Cognitive enhancement by means of TMS and video game training: synergistic effects

by

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A dissertation submitted in accordance with the requirements for the degree of Doctor of Philosophy

at

Universitat Oberta de Catalunya

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April 2018

Abstract

Non-invasive brain stimulation techniques have represented a substantial step forward in the advancement of cognitive neuroscience, especially due to their ability to establish causal links between cognition and the underlying neural substrate of the brain. Among these techniques, transcranial magnetic stimulation (TMS) allows us to modulate the level of cortical excitability of the region underlying the stimulation target with a very high spatial resolution, effectively having an impact on the associated cognitive functions, allowing performance changes that can result in cognitive improvement. However, these changes are often transitory, and there is a need to develop optimized protocols that can potentiate and extend the duration of the stimulation effects so they can be applied in the clinical setting.

Among the cognitive functions that could be enhanced, executive functions are the ones that are more likely to have a visible effect on overall cognition and a greater impact in everyday life. These functions are responsible for the most complex levels of reasoning in human beings, are tightly linked with the rest of the cognitive functions, and are closely related to the concept of general intelligence. The dorsolateral prefrontal cortex (DLPFC) is one of the main brain regions associated with executive functioning, effectively being a central processing hub for these functions, which is also anatomically and functionally interconnected with a wide range of cortical and subcortical structures. Due to these reasons, and backed by the existing literature in this field, the DLPFC was chosen as the target for the non-invasive stimulation in order to achieve cognitive improvement.

The effectiveness of TMS in achieving cognitive changes is potentiated when used in conjunction with a cognitive training emphasizing the targeted cognitive function. The characteristics of the cognitive training are key for achieving the desired near and far-transfer effects. The integration of different cognitive components, the levels of engagement and motivation, and the amount of exposure to the task are factors that must be taken into account to maximize transfer effects. Video games have regained notorious attention in this scientific field, and possesses all the appropriate features to be used for this purpose. They are widespread, they integrate several cognitive processes at once with variable difficulty adjustments, they possess elements that motivate users to spend more time playing, and they are often used for extended periods of time over a person's lifetime, enough to have a real impact on cognition. The joint use of TMS and video game training is expected to create synergistic effects on cognitive performance, enhancing cognitive functions related to the stimulation site and the contexts exposed during video game play.

This thesis provides an in-depth analysis on the topics of cognitive enhancement through TMS, the neural correlates of video games, and cognitive enhancement as a result of video game training (by placing an emphasis on executive functioning) through exhaustive literature reviews. These three pillars have the aim of finding out the best parameters for maximizing the positive impact of TMS and video game training on cognition and the generalization of these effects.

For the experimental stage, an intermittent theta-burst transcranial magnetic stimulation (iTBS) over the right DLPFC has been employed. This protocol was chosen for its capacity of inducing effects comparable to long-term potentiation. Ten stimulation sessions, administered during a two-week period, were performed with the purpose of potentiating the effect of video game training, in combination with a video game training in a 3D platform game with strategy elements that relies extensively on the DLPFC. Four experimental groups were composed by combining the administration of active and sham iTBS stimulation, and the high and low previous video game experience of the participants. Cognitive performance was assessed through a comprehensive neuropsychological battery at three different time points: at the baseline, at the end of the training period, and at a follow-up assessment two weeks after the end of the training.

The results indicated that the effects of the non-invasive brain stimulation on cognitive enhancement in conjunction with the video game training were less notorious and consistent than expected. However, the previous video game experience was found to be determinant for both the baseline performance and for the skill acquisition rate in a series of cognitive domains, particularly processing speed, visuospatial skill, cognitive inhibition and working memory. The reasons behind those changes or the lack thereof have been discussed comprehensively.

These findings provide important implications for the use of cognitive enhancement programs through non-invasive stimulation techniques and for the use of new technologies, such as video games, as coadjutant interventions. Since the cumulative effects of iTBS have barely been tested before in this context, it is not clear whether the low impact on cognition was caused by an inefficient excitation of the cerebral cortex, a sub-optimal choice of the stimulation target or for other unexpected and unexplored reasons. On the other hand, the use of video games has a visible and widespread effect on cognition, both as a result of lifetime video game experience or through shorter video game training programs. Due to their intrinsic characteristics, video games can be successfully used as a tool to study cognition in situations where the use of simpler tasks would be less efficient.

Acknowledgements

Without the support and help of all those who have been involved, this project would not have been a reality. This is why I would like to dedicate this page to all those who, at one time or another, have contributed to make it possible.

Foremost, I would like to express my gratitude to my thesis advisors Dr. Elena Muñoz Marrón and Dr. Diego Redolar Ripoll of the *Universitat Oberta de Catalunya (UOC)*, for their patient guidance, encouragement, and useful critiques of this research work. They have been one of the main pillars during the development of this work and could not have succeed without them.

I am also very grateful and would specially like to thank all my colleagues at the university that contributed this work throughout the doctorate. Especially to Raquel, as her advice and recommendations helped me in many occasions. To Cristina, for her invaluable contribution in reviewing the theoretical framework of the thesis. Also to Isabel, Joan Miquel, Núria, and Quim for their contributions during the initial stages of this project, and to Cecilia, Jesica and Andrea for their personal involvement and support throughout the experimental stages of the doctorate.

I cannot ignore the importance of all the other people who have been involved in this project, with a special mention to all those volunteers who participated in the study.

I must not forget about all the fellow doctorate candidates from UOC's Doctorate School, Aida, Amir, Arun, Lara, Monica, Negar, Pilar, Ronak, Victor…. for their mutual support during the initial stages of the doctorate degree.

My grateful thanks are also extended to the UOC as a whole, first of all for the financial help for carrying out this project, but also for the learning opportunities that were offered during the degree, and its helpful staff that offered guidance when it was needed.

Finally, I must express my very profound gratitude to my parents, Victoria and Miquel, and to my girlfriend, Marina, for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. This accomplishment would not have been possible without them. Thank you.

Marc Palaus

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1. Foreword

In the field of cognitive neuroscience, we are moving forward, gradually, to deepen the understanding of the inner functioning of our brain. The development of new research techniques is essential because, often, the technology and tools available limit the knowledge that can be attained at a given moment. In this sense, the development of non-invasive brain stimulation techniques, together with neuroimaging techniques, has been a great impulse to the progress of this discipline.

On the other hand, there is a tendency to apply neuroscientific knowledge to describe the neural effects of everyday actions, and going further beyond, to explore the impact that these actions can have over our cognition. This is the case of one of the central topics of this dissertation: the effects of video gaming on the brain.

In this thesis, the effects of the use of transcranial magnetic stimulation (TMS), one of the main non-invasive stimulation techniques, have been explored for inducing long-lasting cognitive improvements. When finding the optimum parameters for modulating cortical excitability, the intermittent theta burst stimulation protocol (iTBS) has been chosen due to its promising capacity of achieving long-lasting effects on the cortical activity. In addition, based on scientific evidence of the effects of video game play on brain activity and structure, as well as its potential for cognitive improvement, a video game that had proven effects over the cerebral cortex was chosen as part of the study.

Therefore, an intervention was designed with the aim of achieving plastic changes in the brain by combining iTBS stimulation and video game training that will contribute to amplify the effects of the brain stimulation. The concurrent use of the two techniques is expected to create a synergistic effect, acting in conjunction over the same brain region, mutually potentiating the effects of the two already effective separate interventions.

Executive functions received a preeminent role in this dissertation. These functions, that allow us to regulate our thoughts and behaviors, were the primary object of study. Their implication on our capacity to adapt to the world that surrounds us and their close link to general intelligence makes them especially interesting when studying human cognition and behavior. Achieving improvements in executive functions is out best bet to effectively obtain meaningful changes that affect our everyday life.

The potential impact on cognition that would suppose an improvement in executive capacities was a determinant factor for choosing both the brain stimulation site and the video game used during the training period. The chosen target for stimulation was the dorsolateral prefrontal cortex

(DLPFC), one of the main regions involved in the regulation of executive functions, but also an important cerebral hub responsible for interconnecting many structures in the brain.

However, executive functions are not the only relevant cognitive process that have been studied in this work. This research aims to offer a broader scope, studying a comprehensive selection of cognitive skills, so a wide-spectrum neuropsychological battery has been employed for this purpose, covering the cognitive functions that have been likely affected by the video game play and the TMS.

Thereby, two issues that are currently trending in the world of neuroscience have been dealt with in depth: the use of non-invasive stimulation techniques for cognitive enhancement in healthy people, and the effects of the use of video games in the brain.

The dissertation that you have in your hands corresponds to the doctoral project carried out during the 2014-2018 period at the cognitive neuroscience laboratory (*Cognitive NeuroLab*) of the *Universitat Oberta de Catalunya*, under the supervision of Dr. Elena Muñoz-Marrón and Dr. Diego Redolar-Ripoll.

I hope you enjoy your reading.

Marc Palaus Gallego

Barcelona, 23th May 2018

2. Theoretical Framework and Empirical Evidence

This section is devoted to explaining in depth all the theoretical bases on which this dissertation is based, with the aim of providing all the required background that leads to, and justifies, the research questions and the subsequent experimental stages used in this project, described in section 3.

The first part begins with an explanation of the main group of cognitive functions on which this work is focused: the executive functions. After explaining the definition and the origins of the concept, a detailed taxonomy of how these functions are structured and how can they be measured is provided. Finally, the structural and functional correspondences of the main brain regions responsible for these functions, where the prefrontal lobes have a critical role, are described.

The second part is dedicated to the neuroscience of video gaming, including how video games can be used for the improvement of cognitive performance, an exhaustive review of the underlying neural correlates of video gaming, exploring its structural and functional effects, and, finally, a literature review of the video game training programs and their effects on cognition.

The third and last part is focused on non-invasive brain stimulation, particularly transcranial magnetic stimulation (TMS). Within this sub-section, the technique as well as its effects on the cerebral cortex are described thoroughly, and finishes with its possible applications, with an emphasis on cognitive enhancement in healthy individuals, and providing a state-of-the-art revision on its application on executive functioning.

Together, these three sections provide the entire theoretical basis needed for the development of the experimental stage of this project, featuring the components of cognitive enhancement, video gaming, and non-invasive brain stimulation.

2.1 Executive Functions

2.1.1 What are executive functions?

When we talk about executive functions, we are referring to a complex ensemble of cognitive processes that work together with the aim of directing other abilities and behaviors towards a desired goal. As the name suggests, executive functions play an executive role in cognition, as they modulate the action of other cognitive processes, but are not limited to this aspect. They are also responsible for integrating all the sensory information that reaches the brain and use that information for programming or inhibiting suitable motor actions while acting largely in an unconscious manner. Executive functions give us cognitive flexibility, allowing us to bypass automatic thoughts and behavior in order to think and act in original and creative ways. Otherwise, our behavior would be entirely guided by responses to environmental and endogenous stimuli and we would be unable to prioritize and suppress thoughts, make plans for future actions and foresee the consequences of those actions.

Executive processes have often been compared to the role of an orchestra conductor that is responsible for managing, directing and coordinating the various members of the ensemble. Despite all of them being individually skillful musicians, they are unlikely to produce a harmonious sound by themselves without the intervention of someone in charge. The conductor is responsible for selecting which piece is to be played, deciding the moment they start playing together, controlling the timings, modulating the pace and volume of each section and determining the emphasis of every instrument in each part, to ensure that the final result is harmonious and has an optimal performance (Brown, 2006). The role of executive functions (the orchestra conductor) over more basic cognitive components (individual musicians) is not far from this analogy.

Overall, executive functions arguably represent the highest-order cognitive components and are responsible for the most complex behaviors, such as the capacity for reasoning, abstraction and carrying out complex sequences of planned actions, all of them being factors that are directly correlated with our concept of intelligence. Although these functions are also found in a diverse range of animal species, particularly in higher-order vertebrates, it is in humans where they are most developed, showing a qualitative leap in their potential regarding the rest of the animal kingdom.

There is a tight relationship between these executive processes and the prefrontal lobe, to the extent that the term *frontal functions* is sometimes used as a synonym. Nevertheless, this is an oversimplification since the extent of these functions surpasses the limits of the frontal lobe while at the same time this lobe also devotes extensive regions to other purposes such as motor functioning, reward, emotional processing, social cognition and language production.

The study of executive functions as a research topic is relatively recent. It was not until the 1970s that the specific concept of *executive functions* was first defined (S. Goldstein, Naglieri, Princiotta, & Otero, 2014). However, we can find directly related concepts in the literature as far back as the 1840s, starting with the Phineas Gage case study. This case describes a railroad worker that, as a result of an accident, was pierced with a large iron rod through his frontal lobe, altering his personality and becoming more disinhibited and hyperactive (Ratiu, Talos, Haker, Lieberman, &

Everett, 2004). This event served as a starting point for neuroscientists to deepen in the role of the frontal lobe. During the 1950s, the first differences between automatic and controlled behavior linked with the prefrontal cortex were studied (Broadbent, 1954). This led to the further development of new theoretical models, primarily based on the management of attentional resources, such as the concept of *selective attention*, closely related to executive functions (Shiffrin & Schneider, 1977), while in 1975, Michael Posner (1975) coined the term *cognitive control*, as a more complex system that guided attention. In parallel, Baddeley developed his model of working memory (Alan D. Baddeley & Hitch, 1974), including a *central executive* component, related to the manipulation of short-term memory. Similarly, the model by Norman and Shallice (1986; 1981) suggested that attention was regulated by a *supervisory system*. It was around that time that consensus seemed to indicate that all these processes were located in prefrontal regions. The first time the term *executive* was used when referring to these processes was in 1973 (Pribram, 1973). Since that moment, a myriad of theoretical frameworks flooded the literature and there was little consensus regarding what were the fundamental components, subdivisions and hierarchy of the executive functions, and whether those components were independent or constituted a unitary phenomenon.

While the classification of executive functions has not been completely consolidated, we are slowly reaching a consensus on their key aspects. One of the most accepted categorizations includes the concepts of *shifting*, *updating*, and *inhibition*, while wider conceptualizations including aspects like cognitive flexibility, control over behavioral initiation, planning and organization, self-monitoring, and decision-making seem to be well accepted by the scientific community (for more details see Miyake et al., 2000).

Whereas the terms *executive functions* and *cognitive control* are essentially interchangeable, the former seems to be more restricted to its core concepts while the latter seems to take on a more abstract nuance that allows more degrees of freedom in its conceptualization. Among all the competing models, we considered the classification suggested by Purves (2012) due to its integrative nature.

In this section, we will introduce the anatomy of the frontal lobes, their connectivity and the functional implications of each region in executive-like processes. On a cognitive level, a detailed taxonomy of the executive functions will be elaborated, with an emphasis on the neuroanatomical correlates for each function and studies that provide evidence for every situation.

2.1.2 Taxonomy of executive functions

It is difficult to get a consensus on the classification of executive functions since they are a series of very diverse processes whose hierarchy and the sub-processes they encompass are still not fully understood. However, the key aspect is that all those behaviors are necessary to modify actions that otherwise would be made automatically, allowing to supervise, monitor and flexibly modulate the activity of other cognitive processes, directing them to the achievement of objectives. Contrarily, we would act only by reflexes, in a stereotyped manner and guided by environmental stimuli.

A possible classification, proposed by Purves (2012), is based on the principle that many definitions of executive functions are centered on the concepts of *rules* and *control*. The rules that guide the human behavior, characterized by being abstract and flexible, apply to wide range of contexts that we can identify perceptually and constrain the range of possible actions. In this case, control processes refer to the ability to engage and disengage a particular set of rules depending on the appropriate context.

Based on each context and its pertinent associated behaviors, the effective use of rules can be further subdivided into several components. Rules have to be *initiated* to match stimuli to actions based on current goals, but they also have to be *inhibited* when they are no longer appropriate, and that not only applies to specific actions but also to information processing and social situations. Sometimes a rule is no longer suitable and has to be transitioned to a more convenient one and, in that case, we talk about *shifting* (also known as *task switching*). Finally, sometimes two or more rules have to be integrated in order to form higher-order contingencies for behavior, in which we call *relating* (see Figure 1).

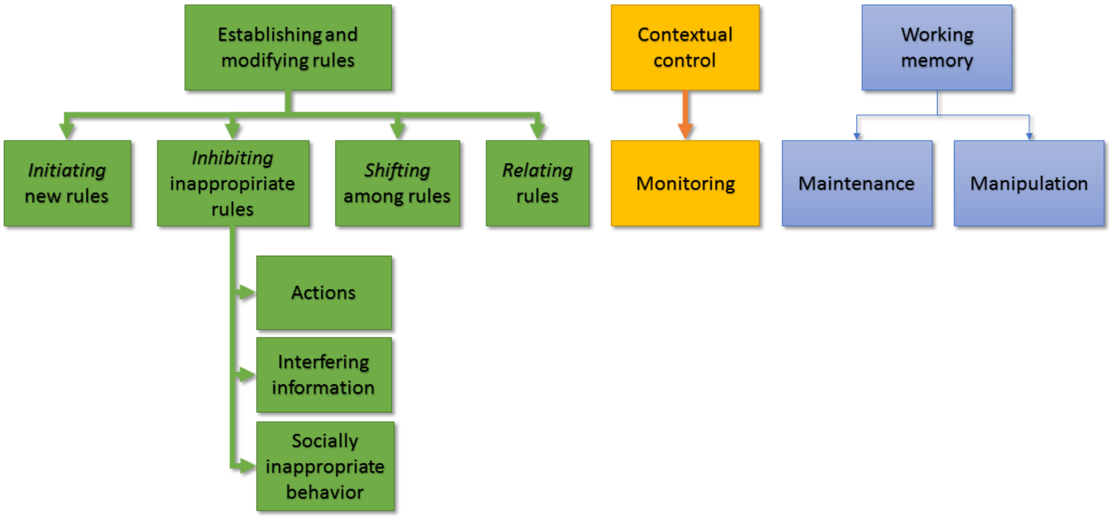

Figure 1. Taxonomy of executive functions, according to Purves et al. (2012). The three main components of this model include functions related to the creation and modification of behavioral rules, monitoring of contextual information and the maintenance and manipulation of short-term information through the working memory.

In order to guide the engagement of other executive functions, the brain requires a *control* component. Rules need to be updated more or less quickly depending on the changes in the environment and resources must be spent to *monitor* the success of behavioral actions and resolve conflicts between actions that might be taken. Therefore, the efficient allocation of these cognitive resources is decisive.

Working memory is another of the key aspects of executive functions and is one of the topics that has sparked more interest in the literature since the advent of the study of the prefrontal cortex. Essentially, it consists of the temporary maintenance and manipulation of information (including rules) that is no longer available to our senses, in order to successfully achieve short-term goals. This information can either be from a distant past, retrieved from the long-term memory, or can be something that has been recently experienced in the environment and held in the short-term memory.

Together, the three divisions proposed in this model, establishment, and modification of rules, contextual control, and working memory, provide a comprehensive categorization of the entire hierarchy of executive functions.

2.1.2.1 Establishing and modifying rules

The first of the three main components involving executive functions deals with the capacity of initiating and inhibiting thoughts and behaviors. When we think about goal-oriented behavior, the first and most basic feature is being able to begin and maintain a new action towards the completion of a goal, which by definition is not driven by external stimuli or by internal predispositions. It is one of the most important aspects of executive functioning since, otherwise, our behavior would be completely instinctive, guided exclusively by the characteristics of the environment, our own physiological needs, and the expectation of a reward through conditioned responses.

Additionally, in order to successfully execute an action aimed at the completion of an objective, inappropriate or distracting information needs to be suppressed, either coming from endogenous or exogenous sources. Our behavior must act accordingly, also suppressing impulsive responses during certain situations that may trigger us to behave in a particular way. Goal-driven behaviors are not something we can simply activate or deactivate, but they rather enter in direct competition with the automatic behaviors that were just described. By default, habits are a powerful source of automatic behavior that are generally adaptive to the environment and require less brain processing power, so we must consciously make an effort if we intend to override them; it is only through the capacity of inhibition that we can keep these automatic behaviors at bay. This capacity for inhibition can also be applied in an interpersonal context, allowing humans to interact with each other appropriately and not just seeking our best interest. This is done by following a series of social norms that help us do what is suitable and needed for each occasion, preventing bad interactions in social contexts with the final objective of achieving long-term goals.

In practice, initiation and inhibition work as complementary functions of executive control. In both cases, executive functions regulate the relative strength of different cognitive or behavioral rules in order to direct and change behavior effectively. In the literature, this complementarity has been reflected in the fact that most sources choose to study them as a unique construct, usually placing more focus in the inhibition aspect, in which several subcomponents have been identified (Purves et al., 2012).

Initiating new rules

The *initiating* component of executive functions is important for responding promptly to changes in the world around us, resulting in adaptive context-specific behaviors, and contributing to motivation. Initiation of targeted behavior has been mostly studied in clinical contexts featuring lateral prefrontal lesions in humans, but these findings are also backed by studies in non-human primates, like in the classical prefrontal studies by Bianchi (1920). Damage in prefrontal regions often features a lack of spontaneity regarding motor movements, complex actions, and mental plans.

Patients with lesions in the lateral prefrontal cortex (PFC) may have preserved verbal and motor abilities, but show personality changes characterized by a lack of proactivity in actions and thoughts, even to the point of disregarding current social relationships. Moreover, these patients do not appear to be concerned about their sudden personality changes or their recent lack of interest in the world around them, even when it implies situations that should cause severe emotional distress, such as the loss of a loved one. The specific impairments associated with the lesion depend on the affected regions; when lateral regions are affected but ventral areas are spared, motor behavior tend to be the most affected aspect, causing apathy, social withdrawal and lack of initiative, where patients only respond to direct commands.

From a lower-level perspective, electrophysiological studies shed some light on how abstract rules might be encoded and initiated in the brain. Evidence shows that, in an experiment in monkeys where several rules are enforced, they are maintained and initiated by different populations of prefrontal neurons, located where our central dorsolateral prefrontal cortex (DLPFC) would be, and are activated accordingly when the situation requires one rule of another, prior to the actual response. These results show that the neural activity reflected the abstraction of rules and principles other than the mere presence of stimuli or activity derived from responding to the items (J D Wallis, Anderson, & Miller, 2001).

Examining the issue from the perspective of a whole neural system, motivation for initiating behavior in the presence of an expected reward seems to be a product of a neural network in which the mesolimbic and mesocortical dopaminergic systems constitute a fundamental core, also involving the DLPFC, the ventral tegmental area (VTA), and the *nucleus accumbens* (nAcc). According to functional magnetic resonance imaging (fMRI) data, the DLPFC was the entry point for reward-related information to this system, and activation in the VTA and the nAcc were directly signaled by this region. Therefore, anticipation for reward was enough to show activity in the DLPFC, whereas activity in the VTA and nAcc was only indirectly linked to reward, determining that the prefrontal region is key for integrating the representation of reward before actually engaging other areas involved in this function and initiating the motivated behavior (Ballard et al., 2011). When rules are complex enough to involve a sequence of actions, individual populations of prefrontal neurons may be responsible for encoding specific steps of that complex rule.

Therefore, the DLPFC seems to be the region in charge of selecting the appropriate action in response to a stimulus. Particularly, the anterior middle frontal gyrus, corresponding to Brodmann area 46, seems to be the region most implicated in initiating and shifting behavior, also coactivating posterior parietal regions. On the other hand, the inferior frontal junction, at the intersection of the inferior frontal sulcus with the inferior precentral sulcus, has an important role in mapping a sensory stimuli to the preparation of the task-specific behavior (Derrfuss, Brass, Neumann, & Von Cramon, 2005).

The basal ganglia are another region that contributes to specific functions within cognitive control, specifically the creation of new rules for behavior. They form a series of loops between the PFC and the basal ganglia that, apart from contributing to motor control, also partake in cognitive and emotional aspects. Particularly, it seems that their interaction with the prefrontal cortex helps to map specific stimulus to particular responses.

Finally, the parietal cortex also has a supporting role in the creation of behavioral rules, particularly those linked to the generation of actions, and representing task-reward associations (Wisniewski, Reverberi, Momennejad, Kahnt, & Haynes, 2015). The region alongside the lateral intraparietal area helps to code the expected value of multiple potential behaviors actions and shows activation when a set of possible actions is actively maintained in the case they might be required in a given context (C. J. Burke & Tobler, 2011).

Inhibiting inappropriate rules

On the same dimension as the initiation of behavior, we find *inhibition*, acting as its complementary process. With inhibition, we refer to the ability of selecting the desired information or behavior by suppressing attention to unimportant or distracting elements from the environment or our internal mental activity that might interfere with our immediate goals. This is done in order to control our own attention, behavior, and thoughts, despite internal predispositions and external temptations, so we can take the most appropriate and rational action. Just like the rest of the executive functions, inhibition is effortful and must be consciously and continuously made in order to avoid being lured by stimuli and be driven by automatic behavior.

The study of inhibition from the perspective of executive functions has allowed detecting three main modalities of inhibitory processes. On one hand, we must make a distinction between behavioral inhibition and inhibition of information that interferes with other mental processes, closely related to the management of attentional resources. On the other hand, a component that will be further explained in its corresponding section, inhibition also has a role in suppressing irrelevant information from the working memory. However, when we talk about cognitive inhibition, which is volitional/effortful, we do not include automatic inhibition processes such as those observed during attentional blink or negative priming tasks.

It is likely that inhibitory control of attention and behavior share common neural substrates, although the two appear to be dissociable to some extent. Factor analysis showed that both modalities of inhibition correlate strongly and can be considered a sole factor (Friedman & Miyake, 2004). Moreover, it is likely that the neural circuits responsible for inhibiting and stopping an action and those for inhibiting an action and shifting to another one are different.

Lesion studies have observed that frontal damage leads to perseveration errors. While that does not seem to affect the learning of new rules, it affects the inhibition of previously learned rules, and the perseveration behavior continues even after receiving negative feedback.

The development of inhibition matches the general trend found in other executive functions. Inhibition performance is much lower in young children (4 to 9 years old) than in adults, measured both in accuracy and in processing speed. That difference in performance is not only observed quantitatively since it also shows some different patterns of response. There are some unique features of inhibition in children compared to adults. In a pure inhibition task, the *hearts and flowers task*, where trials could be congruent (responding at the same side of the stimulus) or incongruent (responding at the opposite side), children were slower and less accurate in a block composed by congruent stimuli than on a block composed by incongruent stimuli. This difference slowly fades as children age, as their brain matures during adolescence (Luna, 2009; Luna, Garver, Urban, Lazar, & Sweeney, 2004), and it is not shown at all in adults, where they are equally fast and accurate in the two blocks (Davidson, Amso, Anderson, & Diamond, 2006). It is important to note that the working memory requirements for the two blocks are the same, as just two rules are held in memory in order to complete the task. The order of presentation of each block did not affect these results, barring the possibility that a worse performance could be due to the need to inhibit the rule from the previous block (Wright & Diamond, 2014). However, when the number of rules that have to be actively maintained increases, it is harder for adults to keep up with the increasing working memory demands compared to children. Moreover, adults were more likely to trade response speed in order to produce more accurate responses, while children showed their impulsiveness by maintaining steady response times at the cost of the accuracy (Davidson et al., 2006).

The early development of inhibitory control is a good predictor of outcomes throughout life, correlating with a wide range of indicators of health and wealth. Children that display better inhibition skills, such as being more persistent and less easily distracted, were associated with lower school dropout rates in adolescence, lower obesity and hypertension rates, lower prevalence of substance abuse, less criminal offenses and greater overall life satisfaction, even after controlling for socio-economic factors and overall intelligence (Moffitt et al., 2011).

Inhibitory control tends to decline in healthy older adults as part of the normal aging process. This is shown in a lower capacity in suppressing interfering visual and auditory stimuli, while the capacity of processing expected stimuli (stimuli which are relevant to a task) seems to better resist the aging process (Gazzaley, Cooney, Rissman, & D'Esposito, 2005). This effect is visible even when the specific properties of the stimuli, like when it is going to appear, are known beforehand (Zanto, Hennigan, Ostberg, Clapp, & Gazzaley, 2010). These top-down suppression impairments in older adults have been correlated with an array of neuroimaging techniques to changes in the prefrontal function (electroencephalography (EEG) and fMRI) and have been replicated in a younger sample using non-invasive brain stimulation techniques (TMS) (Gazzaley & D'Esposito, 2007).

Inhibitory control of attention (Interfering information)

When we are preventing irrelevant or unnecessary information from entering our attentional system in order not to lose our focus in another action in which we are currently engaged, we are referring to the cognitive aspect of inhibition. These distracting elements can be exogenous, if they usually constitute visual or auditory elements from the external environment, or can originate internally (endogenous), such as unwanted thoughts and memories of previously acquired information.

Exogenous stimuli may possess a series of features that make them salient over the rest of the information available in our surroundings, such as bright colors, movement, loud noises, etc. constituting bottom-up stimuli that easily capture our attention. In any case, this interfering information has to be filtered if it is not necessary for our current goal. The kind of attentional control needed to block these distractors has received many names: executive attention, endogenous attention, goal-driven attention, selective attention, top-down attention, etc. The cocktail party effect is a good example of suppression of exogenous distractors: if we need to hear somebody in a noisy environment, we have to make the effort of ignoring all the irrelevant but prevalent noises in order to focus on a single conversation in the middle of the party. Likewise, voluntarily following or searching a visual stimulus in an area densely packed with other visually salient elements also requires the use of cognitive inhibition. For example, when we are searching for some specific object, ignoring the rest of the non-matching objects, or when we are driving and we are only paying attention to the road and the surrounding elements, ignoring other stimuli that may catch our eye, but are irrelevant and may distract us from the main task, affecting our safety.

Similarly, endogenous stimuli, composed by mental representations of reality already stored in our short or long-term memory, can also interfere with our ability to carry out mental tasks. Unwanted thoughts and memories from previous activities have to be actively suppressed to carry out a task effectively. For instance, when reading a text in a foreign language sometimes it is necessary to inhibit the meaning of similar-sounding words to those in our native language since that would complicate our understanding of a text.

In neuropsychology, cognitive or attentional inhibition is assessed using tasks that feature one primary objective and the participant must filter all kinds of interfering information in order not to decrease the performance. Cognitive inhibition is tightly related to working memory, compared to other forms of inhibition, and both show a strong correlation. This is why it is not always easy to assess one aspect without measuring the other.

Cognitive inhibition deficits appear when the lateral PFC is damaged. Patients with lesions in the DLPFC display problems filtering irrelevant information in a delayed match-to-sample task (see Figure 2) with distractors between the sample and the matching stimuli, but if the task did not include distracting info, being a pure working memory task, they showed normal working memory performance. There is some evidence, as measured by the auditory match-to-sample task that attentional networks already modulate sensory regions to avoid task-irrelevant interferences (Purves et al., 2012).

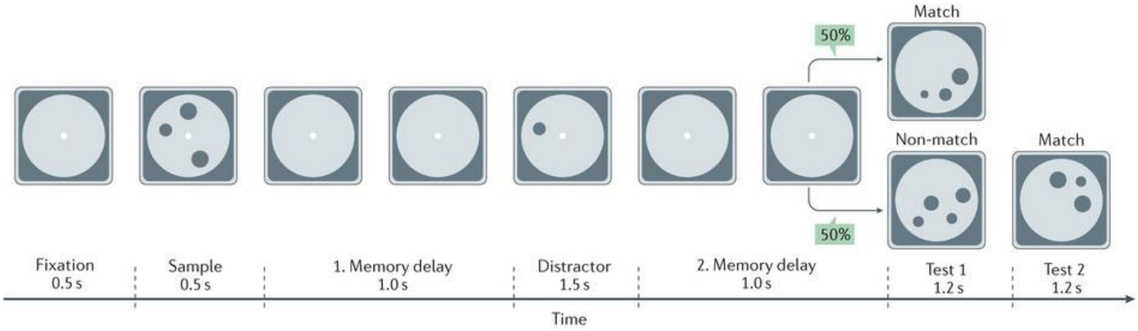

Figure 2. Procedure followed in each trial of the match-to-sample task. After a sample is presented, a distractor appears after a fixed delay. A second delay appears before either a matching or a non-matching sample appears. Adapted from: (Nieder, 2016)

Apart from the role of the lateral PFC in cognitive inhibition, which shows increased activation when actively suppressing information since it is an action that requires effort, the hippocampal formation reduces its activation during that suppression.

Inhibiting actions

The other main form of inhibition is *behavioral inhibition*. This form of inhibition is used when we want to consciously stop a planned action that has already been initiated, or prevent the realization of an action that would have been initiated according to external stimuli or internal predispositions. Although it can be understood as the complementary of behavioral initiation, it probably does not share the same neural substrate. In this case, an action has already been planned and sent to the motor system, and stopping that action involves more than just deactivating the planned action; inhibition requires an effortful and conscious action to suppress the planned response.

One of the main problems with inhibition is the intrinsic difficulty in obtaining measures without involving other cognitive and motor processes. The *horse-race model of inhibition* is an approach that tries to explain and measure this cognitive phenomenon. It describes the ability to inhibit a response as a competition between the tendency to respond a stimulus and the volitional inhibition of that response. Measured in the order of milliseconds, the process that finishes first will be the one that will be shown behaviorally. As a general rule, if the *inhibition* order is given close enough (temporally) to the *respond* order, the action will be inhibited, and the changes of inhibiting that action are lower the more temporally spaced is the *inhibition* order presented. This pattern can easily be represented in the form of a distribution curve.

The horse-race model is used to estimate the precise timing of cognitive inhibition in the *stop-signal reaction time* (SSRT) paradigm. In this task, a *go* trial is always displayed and the subject must respond as fast as possible, measuring the reaction time in milliseconds. In some of the trials, a *stop* signal (in any modality, usually visual or auditory) will be presented soon after, indicating the subject to suppress the previous *go* response. Since the probability of inhibiting will be given by the temporal separation between the two stimuli, the precise temporal appearance of the *stop* signal can be manipulated and the time required to process an inhibition and suppress the response can be calculated. This is usually done using a staircase design where the temporal spacing between the two stimuli is dynamically altered to achieve the optimum correct timing separating the changes of inhibiting and responding.

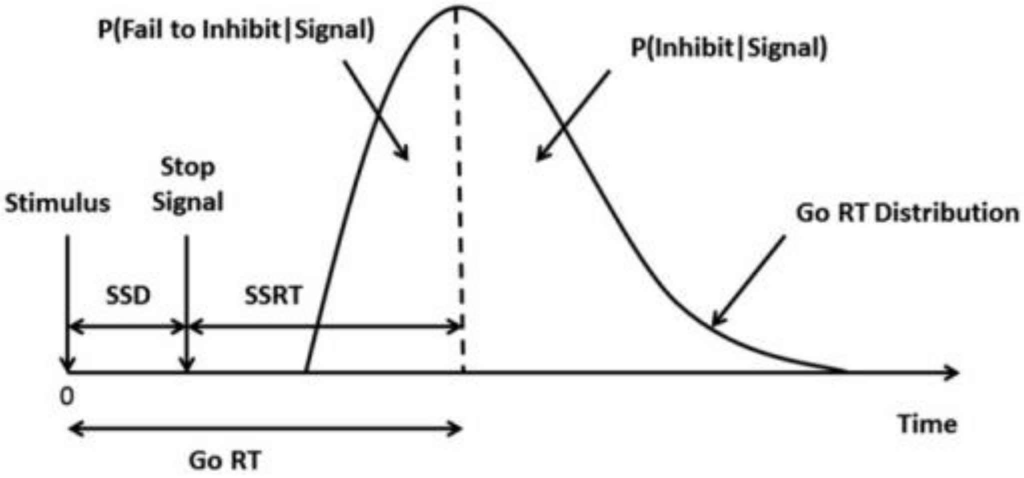

Figure 3. Graphic representation of a trial in the *stop-signal* task, showing the response distribution histogram as a function of time. The "A" point represents the appearance of the "Go" signal, the beginning of the trial. After a variable and very brief moment of time (shorter than the participant's response time), a *stop* signal "B" may appear. If "B" (*Stop*) is presented early enough, the inhibition process will be able to counteract the "A" (Go) response. If "B" (*Stop*) is presented too late, the inhibition process will be unable to finish in time to *stop* the response. The SSRT is, therefore, the time between the presentation of the *Stop* signal ("B") and the temporal moment where the response is inhibited successfully the 50% of the time. Source: (K. L. Evans & Hampson, 2015)

From a neural perspective (Eagle et al., 2008), inhibition process in the SSRT task presents a high involvement of the prefrontal cortex in animal models. Particularly, only lesions in the orbitofrontal cortex seemed to slow down the performance in the SSRT task, although it did not hinder the reaction times in *go* trials. Lesions on the subthalamic nucleus speeded up the latencies in *go* trials, although reduced accuracy in all-Stop trials, concluding that the stopping impairment in independent from the SSRT itself.

The team of Aron et al. (2003) were among the first to consistently link the stop-signal inhibition to the prefrontal lobe in human patients, finding alterations as a result of a lesion on the right inferior frontal gyrus (IFG), but not in the left IFG, in an area connecting the *pars triangularis* and the *pars opercularis*, that showed activation in *stop* trials, regardless of the accuracy, but in the presence of *go* trials, activation is absent.

Bari et al. (2011), also studying the neural substrate of inhibition in rats, found that dorsomedial regions were important for inhibiting already initiated responses. This capacity seems to be mediated by noradrenergic and dopaminergic neurotransmission. Interfering with noradrenergic pathways impaired the stopping ability, while dopaminergic impairments only caused slower *go* responses. They conclude that both orbitofrontal and dorsal prelimbic cortices mediate on the effects of *atomoxetine*, a selective noradrenaline reuptake inhibitor.

Neuropsychological tasks dealing with cognitive inhibition are commonly used in research and the clinical practice (See Table 1), either alone or as part of a wider neuropsychological assessment when evaluating executive performance. The *Stroop* task (Stroop, 1935) is one of the most popular, as it measures the level of interference that a word representing a color painted in a non-matching color produces when the color is read all loud. While this is the classical and most common format of the task, the Stroop paradigm can be applied to other sensory modalities and contexts. For instance, it can be presented in auditory format (Roberts & Hall, 2008), spatial (similar to the Simon effect) (Hilbert, Nakagawa, Bindl, & Bühner, 2014), numerical (Cohen Kadosh, Gevers, & Notebaert, 2011) or even in combination with other emotional tasks (Kappes & Bermeitinger, 2016), to discern the implication and interaction of both cognitive processes.

Assessment of inhibitory control	
Task	**Reference**
Stroop task	(Stroop, 1935)
Simon task	(Simon & Wolf, 1963)
Flanker task	(Eriksen & Eriksen, 1974)
Antisaccade task	(Hallett, 1978)
Delay-of-gratification task	(Mischel & Grusec, 1967)
Go/no-go task	(M. G. Becker, Isaac, & Hynd, 1987)
Stop-signal task	(Lappin & Eriksen, 1966)

Table 1: Common tasks used to assess inhibitory control.

Overall, a task that compares congruent and incongruent stimuli can be considered a Stroop paradigm. In any condition, there will be a facilitating element (usually presented simultaneously, but not necessarily) which will either facilitate or interfere with the main stimuli, and the accuracy and processing speed of each trial is measured. Often, neutral stimuli, not having any facilitating characteristic (such as plain text), are used as a baseline measurement. In the classical paradigm, the facilitating/interfering element is presented simultaneously (usually as a property of the stimuli e.g. color of the text), but paradigms first showing the facilitating/interfering stimuli which will affect how a later stimulus will be processed are common.

Similar to behavioral inhibition, the inhibition of interfering or distracting information has been theorized to work as a race model in which the stimulus that is processed faster (either the interfering information or the inhibition action) is the one which prevails. Both relevant and irrelevant information are processed in parallel. Several theoretical models have been hypothesized to explain the competition between the stimuli, the most common being the *Automaticity* theory, which postulates that one of the two overlapping stimuli is more automatic than the other (in the classical task, reading is more automatic than recognizing the color of a text), due to habit or to intrinsic characteristics. Both stimuli require a certain amount of attentional resources, but in this case, resources must be purposely allocated to ignore (inhibit) the more automatic features of the stimuli, therefore requiring more cognitive resources than just processing the neutral or congruent stimuli. Reading does not need controlled attention (it is automatic), but uses attentional resources dedicated to processing the color of the word, hindering the overall performance. An alternative explanation, the *Parallel distributed processing*, states that different pathways are responsible for the different types of information, and some of these pathways are stronger than others, but not faster. Therefore, the strength of each pathway, when more than one is activated simultaneously, determines the level of automaticity of a task, and the source of interference is the use of the weaker path (in this case, color naming) instead of the stronger one (word reading).

When examined from a neural perspective, neuroimaging techniques show the implication of two main regions, the anterior cingulate cortex (ACC) and the DLPFC. It seems that the ACC is responsible for allocating attentional resources and dealing with error detection, selecting the appropriate response, showing more or less implication depending on the degree of response conflict and response expectancy (Mead et al., 2002). The DLPFC, in this case, seems to be recruited when the interference or conflict appears in order to use top-down mechanisms, the most purely executive aspect of this paradigm, to resolve this conflict. Moreover, the DLFPC would mediate how other regions (mainly posterior areas, like the posterior parietal cortex (PPC)) to favor the most relevant criteria for resolving the conflict (M. Botvinick, 2004; M M Botvinick, Braver, Barch, Carter, & Cohen, 2001; Grandjean et al., 2012). When different modalities of the Stroop paradigm are compared, different subregions of the DLPFC show activation. For instance, when comparing a color-word task with a spatial-word task, a dorsal-ventral dissociation was observed: the color-word task elicited greater activation in inferior frontal regions (BA44) and DLPFC (BA46) than the spatial-word task, which displayed greater activation in areas 8 and 9 of the left middle frontal gyrus (lMFG). Similar dissociations are found in the ACC and posterior areas for the different modalities of the task (Banich et al., 2000).

The Flanker task, a paradigm that also uses congruent and incongruent trials, also seems to share a lot of features with the Stroop task, featuring similar neuroanatomic implications, mainly the ACC and the DLPFC. In this task, the participant must attend a centrally presented stimulus while ignoring the stimuli surrounding it, which may be congruent or incongruent, slowing down the response time in the incongruent trials, as they require more executive processing power.

Another variation of these paradigms is the *antisaccade* task, focusing on visual attention, which consists in inhibiting our natural impulse to look towards salient stimuli. In this task, the participant is told to look away from a stimulus presented on a screen normally in two preset left/right locations. Contrary to other inhibition tasks, the use of eye movements is mediated by a series of regions (frontal eye fields (FEF), supplementary motor area (SMA), thalamus, and putamen) that play a key role regarding the intention of reflexive eye movements, and the involvement of the DLPFC is limited compared to other inhibition tasks, but nevertheless still important (Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991).

The *oddball* and *go/no-go* are a pair of complementary tasks which also implicate the use of cognitive inhibition. Just like the *stop-signal* task, the *go/no-go* is another classic paradigm to study inhibition in which some of the trials (*no-go*) the participant must withhold the impulse to respond when a specific stimulus is displayed, contrary to the *go* trials, that constitute the majority of items of the task, which require a fast motor response right after the appearance of the cue. Apart from measuring the level of accuracy, using the *go/no-go* allows us to obtain a purer value of inhibition reaction times: it can be obtained by subtracting response times in a two-choice paradigm with response times in a go/no-go paradigm. However, some authors argue that the two tasks are not measuring the same effect (Gomez, Ratcliff, & Perea, 2007). The mechanism of this task is related to the one found in the oddball paradigm, in which a series of repetitive stimuli (often with different latencies) is interrupted by a novel or deviant stimuli. The participant's reaction to that stimuli is recorded, usually using functional neuroimaging techniques, without needing to produce a motor response and therefore only requiring sensory and cognitive abilities to process the stimuli. However, due to the lack of measurable correct/wrong trials, the oddball task is not a valid paradigm for measuring inhibiting abilities.

Compared to tasks which require a response for each trial regardless of the inhibition condition (two-choice tasks like Stroop, Flanker or Simon tasks), the Go/No-go (and possibly the stop-signal task) provide a better signal-to-noise ratio (Gordon & Caramazza, 1982). It is generally assumed that these two tasks are analogous and measure the same phenomenon, but comparing the results of the two tasks show that the reality is more complex, possibly because in the go/no-go paradigm the stimulus used for *stop* trials can be associated with the inhibition response and partly automated effect which is not present in the stop-signal task (Verbruggen & Logan, 2008). In the Go/no-go task, the areas which are more implicated are the pre-supplementary motor area (pre-SMA) and the left fusiform gyrus, and when more complex versions of the Go/no-go were used, the right DLPFC and the inferior parietal circuit were recruited, likely as a result of the increasing cognitive demands (that is, a higher use of working memory) (Simmonds, Pekar, & Mostofsky, 2008).

To sum up, there is a variety of methods to measure the capacity of inhibition, although it still needs to be determined if the distinction between inhibition of attention and inhibition of action, and within the different modalities of inhibition of action, are valid when we attempt to observe their neural correlates, since the neural basis for both modalities largely overlap (Diamond, 2014).

Shifting among rules (task switching)

Cognitive flexibility, task switching or set shifting is another of the core executive function, and its correct functioning relies on processes linked to inhibition and working memory. In order to engage in a new task or just keep up switch what is happening in the environment, we must inhibit the current mental representation and redirect our focus of attention to the new set of information, loading it in our working memory and acting appropriately. Cognitive flexibility not only applies to changing to a new task set: on a broader sense, it allows us to acquire new perspectives when trying to solve a problem (what is often called "thinking outside the box") when the traditional approaches do not work anymore.

It is the opposite of mental rigidity. We use shifting in our everyday tasks every time we need to adjust our behavior based on the demands or priorities of our current situation, or a new opportunity unexpectedly arises and we suddenly have to consider it in order to obtain the best possible outcome. A lack of mental flexibility might cause a person to insist on a non-optimal approach to a problem and not consider alternative solutions. Although the concepts of cognitive flexibility, set shifting and task switching might not be technically equivalent, they greatly overlap and their distinction would be equivalent to that between cognitive control and executive functions, where "cognitive flexibility" would represent a broader term and task switching/set shifting a more low-level approach to the same mental phenomenon.

The most common method to assess these functions is by using task switching/set shifting tasks which use a paradigm based on the exposition to two concurrent tasks where only one of them is actively performed based on the presence of a specific cue. For instance, tasks could be as simple as recognizing vowels from consonants, distinguishing one color from another, identifying odd and even numbers, recognizing shapes in figures, or locating the relative position of a stimulus on the screen. Often, these features are bivalent (see Figure 4) so that a stimulus displays features of the two tasks (e.g. a green and odd number), and are arranged so what would be the correct response for one, would be an incorrect answer if following the other task. After a cue before every trial tells the participant which task they must engage, they are expected to respond as fast as possible, and the reaction times, as well as the accuracy, are recorded to assess as indicators for performance.

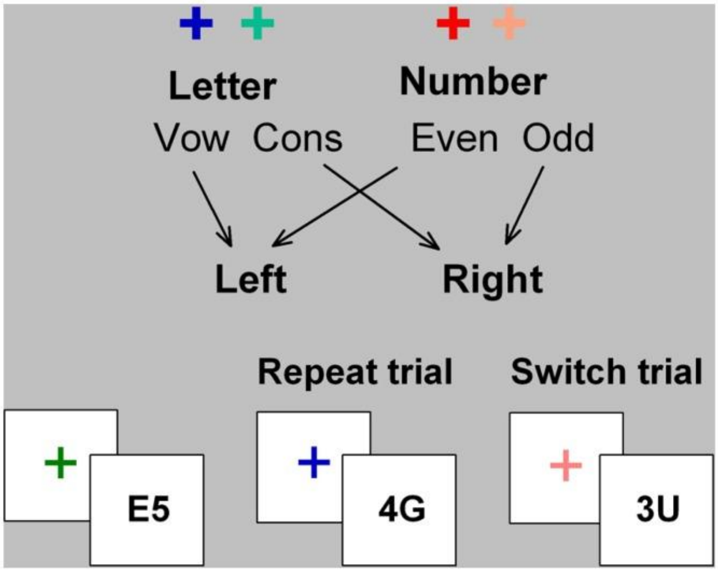

Figure 4. Example of a set-shifting task using bivalent stimuli. In this case, the color of the cue (+) indicates whether the participant must pay attention to the letter or the number that will follow shortly. Adapted from: (Whitson et al., 2014)

Under this paradigm, it is assumed that if the current task is different from the one in the previous trial, an extra effort will be made in order to cancel (inhibit) the mental representation of the previous task and load the rules for the upcoming task, so longer reaction times are expected (reflecting the processing of these steps) compared to trials where the same task appears consecutively. The difference between the two types of trials (*different task* minus *same task*) can act as an indicator of the switching costs. However, that is only valid if we assume that the rules for each task are loaded to the working memory each time a different cue appears, but it is possible that both rules are loaded in parallel and be present in the working memory during the whole administration of the switching task, and the differences in reaction time between consecutive and non-consecutive trials might only account for the selection of the appropriate task. In this case, comparing the performance of a task switching paradigm with a simple or choice-reaction time task, featuring the same kind of stimuli would yield more valid results.

A widely used task and probably the oldest neuropsychological test used to assess set shifting is the Wisconsin Card Sorting Test (WCST) (see Figure 5). In this task, that can be applied in computerized or traditional formats, a deck of cards containing figures varying in color, number and shape are presented to the participant in random order, with the instruction to determine which is the relevant variable for classifying a card, while the criteria change every few cards, and the participant must realize that fact in order to correct the responses according to the new criteria. The number of tries before the participant corrects his criteria and starts responding correctly are counted. However, this task does not provide a value of the latency derived from processing the choice, so it is more frequently used in neuropsychological assessment rather than in neuroscience research.

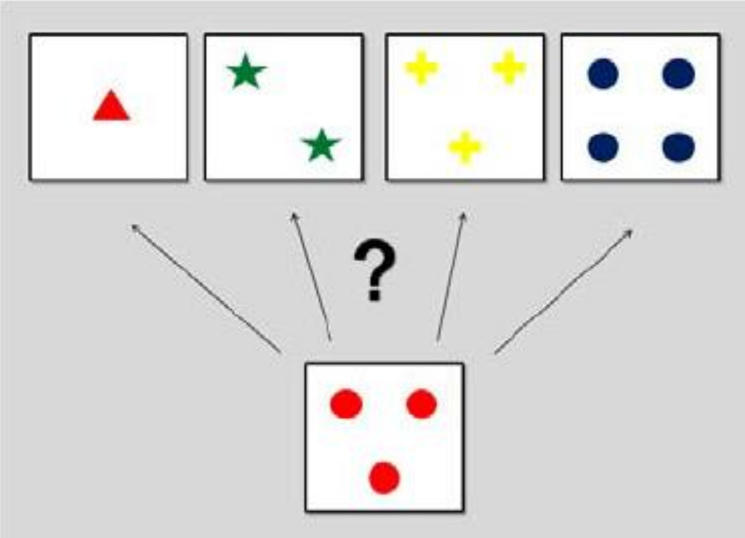

Figure 5. Example trial of the Wisconsin Card Sorting Test (WCST). The participant must choose one card according to one unknown rule (color, shape or number), that changes every several trials. Adapted from: (Youmans, Figueroa, & Kramarova, 2011)

One of the reasons humans have trouble "letting go" from the last rule that worked to successfully accomplish a task has been termed "attentional inertia", which is the tendency to continue to focus attention on what had previously been relevant (Chatham, Yerys, & Munakata, 2012; Kirkham, Cruess, & Diamond, 2003; Kloo & Perner, 2005). Just like any other executive function, task shifting develops with age, with children displaying much more "attentional inertia" compared to adults, getting stuck in a particular way of thinking, fixated on a certain characteristic of an object and being unable to switch to other stimuli or elements of the environment. Neurally, this is displayed as DLPFC activation every time a prepotent tendency is inhibited (Wendelken, Munakata, Baym, Souza, & Bunge, 2012).

Development of cognitive flexibility

Different components of task switching develop at different points along childhood and early adulthood. Perhaps the easiest task that a children as young as 2.5 years old can successfully accomplish (Brooks, Hanauer, Padowska, & Rosman, 2003; Perner & Lang, 2002) is a *within dimension* switching (also known as *reversal task* or *intradimensional shifting*) which consists in training responses to stimulus associated with a particular key mapping and then, in the second half of eh test, reversing the associated keys for each stimulus. The ability to change were you respond is the earliest developed aspect and precedes the development of the capacity to direct one's attentional focus to other stimuli. Children are able to complete the Dimensional Change Card Sort Test (DCCS) (see Figure 6) when they reach the age of 4.5-5, and from even a younger age (3-3.5) if colors are used as the main discrimination criteria (Diamond, 2005; Kloo & Perner, 2005).

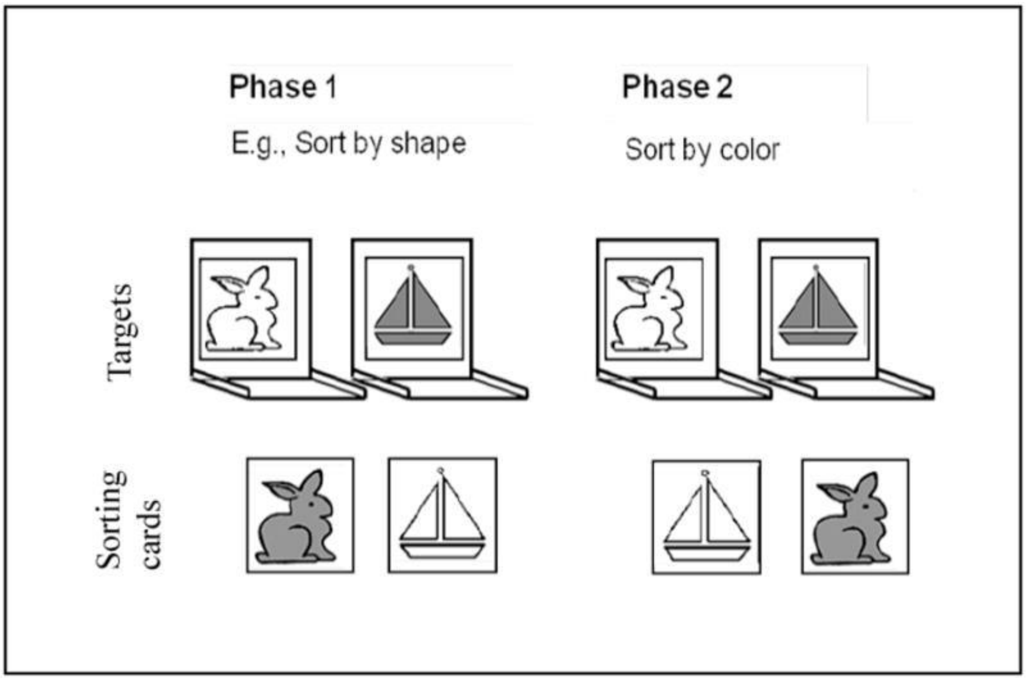

Figure 6. The Dimensional Change Card Sort Test (DCCS) is a task equivalent to a much-simplified version of the Wisconsin Card Sorting Test (WCST) with only two dimensions instead of four, containing just one rule shift during each application, and where the response criterion is reminded at every trial. Source: (Hanania, 2010)

Task switching performance reaches its peak during early adulthood and starts to decline with age. With age, children improve both in accuracy and speed, while aging tends to affect mainly the speed component (Cepeda, Kramer, & Gonzalez de Sather, 2001). Compared to young adults, older adults show slower response times in mixed blocks (where the two tasks can appear mixed one after another) than in single-task blocks. Furthermore, within mixed blocks, they are almost equally slow in repeat and in *switch* trials, but that effect is not found in young adults (Kray & Lindenberger, 2000; Mayr & Liebscher, 2001; Meiran & Gotler, 2001).

The development of executive functions is also linked to how we use them regarding the environmental demands; whereas young children and older adults tens to respond reactively to their environment, older children and young adults adopt a more proactive and anticipatory stance (Czernochowski, Nessler, & Friedman, 2010; Karayanidis, Whitson, Heathcote, & Michie, 2011; Munakata, Snyder, & Chatham, 2012).

Relating rules

The unique cognitive capabilities that can be attributed to the human brain arise, to a large extent, from the precise interaction of all aspects of executive functioning, where one of the main exponents of this synergy is the ability to create complex mental models of the world. The capacity of representing abstract thoughts and concepts is closely linked to frontal functions, as frontal damage often impairs the ability to create high-order abstract representations. A person with frontal lesions may have thoughts that operate only in very concrete and limited ways, either for outer world objects or for the patient's inner experiences. This is further manifested in the ability to arouse and organize, direct and control ideas or feelings under one's own will (K. Goldstein & Scheerer, 1941).

This lack of ability to form abstract representations and behaviors also manifests in the difficulty or refusal of enunciating statements that the patient knows they are false, even when they are explained that they are not true observations in the literal sense, and often these explanations are accompanied by a rigid behavior and being resistant to conviction. This tendency to express literal meanings is also present when they are told to explain the meaning of simple proverbs, fixating in the immediate literal sense and being unable to extract the generalization behind it. Some frontal patients are unable to complete tasks that involve the classification of elements by some rule, such as sorting a series of cards by some criteria, where frontal patients might instead match them by pairs instead, lacking the ability to abstract the general rules and even learn from aids. They also show difficulties integrating sets of information into an inclusive and coherent narrative. When presented with a task consisting of a series of pictures and asked to form a cohesive story with all of them, a frontal patient may be unable to integrate them. Deficits are also shown in the difficulty to understand the reality of non-immediate situations, preferring concrete, real events set in the immediate present rather than in a hypothetical future (K. Goldstein & Scheerer, 1941).

Relating rules offers us the possibility to organize and assign priorities to our actions in order to accomplish a goal. This capacity to structure and plan our behavior is made possible by the identification of the necessary steps and the creation of a hierarchy of subgoals that bring us closer to achieve our objectives (Gazzaniga, Ivry, & Mangun, 2014). A simple task to exemplify the capacity of planning is The Tower of London test (Shallice, 1982), in which the participant must recreate a model pattern formed by a series of beads of different colors, stacked on top of each other at different weights, placed alongside three (or more) possible pegs on a board. To obtain the same pattern as the model, the beads have to be moved in a precise order, which requires planning in advance the series of moves to achieve the goal in an optimal way. Another related task that has been used to measure planning capacity is the Tower of Hanoi, an ancient puzzle game in which different sized disks are moved one by one, where a smaller disk can only be placed on top of a bigger one, with the objective of recreating the initial structure in a separate peg. While also requiring planning capacity, a strategy can be developed easily to achieve the goal, so it is likely that cognitive functions other than planning come into play. These two tasks, in spite of being similar to each other, present a low correlation in performance, casting doubt on their validity (Humes, Welsh, Retzlaff, & Cookson, 1997).

The high order integration of rules seems to be supported by the most frontopolar regions of the brain. In a task where the goal was the integration of two lower-level judgments to form a higher-order one, greater activation of the frontopolar cortex was observed compared to control conditions where only lower-level judgments were needed (R. Smith, Keramatian, & Christoff, 2007). Indeed, it seems that the simplest tasks, especially those involving working memory, show activation patterns limited to posterior frontal regions or even just secondary motor areas. If more challenges are added to a task, the regions that are recruited grow and extend frontally, to more anterior areas. The most abstract are the rules and representations used in the task; the most anterior regions will be recruited, reaching the frontal pole, while more posterior parts are still active as response intentions are translated to concrete movements. The more severe the frontal lesions are, the most difficulties a patient will have to carry out tasks involving abstract representations and judgments, and if presented with a series of tasks that must be carried out in a hierarchical manner (e.g. administering a budget), only the most simple and direct goals will be achieved (Gazzaniga et al., 2014).

2.1.2.2 Contextual control

Another feature of higher-order mental processes consists in knowing whether a series of stimulus-response rules will be enough to achieve a goal, or if less automatic and volitional behavior, mediated by executive control, will be required. Consciously engaging in executive control in order to solve a problem carries a cost over automatic behavior, in the form of cognitive resources. Moreover, executive control can interfere with automatic behavior (when it is already suitable and optimized for the situation) and result in an overall worse performance. To determine when it is cost-effective to engage in conscious behavior, the brain must dedicate resources in monitoring progress of the goal: whether the actions so far have been appropriate and successful to achieve the goal or if more conscious executive processing should be dedicated. Moreover, the processes dedicated to monitoring also should be able to identify the presence of conflicts between actions and resolve them in an optimum way, while efficiently allocating cognitive resources. This higher-level supervision processes dedicated to monitoring behavior are often termed control systems (Purves et al., 2012).

Monitoring

From an attentional perspective, the presence of behavioral control systems was already postulated by Posner and Petersen (2012; 1990), and were classified in three main groups: alertness/vigilance, orienting to sensory stimuli, and conflict monitoring, which is devoted to detect and identify events that require additional resources for their processing. It is this last control system which is responsible for monitoring events of conflict.

It is hypothesized that conflict monitoring is a way to distribute attentional resources in the brain. When a task with high-levels of conflict is carried out, vigilance (sustained attention) must be incremented, which translates into increased activity in the medial frontal cortex that contributes to modulate the activation in other cortical brain regions (Gazzaniga et al., 2014).

In presence of response conflict, one brain region stands out for its key role: the anterior cingulate cortex (ACC) (M M Botvinick et al., 2001; Matthew M Botvinick, Cohen, & Carter, 2004). This is a complex region featuring at least 11 distinct subregions connecting to other grey and white matter areas, like the orbitofrontal cortex, the ventral striatum, and the premotor cortex, and therefore it is likely that the ACC is a key area that mediates decision making, goal-oriented behavior and motor control (Gazzaniga et al., 2014). In neuroimaging studies, activation of the ACC (particularly the dorsal ACC), was observed in three behavioral contexts: 1) overriding of prepotent responses, 2) selection among a set of equally permissible responses (underdetermined responding), and 3) tasks involving the commission of errors, although activation in all three circumstances could be explained by the same phenomenon: the detection of conflict.

Response override of prepotent responses, that is, responses for which immediate reinforcement is available or has been previously associated (Barkley & Murphy, 2006), appear in situations where there is a competition between a correct response and the one being overridden. ACC activity is observed in this context, particularly in incongruent trials of the Stroop task (particularly if precede by congruent trials), although that effect, paired with ACC activation has been also observed in the Flanker task, the Simon task and in the go/no-go paradigm, among others (Matthew M Botvinick et al., 2004).

Underdetermined responding is another circumstance that creates conflict and reliably involves the activation of the ACC when multiple permissible responses compete with each other. Tasks in which ACC activation is observed in presence of underdetermined responding include the stem-completion task (Palmer et al., 2001), the verb generation task (Barch, Braver, Sabb, & Noll, 2000; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997), and even appears in simple motor tasks that including response competition (Frith, Friston, Liddle, & Frackowiak, 1991). The level of activation under this circumstance also depends on the number of alternative responses associated with a stimulus, leading to greater ACC activation when there is more response competition (Barch et al., 2000).

Likewise, the commission of errors is another context in which ACC activation is associated. This behavioral context of response conflict has been extensively studied using EEG and even led to the identification of transient potential named error-related negativity (ERN) (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000). The error-related negativity is a negative-polarity potential that appears in two types of mistaken action: when the participant realized a recent motor movement is incorrect (response ERN) or when feedback is provided informing that an action did not result as expected (feedback ERN) (Purves et al., 2012). The ERN signals are often produced in the context of speeded tasks which allow the participant to respond incorrectly but further processing of the stimuli often leads to a delayed recognition of which would have been the correct response (post-response), therefore activating both the incorrect and correct responses and creating a conflict event, explaining the activation of the ACC.

Specific loci within the ACC corresponding to the processing of these different kinds of conflict monitoring are still a matter of debate. It was first thought that error-related activity and underdetermined responding would appear in the same area within the ACC (Garavan, Ross, Murphy, Roche, & Stein, 2002), although some experiments provided evidence of some specialized localization in each task (T S Braver, Barch, Gray, Molfese, & Snyder, 2001; Kiehl, Liddle, & Hopfinger, 2000; Menon, Adleman, White, Glover, & Reiss, 2001). Moreover, it is not clear if the nature of the feedback ERN can be compared to the more studied response ERN, and whether activation in the ACC comes from the same source (Holroyd et al., 2004; van Veen, Holroyd, Cohen, Stenger, & Carter, 2004). The distinction between purely cognitive tasks and those that include emotional aspects also provided grounds for different localizations in the ACC (see Figure 7). Converging neuroimaging data from meta-analysis found that these executive processes related to monitoring tended to elicit activity in the dorsal part of the ACC, whereas studies which included affective tasks evoked activation in more anterior and ventral parts of the same structure (G Bush et al., 1998).

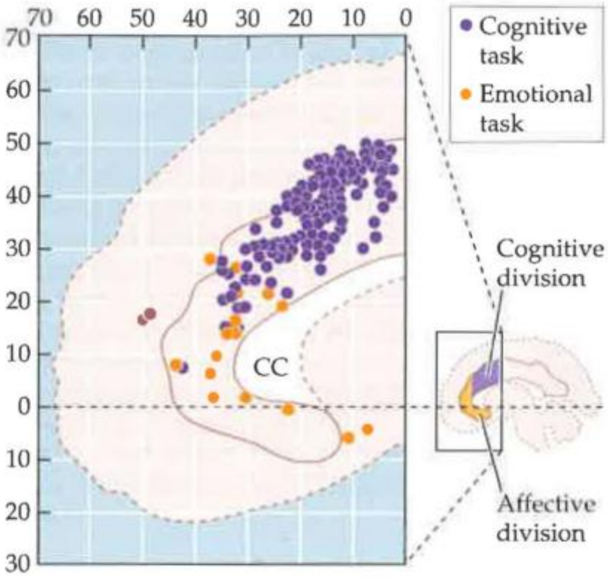

Figure 7. Topographical differences in the anterior cingulate cortex (ACC) when responding to cognitive control demands or emotional processing . Adapted from: (G Bush et al., 1998; Purves et al., 2012)

Nevertheless, the role of the ACC is not fully understood. Beyond monitoring and resolution of conflict, activation in this region has also been observed in situations where a reward is provided, after receiving feedback for an action, or even in processing stages preceding a response to a task, possibly indicating that monitoring of conflict may be carried out in early stages of processing. Moreover, despite the large amount of evidence linking the ACC with response conflict and other aspects of executive functions using functional neuroimaging, it is still not clear whether these activity correlations are enough to attribute a causal role of the ACC in conflict monitoring. Lesion studies have provided evidence in the opposite direction. When studying human subjects, performance in tasks which elicit conflict, such as the Stroop and Go/No-go tasks, do not seem to be affected in persons with lesions, even bilateral, in the dorsal ACC and did not hinder their ability to recognize errors (Lesley K. Fellows & Farah, 2005). It is possible that the role of the dorsal ACC is linked to aspects which might be confounded with cognitive control and often mediate their performance, such as in motivation, reward and emotional processing (George Bush et al., 2002; Shidara & Richmond, 2002). Alternatively, the dorsal ACC could have a role in the control of the autonomic nervous system when it accompanies a cognitive effort in humans (Critchley, 2004; Critchley et al., 2003) or even mediating changes in the autonomic tone without the need of a cognitive factor (Teves, Videen, Cryer, & Powers, 2004), which is a variable that is rarely accounted for, but likely correlates with executive functioning (Lesley K. Fellows & Farah, 2005).

2.1.2.3 Working memory

The processes responsible for inhibition and switching are the executive functions allowing for flexible behavior and aiming towards the completion of our active goals. However, these two groups of processes are insufficient to understand how our goals are kept active in our mind and how we use the available information to complete them. The last main component of executive functions is often called working memory, and it is responsible for maintaining short-term information active and manipulating it in order to produce an output which is relevant for our immediate behavioral objectives.

The information which is manipulated can have its origins in the immediate environment, captures through our senses, or be recovered from our long-term memory. In any case, once the information has been transferred to the short-term memory, it is manipulated in a way that does not require the presence of that information to be immediately available, although the acquisition of further information is possible, especially since the short-term memory is limited, if it is required to complete our goal.

Working memory does not work alone. It is intertwined with other executive functions, especially inhibition, in order to suppress irrelevant information from entering the short-term memory, and it is likely composed of more molecular subunits that work in tandem in order to achieve that manipulation of information.

Due to the current limitations in technology, we cannot directly observe how these subcomponents, which have been hypothesized to exist according to cognitive models, interact with each other to process the information, but a few comprehensive theoretical models have tried to describe the complexity that entails the concept of working memory.

The most influential model, already proposed in the mid-1970s, is Baddeley's model of working memory (Alan D. Baddeley & Hitch, 1974) (see Figure 8), in which a series of separate short-term memory buffers store different modalities of information and all of them are controlled and manipulated by a central control system. In the latest development of this model, three different memory buffers are described: the phonological loop, for auditory and verbal information, the episodic buffer, for integrating information with time sequencing, and the visuospatial sketchpad, which holds visual information. A fourth element of the model, the central executive, acts as a control center and is responsible for supervising, directing and coordinating the information in and out of the three slave memory buffers.

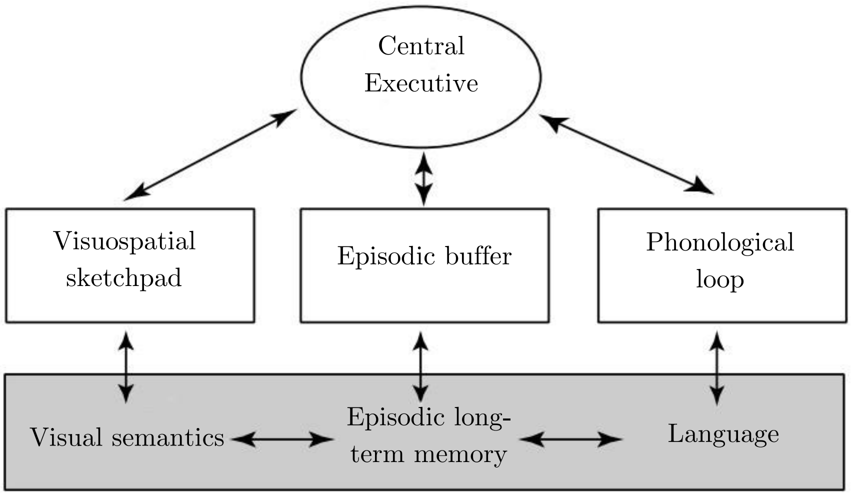

Figure 8. Baddeley's model of working memory, showing the three short-term memory buffers, and the central executive, responsible for managing their contents. Source: (Alan D. Baddeley, 2000)

Cowan's model of working memory (Cowan, 2005) (see Figure 9), termed *Embedded Processes Theory*, involves an alternative and complementary explanation on how working memory operates. According to this theory, working memory are "cognitive processes that are maintained in an unusually accessible state" (Cowan, 1999).

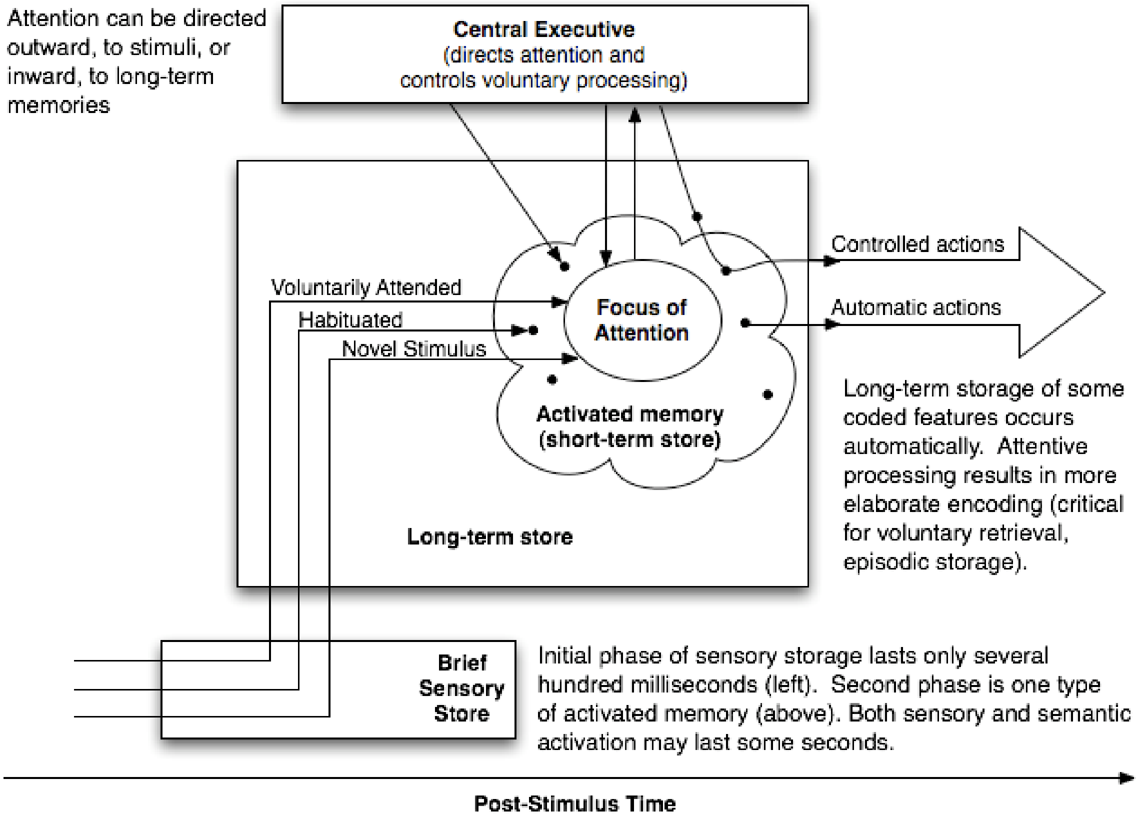

Figure 9. Cowan's *Embedded Processes Theory* of working memory . Adapted from (Cowan, 1999), by Laura B. Dahl (CC BY-NC 2.0).

Under the assumption that attentional processes have a limited-capacity, Cowan postulates that working memory is organized in two embedded levels: 1) activated long-term memory representations that rapidly decay and only remain in that state as long as they are rehearsed, and 2) activated representations under the focus of executive control, with a capacity of holding a maximum of four elements simultaneously. The main difference of Cowan's theory regarding Baddeley's model is the lack of different working memory stores, using a unique long-term memory store instead, arguing that long-term memory representations of sensory information are stored in the respective sensory and association cortices, and that should be reflected in sustained activity in these areas.

Despite the apparent differences, both Baddeley's and Cowan's theories show many points in common, and most of the differences can be explained in terms of different emphasis and terminologies (A. Baddeley, 2012). The activated long-term memory representations would be equivalent to Baddeley's short-term memory buffers, maintained through rehearsal, and the central executive, common in both models, would focus on the representations that will be available to the attentional system. Whereas Baddeley estimated the number of elements that can be maintained under the attentional focus to be seven, Cowan states that the capacity is closer to four "episodes" or "chunks", although they can be composed by more than one item (Cowan, 2005).

The following sections will give more emphasis in Baddeley's model of working memory due to its prominence as a theoretical model and its level of evidence in research. Nevertheless, if we omit Baddeley's deliberate short-term memory buffer division, Cowan's model largely fits in all the explained theoretical concepts, especially regarding the central executive and the sub-components of working memory, and is a theory that must be taken into account when interpreting new results in the literature.

Maintenance of information

The first of the short-term storages of information proposed by Baddeley is the *phonological loop*. The phonological loop, sometimes referred as *articulatory loop*, deals with sound-based representations. It is composed by two subunits: a short-term phonological store that holds transient memory traces, which decays rapidly, and a second mechanism termed *articulatory rehearsal component* which is responsible for keeping the short phonological information alive by continuously repeating it, as if it were an inner voice, and therefore preventing its decay.

Auditory verbal information seems to automatically enter the phonological store, even if it is presented in written form, as it is transformed into phonological information as soon as it is read by silent articulation and encoded in the phonological loop maintaining its temporal order. Evidence shows that humans can retain up to two seconds worth of speech though silent rehearsal (Alan D. Baddeley & Hitch, 1974) although the retention period can be significantly lower if more complex processes, like in a running memory task, are also involved (Cowan, 2001, 2005). It is thought that the separate processing of phonological information in working memory is a key aspect in our capacity of acquiring new languages (Alan D. Baddeley, Gathercole, & Papagno, 1998).

The second short-term memory storage mechanism, the *visuospatial sketchpad*, is specialized in storing visual information for manipulation, and it is completely independent of the phonological loop, as both types of information can be processed simultaneously without interfering with each other (Turnbull, Denis, Mellet, Ghaëm, & Carey, 2005). Functional during briefs periods of time (despite visual information can be stored in long-term memory and accessed indefinitely) that span a few minutes, it allows us to revisit mental image and interact with them in all sorts of spatial tasks.

It is important to note that the visuospatial sketchpad does not correspond to visual sensory memory. Sensory memory briefly holds the information that has been captured by the senses before it is sent to the respective short-term memory storage (the visuospatial sketchpad, in the case of vision). Its capacity is much lower than the short-term buffers, lasting in the order of seconds, while the visuospatial sketchpad can hold information for some minutes.

The visuospatial sketchpad is composed of two subunits (Logie, 1995): the *visual cache*, which stores shape and color information, and the *inner scribe*, which deals with spatial and movement information, including body movements. Furthermore, the inner scribe is responsible for rehearsing and transferring information from the visual cache to the central executive. This is supported by neuroimaging studies where brain activation differences are observed during visual and spatial tasks (Sala, Rämä, & Courtney, 2003), and also by lesion studies where task performance between these two modalities showed differences (Beschin, Cocchini, Della Sala, & Logie, 1997). Moreover, it is likely that his division has some correspondence with the *where* (corresponding to the dorsal stream) and *what* (corresponding to the ventral stream) pathways found in the brain, linked to the spatial and object memory respectively.

The third short-term memory buffer, and the newest addition to the model, is the *episodic buffer* (Alan D. Baddeley, 2000). This short-term storage is dedicated to provide a timeframe reference and integrate information units in the visual, spatial and verbal information, in order to create a single complex structure or episode. It was first designed to fill a gap in the model since none of the other components, including the central executive, could explain how the different kinds of information could be combined. In the sense that provides spatial and temporal information to memories, it resembles the concept of *episodic memory* proposed by Tulving (1989), although in Baddeley's model it is supposed to be a short-term memory (with the possibility to be consolidated onto the long-term memory) which is preserved in densely amnesic patients with impaired long-term memory. Like the two other memory buffers, it is assumed to be limited in capacity since in theory, it would need simultaneous access to the different modalities of short-term memory, each encoded in its own way. It is accessed by the central executive by conscious awareness, so it can influence the contents of the store by placing the focus of attention over certain components of the short-term memory, long-term memory or perception, therefore creating new cognitive representations which can aid in problem-solving.

It is likely that the proposed episodic buffer does not correspond to a single anatomical structure in the brain. Studies dealing with verbal and spatial information in an integrated and unintegrated form (Prabhakaran, Narayanan, Zhao, & Gabrieli, 2000) found greater right frontal activation for integrated information, and more posterior activation in areas also responsible for verbal and spatial working memory, for unintegrated information. However, the precise nature and boundaries of this third component, along with the separation of episodic information between short and long-term memories, is still unclear.

Manipulation of information

All the previous three components are slave processes of the main coordinating mechanism: the *central executive*. It is postulated to be responsible for the selection, initiation, and termination of tasks. In that sense, the central executive could be considered a form of homunculus, since we just translated the most complex parts (and the less well understood) of executive functions to a subcomponent of working memory, creating a redundant mechanism without addressing its fundamental inner workings. Baddeley considered that the central executive is equivalent to the supervisory attentional system (SAS) created by Norman & Shallice (D. Norman & Shallice, 1981; Shallice, 1982), a cognitive device that controls and manages how patterns of thought and behaviors, in a way that allows for the creation of general strategies for problem solving in a conscious way. Again, the model by Normal & Shallice describes a series of operations that do not differ much from the general concept of executive functions: planning and decision making, solving problems which cannot be done by automatic processes, dealing with novel situations and overriding automatic responses when not appropriate. Linking the central executive to the supervisory attentional system implies that it should act as an attention controller, choosing which streams of information should be attended and which should be rejected.

Apart from managing the classical processes of executive functions, the central executive has the ability to select and manipulate information in long-term memory, making it accessible to the three slave systems, and being able to encode it back to the long-term memory. On the whole, due to the lack of knowledge of the precise nature of the central executive, this component of working memory is not well developed in the model (hence, the “homunculus”) and its current role is more of a placeholder until more details about its inner workings are found.

Working memory is unequivocally a product of prefrontal activity. One of the most used paradigms for measuring working memory-related activity is the so-called *delay-period activity*, where the period between the activation of the working memory short-term buffers and the manipulation of that information is observed. That includes visuospatial, non-spatial visual features, auditory and tactile stimuli, task rules, expected rewards and numerical quantities.

The delayed-response paradigm to assess working memory is based on a simple task where the participant (human or not) must respond according to stored internal representations, not available in the environment. The most common presentation (see Figure 10) is a task where a brief visual or acoustic stimulus is presented and then withdrawn. Next, the participant, after introducing a delay of several seconds, must indicate the location of the stimulus. A reward or some sort of feedback is usually given if the response is correct.

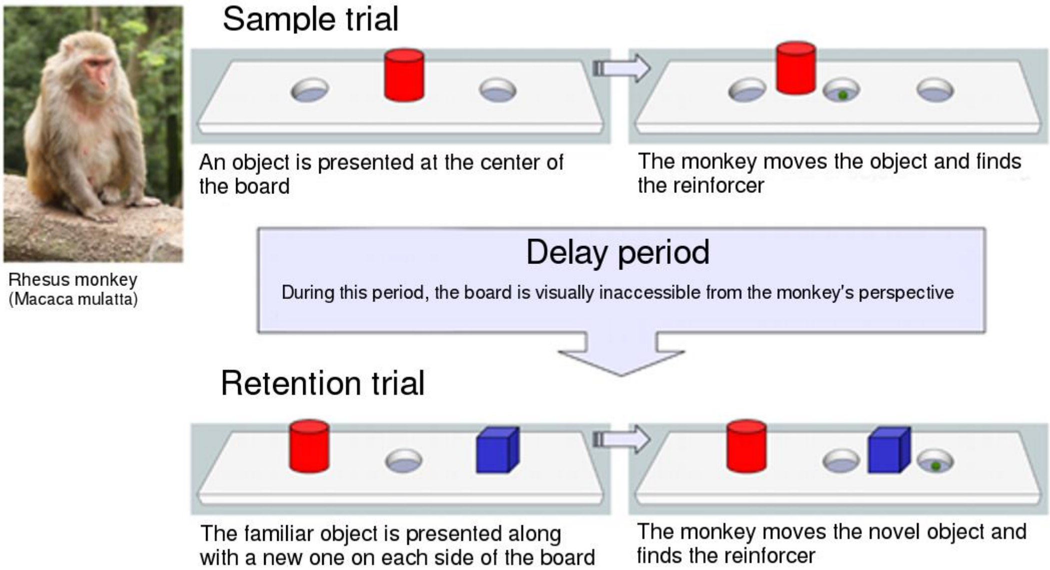

Figure 10. Standard presentation of a delayed-response task using visual stimuli , as used in animal studies using monkeys. Adapted from (Redolar-Ripoll, 2014).

First observed in rhesus monkeys with bilateral prefrontal lesions, where they suffered from severe impairments in this task paradigm (Jacobsen, 1936) it was quickly associated with prefrontal functions and more particularly, with working memory (Fuster, 2015). During the execution of the task, single-neuron activity in the DLPFC was being recorded, and while many neurons showed activity during the visual cue presentation or during the manual response, some prefrontal neurons showed activity associated with the delay period in a tonic and sustained manner. This activity was only observed in trials where the participant responded correctly, but was absent in error trials and trials without reward (Fuster, 1973). However, transient activity due to the visual cue presentation and response period appeared in trials without reward. This supports the hypothesis that the sustained excitation is associated with prefrontal mnemonic processes, while the transient activation during cue presentation and response period are a result of sensory and motor processes, respectively (Funahashi, 2015).

Components of Working Memory

There is still little consensus on which are the fundamental executive processes found in the working memory. Partly, this comes to establishing which types of contents working memory is responsible for processing. The first attempts at this categorization suggested that the *where* and *what* information streams, coming through dorsal and ventral pathways respectively, this information is carried into the frontal lobes, where it is processed. This proposal suggested that dorsal frontal and parietal regions mediate spatial working memory, while ventral frontal and temporal regions mediate object working memory (Nee et al., 2013). Further evidence was able to distinguish between identity-based verbal content from identity-based object content (R. Levy & Goldman-Rakic, 2000), agreeing with the phonological and visual distinction of the theoretical models. Neuroimaging studies were consistent with these different modalities of information, eliciting several activity patterns during working memory task depending on the type of content. For instance, the left IFG (BA44) and ventral left precentral gyrus had a role in verbal maintenance, dorsal aspects of the right premotor cortex and near the caudal superior frontal sulcus in spatial maintenance, and the right IFG in object maintenance (E. E. Smith & Jonides, 1999). Meta-analyses of studies investigating the n-back task supported the notion of the three subdivisions in the prefrontal cortex based on the information modality: left PFC for verbal dominance, dorsal premotor for spatial dominance, and right PFC for object dominance (Owen, McMillan, Laird, & Bullmore, 2005).

These regions account for the temporal maintenance of information, but Baddeley's model suggests that the executive portion of working memory does not discriminate by modality and constitute one unitary module that manages all kinds of information. Studies using fMRI data actually show that the executive component of working memory, when isolated from its maintenance component using refresh tasks (a minimal working memory operation), seems to be located in the mid-DLPFC (Curtis & D'Esposito, 2003; D'Esposito et al., 1998; M Petrides, 2000). This executive component exhibits lateralization in function of the type of content, specially consistent in the case of the left IFG for verbal content (Johnson et al. 2005), and the caudal superior frontal sulcus for spatial content (Courtney et al. 1998), but the association of object content with the right PFC is somewhat variable and inconclusive (Courtney, 2004).

More recent proposals suggest that there is a fourth type of content that can be held in the frontal lobe which represents the most abstract form of information: the storage of rules and goals (Courtney, 2004; Koechlin, Ody, & Kouneiher, 2003). The more abstract is the stored content, the more frontal portions of the prefrontal cortex are recruited, forming a gradient in a rostrocaudal axis (Badre & D'Esposito, 2009). In this case, the rostral regions of the prefrontal cortex showed sustained activation in presence of cues that indicated the immediate engagement of a working memory task, and at the same time interacted with specific caudal regions of the prefrontal cortex depending on the modality of the information to be presented in the upcoming task (Katsuyuki Sakai & Passingham, 2006).

Apart from establishing the different kinds of information which the working memory is able to manage, there is also debate about how to classify its functions. According to the literature on the topic, it is possible to classify the functions of working memory using a four-component categorization: resistance from distractors, resistance for memory intrusions, attentional shifting in working memory and updating the contents of working memory (Friedman & Miyake, 2004; Nee et al., 2013). The implication of the DLPFC in all these functions is clear, but it is difficult to dissociate the role of each function using neuroimaging alone. In the literature, sometimes the same label (DLPFC) is given to a wide range of activation foci (Brass, Derrfuss, Forstmann, & von Cramon, 2005; Courtney, 2004), so it is complicated to dissociate one function from another based on location alone and it is not always clear when different working memory functions are using different regions within the prefrontal cortex. In spite of this, some studies have been able to specify the location of some of these functions to more precise foci (J. K. Roth, Serences, & Courtney, 2006; K Sakai, Rowe, & Passingham, 2002).

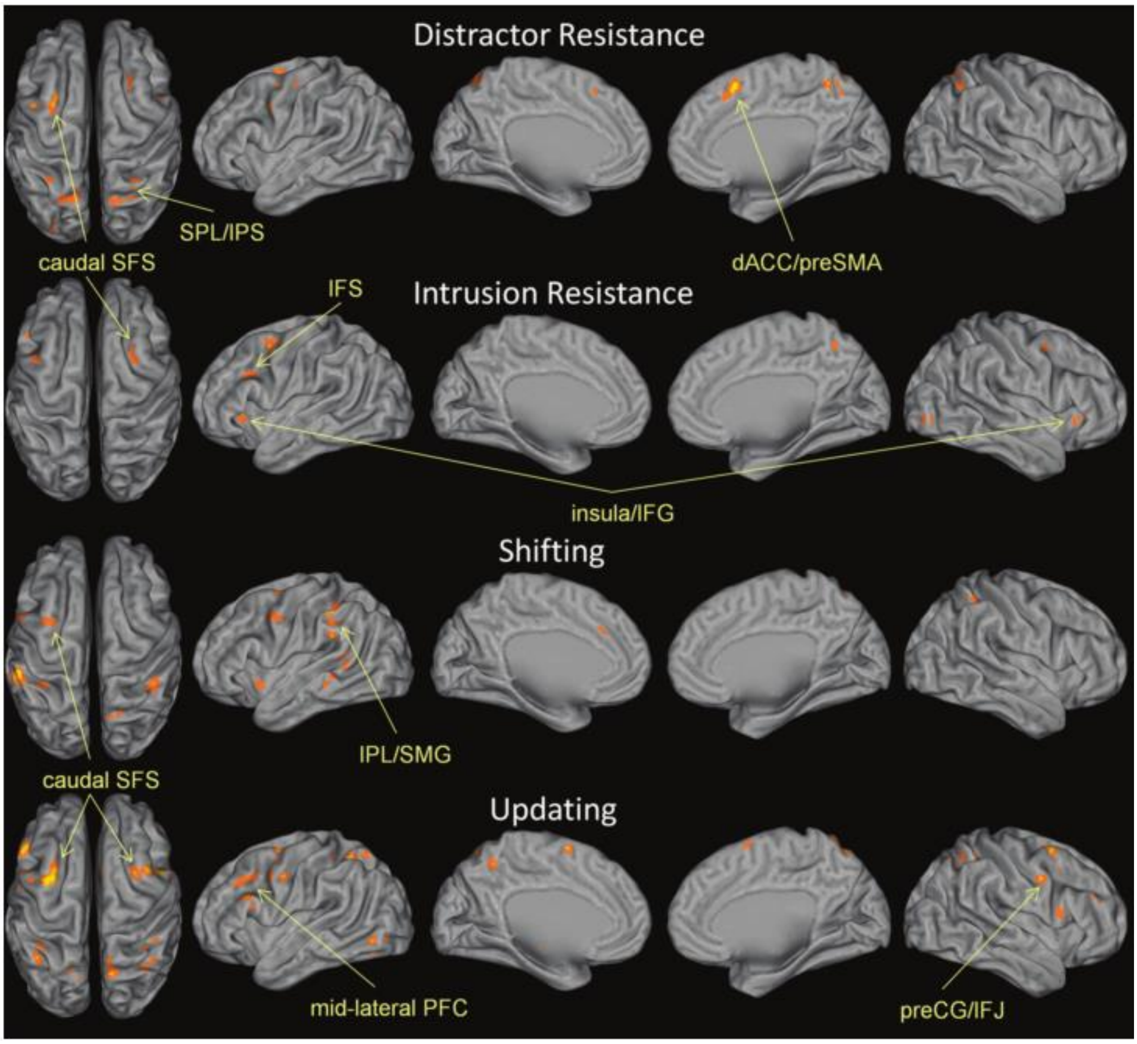

Figure 11: Brain correlates associated with the four main components of working memory . From: (Nee et al., 2013).

Distractor resistance

In order to function properly and sustain complex cognition, working memory has to maintain information while being able to perform secondary tasks. The presence of externals distracters is the main factor that affects working memory performance (Keppel & Underwood, 1962), therefore, the distractor resistance function consists on actively filtering external distractions while either encoding or maintaining information in the working memory (Wager, Spicer, Insler, & Smith, 2014).

Distractor resistance is usually assessed using tasks that consist of memorizing a few units of information (such as groups of letters) during a time interval while, at the same time, doing a secondary task that acts as a distractor (such as counting backward). The greater the time interval dedicated to the secondary task, the smaller is the recall rate of the units of information used in the main task.

The nature of these distracters can be classified in two types: distracters that are perceptually experienced that must be actively ignored in order to remember some other information, and distracters that consist in secondary tasks that have to be carried out while maintaining some other information active. When studying how they affect the performance on working memory, the two types of tasks do not seem to be correlated (Miyake et al., 2000). While the first kind of distracters can be ignored through perceptual filtering mechanisms, at early processing stages (Bundesen, 1990), interference by other tasks probably rely on more active task switching and information selection processes, and indeed correlate with other indices of executive functioning. Moreover, performance in dual-task distracters can be used as a predictor of fluid intelligence (Conway, Kane, & Engle, 2003).

Successful performance in dual-tasks robustly correlate with activity in the lateral and medial PFC during encoding and maintenance of information, but more specifically, when only trials with distractors are used, the pre-SMA was the region which better predicted the performance in this task, particularly in the right hemisphere (see Figure 11) (Nee et al., 2013; Wager et al., 2014). Therefore, while the DLPFC has undoubtedly a key role in complex working memory operations, the pre-SMA is involved with (but not limited to) distractor-resistance.

Intrusion resistance

Intrusion resistance is defined as the effort to mitigate the interference from intrusive memories (Nee et al., 2013), including the difficulty in learning new information because of already existing information, an effect known as proactive interference. Susceptibility to proactive interference is a strong predictor of working memory performance in span tests (Whitney, Arnett, Driver, & Budd, 2001), and span performance on later trials is worsened by performance on earlier trials of a task, partially as a result of proactive interference (May, Hasher, & Kane, 1999). A good resistance to intrusion in working memory is also associated with the capacity of successfully resolving interference from other types of information.

The most common experimental paradigm to study intrusion resistance is the *recent-probes task* (Monsell, 1978), where participants are instructed to memorize a number of items (e.g. letters) during a series of trials, and hold that information in memory for an interval of several seconds, after which they are shown one single item probe and have to decide whether it matches (*positive probe*) one of the items presented previously or not (*negative probe*). In order to study how past trials influence the current one, some of the trials will show a probe containing an item presented in a previous trial, but not in the current (*Recent negative probe*), or trials where the probe contains items not previously presented (*Non-recent negative probe*). The main measures are reaction times and accuracy, showing that recent negative probes slow-down response times and lowers the accuracy. Moreover, when negative probes are presented in consecutive trials, response times are also lower than average (Atkinson & Juola, 1974), showing that the lingering memories of previous items interfere with the task performance.

According to meta-analysis, the most focal point for intrusion resistance is found in the left (Jonides & Nee, 2006) and right mid-ventrolateral prefrontal cortex (VLPFC) (Anderson & Levy, 2009), including the insula and the right IFG (Nee et al., 2013). Since the right IFG is also involved in the inhibition of prepotent responses (Aron, 2007), it is likely that it interacts with different subcortical structures to carry out either function.

Shifting: switching cost

In the case of working memory, *shifting* refers to the process of changing the focus of attention from the contents of the working memory to some other information without replacing it. It is akin to the cognitive flexibility capacity as part of the main classification of executive functioning, though, in this case, it refers exclusively to the narrower sense of manipulating the memory buffers of working memory. Used on an extended basis, shifting leads to performance decreases, as it induces extra costs in the processing of working memory (Liefooghe, Barrouillet, Vandierendonck, & Camos, 2008)

Shifting has been mostly studied with the use of *refresh* tasks in which, for each trial, a stimulus (e.g. written words, drawn objects or abstract patterns) is presented, followed by a delay and the presentation of either another identical stimulus (*repeat* trial), a different one (*read*), or a cue indicating that participants must think of the previous stimulus (*refresh* trial), which are presented intermixed in a random order. Optionally, in order to return brain activity to the baseline and reduce variability among the participants, a simple task required the participant to make a left or right key press in response to arrow before proceeding to the next trial, although paradigms using resting intervals have also been used. Brain activity is meanwhile been recorded using functional neuroimaging techniques, with the objective of capturing the activity characteristically associated with *refresh* trials (M. K. Johnson, Raye, Mitchell, Greene, & Adam, 2003).

Most studies using this paradigm have observed activity in the midlateral PFC in the left hemisphere, although these results are far from being consistent. In a uniform manner, clusters of activation in the left frontal hemisphere were found in the insula, the precentral gyrus, the dorsal anterior cingulate cortex (dACC) and caudal superior frontal sulcus. Inferior parietal activity, located around the left temporoparietal junction has also been consistent as a result of the *refresh* paradigm, indicating a role of this region in shifting attention within working memory (Nee et al., 2013).

Updating

The last function is the capacity of *updating* the contents of the working memory, that is, removing part or the totality of what is stored and replacing that with new information. In some cases, studies are not strict with the terminology and consider shifting and updating as being the same thing, which leads to misleading conclusions when observing the results. In comparison to shifting, updating changes the contents of the working memory, while shifting just changes the focus of attention within those contents.

In experiments exploring the updating function, participants are usually instructed to change what is stored in the working memory at the presence of a cue, by deleting what is currently in the memory buffers and replacing it with new information, either from the environment (e.g. a stimulus that is presented to them) or recalling it from the long-term memory. In some tasks, using the directed forgetting paradigm, participants are required to just partially update the contents of the working memory, by retaining some of the old information that was already present, based on some condition (e.g. retain the lowest numbers in a list) (Sörqvist, 2010). In contrast to the updating function, these tasks usually include trials where the working memory does not need to be updated, either by just holding the information or by including refresh trials alongside the updating trials. Like in the rest of the functions, the stimuli can be presented in a number of modalities, more commonly in visual, spatial, verbal or auditory formats (Nee et al., 2013). Tasks featuring the updating function can be decomposed in three main component processes: retrieval, transformation, and substitution, although not all of them are present in all the occasions (Ecker, Lewandowsky, Oberauer, & Chee, 2010). Retrieval refers to the need to obtain information already placed in the working memory in order to process some new information. If a new information already contains all the information needed for the processing, no retrieval will be needed and the old information will be just overwritten and updated. Transformation refers to the manipulation of the information already present in the working memory. Similarly, if a new information requires no further processing because it is already the desired outcome, no transformation of previously stored information in the working memory will be needed. The last subcomponent, substitution of information, is in charge of substituting the current working memory contents with new information, either directly from the environment or the long-term memory or using the current contents of the working memory (Ecker et al., 2010). While the substitution component is a requisite in an updating task, the lack of it is what characterizes the shifting function of working memory.

When examining its neural basis, it seems that updating involves the interaction between two broad regions: an area formed by midlateral PFC and the inferior frontal junction (an area often underreported because its location (Sundermann & Pfleiderer, 2012)), and the area formed by the superior frontal sulcus and the posterior parietal cortex, associated with the dorsal attentional system (J. K. Roth et al., 2006). Within this dual system, the frontal areas would be responsible for managing the attentional priorities, while the posterior regions specialize in maintaining the attentional focus (Nee et al., 2013).

2.1.3 The neuroanatomy of executive functions

Often, the terms *executive functions* and *frontal function*s are used interchangeably, due to the special relevance of the frontal lobe in these cognitive functions. However, despite being a very important region, recent research has shown that executive functions go further beyond. They consist of a series of interrelated brain systems that combine to provide a flexible control of behavior and direct it in order to achieve goals. On the other side, it is known that the frontal lobe is not only responsible for executive functions; it is also involved for many other aspects, such as motor functioning, reward, emotional processing and social cognition.

Among the structures that are important for executive functions, we find that most of them are located in the prefrontal cortex, which seems to be the main hub for executive processing. However, it is not exclusive from this area since other regions like the posterior PPC, the basal ganglia, and the anterior cingulate cortex (ACC) also have executive roles. While these are the most relevant areas, as found in functional and connectivity studies, many aspects of their microstructure and connectivity are still not known in detail, especially since the prefrontal cortex is a heavily connected area.

In this section, a detailed description of the anatomy of the frontal lobe, its main subdivisions, and which areas are the most important for cognitive control will be provided. The connectivity between the frontal lobe and other regions involved in cognitive control will be the focus of the second part of this section.

2.1.3.1 Anatomy of frontal lobes

The frontal lobe comprises one-third of the brain cortex in humans. It limits at the central sulcus (the fissure of Rolando) and the lateral (Sylvian) fissure. It comprises the PFC, the primary motor cortex, the premotor cortices and the supplementary cortical areas. In humans, it is the last cerebral region to achieve neuronal maturation during our lifetime, not before the late adolescence. It is composed of motor and premotor areas in its posterior sections, whereas in its prefrontal sections it is more specialized in cognitive aspects, being the main hub for executive functions.

Primary motor cortex

The primary motor cortex, or M1, is located in the posterior dorsal section of the frontal lobe. Anatomically, it is located between the central sulcus (or fissure of Rolando) in its posterior part, where it limits with the primary somatosensory cortex, and the precentral gyrus in its anterior (rostral) part, where it limits with supplementary and premotor regions. In its anterior part, it borders the premotor areas. Ventrally, it limits with the insular cortex at the lateral sulcus (Sylvian fissure), it extends all the way up to the dorsal surface of the frontal lobe until the medial longitudinal fissure, and descends towards medial regions where it reaches the superior part of the cingulate cortex (see Figure 12). In the Brodmann classification, it corresponds to the area 4, due to the presence of giant pyramidal cells (Betz cells) in the 5th layer and absence of granular cells in the 4th layer.

One of the features of the primary motor cortex is how motor representation is organized. Analogous to the somatosensory cortex, the primary motor cortex is also somatotopically distributed, that is, each motor region is associated with one specific body part in the contralateral side in an orderly manner, with some degree of overlap, which can be represented as a motor homunculus. Although this cortex follows a topographic representation, the corresponding area in the primary motor cortex it is not proportional to the size of the body part but to the degree of

motor precision which it requires. This is why some body parts, like the arms and legs, show little cortical representation, but the cortical areas for other body parts, like the hands, mouth, and tongue, are disproportionally large.

Figure 12. Location of the primary motor cortex (M1) in the human brain , from a lateral (left) and medial (right) perspective. Adapted from Anatomography (2017) (CC-BY-SA 2.1-ja).

One of the features of the primary motor cortex is how motor representation is organized. Analogous to the somatosensory cortex, the primary motor cortex is also somatotopically distributed, that is, each motor region is associated with one specific body part in the contralateral side in an orderly manner, with some degree of overlap, which can be represented as a motor homunculus. Although this cortex follows a topographic representation, the corresponding area in the primary motor cortex it is not proportional to the size of the body part but to the degree of motor precision which it requires. This is why some body parts, like the arms and legs, show little cortical representation, but the cortical areas for other body parts, like the hands, mouth, and tongue, are disproportionally large.

While this motor cortex not traditionally considered part of the executive network, it is functionally connected to premotor areas, which possess features linked to executive processing. It works together with the secondary motor areas, the posterior parietal cortex and other subcortical regions in the planning and execution of movements.

The primary motor cortex receives inputs from the primary somatosensory area (in the postcentral gyrus), the premotor cortex and thalamic nuclei. The ventral lateral nucleus of the thalamus acts as a relay nucleus that in turn receives inputs from the cerebellum, and the ventral anterior thalamic nuclei provide afferents from the basal ganglia. All these inputs act as modulators of the motor output by providing information about the positioning, timing, and coordination of voluntary movements.

Betz cells project their axons to the brainstem, where they cross at the medulla oblongata and descend through the ventral horn of the spinal cord, being part of the lateral corticospinal tract.

These axons finally reach they target control organs, mainly muscles, and activate the lower motor neurons involved in the control of voluntary movements.

Secondary Motor Area

Premotor cortex

The premotor cortex is located in the middle frontal gyrus right next to the primary motor cortex on its rostral side. It mainly corresponds to BA6, together with the SMA. It has a prominent motor role, and just like the primary motor cortex, stimulation on this region also evokes muscle contractions, although more intensity is needed compared to the M1. Moreover, compared to the primary area, in the premotor cortex, giant pyramidal cells are less common and smaller, and granular cells are present, although not abundant. It also shows a less homogeneous cytoarchitecture, a sign that it is composed of different functional regions. Due to these histological markers, this region seems to be a transition region between the primary motor and prefrontal cortices.

This area can be further subdivided based on histological and functional properties. The most common subdivision is between the dorsal and ventral premotor regions.

a) Dorsal premotor cortex

As the name suggests, the dorsal premotor cortex consists of the dorsal half of the premotor area, anterior to the primary motor cortex and lateral to the SMA (see Figure 13). It is responsible for movements in facial, ocular and proximal muscles, having a role in postural adjustment and to movements oriented to environmental stimuli.

This region also has a role related to the anticipation of future movements and decision-making. Animal studies using primates observed that neurons in the dorsal premotor cortex were active during potential motor plans, which are modulated by the subjective desirability of that plan. It seems that decisions about future motor actions are made through competing processes within the same circuits that guide these actions, since the dorsal premotor cortex still shows activity when a decision is changed in the middle of a task (due the desirability of the plan having changed or that plan no longer exists), regardless of the feedback from the movement itself. So it is likely that this region is still involved in switching the motor action, even once the initial decision has been changed (Pastor-Bernier, Tremblay, & Cisek, 2012).

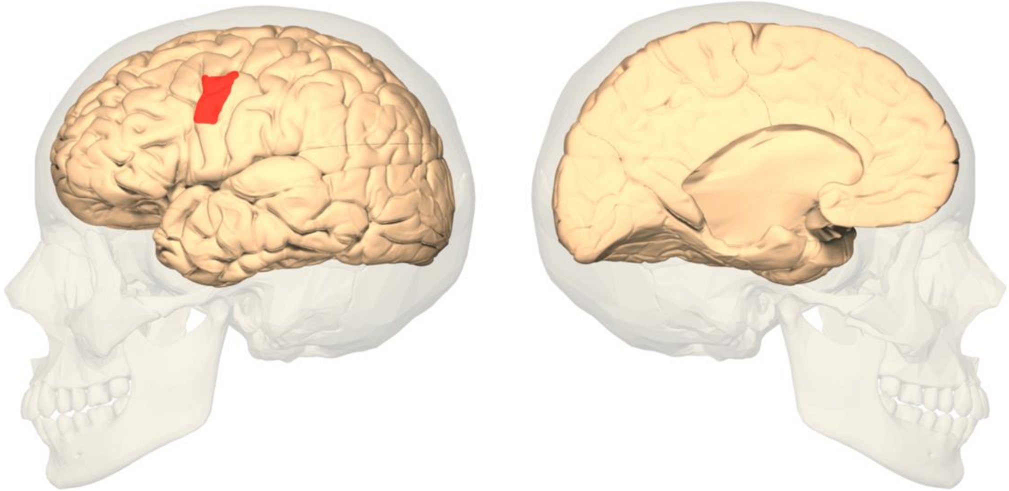

Figure 13. Location of the dorsal premotor cortex (PMd) in the human brain, from a lateral (left) and medial (right) perspective. Adapted from Anatomography (2017) (CC-BY-SA 2.1-ja).

b) *Ventral premotor cortex*

The ventral premotor cortex is much differentiated region located inferior to the dorsal premotor area, alongside the same vertical axis, immediately anterior to the primary motor cortex area related to the mouth and tongue muscles, adjacent to Broca's area (see Figure 14).

It has an important role in the sensory (mainly visual) guidance of hand movements towards external objects. Primate studies provide evidence that this area has a role in determining the position of an object regarding the own body, in order to be able to grab it. This cortical region also seems to be involved during the preparation of a motor action, since it displays activation during *go* signals in cognitive tasks.

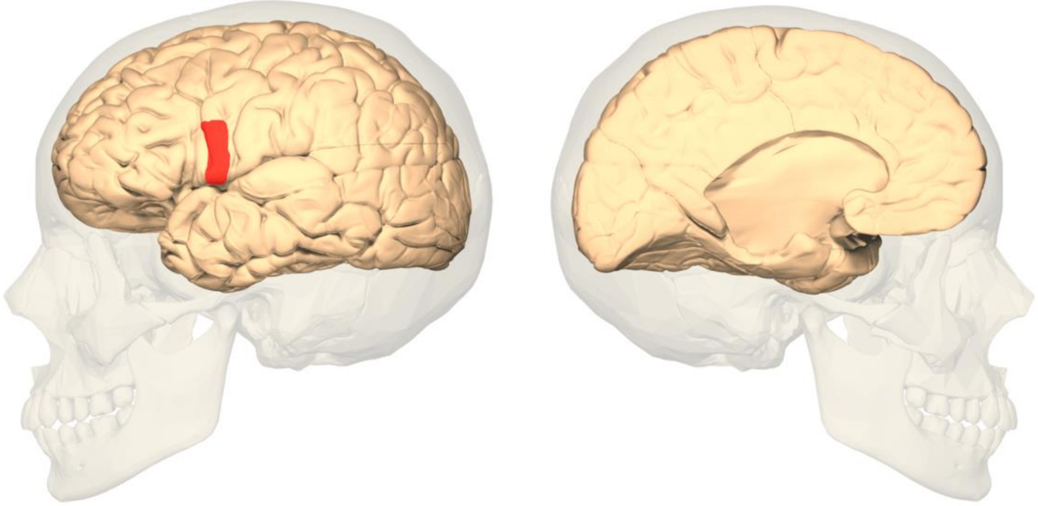

Figure 14. Location of the ventral premotor cortex (PMv) in the human brain, from a lateral (left) and medial (right) perspective. Adapted from Anatomography (2017) (CC-BY-SA 2.1-ja).

This is also the region where the mirror cells were first observed (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992), although since then they have been also found in the SMA, the primary somatosensory cortex and the inferior parietal cortex (Molenberghs, Cunnington, & Mattingley, 2009). The main characteristic of these cells is that they display activation, not only during the performance of a task, but also during the observation of that task being made by another person, and it is speculated that they are an important mechanism for skill learning, or even empathy or language learning (Blakeslee, 2006).

The ventral premotor cortex is also linked to executive components, like perceptual decision-making and performance monitoring. This is supported by the fact that this region, unlike the dorsal premotor cortex, is strongly connected to the adjacent ventral prefrontal cortex in primates (Dum & Strick, 2005). There is evidence that the ventral premotor cortex is involved in the use of sensory information stored in the recent and long-term memory in order to make decisions, execute and evaluate the outcomes of the subject's choices (Dum & Strick, 2005).

Medial or Supplementary motor area (SMA)

The SMA is located on the medial surface of the frontal lobe, in the superior frontal gyrus, anterior to the primary motor cortex, bordering the cingulate cortex in the medial side, and superior to the dorsal premotor cortex in the dorsal side (see Figure 15). Although in other primates it seems to be organized in a somatotopic arrangement, this does not seem to be the case for humans. It corresponds to the upper and inner part of Brodmann area 6 (Geyer, Luppino, & Rozzi, 2012). As it was the case with the primary motor cortex, which was inaccurately referred as M1, this region also received the denomination M2, despite nowadays being an incorrect term.

Its neurons project directly to the spinal cord and its main role is related to the control of movement. It is also strongly connected to the thalamus and epithalamus (Zhang, Ide, & Li, 2012). The precise functions in which it is involved are not completely understood, but four possible functions have been identified: 1) Postural stabilization of the body, 2) Coordinating both sides of the body during bimanual action, 3) Control of movements that are internally generated rather than triggered by sensory events, and 4) Control of sequences of movements. However, it is likely that this area is responsible for other functions. Moreover, its role in the four identified functions is not always consistent, since activation appears during movements that do not comply with the described situations, like in non-sequential, unimanual or stimulus-cued movements.

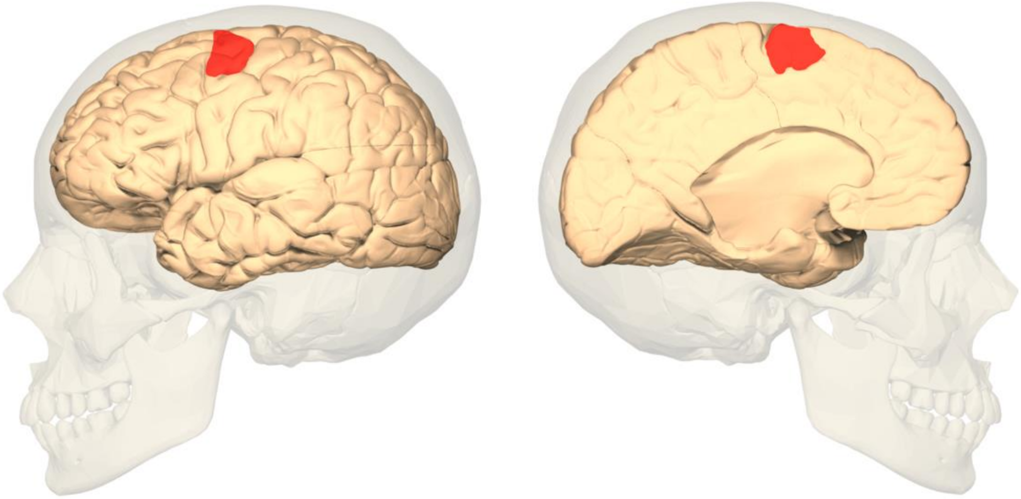

Figure 15. Location of the supplementary motor area (SMA) in the human brain, from a lateral (left) and medial (right) perspective. Adapted from Anatomography (2017) (CC-BY-SA 2.1-ja).

On a cognitive level, this area has shown activation during go signals, either visual, tactile or acoustic, when they are used as a signal to indicate the initiation of a movement. This area also activates during the delay between a go signal and the start of the movement. It is believed to be involved in movement planning and programming, as well as the learning of motor skills.

a) Pre-Supplementary Motor Area (Pre-SMA)

The pre-SMA is the anterior portion of the SMA. It covers approximately the upper and inner parts of the Brodmann area 8 (see Figure 16). It connects extensively to prefrontal areas, but it sends almost no efferent nerves to the primary motor cortex or the spinal cord. Connectivity, however, differs between anterior and posterior regions of the pre-SMA. In contrast to the posterior part, the anterior part is well connected to the prefrontal cortex but not to primary motor areas. The posterior part is heavily connected to the putamen, the pallidum and subthalamic nuclei, while the anterior pre-SMA is better connected to the caudate nucleus in the basal ganglia, showing significant hemispheric asymmetry (Zhang et al., 2012).

Contrary to the rest of the SMA, a motor response is not evoked when stimulation is applied in this area. The activation of this area is seen long before the production of a motor response. It is mainly involved in cognitive aspects of motor control processing, such as the development of motor plans and learning sequences of movements. It also shows activation during cognitive tasks involving motor aspects, such as mental rotation.

The pre-SMA has a key role in executive functions, particularly in controlling those actions that require rapid updating, inhibition or switching, as well as working memory. It is part of an executive control network, together with the IFG and subcortical regions like the thalamus and the striatum. This network is consistently activated during switching and inhibition trials, although the specific role of each component still needs to be researched. As measured in a stop-switching task, the IFG was dissociated from the pre-SMA, and results showed that the pre-SMA by itself has a role in inhibition, but it needs to act together with the IFG to perform in task switching trials (Obeso, Robles, Marrón, & Redolar-Ripoll, 2013)

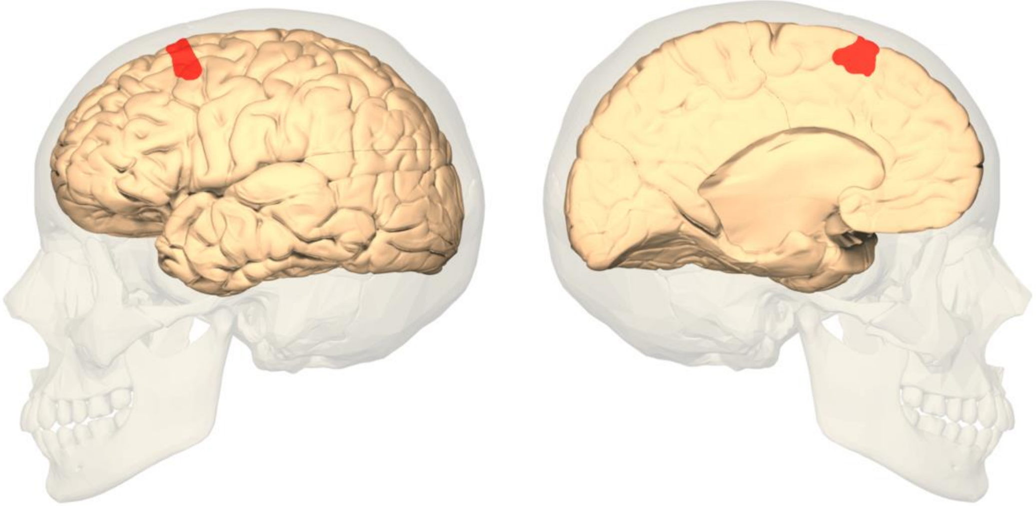

Figure 16. Location of the pre-supplementary motor area (SMA) in the human brain, from a lateral (left) and medial (right) perspective. Adapted from Anatomography (2017) (CC-BY-SA 2.1-ja).

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b) *Supplementary Eye Field*

Also part of the SMA, we find the supplementary eye field. It is located in the rostral portion of the SMA, lateral to the pre-SMA, and it is part of Brodmann area 6 (Luppino, Rozzi, Calzavara, & Matelli, 2003) (see Figure 17). It is heavily connected with other frontal regions, such as the cingulate cortex and subthalamic nuclei. Electrical stimulation in this area induces saccadic movements and coordinated head movements.

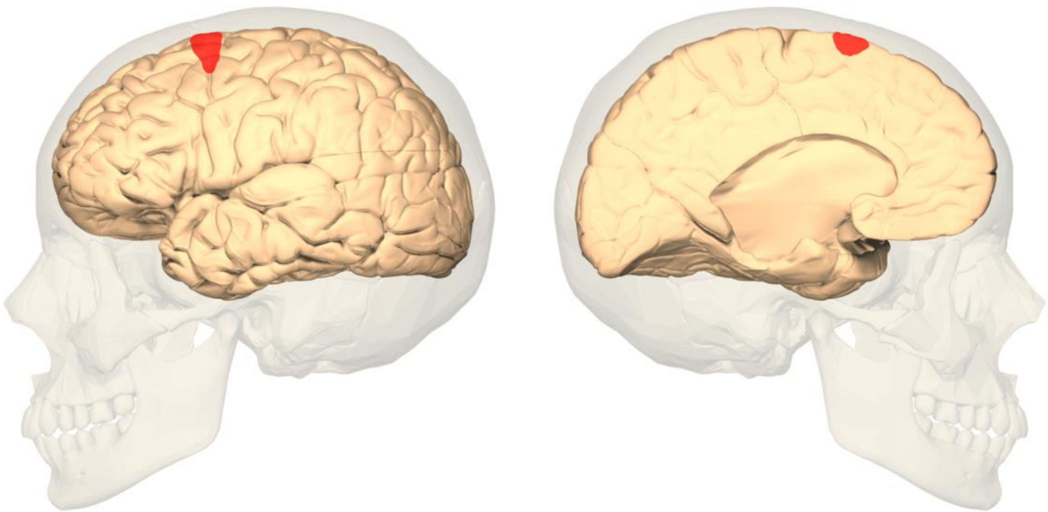

Figure 17. Location of the supplementary eye field (SEF) in the human brain, from a lateral (left) and medial (right) perspective. Adapted from Anatomography (2017) (CC-BY-SA 2.1-ja).

It has an important role in endogenous visual search and visual salience, through top-down attentional and cognitive processes, such as visual exploration based on information retrieved from long-term memory. It works together with the frontal eye fields (FEF), the intraparietal sulcus and the superior colliculus for the generation and control of internally guided saccadic eye movements, particularly contralateral to their location. However, the specific functions for which this area is responsible are still unknown. Studies have found a link between activation in this area and complex cognitive skills, such as spatial transformations, learned transformations and executive functions (Husain, Parton, Hodgson, Mort, & Rees, 2003).

The supplementary eye field has a role in saccade control related to executive functions. Technically, it can be categorized as an anterior region of the SMA. Their main function is evoking exogenous head and eye movements and, possibly, movements of the limbs and torso when an external stimulus enters the visual field. Artificial stimulation of this area produces eye movements, both saccadic and tracking movements.

Stimulation in the supplementary eye field in a non-human primate improved the cognitive performance in a stop-signal task regarding saccade initiation, where the performance also depended on the complexity of the task (Stuphorn & Schall, 2006). In humans, a case study of a man with a lesion in the SEF showed that he lacked control in changing the direction of his eye movement from a previous intention (a behavioral set), which could be categorized as a perseveration error in a task switching paradigm. However, he could monitor and quickly correct his errors. This demonstrates that the supplementary eye field has a role in oculomotor control during response conflict, but not in error monitoring (Husain et al., 2003). Together, these studies provide evidence towards the fact that this region does not only contribute to a motor role in saccade control but also has an executive component in saccade generation.

Some authors consider that the SMA, the pre-SMA, and the supplementary eye fields act together as a “supplementary motor complex”. Anatomically, these regions show little difference and together they form a functional continuum in order to produce voluntary actions. They are also tightly connected with other frontal regions, like the premotor cortex, that allows evoking responses linked to stimuli in the external environment. Therefore, in a way, it could be considered that this “supplementary motor complex” acts as a transition area for both endogenous and exogenous generated motor responses.

Frontal Eye Fields

Outside the SMA, we find the frontal eye fields. They are found in the intersection between the dorsal premotor area (precentral gyrus) and the prefrontal cortex (middle frontal gyrus), where the dorsal and ventral premotor areas meet. They are located in Brodmann area 8 (see Figure 18) (Vernet, Quentin, Chanes, Mitsumasu, & Valero-Cabré, 2014).

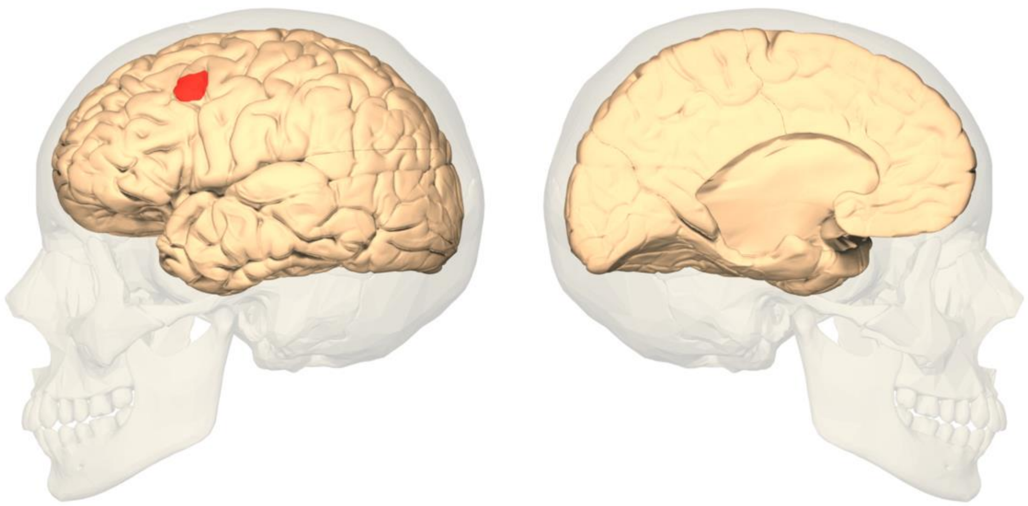

Figure 18. Location of the frontal eye fields (FEF) in the human brain, from a lateral (left) and medial (right) perspective. Adapted from Anatomography (2017) (CC-BY-SA 2.1-ja).

Together with the DLPFC, they are involved in the executive control of saccades, although the more detailed role of each region is not fully understood yet. Current evidence suggests that the DLPFC is needed for this executive control of saccades, that is, to establish an effective intention to perform an eye movement, and also for the suppression against a more automatic pro-saccade response, in order to look away from a visual stimulus and it is likely that the frontal eye fields also have an executive role in this function (Munoz & Everling, 2004). Moreover, the frontal eye fields are needed for visuomotor aspects of anti-saccade (that is, looking away from a stimulus) programming, as observed during a task switching paradigm (Cameron, Riddle, & D'Esposito, 2015). This region is also likely linked to spatial learning, since a disruption in this area altered pro-saccadic reaction times (Liu et al., 2011).

Prefrontal cortex

The prefrontal cortex is located at the most anterior region of the frontal lobe. It is cytoarchitectonically defined by the presence of a granular cell layer (layer IV), unlike the motor cortices, where the presence of giant pyramid cells is predominant. Contrary to what happens in motor and premotor regions, when this area is electrically stimulated it does not evoke movements, a feature that has sometimes been used to distinguish between frontal and prefrontal areas, and is indicative of its predominant cognitive involvement. It comprises the Brodmann areas 8, 9, 10, 11, 12, 44, 45, 46 and 47 (see Table 2.Table 2), showing some degree of overlap with premotor and supplementary areas.

8	**9**	**46**	**44**	**45**	**Lateral 47**	**12**	**Orbital 47**	**11**	**14**	**10**	**24**	**25**
Lateral							Orbitofrontal, Ventromedial, Basal, Orbital			Frontopolar, Anterior, Rostral	Ventral anterior cingulate	Subgenual cingulate
Dorsolateral			Ventrolateral									
Posterior Dorsolateral	Mid-dorsolateral											

Table 2. Main subdivisions of the prefrontal cortex according to their corresponding Brodmann area.

The prefrontal cortex can be further divided into several subregions according to their cognitive correspondences, which are named according to their relative position in the brain. The lateral surface of the prefrontal cortex is often subdivided between its upper and lower regions: the dorsolateral prefrontal cortex (DLPFC) includes the lateral and superior surfaces of the frontal lobe, while directly below we find the ventrolateral prefrontal cortex (VLPFC), extending all the way down to the ventral surface (see Figure 20 and Figure 21). These two regions are sometimes grouped together as «Lateral prefrontal cortex» by some authors.

We find parallel structures on the midline surface of the prefrontal cortex: the dorsal region is termed dorsomedial prefrontal cortex (DMPFC) (see Figure 19), and includes the anterior portion of the cingulate cortex (ACC), while the lower section consists of the ventromedial prefrontal cortex (VMPFC). This area is anatomically equivalent to the orbitofrontal cortex (OFC) and both terms could be used interchangeably (see Figure 23 and Figure 24). However, some authors reserve this term for the lowermost part within the VMPFC, surrounding the eye globes on its superior side, which possesses enough entity to be studied by itself, while using the term *medial orbitofrontal cortex* (mOFC) for the uppermost section of this region.

The anterior part of the frontal lobe, the frontopolar prefrontal cortex or rostral prefrontal cortex, is sometimes mentioned as another subdivision of the prefrontal cortex due to its differential cytoarchitectonic characteristics, corresponding to the Brodmann area 10, and responsible some specialized functions within executive control.

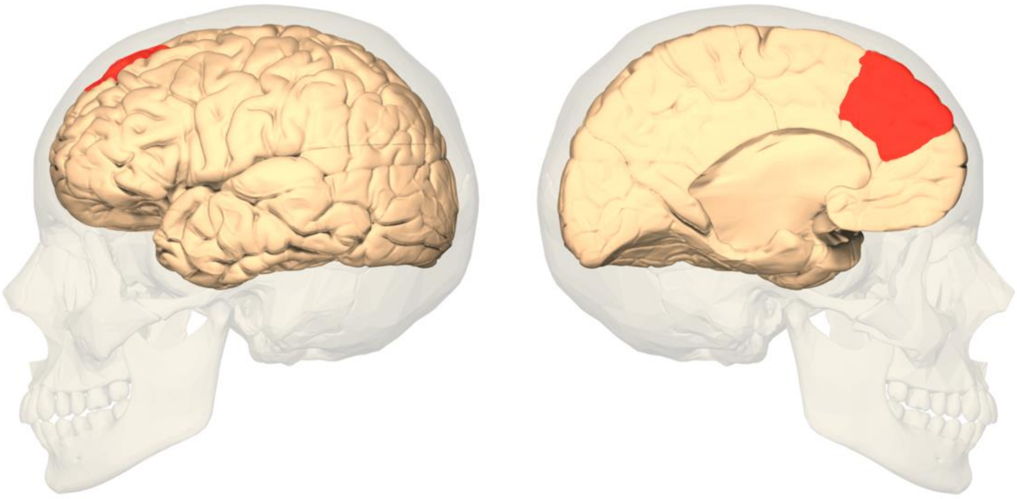

Figure 19. Location of the dorsomedial prefrontal cortex (DMPFC) in the human brain, from a lateral (left) and medial (right) perspective. Adapted from Anatomography (2017) (CC-BY-SA 2.1-ja).

Compared to other brain structures, the prefrontal lobe stands out for its size in humans. Actually, the ontogenetic development of the human brain parallels that of our phylogenetic history, and the development of the associated cognitive capabilities, the most advanced of the animal kingdom, also follows the same trend: the prefrontal cortex is the part of the brain that matures the last, as happens with executive abilities. Counterintuitively, comparing brain sizes among animal species alone is not a good marker for intelligence; otherwise, we would not be able to explain the cognitive capacity of mammals with bigger brains than humans such as elephants or whales.

In spite of that, if we observe the relative sizes of specific brain regions, particularly the prefrontal cortex, we see a meaningful correlation. Brodmann (1912) calculated the relative size of the prefrontal cortex in several mammals. For dogs, it was 7% of the cortex; for cats, 4%; in monkeys, 10%; in great apes, around 20%; and finally, in human beings, it corresponded to 30-35% of the brain. If we already have an idea of the cognitive capacities of these animals, we can establish a direct relationship between the proportional size of the prefrontal cortex and intelligence. Nevertheless, the relative prefrontal size is not a perfect indicator. Despite the existence of a correlation between the frontal and total encephalic size ratio, more thorough studies (Semendeferi, Damasio, Frank, & Van Hoesen, 1997; Semendeferi, Lu, Schenker, & Damasio, 2002) observed that the ratio does not present significant differences between the great apes and humans. In both cases, rations were situated in the 26-33% range, which implies that there must be other aspects that explain the difference in cognitive capabilities between these animals.

Another aspect to consider is the volume of white matter in the frontal lobe, which has also expanded greatly in humans compared to other mammals. This could be indicative that the unique features that make us human are probably due to the interconnection of different cortical regions, and not merely a greater number of neurons in that region (Schoenemann, Sheehan, & Glotzer, 2005).

Lateral Prefrontal cortex

The lateral surface of the prefrontal cortex, comprising those parts of the frontal lobes anterior to the motor and premotor cortices, spans over the inferior, middle and superior frontal gyri. It is commonly subdivided into its upper (dorsal) and lower (ventral) parts, according to their functional anatomy and connectivity (M Petrides & Pandya, 1999, 2002).

Dorsal and ventral regions of the lateral prefrontal cortex feature parallel streams along the rostrocaudal axis, where more anterior regions show involvement when higher levels of abstraction are required. Likewise, another gradient is thought to exist spanning the dorsoventral axis, intertwined with the rostrocaudal axis, and showing specialization when different components of complex tasks, involving level of abstraction and action plans (Koechlin & Hyafil, 2007; Race, Shanker, & Wagner, 2009), or inductive and deductive reasoning strategies (Goel & Dolan, 2004), are mixed together. However, it is still not clear whether these two gradients exist separately or not (Blumenfeld, Nomura, Gratton, & D'Esposito, 2013).

a) Dorsolateral Prefrontal cortex (DLPFC)

Strictly speaking, the DLPFC is not an anatomical structure (as defined by its cytoarchitecture), but a functional one. As such, it roughly corresponds with the Brodmann area 46, although it also extends over the part of the Brodmann area 9 that is adjacent to the dorsal surface of the cortex. Its anterior portion limits with the frontopolar area (Brodmann area 10), while caudally, it borders with the pars triangularis of the IFG, corresponding to Brodmann area 45 (see Figure 20).

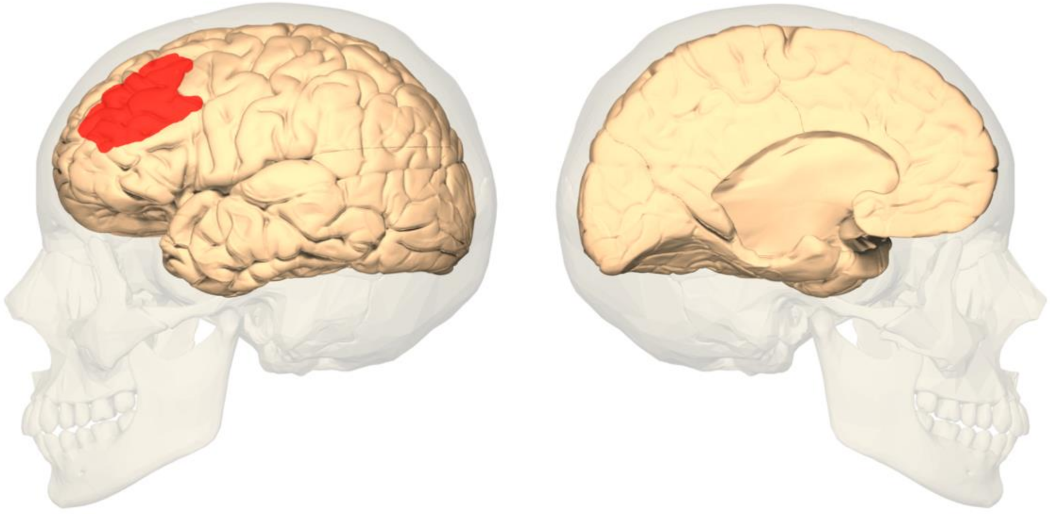

Figure 20. Location of the dorsolateral prefrontal cortex (DLPFC) in the human brain, from a lateral (left) and medial (right) perspective. Adapted from Anatomography (2017) (CC-BY-SA 2.1-ja).

It is a highly connected area, being interconnected with the orbitofrontal cortex, the thalamus, the dorsal caudate nucleus of the basal ganglia, the hippocampus, and primary and association cortices, like posterior temporal, parietal and occipital areas. Additionally, the DLPFC (as opposed to the VLPFC) constitutes the endpoint of the dorsal stream (the "how" system), involved in the guidance of actions and spatial awareness of objects, carrying information originating in the primary visual cortex (V1) in the occipital lobe, and through the parietal lobe.

As a result, the DLPFC is capable of holding representations for complex relationships of rules, needed for deciding which responses to execute, orienting the behavior towards problem-solving. Since this prefrontal region is in charge of integrating and managing information at a very high-level, it is involved in a very wide range of cognitive processes, not limited to the executive functions. The DLPFC is also involved in risky and moral decision making (Greene, Sommerville, Nystrom, Darley, & Cohen, 2001), social cognition and adopting the perspective of someone else (van den Bos, van Dijk, Westenberg, Rombouts, & Crone, 2011), building relationships between items in long-term memory (Murray & Ranganath, 2007), deception and lying (Ito et al., 2012), social cognition and theory of mind (B. L. Miller & Cummings, 2007).

As a whole, it is one of the main hubs for cognitive control, including the management of working memory, cognitive flexibility and planning, decision making, social cognition, conflict solving, and deductive reasoning, making this region one of the most closely linked with the concept of fluid intelligence (Barbey, Colom, & Grafman, 2013).

The DLPFC exhibits some lateralized specializations. When it comes to self-assessment, the right DLPFC seems more involved when dealing with adjectives reflecting personal traits, compared to assessments in other people (Schmitz, Kawahara-Baccus, & Johnson, 2004). More activity in the right DLPFC is also correlated with the capacity of suppressing tempting responses, diminishing risk-taking (E. K. Miller & Cohen, 2001). In complex tasks related to planning capacity, although bilateral activation prevails, it seems that the left DLPFC increased activation when facing goal hierarchy (that is, facing ambiguity in intermediate goals) but lower in search depth (the need to accomplish intermediate goals), while the opposite effect is observed in the right DLPFC (Kaller, Rahm, Spreer, Weiller, & Unterrainer, 2011).

b) Ventrolateral Prefrontal cortex (VLPFC)

The VLPFC is the portion of the lateral prefrontal cortex located in the IFG, limiting dorsally with the inferior frontal sulcus and ventrally by the lateral sulcus (Sylvian fissure). Cytoarchitectonically, it corresponds to Brodmann areas 44, 45 and 47, which have been sometimes considered subregions of the VLPFC due to its functional distinctions (see Figure 21). For instance, the anterior VLPFC (pars orbitalis) correlates with a ventral frontotemporal network associated with top-down processing on memory retrieval, while the mid-VLPFC (pars triangularis) correlates with a dorsal frontoparietal network associated with processing control after memories have been retrieved, supporting the notion of a dorsal-ventral functional distinction within the VLPFC (Barredo, Verstynen, & Badre, 2016).

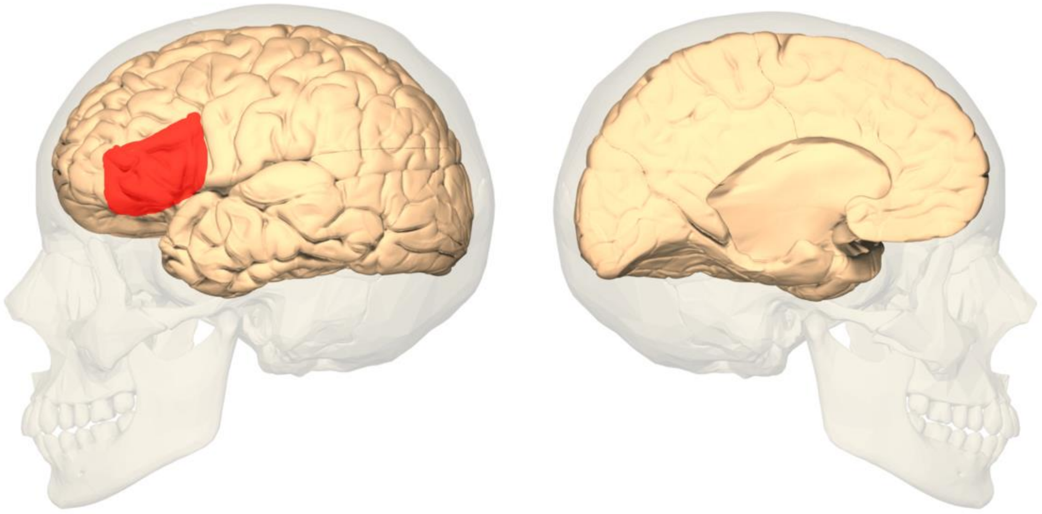

Figure 21. Location of the ventrolateral prefrontal cortex (VLPFC) in the human brain, from a lateral (left) and medial (right) perspective. Adapted from Anatomography (2017) (CC-BY-SA 2.1-ja).

Just like the dorsal pathways terminated in the DLPFC, the ventral pathway (the “what” system), responsible for object recognition and form representation, and linked with the limbic system, comes to an end at the VLPFC. The object attributes resulting from this pathway that are processed in prefrontal regions are dependent on the goals set by the VLPFC, effectively acting as a controller for the ventral pathway.

The VLPFC mediates some of the cognitive processes involved in emotional processing. The VLPFC and the amygdala constitute a neural circuit responsible for the detection of threats and the top-down modulation of negative emotional responses, which works in a coordinated manner with other frontal and prefrontal regions, like the DLPFC, ventromedial prefrontal regions, and the hippocampus.

Another one of the roles of the VLPFC is the management of attention in those cases in which we need to resist temptations and eliminate distractions. Activation in the VLPFC is present while a stimulus needs to be memorized, remaining active during the whole retention period, despite distractions, enabling sustained attention (Postle, 2006), and also shows enduring activation when doing working memory tasks in the presence of distractors (Kane & Engle, 2002).

The VLPFC also shows laterality differences in cognitive processing. Specific forms of cognitive control are associated with subregions of the left VLPFC, such as resolving decision-level conflict (Badre & Wagner, 2007), and tracking decision-level uncertainty (Race et al., 2009) while the right VLPFC seems to be more associated with stopping motor responses and reflexive orienting to abrupt perceptual events occurring outside the focus of attention (B. J. Levy & Wagner, 2011). Laterality activation differences have also been observed depending on mood factors; in depressed subjects, the left VLPFC had higher activation, allowing individuals to maintain their focus on specific problems while minimizing distractions, whereas, in situations of anxiety, the right VLPFC shows more activation, enhancing sustained attention to be able to anticipate hazards.

Frontal Polar Region

Located in the most anterior portion of the prefrontal cortex, the frontopolar region is the area roughly corresponding to Brodmann area 10, constituting the largest cytoarchitectonic area in the brain after having experienced a large increase of volume in recent evolution (Semendeferi, Armstrong, Schleicher, Zilles, & Van Hoesen, 2001). It occupies the more anterior parts of the superior frontal gyrus and the middle frontal gyrus. It is bounded dorsally by Brodmann area 9, caudally by Brodmann area 46 and ventrally by Brodmann areas 47 and 12. On its medial side, it does not reach the cingulate sulcus (see Figure 22). However, functionally speaking there is not an exact correspondence with the cytoarchitectonic structure so, when discussing its cognitive implications, it is most commonly referred as *frontopolar prefrontal cortex*, *anterior prefrontal cortex*, or *rostral prefrontal cortex.*

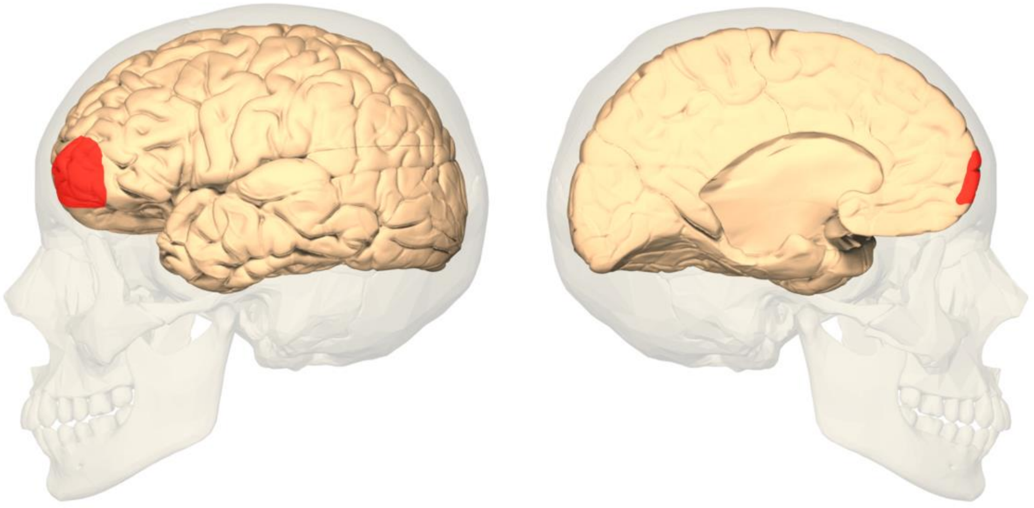

Figure 22. Location of the frontal polar region (FP) in the human brain, from a lateral (left) and medial (right) perspective. Adapted from Anatomography (2017) (CC-BY-SA 2.1-ja).

Regarding connectivity, mostly studied in primates, the frontopolar cortex sends and receives connections to other higher-order association cortices, mainly in the prefrontal cortex, while having low connectivity with primary sensory or motor areas. It is connected to the superior temporal sulcus through the extreme capsule, enabling this region to process auditory and multisensory information. Likewise, the connections leaving through the extreme capsule reach the ventral region of the insula. This region is also connected anterior and posterior cingulate cortex, the retrosplenial cortex, and the amygdala. There are not, however, connections that link this region to parietal, occipital or inferior temporal cortices (Michael Petrides & Pandya, 2007).

It plays a role in the highest level of integration of information, and it is linked with complex cognitive processing such as planning capacity, introspection, retrospective and prospective memory, dissociation of attention, and problem-solving in simultaneous tasks (Buriticá-Ramírez & Pimienta-Jiménez, 2007).

Ventromedial Prefrontal cortex (VMPFC)

The VMPFC is the portion of the prefrontal cortex located at the bottom of the cerebral hemispheres. It does not have a precise demarcation and sometimes surrounding areas are also considered part of the VMPFC. In its most limited form, it refers to the area medial to the orbitofrontal cortex, but under other definitions it can encompass a broad area comprising the lower central region of the prefrontal cortex, overlapping with the orbitofrontal cortex (see Figure 23).

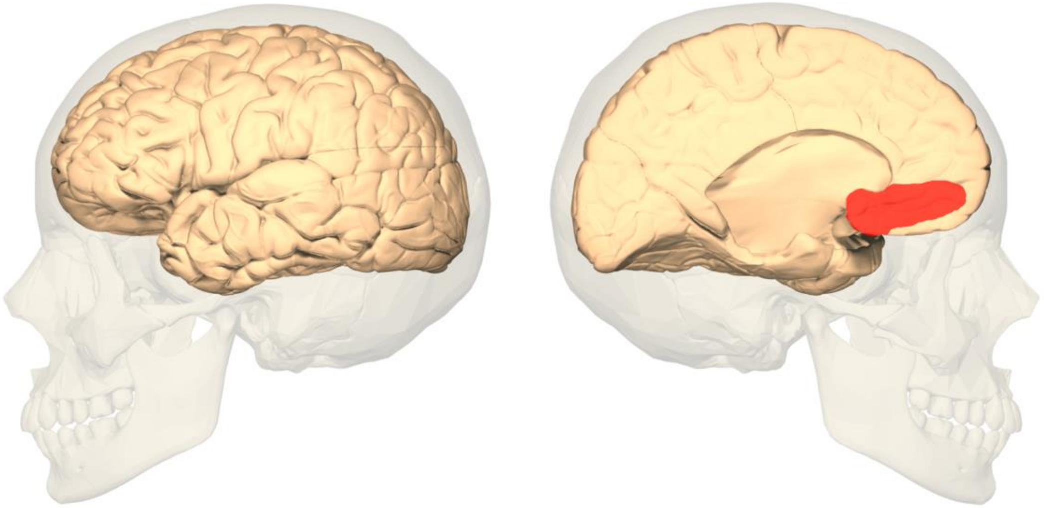

Figure 23. Location of the ventromedial prefrontal cortex (VMPFC) in the human brain, from a lateral (left) and medial (right) perspective. Adapted from Anatomography (2017) (CC-BY-SA 2.1-ja).

Interconnections with the VMPFC include afferents from the ventral tegmental area, the amygdala, the temporal lobe, the olfactory system and the dorsomedial thalamus. In turn, efferent fibers leave towards the temporal lobe, the amygdala, the lateral hypothalamus, the hippocampus, the cingulate cortex and other targets in the prefrontal cortex (Carlson, 2013).

Functionally speaking, the VMPFC is a major node for emotional regulation. Fine distinctions between the VMPFC and the orbitofrontal cortex are not yet well established, but ventromedial regions seem to be more associated with pure emotion regulation, while orbitofrontal regions have a more meaningful role in social cognition. The VMPFC is also involved in decision making, particularly in situations that feature uncertain outcomes, where the uncertainty involves a risk or an ambiguity (L. K. Fellows & Farah, 2007). The detection of irony, sarcasm, and deception also seems to be a role of the VMPFC, as well as the capacity to engage in critical thinking and remain skeptic against false claims and new beliefs (Asp et al., 2012; Zald & Andreotti, 2010). Somehow, the VMPFC is involved in the ability to apply moral judgments to specific situations of the everyday life, since damage in that region preserves the capacity of moral judgment, but are inconsistent in applying these moral principles to their own lives, likely to an impaired use of emotion when reasoning the moral nature of behavior (Carlson, 2013). The VMPFC also plays a major role in the process of extinction, the gradual weakening of a conditioned response, by consolidating the extinction learning. Structurally, grey matter thickness in the VMPFC is associated with more efficient extinction processes (Milad et al., 2005).

Orbitofrontal cortex (OFC)

The orbitofrontal cortex, consisting of Brodmann areas 11 and 47, although occasionally portions of area 10 are included as well, slightly overlapping the frontopolar cortex. Actually, in many contexts, the terms OFC and the VMPFC are considered to refer to the same region and the terms are used interchangeably (L. Phillips, MacPherson, & Della Sala, 2002), adding to confusion regarding the precise location of many prefrontal functions. It receives its name due to its position surrounding the superior part of the orbits of the eyes. If we consider the VMPFC and OFC separate structure, the OFC would be located at the most anterior part of the prefrontal cortex, ventrally to the frontopolar cortex, while the VMPFC would only refer to the most medial areas of the ventral prefrontal hemisphere.

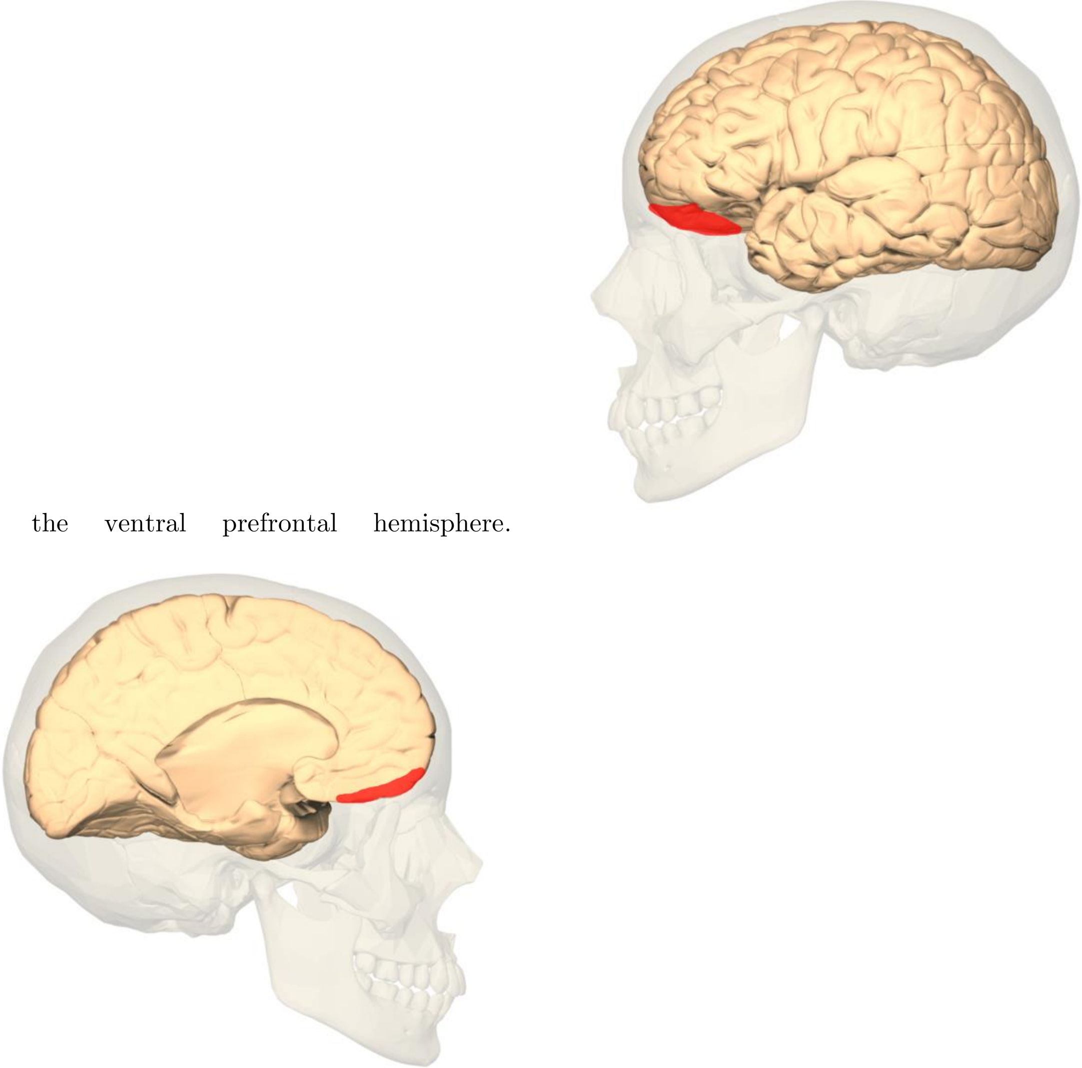

Figure 24. Location of the orbitofrontal cortex (OFC) in the human brain, from a lateral (left) and medial (right) perspective. Adapted from Anatomography (2017) (CC-BY-SA 2.1-ja).

Due to this confusion, it is difficult to attribute specific cognitive functions to one or another region, and there is definitely some degree of overlap between them. Just like the rest of the prefrontal cortices, the OFC has a role in higher-order cognition, and it is particularly involved in decision-making, impulse control, and response inhibition. The precise nature of its function, however, is not completely understood and this is an aspect that is still being debated. Speculation about its role traces back to the case of Phineas Gage, who allegedly experienced a drastic reduction in social inhibition after suffering extensive prefrontal damage, including the OFC and the lateral prefrontal cortices. Its role in impulse control seems to be just related to the inhibition of impulses in tasks where a stimulus-response association is reverted (Stalnaker, Cooch, & Schoenbaum, 2015). In decision-making, the OFC seems to be implicated in those decisions that must be done comparing relative value among several options to find out the optimum choice (Jonathan D Wallis, 2011). The role of the OFC over emotion, due to its interconnections with limbic system structures like the amygdala (Stalnaker et al., 2015), seems to be to modulate bodily changes associated with emotion (e.g. “nervous feelings”, increased perspiration, etc.), especially when faced with the option of making risky choices in decision making and gambling situations (Bechara, Damasio, Tranel, & Damasio, 1997), although the OFC is not completely indispensable for emotionally-guided decisions, as patients with OFC lesions do not seem to display global emotional deficits (Stalnaker et al., 2015).

2.1.3.2 Functional neuroanatomy of executive functions and working memory

Networks underlying executive functions and cognitive control

The functional and cognitive aspects of executive processing can be described based on the connectivity of the regions implicated in this function, a rule that is particularly evident in the frontal cortex. Regarding this aspect, one of the features of the prefrontal cortex is the bidirectional fashion in which most fibers are connected, either directly or indirectly, to other brain regions, more than any other cortical area.

Afferents

The main input to the prefrontal cortex comes from the thalamus, particularly the mediodorsal nucleus of the thalamus, comprising the 80% of the fibers departing from this nucleus, and acting as the main relay hub that conveys information from diverse brain regions to the prefrontal cortex. Within this nucleus, the medial portion, the *pars magnocellularis*, projects to the DLPFC, bringing information from diverse subcortical parts of the brain, particularly those related to the reward system and motor control, such as the *substantia nigra* and the ventral tegmental area (VTA) in the midbrain, the cerebellum, and the *globus pallidus* in the basal ganglia (See Figure 25).

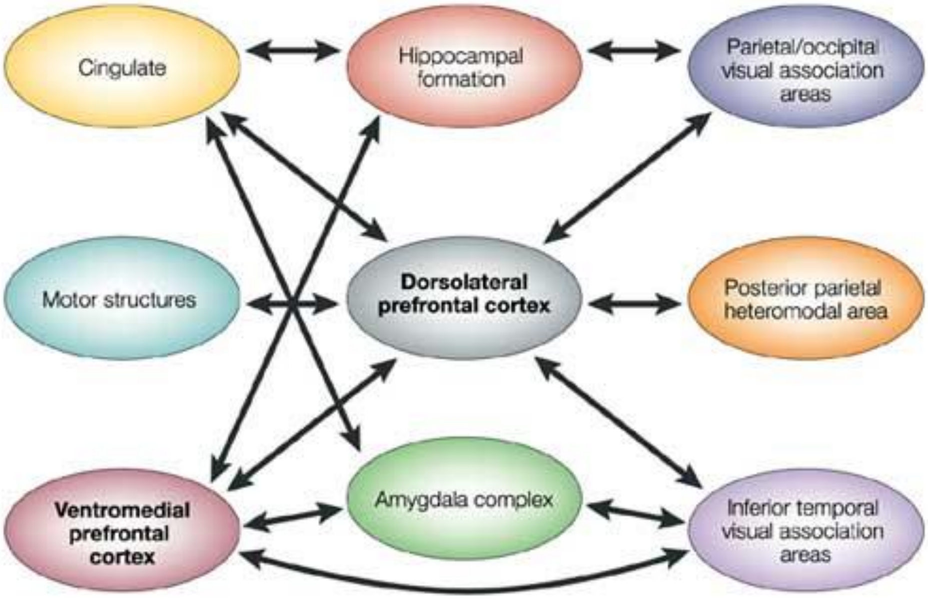

Figure 25: Main connectivity pathways involving the prefrontal cortex. Reciprocal connections to the ventromedial and dorsolateral prefrontal cortices can be observed, from which we can already infer their role in non-emotional and sensory areas and emotional processing areas. Source: (Wood & Grafman, 2003).

Also in the mediodorsal nucleus of the thalamus, another nucleus, the *pars parvocellularis*, projects to the VMPFC. This nucleus receives projections from regions associated with arousal and emotion, like the amygdala complex. The frontal eye fields (FEF), another prefrontal region associated with saccadic and voluntary eye movements, also received projections from the *pars* *parvocellularis*. Finally, the prefrontal cortex also receives inputs from the *pulvinar nucleus* of the thalamus, a nucleus that also projects to the parietal cortex.

Apart from these thalamic connections, the prefrontal cortex receives projections from other cortical and subcortical regions, mainly secondary sensory cortices, with the exception of the orbitofrontal cortex, which receives direct inputs from primary somatosensory, taste and olfactive cortices. Another important bidirectional direct connection to the DLPFC is the PPC, contributing to the important frontoparietal attentional network. The hippocampus, involved in the encoding and retrieval of memory, sends its outputs throughout the prefrontal cortex, the amygdala complex and the VTA, which in turn is primarily connected to the VMPFC.

Efferents

Regarding the outputs from the prefrontal cortex, we find that most fibers are bidirectional, so most of the inputs will have their corresponding efferent fibers, even if they follow an indirect route.

According to this principle, the prefrontal cortex sends fibers to secondary (but not primary) sensory regions, to bilateral premotor regions, and to homologous prefrontal areas through the corpus callosum. The VMPFC sends fibers targeting limbic regions such as the amygdala, the hippocampus, and the cingulate cortex. The hippocampus also receives indirect prefrontal inputs through the entorhinal cortex, an area that is located very close. The prefrontal cortex also sends targets to the hypothalamus, being the only cortical region to do so directly. However, basal ganglia do not match this bidirectionality principle. This region receives inputs from the prefrontal cortex, but these are only corresponded by indirect fibers going to through the *substantia nigra* and the thalamus. There is a reason for this arrangement: the basal ganglia are responsible for controlling the motor output, analogous to how the prefrontal cortex sends its fibers to the premotor regions.

Other regions, cortical and subcortical, relevant in executive functions and working memory

Parietal cortex

The parietal cortex is one of the areas outside of the prefrontal cortex that has a direct involvement in executive functions since it is interconnected with the processing hubs in prefrontal regions forming a frontoparietal network. As such, the parietal cortex is part of the dorsal stream, carrying visuospatial information originating in the primary visual cortex. The parietal cortex has a role in working memory and the direction of attention, especially when it involves a spatial component, but is not limited to that kind of information (Knops, Thirion, Hubbard, Michel, & Dehaene, 2009). The level of recruitment of parietal regions increase when a working memory task becomes more demanding (Diwadkar, Carpenter, & Just, 2000). Moreover, the intraparietal sulcus seems to have a role in processing the manipulation of information in working memory (Koenigs, Barbey, Postle, & Grafman, 2009; Leh, Petrides, & Strafella, 2010), although it is also active while temporally holding information without manipulating it (Molenberghs, Mesulam, Peeters, & Vandenberghe, 2007). In spite of that, although the executive involvement of parietal regions seems clear, their exact role in the whole executive processing is not very well understood.

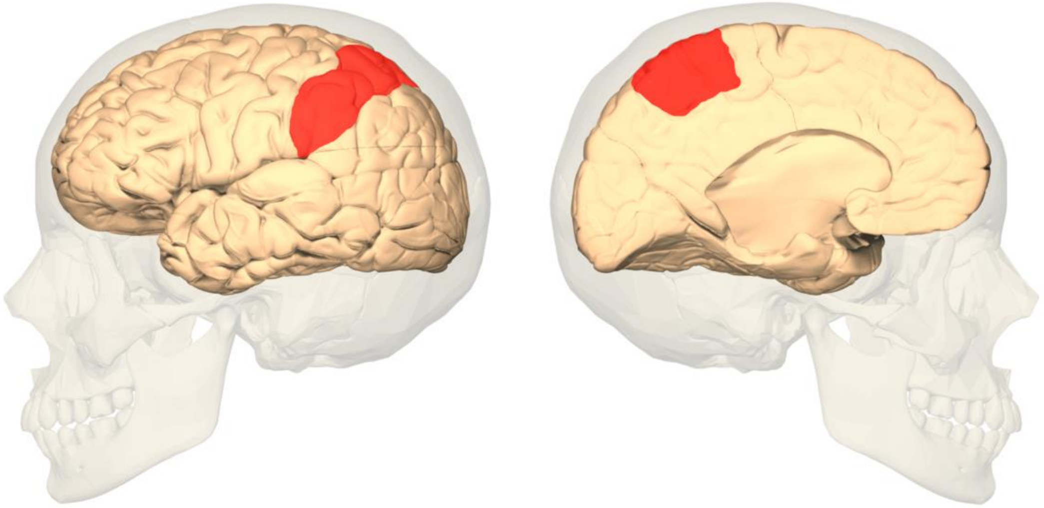

Figure 26. Location of the posterior parietal cortex (PPC) in the human brain, from a lateral (left) and medial (right) perspective. Adapted from Anatomography (2017) (CC-BY-SA 2.1-ja).

Anterior cingulate cortex

The anterior cingulate cortex (ACC) regions (corresponding to the Brodmann area 24), which are adjacent to the pre-supplementary motor cortex, the supplementary motor cortex, and the supplementary eye fields are also involved in the control of movement, as demonstrated by electrically stimulating this area, producing a muscle contraction. It is connected to several thalamic nuclei; however, its specific role in motor functions is still unknown.

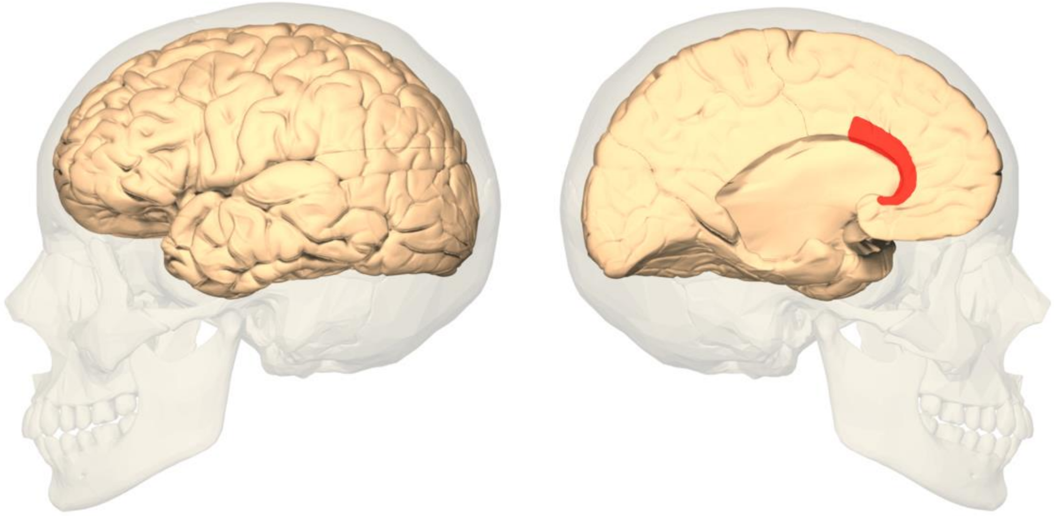

Figure 27. Location of the anterior cingulate cortex (ACC) in the human brain, from a lateral (left) and medial (right) perspective. Adapted from Anatomography (2017) (CC-BY-SA 2.1-ja).

There is a dorsal and a ventral component in the ACC. The dorsal section, connected to the prefrontal and parietal cortices, the motor system, and the frontal eye fields, constitutes a central station for top-down and bottom-up processing that assigns control to other brain areas to act according to the goals. In contrast, the ventral part is more connected to the amygdala, the nucleus accumbens, the hypothalamus, and the anterior insula, and contributes to assessing the salience of emotional and motivational information (Bush, Luu, & Posner, 2000).

The ACC is also involved in the regulation of autonomic nervous system functions, being able to induce parasympathetic modulation in the form of heart rate variability and blood pressure, and as such, it is thought to be a critical structure interfacing between cognition and emotion (Matthews, Paulus, Simmons, Nelesen, & Dimsdale, 2004).

The most prominent cognitive function associated with the ACC is the resolution of conflict that can potentially result in an error, where stimuli that are more competitive elicit more activation in the ACC. Once a conflict has been detected, the ACC then provides cues for other brain regions to cope with the conflict. On a wider scope, the conflict resolution function of the ACC may suppose a key aspect of reward-based learning.

Just like the lateral prefrontal cortex, the dorsomedial prefrontal cortex also features a rostrocaudal gradient of functions, where the most anterior parts implement control at progressively higher levels of abstraction (Blumenfeld et al., 2013).

Basal ganglia

The basal ganglia, particularly the caudate nucleus and the putamen, are a group of subcortical nuclei located at the base of the forebrain which constitute one of the major brain regions that enable executive control, where they seem to have a particularly important role in the context of decisn making. The basal ganglia receive projections from the lateral prefrontal cortex, and only sends indirect projections back to that region via the *substantia nigra* and the thalamus, likely reflecting the role of the basal ganglia in the control of motor output (Purves et al., 2012).

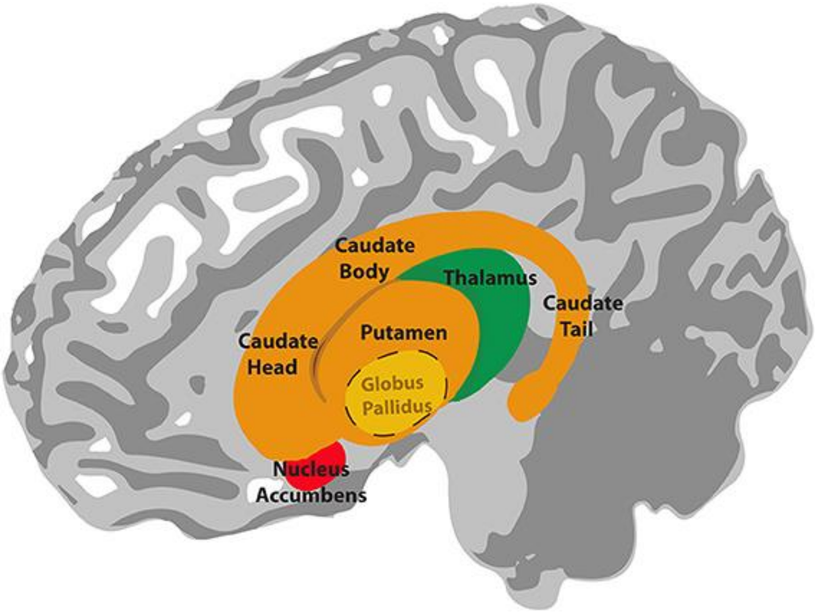

Figure 28. Anatomy of the basal ganglia. Source: (Lim, Fiez, & Holt, 2014) (CC BY 3.0).

Among other three basal ganglia circuits that act as parallel channels of information, there is a well-established circuit (the prefrontal channel, part of the dorsal striatal pathway) integrating the prefrontal cortices and the basal ganglia and another one (the limbic channel, constituting the ventral striatal pathway) integrating limbic structures with other prefrontal regions. The prefrontal channel receives inputs from the PPC and the premotor cortex, enters the basal ganglia through the head of the caudate nucleus, relays in the thalamus and ultimately reaches the prefrontal cortex. On the other hand, the limbic channel has its sources in the temporal cortex, the hippocampus, and the amygdala, and enter the basal ganglia through the nAcc, the ventral caudate and the ventral putamen and, after relaying in the thalamus, they reach the ACC and the OFC.

The basal ganglia have also been implicated in action selection, that is, they contribute to deciding which of several possible behaviors to execute at any given time. They would be responsible for control and regulate activities of the motor and premotor cortical regions in order to perform voluntary movements properly, by having an inhibitory control over a number of motor systems that in some way schedule when a motor system is allowed to become active (Chakravarthy, Joseph, & Bapi, 2010).

The basal ganglia also interact with the prefrontal cortex to support the creation of new rules for behavior, such as the creation of abstract rules, as observed in category learning tasks, which match categories of stimuli to responses. In this case, while the prefrontal cortex would be responsible for coding such abstractions, the basal ganglia would be in charge of the creation of rules that map specific stimulus to specific responses (Cools, Clark, & Robbins, 2004).

2.2 Cognitive Enhancement and Brain Correlates of Video Gaming

When we talk about cognitive enhancement, we include every kind of procedure and technique directed to improve the general cognitive functioning or some of its processes (e.g. attention, memory, language, visuospatial skills, executive functions, etc.), usually focused to help people with cognitive deficits to successfully engage in activities which have been hindered by these impairments. Therefore, the importance of cognitive enhancement is undeniable, being a key aspect to regain independent functioning and quality of life for those who present cognitive deficits, but also helping healthy people in improving cognitive performance.

The development of cognitive rehabilitation is closely linked to the medical advances developed in the early 20th century that contributed to the survival and recovery of brain-injured patients, a substantial fraction of which originated in the context of the wars that ravaged the first half of the century. Their aim was to provide not only physical rehabilitation but also the recovery of cognitive functions, which, if untreated, usually become the most debilitating long-term consequence of the injury. Originally dealing with traumatic brain injuries, rehabilitation therapies were soon adapted to other types of brain injuries, such as cerebrovascular disease, neurodegenerative and psychiatric disorders. The field experienced significant advances during the 70s and 80s, as a result of the progress in cognitive psychology and the treatment of cognitive impairments. From that moment, many new techniques, models, and applications were developed, which set the foundations for the therapies applied today. The scope was not only to treat the impaired cognitive function though, therapies were also developed for social, emotional and behavioral problems, as well as programs for adjusting to disability (Institute of Medicine, 2011).

Used in its narrower sense, “cognitive rehabilitation” or “cognitive training” can refer to the cognitive exercises and activities designed to restore or strengthen cognitive functions. Cognitive rehabilitation must be a comprehensive approach that not only involves the use of tools and activities to recover the hindered function, but must also have to consider contextual environmental and social factors to ensure its success. Therefore, training in compensatory strategies and metacognitive skills is nowadays part of a comprehensive intervention.

Despite the validity and reliability of cognitive rehabilitation interventions having improved steadily, until fairly recently cognitive rehabilitation therapies had relied on traditional methods and did not start to make use of recent technological advances that were present in other areas of neuroscience and psychology, such as the use of neuroimaging and computer-aided therapies. That situation started to change during the 80s and 90s, when many neuropsychological tasks used for assessment and neurorehabilitation tools started to be adapted to computerized formats, improving their efficiency and allowing more flexible administrations, even to the point of allowing customized and supervised home-based rehabilitation programs. Similarly, virtual reality environments started to be a trend in neuropsychology, making possible the use of simulated environments, both for assessment and rehabilitation, where a patient could fully interact with their surroundings, practicing their abilities in a life-like manner.

Currently, the transfer of the trained cognitive functions from the training setting to the application setting (e.g. everyday situations) remains to be the most critical aspect of the intervention and should be considered a goal by itself. However, this is not easily achieved, and many blame the lack of ecological validity of the employed neuropsychological tools, which are sometimes perceived as reductionist. Computerized neuropsychological tasks offer greater ecological validity, but they are still much simpler than the common everyday situations that a patient must cope. Technologies like video games and virtual reality can improve that aspect by simulating situations like those that the patient could encounter in their daily life. Due to the immersive nature of this technology, the level of complexity (e.g. the number of distractors present in a task) can be easily manipulated. This comes at a cost since not all tasks and therapies can be adapted to new formats without losing construct validity, so resources should be devoted to re-validate these tools.

More recently, the spread and popularity of neurocognitive interventions has led to their use in people who would not fit in the category of cognitive impairment. In this case, the use of cognitive rehabilitation in healthy individuals should be more specifically termed *cognitive training* or, if dedicated exclusively to the improvement of current cognitive performance, *cognitive enhancement*. Cognitive training is based on the fact that cognitive abilities can be maintained or improved as a result of mental exercise, just like physical exercise improves fitness. Initially, cognitive training was used as a preventive tool in the context of the normal aging process, but soon the concept spread and the general public embraced it. Many commercial products, such as video games in the *brain training* genre, were released targeting this market, in spite of their lack of evidence and usually without the supervision of a professional, raising more than a few ethical concerns.

2.2.1 Brain correlates of video gaming

In the context of neuroscience and neuropsychology, there has been a growing tendency to employ computer-aided rehabilitation techniques which offer several advantages over more conventional approaches (van Muijden, Band, & Hommel, 2012), allowing for more standardized conditions and frequent feedback to improve motivation. Some of them are mere exercises adapted from previous paper-and-pencil instruments, but some other techniques extend these features and offer customized performance monitoring to be able to dynamically adapt the task difficulty to each user (Institut Guttmann, 2013). But there is one last group of techniques that certainly differs over traditional instruments: the use of virtual environments in the form of video games in order to increase the motivation of the participant in the task while stimulating a wider range of cognitive functions, thereby targeting the lack of ecological validity that characterize pen-and-paper tasks (Anguera et al., 2013).

Before delving into the potential effects that video games can have on the brain and cognition, it is important to take a moment to define what constitutes, and what does not, a video game. A game (of any kind) is a type of play that is structured through rules, that poses a challenge for the player (against the game itself or against another player), and that features some form of interactivity, understood as a bidirectional effect between the player and the game, such as the administration of feedback after some action. Games can involve the use of physical or mental skills, often using both.

Games are a form of entertainment, and their main purpose is to provide fun. Sometimes, secondary purposes are contemplated, such as being educational, teaching abilities, developing physical skills or even being performed at a professional level. For instance, sports are a kind of games that involve mostly physical skills and are often played in the form of professional competitions.

When a game uses an electronic support to carry out its interactivity, then we talk about electronic games. Video games are the main representatives of this category, although not all electronic games are video games; pinball machines, slot machines, and audio games are examples of electronic games that do not fit in the category of video games. Then, what is exactly a video game? The key aspect of video games is that they carry out the interactivity through a user interface that generates visual feedback in a screen or display.

There are debates about the nature of a “game” that meets all the requisites for being a video game except that its main purpose is not to entertain, like what happens in the case of simulators, particularly flight simulators. Some argue that since the main goal is to act as a training tool, simulators, which often do not have specific goals, cannot be categorized as video games. Despite being used to train abilities (e.g. fly a plane), this kind of learning cannot be considered cognitive enhancement as we know it, since it is not focused to improve basic cognitive abilities, but rather teaching a very specific skill, involving technical knowledge and procedural learning, through near-transfer.

There is still a big difference between video games created in a laboratory with a research purpose in mind, and video games intended for public consumption. Purpose-made video game instruments for cognitive rehabilitation are often centered in the completion of simple tasks with adjusted levels of difficulty, although often feature poorly executed graphics and gameplay which may weaken the motivation of the participant. On the other hand, commercial video games do not have this problem, offering much more complex situations in highly detailed and polished environments, at the expense of the lack of control over the in-game variables, situations, and scenarios.

When it comes to assessing the validity of an intervention there are several ways in which performance on cognitive functioning can be measured, but can be summarized in two non-exclusive main categories: either by means of neuropsychological testing or by employing structural and functional neuroimaging techniques. Volumetric and functional changes in the brain after being exposed to rehabilitation therapy have been observed in previous studies (e.g. de Lange et al., 2008; Prosperini, Piattella, Giannì, & Pantano, 2015), showing that rehabilitation not only helps improving neuropsychological functioning but it also induces the corresponding changes in the brain. Actually, that was the expected result, as any change in cognitive abilities will have a neural correlate in brain's tissue and activity, even if it is small enough and undetectable by current technology.

There are precedents (e.g. Simone Kühn, Gleich, Lorenz, Lindenberger, & Gallinat, 2013) of the use of commercial video games in producing structural changes in the brain in areas responsible for certain cognitive functions, such as attention, visuospatial reasoning, fine-motor skills, or problem-solving abilities. These results offer encouraging prospects in the use of commercial video games in neuropsychological rehabilitation as well as cognitive function enhancement in healthy people.

Although cognitive enhancing and rehabilitation through the use of video game training seems to be one popular option at the current moment, efficacy data from studies dealing with video game training still shows mixed results (Powers, Brooks, Aldrich, Palladino, & Alfieri, 2013). For this reason, it seems a good idea to combine the potential effect of video game training with other techniques capable of inducing brain plasticity, creating a synergic effect and multiplying the impact of the application of each method separately.

Despite this potential and the current growth of the field, research in video games from the perspective of neuroscience has been developing in an unstructured manner and without any specific guidelines. The result of this is a quite large body of literature that provides lots of neuroimaging and behavioral data but lacking cohesion, and from which it is quite hard to draw any conclusions. With the aim of bringing order to this whole situation, the best possible course of action was to elaborate a systematic compilation of all studies that used video games alongside neuroimaging techniques. The following article, written by the research group implicated in this work, and me as the first author (2017), provides a systematic review of neural changes associated with video gaming and their associated cognitive implications are discussed in length.

frontiers
in Human Neuroscience

REVIEW
published: 22 May 2017
doi: 10.3389/fnhum.2017.00248

Neural Basis of Video Gaming: A Systematic Review

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Background: Video gaming is an increasingly popular activity in contemporary society, especially among young people, and video games are increasing in popularity not only as a research tool but also as a field of study. Many studies have focused on the neural and behavioral effects of video games, providing a great deal of video game derived brain correlates in recent decades. There is a great amount of information, obtained through a myriad of methods, providing neural correlates of video games.

Objectives: We aim to understand the relationship between the use of video games and their neural correlates, taking into account the whole variety of cognitive factors that they encompass.

Methods: A systematic review was conducted using standardized search operators that included the presence of video games and neuro-imaging techniques or references to structural or functional brain changes. Separate categories were made for studies featuring Internet Gaming Disorder and studies focused on the violent content of video games.

Results: A total of 116 articles were considered for the final selection. One hundred provided functional data and 22 measured structural brain changes. One-third of the studies covered video game addiction, and 14% focused on video game related violence.

Conclusions: Despite the innate heterogeneity of the field of study, it has been possible to establish a series of links between the neural and cognitive aspects, particularly regarding attention, cognitive control, visuospatial skills, cognitive workload, and reward processing. However, many aspects could be improved. The lack of standardization in the different aspects of video game related research, such as the participants' characteristics, the features of each video game genre and the diverse study goals could contribute to discrepancies in many related studies.

Keywords: addiction, cognitive improvement, functional changes, internet gaming disorder, neural correlates, neuroimaging, structural changes, video games

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Received: *16 September 2016*
Accepted: *26 April 2017*
Published: *22 May 2017*

Citation:
Palaus M, Marron EM, Viejo-Sobera R and Redolar-Ripoll D (2017) Neural Basis of Video Gaming: A Systematic Review.
Front. Hum. Neurosci. 11:248.
doi: 10.3389/fnhum.2017.00248

INTRODUCTION

Nowadays, video gaming is a highly popular and prevalent entertainment option, its use is no longer limited to children and adolescents. Demographic data on video gaming shows that the mean age of video game players (VGPs) (31 years old, as of 2014) has been on the rise in recent decades (Entertainment Software Association, 2014), and it is a common activity among young adults. Moreover, the increasing ubiquity of digital technologies, such as smart-phones and tablet computers, has exposed most of the population to entertainment software in the form of casual video games (VGs) or gamified applications. Therefore, an important segment of society, over 30% in tablet computers and 70% in smart phones, has been exposed to these technologies and can be considered now, in some form, casual gamers (Casual Games Association, 2013).

It is not uncommon to hear both positive and negative health claims related to VGs in the mass media. Most of the time, these are unverified and sensationalist statements, based on "expert" opinions, but lacking evidence behind them. On the other side, as VGs become more complex (due to improvements in computer hardware), they cater to audiences other than children, appealing to older audiences, and VGs have gained prevalence as a mainstream entertainment option. Consequently, the number of people who spend hours daily playing these kinds of games is increasing.

There is interest in knowing the possible effects of long-term exposure to VGs, and whether these effects are generally positive (in the shape of cognitive, emotional, motivation, and social benefits) (e.g., Granic et al., 2014) or negative (exposure to graphic violence, contribution to obesity, addiction, cardio-metabolic deficiencies, etc.) (e.g., Ivarsson et al., 2013; Turel et al., 2016). Moreover, VGs possess a series of intrinsic features which make them suitable for use in experimental procedures: they seem to increase participants' motivation better than tasks traditionally used in neuropsychology (e.g., Lohse et al., 2013) and, in the case of purpose-made VGs, they offer a higher degree of control over the in-game variables.

For all the reasons mentioned above, VGs have recently sparked more scientific interest. The number of publications that study or use some form of gaming has been increasing, since 2005, at a constant rate of 20% per year. While during the 90's around 15 VG-related articles were published per year, in 2015 that number was over 350 (see **Figure 1**).

However, the concept of VG is extremely heterogeneous and within the category we find a myriad of hardly comparable genres. The behavioral effects and the neural correlates derived from the use of VGs depend both on the nature of the VG, the exposition to the game (hours of game play, age of onset, etc.) (Kühn and Gallinat, 2014), and, to a large extent, the individual characteristics of each participant (Vo et al., 2011).

Furthermore, due to the popularity of VG genres where graphic violence is prevalent (shooters, survival horror, fantasy), many studies have chosen to focus on this variable. Therefore, there is a reasonable amount of scientific literature devoted to the study of violent behaviors and violence desensitization as a consequence of violence in VGs (e.g., Wang et al., 2009; Engelhardt et al., 2011). Lastly, in particular since the emergence of online VG play, there are concerns about the addictive properties of VGs, akin to gambling and substance abuse, consequently making it another recurrent topic in the literature (e.g., Young, 1998).

For the time being, this whole body of knowledge is a complex combination of techniques, goals and results. On one hand, there are articles which study the effects of VG exposure over the nervous system and over cognition (e.g., Green and Seitz, 2015); it seems that there is solid evidence that exposure to certain kinds of VGs can have an influence on behavioral aspects, and therefore, we should be able to appreciate changes in the neural bases (Bavelier et al., 2012a). Actually, assessing the cognitive and behavioral implications of VG exposure has already been the object of study in recent systematic reviews and meta-analysis that used neuropsychological tasks to measure the influence of these games in healthy individuals. This is highly relevant since they evaluate the possible transfer effects of VG training to wider cognitive domains, providing a global perspective on how experimental and quasi-experimental designs differ in the size of the effect depending on the cognitive function (Powers et al., 2013), and how aging interferes with cognitive training by means of computerized tasks (Lampit et al., 2014) and VGs (Toril et al., 2014; Wang et al., 2016). Knowledge obtained about transfer effects is very important since it allows us to establish a link between VGs and cognition, indirectly helping us understand its neural basis, which in this case acts as a bridge between them. From an applied perspective, this knowledge can be used to design more effective rehabilitation programs, especially those focusing on older populations, keeping the most

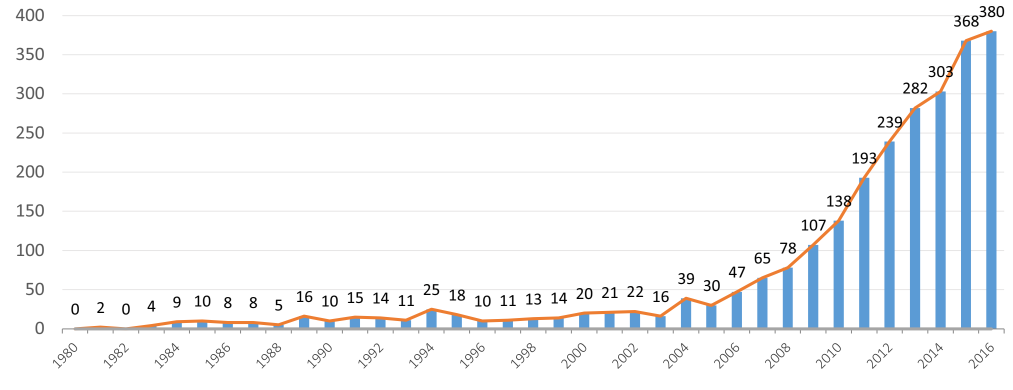

FIGURE 1 | Increasing trend in VG-related articles. Since 2005, the average annual growth is around 20%. (Source: MEDLINE).

useful components and reducing those which are shown to have less benefits.

On the other hand, VGs have been used as a research tool to study the nervous system. In this group of studies, it is common to find exposure to VGs as the independent variable, especially in most studies that use unmodified commercial VGs. However, it is not unusual to employ custom designed VGs, such as the widely used Space Fortress, where in-game variables can be fine-tuned to elicit certain mental processes in consonance with the research hypothesis (e.g., Smith et al., 1999; Anderson et al., 2011; Prakash et al., 2012; Anderson et al., 2015). Nevertheless, in both cases, the study of the VG exposure over the nervous system and the use of VGs as a research tool, VGs are used to obtain information about the underlying neural processes relevant to our research interest.

As yet there is no systematic review on this topic. The aim of this article is to gather all the scientific information referring to neural correlates of VGs and synthesize the most important findings. All articles mentioning functional and structural changes in the brain due to video gaming will be analyzed and information about the most relevant brain regions for each kind of study will be extracted; the main objective of many VG-related articles is not to study their neural correlates directly. Studies focusing on the addictive consequences or the effects of violence will be categorized independently.

Our final goal is to highlight the neural correlates of video gaming by making a comprehensive compilation and reviewing all relevant scientific publications that make reference to the underlying neural substrate related to VG play. This is the first effort in this direction that integrates data regarding VGs, neural correlates and cognitive functions that is not limited to action-VGs or cognitive training programs, the most frequently found research topics.

METHODS

In order to structure reliably the gathered information in this systematic review, the guidelines and recommendations contained in the PRISMA statement (Liberati et al., 2009) have been followed.

Eligibility Criteria

All articles which included neural correlates (both functional and structural) and included VG play in the research protocol or studied the effects of exposure to VGs were included in the review. Both experimental and correlational studies were included. No restrictions regarding publication date were applied.

Healthy participants of any age and gender were considered. Studies include both naive and experienced VG participants. Participants that reported gaming addiction or met criteria for internet gaming disorder (IGD) were also included in the review owing to the interest in observing neural correlates in these extreme cases. Other pathologies were excluded in order to avoid confounding variables.

Articles employing several methodologies were included. These can be organized into three main groups: studies where naive participants were trained in the use of a VG against a control group, studies comparing experienced players vs. non-gamers or low-experience players, and studies comparing differential characteristics of two VG or two VG genres.

The primary outcome measures were any kind of structural and functional data obtained using neuroimaging techniques including computerized tomography (CT) scan, structural magnetic resonance imaging (MRI), functional MRI (fMRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), magneto encephalography (MEG), transcranial direct current stimulation (tDCS), electroencephalogram (EEG), event-related potentials (ERP), event-related spectral perturbation (ERSP), steady state visually evoked potential (SSVEP), Doppler, and near-infrared spectroscopy (NIRS), following or related to VG use.

Information Sources

Academic articles were located using two electronic databases: MEDLINE and Web of Science, and by scanning reference lists in other studies in the same field. Only the results from these two databases are reported since results from other sources (Scopus, Google Scholar) did not provide any relevant new results. The search was not limited by year of publication and only articles published in English, Spanish, or French were considered for inclusion. The first studies relevant to the topic are from 1992, while the most recent studies included in this review were published in February 2016.

Search

A systematic search was performed using a series of keywords which were expected to appear in the title or abstract of any study containing neural correlates of VGs. These keywords were grouped in two main categories. First of all, a group of keywords trying to identify articles which used VG as a technique or as a study goal. These keywords included search terms related to "video games" proper (in different orthographic variants), types of players (casual, core, and hardcore gamers) and references to serious gaming. In second place, two groups of keywords were used to detect articles which studied the neural basis: (1) keywords related to anatomical features, such as structural or functional changes, gray, or white matter (WM) volumes, cortical features, and connectivity and (2) keywords which mentioned the neuroimaging technique used to obtain that data, such as EEG, MRI, PET, or NIRS. (See Appendix)

Study Selection

Due to the large amount of results obtained by the previous search terms, strict exclusion criteria were applied to limit the final selection of studies. The same criteria were applied in a standardized way by two independent reviewers, and disagreements between reviewers were resolved by consensus. Due to high variability in the terminology and the diversity of keywords used in the search, a large number of false positive studies (65% of items found) appeared during the review process (see **Figure 2**).

By performing a search using standardized terms, a list of studies from the two databases was extracted. A large number of studies (62% of those that met the inclusion criteria) were found

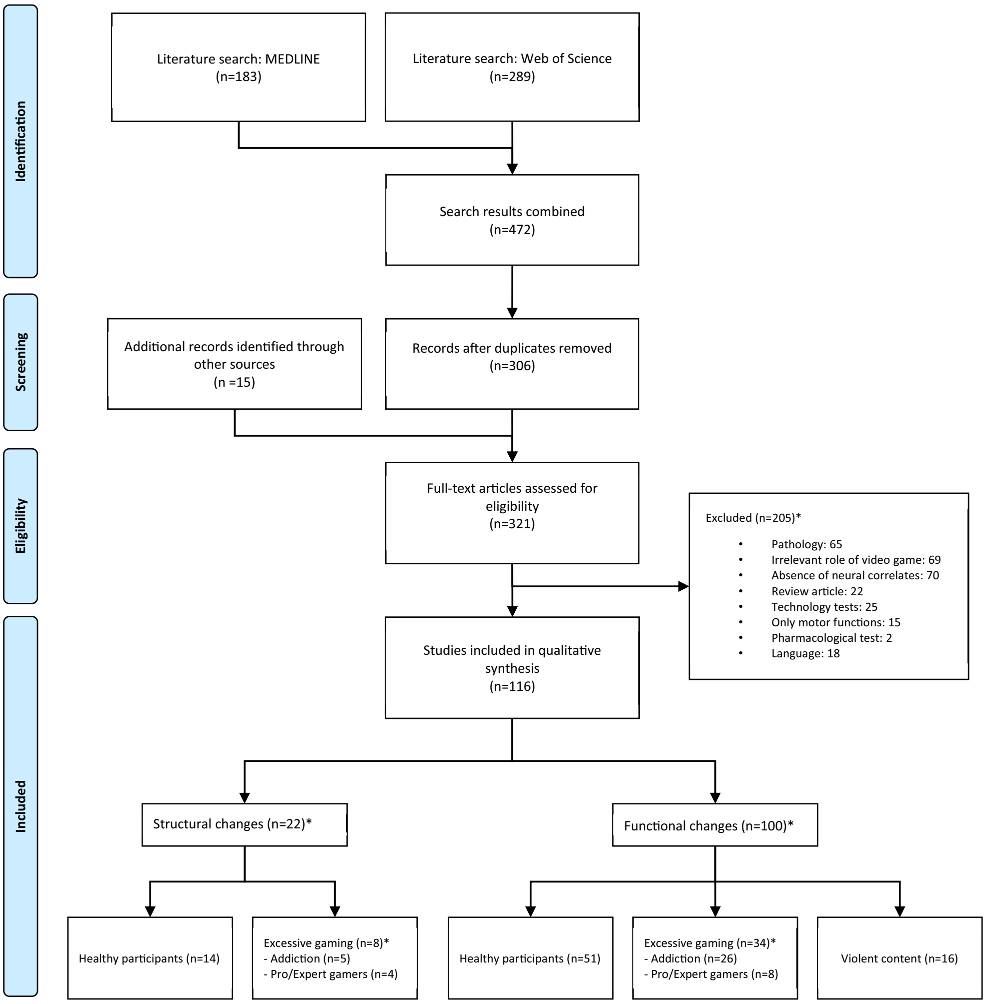

FIGURE 2 | Study selection diagram flow. *Articles in these sections may not be mutually exclusive.

to be duplicates in both databases, so a careful comparison was made in order to merge the references.

No unpublished relevant studies were considered. Studies relevant to the topic but not published in peer-reviewed journals, such as conference posters and abstracts were considered.

Data Collection Process

All the relevant information was classified in a spreadsheet, according to the variables listed below. Variables related to violence and abuse of VGs were also categorized, since a significant portion of the studies focused on these behaviors. A small number of articles ($n = 7$) were found in sources other than the two databases, mainly through references in other articles.

For each study, the following data was extracted: (1) characteristics of the sample, including sample size, average age and range, inclusion and exclusion criteria, and gaming experience; (2) aim of the study, specially noting if it is focused on gaming abuse or exposure to violent content; (3) name and genre of the VG used during the study, if applicable; (4) study design; (5) main neuroimaging technique applied in the study, and whether the technique was applied while participants played; (6) functional and structural neural correlates observed in the study. Studies were then classified in several groups as to whether they provided structural or functional data, and whether they addressed violent or addictive aspects.

Moreover, in order to understand the outcomes derived from the neural correlates, most of the studies establish a connection between these correlates and their cognitive correspondence, either by directly measuring the outcomes using cognitive tasks and questionnaires, or by interpreting their results based on existing literature.

In the discussion section of this review, we attempted to summarize the main findings by associating the neural changes to their cognitive and behavioral correspondences. Whereas, in many cases the original articles provided their own explanation for the phenomena, we also worked on integrating the general trends from a cognitive perspective. We therefore indicate which studies provide and interpret empirical cognitive or/and behavioral data (non-marked), those which discuss cognitive or/and behavioral implications without assessing them (marked with *), and those which did not provide any cognitive nor behavioral information (marked with **).

RESULTS

Study Selection

The combined search of MEDLINE and Web of Science provided a total of 306 unique citations. Of these, 205 studies were discarded because they did not seem to meet the inclusion criteria after reviewing the abstract. The main reasons for exclusion were: being a review article ($n = 22$), absence of neural correlates ($n = 70$), presence of pathology in the participants ($n = 65$), not being related to VGs or using simple computerized tasks which could not be considered VGs ($n = 69$), testing of new technologies in which the brain correlates were a mere by-product ($n = 25$), articles focused on motor functions ($n = 15$), pharmacological studies ($n = 2$), and finally, articles in languages other than English, Spanish, or French ($n = 18$). Excluded articles often met more than one exclusion criteria. As mentioned in the eligibility criteria, an exception were those articles in which the pathology consisted of gaming overuse or addiction and articles which featured psychopathology and included groups of healthy participants from whom neural data was provided.

Fifteen extra articles that met the inclusion criteria were found after examining the contents and following the references in the previously selected studies. As expected, articles written in English comprised the vast majority; among the rest (8.9%), 10 of them (4.9%) were discarded from the review solely for language reasons. No unpublished relevant studies were considered. Studies relevant to the topic but not published in peer-reviewed journals, such as conference posters and abstracts were considered. Ultimately, a total of 116 studies were identified for inclusion in the review (see flow diagram in **Figure 2**).

Most studies ($n = 100$; 86.2%) provided functional data, while only 22 (18.9%) of them studied structural changes in the brain. A few ($n = 6$; 5.2%) provided both structural and functional data. A significant number of the studies focused their attention on excessive playing or VG addiction. That was the case for 39 (33.6%) of the reviewed articles, so we considered it appropriate to analyze them in their own category. Likewise, 16 studies (13.8%) focusing on the violent component of VGs were also placed in their own category. These categories were not always exclusive, but there was only one case where the two criteria were met. (See **Table 1** for a breakdown by category).

Characteristics of Included Studies

Based on their methodology, studies in this review could be classified as experimental ($n = 54$; 46.6%), randomly assigning the participant sample to the experimental groups, and quasi-experimental ($n = 62$; 53.4%), where the groups were usually constructed according to the participants' characteristics. While studies involving excessive gaming almost always followed a quasi-experimental design comparing experienced gamers against low-experience VG players, articles studying normal gaming and the effects of violence exposure used both experimental and quasi-experimental designs. A fraction of the studies ($n = 15$; 13%), both experimental and quasi-experimental, compared the results to a baseline using a pretest-posttest design. That was the case for most studies involving a training period with VGs.

TABLE 1 | Article breakdown by category.

	Structural	Functional	Both	Total
All	22	100	6	116
Healthy (Non excessive, non-violent)	14	51	3	62
Excessive gaming	8	34	3	39
Excessive gaming, IGD	5	26	2	29
Excessive gaming, Non-IGD	3	8	1	10
Violence	0	16	0	16
Violence + Excessive gaming	0	1	0	1
	Only structural	**Only functional**		
	16	94		

IGD, Internet Gaming Disorder.

The cumulative sample included in this review exceeds 3,880 participants. The exact number cannot be known since participants could have been reused for further experiments and in some cases the sample size was not available. Most studies used adolescents or young adults as the primary experimental group, since that is the main demographic target for video gaming. In many cases, only male participants were accepted. In the cases where VG experience was compared, the criteria varied greatly. For the low video gaming groups, VG usage ranged from <5 h/week to none at all. For the usual to excessive VG groups, it could typically start at 10 h/week. In some cases, where the level of addiction mattered, the score in an addiction scale was used instead.

In more than half of the studies ($n = 67$; 57.8%) participants actually played a VG as part of the experimental procedure. In the rest, either neural correlates were measured in a resting-state condition or VG related cues were presented to the participants during the image acquisition.

Structural changes in the gray matter (GM) were measured in the form of volumetric changes, whereas WM was assessed using tractography techniques. Functional changes were typically measured comparing activation rates for different brain regions. Nearly half ($n = 55$; 47.4%) of the assessed studies used fMRI as the neuroimaging technique of choice, while other functional techniques remained in a distant second place. Functional connectivity was assessed in several studies employing resting-state measures. EEG in its multiple forms was also widely used ($n = 32$; 27.6%) to obtain functional data, either to measure activation differences across regions or in the form of event related potentials. (See **Table 2** for a breakdown by neuroimaging technique).

The high variability in the study designs, participants and objectives meant we focused on describing the studies, their results, their applicability, and their limitations on a qualitative synthesis rather than meta-analysis.

Structural Data

Data regarding structural changes following VG use was available from 22 studies, fourteen of which provided structural data for more than 800 participants that had a normal VG use and included both VGPs and non-VGPs (see **Table 3**). The remaining eight studies examined aspects concerning the excessive or professional use of VG (see **Table 4**).

In studies dealing with healthy, non-addicted participants, eight studies used MRI to provide structural information for the GM, while six focused on the WM using diffusion tension imaging (DTI).

Three studies compared lifetime VG experience prior to the study, while the rest used a training paradigm where participants were exposed to a VG during the experimental sessions prior to the neuroimaging procedure and compared to a baseline. Seven studies provided WM integrity data using the DTI technique while the rest analyzed cortical thickness variations using regular structural MRI.

The most researched areas in studies examining volumetric differences found relevant changes in prefrontal regions, mainly the dorsolateral prefrontal cortex (dlPFC) and surrounding areas, superior and posterior parietal regions, the anterior cingulate cortex (ACC), the cerebellum, the insula, and subcortical nuclei, as well as the striatum and the hippocampus. In addition to this, structural connectivity studies observed changes in virtually all parts of the brain, such as in fibers connecting to the visual, temporal and prefrontal cortices, the corpus callosum, the hippocampus, the thalamus, association fibers like the external capsule, and fibers connecting the basal ganglia.

Functional Data

A 100 articles provided functional data combined with VG use. Of these, around half ($n = 51$) were studies which did not include violence or addiction elements (See **Table 5**). A third ($n = 34$) corresponded to articles aiming at understanding the neural bases of IGD (See **Table 6**), often drawing parallels with other behavioral addictions and trying to find biomarkers for VG addiction. The rest ($n = 16$) were devoted to study the effects of violence exposure in VGs (See **Table 7**). In total, these studies provided functional data for 3,229 experimental subjects, including control groups. Note that there is some overlap with the structural section, since a few ($n = 6$) studies provided both structural and functional data.

The rich diversity of methodologies and research goals means that the study of functional brain correlates covers practically all regions of the brain. The most studied areas are found in frontal and prefrontal regions and are concerned with high-order cognitive processes and motor/premotor functions. Activity changes in parietal regions, like the posterior and superior parietal lobe, relevant for diverse functions such as sensory integration and visual and attentional processing, are also a common find. The anterior and posterior cingulate cortices, together with other limbic areas, such as the amygdala, and the entorhinal cortex, display activity changes possibly as a consequence of learning and emotion processing and memory. Structures in the basal nuclei also have a prominent role, particularly the striatum, in studies related to VG addiction. Finally, we must not overlook a series of brain regions which do not appear as frequently, such as occipital and temporal cortices, the cerebellum, the thalamus, and the hippocampus, where distinctive activity patterns have also been observed as a result of VG play.

TABLE 2 | Neuroimaging techniques used in the reviewed studies.

Technique	N	%
Electrophysiological methods	32	27.6
EEG (standard)	13	11.2
ERP	16	13.8
ERSP	1	0.9
SSVEP	2	1.7
MRI	70	60.3
MRI (structural)	15	12.9
fMRI	55	47.4
NIRS	8	6.9
SPECT	2	1.7
PET	2	1.7
Doppler	1	0.9

EEG, Electroencephalography; ERP, Event-related potentials; ERSP, Event-related spectral Dynamics; fMRI, Functional magnetic resonance imaging; MRI, Magnetic resonance imaging; NIRS, Near-infrared spectroscopy; PET, Positon emission tomography; SPECT, Single-photon emission computed tomography; SSVEP, Steady-state visual evoked potential.

DISCUSSION

Due to the given amount of data provided in the reviewed articles, we decided to categorize all the information based on the cognitive functions which are associated with the neurophysiological correlates, rather than focusing on the main research goal for each study. Thus, the discussion has been grouped into six main sections: attention, visuospatial skills, cognitive workload, cognitive control, skill acquisition, and reward processing. These cognitive processes are not clearly independent since they present some degree of overlap. This is particularly relevant in the cases of cognitive workload, which may be linked to virtually any cognitive function, and attention, which is also closely related to cognitive control, among other functions. Nevertheless, after analyzing the literature, virtually all the articles included in this review focused on one or more of the mentioned cognitive functions in order to explain their findings. Thus, the proposed categories have sufficient presence in the literature to justify their use as separate domains for the study of cognition. While they should not be understood as independent aspects of cognition, the chosen categorization will allow a link between the underlying neural correlates and corresponding behavior to be easily established.

Within each one of the sections, structural and functional correlates are discussed according to their contributions to cognitive functioning, including possible inconsistencies between studies and the presence of transfer effects. Owing to the close link between VG violence, limbic and reward systems, and the possible abnormal reward mechanisms in addicted players, studies previously classified with violence in VGs and VG addiction are predominantly discussed in the reward processing section.

TABLE 3 | Studies providing structural data dealing with healthy, non-expert participants.

Ref.	Year	*N*	Age	Sample	VP experience	VG genre	Technique	Design	Neural correlates
Erickson et al., 2010	2010	39	(18–28)	Healthy young adults	<3 h/week	Action, shooter	MRI	Experimental (randomized)	Predictors of skill acquisition: ▲ DS ▲ VS
Basak et al., 2011	2011	20	70.1 ± 4.81	Healthy older adults	Low VGP (<1 h/week)	Real time strategy	MRI	Quasi-experimental (one group pretest-posttest)	Predictors of skill acquisition: ▲ MFG (left) ▲ PoCG (left) ▲ dlPFC (left) ▲ ACC (right) ▲ Cerebellum
Vo et al., 2011	2011	34	(18–28)	Healthy young adults	Low or Non-VGP	Action, shooter	MRI	Experimental (crossover)	Skill acquisition: ▲ DS
Colom et al., 2012	2012	20	18.95 ± 2.65	Healthy young adults, female	Low or Non-VGP	Puzzle, Brain training	MRI (DTI)	Experimental (randomized with pretest)	After VG training: Gray matter: ▲ PFC (BA9 & BA10) ▲ Small temporal and parietal regions White matter: ▲ HC cingulum ▲ ILF
Kühn et al., 2013	2013	48	24.1 ± 3.8	Healthy young adults	Low or Non-VGP	Action, 3D platforms	MRI	Experimental (randomized with pretest)	After VG training: ▲ HC (right) ▲ dlPFC (right) ▲ Cerebellum
McGarry et al., 2013	2013	7	(60–85)	Healthy older adults	–	Real time strategy	MRI	Quasi-experimental (one group pretest-posttest)	After VG training: ▲ SPG ▲ Lateral IFG ▲ PrCG ▲ FG
Kühn and Gallinat, 2014*	2014	62	28.4 ± 6.07	Healthy young adults, male	Low or Non-VGP ($n = 48$) Excessive ($n = 9$) IGD ($n = 5$)	–	MRI	Quasi-experimental (retrospective)	VG experience: ▲ Entorhinal cortex ▲ HC Game genre: ▲ Entorhinal cortex
Kühn et al., 2014*	2014	152	14.4 ± 0.03	Healthy adolescents	12.6 ± 12.9 h/week	–	MRI	Quasi-experimental (retrospective)	VG experience: ▲ dlPFC (left) ▲ MFG(left) ▲ SFG (left) ▲ FEF (left)
Strenziok et al., 2013	2014	–	(>60)	Healthy older adults	–	Real time strategy Puzzle, Brain training	MRI (DTI)	Experimental (randomized)	After VG training: ▼ Splenium of CC

(Continued)

TABLE 3 | Continued

Ref.	Year	*N*	Age	Sample	VP experience	VG genre	Technique	Design	Neural correlates
Strenziok et al., 2014	2014	42	69.21 ± 4.9	Healthy older adults	–	Action, shooter Real time strategy Puzzle, Brain training	MRI (DTI)	Experimental (randomized with pretest)	After VG training (white matter AD): All 3 groups: ▲ Lingual gyrus (left) ▲ Thalamus (right) Brain training vs. Action shooter: ▲ TO junction (right) Brain training vs. Strategy: ▲ POT junction (right)
Szabó et al., 2014**	2014	56	36.8 ± 10.3	Healthy adults	Low or Non-VGP	Action, 3D platforms	MRI	Experimental (randomized with pretest)	After VG training: ▲ HC (right)
Zhang et al., 2015	2015	45	16.9 ± 2.2 (VGP) 17.1 ± 1.3 (Non-VGP)	Healthy adolescents, male	VGP (19 h/week) Low or Non-VGP (<2 h/week)	Racing Role playing, MMORPG Dance Action, First Person Shooter	MRI (DTI)	Quasi-experimental (retrospective)	VGP vs. Non-VGP (White matter FA): ▲ CST (left) ▲ SLF (left) ▲ ILF ▲ IFOF
Kim Y. H. et al., 2015*	2015	31	29.0 ± 4.1	Healthy young adults	VGP (>3 h/week) Non-VGP (<10 h/year)	Real time strategy	MRI (DTI)	Quasi-experimental (with control group)	VGP vs. Non-VGP: White matter connectivity: ▲ EC (right) & Visual cortex ▲ IFG (right) & ACC
Takeuchi et al., 2016	2016	240	11.1 ± 2.7	Healthy children	0.8 ± 0.75 h/week	–	MRI (DTI)	Quasi-experimental (cross-sectional)	VG experience: ▲ PFC (bilateral) (GM & WM) ▲ ACC ▲ Lateral & Medial temporal cortex ▲ BG ▲ FG ▼ Genu of de CC (Specific areas) ▼ Body of the CC ▼ ACR (bilateral) ▼ SCR (right)
Takeuchi et al., 2016	2016	189	(5.7–16.6)	Healthy children	–	–	MRI (DTI)	Quasi-experimental (longitudinal)	VG experience: ▲ Cluster 1: BG (Gm & WM) (left) Medial temporal lobe (left) Thalamus (bilateral) ▲ Cluster 2: Insula (right) Putamen (right) Thalamus (right) ▲ Cluster 3: MTG & ITC (left) FG Occipital lobe (left)

ACC, Anterior cingulate cortex; ACR, Anterior corona radiata; AD, Axial diffusivity; BA, Brodmann area; BG, Basal ganglia; CC, Corpus callosum; CST, Corticospinal tract; dlPFC, Dorsolateral prefrontal cortex; DS, Dorsal striatum; DTI, Diffusion tensor imaging; EC, External capsule; FA, Fractional anisotropy; FEF, Frontal eye fields; FG, Fusiform gyrus; GM, Gray matter; HC, Hippocampus; IFG, Inferior frontal gyrus; IFOF, Inferior frontooccipital fasciculus; IGD, Internet Gaming Disorder; ILF, Inferior longitudinal fasciculus; ITC, Inferior temporal cortex; MFG, Middle frontal gyrus; MRI, Magnetic resonance imaging; MTG, Middle temporal gyrus; PFC, Prefrontal cortex; PoCG, Post central gyrus; POT, Parieto-occipito-temporal; PrCG, Pre-central gyrus; SCR, Superior corona radiata; SFG, Superior frontal gyrus; SLF, Superior longitudinal fasciculus; SPG, Superior parietal gyrus; TO, Temporo-occipital; VG, Video game; VGP, Video game player; VS, Ventral striatum; WM, White matter. Articles marked with an asterisk (*) discuss cognitive implications without directly assessing this dimension. Articles marked with a double asterisk (**) did not provide either empirical cognitive data nor discuss cognitive implications. The rest of the articles (non-marked) have measured cognitive correlates with specific tasks.

TABLE 4 | Studies providing structural data dealing with VG experts or excessive gaming.

Ref.	Year	*N*	Age	Sample	VG experience	VG genre	Technique	Design	Neural correlates
Han et al., 2012a	2012	55	20.9 ± 2.0 (IGD) 20.8 ± 1.5 (Pro) 20.9 ± 2.1 (Control)	Young adults, male	IGD (9.0 ± 3.7 h/day) Professional VGP (9.4 ± 1.6 h/day) Low or Non-VGP (1.0 ± 0.7 h/day)	Real time strategy	MRI	Quasi-experimental (with control group)	IGD vs. Control: ▲ Thalamus GM (left) ▼ ITG (bilateral) ▼ MOG (right) ▼ IOG (left) Professional vs. Control: ▲ CG (left) ▼ MOG (left) ▼ ITG (right) Professional vs. IGD: ▲ CG (left) ▼ Thalamus (left)
Hou et al., 2012*	2012	14	20.40 ± 2.30 (IGD) 20.44 ± 1.13 (Control)	Young adults	IGD (>8 h/day) Low or Non-VGP (<5 h/day)	–	SPECT	Quasi-experimental (with control group)	IGD vs. Control: ▼ Striatum volume ▼ Striatum weight ▼ Striatum/whole brain ratio
Hyun et al., 2013	2013	23	19.8 ± 1.7	Healthy young adults, male	Professional VGP (9.2 ± 1.6 h/day)	Real time strategy	MRI	Quasi-experimental	Career length: ▲ SFG (right) ▲ SPG (right) ▲ PrCG (right) Winning rates: ▲ PFC
Tanaka et al., 2013	2013	50	24.1 ± 2.9 (Experts) 22.4 ± 3.42 (Control)	Healthy young adults, male	Expert VGP (21.4 ± 10.0 h/week) Low or Non-VGP (<2 h/week)	Action, fighting	MRI	Quasi-experimental (with control group)	Experts vs. Non-experts: ▲ PPC (right)
Yuan et al., 2013a	2013	36	19.4 ± 3.1 (IGD) 19.5 ± 2.8 (Control)	Young adults, male	IGD (10.2 ± 2.6 h/day) Low or Non-VGP (0.8 ± 0.4 h/day)	Role playing, MMORPG	MRI	Quasi-experimental (with control group)	IGD vs. Control: ▲ Precentral cortex (left) ▲ PCu ▲ MFG ▲ ITC ▲ MTG ▼ lOFC (left) (Impaired task performance) ▼ Insula ▼ Lingual gyrus ▼ PoCG (right) ▼ Entorhinal cortex ▼ IPC

(Continued)

TABLE 4 | Continued

Ref.	Year	*N*	Age	Sample	VG experience	VG genre	Technique	Design	Neural correlates
									IGD duration: ▲ Precentral cortex (left) ▲ PCu ▲ Lingual gyrus
Xing et al., 2014	2014	34	19.1 ± 0.7 (IGD) 19.8 ± 1.3 (Control)	Young adults	IGD (9.5 ± 1.3 h/day; 65.7 ± 11.6 IAT) Control (2.2 ± 1.4 h/day; 29.2 ± 4.5 IAT)	Action, Real time strategy	MRI (DTI)	Quasi-experimental (with control group)	IGD vs. Control (FA): ▼ SN tract (right)
Gong et al., 2015*	2015	57	23.26 ± 0.4 (Experts) 22.36 ± 0.38 (Amateurs)	Healthy young adults	Expert VGP (46.67 ± 2.1 h/week) Amateur VGP (14.2 ± 1.1 h/week)	Action, Real time strategy	MRI	Quasi-experimental (with control group)	Experts vs. Amateurs): ▲ Insula (left) ▲ Short insular gyri ▲ Long insular gyrus ▲ Central sulcus
Jin et al., 2016*	2016	46	19.12 ± 1.05 (IGD) 18.76 ± 1.81 (Control)	Adolescents	IGD (5.32 ± 2.10 h/day) Low or Non-VGP (2.07 ± 1.39 h/day)	Action, Real time strategy	MRI	Quasi-experimental (with control group)	IGD vs. Control: ▼ dlPFC ▼ OFC ▼ ACC ▼ SMA (right)

ACC, Anterior cingulate cortex; CG, Cingulate gyrus; dlPFC, Dorsolateral prefrontal cortex; DTI, Diffusion tensor imaging; FA, Fractional anisotropy; GM, Gray matter; IGD, Internet gaming disorder; IOG, Inferior occipital gyrus; IPC, Inferior parietal cortex; ITC, Inferior temporal cortex; lOFC, Lateral orbitofrontal cortex; MFG, Middle frontal gyrus; MMORPG, Massively multiplayer online role-playing game; MOG, Middle occipital gyrus; MRI, Magnetic resonance imaging; MTG, Middle temporal cortex; OFC, Orbitofrontal cortex; PCu, Precuneus; PFC, Prefrontal cortex; PoCG, Post-central gyrus; PPC, Posterior parietal cortex; PrCG, Pre-central gyrus; SFG, Superior frontal gyrus; SMA, Supplementary motor area; SN, Salience network; SPECT, Single-photon emission computed tomography; SPG, Superior parietal gyrus; VGP, Video game player. Articles marked with an asterisk (*) discuss cognitive implications without directly assessing this dimension. Articles marked with a double asterisk (**) did not provide either empirical cognitive data nor discuss cognitive implications. The rest of the articles (non-marked) have measured cognitive correlates with specific tasks.

TABLE 5 | Studies providing functional data dealing with healthy, non-expert participants, without violent content.

Ref.	Year	*N*	Age	Sample	VG experience	VG genre	Technique	Design	Neural correlates
Kelley et al., 1992**	1992	21	31.4 ± 7.8	Healthy adults	–	Breakout	Doppler	Experimental (crossover)	VG play vs. Baseline: ▲ MCA (bilateral) ▲ PCA (left)
Brookings et al., 1996	1996	8	(21–29)	Healthy adults	Air traffic controllers	Simulation	EEG	Experimental (crossover)	Task difficulty (measured in Theta power): High vs. Low difficulty: ▲ F8, C3, Cz, T4, P3, Pz, P4 Medium vs. Low difficulty: ▲ C3, P3, Pz Overload condition vs. Low difficulty: ▲ F3, C3, Pz Overload condition vs. Medium difficulty: ▲ T6, O2 Overload condition vs. High difficulty: ▲ F7, F3, Fz, C3
Koepp et al., 1998**	1998	8	(36–46)	Healthy adults, male	–	Action	PET	Quasi-experimental (with pretest)	VGP vs. baseline: ▼ Striatum (dopamine binding) Performance level: ▼ VS (dopamine binding)
Pellouchoud et al., 1999*	1999	7	(9–15)	Healthy children	–	Puzzle	EEG	Experimental (crossover)	Gameplay vs. resting: ▲ Frontal midline theta (6–7 Hz) ▼ Posterior alpha (9–12 Hz) ▼ Central mu (10–13 Hz)
Smith et al., 1999	1999	6	(22–25)	Healthy young adults	–	Action, shooter	EEG	Quasi-experimental (with pretest)	VG Post vs. Pre: ▼ Central alpha waves ▲ Primary motor cortex alpha waves ▲ Frontal midline theta waves
Izzetoglu et al., 2004*	2004	8	(18–50)	Healthy adults	–	Action, strategy	NIRS	Experimental (crossover)	VG difficulty: ▲ dlPFC (bilateral)
Matsuda and Hiraki, 2004*	2004	6	(23–29)	Healthy young adults	–	Action, First Person Shooter Rhythm Puzzle	NIRS	Experimental (crossover)	VG play vs. rest: ▼ dPFC Viewing VG or non-VG images: ▼ dPFC Fast vs. slow finger tapping: ▲ dPFC Left vs. right finger tapping: ▲ dPFC
Matsuda and Hiraki, 2006*	2006	13	(7–14)	Healthy children	–	Action, fighting Puzzle	NIRS	Experimental (crossover)	Children (VG play vs. rest): ▼ dPFC Children vs. Adults (VG play): = dPFC
Nagamitsu et al., 2006**	2006	12	8 (7–10) (children) 34 (26–44) (adults)	Healthy children Healthy adults	Low and High VGP (>2 h/day) Non-VGP	Action, 2D Platforms	NIRS	Quasi-experimental (with control group)	During VG play: ▲ PFC (bilateral) in 4 adults ▼ PFC (bilateral) in 2 children ▲ PFC & Motor cortex (bilateral) correlation

(Continued)

TABLE 5 | Continued

Ref.	Year	*N*	Age	Sample	VG experience	VG genre	Technique	Design	Neural correlates
Salminen and Ravaja, 2007**	2007	25	23.8	Healthy young adults	VGP (>once a month)	Action, 3D Platforms	EEG	Experimental (crossover)	While playing: Picking up item: ▼ Central theta waves ▼ Frontal high alpha waves ▲ Frontal beta waves Falling: ▼ Central theta ▲ Fronto-central beta waves Reaching goal: ▲ Parietal theta waves ▼ Frontal low alpha waves ▲ Frontal high alpha waves ▼ Central high alpha waves ▲ Parietal high alpha waves ▼ Frontal beta waves ▲ Central beta waves
Sheikholeslami et al., 2007**	2007	2	–	Healthy participants	–	Sports	EEG	Quasi-experimental (with pretest)	Gaming vs. resting: ▲ Frontal midline theta waves ▼ Parietal alpha waves & slow increase
Corradi-Dell'Acqua et al., 2008*	2008	17	–	Healthy young adults	–	Custom VG	fMRI	Experimental (factorial design)	VG character controlled synchronously: Agency vs. Control: ▲ MCG (left) ▲ MFG Agency vs. Control (when changing spatial positions): ▲ POT junction (right)
Russoniello et al., 2009	2009	69	–	–	–	Puzzle	EEG	Experimental (randomized)	VGP vs. Control: ▼ Frontal alpha waves (left)
Bailey et al., 2010	2010	51	(18–33)	Healthy young adults	Low VGP (1.76 ± 4.75 h/week) High VGP (43.4 ± 16.0 h/week)	Action	EEG (ERP)	Quasi-experimental (with control group)	High VGP vs. Low VGP: ▼ Medial frontal negativity amplitude ▼ Frontal slow wave amplitude
Han et al., 2010b*	2010	21	24.1 ± 2.6	Healthy young adults	Low VGP (<1 h/day) High VGP (>1 h/day)	Action, fighting	fMRI	Quasi-experimental (with control group and pretest)	Excessive VGP vs. Control: ▲ ACC ▲ OFC
Anderson et al., 2011*	2011	20	23.6	Healthy young adults	VGP (low, medium and high)	Action, shooter	fMRI	Experimental (crossover)	During VG play: ▲ Hand motor regions (bilateral) ▲ ACC ▲ PPC ▲ LIPFC ▲ CN ▲ FG
Maclin et al., 2011	2011	39	(19–29)	Healthy young adults	Low or Non-VGP (<3 h/week)	Action, shooter	EEG (ERP)	Experimental (crossover)	Post vs. Pre-training ▼ P300 amplitude (VG "hits") ▼ P300 amplitude (oddball tones) ▲ P300 amplitude (VG "enemies") ▼ Delta power (VG "hits") ▲ Delta power (oddball tones) ▲ Alpha power (VG "hits")

(Continued)

TABLE 5 | Continued

Ref.	Year	*N*	Age	Sample	VG experience	VG genre	Technique	Design	Neural correlates
									▲ Alpha power (oddball tones) ▲ Delta power (VG “enemies”) ▲ Alpha power (VG “enemies”) ▲ Parietal (Pz) theta power (VG “enemies”) ▲ Parietal (Pz) delta power (VG “enemies”) Oddball task inside VG vs outside game ▼ P300 amplitude
Mishra et al., 2011	2011	41	21 (VGP) 24 (Non-VGP)	Healthy young adults, male	VGP (9.0 ± 2.7 h/week) Non-VGP (0 h/week)	Action	EEG (SSVEP)	Quasi-experimental (with control group)	VGP vs. Non-VGP: ▲ Suppression SSVEP to unattended peripheral sequences ▲ P300 amplitude
Bavelier et al., 2012a	2012	26	20.50	Healthy young adults	VGP (>5 h/week) Low or Non-VGP (<5 h/week)	Action, First Person Shooter	fMRI	Quasi-experimental (crossover, with control group)	As attentional demands increased: Non-VGP vs. VGP: ▲ FPN
Cole et al., 2012*	2012	57	25.3 ± 9.4	Healthy young adults	–	Action, shooter	fMRI	Experimental (randomized)	VG onset: ▲ CN ▲ NAcc ▲ PHG VG gameplay: ▲ Thalamus ▲ Posterior insula ▲ Putamen ▲ Motor regions ▼ Parietal cortex ▼ Medial PFC VG offset gameplay: ▲ Anterior insula ▲ ACC VG group vs. Control: ▲ CN ▲ NAcc ▲ PHG
Lee H. et al., 2012	2012	75	21.57 ± 2.58	Healthy young adults	Low or Non-VGP (<4 h/week)	Action, shooter	fMRI	Experimental (randomized)	Full emphasis vs. Hybrid variable-priority training (post-training): ▲ PCu (left) ▲ Lateral occipital cortex (left) ▲ Intracalcarine cortex (left) ▲ SFG (right) Post vs. Pre training: ▼ Intracalcarine cortex (bilateral) ▼ Lingual gyrus (bilateral) ▼ Lateral occipital cortex (bilateral) Hybrid variable-priority training vs Control: ▼ dlPFC VG skill improvement: ▼ Intracalcarine cortex (right)
Han et al., 2012a*	2012	19	20.5 ± 1.5	Healthy young adults, male	–	Action, First Person Shooter	fMRI/MRI	Experimental (crossover)	VG vs. Neutral stimuli: ▲ IFG (left) ▲ PHG (left) ▲ Parietal lobe (bilateral) ▲ Thalamus (bilateral) ▲ Cerebellum (right)

(Continued)

TABLE 5 | Continued

Ref.	Year	*N*	Age	Sample	VG experience	VG genre	Technique	Design	Neural correlates
									VG training amount: ▲ Medial frontal lobe (right) ▲ PrCG (bilateral) ▲ PoCG (right) ▲ PHG (right) ▲ PCu (left)
Havranek et al., 2012	2012	20	23.5 ± 3.83	Healthy young adults	VGP (>11.7 h/week) Non-VGP (0.2 h/week)	Role-playing	EEG	Experimental (factorial)	1st person view vs. 3rd person view: ▼ Parietal alpha ▼ Occipital alpha ▼ Limbic cortex alpha Active VGP vs. Passive VGP: ▲ Frontal theta
Klasen et al., 2012*	2012	13	(18–26)	Healthy young adults, male	VGP (15.1 ± 9.0 h/week)	Action, First Person Shooter	fMRI	Experimental (crossover)	Success vs. failure events: ▲ Head of the CN ▲ NAcc ▲ Putamen ▲ Cerebellum ▲ Thalamus ▲ SPG ▲ Motor and premotor areas High vs low focus (presence of enemies): ▲ Cerebellum ▲ Visual areas ▲ PCu ▲ Premotor areas ▼ IPS (bilateral) ▼ OFC ▼ rACC Goal-oriented vs exploratory: ▼ IPS (bilateral) ▲ FFA ▼ dACC ▼ PCu High vs Low control: ▲ Visual areas ▲ Cerebellum ▲ Thalamus ▲ Motor areas ▼ Temporal poles (bilateral) ▼ AG (bilateral)
Liu et al., 2012	2012	68	19.7 ± 2.0	Healthy young adults	–	Racing	NIRS	Experimental (randomized)	Extrinsic orders & Intrinsic orders vs. Control: ▲ Prefrontal activation Extrinsic orders vs. Intrinsic orders: ▲ Prefrontal activation (globally) ▼ Prefrontal activation (in subsequent VG trials)
Mathewson et al., 2012	2012	39	(18–28)	Healthy young adults	Low or Non-VGP (<3 h/week)	Action, shooter	EEG (ERSP)	Experimental (crossover)	Learning rate predicted by: ▲ Frontal alpha power ▲ Alpha ERSPs ▲ Delta ERSPs

(Continued)

TABLE 5 | Continued

Ref.	Year	*N*	Age	Sample	VG experience	VG genre	Technique	Design	Neural correlates
Prakash et al., 2012	2012	66	22 ± 2.90 (Fixed emphasis training) 20.86 ± 2.19 (Hybrid variable-priority training) 21.48 ± 2.71 (Control)	Healthy young adults	Low or Non-VGP (<4 h/week)	Action, shooter	fMRI	Experimental (randomized)	Post vs. Pre (all groups): ▼ MFG (right) ▼ SFG (right) ▼ vmPFC HVT vs. Control: ▼ MFG (right) ▼ SFG (right)
									▼ vmPFC HVT vs. FET: ▼ MFG (right) ▼ SFG (right) ▼ vmPFC ▼ Motor cortices ▼ Sensory cortices ▼ Posteriomedial cortex
Subhani et al., 2012**	2012	10	(19–25)	Healthy young adults	–	Racing	EEG	Quasi-experimental (with pretest)	Gaming vs. rest: ▲ Global theta Fz/alpha Pz ratio
Voss et al., 2012	2012	29	22.24 ± 2.90	Healthy young adults	Low or Non-VGP (<3 h/week)	Action, shooter	fMRI	Experimental (randomized)	Post vs. Pre-training (FC): Changes in the DMN
Wu et al., 2012	2012	16	21.3 (Experimental) 22 (Control)	Healthy young adults	Non-VGP	Action, First Person Shooter	EEG (ERP)	Experimental (randomized with pretest)	FPS vs. Non-action: =N100 amplitude =P100 amplitude ▲ P200 amplitude ▲ P300 amplitude
Anguera et al., 2013	2013	46	67.1 ± 64.2	Healthy older adults	Low or Non-VGP (<2 h/month)	Racing	EEG	Experimental (crossover)	After VG training: ▲ Midline frontal theta power ▲ Frontal-posterior theta coherence
Bailey and West, 2013**	2013	31	20.40 ± 2.01 (Action) 21.77 ± 4.02 (Non-action) 24.22 ± 8.43 (Control)	Healthy adults	Non-VGP (0 h/week)	Action, First Person Shooter Puzzle, Brain Training	EEG (ERP)	Experimental (randomized)	After VG training: Action VG vs. Control: ▲ Frontal amplitude (right) ▲ Posterior amplitude (right) Non-action VG vs. Control: ▲ N200 amplitude ▲ P300 amplitude ▼ Sustained modulation centralparietal region (left) ▲ Sustained modulation frontal region Post vs Pre: Action & Non-action VG vs. Control: ▲ P300 amplitude
Berta et al., 2013	2013	22	26.3 ± 5.5	Healthy young adults	VGP and Non-VGP	Action, shooter	EEG	Experimental (crossover)	VG difficulty differences in: Alpha frequency Low-beta frequency Mid beta frequency
Khairuddin et al., 2013*	2013	29	21.73 ± 1.59	Healthy young adults	–	Racing	EEG	Experimental (crossover)	3D vs. 2D VG play: ▲ Occipital CPEI complexity ▲ Occipital Hjorth complexity ▲ Temporal Hjorth complexity

(Continued)

TABLE 5 | Continued

Ref.	Year	*N*	Age	Sample	VG experience	VG genre	Technique	Design	Neural correlates
Krishnan et al., 2013	2013	24	–	–	Action VGP (9 h/week) Non-action VGP (15 h/week)	Action, First Person Shooter Role-playing	EEG (SSVEP)	Quasi-experimental (with control group)	Non-action VGP: (Hit rate at attended 8.6 Hz flicker) ▲ Parietal activation (task difficulty at attended 8.6 flicker) ▲ Frontal activation Action VGP: (Hit rate at ignored 3 Hz flicker) ▲ Parietal activation (task difficulty at ignored 3 Hz flicker) ▲ Frontal activation
Mathiak et al., 2013	2013	13	(18–26)	Healthy young adults, male	VGP (>5 h/week)	Action, First Person Shooter	fMRI	Quasi-experimental (crossover)	Decrease of positive affect: ▲ Insula (bilateral) ▲ Amygdala (bilateral) Increase of negative affect: ▼ vmPFC (bilateral) ▼ PCu ▼ HC
Martínez et al., 2013	2013	20	18.95 ± 2.65	Healthy young adults, female	Low or Non-VGP	Puzzle, Brain training	fMRI	Experimental (randomized, with pretest)	Post vs. pre-training (resting state): ▲ Parietofrontal correlated activity VG training vs. control group (resting state): ▲ PCu (bilateral) ▲ PCC ▲ Retrosplenial cortex ▲ Inferior parietal/supramarginal (B40) ▲ TPJ ▲ TO junction ▲ PTC (BA21, 22) ▲ Temporal pole (left) ▲ IFG (left) ▲ dlPFC & vmPFC (BA10, 11) (bilateral) ▲ MFG (BA9) (left) ▲ ACC (BA24, 32) ▲ Cuneus (BA18, 19) (bilateral) ▲ Cerebellum (bilateral) ▲ Thalamus
McGarry et al., 2013	2013	7	(60–85)	Healthy older adults	–	Strategy	fMRI	Quasi-experimental (with pretest)	After VG training (FC): ▲ PPC & AG
Tachtsidis and Papaioannou, 2013**	2013	30	24.00	Healthy young adults	≪Some≫ experience in VG	Action, fighting Puzzle	NIRS	Experimental (randomized with pretest)	VG playing vs. baseline: ▲ PFC Fighting vs. puzzle game: ▲ PFC (1st third of gameplay) ▼ PFC (3rd third of gameplay)
Hahn et al., 2014	2014	27	25.5 ± 4.18 (VGP) 24.5 ± 2.85 (Non-VGP)	Healthy young adults	VGP (>4 h/week) Non-VGP (0 h/week)	Role-playing, MMORPG	fMRI	Quasi-experimental (with control group)	VGP vs. Non-VGP (reward anticipation): ▼ VS VGP vs. Non-VGP (resting-state): ▲ VS regional homogeneity (right)
Nikolaidis et al., 2014	2014	45	21.74 ± 5.09	Healthy young adults	Low or Non-VGP (<4 h/week)	Action, shooter	fMRI	Experimental (crossover)	Post vs. Pre-training (predictors of working memory performance): ▲ Superior parietal lobule ▲ PoCG ▲ PCu
Strenziok et al., 2014	2014	46	69.21 ± 4.9	Healthy older adults	–	Action, Shooter real time strategy puzzle, Brain training	fMRI	Experimental (randomized with pretest)	Puzzle & Shooter vs. Strategy (FC): ▼ SPG & ITG

(Continued)

TABLE 5 | Continued

Ref.	Year	*N*	Age	Sample	VG experience	VG genre	Technique	Design	Neural correlates
Yoshida et al., 2014*	2014	20	22.3 ± 1.2	Healthy young adults	–	Puzzle	NIRS	Experimental (crossover)	Flow vs. boredom condition: ▲ vlPFC (bilateral) ▲ dlPFC (bilateral) ▲ Frontal pole areas (bilateral)
Anderson et al., 2015	2015	40	24.0	Healthy young adults	–	Action, shooter	fMRI	Experimental (crossover)	Predictor of VG skill: ▲ DS (right) ▲ Sequential structure of whole brain activation
Hsu et al., 2015	2015	41	26.3	Healthy young adults	–	Racing	tDCS	Experimental (crossover)	Anodal tDCS vs. Sham: ▲ dlPFC (left) enhanced multitasking performance 2nd session vs. 1st session: ▲ dlPFC (left) decreased multitasking cost
Kim Y. H. et al., 2015*	2015	31	29.0 ± 4.1	Healthy young adults	VGP (>3 h/week) Non-VGP (<10 h/year)	Strategy	fMRI	Quasi-experimental (with control group and pretest)	VGP vs. Non-VGP: ▲ IFG (right) ▲ ACC ▲ Striatum
Liu T. et al., 2015	2015	51	21.0 ± 2.2	Healthy young adults	Low and High VGP	Racing	NIRS	Experimental (factorial)	Single vs. Paired (low VGP group) ▲ PFC Low vs. High VGP (paired group) ▼ PFC
Lorenz et al., 2015	2015	50	23.8 ± 3.9 (Experimental) 23.4 ± 3.7 (Control)	Healthy young adults	Low or Non-VGP (0.7 ± 1.97 h/month)	Action, 3D Platforms	fMRI	Experimental (randomized)	Post vs. Pre-test (reward anticipation, VG training & control group): ▼ VS Post vs. Pre-test (VG training group): =VS Post vs. Pre-test (control group) ▼ VS
McMahan et al., 2015	2015	30	20.87 (18–43)	Healthy adults	Low and High VGP (20% >20 h/week)	Action, 2D Platforms	EEG	Experimental (crossover)	High vs. Low intensity VG events: ▲ Betta power ▲ Gamma power
Patten et al., 2015	2015	–	–	–	Low or Non-VGP VGP	–	EEG (ERP)	Quasi-experimental (with control group)	VGP vs. Non-VGP: ▼ Latency Pd component
West et al., 2015	2015	59	23.88 ± 3.94 (Action) 24.36 ± 3.68 (Non-action)	Healthy young adults	Action VGP (17.9 ± 10.44 h/week) Non-Action VGP (0 h/week)	Action, First Person Shooter, Adventure	EEG (ERP)	Quasi-experimental (with control group)	Action vs. Non-VGP: ▼ Visual cortex amplitude (N2pc) in near condition. ▲ Visual cortex amplitude (N2pc) in far condition ▲ P3 component amplitude in targets.

ACC, Anterior cingulate cortex; AG, Angular gyrus; CN, Caudate nucleus; CPEI, Composite permutation entropy index; dACC, Dorsal anterior cingulate cortex; dlPFC, Dorsolateral prefrontal cortex; DS, Dorsal striatum; EEG, Electroencephalography; ERP, Event-related potentials; ERSP, Event-related spectral dynamics; FFA, Fusiform face area; FC, Functional connectivity; FG, Fusiform gyrus; fMRI, Functional magnetic resonance imaging; FPN, Frontoparietal network; HC, Hippocampus; IFG, Inferior frontal gyrus; ITG, Inferior temporal gyrus; IPS, Intraparietal sulcus; liPFC, Lateral inferior prefrontal cortex; MCA, Middle cerebral artery; MCG, Middle cingulate gyrus; MFG, Middle frontal gyrus; MRI, Magnetic resonance imaging; NAcc, Nucleus accumbens; NIRS, Near-infrarred spectroscopy; OFC, Orbitofrontal cortex; PCA, Posterior cerebral artery; PPC, Posterior cingulate cortex; PCu, Precuneus; PFC: Prefrontal cortex; PHG, Parahippocampal gyrus; PoCG, Post central gyrus; POT, Parieto-occipito-temporal; PPC, Posterior parietal cortex; PrCG, Pre-central gyrus; PTC, Posterior temporal cortex; rACC, Rostral anterior cingulate cortex; SFG, Superior frontal gyrus; SPG, Superior parietal gyrus; SSVEP, Steady state visually evoked potential; tDCS, Transcranial direct current stimulation; TO, Temporo-occipital; TPJ, Temporo-parietal junction; VG, Video game; VGP, Video game player; vmPFC, Ventromedial prefrontal cortex; VS, Ventral striatum. Articles marked with an asterisk (*) discuss cognitive implications without directly assessing this dimension. Articles marked with a double asterisk (**) did not provide either empirical cognitive data nor discuss cognitive implications. The rest of the articles (non-marked) have measured cognitive correlates with specific tasks.

TABLE 6 | Studies providing functional data dealing with VG experts or excessive gaming.

Ref.	Year	*N*	Mean age (range)	Sample	VG experience/Addiction	VG genre	Technique	Design	Neural correlates
Thalemann et al., 2007*	2007	30	Young adults, male	28.75 ± 6.11 (Excessive VGP) 25.73 ± 8.14 (Control)	Excessive VGP (4.31 ± 2.17 h/day) Casual VGP (0.25 ± 0.46 h/day	–	EEG (ERP)	Quasi-experimental (with control group)	Excessive vs. Casual VGP (exposition to gaming cues): ▲ Pz ▲ P4
Allison and Polich, 2008**	2008	14	23.5 ± 5.1	Healthy young adults	Expert VGP (>10 h/week)	Action, First Person Shooter	EEG (ERP)	Experimental (crossover)	Correlated with gaming workload: ▼ N100 amplitudes (largest in Cz, smallest in Pz) ▼ P200 amplitudes (largest in Cz) ▼ N200 amplitudes (largest in Cz) ▼ sP300 amplitudes (largest in Pz, smallest on Fz)
Ko et al., 2009*	2009	20	(21–25)	Young adults, male	IGD (>30 h/week) Control (<2 h/day)	Role playing, MMORPG	fMRI	Quasi-experimental (with control group)	IGD vs. Control (exposition to gaming pictures): ▲ OFC (right) ▲ NAcc (right) ▲ ACC & Medial frontal cortex (bilateral) ▲ dlPFC (right) ▲ CN (right)
Granek et al., 2010*	2010	26	24 ± 3.1 and 26 ± 4.6	Healthy young adults, male	Expert VGP (12.8 ± 8.6 h/week) Non-VGP	–	fMRI	Quasi-experimental	Expert VGP vs. Non-VGP: ▲ SFG ▲ dlPFC (including MFG (BA 46) & IFG) ▲ vlPFC (including IFG (BA 45), ventro-orbital frontal gyrus (BA 47) and rostral lateral sulcus (BA 45) ▲ PPC (including parietooccipital sulcus (BA 7, 19), PCu (BA 7), IPS (BA 7) and IPC (BA 7)
Liu et al., 2010*	2010	38	Young adults	21.0 ± 1.3 (IAD) 20.0 ± 1.8 (Control)	IAD (=6 h/day) Non-IAD	–	fMRI	Quasi-experimental (with control group)	IAD vs. Control (Regional homogeneity): ▲ Cerebellum ▲ Brainstem ▲ CG (right) ▲ PHG (bilateral) ▲ Frontal lobe (rectal gyrus, IFG & MFG) (right) ▲ SFG (left) ▲ PCu (left) ▲ PoCG (right)

(Continued)

TABLE 6 | Continued

Ref.	Year	*N*	Mean age (range)	Sample	VG experience/Addiction	VG genre	Technique	Design	Neural correlates
						–			▲ MOG (right) ▲ ITG (right) ▲ STG (left) ▲ MTG
Doty et al., 2011*	2011	14	–	–	VG Dependent VG Non-dependent	Action, First Person Shooter	EEG (ERP)	Quasi-experimental (with control group)	Dependent vs. Non-dependent group: ▼ PFC (Pre-event) ▼ PFC Theta waves (Post-event) ▼ Prefrontal and frontal regions (general activation)
Dong et al., 2012*	2012	29	24.2 ± 3.5 (IAD) 24.6 ± 3.8 (Control)	Young adults, male	IAD (>80% time playing VG) Control (16.3 ± 4.3 Young's scale score)	–	fMRI	Quasi-experimental (with control group)	IGD vs. Control (Regional Homogeneity): ▲ Brainstem ▲ IPC ▲ Posterior cerebellum (left) ▲ MFG (left) ▼ ITG (left) ▼ Occipital lobe (left) ▼ PoCG (left) ▼ MCG (left)
Ding et al., 2013*	2013	41	16.94 ± 2.73 (Internet addiction group) 15.87 ± 2.69 (Control group)	Adolescents	Internet Addiction (26.44 ± 21.47 h/week; CIAS 64.59 ± 6.43) Control (10.50 ± 11.60 h/week; CIAS 45.70 ± 7.81)	–	fMRI	Quasi-experimental (with control group)	IGD vs. Control (FC): ▲ Bilateral cerebellum posterior lobe & MTG ▼ IPC (bilateral) & ITG (right)
Feng et al., 2013*	2013	33	16.93 ± 2.34 (IGD) 16.33 ± 2.61 (Control)	Adolescents	IGD (25.47 ± 17.89 h/week; 66.73 ± 3.01 Chen Internet Addiction Scale) Control (9.28 ± 12.90 h/week; 40.50 ± 8.42 Chen Internet Addiction Scale)	–	fMRI	Quasi-experimental (with control group)	IGD vs. Control: ▲ ITC/FG (left) ▲ PHG/Amygdala (left) ▲ Medial frontal lobe /ACC (right) ▲ Insula (bilateral) ▲ MTG (right) ▲ PrCG (right) ▲ SMA (left) ▲ CG (left) ▲ IPC (right) ▼ MTG (left) ▼ MOG (left) ▼ CG (right)

(Continued)

TABLE 6 | Continued

Ref.	Year	*N*	Mean age (range)	Sample	VG experience/Addiction	VG genre	Technique	Design	Neural correlates
Kätsyri et al., 2013a*	2013	11	25.6 (22–33)	Healthy young adults, male	VG Experts (>10 h/week)	Action, First Person Shooter	fMRI	Experimental (crossover)	Winning vs. Losing: ▲ omPFC Active vs. Vicarious playing: ▼ Midbrain ▼ Striatum (especially anterior putamen, in loss events)
Kätsyri et al., 2013b*	2013	17	24.8 (20–33)	Healthy young adults, male	VG Experts (>10 h/week)	Action, First Person Shooter	fMRi	Experimental (crossover)	Winning vs. Losing: ▲ vmPFC ▲ VS ▲ DS Winning condition (FC): ▲ VS & ▲ Insula (right) ▲ VS & ▲ DS ▲ VS & ▲ PrCG & PoCG ▲ VS & ▲ Visual association cortices Human vs. Computer opponent: ▲ vmPFC ▲ DS
Ko et al., 2013*	2013	45	24.67 ± 3.11 (IGD) 24.80 ± 2.68 (Remission) 24.47 ± 2.83 (Control)	Young adults, male	IGD IGD in remission Control (Non-IGD)	Role playing, MMORPG	fMRI	Quasi-experimental (with control group)	IGD vs. Control (exposition to gaming cues): ▲ dlPFC (bilateral) ▲ PCu ▲ PHG (left) ▲ PCC ▲ ACC (right)
Kim et al., 2013	2013	5	18 ± 0	Adolescents, male	IGD (>4 h/day) Control (0 h/day)	–	EEG (ERP)	Quasi-experimental (with control group and pretest)	Pre vs. Post course: ▲ P300 fronto-central areas (bilateral) IGD vs. Control (current density, post-course): ▼ Midline paracentral lobule ▼ PCu
Latham et al., 2013	2013	31	23.27 ± 0.88 (VGP) 25.69 ± 1.19 (Non-VGP)	Healthy young adults, male	Expert VGP (34.67 ± 5.01 h/week) Non-VGP	Action, shooter; Strategy or Role Playing, MMORPG	EEG (ERP)	Quasi-experimental	Expert VPG vs. Low VPG: Earlier Visual N1

(Continued)

TABLE 6 | Continued

Ref.	Year	*N*	Mean age (range)	Sample	VG experience/Addiction	VG genre	Technique	Design	Neural correlates
Song et al., 2013*	2013	39	Healthy young adults, male	20.5 ± 1.6 (2D) 20.4 ± 2.1 (3D)	Professional VGP (2D strategy VG) Professional VGP (3D strategy VG)	Real time strategy	fMRI	Quasi-experimental (with control group)	2D vs. 3D strategy game: ▲ SFG (right) ▲ Medial frontal gyrus (bilateral) ▲ Occipital lobe (right) ▼ MFG (left) ▼ FG (left) ▼ Cerebellum (left)
Yuan et al., 2013b	2013	36	Adolescents and young adults	19.4 ± 3.1 (IGD) 19.5 ± 2.8 (Control)		Role playing, MMORPG	fMRI	Quasi-experimental (with control group)	IGD vs. Control: ▲ medial OFC (left) ▲ PCu (left) ▲ SMA (left) ▲ PHG (right) ▲ MCG (bilateral)
Chen et al., 2014	2014	30	24.67 ± 3.12 (IGD) 24.47 ± 2.83 (Control)	Young adults, male	IGD (>4 h/day; 76.00 ± 12.09 Chen Internet Addiction Scale) Control (26.0 ± 0.0 Chen Internet Addiction Scale)	Role playing, MMORPG	fMRI	Quasi-experimental (with control group)	IGD vs. Control: ▼ SMA (right) ▼ preSMA (right)
Tian et al., 2014*	2014	12	Young adults, male	23.5 ± 2.58 (IGD) 22.7 ± 1.27 (Control)	IGD (77.6 ± 6.8 Young's scale score) Control (28.7 ± 3.7 Young's scale score)	Role playing, MMORPG	PET	Quasi-experimental (with control group and pretest)	IGD vs. Control (glucose metabolism): ▲ Cuneus (right) ▲ Calcarine (right) ▼ Medial temporal cortex (left) Within group (monoamine receptors): ▲ Correlation with IGD severity ▼ Putamen ▼ OFC/cerebellum ratio Glucose vs. monoamine: ▲ Striatum/cerebellum ratio ▲ OFC/cerebellum ratio
Wee et al., 2014*	2014	33	Adolescents	17.3 ± 2.6 (IAD) 17.7 ± 2.5 (Control)	IAD (4.8 ± 22 h/day; 62.4 ± 17.1 Young's Internet Addiction Scale) Control (1.3 ± 0.6 h/day; 37.0 ± 10.6 Young's Internet Addiction Scale)	–	fMRI	Quasi-experimental (with control group)	IAD vs. Control (FC): Frontal, occipital, and parietal lobes

(Continued)

TABLE 6 | Continued

Ref.	Year	*N*	Mean age (range)	Sample	VG experience/Addiction	VG genre	Technique	Design	Neural correlates
Xing et al., 2014	2014	34	Young adults	19.1 ± 0.7 (IGD) 19.8 ± 1.3 (Control)	IGD (9.5 ± 1.3 h/day; 65.7 ± 11.6 IAT) Control (2.2 ± 1.4 h/day; 29.2 ± 4.5 IAT)	Action, Real time strategy	fMRI	Quasi-experimental (with control group)	IGD vs. Control (FC): =FC
Gong et al., 2015*	2015	57	23.26 ± 0.4 (Experts) 22.36 ± 0.38 (Amateurs)	Healthy young adults	Expert VGP (46.67 ± 2.1 h/week) Amateur VGP (14.2 ± 1.1 h/week)	Action, Real time strategy	fMRI	Quasi-experimental (with control group)	Experts vs. Amateurs (FC): ▲ Between insular regions (especially left) VG experience (FC): ▲ Insular functional integration (left)
Han et al., 2015	2015	47	15.2 ± 1.9 (IGD) 14.9 ± 1.9 (Control)	Adolescents, male	IGD (>30 h/week) Non-IGD	Role playing Real time strategy First Person Shooter Others	fMRI	Quasi-experimental (with control group)	IGD vs. Control: ▲ FEF (left) to dACC ▲ FEF (left) to anterior insula (right) ▲ dlPFC (left) to TPJ (left) ▲ dlPFC (right) to TPJ (right) ▲ Auditory cortex (right) to motor cortex (right) ▲ Auditory cortex (right) to SMA ▲ Auditory cortex (right) to dACC
Hong et al., 2015*	2015	23	13.4 ± 2.31(IGD) 14.81 ± 0.87(Control)	Adolescents, male	IGD (14.25 ±1 2.12 h/week; 57.00 ± 17.39 Young Internet Addiction Test) Controls (16.86 ± 6.51 h/week; 38.36 ± 7.31 Young Internet Addiction Test)	–	fMRI	Quasi-experimental (with control-group)	IGD vs. Control (FC): ▼ Dorsal putamen & (Posterior insula, parietal operculum) Internet addiction scores (FC): ▲ Dorsal putamen & PoCG (bilateral)
Kim H. et al., 2015*	2015	31	21.63 ± 5.92 (IGD) 25.4 ± 5.29 (Control)	Young adults, male	IGD (5.95 ± 2.27 h/day; 75.81 ± 4.72 Young's Internet Addiction Test) Control (<2 h/day; 23.80 ± 14.81 Young's Internet Addiction Test)	–	fMRI	Quasi-experimental (with control group)	IGD vs. Control (Regional Homogeneity): ▲ PCC ▼ STG (right) Internet addiction scores correlated in (Regional Homogeneity): ▲ Medial frontal cortex ▲ PCu/PCC ▲ ITC (left)

(Continued)

TABLE 6 | Continued

Ref.	Year	*N*	Mean age (range)	Sample	VG experience/Addiction	VG genre	Technique	Design	Neural correlates
Lee et al., 2015	2015	38	Adolescents, male	13.6 ± 0.9 (IGD) 13.4 ± 1.0 (Control)	IGD Control (Non-IGD)	–	fMRI	Quasi-experimental (with control group)	IGD vs. Control (Angry facial stimuli): ▼ dACC ▲ Insula ▼ PPC ▲ FG IGD vs. Control (FC): ▲ (Insula & ▼ dlPFC, ▼ MTG, ▼ cerebellum, PPC)
Liu J. et al., 2015*	2015	40	Young adults	21.4 ± 1.0 (IGD) 20.8 ± 1.1 (Control)	IGD (=6 h/day in internet) Control (<3 h/day in internet)	Role playing, MMORPG	fMRI	Quasi-experimental (with control group)	IGD vs. Control: ▲ SPG (right) ▲ Insular lobe (right) ▲ PCu (right) ▲ CG (right) ▲ STG (right) ▲ Brainstem (left) ▲ Frontal cortex
Luijten et al., 2015	2015	45	Young adults, male	20.83 ± 3.05 (IGD) 21.38 ± 3.03 (Control)	IGD (Video game Addiction Test score = 2.5) Control (Video game Addiction Test score = 1.5)	–	fMRI	Quasi-experimental (with control group)	IGD vs. Control: ▼ IFG (left) ▼ IPC (right)
Wang et al., 2015*	2015	31	Adolescents	16.94 ± 2.73 (IGD) 15.87 ± 2.69 (Control)	IGD (64.59 ± 6.43 Chen Internet Addiction Scale) Control (45.70 ± 7.81 Chen Internet Addiction Scale)	–	fMRI	Quasi-experimental (with control group)	IGD vs. Control (FC): ▼ SFG (orbital part) (bilateral) ▼ IFG (orbital part) ▼ MFG ▼ SFG
Dong and Potenza, 2016	2016	36	21.33 ± 2.18 (IGD) 21.90 ± 2.33 (Control)	Young adults, male	IGD (>80% online time) Low or Non-VGP	–	fMRI	Quasi-experimental (with control group)	IGD vs. Control: ▼ ACC ▼ PCC ▼ MTG ▼ IFG (RT) ▼ STG (RT)

(Continued)

TABLE 6 | Continued

Ref.	Year	*N*	Mean age (range)	Sample	VG experience/Addiction	VG genre	Technique	Design	Neural correlates
Gong et al., 2016	2016	45	23.3 ± 4.3 (Experts) 22.3 ± 3.46 (Amateurs)	Healthy young adults, male	Experts (ELO > 1,800) Amateurs (ELO < 1,200)	Action, Real time strategy	fMRI	Quasi-experimental (with control group)	Action VG Experts vs. Amateurs: ▲ SN & CEN (global characteristics) ▲ Local regions of SN & CEN (nodal characteristics) ▲ SN & CEN (FC)
Han et al., 2016	2016	102	20.2 ± 3.2 (IGD) 20.2 ± 2.9 (Control)	Adolescent or young adults, male	IGD (>30 h/week) Low or Non-VGP	Role playing Real time strategy First Person Shooter Others	fMRI	Quasi-experimental (with control group)	IGD vs. Control (During executive task): ▲ Lateral occipital cortex (right) ▲ PCu
Jin et al., 2016*	2016	46	19.12 ± 1.05 (IGD) 18.76 ± 1.81 (Control)	Adolescents	IGD (5.32 ± 2.10 h/day) Low or Non-VGP (2.07 ± 1.39 h/day)	Action, Real time strategy	fMRI/MRI	Quasi-experimental (with control group)	IGD vs. Control (FC): ▼ (dlPFC, OFC, ACC & SMA) & (Insula, temporal cortices, occipital cortices) ▼ (dlPFC, OFC, ACC & SMA) & (DS, pallidum, thalamus)
Park et al., 2016	2016	36	Young adults, male	24.2 ± 3.2 (OGA-CBT) 23.6 ± 2.7 (OGA-VRT) 23.3 ± 2.9 (Control)	IGD (>30 h/week) Control (<3 h/week)	–	fMRI	Quasi-experimental (with control group)	IGD vs. Control (baseline, ALFF): ▼ MFG (right) IGD vs. Control (baseline, FC) ▼ Cortico-striatal limbic circuit
Zhang et al., 2016	2016	115	Young adults	22.28 ± 1.98 (IGD) 23.02 ± 2.09 (Control)	IGD (78.36 ± 8.43 Chen Internet Addiction Scale) Control (43.49 ± 9.64 Chen Internet Addiction Scale)	–	fMRI	Quasi-experimental (with control group)	IGD vs. Control (FC): ▲ (Anterior insula & ACC, Putamen, Angular gyrus, PCu) ▲ (Posterior insula & PoCG, PrCG, SMA, STG) IGD severity (FC): ▲ (Anterior insula & Angular gyrus, STG) ▲ (Posterior insula & STG)

ACC, Anterior cingulate cortex; CEN, Central executive network; CG, Cingulate gyrus; CIAS, Chen's Internet addiction scale; CN, Caudate nucleus; dACC, Dorsal anterior cingulate cortex; dlPFC, Dorsolateral prefrontal cortex; DS, Dorsal striatum; FC, Functional connectivity; FEF, Frontal eye fields; FG, Fusiform gyrus; IFG, Inferior frontal gyrus; IGD, Internet gaming disorder; IPC, Inferior parietal cortex; IPS, Intraparietal sulcus; ITC, Inferior temporal cortex; ITG, Inferior temporal gyrus; MCG, Middle cingulate gyrus; MFG, Middle frontal gyrus; MOG, Middle occipital gyrus; MTG, Middle temporal gyrus; NAcc, Nucleus accumbens; OFC, Orbitofrontal cortex; omPFC, Orbitomedial prefrontal cortex; PCC, Posterior cingulate cortex; PCu, Precuneus; PFC, Prefrontal cortex; PHG, Parahippocampal gyrus; PoCG, Post-central gyrus; PrCG, Pre-central gyrus; preSMA, Pre-supplementary motor area; SFG, Superior frontal gyrus; SMA, Supplementary motor area; SN, Salience network; SPG, Superior temporal gyrus; STG, Superior temporal gyrus; TPJ, Temporo-parietal junction; vlPFC, Ventrolateral prefrontal cortex; VS, Ventral striatum. Articles marked with an asterisk (*) discuss cognitive implications without directly assessing this dimension. Articles marked with a double asterisk (**) did not provide either empirical cognitive data nor discuss cognitive implications. The rest of the articles (non-marked) have measured cognitive correlates with specific tasks.

TABLE 7 | Studies providing functional data focused on the violent contents of VG.

Ref.	Year	*N*	Sample	Age	VG experience	VG genre	Technique	Design	Neural correlates
Bartholow et al., 2006	2006	39	Healthy young adults	19.50	Violent VGP Non-violent VGP	"Violent" VG "Non-violent" VG	EEG (ERP)	Quasi experimental (with control group)	Violent vs. Non-violent: ▼ P300 amplitudes
Mathiak and Weber, 2006*	2006	13	Healthy young adults, male	(18–26)	VGP (15.1 ± 9.0 h/week)	Action, First Person Shooter	fMRI	Quasi-experimental	During violent scenes: ▲ dACC ▼ rACC ▼ Amygdala
Weber et al., 2006*	2006	13	Healthy young adults	23.00 (18–26)	VGP (15.1 h/week)	Action, First Person Shooter	fMRI	Experimental (crossover)	During virtual violence exposure: ▼ Amygdala ▼ ACC
Wang et al., 2009	2009	44	Healthy adolescents	14.8 ± 1.2 (Violent group) 15.0 ± 1.1 (Non-violent group)	–	Sports, Racing Action, First person shooter	fMRI	Experimental (randomized)	Violent vs. Non-violent (Counting Stroop task): ▼ PFC Violent vs. Non-violent (Counting Stroop task, FC): ▼ dlPFC & ACC (left) Violent vs. Non-violent (Emotional Stroop task): ▲ Amygdala (right) ▼ Medial PFC Violent vs. Non-violent (Emotional Stroop task, FC): ▼ Amygdala & Medial PFC (non-violent group) =FC (violent group)
Hummer et al., 2010	2010	45	Healthy adolescents	14.9 ± 0.3 (Non-violent) 14.5 ± 0.3 (Violent)	–	Sports, Racing Action, First Person Shooter	fMRI	Experimental (randomized)	Violent vs. Non-violent (Go/No-go): ▼ dlPFC (right) Non-violent VG (FC): ▼ dlPFC & ▲ PCu
Regenbogen et al., 2010*	2010	22	Healthy young adults, male	25.9 ± 2.9	VGP (131 h/year violent VG) Low or Non-VGP (6 h/year violent VG)	Violent VG	fMRI	Quasi-experimental (with control group)	Real vs. Non-violent content (VGP): ▲ IFG (right) ▲ Lingual gyrus (left) ▲ STG Virtual vs. Non-violent content (VGP): ▲ IFG (bilateral) ▲ Occipital cortex ▲ PoCG ▲ MTG (right) ▲ FG (left) Real vs. Non-violent content (Control): ▲ Frontal regions (left) ▲ Insula ▲ SFG Virtual vs. Non-violent content (Control): ▲ Posterior regions

(Continued)

TABLE 7 | Continued

Ref.	Year	*N*	Sample	Age	VG experience	VG genre	Technique	Design	Neural correlates
Bailey et al., 2011*	2011	48	Healthy young adults, male	19.73 ± 1.28 (low VGP) 19.87 ± 3.52 (high VGP)	Low VGP (3 h/week) High VGP (33 h/week)	"Violent" VG	EEG (ERP)	Quasi-experimental (with control group)	High vs. Low VGP: (Negative & violent) vs. (neutral and positive) stimuli: ▼ FCz (@125 ms) ▼ Oz (@280 ms) Early posterior negativity (EPN) ▲ PO4 & F9 (500-1000 ms) Late positive potential (LPP) High (positive & violent vs. neutral stimuli) vs. Low VGP (Positive vs. neutral stimuli): ▼ Fpz (@100 ms) ▲ C3, CP3 (400–900 ms) ▼ Iz (400–900 ms) Low vs. High VGP (negative vs. violent stimuli): ▲ F9 (sustained) ▲ TP8 (sustained) ▲ PO9 (@300 ms)
Engelhardt et al., 2011	2011	70	Healthy young adults	(18–22)	Violent VGP Non-violent VGP	Action, First Person Shooter, Adventure Action, Adventure, Sports, Platforms	EEG (ERP)	Quasi-experimental (with control group)	Violent vs. Non-violent: ▼ P3 component at parietal (P3, Pz, and P4) regions
Mathiak et al., 2011*	2011	13	Healthy young adults, male	22.7 ± 2.0	VGP (15.1 ± 9.0 h/week)	Action, First Person Shooter	fMRI	Quasi-experimental	(Failure & success events) vs. Baseline: ▲ Visual cortex Failure vs. Success events: ▼ OFC ▼ CN Negative vs. Positive affect (only failure events): ▼ Temporal pole (right)
Montag et al., 2012*	2012	40	Healthy young adults, male	23.33 ± 4.45	Experienced VGP in First person Shooters (18.83 ± 9.12 h/week) Low or Non-VGP (2.00 ± 3.82 h/week)	Action, First Person Shooter	fMRI	Quasi-experimental (with control group)	VGP vs. Control (during negative emotional stimuli): ▼ Lateral medial frontal lobe (left) VGP vs. Control (during VG cues): ▲ Frontal regions ▲ Temporal regions
Chou et al., 2013*	2013	30	Healthy young adults	24.67 ± 4.7	VGP (3.1 h/week)	Action, Fighting Action, 3D platforms	SPECT	Experimental (crossover)	Post vs. Pre-training: ▼ PFC ▲ Temporal cortex ▲ Occipital cortex Violent vs. Non-violent VG: ▼ dACC (in males)

(Continued)

TABLE 7 | Continued

Ref.	Year	*N*	Sample	Age	VG experience	VG genre	Technique	Design	Neural correlates
Lianekhammy and Werner-Wilson, 2015*	2015	45	Healthy adolescents	14.3 ± 1.5	Brain training VG group (4.8 ± 10.6 h/week) Violent VG group (17.7 ± 17.4 h/week) Non-violent VG (9.3 ± 8.4 h/week)	Puzzle Action, First Person Shooter Action, 3D platforms	EEG	Experimental (randomized)	High empathy vs. Low empathy: ▲ Right hemisphere frontal EEG asymmetry scores (violent and non-violent) ▲ Right hemisphere High vs. Low helpfulness: ▲ Left hemisphere (non-violent group)
Liu Y. et al., 2015	2015	49	Healthy young adults	20.76 ± 1.76	–	Strategy Sports, Racing	EEG (ERP)	Experimental (randomized)	Prosocial vs. Neutral VG: ▼ P300 amplitudes
Petras et al., 2015	2015	30	Healthy adults	25.96 (18–44)	21 Non habitual VGP (<once a week) 9 Habitual VGP (=once a week)	Action, Shooter	EEG (ERP)	Experimental (randomized, factorial)	Egocentric vs. Bird-view perspective: ▲ N1 amplitudes (shoot task) ▼ Pre-stimulus alpha power (shoot task)
Zvyagintsev et al., 2016*	2016	18	Healthy young adults, male	25.1 ± 2.7	VGP (>5 h/week)	Sports, Racing (Violent)	fMRI	Experimental (crossover)	Violent vs. Non-violent (FC): ▼ Sensory-motor networks ▼ Reward network ▼ DMN ▼ FPN (right)

3D, Three-dimensional; ACC, Anterior cingulate cortex; CN, Caudate nucleus; dACC, Dorsal anterior cingulate cortex; dlPFC, Dorsolateral prefrontal cortex; DMN, Default mode network; EEG, Electroencephalography; ERP, Event-related potentials; FC, Functional connectivity; FG, Fusiform gyrus; fMRI, Functional Magnetic Resonance Imaging; FPN, Frontoparietal network; IFG, Inferior frontal gyrus; MTG, Middle temporal gyrus; OFC, Orbitofrontal cortex; Pcu, Precuneus; PFC, Prefrontal cortex; PoCG, Post-central gyrus; rACC, Rostral anterior cingulate cortex; SFG, Superior frontal gyrus; SPECT, Single-photon emission computed tomography; STG, Superior temporal gyrus; VG, Video game; VGP, Video game player. Articles marked with an asterisk (*) discuss cognitive implications without directly assessing this dimension. Articles marked with a double asterisk (**) did not provide either empirical cognitive data nor discuss cognitive implications. The rest of the articles (non-marked) have measured cognitive correlates with specific tasks.

Attention

Attentional resources are one of the main cognitive domains in which VGs are involved and one of the most researched. The involvement of attentional networks during gameplay is closely related with other brain regions responsible for cognitive control, especially when more complex operations toward a specific goal are required. Many brain regions are involved in attention, particularly nodes in the dorsal frontoparietal system, mediating top-down attentional processes in goal-oriented behavior, but also nodes in the ventral network, responsible for bottom-up sensory stimulation (e.g., Vossel et al., 2014) dealing with those salient stimuli to which the player must pay attention.

There is evidence that VGPs display enhanced performance in a range of top-down attentional control areas, such as selective attention, divided attention, and sustained attention (Bavelier et al., 2012b). The ACC is an area that consistently shows functional activity during VG play due to its involvement as the main hub in top-down attentional processes (selective or focused attention) and goal-oriented behavior (e.g., Anderson et al., 2011*; Bavelier et al., 2012b).

Non-VGPs, compared to VGPs, showed greater frontoparietal recruitment, a source of selective attention, as task demands increased, showing that habitual gamers have more efficient top-down resource allocation during attentional demanding tasks (Bavelier et al., 2012a). That resource optimization effect can also be observed in attentional control areas, such as the right middle frontal gyrus (MFG), right superior frontal gyrus (SFG), and the ventromedial prefrontal cortex (vmPFC) (Prakash et al., 2012*). Functional connectivity changes in the attentional ventral stream, particularly in occipitotemporal WM, responsible for bottom-up reorienting toward novel stimuli, have also been observed as a result of VG training and were linked to cognitive improvement (Strenziok et al., 2014*). Integration between attentional and sensoriomotor functions has been observed in expert VGPs in the form of increased structural GM and functional connectivity in anterior and posterior insular sub regions where long-term exposure to attentional VG demands coordinated with the fine skills involved in using the VG controller may have resulted in plastic changes in these two regions that are respectively involved in attentional and sensoriomotor networks (Gong et al., 2015*).

Using electrophysiological techniques, it seems that VG play correlates with an increment of the frontal midline theta rhythm, associated with focused attention (Pellouchoud et al., 1999*), and increases with VG practice (Sheikholeslami et al., 2007**; Smith et al., 1999), both in an action and a puzzle VG, attributable to ACC activity. Likewise, amplitudes in the P200 (Wu et al., 2012), an early visual stimuli perceptual component, and P300 components (Mishra et al., 2011; Wu et al., 2012), which involved in early stages of decision-making, were also linked to top-down spatial selective attention improvements after training and lifetime exposure to action VG. Action VGPs and non-action VGPs seem to respond differently in the way they deploy attention to central and peripheral targets in visual attention tasks, as measured by the N2pc component (West et al., 2015), which is also linked to selective attention.

If we consider different VG genres, it seems that action VGs are better at improving selective attention than other slow-paced VGs such as role-playing games (RPG) (Krishnan et al., 2013), puzzle (Green and Bavelier, 2003), or strategy VGs (Tsai et al., 2013) which require high planning skills and other forms of proactive cognitive control. This is probably due to the extensive use of attentional systems, paired with precise timings that action VGs require. While these improved attentional skills are typically observed in habitual VGPs, it is possible to achieve long-lasting improvements as a result of a single VG training procedure (Anguera et al., 2013).

Visuospatial Skills

Visuospatial skills encompass processes that allow us to perceive, recognize, and manipulate visual stimuli, including visuomotor coordination and navigational skills, and VGs are predominantly interactive visual tasks.

The areas implicated in visuospatial processing have traditionally been classified along a visual ventral stream (responsible for object recognition) and a visual dorsal stream (responsible for spatial location). Both depart from the visual cortex, in the occipital lobe, and reach the posterior parietal cortex (dorsal stream) and the inferior temporal cortex (ventral stream). More recent proposals have refined that model, broadening the traditional conceptualization of the two-stream model (for further details see Kravitz et al., 2011). Among other nodes, the role of the hippocampus stands out for its function in higher order visual processing and memory (Kravitz et al., 2011; Lee A. C. H. et al., 2012).

Neural correlates related to visuospatial skills have been detected in relationship with structural volume enlargements of the right hippocampus (HC), both in long-term gamers and experimentally after a VG training period (Kühn et al., 2013; Kühn and Gallinat, 2014*). Increased hippocampal volumes were also found by Szabó et al. (2014**), although the authors do not attribute that effect to the VG training. The entorhinal cortex, associated with navigational skills (Schmidt-Hieber and Häusser, 2013), which together with the HC is involved in spatial memory (Miller et al., 2015), was also correlated with lifetime experience in logic/puzzle and platform VG (Kühn and Gallinat, 2014*).

Decreased activation in occipitoparietal regions, associated with the dorsal visuospatial stream (Goodale and Milner, 1992), has also been linked to improved visuomotor task performance, suggesting a reduction of the cognitive costs as a consequence of the VG training, dependent on the training strategy used in the VG (Lee H. et al., 2012). Earlier N100 latencies in the visual pathways are another feature found in long-term VGPs, which may contribute to faster response times in visual tasks after years of practice (Latham et al., 2013).

Reduced WM integrity in interhemispheric parietal networks for spatially-guided behavior could be another symptom for a decreased reliance on specific visuospatial networks after VG training as performance improved (Strenziok et al., 2013*). However, other studies found that increased WM integrity in visual and motor pathways was directly responsible for better visuomotor performance in long term VGPs (Zhang et al., 2015*). Despite these connectivity changes, brain functional differences between VGPs and non-VGPs do not always reflect performance in visuospatial skills, which were best predicted by non-visual areas (Kim Y. H. et al., 2015*).

Cognitive Workload

Brain activation patterns depend on the cognitive demands of the environment and also on the associated level of workload (Vogan et al., 2016), which is directly related to the allocation of resources to the working memory and its associated attentional processes (Barrouillet et al., 2007). When we manipulate this variable and observe its neural correlates, it is likely that we are seeing the result of neural recruitment mechanisms as the cognitive demands increase (Bavelier et al., 2012a). VGs have often been employed to obtain cerebral measures of cognitive workload, given the ability to adjust many of their features, particularly in a purpose-made VG, such as the popular Space Fortress. Due to the nature of this task, it is likely that functional changes related to the manipulation of cognitive load appear along the attentional networks and in specific key nodes related to executive functions, mainly in prefrontal and parietal cortices.

Cognitive workload is not a unitary concept; some studies have been able to identify different activation patterns by manipulating the difficulty of a task (e.g., Anderson et al., 2011*). Namely, the number of stimuli appearing simultaneously on the screen and the complexity of each stimulus seem to elicit different responses from the brain. For instance, in the context of an air traffic control simulator, when directly manipulating the task difficulty by increasing the number of planes that a participant had to attend, the theta band power increased (Brookings et al., 1996). Theta band power also displayed higher power compared to a resting condition, and gradually increased during gameplay (Sheikholeslami et al., 2007**). The theta band seems to be directly related to the level of cognitive demand in a wide range of cognitive abilities, such as attention, memory, and visuospatial processes, although this finding is not universal and decreased theta band power has been observed as a feature of sustained attention. So it appears that it is both related to task complexity and levels of arousal and fatigue. On the other hand, beta band power seemed to be more associated with the complexity of the task, especially in frontal and central areas, likely indicating a qualitative change in the cognitive strategy followed by the participant or the type of processing done by the brain (Brookings et al., 1996).

Assessing cognitive workload with ERP shows that during VG play, amplitudes tend to correlate negatively with game difficulty in expert VGPs, with most ERP (P200, N200) having its maximum amplitude in frontoparietal locations, with the exception of the P300, being larger in parietal regions (Allison and Polich, 2008). This is consistent with previous literature about cognitive workload related to attention and working memory demands and ERP peak amplitude decrements (Watter et al., 2001).

Frontoparietal activity, linked to attentional processes, also exhibits recruitment effects as game difficulty increases, which also affects reaction times, making them slower (Bavelier et al., 2012a). As mentioned above, comparing habitual VGPs with non-VGPs, it appears that the former show less recruitment of frontoparietal networks when compared to the non-gamers, which could be attributed to their VG experience and the optimization of their attentional resources (Bavelier et al., 2012a). Increased blood flow in prefrontal areas like dlPFC was also associated with increasing cognitive demands related to attention, verbal and spatial working memory and decision making (Izzetoglu et al., 2004*).

The intensity of the events displayed in the VG was also linked with certain electrophysiological correlates. High intensity events, such as the death of the VG character, were associated with increased beta and gamma power when compared with general gameplay (McMahan et al., 2015).

Cognitive Control

During the course of a VG, the player can encounter many situations in which he has to use one of several possible actions. For instance, while playing a game, the player might be required to interrupt and quickly implement an alternate strategy, or manipulate a number of elements in a certain way in order to solve a puzzle and progress in the storyline. All these abilities can be characterized under the “umbrella” of cognitive control, which includes reactive and proactive inhibition, task switching and working memory (Obeso et al., 2013). These cognitive control aspects are key to overcoming the obstacles found the VG. In fact, they are frequently used in parallel (Nachev et al., 2008) in order to engage in goal-directed behavior. These processes have their neural substrate in the prefrontal cortex, supported by posterior parietal areas and the basal ganglia (Alvarez and Emory, 2006). Therefore, most changes regarding cognitive control observed after VG play will likely be detected in these regions.

Indeed, prefrontal regions are one of the brain areas in which GM volumetric changes have been observed as a result of a cognitive training with a VG, which is remarkable if we consider that the common VG training period spans from a few weeks to a couple of months. These regions, such as the dlPFC, determinant for cognitive control (Smith and Jonides, 1999), show volumetric changes that seem to correlate with VG performance and experience, likely as a result of the continuous executive demands found in a VG, such as attentional control and working memory (Basak et al., 2011). These volumetric changes even result in correlations with transfer effects in cognitive control tasks (Hyun et al., 2013). Volumetric-behavioral correlations work both ways, since individuals with decreased orbitofrontal cortex (OFC) volumes as a consequence of VG addiction show poorer performance in similar tasks (Yuan et al., 2013a).

During VG play, these prefrontal regions increase their activation in response to the cognitive demands (game difficulty) and display a positive correlation with performance measures (Izzetoglu et al., 2004*). Still, prefrontal activity is not only affected by the complexity of the task, but also by the nature of the task and the individual differences of the participants (Biswal et al., 2010). Some research groups have found deactivation of dorsal prefrontal regions during gameplay. A possible explanation for this phenomenon could be the interference effect of attentional resources during visual stimuli, since activity in the dlPFC remained stable while passively watching a VG, but not while actively playing it (Matsuda and Hiraki, 2004*). Likewise, the same team also found that finger movement while handling the game controller did not seem to contribute as a source of prefrontal deactivation. Further studies also noted that the observed prefrontal deactivation was not affected by age or performance level (Matsuda and Hiraki, 2006*), although some authors have challenged that finding, claiming that prefrontal activation during video gaming was age-dependent, where most adults tended to show increased prefrontal activity while it was attenuated in some of the children. So prefrontal activation could be a result of age, game performance, level of interest and attention dedicated to the VG (Nagamitsu et al., 2006**).

It has been possible to establish a causal relationship between dlPFC activation and cognitive control using non-invasive stimulation methods. Stimulating the left dlPFC using tDCS results in a perceptible improvement in multitasking performance in a three-dimensional VG (Hsu et al., 2015).

Changes in functional activity after a training period in other executive-related nodes, such as the superior parietal lobe (SPL) have also been associated with working memory improvements (Nikolaidis et al., 2014).

Connectivity-wise, Martínez et al. (2013) found resting-state functional connectivity changes in widespread regions (frontal, parietal, and temporal areas) as a result of a VG training program, which were attributed to the interaction of cognitive control and memory retrieval and encoding.

Despite the observed structural and functional changes in prefrontal areas, executive functions trained in a VG show poor transfer effects as measured with cognitive tasks (Colom et al., 2012; Kühn et al., 2013). Others, showing neural correlates related to executive functions, visuospatial navigation and fine motor skills, failed to observe far transfer effects even after a 50 h training period, as measured by neuropsychological tests (Kühn et al., 2013). By studying lifelong experts or professional gamers, some studies have detected structural GM changes that correlated with improved executive performance, involving posterior parietal (Tanaka et al., 2013), and prefrontal (Hyun et al., 2013) regions. Regarding structural connectivity, WM integrity changes in thalamic areas correlated with improved working memory, but integrity of occipitotemporal fibers had the opposite effect (Strenziok et al., 2014). VG experience also seems to consolidate the connectivity between executive regions (dlPFC and the posterior parietal cortex -PPC-) and the salience network, composed by the anterior insula and the ACC, and responsible for bottom-up attentional processes (Gong et al., 2016).

Different VG genres seem to affect which cognitive skills will be trained. Training older adults in a strategy VG seemed to improve verbal memory span (McGarry et al., 2013), but not problem solving or working memory, while using a 2D action VG improved everyday problem solving and reasoning. Transfer effects were even more relevant in the case of a brain training/puzzle VG, where working memory improvements were also observed (Strenziok et al., 2014). Using a younger sample, working memory improvements were detected after training with a 2D action VG (Space Fortress, Nikolaidis et al., 2014). Nevertheless, training periods found in scientific literature vary greatly and it is difficult to ascertain if a lack of transferred skills cannot be due to a short training period.

Regarding electrophysiological methods, electroencephalography studies have shown functional correlations with alpha oscillations in the frontal cortex that could reflect cognitive control engagement in the training VG (Mathewson et al., 2012).

Skill Acquisition

Several studies have attempted to determine which regions could act as predictors for skill acquisition. Since this is a domain in which multiple cognitive functions are involved, volumetric and functional changes will appear in a wide range of cortical regions. Most of the learning in VGs is non-declarative, including visuospatial processing, visuomotor integration, and motor planning and execution. Improvements in these areas will generally lead to decreased cortical activation in the involved areas due to the optimization of resources, whereas this is not the case for striatal and medial prefrontal areas, which display a distinctive pattern of activation and typically increase their activity due to skill acquisition (Gobel et al., 2011).

Striatal volumes were determined as predictors for skill acquisition, although structural changes in the hippocampal formation were not (Erickson et al., 2010). Particularly, the anterior half of the dorsal striatum was the region which more accurately predicted skill acquisition in a complex VG (Vo et al., 2011). Other areas identified as predictors were the medial portion of the Brodmann area 6, located in the frontal cortex and associated with motor control in cognitive operations and response inhibition and the cerebellum, likely associated with motor skill acquisition (Basak et al., 2011). The same authors also considered the post-central gyrus, a somatosensory area that could be related to a feedback mechanism between prefrontal and motor regions, while the volume of the right central portion of the ACC also correlated with skill acquisition and is responsible for monitoring conflict. Finally, dlPFC volumes, with a central role on the executive functions, also showed correlation with VG performance over time (Basak et al., 2011).

On a functional level, Koepp et al. (1998**) was the first team to identify a relationship between striatum activity, associated with learning and the reward system, and performance level in a VG. The study by Anderson et al. (2015) also support the notion that the striatum, particularly the right dorsal striatum, composed of the caudate nucleus and the claustrum, is a key area in skill acquisition. However, the same team was able to predict learning rates more accurately by comparing whole sequential brain activation patterns to an artificial intelligence model.

Learning gains seemed to be best predicted by individual differences in phasic activation in those regions which had the highest tonic activation (Anderson et al., 2011*). Differences related to learning rates were also observed in the activation of the default mode network, especially when different training strategies were employed by the participants. Using electrophysiological methods, the best predictors were the alpha rhythms (Smith et al., 1999), particularly frontal regions, and alpha and delta ERSP, which are associated with cognitive control (task switching and inhibition) and attentional control networks (Mathewson et al., 2012). Frontal midline theta rhythms, linked with focused concentration and conscious control over attention, seemed to increase over the course of the training sessions with a VG (Smith et al., 1999).

Reward Processing

Addiction

VG addiction is understood as an impulse-control disorder with psychological consequences, not unlike other addictive disorders, especially non-substance addictions such as pathological gambling (Young, 1998). Internet Gaming Disorder (IGD) has been recently proposed for inclusion as a psychiatric diagnosis under the non-substance addiction category in the Diagnostic and Statistical Manual for Mental Disorders 5th ed. (DSM-5) (American Psychiatric Association, 2013), with its diagnostic criteria being adapted from those of pathological gambling. Efforts in order to find a consensus regarding its assessment are still ongoing (Petry et al., 2014). In some cases, VG addiction is included as a subset within the broader definition of Internet addiction, although this categorization is not always consistent, since many VGs in which addiction is studied do not have an online component. Several instruments have been developed to assess gaming addictions: the Internet Addiction Test (IAT) by Young (1998) and the Chen Internet Addiction Scale (CIAS) (Chen et al., 2004) being the most used in research and clinical practice.

Within the VG literature, there is a great deal of interest in knowing the neurobiological basis of VG addiction and whether it can be related to other behavioral addictions by observing abnormal reward processing patterns. This seems to be the case, since many regions involved in the reward system have been found affected in people with VG addiction (e.g., Liu et al., 2010*; Hou et al., 2012*; Hahn et al., 2014). Among the complex set of structures that are involved in the reward system, the cortico-ventral basal ganglia circuit is the center of the network responsible for assessing the possible outcomes of a given behavior, especially in those situations where, during a goal-oriented behavior, complex choices must be made and the value and risk of secondary rewards must be weighed (Haber, 2011).

Differential structural and functional changes in addicted individuals can be found throughout the reward system. The main components of this circuit are the OFC, the ACC, the ventral striatum, ventral pallidum, and midbrain dopaminergic neurons (Haber, 2011), but many other regions seem to be involved in the wider context of addiction.

By exposing the participants to gaming cues, it is possible to elicit a craving response and study which regions show stronger correlation in IGD patients compared to controls. The model proposed by Volkow et al. (2010) involves several regions, which are mentioned consistently across studies, to explain the complexity of the craving. First, the precuneus, which showed higher activation in addicted individuals (Ko et al., 2013*), is an area associated with attention, visual processes, and memory retrieval and integrates these components, linking visual information (the gaming cues) to internal information. Regions commonly associated with memory and emotional functions are also involved: the HC, the parahippocampus and the amygdala seem responsible for providing emotional memories and contextual information for the cues (Ding et al., 2013*), regions where subjects showed higher activation (O'Brien et al., 1998). Central key regions of the reward system, like the limbic system and the posterior cingulate have a role in integrating the motivational information and provide expectation and reward significance for gaming behaviors (O'Doherty, 2004). The OFC and the ACC are responsible for the desire for gaming and providing a motivational value of the cue-inducing stimuli (Heinz et al., 2009), contributing to the activation and intensity of the reward-seeking behavior (Kalivas and Volkow, 2005; Brody et al., 2007; Feng et al., 2013*). In the last step, prefrontal executive areas such as the dlPFC have also shown involvement during craving responses (Han et al., 2010a*; Ko et al., 2013*), and are linked to the formation of behavioral plans as a conscious anticipation of VG play. All these frontal regions[dlPFC, OFC, ACC, and the supplementary motor area (SMA)] tend to show reduced GM volumes in participants with IGD (Jin et al., 2016*).

Striatal volumes, particularly the ventral striatum, responsible for a key role in reward prediction, were reduced in people with excessive internet gaming compared to healthy controls (Hou et al., 2012*) and in the insula, with its role in conscious urges to abuse drugs (Naqvi and Bechara, 2009).

Overall, these features are characteristic of reward deficiencies that entail dysfunctions in the dopaminergic system, a shared neurobiological abnormality with other addictive disorders (Ko et al., 2009*, 2013*; Cilia et al., 2010; Park et al., 2010; Kim et al., 2011).

Several regions seem to be related to the intensity of the addiction. In a resting state paradigm, connectivity between the left SPL, including the posterior cingulate cortex (PCC), and the right precuneus, thalamus, caudate nucleus, nucleus accumbens (NAcc), SMA and lingual gyrus (regions largely associated with the reward system) correlated with the CIAS score, while at the same time, functional connectivity with the cerebellum and the superior parietal cortex (SPC) correlated negatively with that score (Ding et al., 2013*). The distinctive activation and connectivity patterns related to the PCC (Liu et al., 2010*), an important node in the DMN and reward system (Kim H. et al., 2015), could be used as a biomarker for addiction severity, both in behavioral and substance dependence. As the addiction severity increases, changing from a voluntary to a compulsive substance use, there is a transition from prefrontal to striatal control, and also from a ventral to a dorsal striatal control over behavior (Everitt and Robbins, 2005), Matching evidence in the form of weaker functional connectivity involving the dorsal-caudal putamen has been found in IGD patients (Hong et al., 2015*).

It is important to note that, even controlling the amount of time playing VGs, professional and expert gamers display very different neural patterns compared to addicted VGPs. Gamers falling into the addiction category show increased impulsiveness and perseverative errors that are not present in professional gamers and, on a neural level, they differ in GM volumes in the left cingulate gyrus (increased in pro-gamers) and thalamus (decreased in pro-gamers), which together may be indicative of an unbalanced reward system (Sánchez-González et al., 2005; Han et al., 2012b).

Exposure to Violent Content

Many articles use violent VGs in their designs as a way to study the effects of violence exposure, emotional regulation and long-term desensitization. Exposure to violent content has been associated with reduced dlPFC activity and interference in executive tasks (inhibition, go/no-go task) (Hummer et al., 2010), which cannot be interpreted without studying the link with the limbic and reward systems. It is likely that repeated exposure to violent content will trigger desensitization processes that affect regions linked to emotional and attentional processing, particularly a frontoparietal network encompassing the left OFC, right precuneus and bilateral inferior parietal lobes (Strenziok et al., 2011). It is hypothesized that this desensitization may result in diminished emotional responses toward violent situations, preventing empathy and lowering the threshold for non-adaptive behaviors linked to aggressiveness (Montag et al., 2012).

Limbic areas are associated with violence interactions, shown by the activation changes detected in the ACC and the amygdala in the presence of violent content (Mathiak and Weber, 2006*; Weber et al., 2006*). Lateral (especially left) prefrontal regions might be involved as well, integrating emotion and cognition and therefore working as a defense mechanism against negative emotions by down-regulating limbic activity (Montag et al., 2012). Wang et al. (2009) also provided evidence of that regulation mechanism by observing differing functional correlations between the left dlPFC and the ACC, and medial prefrontal regions & the amygdala during an executive task after a short-term exposure to a violent VG.

The reward circuit also seems to be implicated in the presence of violent content. Activation decreases in the OFC and caudate appeared in the absence of an expected reward. However, it does not seem that violence events were intrinsically rewarding (Mathiak et al. (2011*). Zvyagintsev et al. (2016*) found that resting-state functional connectivity was reduced within sensory-motor, reward, default mode and right frontotemporal networks after playing a violent VG, which could be linked to short-term effects on aggressiveness.

Gender differences in neural correlates were observed in one study (Chou et al., 2013*) after being exposed to violent content, with reduced blood flow in the dorsal ACC after playing a violent VG in males, but not females, possibly as a result of the role of the ACC in regulating aggressive behavior in males.

The effect of certain personality traits, particularly empathy, have been assessed using violent VG exposure (Lianekhammy and Werner-Wilson, 2015*). However, while empathy scores correlated with neural activity (frontal asymmetry during EEG), they were not affected by the presence of violent content. Markey and Markey (2010) found that some personality profiles, especially those with high neuroticism and low conscientiousness and agreeableness, are more prone to be affected by the exposure to violent VGs.

VG player's perspective may also be determinant to the level of moral engagement; while ERP N100 amplitudes were greater during a first person violent event, if the player was using a distant perspective, general alpha power was greater, which is indicative of lower arousal levels (Petras et al., 2015).

Montag et al. (2012), observed that regular gamers have been habituated to violence exposure and show less lateral prefrontal activation, linked to limbic down-regulation, compared to non-gamers. However, gamers have not lost the ability to distinguish real from virtual violence, as Regenbogen et al. (2010*) found, although that also depended on each person's learning history.

While attenuated P300 amplitudes have been linked to violence desensitization, both in short and long term exposure (Bartholow et al., 2006), these amplitudes did not increase using a pro-social VG (Liu Y. et al., 2015). Engelhardt et al. (2011), experimentally linked the lower P300 amplitudes to violence desensitization and their effects on aggression. Bailey et al. (2010) also supported the link between violent VG exposure and desensitization to violent stimuli, associating it with early processing differences in attentional orienting.

Flow

Flow and boredom states during VG play have also been the subject of research using neural correlates. The concept of flow, described by Csikszentmihalyi (1990), is understood as a mind state of being completely focused on a task that is intrinsically motivating. Among other characteristics, the state of flow implies a balance between the task difficulty and the person's skills, the absence of ambiguity in the goals of the task, and is commonly accompanied by a loss of awareness of time. Considering that the concept of flow is a complex construct which itself cannot be directly measured, it is necessary to operationalize its components. Some authors have identified some of these components as sustained attention (focus), direct feedback, balance between skill and difficulty, clear goals and control over the activity (Klasen et al., 2012*) and it has been theorized to be firmly linked to attentional and reward processes (Weber et al., 2009).

VGs provide the appropriate context in which flow states are encouraged to occur, since feedback is offered continuously and the level of difficulty is programmed to raise progressively, in order to match the improving skills of the player (Hunicke, 2005; Byrne, 2006). Therefore, VGs are perfect candidates to operationalize the components involved in the flow theory.

During gameplay in an action VG, Klasen et al. (2012*) could not relate the feedback component to any meaningful neural activity, but the four remaining flow-contributing factors showed joint activation of somatosensory networks. Furthermore, motor regions were implicated in the difficulty, sustained attention and control components. Together, the authors identify this sensorimotor activity as a reflection of the simulated physical activity present in the VG, which can contribute to the state of flow. The rest of the components elicited activity in several different regions. The reward system was involved in the skill-difficulty balance factor, observed by activation in the ventral striatum and other basal nuclei, rewarding the player in successful in-game events. In addition to activity in reward regions, this factor also correlated with simultaneous activity in a motor network comprised of the cerebellum and premotor areas. The factor comprising concentration and focusing during the VG was associated with changes in attentional networks and the visual system, as players switched away from spatial orientation to processing the numerous elements of the VG in high focus settings. Goal-oriented behavior showed decreased activity in the precuneus and regions of the ACC, while activity in bilateral intraparietal sulcus and right fusiform face area (associated with face processing) increased, which the authors explain as a result of a shift from navigation in a known environment to seeking new game content (Klasen et al., 2012*).

When manipulating the VG settings to elicit states or boredom, operationalized as the absence of goal-oriented behavior, one of the main aspects of flow, affective states appear. While the lack of goal-directed behavior resulted in an increase of positive affect, the neural correlates were characterized by lower activation in the amygdala and the insula (Mathiak et al., 2013). However, a different neural circuit was responsible when negative affect increased, characterized by activation in the ventromedial prefrontal cortex and deactivation of the HC and the precuneus, that seemed to counteract the state of boredom, possibly by planning future actions during inactive periods (Mathiak et al., 2013). Involvement of frontal regions was also observed by Yoshida et al. (2014) related to flow and boredom states. During the state of flow, activity in bilateral ventrolateral prefrontal cortex (vlPFC) [comprising the inferior frontal gyrus (IFG) and lateral OFC] increased, and it decreased when participants were subject to a boredom state. The OFC is linked to reward and emotion processing (Carrington and Bailey, 2009), and monitoring punishment (Kringelbach and Rolls, 2004). However, this study employed boredom differently, using a low difficulty level in the VG instead of the suppressing goal-directed behavior.

Brain-computer interfaces, using electrophysiological methods to measure brain activity, have been able to differentiate states of flow and boredom, created by adjusting the level of difficulty of a VG. The EEG frequencies that were able to discern between flow states were in the alpha, low-beta and mid-beta bands, measured in frontal (F7 and F8) and temporal (T5 and T6) locations (Berta et al., 2013).

Gender Differences

Although some studies have already discussed the presence of gender differences in cognitive processes related to VG playing, the lack of studies dealing with this topic and providing neural data are notable. The most relevant study of gender differences (Feng et al., 2007*) found that a 10-h training in an action VG (but not in a non-action VG) was enough to compensate for baseline gender differences in spatial attention, and to reduce the gap in mental rotation skills. Whether the initial difference was innate or a product of lesser exposure to this kind of activities in women is a matter of debate (Dye and Bavelier, 2010). Actually, one of the reasons men do not improve as much as women could be explained by a ceiling effect due to previous exposure to VGs. On the other hand, women with less experience in these activities are able to achieve equal performances in visuospatial skills that reach the same ceiling effect with a short training period. In this respect, Dye and Bavelier comment on the possible effects of lifetime VG exposure since the gender gap in attentional and non-attentional skills is smaller or non-existent during childhood compared to adult life, and the greater development of these skills in male individuals is partially due to games targeting a male audience.

Other authors (Ko et al., 2005) have focused on other psychosocial factors to explain gender differences in online VG addictions. Considering most online VGPs are men and this difference is also observed in addiction cases, they studied the possible factors and observed that lower self-esteem and lower daily life satisfaction are determinant in men, but not women. They attribute these differences to the reasons on why they play VGs: while men declared to play to pursue feelings of achievement and social-bonding, it was not the case for women. This aspect is not new to VG addiction and is shared aspect with other addictions. It is likely that VGs are used as a way to cope with these problems, leading up to the development of the addiction.

LIMITATIONS

The study of neural correlates of VGs entails a number of inherent difficulties. The main limitation encountered during the development of this review was the dual nature of studies with regard to VGs as a research tool or as an object of study. The lack of standardization in study objectives is another limitation that should be addressed. Despite the recent popularity of VG-related studies, there are a multitude of similar research lines that offer hardly comparable results, making it difficult to draw general conclusions. We aimed to unify all sorts of studies in order to interpret and generalize the results.

First of all, we compared a large number of studies that not only used completely different techniques, but also had very heterogeneous research goals. We grouped them together with the aim of extracting all the available neuroimaging information, but it is likely that some information that would have been relevant for us was missed in the studies because their research objectives differed greatly from our own. In fact, in certain cases, VGs were almost irrelevant to the aim of the study and were only used as a substitute for a cognitive task, so the provided results may not directly reflect the VG neural correlates. Similarly, VGs were sometimes used as tools to provide violence exposure or to study the effects of behavioral addictions without the VG being the central object of study.

Another issue was the lack of a proper classification for VG genres. While the most common division is between action and non-action VGs, it would be interesting to establish which variables determine this classification. For instance, both first person shooters and fighting games could be considered action VGs. Both demand quick response times and high attentional resources, but first person shooter games require much higher visuospatial skills while fighting games do not. Consequently, efforts should be made to determine which aspects of each VG genre are related with each cognitive process and its associated neural correlates.

Apart from these aspects, comparisons between gamers and non-gamers are common in VG literature. Nevertheless, there is no consensus on the inclusion requirements for each group and it seems that no scientific criterion has been used to establish a cut-off line. Current dedication to VGs, measured in hours per week, seems to be the most common classification method. Non-gamer groups sometimes are so strict as to exclude any gaming experience, but on other occasions, for the same category, several weekly VG hours are tolerated. This is problematic since, in some cases, cognitive changes have been found after just a few weeks of VG training. However, in most cases, the onset age of active VG play, which is a particularly relevant aspect (Hartanto et al., 2016), is not taken into account. Another relevant variable, which tends to be forgotten, is lifetime VG experience, usually measured in hours. Moreover, despite the clearly different outcomes caused by different VG genres, this variable is not included when describing a participant's VG experience. Therefore, VG experience should be measured taking into account all the variables mentioned above: onset age, lifetime VG experience (in hours), current VG dedication (hours per week) and VG genres.

With regard to this review, it was really difficult to extract all the relevant information because of the limitations of the existing literature about the topic. But we did our best to clarify the results and to extract valuable conclusions.

Another limitation was the link between neural changes and cognitive functions. The neural correlates of VGs are the focus of this review, and we found it essential to complement this data by discussing their cognitive implications. In most cases these implications were directly assessed by the individual studies, but in some cases they were extrapolated based on previous literature. Furthermore, even when functional or structural changes are detected, they do not always reflect cognitive changes. This may be due to a lack of sensitivity in the cognitive and behavioral tasks employed. In order to detect both neural and cognitive changes, specific research designs, with sufficiently sensitive measurements of the three dimensions (functional, structural, and cognitive) are needed. Ideally, to determine when each change starts to appear as a result of VG exposure, an experimental design, including a VG training period, should be used. In this design, the neural and cognitive data would be assessed along a series of time points until the three types of changes were detected. An exhaustive discussion of the cognitive implications of VGs is beyond our scope since there are already other works that deal with this particular issue (Powers et al., 2013; Lampit et al., 2014; Toril et al., 2014; Wang et al., 2016).

Efforts should be made to systematize VG-related research, establishing VG training protocols and determining the effects of lifetime VG exposure, in order that more comparable results can be obtained and to improve the generalizability of results.

CONCLUSIONS

The current work has allowed us to integrate the great deal of data that has been generated during recent years about a topic that has not stopped growing, making it easier to compare the results of multiple research groups. VG use has an effect in a variety of brain functions and, ultimately, in behavioral changes and in cognitive performance.

The attentional benefits resulting from the use of VG seem to be the most evidence-supported aspect, as many studies by Bavelier and Green have shown (Green and Bavelier, 2003, 2004, 2006, 2007, 2012; Dye et al., 2009; Hubert-Wallander et al., 2011; Bavelier et al., 2012b). Improvements in bottom-up and top-down attention, optimization of attentional resources, integration between attentional and sensorimotor areas, and improvements in selective and peripheral visual attention have been featured in a large number of studies.

Visuospatial skills are also an important topic of study in VG research, where optimization of cognitive costs in visuomotor task performance is commonly observed. Some regions show volumetric increases as a result of VG experience, particularly the HC and the entorhinal cortex, which are thought to be directly related to visuospatial and navigational skills. Optimization of these abilities, just like in attention and overall skill acquisition, is usually detected in functional neuroimaging studies as decreased activation in their associated pathways (in this case, in regions linked to the dorsal visual stream). It is likely that the exposure to a task first leads to an increase of activity in the associated regions, but ultimately, as the performance improves after repeated exposures, less cortical resources are needed for the same task.

Likewise, although not always consistent, even short VG training paradigms showed improvements in cognitive control related functions, particularly working memory, linked to changes in prefrontal areas like the dlPFC and the OFC. How to achieve far transfer in these functions remains one of the most interesting questions regarding cognitive control. Despite VGs being good candidates for cognitive training, it is still not well-known what the optimum training parameters for observing the first effects are. It seems intuitive that longer training periods will have a greater chance of inducing far transfer, but how long should they be? We also commented on how VG genre can have differential effects on cognitive control, so we cannot expect to observe these effects without first controlling this variable, since different VG genres often have little in common with each other.

Cognitive workload studies have offered the possibility of observing neural recruitment phenomena to compensate for the difficulty and complexity of a cognitive task and a number of studies have pointed to the importance of frontoparietal activity for this purpose.

It has been also possible to link skill acquisition rates with certain cerebral structures. Several brain regions are key in this regard, mainly the dlPFC, striatum, SMA, premotor area, and cerebellum. Moreover, as suggested by Anderson et al. (2015), models of whole-brain activation patterns can also be used as an efficient tool for predicting skill acquisition.

The role of the reward system is always present when we talk about VGs, due to the way they are designed. Addiction has a heavy impact throughout the neural reward system, including components like the OFC, the ACC, the ventral striatum, ventral pallidum, and midbrain dopaminergic neurons, together with diverse regions that have support roles in addiction. The role of structures that link addiction to its emotional components, such as the amygdala and the HC should not be underestimated.

Limbic regions work together with the PCC to integrate the motivational information with the expectation of reward.

Exposure to violent content has implications regarding the reward circuits and also emotional and executive processing. Reduced functional connectivity within sensory-motor, reward, default mode and right frontotemporal networks are displayed after playing a violent VG. The limbic system, interacting with the lateral prefrontal cortex, has a role in down-regulating the reaction to negative emotions, like those found in violent contexts, which may lead to short-term violence desensitization.

Despite the difficulties in locating the main components of flow in the brain, it seems that several networks are involved in this experience. General activation of somatosensory networks is observed while being in this state, whereas activation in motor regions is only linked to three components of flow: skill-difficulty balance, sustained attention and control over the activity. The reward system has key implications in the experience of flow, showing that the ventral striatum and other basal ganglia are directly linked to the skill-difficulty balance in a task. When seeking new content in order to avoid boredom, the bilateral intraparietal sulcus and the right fusiform face area seem to be the most implicated regions. During a flow-evoking task, the absence of boredom is shown by activity in the IFC, the OFC, and the vmPFC. Flow is also linked to emotional responses, and both positive and negative affect during a VG have shown changes in the amygdala, insula, vmPFC and the HC.

It is also worth commenting on the negative effects of VGs. While much has been written about the possible benefits of VG playing, finding articles highlighting the negative outcomes in non-addicted or expert VGPs is much less common. To our knowledge, only four studies pointed out neural correlates which predicted hindered performance in a range of cognitive domains. VG use has been linked with reduced recruitment in the ACC, associated with proactive cognitive control and possibly related to reduced attentional skills (Bailey et al., 2010). Likewise, exposure to violent content in VG is associated with lower activity in the dlPFC, interfering with inhibitory control. The same team (Bailey and West, 2013) observed how VG play had beneficial effects on visuospatial cognition, but in turn had negative effects on social information processing. Lastly, VG exposition has been linked to delayed microstructure development in extensive brain regions and lower verbal IQ (Takeuchi et al., 2016).

Finally, although this review is focused on the neural correlates of VG, not their cognitive or behavioral effects, we believe in the importance of integrating all these aspects, since raw neuroimaging data often offer little information without linking it to its underlying cognitive processes. Despite the fact that this integration is increasingly common in the literature, this is not always the case and it is an aspect that could be addressed in future studies.

AUTHOR CONTRIBUTIONS

All authors had an equal involvement during the process of making this review article. The article's design, data acquisition, and analysis of its content has been made by consensus among all the authors.

FUNDING

This study has been supported by the doctoral school of the Open University of Catalonia, Spain, under the IN3-UOC Doctoral Theses Grants Programme 2013-2016 (http://in3.uoc.edu). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ACKNOWLEDGMENTS

We would like to sincerely thank our colleague Cristina García Palma for her assistance during the whole process of extracting and processing information from the scientific databases and for her valuable contributions during the course of this work. We would also like to express our gratitude to Nicholas Lumsden, who assisted in the proof-reading and English-language correction of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnhum.2017.00248/full#supplementary-material

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer JMRA and handling Editor declared their shared affiliation, and the handling Editor states that the process nevertheless met the standards of a fair and objective review.

2.2.2 Video game training programs for cognitive enhancement

Once the effects that video games can have on brain structures and functioning, and their possible cognitive implications, have been discussed, it is reasonable to deepen to what extent video games can actually be used for the purpose of enhancing cognitive abilities. More importantly, due to the broad nature of the video game concept, it is necessary to identify those decisive factors that can lead to cognitive changes, to what extent it is possible to improve cognition, which cognitive domains are the most susceptible to improvement, the duration of these effects, the possible adverse effects and, lastly, what are the potential practical applications of video games used as a cognitive rehabilitation tool.

There are several reasons why video games are in the spotlight when studying potential cognitive enhancement tools. First, if treated like a learning device, video games involve predominately active forms of learning. The player is achieving knowledge and skills by participating in the game in a conscious and deliberate manner, continuously assessing their own degree of control, and not merely absorbing those skills through passive methods characterized by the lack feedback, as could be watching instructional videos. Although not being the classical setting in which active learning is applied, compared to passive methods, an active learning approach leads to better integration and consolidation of the presented materials (Michael, 2006). Moreover, video game players rarely focus on one single video game, and even if that was the case, most video games usually include a wide range of contexts and skills that the player must master in order to achieve its objectives. That variety of situations is key for promoting the generalization of learning (Schmidt & Bjork, 1992) since we tend to face the problems we encounter in our daily life by applying solutions that previously proved effective in similar situations. Generalization, understood as the influence from the improvement of one mental function on the efficiency of a related one (Woodworth & Thorndike, 1901), through the exposure to different situations is also a key aspect when trying to achieve the transfer of knowledge and skills across multiple domains.

Not all video games train the same set of skills. A puzzle video game and an action video game both feature electronic visual elements and interactivity, but the similarities end here. The cognitive skills required for successfully playing a certain game are different for each genre. For instance, considering the popular and simple game of Tetris, in which figures composed by four squares (*tetrominoes*) forming different shapes appear one by one and the player must rotate and move them to optimally fit them at the bottom without empty gaps. The figures are processed by visual skills, the key presses to manipulate the figure are controlled by the motor skills, and spatial skills are responsible for changing the orientation of the figures and fitting them at the bottom. While a figure is being manipulated, the next one already appears in one side of the screen, relying on peripheral visual processing, so the player can plan his actions accordingly, requiring the use of executive functions. All of that during the presence of a time constraint, favoring processing speed. If a simple puzzle game already involves a myriad of cognitive skills, it is expected that other genres featuring more complex environments will arguably face greater demands in processing task-relevant information (Powers et al., 2013).

Another unique feature of video games is the dynamic adjustment of the difficulty level throughout the game. To truly pose a challenge, a video game cannot have a stable difficulty level. Otherwise, if initially set too high, the game would be too hard for the player and would result in frustration and its abandonment. On the contrary, if set too low, the player would quickly learn the basic skills and the game would soon become too easy and predictable, resulting in boredom and, again, the abandonment of the game. For a game to maintain the player's involvement throughout its progress (see discussion on Flow, on section 2.2.1), it needs to create an increasing learning curve, as it is expected that players will improve their skills with practice. In games featuring a more linear development, the difficulty can be globally programmed to increase gradually, but more advanced designs balance the difficulty by dynamically controlling the presence of those elements which make the game harder (e.g. number and difficulty of enemies, number and location of power-ups, addition of time constraints, smarter artificial intelligence, etc.) by analyzing the competence and performance of the player (Byrne, 2006; Hunicke, 2005). As a whole, the dynamic difficulty balancing results in the fact that gamers will be constantly improving their skills in order to progress in the game, effectively turning it into a continuous learning device.

In addition to the variable difficulty level, video games also try to maintain the interest of the player by carefully adjusting the administration of reinforcements during gameplay. Most of these rewards are external, in the sense of in-game features that provide some sense of reinforcement or corrective information to how the player is performing, such as scores, achievements, unlocked features, etc., which can also be delivered in the form of vicarious reinforcement when observing another player, watching pre-recorded gameplay, and video game cutscenes (Reigeluth & Schwartz, 1989). In addition, playing video games can also elicit internal rewards, derived from the own player's sense of self-efficacy and satisfaction with his progress, or the possible social interactions (competitive and collaborative) resulting from the game (Shegog, 2010).

The presence of continuous reinforcement elements, and the way a game's storyline is divided into sections defining the length of a gaming session, increases the amount of time a player spends in the game. This is another relevant factor since time spent on a task has been shown to be one of the factors that better correlates with achievement (Garity & Butts, 1984). Therefore, since the intrinsic characteristics of video games encourage gamers to keep playing, the lengthening the amount of time exposed to the task would theoretically promote the learning of skills associated with the game. Moreover, there is another effect related to the time spent in the game that contributes to the consolidation of the learned skills, and it is the fact that gamers are exposed to video games during wide periods of time, comprising weeks, months or even years. When a learning process is distributed throughout spaced intervals of time, the learning of skills and knowledge is better consolidated (A. D. Baddeley & Longman, 1978).

When a task is purposely designed to keep its user engaged and motivated by administering precisely studied contingent reinforcements, almost like an operant conditioning chamber, it ceases to be a simple entertainment option to enter the domain of behavioral psychology (Hopson, 2001). There is always the risk that these carefully crafted game mechanics, if abused, end up inducing impulse control disorder and developing symptoms of addiction on vulnerable populations, derived from its effects on the reward system of the brain (see section 2.2.1, *Reward Processing*). This is especially relevant in the case of online multiplayer games, where the social component of playing is added to the fact that these games are designed not to have a clear and conclusive end. All this behavior-oriented design that video games possess, which can constitute potential sources for developing addictive behaviors, not unlike gambling, inevitably raised some ethical questions (D.

Becker, 2002). Because of that, some voices have spoken in favor of some kind of regulation to avoid making video games deliberately addictive (C. Shawn Green & Seitz, 2015).

All the points discussed above set the basis for assuming that video games have an actual effect on our cognition, possessing an ideal set of characteristics for training skills, and therefore could work as effective tools for the advantageous modification of cognition and behavior. It would be expected that a repeated exposure to a video game would result in the improvement of multiple aspects of cognition directly related to the game performance, but it is not clear whether these improvements would also transfer to non-gaming situations. This is currently a debated question in the field, with both supporters (Bavelier, Green, Pouget, & Schrater, 2012) and skeptics (Lee et al., 2012). The next section will be dedicated to explore the effectiveness of cognitive rehabilitation and enhancement programs using video games, and to determine the optimum parameters for a training program.

2.2.2.1 Method description

The cognitive effects of video gaming can be studied from two methodological standpoints: either using experimental or quasi-experimental designs. The difference is mainly determined by how the sample is acquired and assigned to the corresponding experimental conditions, in this case, the *gamers* and *non-gamers* groups. Each design has its advantages and disadvantages. Quasi-experimental designs most often imply classifying the participants depending on their previous video game experience, usually between *High gamers* and *Low or non-gamers.* This design does not allow for random assignment and may suffer from some biases, mainly selection bias, since habitual gamers are more likely to be interested in participating in this kind of studies. It is also reasonable to postulate the existence of some cognitive aspects that may mediate if a person will become a regular gamer; for instance, a person with low attentional and processing speed skills may feel less inclined to play fast-paced action video games since the experience would not be as enjoyable, and therefore preferring other genres or completely abstaining from playing video games. In addition, some video games are also oriented to certain demographics. For example, gender differences in video gaming are notorious in both the male/female ratio and the type of games that attract each gender. These biases add confounding variables to the design, affecting its internal validity and, ultimately, the interpretation of the results.

On the other hand, experimental designs offer a higher degree of control, allowing for the perfectly random assignment of participants to the experimental conditions and creating equal groups, eliminating most kinds of selection bias. In experimental designs, participants, often with few or no video game experience, are trained during a period of time, and a series of assessments measure the presence of cognitive changes which in this case can be only attributed to the independent variable, the video game training period. Unfortunately, longer training periods increase the likelihood of achieving cognitive enhancement, meaning that experimental designs tend to be more time-consuming and expensive, and often translate to lower sample sizes. Therefore, finding the exact point where more exposure to video games does no longer increase cognitive performance is one of the key aspects to optimize these training programs.

Quasi-experimental studies are more suited to understand the long-term effects of exposure to video games, an information that is not feasible to study using experimental designs, since the training periods tend to be shorter, over a period spanning days to months. In their methodology, most studies make the distinction between low or non-video game players to control the level of video game exposition their participants had. Quasi-experimental designs can also be carried out in a single point in time since the participants are already selected according to the independent variable and generally do not need a training period. Unlike the previous section 2.2.1 where both experimental and quasi-experimental were considered to understand the neural correlates of video games, since this section is oriented to find potential training programs which involve benefits at the cognitive level, only experimental designs have been considered, although occasionally, comparisons with equivalent quasi-experimental designs have been made if they help to better understand the results.

To date, three main meta-analyses have been carried out assessing the cognitive effect of video game training in healthy individuals. While they share the object of study and show some degree of overlap, they use slightly different methodologies and therefore provide different perspectives on this subject. The first one, published by Powers et al. (2013), intended to carry out an inclusive review of experiments and quasi-experiments using video game training programs on healthy adults with control groups, and classified the possible cognitive improvements among five domains (auditory processing, executive functions, motor skills, spatial imagery, and visual processing), using only commercial video games, regardless of the genre. The second meta-analysis, carried out by Wang et al. (2016), had a similar approach, but focused only in action video games, and placing more emphasis on discerning the effects of age, comparing young and older adults. In their review, the authors chose to classify cognitive improvements in five main domains: processing speed/attention, visuospatial ability, executive function, and memory. A third review made by Toril et al. (2014) focused on cognitive training with video games in older populations, a key aspect if we want to be able to apply these training programs to cognitive rehabilitation since it is the largest demographic segment that probably will take advantage of cognitive enhancement and rehabilitation. Among other moderator variables, they measured the effects of video gaming on five cognitive domains: memory, attention, reaction time, executive functions, and a global measure of cognitive performance.

The studies included in the three reviews are displayed in the table below (see Table 3), containing a comprehensive list of the main results, including the most relevant aspects of the video game training interventions, such as the age of the participants, the video game genre, the duration of the training and its impact on cognition.

Lastly, and already beyond the general scope of this section, it is worth mentioning a fourth review article by Stanmore et al. (2017) focused on the so-called *exergames*, games characterized by the use of physical activity as part of the requirements to complete the objectives of the game. Examples of this are the technologies used in the Nintendo Wii, the Xbox Kinect, and omnidirectional treadmills, effectively combining aerobic exercise with cognitive training, which have been attributed additive effects (Shatil, 2013). It is worth noting that a similar category of games was already considered by the review by Powers et al. (2013) under the name of *Mimetic* video games.

Authors	Year	N	Ages	Game	Genre	Training duration	Cognitive domain / measures	Outcome	Powers 2013	Wang 2016	Toril 2014
Gagnon	(1985)	58	18-31	Battlezone (3D) Targ (2D)	Shooter	1 week, <1.5h/day (5h)	Motor Skills & Spatial imagery	Game scores correlated with spatial task	✓		
Miller & Kapel	(1985)	88	11-13	Robot Blast, Pharaoh's Needle, Hamlet, 3D Maze, Factory	Puzzle	3 weeks	Executive functions, Spatial imagery	Transfer effects to improved spatial abilities	✓		
Dorval & Pepin	(1986)	70	22	Zaxxon	Shooter	8 sessions, 5x/session	Spatial imagery	Improved spatial scores	✓		
Drew & Waters	(1986)	13	61-78	Atari Crystal Castles	Arcade	8 weeks, 12x/week	Executive functions, Motor skills	Improved psychomotor speed and global cognition	✓		✓
Gagnon	(1986)	60	18-40	Battlezone	Shooter	30 minutes	Spatial imagery	No differences were observed	✓		
Clark, Lanphear & Riddick	(1987)	14	57-83	Pac Man Donkey Kong	Arcade, platformer	7 weeks, 120 min/week (14h)	Spatial stimulus-response (S-R) compatibility	Improved reaction times	✓	✓	✓
McClurg & Chaille	(1987)	57	10-15	The Factory Stellar 7	Puzzle, Shooter	5 weeks	Spatial imagery	Improved spatial ability	✓		
O'Banion	(1983)	30	7-8	Sink the Ship Nightmare Gallery	Arcade	7 weeks, 40 min/week (4.67h)	Motor skills, Visual processing	Improved eye-hand coordination, reaction times	✓		
Orosy-Fildes & Allan	(1987)	20	25.4	Centipede	Arcade	15 minutes	Visual processing	Improved reaction times	✓		
Dustman et al.	(1992)	60	62-71	Breakout, Galaxian, Frogger, Kaboom, Pacman, etc.	Arcade	11 weeks, 3x/week	Attention, Response speed, Visual processing, Executive functions	Visuomotor coordination: Improved reaction times			✓
Gopher, Weil & Bareket	(1994)	58	18-20	Space Fortress	2D Shooter, custom video game	45-60min x 8 sessions (6-8h)	Attention, Cognitive workload	Transfer effects, better flight performance	✓		
Okagaki & Frensch (Exp 1)	(1994)	28	19.93	Tetris	Puzzle	30min x 12 sessions (6h)	Spatial imagery, Visual processing	Improved reaction times	✓		
Okagaki & Frensch (Exp 2)	(1994)	28	19.85	Tetris	Puzzle	30min x 12 sessions (6h)	Spatial imagery	Improved reaction times	✓		

Authors	Year	N	Ages	Game	Genre	Training duration	Cognitive domain / measures	Outcome	Powers 2013	Wang 2016	Toril 2014
De Lisi & Cammarano	(1996)	56	18-42	Blockout Solitaire	Puzzle	30min x 2 sessions (1h)	Spatial imagery	Improved mental rotation performance	✓		
Subrahmanyam & Greenfield	(1994)	56	10-11	Marble Madness	Platformer	45min x 3 sessions (2h15m)	Spatial imagery	Improved spatial skills	✓		
Golstein et al.	(1997)	22	72-85	SuperTetris	Puzzle	5 weeks, 300min/week (25h)	Reaction times, Executive functions	Improved reaction times. Experimental and control group improved executive functions	✓		✓
Fery & Ponserre	(2001)	50	19.7	Golf	Sports	20 trials, 1 session	Motor Skills	Far-transfer from video game to real-life activity	✓		
De Lisi & Wolford	(2002)	47	8-9	Tetris	Puzzle	30min x 11 sessions (5.5h)	Spatial imagery	Improved spatial skills	✓		
Sims & Mayer (Exp 2)	(2002)	16	Young adults	Tetris	Puzzle	1h x 14 sessions (14h)	Spatial imagery	Improved spatial skills	✓		
Kearney	(2005)	14	Adults (>20)	Counter-Strike	First person shooter	-	Executive functions	Enhanced multitasking skills	✓		
Boot	(2007)	82	21.40, 21.35, 21.50 & 21.74	Tetris Rise of Nations Medal of honor	Puzzle, Real-time strategy, First person shooter	1.5h x 15 sessions (21.5h)	Executive functions, spatial imagery, visual processing	No transfer effects	✓		
Feng, Spence & Pratt (Exp 2)	(2007)	20	18-32	Medal of Honor: Pacific Assault	First person shooter	1-2h x 4 weeks (10h)	Visual processing	Improved accuracy	✓		
Smith, Morey, & Tjoe	(2007)	74	~20	Copy-Cat	Puzzle	12 game levels	Spatial imagery	Improved use of visual strategies	✓		
Green & Bavelier (Exp 2)	(2007)	32	21.3 21	Unreal Tournament 2004	First person shooter	+2h/day (30h)	Visuospatial / Visual processing	Lower crowding threshold	✓	✓	
Basak et al.	(2008)	39	69.89 68.88	Rise of Nations	Real time strategy	1.5h x 15 sessions (23.5h)	Executive functions, attention, visuospatial	Transfer effects	✓	✓	✓

Authors	Year	N	Ages	Game	Genre	Training duration	Cognitive domain / measures	Outcome	Powers 2013	Wang 2016	Toril 2014
Belchior et al.	(2007)	58	67-84	Tetris	Puzzle	4-5weeks, 3x/week	Memory, executive function, visuospatial abilities	Improved visual attention, but not transfer effects			✓
Cherney	(2008)	61	17-23	Antz Racing Extreme Tetris	Racing Puzzle	2 weeks or 3 days (4h)	Spatial imagery	Improved spatial skills	✓		
Cohen et al. (Exp 2)	(2008)	23	18-29	Unreal Tournament	First person shooter	3-5h/week (12h)	Visual processing	Improved visual skills	✓		
Cohen, Green & Bavelier (Exp 1)	(2008)	23	18-29	Unreal Tournament	First person shooter	3-5h/week (12h)	Attentional blink	Improved attentional skills	✓		
Green (Exp. 5)	(2008)	23	Adults	Death Match Call of Duty Tetris	First person shooter Puzzle	1h/day x 10 days (10h)	Auditory processing, Visual processing	Improved accuracy	✓		
Torres	(2011)	43	60-86	Super Granny Zoo Keeper Penguin Push Bricks "memory games"	Puzzle	8 weeks, 1/week	Comprehensive dementia cognitive battery	Less cognitive decline			✓
Cassavaugh & Kramer	(2009)	21	71.7	Beckman Institute Driving Simulator	Driving	2-3 weeks, 8 sessions	Attention, working memory, manual control	Improved reaction times			✓
Nelson & Strachan (Exp 1)	(2009)	20	19-23	Unreal Tournament Portal	First person shooter, puzzle	15min x 4 sessions (1h)	Visual processing	Faster response times but lower accuracy	✓	✓	
Nelson & Strachan (Exp 2)	(2009)	10	19-22	Unreal Tournament Portal	First person shooter, puzzle	15min x 4 sessions (1h)	Visual processing	Faster response times but lower accuracy	✓	✓	
Li, Polat, Makous & Bavelier	(2009)	31	19-27	Unreal Tournament 2004 Call of Duty 2 The Sims 2	First person shooter	<10h/week x 9 weeks (50h)	Visual processing	Improved contrast sensitivity	✓	✓	
Spence, Yu, Feng & Marshman	(2009)	20	17-23	Medal of Honor	First person shooter	1-2h x <4 weeks (10h)	Visual processing	Improved visuospatial skills, gender leveling	✓		
Ackerman et al.	(2010)	78	50-71	Wii Big Brain Academy	Brain training	4 weeks, 5x/week	Cognitive and perceptual speed	No significant transfer effects			✓
Boot et al.	(2010)	38	21.79 22.70	Space Fortress	2D Shooter, custom video game	3-5sessions/week (20h)	Executive functions, visual processing	Different training strategies obtained different learning rates.	✓		

Authors	Year	N	Ages	Game	Genre	Training duration	Cognitive domain / measures	Outcome	Powers 2013	Wang 2016	Toril 2014
Li, Polat, Scalzo & Bavelier	(2010)	25	26 & 24.7	Unreal Tournament 2004	First person shooter	2h/day (50h)	Attention	Improved reaction times and enhanced sensitivity		✓	
Masson, Bub & Lalonde	(2011)	51	11-15	Enigmo Railroad Tycoon 3	Puzzle/physics Strategy	1h x 6 sessions (6h)	Motor skills	Improved physics calculation	✓		
O'Leary, Pontifex, Scudder, Brown & Hillman	(2011)	36	18-25	Mario Kart Wii Fit	Racing, exergame	20min x 4 sessions (1h20m)	Executive functions	No improvements in cognitive control compared to physical exercise	✓		
Peretz et al.	(2011)	121	60-77	CogniFit Personal Coach	Brain training	12 weeks, 3x/week	Comprehensive cognitive battery	Improved focused and saturated attention, memory recognition, and mental flexibility			✓
Sosa	(2012)	31	74	Brain Age	Brain training	5 weeks, 1/week	Memory, processing speed, executive functions	Improved "syllable (time)", "arithmetic (time) and Stroop performance			✓
Stern et al. (Exp. 1)	(2011)	40	66.34 66.95	Space Fortress (emphasis change)	2D Shooter, custom video game	1h x 36 sessions (36h, during 12 weeks)	Executive function, visuospatial, memory, attention, language, processing speed	Improvement in one measure of executive control		✓	
Stern et al. (Exp. 2)	(2011)	40	66.34 66.96	Space Fortress (active or passive control)	2D Shooter, custom video game	1h x 36 sessions (36h, during 12 weeks)	Executive function, visuospatial, memory, attention, language, processing speed	No improvement		✓	
Colom et al.	(2012)	20	18.95	Professor Layton and The Pandora's Box	Brain training	4 weeks, 4h/week (16h)	Executive functions, reasoning	No difference in intelligence scores		✓	
Green, Sugarman, et al. (Exp. 4)	(2012)	36	25.7 24.7	Unreal Tournament Call of Duty	First person shooter	6-14 weeks (50h)	Executive functions	Improved response times and executive functioning	✓		
Lee et al.	(2012)	75	18-30	Space Fortress	2D Shooter, custom video game	2h x 15 sessions (30h)	Executive functions, visual processing	Improved visuospatial processing	✓		

Authors	Year	N	Ages	Game	Genre	Training duration	Cognitive domain / measures	Outcome	Powers 2013	Wang 2016	Toril 2014
Maillot, Perrot & Hartly	(2012)	32	73.47 (65-75)	Nintendo Wii	Casual, exergame	1h x 24 sessions (24h)	Executive functions, processing speed, visuospatial	Improved physical function, executive control, and processing speed, but no visuospatial skills	✓	✓	✓
McDougall & House	(2012)	41	74	Nintendo Brain Training	Brain training	6 weeks	General intelligence tests	Improved Backward Digit Span			✓
Nouchi	(2012)	28	69	Brain Age	Brain training	15min/day x 5 sessions/week x 4 weeks (5h)	Executive functions, attention, processing speed	Improved executive function and processing speed			✓
Sanchez	(2012)	60	Young adults	Halo: Combat Evolved Word Whomp	First person shooter	25 min	Visuospatial	Enhanced visuospatial performance	✓	✓	
Staiano, Abraham & Calvert	(2012)	54	15-19	Wii Sports	Sports Exergame	30min/day x 5 sessions/week x 10 weeks (25h)	Executive function	Improved executive skills	✓		
Valadez & Ferguson	(2012)	100	18-45	Red Dead Redemtion Fifa 2010	Action-Adventure, Sports	15 or 45 minutes	Spatial imagery	No effects	✓		
Van Muijden et al.	(2012)	72	60-77	Anagram Falling bricks	Puzzle	7 weeks (24.5h)	Executive functions, attention, reasoning	Improved cognitive inhibition and inductive reasoning			✓
Whitlock, McLaughlin & Allaire	(2012)	39	60-77	World of Warcraft	MMORPG	1h/day x 2 weeks (14h)	Executive functions, spatial imagery, visual processing	Improved attention and spatial orientation	✓		
Wu et al.	(2012)	25	18-27	Medal of Honor	First person shooter	Several <2h sessions (10h)	Visual processing	Improved visual attention	✓		
Anguera et al.	(2013)	46	67	Neuroracer	Racing / custom video game	4 weeks	Cognitive control	Transfer effects			✓
Belchior et al.	(2013)	27	74.8	Medal of Honor	First person shooter	1.5h x 6 sessions (9h)	Processing speed	Transfer effects		✓	
Boot et al.	(2013)	40	74	Brain Age	Brain training	1h/day x 5 sessions/week x 12 weeks (60h)	Perceptual speed, memory, selective attention/executive control, reasoning ability	No transfer effects			✓
Boot et al.	(2013)	34	73 & 72	Mario Kart DS	Racing	1h/day x 5 sessions/week x 12 weeks (60h)	Perceptual speed, memory, selective attention/executive	No transfer effects		✓	✓

Authors	Year	N	Ages	Game	Genre	Training duration	Cognitive domain / measures	Outcome	Powers 2013	Wang 2016	Toril 2014
							control, reasoning ability				
Bozoki et al.	(2013)	60	60-80	"Online video games"	Puzzle	6 weeks	Psychomotor speed, attention, decision making, working memory, learning	No transfer effects, small effect sizes			✓
Wu & Spence	(2013)	60	18-25	Medal of Honor: Pacific Assault Need for Speed: Most Wanted Ballance	First person shooter Driving Puzzle	1-2h x session (10h)	Processing speed	Improvements in speed and accuracy		✓	
Blacker et al.	(2014)	34	20.41 20.65	Call of Duty: Modern Warfare The Sims 3	First person shooter	1h x 30 sessions (30h)	Executive functions, working memory	Transfer effects in working memory		✓	
Cherney et al.	(2014)	40	20.5	Wii Fit (Segway circuit) Crazy Taxi	Exergame Driving	0.5h x 2 (1h)	Visuospatial	Improved mental rotation, gender leveling		✓	
Seçer & Satyen	(2014)	29	70	Pac Man	Arcade	3h x 3 sessions (9h)	Processing speed	No transfer effects		✓	
Schubert et al.	(2015)	42	24.7 21	Medal of Honor	First person shooter	1h x 15 sessions (15h)	Executive function, processing speed, working memory, visuospatial	Improved processing speed on visual attention		✓	
Green & Bavelier (Exp. 3)	(2006a)	32	21.3 21.0	Unreal Tournament 2004 Tetris	First person shooter	2h/day, 5-8h/week (30h)	Visual processing	Improved visual attention	✓	✓	
Green & Bavelier (Exp. 2)	(2006b)	17	20.4 19.7	Medal of Honor: Allied Assault Tetris	First person shooter	10 sessions	Visual processing	Improved enumeration performance	✓	✓	

Table 3. Comprehensive list of studies using video game training to improve cognition, as reviewed by Powers et al. 2003; Toril et al. 2014; and Wang et al. 2016.

Global effects

The meta-analysis by Powers et al. (2013), comparing 46 experiments, found that the training period had a small-to-medium mean effect size (see Table 4), showing that, overall, video games were successful in enhancing information processing skills. Since that group categorized the main moderator variables in several categories, they could do comparisons within the studies and study the heterogeneity for both the individual studies and the comparisons. The heterogeneity was significant when doing these comparisons but was only marginal at the level of studies, indicating that 24% of the heterogeneity within the sample was caused because of the true variability between the studies (see Table 4). Regarding the effect sizes for the main cognitive domains, all of them were significant with the exception of auditory processing, possibly due to the low number of studies that considered it. The largest effect size was found in motor skills, whereas the rest of the domains (e.g. spatial imagery and visual processing) showed small magnitudes, even negligible in the case of executive functions (see Table 4). Since that meta-analysis also provided data for quasi-experiments, it is worth mentioning that studies using quasi-experimental designs found overall larger effects compared to true experiments. This is probably due to already discussed self-selection effect where habitual video game players are more prone to participate in this kind of studies, and also to the presence of Hawthorne effects, where players might expect to perform better due to their previous experience and try to act accordingly, altering their performance.

True experiments	Level of Analysis	Cohen's d	CI (95%)		Z	p-value (Z)	N	Q	df (Q)	p-value (Q)	I²
			Lower	Upper							
Studies (46)	Fixed	0.45	0.35	0.56	8.33	.001	1621	59.04	45	.078	23.78
	Random	0.48	0.35	0.6	7.43	.001					
Comparisons (251)	Fixed	0.28	0.23	0.32	12.5	.001	9090	670.77	250	.001	62.73
	Random	0.33	0.25	0.4	8.78	.001					

Table 4. Summary of effect sizes for overall effects at the level of studies and comparisons, for true experiments. Adapted from Powers et al. (2013).

The study by Wang et al. (2016) found that, after analyzing 20 studies, video games had a moderate effect size on cognition, characterized by a high variability across the studies (see Table 8). By cognitive domain, action video games had moderate impacts on visuospatial skills and processing speed and attention. The effect was slightly lower for executive functions. In the last place, enhancement of memory function showed a smaller effect size compared to the other functions (see Table 8). These results are comparable to those obtained in the meta-analysis by Powers et al. (2013), which found moderate overall effect sizes (see Table 4).

Toril et al. (2014), focusing on 20 studies characterized by having older participants, also observed a moderate mean effect size across all studies before considering any moderator variables, but without achieving a significant heterogeneity, indicating that indeed video game training was successful in improving cognitive functions in older populations (see Table 5). Observing individual cognitive domains, their effects were heterogeneous, with the largest effect sizes found in reaction times, followed by memory, global cognitive performance, and finally attention. Executive functions, on the other hand, did not reach the level of significance in this group of studies (see Table 9). Overall, these results agree with those found in the two other meta-analyses, finding moderate effect sizes in cognition enhancement as a result of video game training, an encouraging finding since cognitive functions tend to decline as a result of normal aging processes.

Number of studies	Cohen's d	CI (95%)		Q (19)	p-value (Q)	I^2
		Lower	Upper			
20	0.37	0.26	0.48	23.95	> .05	20.69%

Table 5. Overall effect size by incorporating all the effect sizes from individual studies. Adapted from Toril et al. (2014).

Cognitive domain

When considering all kinds of video games, the analysis by Powers et al. (2013), confirmed that experimental designs in video game training showed robust effects in improving cognition, being motor skills the most benefited from this training but also showing positive effects on other cognitive functions (see Table 6). The notable exception here is the low effect on executive functions, that were the most resistant to change. When examining more carefully the skills included in executive functions, Powers et al. (2013) decided to divide them into a set of subskills, comprising *Executive function battery, Dual/multitasking, Inhibition, Intelligence, Task switching* and *Working/short-term memory.*

Cognitive domain	Cohen's d	CI (95%)		Z	p-value (Z)	k	N	Q (df)	p-value (Q)
		Lower	Upper						
Auditory processing	0.45	-0.47	1.36	0.96	.339	1	50		
Executive functions	0.16	0.05	0.27	2.83	.005	89	3721		
Motor skills	0.76	0.54	0.98	6.65	.001	15	627		
Spatial imagery	0.43	0.34	0.53	8.63	.001	77	2617		
Visual processing	0.36	0.17	0.54	3.8	.001	64	2075		
Between-classes effect								26.65 (4)	0.01

Table 6. Summary of effect sizes for true experiments moderated by cognitive domain. Adapted from Powers et al. (2013).

Further exploring the subskills within executive functions, only inhibition tasks were found to significantly moderate cognition in true experiments (see Table 7).

Cognitive domain	Cohen's d	CI (95%)		Z	p-value (Z)	k	N	Q (df)	p-value (Q)
		Lower	Upper						
Exec function battery	0.14	-0.14	0.68	0.49	.623	2	111		
Dual/multitasking	0.17	-0.16	0.49	1.00	.317	12	546		
Inhibition	0.39	0.15	0.63	3.24	.001	17	737		
Intelligence	0.06	-0.23	0.35	0.43	.668	19	790		
Task switching	0.06	-0.33	0.45	0.30	.766	10	437		
Working/short-term memory	0.12	-0.03	0.27	1.57	.118	24	1100		
Between-classes effect								4.69 (5)	0.455

Table 7. Summary of effect sizes for executive functions moderated by sub-skill, for true experiments. Adapted from Powers et al. (2013).

When only action video games are considered (Wang et al., 2016), moderate benefits are achieved in the domains of attention and processing speed, analyzed together, (see Table 8), consistent with previous findings. Action video game players saw enhancement in different aspects of attention, like sustained attention, visual selective attention and divided attention (Feng et al., 2007; C. Shawn Green & Bavelier, 2003; Greenfield, 2014). During gameplay, participants benefited from improved sustained attention and general concentration, as well as an optimized use of the attentional resources, allocating more resources to the task they are performing at a given moment, resulting in an overall better efficiency. Likewise, participants also increased the spatial resolution of their visual processing across the visual field (C. Shawn Green & Bavelier, 2007).

Visuospatial skills were also subject to a moderate degree of enhancement. Action video games require the player to manipulating visuospatial information and navigating in 3D environments in a goal-directed manner. Previous studies had shown that visuospatial skills presented some plasticity in healthy adults, and video games proved to be an appropriate tool for transferring the enhancement effects in this cognitive function.

Regarding executive functions, the effect was smaller, although significant. The effect was lower, even negligible, in older adults, whereas younger adults show greater executive improvements as a result of training. Moreover, it is likely that the kind of video games also took part on these differences, with action video games being more suitable for improving this function as a result of the kind of activity that is trained during gameplay.

Enhancement of memory also showed a small effect, although very few studies examined this domain, and all of them did so in older populations, so the results may not be as consistent as the other cognitive functions that were analyzed. Nevertheless, these significant improvements tell us that plasticity in memory functions is preserved even in older adulthood and is susceptible to being trained.

	Effect size					Heterogeneity			Egger's test	
				CI (95%)						
Cognitive domain	Number of studies	Cohen's d	SE	Lower	Upper	Q	p-value (Q)	I^2	t	p-value (t)
Overall cognition	20	0.58	0.1	0.37	0.78	103.57	< .001	81.67	1.84	.082
Processing speed / attention	12	0.5	0.18	0.14	0.85	81.69	< .001	86.53	0.15	.883
Memory	3	0.33	0.19	-0.05	0.71	< .001	.998	< 0.001	0.29	.822
Visuospatial ability	10	0.54	0.12	0.3	0.77	15.37	.081	41.43	0.78	.458
Executive function	9	0.49	0.17	0.15	0.83	51.19	< .001	84.37	0.13	.898

Table 8. Main findings of action video game training by cognitive domain. Adapted from Wang et al. (2016).

In older adult samples, examined by the team led by Toril (2014), some interesting patterns arise. Attention was the cognitive domain that experienced better improvements as a result of the video game training (see Table 9), probably reducing distractibility by improving attention filtering, a function that tends to decline with age and is associated with frontal functions, and also improved alertness, supported by wider neural networks. Regarding the speed of processing, as measured with reaction time tasks, it also improved as a result of training, likely as a result of the strict timings that some video games require. Likewise, the retention of information is a common element in many games, which may have led to the memory improvements also detected in this meta-analysis. The use of general intelligence tests for assessing the transfer effects also showed positive results, although to a lesser extent than those measured in specific cognitive functions. On a negative note, executive functions did not seem to be affected by the training in older adults.

Cognitive domain	Cohen's d	SE	Z	p-value (Z)	CI (95%)

					Lower	Upper
Memory	0.39	0.12	3.08	< .01	0.01	0.64
Attention	0.37	0.10	3.67	< .01	0.17	0.57
Reaction time	0.63	0.10	5.93	< .01	0.42	0.84
Cognitive function	0.38	0.12	3.07	< .01	0.13	0.62
Executive functions	0.16	0.13	1.2	> .05	-0.10	0.42

Table 9. Effect sizes by cognitive domain in older adults. Adapted from Toril et al. (2014).

When comparing cognitive domains among the three meta-analyses, some shared conclusions arise. The lack of transfer effects in executive functions was a shared conclusion in the general meta-analysis by Powers et al. (2013) and the one by Toril et al. (2014), which studied older samples, although in the review by Wang et al. (2016), using only action video games did find statistically significant results in this functions, implying that game genres requiring fast reaction times and precise hand-eye coordination are more successful in improving cognitive functioning. For some reason, the domain of attention was not considered in Power's meta-analysis, but it consistently achieved moderate effects when studied in relation to action video games and older populations. Visual and spatial skills also seemed to be benefited from video game training, achieving greater effects when trained with action video games. Finally, the evidence indicates that memory functions also respond to the effects of training, although in a smaller magnitude, when examined both with action video games and in adult populations.

Modulators of the training effects

Video game genre

When we talk about video games, there is a tendency to group them all together, as if they were one unitary concept. While they likely have some general effects, video game genres can be so different that it is safe to assume that, cognitive wise, they are hardly the same. With some exceptions, video games can easily be classified in genres based on their content and how a user interacts with it. The main division used in the literature is between action and non-action video games, based on the speed and precision with which the player must react to the game. Just like other fictional works, genres are numerous, and there is not always a clear-cut division between one genre and another. Furthermore, they can be categorized both by type of gameplay (e.g. shooter, role-playing game, puzzle, platformer, etc.) or by their content (e.g. fantasy, science fiction, adventure, horror, etc.), where the former division makes more sense if we intend to study them from the perspective of their cognitive effects.

Powers et al. (2013) classified the video games used for cognitive training into five main groups: *Action/violent* games, which comprised *shooter games* (e.g. Medal of Honor, Unreal Tournament, etc.), *mimetic games*, in which the player has to imitate the actions on the screen (e.g. Wii games such as Wii Sports and Wii Fit), *Non-action* games, which comprised simulation, education and sports games (e.g. Word Whomp, Mario Kart, The Sims, etc.) and finally *puzzle* games, which emphasized problem-solving skills (e.g. Tetris). The targeted game type had an effect on cognition. *Mimetic* game training showed larger effects compared to *action/violent* game training and *puzzle* game training, and marginally larger effects compared to *non-action* video games. Whereas in quasi-experimental designs, action video games were more beneficial for inducing cognitive changes, that was not the case when using experimental designs, and the magnitude of the changes was similar in action and non-action video games, and still lower than in mimetic games (although the latter were studied in one single article, so results must be interpreted cautiously). Usually, experiments are designed in a way that a particular video game genre is chosen according to the expected cognitive improvements in one specific domain. For instance, puzzle games have been used to study the spatial imagery domain, whereas first-person shooters are associated with the visual-processing domain, and it is likely that the potential improvements of training in one particular game are closely tied to the cognitive demands of that genre. However, the insufficient volume of research comparing individual video game genres with specific cognitive domains does not allow for generalizations at the current moment.

Genre	Cohen's d	CI (95%)		Z	p-value (Z)	k	N	Q	p-value (Q)
		Lower	Upper						
Action/Violent	0.22	0.13	0.3	4.94	0.001	135	5410		
Mimetic	0.95	0.66	1.23	6.58	0.001	20	684		
Nonaction	0.52	0.31	0.73	4.9	0.001	16	510		
Puzzle	0.3	0.16	0.45	4.03	0.001	76	2486		
Between-classes effect								28.06 (3)	0.001

Table 10. Effect sizes by video game genre. Adapted from Powers et al. (2013).

Toril et al. (2014), facing the diversity of video games that were used in the studies of their meta-analysis, divided video games into two main groups: *simple* and *complex*. Simple games are those that do not involve complex cognitive demands, while complex video games require the recruitment of many perceptual and cognitive skills. While it was expected that games that are more complex had a bigger impact on cognition, no significant differences between the two types of games were detected (see Table 11), and there even was a small trend suggesting that simpler games might be more beneficial. Regular video games were also compared with “brain training” video games. The differences between these two groups were characterized by lack of significant heterogeneity where regular video games showed slightly higher effect sizes compared to brain training activities but, overall, both game groups can be considered to have equal effects.

Variable	Level	Cohen's d	SE	Q (1)	p-value (Q)	I2	Z	p-value (Z)	CI (95%)	
									Lower	Upper
Type of game	Simple	0.42	0.08	0.55	> .05		5.00	< .01	0.25	0.58
	Complex	0.33	0.07				4.38	< .01	0.18	0.48
Type of program	Video games	0.40	0.07	0.27	> .05		5.25	< .01	0.25	0.55
	Brain training	0.34	0.08				4.04	< .01	0.17	0.50

Variable	Level	Cohen's d	SE	Q (1)	p-value (Q)	I^2	Z	p-value (Z)	CI (95%)	
									Lower	Upper
Type of game	Simple	0.42	0.08	0.55	> .05		5.00	< .01	0.25	0.58
	Complex	0.33	0.07				4.38	< .01	0.18	0.48
Type of program	Video games	0.40	0.07	0.27	> .05		5.25	< .01	0.25	0.55
	Brain training	0.34	0.08				4.04	< .01	0.17	0.50

Table 11. Effect sizes by type of video game. Adapted from Toril et al. (2014).

Global duration

According to the principles that lead to the generalization of cognitive skills, spacing the acquisition of knowledge during a period of time should derive in a better consolidation of that knowledge, compared to the learning of the same volume of knowledge in a short interval. Following this principle, it would make sense that studies featuring longer training periods and a higher global duration would result in larger transfer effects to cognition, but this is not always the case.

Powers et al. (2013) divided the total length of the training into two groups, 10 hours or more, and less than 10 hours, and found that the effect sizes were comparable among the two groups, likely due the fact that participants quickly adapt their cognitive processes to the features of the game, and therefore, extensive training periods are not needed.

Consistent among the three meta-analyses, the cognitive effects of video game training were modulated by several moderator variables, among which the duration of the training sessions, the number of sessions and the total duration of the training program showed negative correlations with the effect sizes of the training (Wang et al., 2016).

The fact that the amount of training correlated negatively may be explained by a decrease of motivation to continue playing the as participants spend more time on training. It has been postulated to be an effect of the *temporal discounting* hypothesis (L. Green, Fristoe, & Myerson, 1994), in which people tend to give less value to rewards the more distant in time they are expected. Longer training periods may, therefore, dilute the benefits of taking part in a study and the participant loses the motivation, leading to a lower training efficacy. However, a careful review of the articles included in the meta-analysis did not give support to that idea, as repeated cognitive measures along the training period showed continuous improvement in the game performance, an effect that is hardly compatible with a lack of motivation. It is possible that this effect can be better explained under the perspective of a more comprehensive model, taking into account several elements, such as the levels of arousal, engagement, reward, feedback, and level of enjoyment during the gameplay, which together could contribute to a state of flow (Csikszentmihalyi, 1990) during the task.

In older populations, shorter training periods (from one to six weeks) were, in fact, better at improving cognition than longer interventions (seven to twelve weeks) (see Table 12). This result has positive implications since it means that less time-consuming interventions work just as well, or even better, than long training periods. The authors attribute this result to the lack of motivation observed in older participants when the training period is too long, also concordant with the *temporal discounting* hypothesis, and the expected rewards (which often are not subjectively perceived) do not compensate the investment in the task. They comment that in many cases, although participants begin with high motivation, the only factor that keeps them from abandoning is the affective link or personal relationship with the experimenter. Another reason for this lack of motivation may stem from the fact that video games do not usually cater to older populations, both in its contents and in the difficulty level, and therefore they may not be perceived as enjoyable as it would happen with younger participants.

Training duration	Cohen's d	SE	Q (1)	p-value (Q)	I²	Z	p-value (Z)	CI (95%)	
								Lower	Upper
Short	0.49	0.08	3.73	0.05	73.19%	5.59	< .01	0.32	0.67
Long	0.26	0.08				3.03	< .01	0.09	0.43

Table 12. Effect sizes of the video game training moderated by the total length of the training program. Adapted from Toril et al. (2014).

Age

The age of the participants is another of the moderating variables that is thought to have a larger impact on skill acquisition and cognitive enhancement. It is assumed that younger participants would display more plasticity effects compared to older populations. Moreover, one factor that is not often considered is the onset age of video game play. According to Hartanto et al. (2016), there is a critical period during which the brain is more prone to consolidating the cognitive enhancement produced by video games, even surpassing the effect of recent video game playing, as measured in an executive skill (task switching). Specifically, those participants who started playing video games before the age of twelve possessed greater executive skills, regardless of the amount of current video gaming. It would be interesting to know if the same effect appears when other cognitive functions are measured and if they all share the same critical age threshold.

Powers et al. (2013) divided the participant's age into four main groups in order to assess its effects as a moderator variable: youth (3-17), young adults (18-22), adults (23-54) and older adults (+55). Age moderated the effects of the training especially in older adults, more than in young adults or adults but, nevertheless, demonstrating the benefits of video gaming across all ages (see Table 13). Due to the small sample of experiments, these data should be interpreted with caution, until more studies consolidate this trend.

Age	Cohen's d	CI (95%)		Z	p-value (Z)	k	N	Q (3)	p-value (Q)
		Lower	Upper						
Youth (3-17 years)	0.40	0.17	0.64	3.34	0.001	28	1080		
Young adults (18-22 years)	0.22	0.12	0.32	4.21	0.001	121	4407		
Adults (23-54 years)	0.28	0.16	0.41	4.37	0.001	55	2206		
Older adults (>55 years)	0.63	0.44	0.82	6.45	0.001	43	1397		
Between-classes effect								14.41	0.002

Table 13. Effect sizes of video game training moderated by age group. Adapted from Powers et al. (2013).

Wang et al. (2016) found age differences on how action video games enhanced cognition, by comparing young adults against older adults (see Table 14). Whereas the magnitude of the overall changes is moderate for young adults, in older adults the magnitude was lower, although they still experienced benefits from the action video game training. In both cases, the studies showed significant heterogeneity, respectively, without evidence of publication bias. Moreover, the magnitude of the effect size was significantly higher in young adults.

Disaggregated by cognitive domain, the meta-analysis by Wang et al. (2016) found that young adults benefited most from processing speed and attention, visuospatial ability and executive functions, with large to moderate effect sizes (see Table 14). However, in older adults, training in video games seems to be beneficial, primarily, for improving executive functions, followed by processing speed and attention, memory, and visuospatial skills. In any case, the effect size for older adults is still lower than for younger adults when the different cognitive domains are analyzed separately, although the only significant difference between those two groups was in processing speed and attention. The authors agree that due to the small number of studies comparing young and older adults, these results must be treated with caution. It is worth considering that for all these cases, the authors demonstrated that the publication bias was insignificant.

Age / Cognitive domain	**Effect size**					**Heterogeneity**			**Egger's test**	
	Number of studies	**Cohen's d**	**SE**	**CI (95%)**		**Q**	**P**	**I^2**	**t**	**P**
				Lower	**Upper**					
Young adults										
Overall cognition	12	0.75	0.16	0.43	1.07	42.27	< .001	73.97	10.00	.287
Processing speed/Attention	4	0.81	0.47	0.11	1.73	19.82	< .001	84.86	0.30	.790
Visuospatial ability	6	0.70	0.12	0.46	0.94	3.94	.559	< 0.001	2.09	.105
Executive function	4	0.64	0.22	0.01	1.29	14.87	< .01	79.88	2.00	.637
Older adults										
Overall cognition	8	0.38	0.13	0.12	0.64	48.14	< .001	85.46	0.36	.728
Processing speed/Attention	8	0.37	0.20	-0.02	0.76	54.59	< .001	87.18	0.55	.601
Memory	3	0.33	0.19	-0.03	0.71	0.00	.998	0.00	0.29	.882
Visuospatial ability	4	0.29	0.20	-0.10	0.68	7.15	.067	58.05	0.92	.455
Executive function	5	0.40	0.22	-0.04	0.84	14.87	< .001	88.96	0.32	.773

Table 14. Effect sizes by age group and cognitive domain. Adapted from Wang et al. (2016).

When specifically studying older adults, two age groups were made: 60-70 and 71-80. It appears that the older the participants, the most they benefit from the video game training (see Table 15). An explanation for this would be the lower baseline scores that characterize old age. Not only they show greater improvements overall, but their final cognitive performance is even greater than the slightly younger samples at the end of the intervention (Toril et al., 2014). It should be noted that older populations tend to use less new technologies, and the sudden exposition to video games in the experimental setting could cause some catch-up effect, achieving larger effects that those who are more familiar with new technologies.

Age group	**Cohen's d**	**SE**	**Q (1)**	**p-value (Q)**	**I^2**	**Z**	**p-value (Z)**	**CI (95%)**	
								Lower	**Upper**
60-70	0.3	0.07	4.50	< .01	77.77%	4.27	< .01	0.16	0.44
71-80	0.57	0.11				4.98	< .01	0.34	0.79

Table 15. Effect sizes by age group in elderly participants. Adapted from Toril et al. (2014).

Control group

The type of control group used in video game training experiments can also act as a moderator variable. The effect size tends to be greater in those studies that use passive control groups compared to studies with active control groups. Passive control groups are those in which participants did not receive any kind of intervention, whereas in the active control groups, participants received some kind of training not related to video games, such as doing paper-and-pencil activities, three-dimensional puzzle games, passively watching contents on a monitor, or even playing another video game from a genre related to the one used in the experimental group. Passive control groups, apart from being more prone to the presence of confounding variables, participants assigned to that group would generally have fewer expectations compared to the experimental and active control groups. The more similar are the experimental and control groups, the lower will be the magnitude of the effects. Therefore, studies which use passive control groups will generally obtain greater effect sizes, since active control groups will be more similar to the experimental condition with the video game training (Huntley, Gould, Liu, Smith, & Howard, 2015). In the analyzed literature, there is not enough evidence to make an overall assumption and support this claim, since most studies in action video games with active control groups are done in young adults, while passive control groups are used when participants are older adults, and even ignoring this factor, studies with active control groups generally achieve larger effect sizes (Wang et al., 2016).

When considering not only action video games, Powers' group found that the type of control group did not work as a moderator variable in true experiments. In other words, passive control groups did not yield smaller effects than active control groups. The authors believe that the reason behind this may be related to the participants' expectations and possible placebo-like effects in the control groups (Powers et al., 2013).

Regarding the effects in studies using older participants, not many of the included articles featured active and passive control groups in the same study. There is a factor which is often neglected, and it is the fact that in the experimental and active control groups there are social interactions between the participant and the experimenter, whereas social contact is absent in passive control groups. This social contact could have an influence on the levels of motivation and affect the results of the cognitive training, likely having a small but positive effect on cognition.

Gender

The team by Powers et al. (2013) measured the effect of cognitive training male only, female only or mixed groups. The effects of training equally affected men and women, and the meta-analysis did not detect any significant difference between the two groups, although again, not many studies deal with this factor and more research is needed regarding gender differences. This contrasts with the findings in quasi-experimental designs, where men only and mixed groups obtained benefits from training, but not those groups comprised exclusively of women. The authors attribute this effect to the differences on how men and women choose to play video games, leading to different information-processing outcomes. Moreover, mixed and female-only groups are less common in the literature, due to the fact that fewer women volunteer in this kind of studies, contributing to the selection bias.

2.2.2.2 Practical applications of video games on cognition

The precise mechanisms of how video game training improves cognition are still not well understood. The generalization of learned aspects is key to the success of an intervention. When it comes to measuring the degree of generalization, the transfer effects can be understood in several ways. For a cognitive training to be successful, the learned skills should transfer to different situations in real-life (far-transfer), not only contexts almost identical to the training context (near-transfer). It is not enough for a participant or a patient to improve in a specific task (a video game, in this case) if that learning does not translate to better skills in their everyday life. In the case of video game training, by performing neuropsychological assessments at different time points alongside the training period, it is possible to determine the effectiveness of that program in enhancing a set of cognitive functions in a more general manner. Another aspect is the maintenance of these effects. Sometimes a learned knowledge or skill starts to fade as time passes. A truly effective training program should produce cognitive changes that will withstand the passage of time. Unfortunately, longitudinal designs where participants' skills are monitored, in the medium or long-term are scarce. Spacing a training period over a greater span of time should, in theory, help consolidate a learning and ensure retention of skills, but a careful review of the literature shows us that this is not the case with cognitive training with video games, where the lack of motivation does not compensate for the longer training periods. Moreover, it is possible that explicit memory benefits from that spanning factor, but video game training enhances, in most cases, elements in the implicit memory in the form of procedural learning, which may not be influenced from this effect.

Among video game genres, action video games seem to enhance cognition in a more widespread way, likely due to its requirements of rapid and accurate reactions, and good command of attentional processes, such as attention switching and divided attention (C. Shawn Green & Seitz, 2015). At the at the same time, action video games include unpredictability factors, quick presentations with high perceptual load, selections between multiple action plans and emphasis on peripheral processing (Hubert-Wallander, Green, Sugarman, & Bavelier, 2011; Oei & Patterson, 2013). Some authors (Bavelier et al., 2012) have proposed that the broad transfer effects of these games can be explained with the *learning to learn theory* (Harlow, 1949), where patterns are picked from a series of learning experiences. The action video game training may improve top-down and probabilistic inference capabilities, as the game makes the player engage in a wide range of tasks. As discussed in section 2.2.1, action video games facilitate brain plasticity in adults in a number of ways, affecting structurally and functionally widespread brain regions that could be a reflection of the cognitive transfer effects in all these domains.

The lack of far-transfer effects related to executive functions, such as multitasking, non-verbal intelligence, task switching and working memory, found in non-action video games is concerning. If one of the aims is to make healthy people smarter, changes in executive functions are of vital importance. Commercial video games marketed as “brain training”, which became popular a few years ago, often claim that they will improve reasoning, general intelligence, and working memory, but the lack of benefits of these games, as measured in true experiments, contradict all these claims (Kable et al., 2017). Moreover, this kind of games tend to use “gamified” versions of neuropsychological tasks used for the assessment of cognitive functioning, and therefore the learning effects should be more easily detectable since no far-transfer is required. However, this is not the case, further invalidating the effectiveness of these “brain training” games (Powers et al., 2013).

Among the direct practical applications of cognitive training (with video games or otherwise) are those linked to the enhancement of academic performance, in the case of healthy people, cognitive stimulation for healthy older adults, and cognitive rehabilitation for those who suffer mild cognitive impairments. To date, no study has explored the possibility of applying video game training to directly improve academic or work performance. This issue has been already dealt with in correlational studies that found the positive effect that video games have on academic outcomes

(Posso, 2016), although it is hard to assume a direct causal relationship. Regarding cognitive stimulation and rehabilitation, the meta-analysis by Toril et al. (2014) offers a good overview of the possibilities of video games in the potentiation of cognitive skills that decline with age, and it is especially promising since the most benefited seems to be those participants with older age. Let us not forget all these studies were carried out with healthy individuals, and the observed transfer effects may not be present in the case of cognitively impaired patients. One recent article (Savulich et al., 2017) explored whether video games could improve cognitive functioning in persons with early memory problems derived from schizophrenia. These mild cognitive impairment patients were trained in a casual video game and showed improved performance in a memory task, which was also modulated by the level of motivation of the participant. Classical cognitive stimulation programs, encompassing a wide range of activities to engage and stimulate a patient, have been proved effective (with small to moderate effect sizes) in improving general cognition in dementia. However, there was no sign that these effects could be replicated with cognitive training on standardized tasks (Huntley et al., 2015), as it could be the case of video game training. In any case, the evidence on the effectiveness of video game training for cognitive impairment is still scarce, and whether impaired patients or the population at high risk for developing dementia may benefit from these training programs is still unclear (Robert et al., 2014).

2.3 Non-Invasive Brain Stimulation Techniques and Cognitive Enhancement

2.3.1 Method description: Non-invasive brain stimulation

The study of the brain has always been plagued with difficulties. One of the main goals of neuroscience has been how to have an effective influence on the brain in living people while causing the least possible harm, even none if possible.

Non-invasive brain stimulation techniques comprise a series of techniques aimed at producing temporary changes in cerebral activity while minimizing the level of invasiveness, that is, that they do not require an incision or insertion in the body in order to be effective. Their effects tend to be short-lived and harmless to the subject to which it is applied, so one of the benefits is that it can actually be used for research in healthy participants. These techniques can even facilitate or suppress changes in cortical excitability which can outlast the duration of the stimulation (Hummel & Cohen, 2005), so they can be used as a therapeutic approach in diseases with brain activity dysfunctions.

The techniques used for neurostimulation and neuromodulation can be categorized whether they use magnetic fields, electrical current or light as the energy input used to induce cortical changes (see Table 16).

Among the diversity of available techniques, two of them stand above the rest regarding their proven effectiveness and how often they are used in clinical practice and scientific literature: transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES), in its direct current modality (tDCS). Both of them share a common mechanism, using suprathreshold currents in the brain to achieve changes in its excitability. After a brief introduction to the main non-invasive stimulation techniques, most of this chapter will be dedicated to TMS, where its physical principles, their main modalities and safety and ethical aspects will be explained.

2.3.1.1 Transcranial electrical stimulation (tES)

The use of electricity in medical contexts is not new. Ignoring all the pre-scientific applications of magnetic and electrical fields that plagued the past, the thorough study of this topic began at the start of the 20th century. Transcranial electrical stimulation encompasses a series of techniques of non-invasive stimulation using electrical currents that are applied to the brain, using one or more electrodes, mostly aimed at research and clinical purposes.

Transcranial direct current stimulation (tDCS)

Within the modern electrical stimulation techniques, this is by far the most used variant. A direct current, usually driven from batteries, is applied at 1-2mA over 5-20 minutes (Paulus, 2011), letting subthreshold electrical currents flow through the encephalic mass during that period of time. The placement of the anode and the cathode matters, since each one has unique properties. Commonly, placed over the target region, the anode is used to induce cortical excitability meanwhile the cathode induces cortical inhibition. Despite not having a high spatial resolution, a new device has been developed that allows a different electrode configuration, using a ring of cathodes around the anode, or a ring of anodes around the cathode in order to increase or decrease, respectively, cortical excitability in the target area. This technique, called high-definition tDCS (HD-tDCS), allows much more precision in the stimulation.

Transcranial alternating current stimulation (tACS)

Similar to tDCS, this variant applies alternating current using a bipolar electrode arrangement, where a single sinusoid wave at 10-40Hz with a peak intensity of 0.4 to 1mA (Paulus, 2011) at less than 20V flows through the brain. tACS has the potential to synchronize or desynchronize activity between targeted brain regions and could be used to design individualized interventions aimed at coupling or decoupling activity between specific brain regions (Santarnecchi et al., 2015). The HD-tACS is also possible with the aim of reaching more localized stimulation.

Transcranial random noise stimulation (tRNS)

Whereas tACS featured a single wave applied at a regular frequency, tRNS also uses alternating currents, but at random frequencies within a given spectrum (0.1-640Hz) (Paulus, 2011). As it uses alternating current, the anode and cathode are probably polarity-independent (Miniussi, Harris, & Ruzzoli, 2013). Apart from clinical applications, this variant has also been used to study cognitive enhancement in healthy people (Santarnecchi et al., 2015). Once again, HD-tRNS is used to obtain more precise stimulation.

Name	Energy modality	Main uses	Focality	Invasiveness	Advantages	Limitations
Transcranial magnetic stimulation (TMS)	Magnetic field	Research, assessment of nerve integrity, treatment of psychiatric and cognitive disorders, cognitive enhancement	Very focal (in the order of mm)	Low (no preparation is needed, just place the coil and stimulate). Short stimulation periods.	Application in central and peripheral nervous system. Possible substitute for electroconvulsive therapy (ECT) for treatment of depression.	Expensive Some modalities may induce discomfort.
Transcranial electrical stimulation (tES)	Electrical field	Cognitive enhancement, psychiatric disorders (depression), treatment of motor dysfunctions.	Low. Improved with the HD-tDCS modality.	Low (requires positioning of the electrodes, application of gel and stimulation lasts tens of minutes)	Much cheaper than TMS. Very portable. Easier to apply.	Inconclusive results. Longer application times. Uncomfortable sensations.
Transcranial photobiomodulation / Transcranial laser stimulation (TLS)	Infrared light	Research, Cognitive enhancement, stroke/traumatic brain injury rehabilitation.	Relatively focal.	Low (requires positioning of the lasers/LED)	Relatively cheap. Safe.	Recent. Low volume of research. Very experimental.
Transcranial static magnetic field stimulation (tSMS)	Magnetic field	Still in experimental stages.	Low.	Low. Relatively long stimulation periods	Low cost, simplicity.	Low volume of research. Very experimental.

Table 16 Modalities of non-invasive stimulation techniques.

2.3.1.2 Transcranial magnetic stimulation (TMS)

Origins and basic principles

Despite the TMS technique being quite recent, it is based on the principles of electromagnetic induction discovered by Michael Faraday, a 19th-century British physicist and chemist that studied electromagnetism and is known, mainly, for the discovery of electromagnetic induction in 1831 (Faraday & Day, 1999).

According to the laws of classical electromagnetism, in particular Ampère's law, passing a direct electrical current through a conductor, such as a wire, creates a circular magnetic field perpendicular to the plane in which the current flows (see Figure 29), where its strength is directly proportional to the current that passes through it. If the same conductor is shaped in the form of a coil (solenoid), different properties emerge from this circuit: all the individual magnetic fields generated by the separate turns of the conductor are forced to pass through the center of the coil, adding their strength, and resulting in a much larger magnetic field. The greater number of turns of the conductor, the stronger the field produced is going to be, particularly on the inside of the solenoid. Therefore, the strength of the magnetic field will directly depend on the strength of the electrical current and the number of turns in the coil.

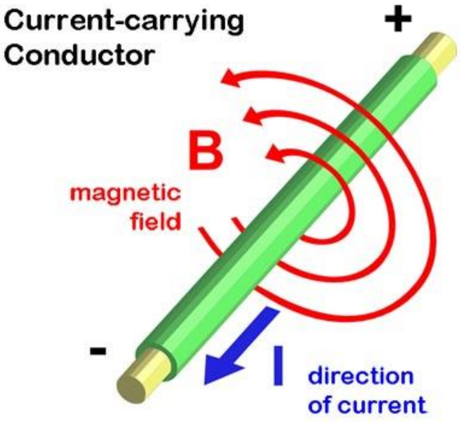


Figure 29. Schematic representation of Ampère's law. A direct electrical current that passes through a conductor creates a circular magnetic field perpendicular to the plane in which the current flows. Source: Wikimedia Commons (CC BY-SA 3.0)

Because of this principle, energy is stored in the coil's magnetic field as long as the current flows and this effect can be used in a number of practical applications, such as electromagnets, electrical transformers, and magnetic inductors. The magnetic field flows in a particular direction through the center of the solenoid, which is determined by the direction of the passing electrical current through the conductor. When observed from the top of the conductor, the magnetic field will flow in a counter-clockwise manner. An easy way of visualizing its direction is by using Fleming's "right-hand rule": by curling the fingers of your right hand, the thumb will always point in the direction of the current, and the curl of the fingers represent the direction of the magnetic field (see Figure 30). This also entails that by reversing the current, we also reverse the magnetic field.

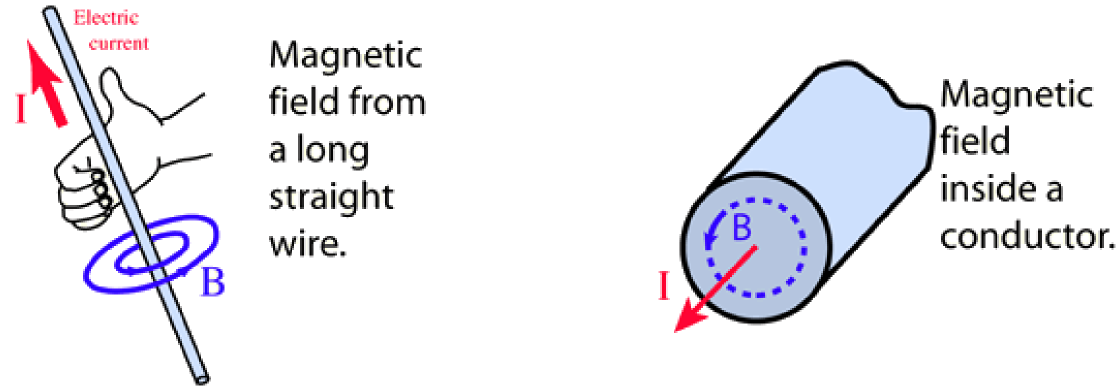


Figure 30. Representation of the direction of the magnetic field flow as a result of the direction of an electrical current through a conductor. From a top-down perspective, the magnetic field will always flow in a counter-clockwise manner.

Furthermore, according to Faraday's law of electromagnetic induction, a changing or moving magnetic field will induce an electrical current in a stationary conductor placed nearby, which will be directly proportional to the strength of the field (see Figure 31). By using this effect, electrical energy can be generated and applied in many contexts, such as electrical motors, wireless chargers or neurostimulation.

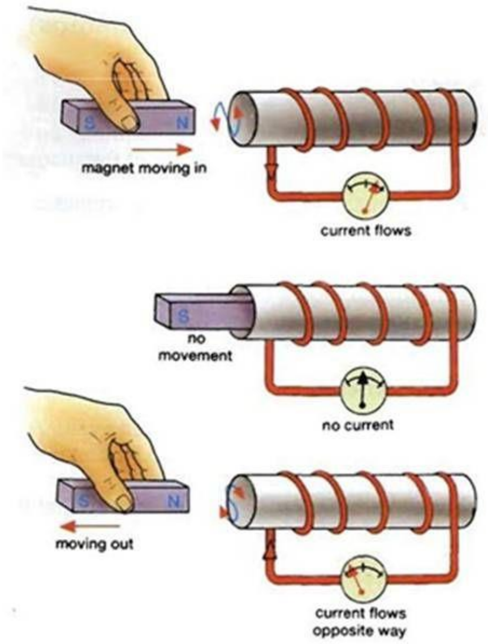


Figure 31. Schematic representation of electromagnetic induction. A changing magnetic field will induce an electrical current in a nearby stationary conductor, proportional to the strength of the field. According to Lenz's laws, the direction of the induced current will flow as to oppose the changing magnetic field producing it. Source: Johnson, 2001.

It was not until the end of the 20th century that this idea was used for the study of the brain. In 1985, a team led by Anthony Barker were the first team to apply the properties of electromagnetic induction to modulate the activity of the brain cortex, taking advantage of the neurophysiological properties of the cerebral cells (Barker, Jalinous, & Freeston, 1985). They developed the first modern device, a single induction coil not much different from the ones used nowadays, that acted as an electromagnetic inductor and was capable of depolarizing neurons in the brain cortex located directly underneath the scalp by emitting short magnetic pulses. Being the first team to use this technique, they applied it to assess the integrity of the corticospinal pathway through the activation of the motor cortex in human beings, evoking contralateral movements in a non-invasive, safe and painless way.

The actual transcranial magnetic stimulator consists in a copper coil isolated by a plastic enclosure, connected to a power source composed by a series of condensers, which are capable of holding and providing thousands of amperes in the order of milliseconds and a thyristor, a type of transistor, which regulates the current flow (see Figure 32). The electrical current needed to generate a magnetic field strong enough to be used to stimulate the brain cortex is in the range of 7-10kA, which is applied in the form of a single pulse which lasts around 1ms. In these conditions, a magnetic field up to 2.5T will be generated, a strength comparable to that of a magnetic resonator (for more detailed technical and physiological aspects of the technique, check the specifications by The MAGSTIM Company LTD (2009)). Since the intensity of the magnetic field is inversely proportional to the square of the distance, the coil has to be placed as close as the location of the stimulation target as possible. Other factors that will affect the strength of the magnetic field needed to stimulate the cortex will be the different conductances and resistances of the tissues that surround the cerebral cortex (hair, scalp, cranial vault, cerebrospinal fluid, and meninges) and the excitability and orientation of the cortex neurons. Once the pulse has crossed the cranial tissues, the intensity of the current will be in the order of a few mA. Due to these reasons, TMS is normally used for stimulating cortical areas, and reaching deeper brain regions is a complicated feat without the use of other technologies.

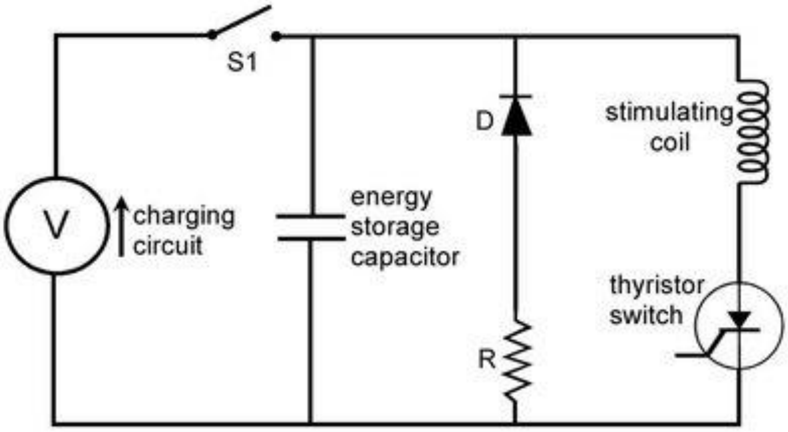


Figure 32. TMS circuit diagram. Source: Alvaro Pascual-Leone, Davey, Rothwell, Wasserman, & Puri, 2002

The basis for transcranial stimulation is the depolarization of neural membranes in order to initiate actions potentials. Both TMS and tES stimulate the axons of the neurons, particularly large diameter myelinated axons, instead of the cell bodies, since the soma has a higher threshold due to a greater electrical time constant (D. Burke, Bartley, Woodforth, Yakoubi, & Stephen, 2000).

Induced currents in the brain have an important directional component. In TMS, most currents flow in parallel to the surface of the brain, not perpendicularly to the gray matter. The stimulation threshold directly depends on the direction of the current. Using this technique, the depolarization often occurs at the point where the axon bends out of the field and the change in electrical field is greatest (Rossini et al., 2015).

The effect of the stimulation ultimately depends on which neural circuits are recruited. These circuits are not necessarily only those that anatomically correspond to the stimulated area, and it is possible to achieve depolarization in distal regions, which are functionally or anatomically connected to the target site. This is the reason connectivity studies are even very important to understand the targets of the TMS activation in the brain.

Types of coils

The distribution of the magnetic field and therefore the focality and penetration of the stimulus can be controlled by using different kinds of stimulation coils. The most commonly used designs are based on two basic models: one of them featuring a single circular coil, and another one featuring two intersecting coils in a figure-of-eight shape (see Figure 33). The first one, being the original coil that was developed with the TMS technique, features a strong and uniform magnetic field alongside the coil circumference that decreases towards the center and the exterior of the ring. Since the magnetic field it produces is relatively distributed, it is possible to cover large areas of the brain or even to stimulate regions in both hemispheres at the same time. However, the magnetic field it creates is diffuse and therefore less powerful, which translates it into a lower penetration power, overall making it less suitable for many applications.

On the other hand, the figure-of-eight coil achieves a focalized magnetic field right at the intersection between the two coils, achieving a much a much higher precision (see Figure 34). Due to these reasons, the figure-of-eight coils are the most frequently used in basic neuroscience research, such as brain mapping, and in clinical settings. In order to achieve this level of precision, the coil is required to be positioned exactly above and parallel to the stimulation site, and any slight deviation will change the properties of the induced current, altering the intended effects. The size of the coils also determines some of these properties; the smaller the coils, the more focal the stimulation will be, but they will tend to overheat faster (Rossini et al., 2015), allowing for shorter stimulation sessions since most TMS devices will automatically disable themselves for safety reasons if a temperature threshold (41ºC, according to medical protocols) is reached, so as to avoid burning sensations (US20110218381 A1, 2011).

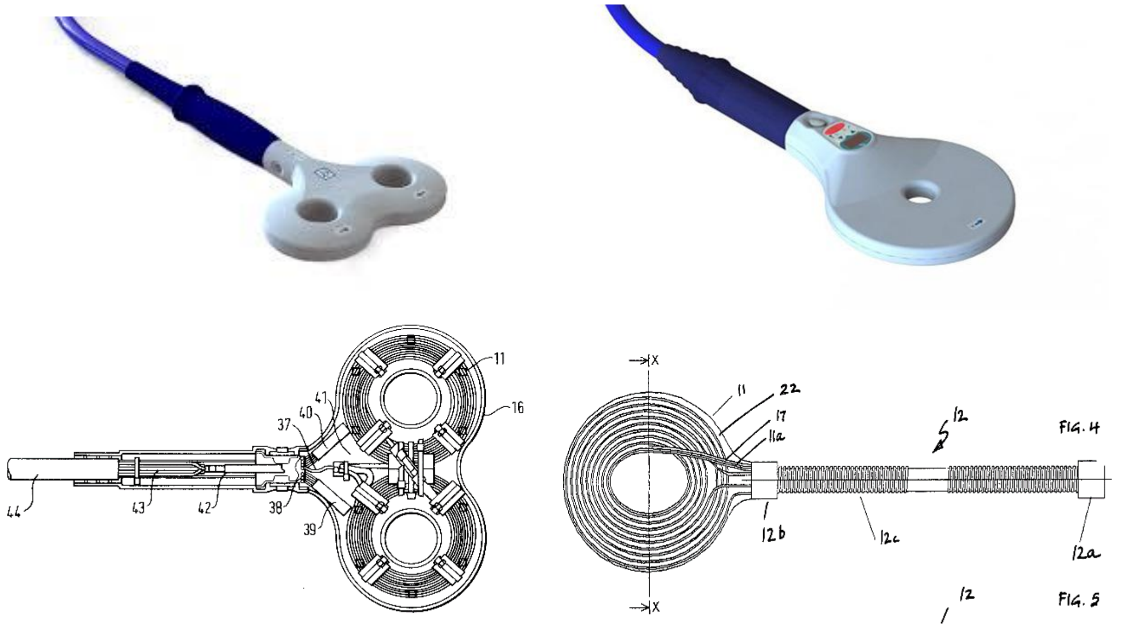


Figure 33. Main types of TMS coils. Most coils are based on these two basic designs: the figure-of-eight coil, used when precision is important, and the circular coil, when a larger area needs to be stimulated. (Source: ©Magstim; Mould, 2001; Phillips & Thomas, 2009)

On the other hand, the figure-of-eight coil achieves a focalized magnetic field right at the intersection between the two coils, achieving a much a much higher precision (see Figure 34). Due to these reasons, the figure-of-eight coils are the most frequently used in basic neuroscience research, such as brain mapping, and in clinical settings. In order to achieve this level of precision, the coil is required to be positioned exactly above and parallel to the stimulation site, and any slight deviation will change the properties of the induced current, altering the intended effects. The size of the coils also determines some of these properties; the smaller the coils, the more focal the stimulation will be, but they will tend to overheat faster (Rossini et al., 2015), allowing for shorter stimulation sessions since most TMS devices will automatically disable themselves for safety reasons if a temperature threshold (41ºC, according to medical protocols) is reached, so as to avoid burning sensations (US20110218381 A1, 2011).

The spatial and temporal resolution can further be improved by combining TMS with other neuroimaging techniques, such as structural and functional MRI, or positron emission tomography (PET). Thanks to this combination, the effectiveness of TMS can be greatly improved, achieving a greater precision in the study of brain activity and human cognition, which is especially relevant in the field of cognitive neuroscience.

In order to overcome the low penetration power of TMS, a third and less commonly employed type of coil is used in a protocol termed *deep TMS*. The coil, in the shape of an H letter (see Figure 35), is able to reach deeper regions without over-stimulating superficial regions due to its design, which creates a distributed magnetic field near the coil surface, but maintains the strength of the magnetic field up to a certain distance. Due to its larger size, most of the time this kind of coil is used pre-mounted within a helmet, which is ready to target specific brain areas, and are mostly used in clinical settings to treat psychiatric disorders, particularly major depression (Bersani et al., 2013).

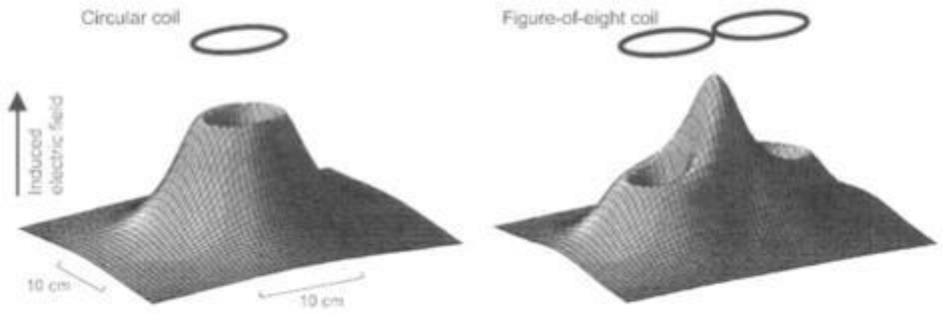


Fig. 2. The strength of the electric field induced in a spherical volume conductor below a circular (*left*) and a figure-of-eight coil (*right*). Reprinted from (Ilmoniemi *et al.*, 1999), with permission of Begell House, Inc.

Figure 34. Pattern of the electric field determined by the shape of the magnetic coil (from Hallett, 2007 – with permission). Two magnetic coils with different shapes (circular and figure-of-eight, respectively) and their resultant electric fields. (Ilmoniemi, Ruohonen, & Karhu, 1999)

Nonetheless, there is always a depth-focality tradeoff, as the improved penetration of the magnetic field is a direct result of using higher stimulation intensities, and it is currently not possible to avoid stimulating superficial areas as well (Deng, Lisanby, & Peterchev, 2013). Therefore, this type of coil cannot achieve the precision of a figure-of-eight coil, likely creating unwanted effects on other brain circuits.

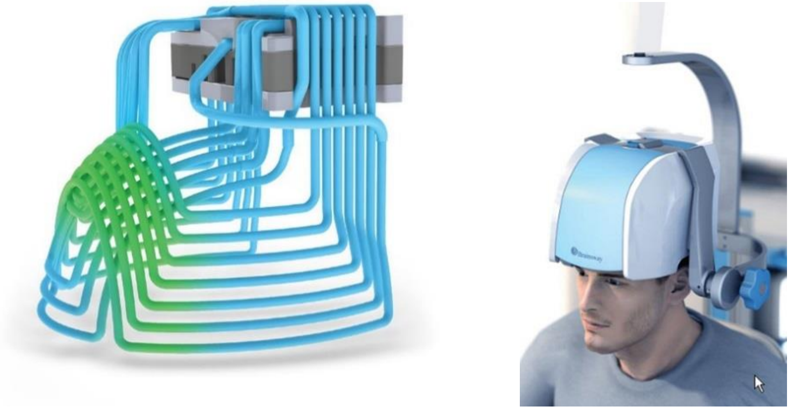


Figure 35. H-coil configuration used in deep TMS, used for stimulating deeper brain regions. These coils are usually mounted inside a helmed due to their size and are commonly used in clinical contexts. (© Brainsway Ltd.® 2014)

Stimulation protocols and parameters

The effectiveness of a TMS intervention, in the clinical practice or in research, will also depend on the stimulation protocol used, which will be comprised by a combination of the stimulation paradigm applied, the intensity delivered and the frequency of the stimulation.

Stimulation paradigm

In research contexts, TMS can be applied in online and offline paradigms. In the first one, the application of the stimulation is done concurrently to the administration of a task to the participant, and it is mainly used to deepen in the knowledge about the temporal implications of a delimited cerebral region over specific cognitive functions.

On the contrary, in the offline paradigm both aspects, stimulation and task, are dissociated, so the TMS and the task administration are not applied at the same time. This paradigm is used in order to know the effect of TMS beyond the stimulation period over a specific cognitive function.

Similarly, the TMS can also be used concurrently or dissociated in time with neuroimaging techniques, in order to acquire more knowledge about the effects of the application of stimulation on brain activity. The concurrent use of both techniques allows obtaining temporospatial information of the immediate effects of TMS on neural activity, since the neuroimaging shows, in real time, the changes induced by TMS in brain activation, both in the areas where the stimulation is applied and in the brain regions connected with them.

On the other hand, neuroimaging acquired before the application of the TMS is very useful for the guidance of a posterior stimulation, since a neuronavigation system can be used to apply the TMS in an exact cerebral location and hold said location throughout the duration of stimulation protocol, thus increasing the accuracy of the technique. Moreover, fMRI provides information about the activation pattern that exists during the performance of experimental tasks, which is very useful in basic neurosciences studies, since it helps us to define the optimum temporal window and spatial location to perform the stimulation.

Finally, neuroimaging can be acquired after the stimulation. This approach allows us to observe the patterns of brain activation induced by the stimulation protocol and can provide information about the functional reorganization processes potentiated by TMS. Since the TMS effects are temporally limited, the neuroimaging should be recorded as soon as possible to ensure that short-term effects are also captured.

Stimulation intensity

The clinician or experimenter can control the levels of energy that will flow through the TMS coil. In order to determine the suitable stimulation intensity, the motor threshold must be determined for each participant individually before the stimulation.

The motor threshold is defined as the lesser intensity needed to induce a motor evoked potential (MEP) of minimum amplitude, or a visible contraction of the first dorsal interosseus muscle of the hand in 50% of the trials, applying one single TMS pulse over the motor cortex.

Whether the muscle should be in resting state or slightly contracted, will depend on the stimulation protocol that will be applied afterword. In the case of the resting motor threshold, the amplitude of the MEP must be larger than 50 μV, whereas in the active motor threshold it must be higher than 100 μV (Rossini et al., 2015). The reason behind this difference is that a given stimulation intensity will have a bigger effect when it is applied to an active brain, compared to when the brain is in resting state. This phenomenon occurs because the applied magnetic stimulus evokes cortical synaptic activity, and such evocation is more effective when the postsynaptic neurons are active when the stimulus is applied. For this reason, the motor threshold is generally lower on an active state compared to resting state, since lower stimulation intensity is needed to obtain the same effect on the muscle.

It is important to note that the intensity of the induced current decreases significantly as it penetrates the brain. This is why it is only possible to directly stimulate cortical areas with TMS. Actually, it is not exactly an isolated brain region that we are stimulating, but a brain network, since the stimulation will also have an effect on cortical and subcortical areas structurally and functionally interconnected with the target region.

Stimulation frequency

Depending on the frequency of the magnetic pulses applied to the cortex, TMS can be classified into three main groups, which will produce different effects on brain activity and are used for different purposes.

a) Single-pulse TMS

In single-pulse TMS, a single magnetic field characterized by a very short duration is applied. Depending on its intensity, the pulse may be able to depolarize an entire population of neurons underneath the stimulation site and thus evoking a certain phenomenon (such as a movement or a perception) or create a transient alteration in brain activity. Therefore, if the stimulated area is required for the development of a particular cognitive task, its performance will be altered for a very brief period of time, since the single-pulse TMS will disrupt that neural network for a few milliseconds.

The temporal resolution of single-pulse TMS is excellent, making it a very suitable technique for the study of the mental chronometry in cognitive processes since it offers precise information about the moment in which a brain activity in a concrete area contributes to the execution of a specific task. Thus, applied over the motor cortex, TMS allows us to research the chronometry of the motor cortex involvement in the execution of motor sequences; applied over the somatosensory cortex, provides clues on the course of tactile perception; and applied over the occipital cortex, allows us to explore the chronometry of the detection and perception of visual stimuli, etc.

b) Paired-pulse TMS

In the paired-pulse TMS, several pulses of identical or different intensity are produced, separated by a variable inter-stimulus interval of several milliseconds, either in the same brain region (with a single stimulation coil) or in different cortical areas (using two or more coils). The production of two or more pulses in a specific cortical area improves the effectiveness of the technique and the duration of its effects, and induces short-term intracortical modulation and plasticity effects.

The application of paired pulses in different cortical areas allows the study of intracortical inhibition and facilitation circuits within the same cerebral hemisphere, as well as the study of interhemispheric connectivity.

c) Repetitive TMS

Repetitive TMS (rTMS) is characterized by the application of pulse trains whose frequency will be the main determinant of its effects. It uses a special type of stimulator that is able to deliver high-frequency pulses (1 to 20Hz) (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). Based on the pulse frequency and its effects on the motor cortex, it is often grouped into two main categories:

low and high-frequency rTMS, which will exert a different modulating effect on cortical excitability.

Broadly speaking, low-frequency or slow rTMS (≤ 1 Hz) (see Figure 36A) possesses an inhibitory effect in brain activity, while high-frequency or fast rTMS (>1 Hz) (see Figure 37B) tends to induce an increment in the cortical excitability of the stimulated area (Rossi et al., 2009).

A tradeoff of rTMS is its lower temporal resolution compared to single-pulse TMS, but that effect can be used to our benefit, since it will allow us to modify the excitability of the stimulated cortical area (either increasing or decreasing it) and more distal areas to which it is functionally linked (Paus & Barrett, 2004), allowing to study the pathway integrity. Therefore, it is a very useful technique for the localization of brain regions involved in a specific cognitive function.

Furthermore, this technique allows us to generate transient "virtual lesions", by selectively blocking during a period of time the specific neural networks responsible for certain cognitive functions (Pascual-Leone, Walsh, & Rothwell, 2000). This feature makes rTMS a very valuable tool in neuropsychological research since it will provide us the opportunity to gain more precise knowledge about neuropsychological syndromes that are described in clinical practice and offers the possibility of validating neuropsychological models of cerebral functioning proposed from a basic perspective. In addition, it allows extrapolating theoretical models based on animal research to a human perspective in a safe way.

Likewise, rTMS will enable studies with delayed paradigms, in which the magnetic stimulation and the execution of a task are temporally spaced, as the effects of rTMS last longer than the stimulation period. The duration of the effects depends on the stimulation protocol, the intensity of the magnetic field and the duration of the stimulation protocol that has been used (Di Lazzaro et al., 2011). In addition to this, the cognitive effects over the stimulated area can be due to the direct modulation of the area responsible for the cognitive function, but can also be achieved by stimulating or inhibiting a brain region which competes with the target cognitive function, or even by the indirect effects of stimulating an area which is functionally connected to the target region (Luber & Lisanby, 2014). Moreover, rTMS's ability to induce long-term modulation of the cortical excitability makes it possible to be used as a therapeutic approach in neurological, neuropsychological and psychiatric disorders associated with alterations in brain activity.

Low frequency rTMS

This modality is usually applied at 1Hz, although alternative protocols, ranging from 0.1 to 0.9Hz have been studied, using one single-pulse train lasting 10 to 20 minutes (see Figure 36). After the stimulation of the motor cortex, the MEP showed a reduced amplitude. However, its effects are not always as consistent as in high-frequency rTMS (de Jesus et al., 2014).

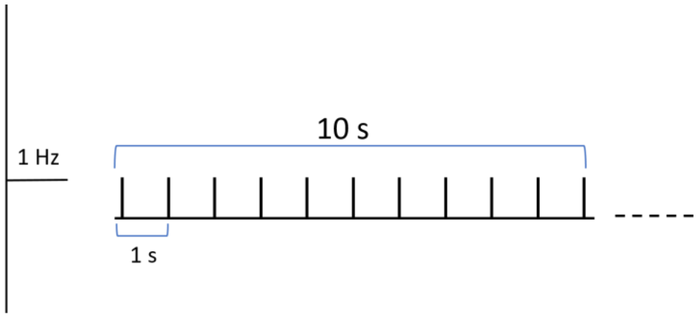


Figure 36. Representation of a low-frequency rTMS configuration at 1Hz. This rTMS modality tends to decrease cortical excitability, as measured over the motor cortex (Rossi et al., 2009).

High frequency rTMS

Frequencies from 5 to 20Hz (or even higher) are applied to the brain cortex in intensities ranging from subthreshold to 150% of the motor threshold (see Figure 37). Contrary to low-frequency rTMS, this variant achieves increased MEP amplitudes. The outlasting effects over brain excitability of this modality seem to depend on the intensity and the duration of the stimulation, being weaker when lower intensities are used. Furthermore, it seems that these effects and the intensity and number of pulses do not show a linear effect (Bear, 2003; Chen et al., 1997).

However, these excitatory and inhibitory effects that characterize high and low rTMS have been measured in the motor cortex and in clinical populations, and it is not entirely known if this data can be exported to other brain regions and in healthy participants.

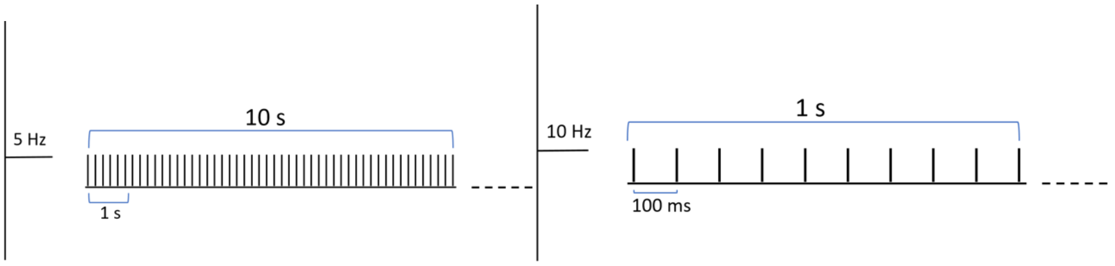


Figure 37. Representation of two high-frequency rTMS configurations, at 5Hz and 10Hz respectively. This rTMS modality tends to increase cortical excitability, as measured over the motor cortex (Rossi et al., 2009).

Theta Burst (TBS)

The theta burst stimulation protocol (TBS), developed by Huang et al. (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005), constitutes a rTMS paradigm that consists of trains of three pulses applied at 50Hz, up to a total of 600 pulses. This pattern of stimulation has been extensively used in basic neuroscientific research in order to induce plasticity through long-term potentiation (LTP) and long-term depression (LTD) in animal brain slices, and was adapted for its use in humans replicating the original pattern in TMS (Capocchi, Zampolini, & Larson, 1992; Larson & Lynch, 1989; Rose & Dunwiddie, 1986). While LTP involves the strengthening of the connection between two neurons, LTD has the opposite effect and induces the weakening of the connection between neurons. It is thought that these effects are achieved mainly through a modification of synaptic transmission ability. It is not clear whether a single stimulation session is enough to induce these LTP and LTD phenomena, although it is enough to induce excitatory or inhibitory effects on the cortex, lasting tens of minutes after the stimulation, with more consistent and longer lasting effects (Iezzi et al., 2011), and shorter stimulation times compared to classical rTMS protocols. When using a protocol consisting of several TBS sessions separated by a time interval, the excitability changes are greater than for each session separately (Goldsworthy, Pitcher, & Ridding, 2012). It is currently the TMS protocol that offers better results in eliciting sustained activation or inhibition in the human cortex, and due to its efficacy is one of the most used in research and the clinical practice. Following these principles, two paradigms have been developed that evoke opposite effects on the nervous system:

- **Continuous TBS (cTBS):** this paradigm was designed to evoke LTD-like effects and consists of trains of three pulses applied at 50Hz (repeated five times per second) in a continuous manner (see Figure 38), usually emitted at an intensity equivalent to the 80% of the active motor threshold (AMT). This entails that the total duration of the stimulation protocol is 40 seconds. Regarding the intensity, at 70% of the motor threshold, cTBS induces an electrical field of 50-80mV/mm. Although it was originally designed to be applied to the primary motor cortex, nowadays it is used in the stimulation of other cortical areas, obtaining similar effects.

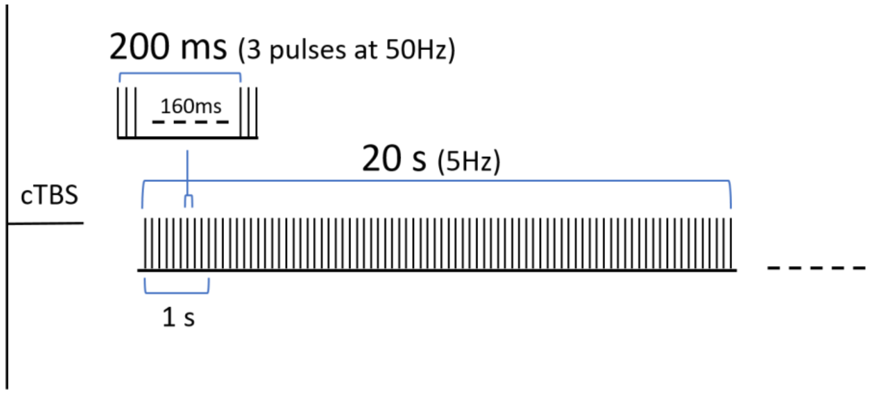


Figure 38. Schematic representation of the continuous Theta Burst Stimulation protocol (cTBS), where a single train of 600 pulses are delivered in bundles of 3 pulses at 50Hz, and each bundle repeated at 5Hz.

- **Intermittent TBS (iTBS):** this paradigm was designed to induce LTP-like effects and, unlike the continuous variation, in this paradigm the pulse trains last only 2 seconds and are spaced 8 seconds until the next train (see Figure 39). Therefore, the 3 pulses at 50Hz will be applied every 10 seconds, and the whole stimulation, equally consisting of 600 pulses, will take 200 seconds. Compared to cTBS, it seems that the intermittent paradigm shows longer-lasting effects over the cerebral cortex (Goldsworthy et al., 2012).

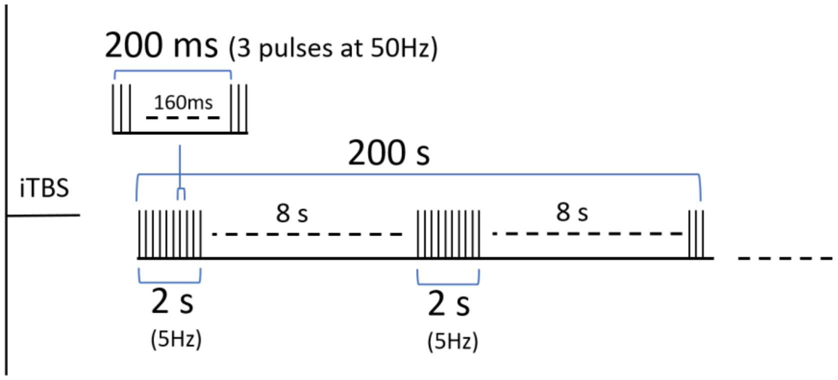


Figure 39. Schematic representation of the intermittent Theta Burst Stimulation protocol (iTBS), where an adapted stimulation of the protocol used for cTBS is temporally spaced. Every 10 seconds, the stimulation is applied during 2 seconds, followed by a resting interval of 8 seconds, until the 600 pulses have been delivered, lasting a total of 3 minutes and 20 seconds.

Overall, the main advantage of TBS over standard rTMS is the longer duration of its effects, up to 20 minutes for the iTBS modality and up to 60 minutes for the complete cTBS protocol (Suppa et al., 2016), with shorter stimulation times. However, even using these standardized protocols there are other factors that may affect cortical excitability, such as the time of the day, the release of cortisol, the shape of the coil, the intensity and direction of the current, the intrinsic brain activity during the stimulation (state-dependency), and interpersonal differences in response to the stimulation. All these are important aspects that should be controlled as far as possible in order to minimize the variability. Moreover, different brain regions might respond differently to the stimulation, so the excitatory/inhibitory effects observed in motor areas may not be always transferable to other areas. Evidence about the effects of these stimulation protocols in several brain regions is still needed to avoid unwanted paradoxical effects.

Long-term potentiation (LTP) and long-term depression (LTD)

The long-term effects of TMS, which are achieved by modulating lasting changes in corticospinal excitability, are thought to involve long-term potentiation/depression (LTP/LTD)-like effects on cortical synapses. TBS stimulation patterns are the key to determine the direction of change in synaptic efficiency.

It is likely that TBS stimulation produces a mixture of both excitatory and inhibitory effects, which may be responsible for the long-term changes. A model developed by Huang et al. (2011) aims to explain how these mechanisms lead to long-lasting changes in synaptic plasticity at a cellular level. The authors limit the scope to NMDA receptors of glutamatergic synapses since these are the type of receptors that are better understood.

Cortical activation leads to Ca2+ entry through the NMDA channel. The authors hypothesize that processes leading to LTP depend on the entry rate of Ca2+, while processes leading to LTD depend on the amount of Ca2+ that enter the neuron. TBS produces a mix of excitatory and inhibitory effects, leading to potentiation or depression, and its final outcome will depend on the net sum of these two effects.

This process is thought to be carried out in three stages: First, each burst of three pulses at 50Hz result in the build-up of a trigger factor (e.g. post-synaptic Ca2+ influx) that eventually leads to lasting changes in synaptic efficacy. The concentration of the trigger factor decays exponentially after each burst.

Secondly, the trigger factor leads to the production of a *facilitatory* or an *inhibitory* substance designed to be equivalent to activation of different types of protein kinases. The temporal pattern of Ca2+ influx is key for LTP induction, while the sustained level of Ca2+ is important for LTD. Therefore, the facilitation effect accumulates according to the rate of increase in the trigger factor, whereas the inhibition effect accumulates more slowly according to the overall level of the trigger factor, and both decay exponentially with time.

In the last stage, the final level of the two substances interacts with two corresponding slower processes that may be analogous to phosphorylation/dephosphorylation of membrane-bound ion channels responsible for the production of LTP/LTD. The net effect on cortical excitability is modeled as the sum of these positive and negative after-effects.

Therefore, following cTBS, suppression is larger than facilitation and the MEPs are suppressed for many minutes. The opposite occurs after iTBS, whilst after imTBS, suppression and facilitation are matched and there is virtually no net effect on MEP amplitudes.

2.3.2 Applications

2.3.2.1 TMS as a research tool

Since TMS allows in-vivo human brain research, it is possible to use the technique to study the cognitive, emotional and behavioral processes in humans. In addition, contrary to neuroimaging techniques that merely display a correlational image of the neural activity, TMS allows establishing causal effects.

In basic and clinical research, TMS can be used to study the chronometry of a specific brain function, the implication of different brain regions in a particular cognitive function, and to assess the function of intracortical and interhemispheric connectivity.

One relevant characteristic of TMS is the concept of *online interference* since TMS is able to facilitate or hinder the performance in a given cognitive process. In the most basic level, it consists on the temporal disruption of a cognitive function by modifying the activity of the neural region associated with the processing of the said function. In other words, it is a great alternative method to classical lesion studies, due to the possibility of generating *virtual patients* in healthy samples. Compared to these, *virtual lesions* have several advantages: a) they allow the use of healthy participants, discarding the problems that the clinical situation of a patient may cause. Secondly, they can be used to extract logical inferences on the brain functioning from simpler observations and contribute to theoretical cognitive models. Virtual lesions created with TMS are transitory and very specific (due to its spatial resolution), while lesions in clinical patients may cause both direct interferences on cognitive functions and compensatory effects that the patient develops over time, not knowing which ones correspond to the extent of the lesion. TMS can be repeated during several sessions, and carry out retests of the hypothesis in the same or different participants. Lastly, with TMS is possible to separate high-order cognitive functions to its more basic aspects, in order to study its components separately. On this point, it is worth mentioning that information processing, especially that of high-order functions, is often carried out by a network of nodes located in different sites across the brain, so stimulating just one specific node might not yield the expected effect.

2.3.2.2 TMS as a therapeutic tool

TMS represents a powerful tool in the treatment of disorders linked to the nervous system, particularly in neuropsychological rehabilitation, and to psychiatric disorders, and can effectively work as a complement for conventional therapeutic approaches.

The first clinical use of TMS was to assess the integrity of the corticospinal pathway. Taking the motor cortex as a reference, a MEP is measured in a series of body muscles. It is important to note that the threshold needed to evoke the MEP is different in each muscle; it is lower for the hand and forearm, and it rises as we move to proximal areas of the body and the lower limbs. In addition, the MEP can change from one session to the following, to an effort must be made in order to control all external factors that may modify this value.

The potential of rTMS resides in its capacity to induce changes in cortical excitability, by increasing the plastic capacity of the brain and facilitating the recovery or reorganization of the affected neural networks and restoring balance in brain interhemispheric interactions. TMS, therefore, acts as a guide for the natural plasticity processes in the brain, supporting those that result in adaptive changes and inhibiting those that could be disruptive. Therefore, it enables a better recovery or reorganization of the dysfunctional neural networks responsible for the altered cognitive function, since it contributes to reinforcing these networks. In any case, TMS should not constitute a treatment by itself, but a complement to improve the efficacy of a wider intervention. It is also important to assess if the improved brain functioning is temporally stable, as this will determine how the treatment protocol will be established for each condition and if it is clinically feasible.

The beneficial effects of TMS are dependent on the activation status of the stimulated area. The effects over a neural circuit will be greater when the circuit is active during the stimulation. For that reason, combining TMS and conventional cognitive rehabilitation seems the to be a very good option in order to provide a comprehensive approach in neuropsychological rehabilitation, achieving stronger effects than using the two treatments separately and reducing the time period required for the treatment, accelerating the patient's recovery.

The usefulness of TMS in cognitive rehabilitation lie on the fundamental principle that the brain has the ability to recover from damage by reorganizing its neural networks in order to maximize its recovery. Thus, altered cognitive functions after the onset of brain damage can be restored or compensated, at least partially, thanks to adaptive changes in neural circuits. This plastic capacity is influenced by a large number of factors, such as the location and extension of the injury, the stage of alteration, the age at which the damage occurred, the individual's cognitive reserve, etc. Therefore, the rehabilitation of cognitive acquired brain damage is an option with TMS. By means of this technique, it is possible to compensate interhemispheric imbalance, one of the agents causing deficits like aphasia or neglect, as well as directly stimulating the affected cortical area and surrounding regions to hasten the recovery of the altered function.

The use of TMS as a therapeutic tool for acquired or neurodegenerative brain damage has grown exponentially the last few years [see Lefaucheur et al. (2014) for a systematic review]. Recent research can be found dealing with the use of TMS as a therapeutic approach in Parkinson's disease, Alzheimer's dementia, traumatic brain injury, stroke and other neurological or neuropsychological disorders associated with cognitive impairment (C. Clark, Cole, Winter, Williams, & Grammer, 2015; Demirtas-Tatlidede, Vahabzadeh-Hagh, & Pascual-Leone, 2013; A. Evans, 2008; Luber & Lisanby, 2014; Wagle Shukla et al., 2015). However, there are still few conclusive results, since there is a need to improve the level of evidence based on a medical approach, providing double-blind, placebo-controlled and cross-over trials in order to obtain solid proof of the usefulness of TMS in these conditions.

Psychiatric disorders are also characterized by functional and structural neural imbalances that make them suitable for treatment using non-invasive brain stimulation. TMS has been used for over two decades in this regard, stimulating cortical areas related to impaired brain circuits and modulating their activity. When this procedure is applied repeatedly, it can result in long-term changes that interrupt the development of the disorder. Compared to pharmacological treatments, TMS shows less secondary effects and better treatment fidelity, and there is the possibility of combining the two treatments for better outcomes (Lefaucheur et al., 2014).

When developing treatment protocols for clinical conditions, it is important to assess which is the optimal procedure to follow. First, the stimulated target must be selected based on theoretical models of the condition as well as clinical experience. Whether or not a neuronavigation system is crucial for the treatment has to be determined, as it would greatly increase its price and complexity. The duration of the intervention must be set, since it is possible that the first effects start to appear a few weeks into the treatment, and studies using one or two-week protocols are usually insufficient to detect changes. Once the positive outcome of the intervention has been established, it is important to observe how long do these changes last. It is possible that less frequent follow-up stimulation sessions are required to maintain the beneficial effects of TMS over long periods of time (Lefaucheur et al., 2014).

Major depression is the most studied disorder in which TMS has been found effective and has been approved for the US Food and Drug Administration (FDA) for pharmacoresistant cases, being a viable alternative to the more invasive electroconvulsive therapy (Perera et al., 2016). Although the evidence is still not conclusive, there is ongoing research on the efficacy of TMS in other disorders, such as schizophrenia, bipolar disorder, anxiety disorders, post-traumatic stress disorder and substance abuse (Cristancho, Cristancho, & O'reardon, 2013).

2.3.2.3 TMS for cognitive enhancement

The improvement of cognitive processing has been one of the targets of non-invasive stimulation techniques, sometimes as part of the research design, sometimes as a standalone goal on its own. As has already been explained, there are several variables that will determine the effects of the stimulation using TMS, among them the location and parameters of the stimulation must be highlighted.

The first reports of cognitive enhancement are contemporary to the development of the technique, when some of the first research experiments with this technique evoked faster response times in simple reaction tasks (Pascual-Leone et al., 1992) and small effects (although non-significant) over memory (Pascual-Leone et al., 1993; Wassermann et al., 1996). It is thought that these effects were not a direct result of the stimulation on the cortex, but the change in reaction times could be explained by a general psychological attention effect (Terao et al., 1997). In any case, the number of articles reporting changes in cognitive performance using TMS is numerous.

At first, the effects of TMS were explained as an interfering activation of a population of neurons that altered the normal cognitive processing, acting, in practical terms, as a temporary virtual lesion. To explain the counterintuitive idea that this cognitive disruption could result in positive cognitive changes, it was speculated that TMS could selectively disrupt distracting or competing stimulus on a certain cognitive task, freeing resources relevant to that task in order to process the information more efficiently. This mechanism was termed *paradoxical facilitation* (Walsh et al. 1998). However, that was not a satisfactory explanation in cases where the stimulation target was thought to be a key area for the processing of a specific task, leading to think that TMS could not only induce a disruptive effect, but under some circumstances also a facilitating one, being determined not only by the location, but also by the precise stimulation parameters (frequency, duration, timing, etc.). In any case, in the early stages of TMS research, where the technique was used for its disruptive properties, improvements usually appeared as an unexpected side effect.

The review by Luber et al. (2014) provides a comprehensive account of instances of cognitive enhancement through TMS, ranging from faster processing speeds to improved performance in attention, memory, and language tasks. As that team observed, superior cognitive abilities could be achieved with different TMS paradigms, including single-pulse, paired-pulse, repetitive TMS (in either high or low frequencies) and TBS. Despite evoking different effects on the cerebral cortex, they achieve their enhancing effects through different mechanisms. These mechanisms can be grouped in three main classes, although these are only possible explanations for the observed effects of TMS and are not definitive categories: *nonspecific effects of TMS*, the *direct modulation of a cortical region or network* resulting in more efficient processing, and finally the *disruption of competing or distracting processing.*

Enhancement via nonspecific effects of TMS

This kind of enhancement is not produced by the direct effects of the TMS stimulation on the cortical processing of a task. On the contrary, these type of effects, called *intersensory facilitation* (or *multisensory integration*), occurs if the response to a stimulus, or a set of stimuli, from one sensory modality is in some way furthered by concurrent stimulation of one or more other sensory modalities (D. A.-E. Roth et al., 2012). Enhancements produced by this effect can occur in three ways: Faster reaction times, a lower sensory threshold for detecting stimuli, or an increased rate of stimuli recognition, identification or classification, or in qualities of these stimuli (such as brightness or loudness). In the case of TMS, when a pulse occurs temporally close to the onset of a stimulus that a participant must respond, a psychological effect not related to the momentary disruption of the stimulation may increase average response times. It can also occur in repeated TMS protocols, when the effects of the stimulation on the vertex (thought to be a control location with no cognitive effects) produced similar outcomes to other locations (which should be directly related to a task) but these effects did not happen in a group that did not receive TMS stimulation (e.g. (Campana, Cowey, & Walsh, 2002)). Even in offline TMS protocols, non-specific enhancement effects can be present. In these cases, some authors have theorized that the improvements could have been produced by a general state of arousal rather than the effects of the stimulation (Drager, Breitenstein, Helmke, Kamping, & Knecht, 2004).

Enhancement mechanism involved with direct TMS to task-related cortex

This is the most direct effect TMS can have over the neural activity needed to perform a task. Even simple-pulse designs have been found to be effective in enhancing performance, as a result of a potentiation of the local neural activity for a brief period. Already in some animal models, stimuli detection could be improved with a single direct electrical stimulation of neurons a few millisecond before the presentation of a target, suggesting that the additional neural activity brought the neural response to the stimulus above the threshold of awareness, explaining how TMS stimulation (in humans) could have equivalent effects (Grosbras & Paus, 2002).

Online repeated TMS paradigms have also been used to facilitate cortical processing. A proposed mechanism for that effect is based on the increase in excitatory post-synaptic potentials, a short-lived form of synaptic plasticity named *post-tetanic potentiation.* A competing explanation is based on the theory that rTMS trains are based on neural dynamics that mimic the oscillatory behavior in cortical integration, affecting the performance of several cognitive domains, with the potential to enhance it. For instance, a 2 second rTMS trains at the individual alpha frequency

(IAF) preceding a stimulus enhanced performance in a mental rotation task (Klimesch, Sauseng, & Gerloff, 2003). These effects are greatly dependent on the frequency of the TMS pulses as even slight variations can cause the opposite effect. It is possible that the optimum frequency differs from one cognitive function to the other, as the oscillatory behavior may vary, and the nature of the task can also affect the effectiveness of the stimulation (Romei, De Haas, Mok, & Driver, 2011). The theta rhythm (4-7Hz) may have a more global effect, affecting neural networks across large cerebral regions, and can have an effect on memory and attention (Sirota et al., 2008). A significant number of studies using 5Hz rTMS also achieved enhancement of executive functions, and this paradigm is nowadays frequently used to study cognitive enhancement.

On the other side, offline TMS paradigms offer longer lasting effects, ranging from a few minutes to up to 2 hours in some circumstances (Tegenthoff et al., 2005), compared to online models, and are known to improve performance when applied before a cognitive task. In this case, the persistence of the effects through a longer period of time can be indicative of LTP-like plasticity effects (Bliss, Collingridge, & Morris, 2003), but modulation of cortical inhibitory systems can also play a role (Funke & Benali, 2010). These effects have been observed in the motor and somatosensory cortex, and can be perceived with EEG techniques as an increased or decreased cortical activation. It is likely that improved performance following offline TMS stimulation is caused by Hebbian learning processes as a result of the facilitation in the co-activation of input neurons, changing the synaptic strength (Tegenthoff et al., 2005). Due to this principle, TMS has the potential to accelerate skill acquisition, by stimulating a cortical region associated with the skill together while that ability is exercised. Another advantage of offline TMS paradigms for cognitive enhancement is the relatively large temporal window in which the stimulation can be applied in order to observe improvements in skill performance. These improvements may occur before, during or after the stimulation period with satisfactory results (Thickbroom, 2007), and the enhanced skills can persist even beyond the cortical activity changes induced by the TMS (Boyd & Linsdell, 2009).

Evidence has shown that enhancement by directly stimulating the responsible cortical area can be achieved in a variety of TMS paradigms: single-pulse, a short train of pulses or multiple trains applied offline. Moreover, the best results are achieved when the stimulation is applied immediately before performance and high frequency rTMS paradigms are used (Luber & Lisanby, 2014). The exception are online TMS paradigms that apply the stimulation exactly during the cortical processing of a stimuli, which enhance performance based on a suggested *stochastic resonance* effect, where the stimulation provides a boost (by adding neural noise) to the detection or processing of a stimuli that otherwise would be too weak to be processed properly (Miniussi, Ruzzoli, & Walsh, 2010). For instance, applying the same TMS paradigm at different levels of the motor threshold could induce opposite effects in the participants, enhancing or disrupting the processing of a visual stimulus respective to a baseline (Schwarzkopf, Silvanto, & Rees, 2011).

When attempting to maximize the effects of the cortical stimulation for promoting the acquisition of a skill, the order in which the skill training and the stimulation are applied is a decisive factor. Animal studies in hypothalamic intracranial self-stimulation have shown that, after being trained in a particular skill and tested 24 hours later, those who received the stimulation immediately after the acquisition session had a better retention of the task, whereas the group that received stimulation right before the delayed testing session did not maintain the effects of the skill training (Redolar-Ripoll, Aldavert-Vera, Soriano-Mas, Segura-Torres, & Morgado-Bernal, 2002). The effects of TMS have also been found to be dependent on the time point in which the stimulation is applied, as demonstrate the cases where opposite effects (either facilitatory or disruptive) were achieved only changing the precise moment of the stimulation regarding a cognitive process. Generally speaking, when TMS is applied after the cognitive process, neural populations will be at a baseline level of activity, whereas during the cognitive process, involved neurons will be strongly activated and uninvolved regions may even be inhibited, and the stimulation will have an effect with the neurons under their current, imbalanced state (Silvanto & Muggleton, 2008). When a non-invasive brain stimulation is applied during or after a task or skill training, a state-dependent TMS approach is being used. It is important to know the fine functional, physiological, and anatomical properties of the networks being targeted with the stimulation since that will determine the most appropriate stimulation protocols for each case and the success in achieving significant behavioral changes (Romei, Thut, & Silvanto, 2016).

Enhancement via "addition-by-subtraction"

The third kind of mechanism for cognitive improvement is based on the principle that, by disrupting processes that compete or distract from the main task, the general performance is enhanced. TMS pulses can be applied to shortly disrupt cortical activity in a specific area responsible for processing a certain characteristic of a stimulus. For instance, in a visual search task where stimuli present a series of characteristics, such as motion and color, and the participant has to focus in one of them, it is possible to improve the baseline performance by inhibiting areas in the visual cortex responsible for processing the non-target feature (Walsh et a. 1998). In this regard, disruptive TMS protocols are commonly used. The 1Hz rTMS, which is thought to lower local cortical excitability, is a good candidate for producing performance enhancements though *addition-by-subtraction*. If the pulse trains are long enough (10-20 minutes), the effects can be comparable to a temporal lesion (Pascual-Leone, Bartrés-Faz, & Keenan, 1999). Another form of *addition-by-subtraction* enhancement, also studied with 1Hz rTMS, is in the form of cross-hemispheric inhibition (Hilgetag, Théoret, & Pascual-Leone, 2001). In this case, rTMS temporarily releases one of the hemispheres from excessive inhibition from the other, which in occasions can show hyperactivity when processing certain information, hindering the processing power. This kind of enhancement, which has been used extensively for the rehabilitation of stroke (by inhibiting the healthy hemisphere and therefore promoting a better functioning on the damaged one), can also be used for cognitive enhancement when the cognitive functions responsible for processing a stimulus possess some laterality. Many TMS protocols whose effect is to down-regulate cortical excitability can also be valid for cognitive enhancement through the addition-by-subtraction mechanism, such as cTBS (Kalla, Muggleton, Cowey, & Walsh, 2009) or higher frequencies such as short trains of pulses at 10Hz (Hayward, Goodwin, & Harmer, 2004) or 12Hz (Harris, Benito, Ruzzoli, & Miniussi, 2008). Therefore, addition-by-subtraction can be evoked by either disrupting ongoing processing with single-pulse TMS or high-frequency TMS, or by down-regulating the cortical excitability by using longer trains of 1Hz rTMS or continuous thetaburst TMS.

Overall, this mechanism works by "disrupting or inhibiting an inessential or less essential but competing part of one or more functional brain networks involved in a task resulting temporary network reorganization" (Luber & Lisanby, 2014).

Cognitive enhancement as a zero-sum proposition

Cognitive enhancement using non-invasive brain stimulation has been suggested to come at cost of the performance in other cognitive domains. Under that perspective, enhancements are not just an improvement on some cognitive functions, but a re-allotment of the already existing finite processing resources of the brain. That is, cognitive enhancement can be viewed within the framework of a zero-sum game (Brem, Fried, Horvath, Robertson, & Pascual-Leone, 2014; Luber, 2014).

A zero-sum game is a theoretical concept based on the physical principle of conservation of energy in a closed system. In such a game, the total gains among all the players equal zero, and if some players win a certain amount, the rest must compensate and therefore must have lost an equal amount. Extending this concept to cognitive processing, Brem et al. (2014) postulated that cognitive enhancements (gains) are balanced by costs within the system, implying that some other functions must have had a loss of performance. Strictly speaking, the brain cannot be considered a closed system, and that theoretical framework is more of an analogy, but it can be used to explain why some cognitive processes exhibit limited capacities. This is especially relevant in executive functions, where these constraints have been better studied, like the classic cocktail party effect, related to selective attention, and the 7±2 magic number, relying on working memory (Cherry, 1953; G. A. Miller, 1956).

The concept of the brain as a limited capacity phenomenon is not new, and analogies borrowing from computer science and economics were not uncommon in the preceding decades. Under this assumption, the central executive processor tries to allocate these resources in an optimal manner to provide a better performance. The way this processing power is deployed will result in different cost/benefit phenomena, the better studied of which is the speed-accuracy tradeoff, where response times are improved at the cost of lower precision on a task, and vice versa. This effect has been observed in non-invasive brain stimulation studies, for instance in detecting visual stimuli, that after applying inhibitory rTMS improved accuracy in the ipsilateral visual field, but reduced the accuracy in the contralateral hemifield (Hilgetag et al., 2001). In another case, when TMS was used to disrupt cortical activity related to motion processing in the presence of stimuli showing different features, those featuring motion were processed more slowly, while the rest (that did not include the motion variable) elicited faster response times (Walsh, Ellison, Battelli, & Cowey, 1998). These are two examples of how induced cognitive enhancement by TMS resulted in unexpected costs in other cognitive areas. This kind of cognitive enhancement has been termed *addition by subtraction* by Luber et al. (2014), and these authors were able to identify that almost half of the studies included in their review (26 out of 62) could be placed in this category. According to these authors, the mechanism behind "Addition by subtraction" lies in the inhibition or disruption of non-essential (or less essential) but competing parts of functional brain networks involved in a particular task, which ends up involving a temporal reorganization of these networks.

While the hypothesis does not contradict the zero-sum framework exposed previously, most of the time it is hard to identify the source of the cost. In some cases, an observed enhancement can be due to the disruption of a network responsible for an overlearn tendency (Oliveri et al., 2010), which resulted adaptive for a specific task, and participants became more efficient. While still presenting a cost, the overall result is positive, so it is safe to assure that not all costs derived from cognitive enhancement will translate as other impaired functions, especially if that means faster learning rates.

Whereas 26 out of 62 studies in the review by Luber et al. (2014) fitted this framework, the rest do not. These were studies characterized by the direct stimulation of the region responsible for processing a specific task. In these cases, the enhancement could be explained by the stimulation “adding” to the resources available for a task e.g. decreasing the threshold needed for detecting a stimulus, without the loss of resources in other functions (Miniussi et al., 2010).

In all these cases, the acute effects of non-invasive brain stimulation were examined, but if paradigms oriented towards producing long-term changes are desired, the zero-sum framework is not particularly useful. To produce these long-lasting improvements, the repeated application of non-invasive stimulation during several sessions is needed to achieve a cumulative effect (Thut & Pascual-Leone, 2010), but also the changes are more likely to be permanent if the stimulation is applied concurrently with a certain task, related to the stimulation target, so Hebbian synergies are created, improving the performance in that domain (Thickbroom, 2007). However, the optimal parameters for achieving long-term changes are still unknown, and only the sum of the evidence will help create more appropriate enhancement paradigms for accelerating the learning of desired skills (Luber & Lisanby, 2014).

The reason why these long-term changes are probably not suitable for the zero-sum paradigm is that the brain continually learns and reorganizes itself to deal with new situations. For example, the automation of complex behavior, such as driving, relieves resources from the executive processing networks, so they are able to process other information, effectively achieving some form of cognitive enhancement without implying an associated cost. By stimulating a brain that already is, in some way, improving itself, we are just taking advantage of these naturally occurring processes to further enhance cognition.

Cognitive enhancement of executive functions through TMS

The enhancement of cognitive functioning in healthy individuals with non-invasive brain stimulation has experienced a growing interest in the recent years. Compared to other brain stimulation techniques, such as tDCS, TMS has the advantage of having greater spatial and temporal resolution, and the possibility of combining its use with neuroimaging techniques in order to stimulate a very specific cortical region thought neuronavigation systems.

Thanks to the review by Luber and Lisanby (2014), the facilitating effects of TMS could have been categorized by cognitive functions and also by enhancement mechanism. A significant number of studies were successful in achieving an enhancement in executive control, which, for their nature, represent the higher-order cognitive functions and the ones closer to general intelligence.

Table 17 features a list of studies that used TMS to enhance different aspects of executive functions, stating the target region, the stimulation protocol, the targeted cognitive domain and the type improvement that was achieved.

As can be seen from the table, most studies use either single-pulse TMS, to disrupt cognitive processing during the completion of a task (online), more frequently, offline high-frequency (>10Hz) repetitive TMS used to increase cortical excitability prior to the cognitive assessment, in occasions, applied throughout several sessions.

The target regions for executive functioning enhancement were, unsurprisingly, those areas directly related to the processing of several aspects of these functions (see Figure 40). For instance, targeting prefrontal areas like the DLPFC is common, in either hemisphere, and is used as a target for the improvement of processes related to working memory, set switching and inhibition. Another prefrontal region, the OFC, is also commonly stimulated and was targeted to enhance visual and emotional short-term memory, as well as task switching and visual working memory. A related area, the ACC was targeted in some studies to enhance inhibition in the Stroop task. The stimulation of parietal areas was also present, and was used as a way to enhance specific components of executive tasks, such as phonological or spatial information.

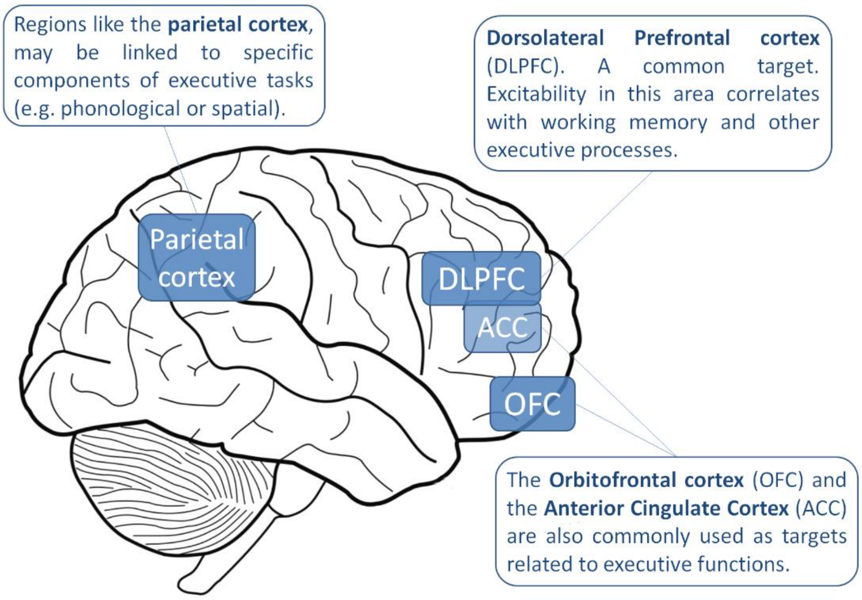


Figure 40. Main target regions for the enhancement of executive functions through TMS. Source: Palaus et al., (2015).

Most improvements were present in the form of faster response times, without any accuracy tradeoff, but a better accuracy or an improved overall performance were present in some cases, although the variability among studies was high. Overall, it seems feasible to use TMS to induce cognitive enhancement to executive functions, but results are far from consistent, and only in a few cases the general performance (often in the form of task accuracy) was improved, being faster response times a much more common outcome. The diversity of experimental designs used in the literature, the little sample sizes, the different targets for the stimulation and the different stimulation protocols may have had a big role on whether these executive changes were successful.

Reference	Domain	n	Region	Stimulation Protocol	Mode	Mechanism	Main findings
Boroojerdi et al. (2001)	Visual analogic reasoning	16	right PFC	rTMS 5Hz 90% MT	Offline	Direct cortical stimulation	Lower RT
Cattaneo et al. (2008)	Visual short-term memory	14	visual cortex (V1/V2)	TMS Single-pulse 65% MT	Online	Direct cortical stimulation	Lower RT
Evers et al. (2001)	Inhibition (go/no-go)	14	left & right DLPFC	rTMS 20Hz 95% MT	Offline	Direct cortical stimulation	Lower RT
Gaudeau-Bosma et al. (2013)	Working memory (n-back)	20	left DLPFC	rTMS 10Hz 110% MT	Offline	Direct cortical stimulation	No improvement
Hannula et al. (2010)	Tactile memory	6	middle frontal gyrus	TMS Single-pulse 120% MT	Online	Direct cortical stimulation	Lower RT
Hayward et al. (2004)	Inhibition (Stroop)	12	ACC	rTMS 10Hz 110% MT	Online	Addition-by-subtraction	Better performance
Hayward et al. (2007)	Inhibition (Stroop)	7	ACC	rTMS 10Hz 110% MT	Online	Direct cortical stimulation	Better performance
Hwang et al. (2010)	Inhibition / vigilance (Continuous performance test)	17	left DLPFC	rTMS 10Hz 90% MT	Offline	Direct cortical stimulation	Better accuracy
Jahanshahi et al. (1998)	Working memory (Number generation)	11	left DLPFC	rTMS 20Hz 100% MT	Online	Direct cortical stimulation	Better performance
Kirschen et al. (2006)	Verbal working memory	30	left inferior parietal	TMS Single-pulse 120% MT	Online	Addition-by-subtraction	Better accuracy & Lower RT
Luber et al. (2007)	Visual working memory	44	left DLPFC & midline parietal cortex	rTMS 5Hz 100% MT	Online	Direct cortical stimulation	Lower RT

Reference	**Domain**	**n**	**Region**	**Stimulation Protocol**	**Mode**	**Mechanism**	**Main findings**
Luber et al. (2008)	Visual working memory	17	upper left middle occipital gyrus & midline parietal cortex	rTMS 5HZ 100% MT	Online	Direct cortical stimulation	Lower RT
Luber et al. (2013)	Visual working memory, task switching	27	left OFC	rTMS 5HZ 100% MT	Online	Direct cortical stimulation	Lower RT
Sauseng et al. (2009)	Visual short-term memory	21	right/left PPC	rTMS 10Hz 110% MT	Online	Addition-by-subtraction	Better accuracy
Schutter & van Honk (2006)	Visual/Emotional short-term memory	12	left OFC	rTMS 1Hz 80% MT	Offline	Addition-by-subtraction	Better accuracy
Vanderhasselt et al. (2006b)	Set switching	22	right DLPFC	rTMS 10Hz 110% MT	Offline	Direct cortical stimulation	Lower RT
Vanderhasselt et al. (2006a)	Inhibition (Stroop)	28	left DLPFC	rTMS 10Hz 110% MT	Offline	Direct cortical stimulation	Lower RT
Vanderhasselt et al. (2007)	Inhibition (Stroop)	20	right DLPFC	rTMS 10Hz 110% MT	Offline	Direct cortical stimulation	Lower RT
Yamanaka et al. (2010)	Spatial working memory	52	right/left PC (P4)	rTMS 5Hz 100% MT	Online	Direct cortical stimulation	Lower RT
Yamanaka et al. (2014)	Spatial working memory	38	right/left PC (P4)	rTMS 5Hz 100% MT	Online	Direct cortical stimulation	No improvement

Table 17. Studies that dealt with cognitive enhancement in healthy individuals with effects over the executive functions. Source: (Luber & Lisanby, 2014; Palaus et al., 2015)

3. Experimental work

3.1 Objectives and hypothesis

In the previous sections, two methods for inducing changes in the brain and its cognitive functions have been explored: video games, and non-invasive brain stimulation techniques. Both are relatively new techniques in neuroscience that currently enjoy a moment of popularity as research tools. In spite of this, they rarely have been used together. One of the few cases was the study developed by Anguera et al. (2013) in which they used a custom-made racing video game paired with TMS in older adults, successfully enhancing cognition and achieving near and far-transfer effects.

Having reviewed the neural effects of video game and knowing how they can be used for cognitive enhancement, together with the optimum parameters for TMS stimulation to modulate cortical activity, leads us to assume that non-invasive brain stimulation may show a positive interaction effect when used in conjunction with a video game training. This could be especially notorious when applying TMS to the target area where the video game training has its main effect. Therefore, the two techniques used together would be able to evoke synergistic effects, potentiating the action of the two already effective separate interventions.

3.1.1 Objectives

The main objective of this research is to study, in healthy young adults, the combined effects of video game training and rTMS (and more specifically the iTBS protocol) in enhancing cognitive functions, with a special focus on the executive functions.

The specific objectives to be achieved are as follows:

- To demonstrate the effectiveness of the intervention in improving cognitive functions by directly strengthening specific neuropsychological processes linked to the cognitive skills targeted during the video game training (near-transfer).
- To demonstrate the effectiveness of the intervention in improving cognitive functions, facilitating the learning and consolidation of new cognitive skills, by exploring the degree of generalization to other cognitive functions (far-transfer).
- To demonstrate that synergistic effect of the two components of the intervention (iTBS and video game training) applied together lead to greater cognitive enhancement, in near and far-transfer.
- To identify the variables that act as predictors of cognitive improvement after the intervention.

3.1.2 Hypotheses

The following hypotheses are proposed:

- Participants who undergo active iTBS stimulation combined with video game training will show more near-transfer improvement effects, as assessed by an analogous video game task, compared to the control group.
- Participants who undergo active iTBS stimulation combined with video game training will show better performance in processing speed compared to the control.
- Participants who undergo active iTBS stimulation combined with video game training will show better performance in attention compared to the control.
- Participants who undergo active iTBS stimulation combined with video game training will show better performance in visuospatial skills compared to the control.
- Participants who undergo active iTBS stimulation combined with video game training will show better performance in executive functions compared to the control.
- Participants who undergo active iTBS stimulation combined with video game training will show better performance in measures of general intelligence compared to the control group.

3.2 Methods

3.2.1 Participants

32 participants took part in this research. All but five completed all the phases of the study. Of those who interrupted their participation, two of them did it because discomfort during the stimulation, two more due to incompatibility of schedules, and one because of personal reasons.

The final sample was composed of 27 participants (14 women [51.9%] and 13 men [48.1%]), aged 18-40 (29.44±6.28). All of them were healthy individuals and met the inclusion criteria for participation (see below) and for both MRI and TMS (see annex 8.1 and 8.2 for more details).

The inclusion and exclusion criteria for participation in the study are the following:

- Male and female participants.
- Age ranging from 18 to 40 years.
- Free from any mental illness or cognitive impairment.
- Not being regular video game users (< 3h per week) for the last 6 months.
- Had never played the specific game used during the training (*Super Mario 64*) or any of its sequels (*Super Mario Sunshine*/*Galaxy*) in the 3D platform genre.

The reason behind the current three hour per week video game usage limit is rooted in the literature. It is common to establish a cut-off point for selecting low or non-video game players in order to avoid the possible confounding effects of current video game play when the experimental procedure includes video game training. In this case, 3h per week is a common threshold for studies researching the cognitive effects of video game training (e.g. Maclin et al., 2011; Mathewson et al., 2012; Voss et al., 2012). In addition, the sampling process excluded those participants who had ever played the target video game used in this study, or games directly related to it, since there is the risk that the expected cognitive changes after the training period may have been already potentiated by a previous experience in this specific video game or its sequels.

In the final sample, 19 of the 27 participants had not played at all for the last six months before their participation. Of those who played, five of them played up to 1 hour per week, and three played from 1.5 to 2.5 hours per week, but only casual games (e.g. *Candy Crush* or *Clash of Clans*).

3.2.2 Experimental design

The present research was conducted through an experimental randomized 2x2 factorial design with repeated measures.

Each participant was randomly assigned to one of the two experimental groups based on the TMS stimulation conditions: active iTBS and sham stimulation groups. This is a between-subject study, so participants that were assigned to one experimental condition did not take part in the other.

After analyzing the data taking into account these two groups, we decide to divide them into four groups, in order to find more meaningful results. Based on previous literature (see Palaus et al., 2017), a logistic regression model was performed (see section 3.3.5) in order to identify the best predictors of the cognitive improvement after the training. Considering age, gender and previous video game experience as possible predictor variables, results showed that participant's previous video game experience was the strongest predictor of cognitive changes related to executive functioning (see section 3.3.2).

In this regard, previous video game experience was defined as having played regularly at least during some period in their life following the following criteria:

- More than 3 hours per week.
- Starting before adolescence (14 years old or younger).
- Playing for extended periods of time (sustained for at least one year).

For this reason, the previous video game experience was incorporated as a new independent variable in the experimental design. Experienced video game players (*Exp*) were considered all participants that met the previous criteria (n=12), while the rest were classified as non-experienced video game players (*NoExp*) (n=15). Among experienced players, five of them had played for more than two hours a day (up to eight hours a day) while the rest spent about three to five hours per week playing video games. The regular video game play during the lifespan was also relevant, most of them starting in early childhood (around six years old) and while some of them stopped playing regularly after adolescence (three of them), the rest of them continued playing until early adulthood. Considering the non-experienced group, most of them had played either sporadically at some point of their life (usually on a weekly basis), during short timespans (one to four years) or starting past adolescence.

Since the TMS stimulation modality is a variable that was manipulated and assigned randomly to the participants, the study follows an *experimental design.* As one of the independent variables is manipulated but the other is a personal variable, it constitutes a *P x E (Person by Environment) factorial design.* Each independent variable contains two levels (active or sham stimulation, and high or low video game experience), therefore, being a 2 x 2 design with four total conditions (see Table 24). Each condition has been applied to a different group of subjects, and none of them participated in more than one condition, thus constituting a *between-subject design.*

Finally, the effects of the independent variables over the dependent variables have been measured at three different time points, therefore constituting a *repeated measures model.*

Uniting all the above, this study can be characterized as a randomized factorial design with repeated measures.

		Video game experience	
		Non-experienced (NoExp)	**Experienced (Exp)**
Stimulation type	**Sham iTBS**	Sham iTBS / Non-experienced	Sham iTBS / Experienced
	Active iTBS	Active iTBS / Non-experienced	Active iTBS / Experienced

Table 18. Factorial matrix displaying the two independent variables compared in the study.

3.2.3 Materials

The materials required for this experiment can be grouped into three categories:

First, for the neuropsychological assessment, selected tests (mainly focused on executive functioning) were used. All the employed tests have been developed or adapted on purpose for this research, although they are based on standard neuropsychological tasks (see the Neuropsychological assessment sections in 3.2.4.2 and 3.2.4.4). All the tests, but one, were electronically applied using a desktop computer with a 17" CRT screen, 85Hz and a standard QWERTY keyboard, and displayed through the E-Prime Studio software.

Secondly, the video game employed to perform the training was *Super Mario 64* for Nintendo 64 console, the same video game used in previous studies (Kühn et al., 2014, 2013) in order to preserve its validity. Due to the game being released almost 20 years ago and the impossibility of finding the original system and adapting it to our experimental conditions, an emulator software was used, which allowed for the creation of different save states for each participant, and its syncing between the different computers of the Cognitive NeuroLab, where the whole study was carried out. Participants played the video game using an original Nintendo 64 controller, connected to the computer using a USB adapter. During the pre and post-assessment sessions, a spin-off of the game, called *Super Mario Star Road* was employed.

Finally, in third place, the Cognitive NeuroLab infrastructure counts with all the required equipment necessary for the application of the TMS:

- Transcranial magnetic stimulator system (TMS) *Magstim Super-Rapid Stimulator 2* (Magstim, Whitland, Dyfed, UK).
- 70mm figure-of-eight TMS coil.
- Neuronavigation system in order to precisely localize the stimulation sites, including a Brainsight frameless stereotaxic system (Rogue Research, Montreal, Canada) and an infrared tracking System (Polaris, NorthernDigital, Waterloo, Canada).

3.2.4 Procedure

This section provides a systematic description of the procedure of the research, including the schedule of the assessment and training sessions, the specific parameters of the structural MRI, a detailed account of the neuropsychological battery used for assessing the participant's cognitive performance, and the TMS stimulation parameters.

A timeline overview of the whole experimental procedure is presented in figure 41. In addition, Table 19 includes a timeline of the experimental stages following the SPIRIT recommendations (Chan et al., 2013). These stages and all the procedures they contain are explained in detail in the sections below.

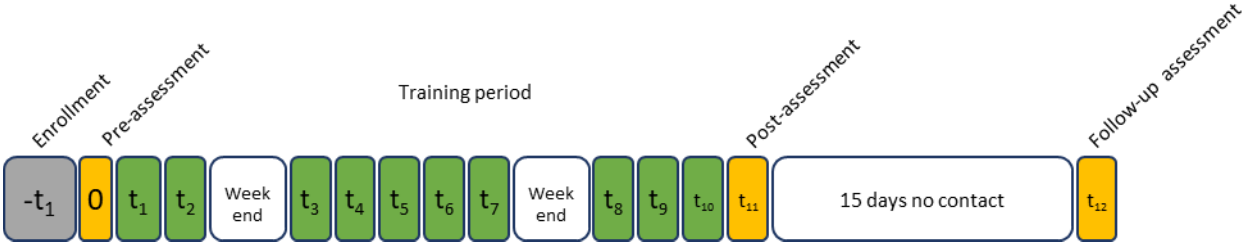


Figure 41. Timeline overview of the whole experimental procedure for this study. Elements in orange correspond to the cognitive assessments and elements in blue-green correspond to the video game training and TMS sessions.

	STUDY PERIOD						
	Enrollment	**Pre-assessment**	**Training period**			**Post-assessment**	
TIMEPOINT	t_{-1}	**0**	t_1	t_2- t_9	t_{10}	t_{11} (post)	t_{12} (15 day follow-up)
RECRUITMENT AND ALLOCATION							
Eligibility screening	X						
Magnetic resonance imaging	X						
Informed consent		X					
Socio-demographic and video game usage data collection		X					
Group allocation		X					
TRAINING PERIOD							
1.5h Video game play			◆—	—	—◆		
TMS administration			◆—	—	—◆		
ASSESSMENTS:							
Active motor threshold			X				
TMS screening			X	X	X		
Video game survey			X	X	X		
Beck depression inventory		X				X	
Mini Mental State Examination			X	X	X		
Reaction time tasks		X				X	X
Raven's progressive matrices		X				X	
3-Back task		X				X	X
Mental rotation task		X				X	X
Digit span tasks		X				X	X
Five-Point test						X	
Stop-switching task		X				X	X
Matchstick task						X	
Video gaming skills		X				X	

Table 19. Schedule of the experiment following SPIRIT recommendations (Chan et al., 2013).

3.2.4.1 Enrollment

Participants were recruited from a number of means: informative posters and leaflets were displayed at the *Universitat Oberta de Catalunya* (UOC), the *Universitat de Barcelona* (UB), the *Universitat Autònoma de Barcelona (UAB)*, and the *Hospital de la Santa Creu i Sant Pau* in Barcelona. University students and personnel were also informed in person, through email, and using social networks. In order to take part in the experiment, each subject signed a written informed consent describing all the procedures that were carried out during the research, as well as any possible health risk and safety hazard (see the informed consent form in Annex 8.3).

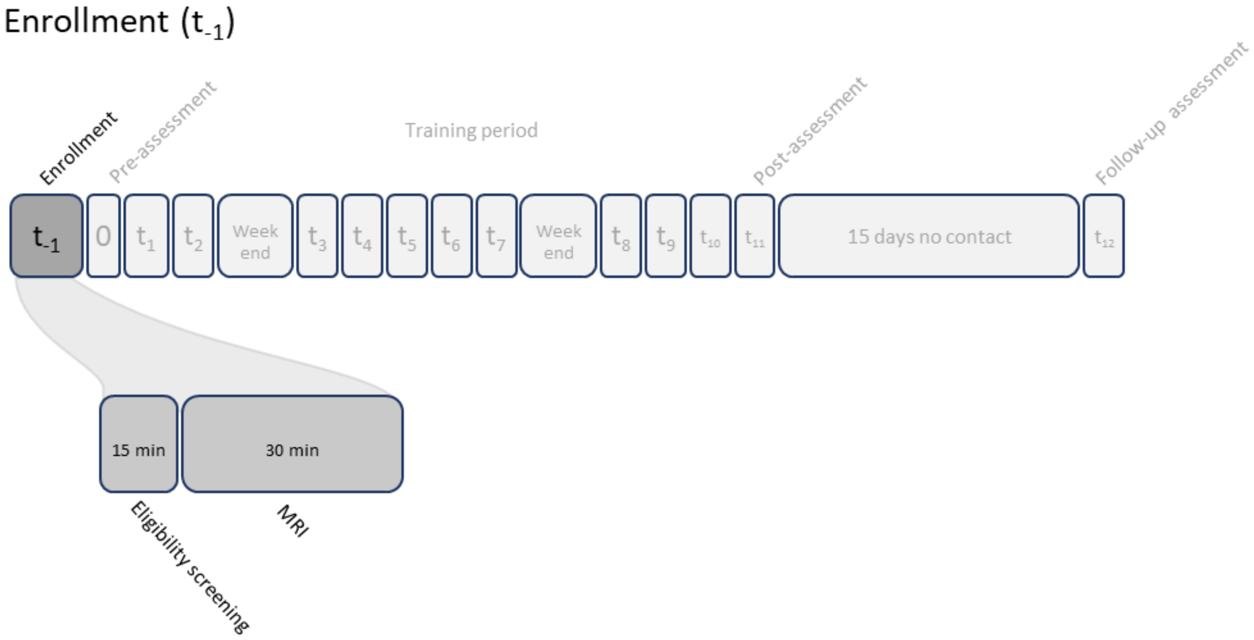


Figure 42. Timeline of the enrollment stage (t-1), including the eligibility screening and the acquisition of the structural MRI.

Eligibility screening

Upon contacting each participant, they completed an online form containing questions regarding the inclusion and exclusion criteria for participation. The form included demographic aspects, the level of exposure to the training video game, current video game usage, health conditions, and an exhaustive list of criteria related to their ability to undergo MRI and TMS (see sections 8.1 and 8.2 in the annex).

Magnetic resonance imaging acquisition

In order to detect any possible structural brain anomaly that could act as exclusion criteria for the TMS stimulation, and to use the neuronavigator to precisely locate the stimulation point, a structural MRI scan was obtained for each participant.

A first batch of participants was scanned using a Siemens MAGNETOM Essenza MRI Scanner, with a 1.5 Tesla magnetic field at the *Hospital de Mollet del Vallès.* A 3D T1 multiplanar reconstruction (MPR) transversal sequence was acquired, with a 256x256-resolution matrix and a 256mm field of view (FOV). Each slice had a 1mm thickness and had a 50% distance factor (spacing between slices). The repetition time (TR) was 1930ms and the echo time (TE) lasted

5.12ms, with a total acquisition time (TA) of 5 minutes and 8 seconds. The phase encoding direction was right to left (ROW), with a sagittal orientation.

Due to the relocation of the laboratory, a later batch of participants was scanned using a Philips Medical Systems Achieva 401, with a 1.5 Tesla magnetic field at the *Hospital de la Santa Creu i Sant Pau*. A 3D T1 multiplanar reconstruction (MPR) transversal sequence was also acquired, with a 256x256-resolution matrix, with a voxel size of 0.9375x0.9375mm and an 8° flip angle. 180 slices were captured, and each slice had a 1mm thickness and had a 1mm spacing between slices. The repetition time (TR) was 8.230ms and the echo time (TE) lasted 3.794ms. The phase encoding direction was right to left (ROW), with a sagittal orientation.

An informed consent, provided by the Radiology Service of the hospitals, was signed by all participants before acquiring the resonance image.

3.2.4.2 Pre-assessment

The pre-assessment stage included explaining the experiment to the participants in detail, signing the consent form, allocating them randomly to the experimental group, interviewing participants about their gaming habits and performing the baseline cognitive assessment. In total, the pre-assessment had an approximate duration of 130 minutes. A detailed account of the procedures carried out during the pre-assessment stage can be seen in Figure 43.

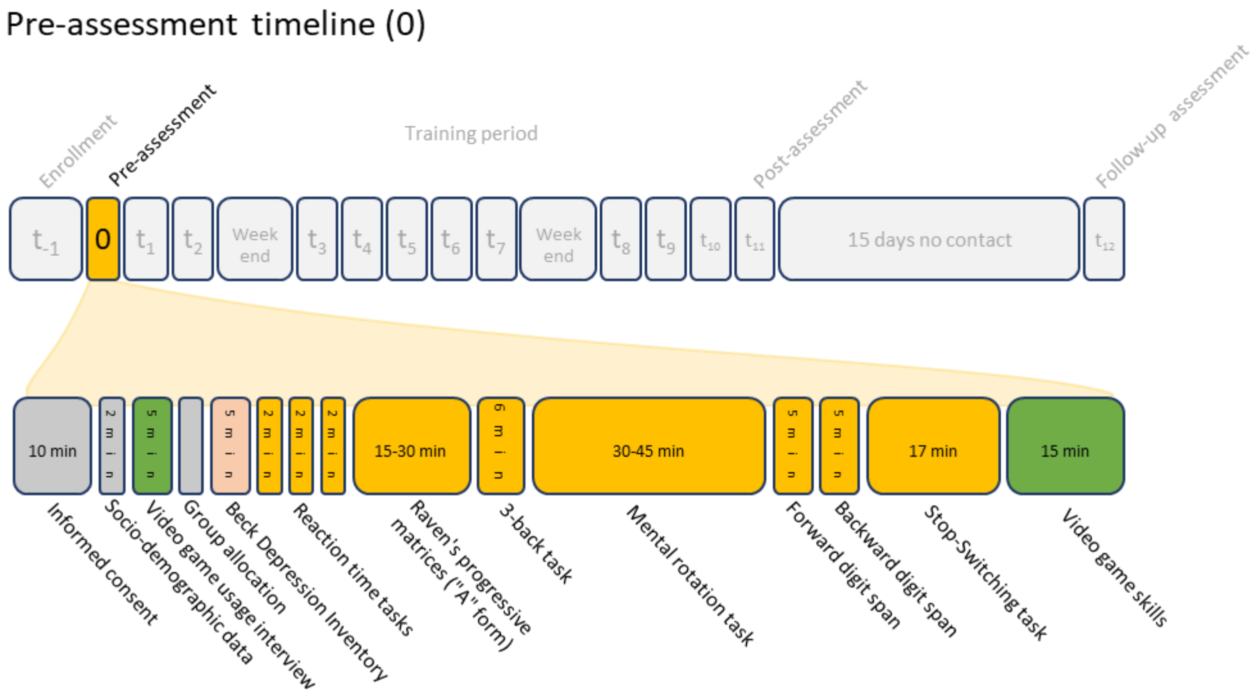


Figure 43. Timeline of the pre-intervention assessment stage. Elements in yellow correspond to the cognitive assessments and elements in green correspond to aspects related to video gaming.

Informed consent

The full informed consent form that subjects signed prior to their participation can be seen in Section 8.3 in the annex. It emphasized the voluntary aspect of the participation, the structure of the study, the possible side-effects of the non-invasive brain stimulation, and details about the confidentiality of the data.

Ethical and legal aspects

Patients' participation was voluntary, after being informed about the objectives of the study and after signing the consent form. The participants were free to withdraw from the study at any time. The researchers agreed to respect all the established current legislation regarding clinical research (WMA Declaration of Helsinki, 2004; Law 41/2002 on patient autonomy). This project was also approved by the Ethics Committee of the Universitat Oberta de Catalunya (UOC).

In accordance with Organic Law 15/1999 on the Protection of Personal Data, any data collected from the participants was treated with strict confidentiality. A coded identification (ID) of sequential numbers and combination of letters was used for all results and data acquired. The only nominal identification appeared on the informed consent.

Possible risks, side effects and discomforts

TMS has been used in research for more than 20 years and safety guidelines have been developed. In this study, all the all safety recommendations for the TMS protocol used are followed (Rossi et al., 2009). Although following safety recommendations, some side effects may occur (see Section 8.3).

Although TMS has been used worldwide since 1984, there could be complications that are as yet unknown. For this reason, a doctor was always on call during application of the TMS to decide what steps were to be taken in case of the occurrence of any side effects.

Socio-demographic, video game usage and mood data collection

Once participants were selected for their participation, their demographic information (age, gender, and level of education) was recorded and they were briefly interviewed in order obtain a general perspective of their video gaming habits. Using a structured interview with open questions, we tried to cover all aspects which have been found relevant in the literature regarding video game experience. We first started by asking them if they currently play any video game, explicitly including any casual games (played in a web browser or on a mobile phone), and how often did they play. Next, we asked if they possessed any video consoles at home or a computer they used for playing. Following that, we asked about past video gaming habits. We grouped the answers into two categories, whether they played before and after the adolescence (using the cut-line of 12 years old in ambiguous responses). For both categories, we asked participants about the age of start and whether they played on a regular basis or just occasionally, to see whether they could have been considered casual, core or hardcore gamers at each point of their lives. In addition to this, we also asked about the genres of the video games that they have played during their life and wrote down any specific game title that they mentioned during the interview. Aggregating all this information, participants were classified between experienced and non-experienced video game players, where the most decisive factor was whether or not had been core or hardcore players before adolescence.

In order to observe any possible effects of the stimulation on the participant’s mood, the Spanish adapted version of the Beck Depression Inventory (BDI-II) (Beck, 1972; Beck, Steer, Ball, &

Ranieri, 1996; Sanz, J., García-Vera, M. P., Espinosa, R., Fortún, M., & Vázquez, 2005), which is part of the recommended safety guidelines, was applied on the first and last sessions.

Group allocation

The allocation to the different experimental groups was performed at this point. The assignment to the sham or active iTBS groups was done with the help of a computerized random number generator that divided the sample in two random groups. Regarding the assignment to the experienced or non-experienced video game player groups within each experimental group, participants were separated according to the criteria related to previous video game usage (see section 3.2.2), taking into account the answers in the guided interview.

Neuropsychological assessment

A neuropsychological battery was designed to cover a wide range of cognitive processes, including processing speed, attention, visuospatial processing, executive functions, and general intelligence. All tasks except the 5-point test were adapted to an electronic format using the E-prime computerized experiment suite in order to obtain more precise measurements. Responses were registered using a standard computer keyboard, and the tasks were presented in a 17" CRT monitor, that according to E-Prime recommendations provide faster refresh rates that result in more accurate response times. Responses were introduced in a consistent manner by the same keys across all tasks, where the letter J always acted as an affirmative response, and K as the negative. Additional keys, such as the spacebar or the numerical keypad, were used in the tasks that required it.

Participants were assessed at three time points during their participation in the experiment: before the training, after the end of the training, and two weeks after the end of the training. Not all the tasks were used in the three assessments; those suffering from significant learning effects and lacking parallel versions were omitted in the third assessment. While the two first assessments were designed to be completed in around one hour and a half, the third one was shorter, lasting around one hour (see the list of tasks in the application order in Table 20).

Task	Domain	Time
Simple Reaction Time	Processing speed	2 min
Direction Choice Reaction Time	Processing speed	2 min
Color Choice Reaction Time	Processing speed	2 min
Raven's Progressive Matrices	Abstract reasoning / Fluid intelligence	15-30 min
3-back	Working memory	6 min
Mental Rotation	Visuospatial processing	30-45 min
Forward Digit Span	Attentional / Memory span	5 min
Backward Digit Span	Attentional span / Working memory	5 min
5-point test	Executive functions (design fluency)	3 min
Stop- Switching	Executive functions (inhibition / task switching)	17 min
Matchstick	General intelligence (insight problem solving)	10-20 min

Table 20. Neuropsychological assessment protocol applied at three time points during the participation in the experiment.

Reaction time tasks

The neuropsychological battery started by testing visual processing speed in three different tasks. Since reaction times are a component of virtually any cognitive task (Romei et al., 2016), measuring simple and choice reaction times may be useful for getting an estimation of each participant's average processing speed through a sensory-motor response. While simple reaction times offer us a basic processing speed measure, choice reaction times, also take into account the delay originating from the participant's decision.

The simple reaction time task was designed to measure the minimal time needed to respond to a stimulus, and it is considered a basic measure of processing speed. At the beginning of each trial, the participant was presented a fixation point in a dark background. After a brief pause (that varies from 1100 to 3100ms), a five-centimeter-wide white circumference appeared in the middle of the screen that remains on the screen until the participant responded. The participant was instructed to press the letter J with the right index finger as soon as possible (see Figure 44).

In the choice reaction task the same stimulus was presented on the left or the right side of the screen. The participant had to press J (left) or K (right) as quick as possible depending on where it appeared.

The color reaction time task was also a choice reaction time task, where the stimulus appeared in the center of the screen but it could be blue or red instead of white. Again, the participant had to press J (blue) or K (red) with their index and middle fingers of their right hand, respectively, regardless of their hand dominance, according to the color of the stimulus. This created an additional difficulty since the position of the keys is not intuitive of the characteristics of the stimulus presented on the screen and the participant had to remember and process that information.

The three tasks were preceded by the instructions that were presented on the screen, showing examples of the stimuli they should expect and which keys they had to press in each case. Each task was composed of 20 trials, where a response was required for each one of them, and the target appeared randomly after four fixed intervals (1100, 1700, 2300 and 3100ms) in order to avoid the participant anticipating the appearance of the stimulus based on a fixed rhythm. The reaction time after each target was presented was measured in milliseconds. Each of the reaction time tasks took about 1 minute to complete. Regarding the data analysis, the first trial was not included since its reaction times could not be representative of the rest of the participant's performance due to the unexpected factor at the beginning of starting the task.

En esta tarea aparecerá el siguiente estímulo repetidamente:

Tu objetivo consiste en pulsar la tecla

J

lo más rápidamente posible en cuanto aparezca el estímulo.

Pulsa cualquier tecla para empezar

En el centro de la pantalla aparecerán los siguientes estímulos aleatoriamente:

Debes responder lo más rápidamente posible en cuanto aparezca uno de ellos:

Pulsando J si el estímulo es de color azul.

Pulsando K si el estímulo es de color rojo.

Pulsa cualquier tecla para empezar

Figure 44. Instructions screen for the simple and color choice reaction time tasks. During the tasks, only the white or blue/red circumference appeared at the center of the screen at irregular intervals.

Simple reaction time latencies have shown correlation with measures of fluid intelligence (Sheppard & Vernon, 2008).

Raven's progressive matrices

In order to obtain a measure of the participant's abstract reasoning, an indicator of fluid intelligence, a modified version of the Raven's Standard Progressive Matrices (Raven, 1936; Raven & Court, 2014) was used. Designed to provide a value of the G factor, it is not as affected by the educational attainment of the participant as other intelligence tests that deliberately include measures assessing crystallized intelligence. It is designed as a non-verbal test composed of 60 items grouped in 5 sets, which generally appear in order of increasing difficulty. In order to suit the task to our assessment, the test was divided into two 31-item parts balanced in difficulty. The first 31-item group (form A) was presented in the pre-training assessment and the other (form B) in the post-training assessment.

Each item maintained the format of the original test, being composed by a design where a fragment was always missing, and several response options (6 to 9) were shown at the bottom of the screen (see Figure 45). Each possible option was numbered and the participant had to select the missing piece that completed the main pattern using the numerical keypad.

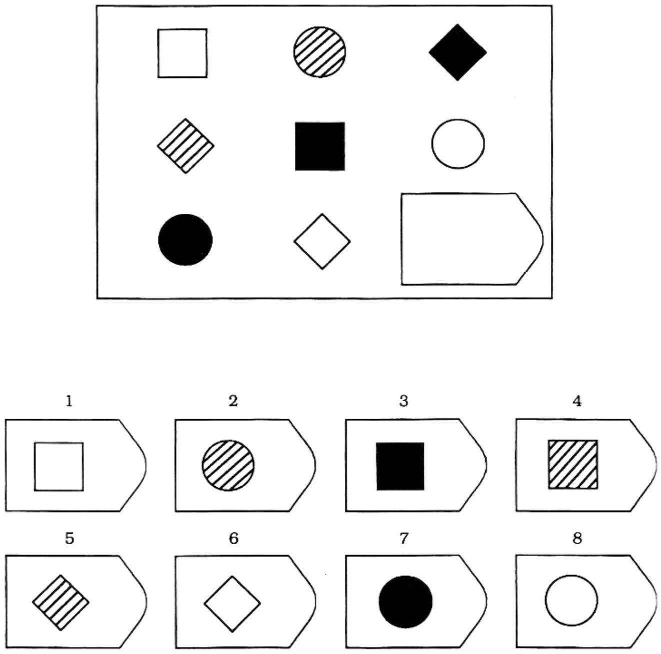


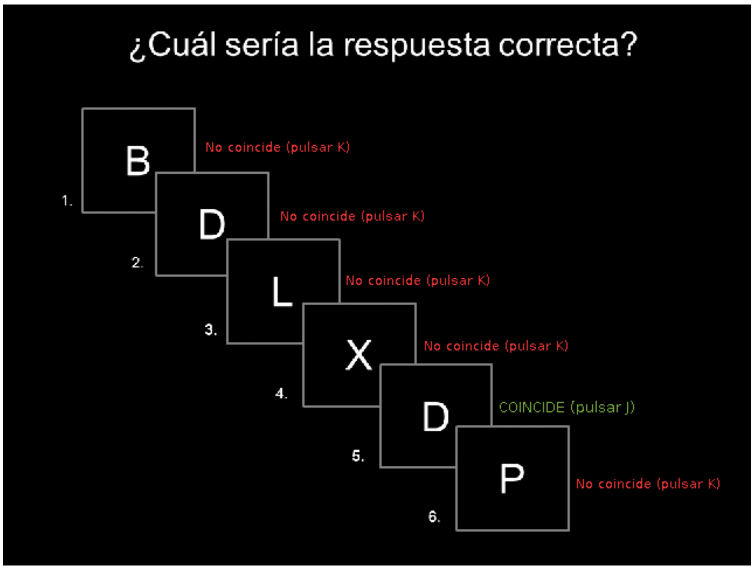
Figure 45. Sample item during the Raven's Progressive Matrices task, as shown on screen during the assessment. Participants had to select the appropriate response by using the number pad as soon as they knew the answer.

In this task, the instructions prior to the task did not include any examples. The response time for each item and the total number of correct answers was measured. While the response times were important, participants were told to answer once they were sure of their choice and there was no time limit for this test. It usually took around 15 minutes to complete each part of the test, although the participant's response pattern could be highly variable, some taking more than twice the time.

3-back task

A 3-back task, based on a modification (Salat, Kaye, & Janowsky, 2002) of a popular sequential letter task in working memory fMRI studies (Todd S Braver et al., 1997; J. D. Cohen et al., 1997), which in turn is a form of the n-back paradigm (Kirchner, 1958) was used as a measure for working memory performance. In this task, random letters appeared in the center of the screen at a constant rate (one every three seconds), only showing one letter. Participants had to try to remember the letter sequence and indicate whether the letter currently presented in the screen was the same letter that appeared three positions before, in a continuous fashion. A response was required for each trial, pressing the letter J with the right index finger for an affirmative response (target), and the letter K with the middle finger for a negative answer (non-target).

First, participants were taught the task using examples (see Figure 46) and did a short practice (20 trials) up to two times before starting the real task. If the participant achieved a 60% success rate the first time, the program automatically skipped to the main task. The main assessment was composed of 63 trials (20 targets + 60 non-targets + 3 initial items that were not computed) that were equivalent for all participants. Items could be composed of any consonant of the alphabet and were presented in white against a black background in Arial font size 30 (1.4 x 1-1.5 cm). The stimulus duration was 500ms with a 2500ms interstimulus interval between each letter. Overall, the approximate duration of the task was 6 minutes, including the examples and the practice.



¿Cuál sería la respuesta correcta?

Figure 46. Example screen used to teach participants how to respond to the n-back task, preceding a 20-item practice and the main task.

The variables analyzed from this task was the accuracy rate and the reaction times. A sensitivity index (d') was extracted using the following formula:

$$d' = Z(hit\ rate) - Z(false\ positive\ rate)$$

Mental rotation task

This task is based on the classic 1971 mental rotation test designed by Shepard et al. (1971).

In this task, a couple of three-dimensional objects appeared in the screen, one of each rotated in relation to the other, and participants had to indicate whether the pair of objects actually corresponded to the same figure or not. The premise of this task is that participants will mentally rotate one of the figures in order to match with the other, and the response time will be a direct indicator of the item difficulty, characterized by the degrees of rotation between the two figures.

The task was designed to mimic the looks and mechanics of the original experiment. All figures were composed by stacking a number of cubes together, forming a 3D shape. There were 5 different figures (see Figure 47), and each one also had its mirrored counterpart. The figures were displayed in a neutral grey color and the edges of the composing cubes were outlined in black, to provide better contrast and easier identification against the white background.

Each figure and its mirrored version were rotated in 20º steps, from 0 to 180º, either in X and Z planes, but not both at the same time. Any resulting image where the figure could not be easily identified at first glance were discarded from the task. This generated a pool of 148 figures (around 30 of each type) from which the task selected and displayed to the participant.

Items, composed of pairs of figures of the same type, were generated dynamically at the start of the task. The number of items of each type and the difference in rotation degrees between the two displayed figures was controlled, and there was approximately the same number of matching items, composed by two non-mirrored figures, and non-matching items, composed by a normal and a mirrored figure.

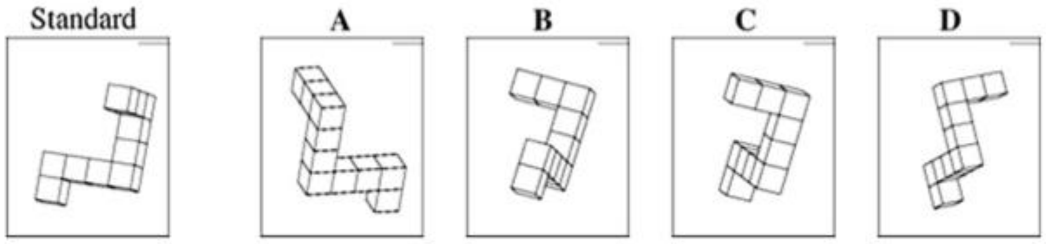


Figure 47. The five figures present during the mental rotation task, rotated in either the X or Z axis.

Previous to the main task, participants completed an example consisting of 4 items sorted in order of complexity: (1) two identical non-rotated figures, 2) two mirrored non-rotated figures, 3) two identical figures with a slight rotation in the X-axis, 4) two identical figures rotated in the Z-axis), and 4 more items representative of the main task. After each practice item, a feedback was given whether the participant's response was correct or not. Subjects were instructed to answer avoiding mistakes while being as quick as possible. Consistent with the rest of the tasks in the battery, the key J, pressed with the index finger, worked as an affirmative response, and the key K, pressed with the middle finger, as a negative response. During the main task, no feedback was given, and a brief pause of 10 seconds appeared after completing 10 items. A longer pause of one minute was programmed in the middle of the task.

The duration of the task highly depended on the participant's performance, since there was a fixed number of items (200) and there was no time limit to respond. Therefore, completion times usually took around 30 minutes.

Digit span task: forward and backward

We administered a computerized version of the subtest included in the Weschler Adult Intelligence Scale III (WAIS-III) (Wechsler, 1999). In this test, participants had to listen and remember a string of digits and repeat them with the only aid of their memory. The digits were pre-recorded, were presented in a random order in a monotone voice, and were paced one digit per second. Random number sequences composed of the numbers 1 to 9 (0 not included) were generated for every trial, and digits could be repeated within the same trial. The task started with just two digits, and increased by one digit every two trials, with no limit regarding the maximum span. The task ended when the participant failed two series of the same length. The maximum length of the string (span) attained and the number of series correctly completed were recorded.

In the forward digit span task, the subject had to repeat the digits in direct order, as previously heard, while the examiner annotated the response. In the backwards digit span, task subject had to respond the series in reverse order. Before each sub-task, instructions and a 3-digit example were provided.

The forward digit-span task is supposed to provide a measure of attention span, while the backward digit-span task also involves executive processing, particularly the working memory capacity.

Stop-switching task

Next, a test using a Stop-Switching paradigm (Logan, Cowan, & Davis, 1984; Obeso et al., 2013) was applied, focused on its heavy executive functioning component. This task was a combination of classic go/no-go task (inhibition) and a task switching paradigm (set-shifting). The result was a task that, under the appearance of a simple choice reaction time task, included *stop* and *switch* trials.

A white arrow at the center of the screen in a black background, pointing to the left or right told participants which key they had to press (J for left, R with right, with the index and middle finger of their right hand) as soon as they saw the arrow, measuring their reaction time. Combined with these go trials, *stop* and *switch* trials were inserted.

During a *stop* trial, the white arrow appeared briefly and shortly after a white cross would appear in its place (*stop* signal). Participants had to try to inhibit their already initiated response. However, if the white arrow turned blue, it indicated a *switch* trial, and the participant was instructed to press the spacebar with their right thumb as quickly as possible (see Figure 48).

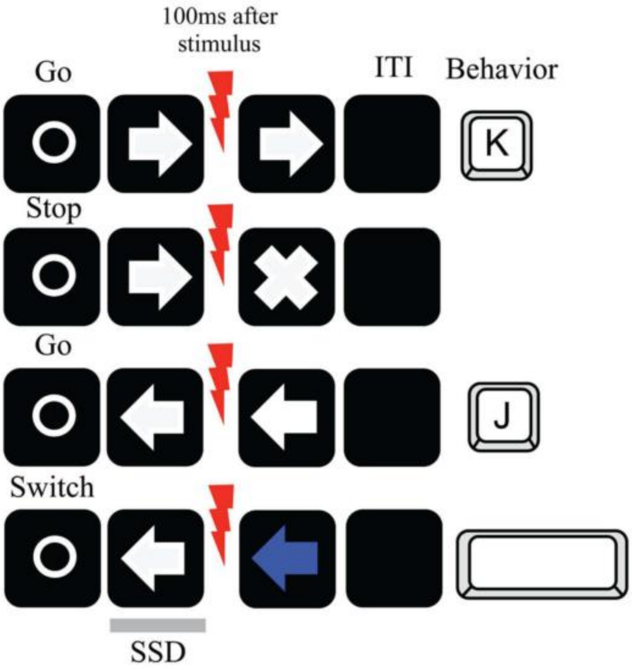


Figure 48. Stimuli used during the Stop-switching task, featuring *go*, *stop* and *switch* trials. Adapted from Obeso et al. (2013).

The interval between the white arrow and the cross sign in *stop* trials (stop-signal delay, SSD) was variable and depended on the participant's correct response rate (for more details, see Obeso et al., 2013). The reason behind this variable delay was to find the SSD in which the participant responded correctly at the 50% of the *stop* trials, necessary for obtaining the value of the stop-signal reaction time (SSRT) (see Figure 3) using the integration method (Band, van der Molen, & Logan, 2003), the reaction time that each participant needed to process the inhibition response. The SSD varied according to a staircase method; it increased 50ms for each successful inhibition and decreased by 50ms each time the participant could not inhibit and gave an invalid response.

The staircase method also was applied for the *switch* trials, but using a reverse paradigm: the delay was reduced in 50ms for each incorrect switch trial and was increased in 50ms for each successful switch trial, up to a limit of 1000ms.

Participants were instructed to answer as fast as possible, just like in a reaction time task, and not to wait for a *stop* or *switch* signal, all while trying to answering correctly to all the stimuli. However, strategies consisting in answering for a few milliseconds after the *go* signal in order to improve their detection rate are commonly reported in the literature.

The inter-trial interval was also variable and ranged from 1000 to 2500ms. In total, there were four blocks of trials consisting of 72 *go*, 18 *stop*, and 18 *switch* trials per block (108 total trials per block). Including the instructions and a brief initial practice session, the task had an approximate duration of 15 minutes.

Video gaming skills

Participants were instructed to play in a video game that shared the same mechanics as the one they would play during the training for the following days. This was done for several reasons: 1) to control previous video game experience as a possible confounding variable (see section 3.2.1), 2) to obtain a general impression of their video game ability, and 3) to obtain a baseline performance that would be compared to a later performance in the same video game the at the end of the second cognitive assessment.

Participants were then instructed to play for 15 minutes and their screen was recorded during that time. After a brief explanation of the main controls of the game, they were told the objective they had to achieve: to reach the top of a raised area, jump across some floating platforms to reach a fortress, and defeat the enemy inside the fortress. Unfortunately, being a commercial video game, there were no internal variables that could be used as a measure of their performance, so it had to be qualitatively measured.

In order to overcome the qualitative nature of this task, both performances were compared and a score was given to each participant based on the achievement of the mentioned game objectives. Generally, 15 minutes was not enough for the usually inexperienced participants to complete these objectives, which had the unintended effect to avoid a ceiling effect in their performances.

3.2.4.3 Training period

The training period constituted the central block of the study. The central features of this stage are the video game training and the TMS stimulation, but some other procedures were included as well.

The first session was slightly different from the rest, as some additional procedures needed to be carried out, such as the measurement of the active motor threshold and the participant's mood (see Figure 49 for a detailed account of all procedures carried out during the first training session). This session had an approximate duration of 120 minutes.

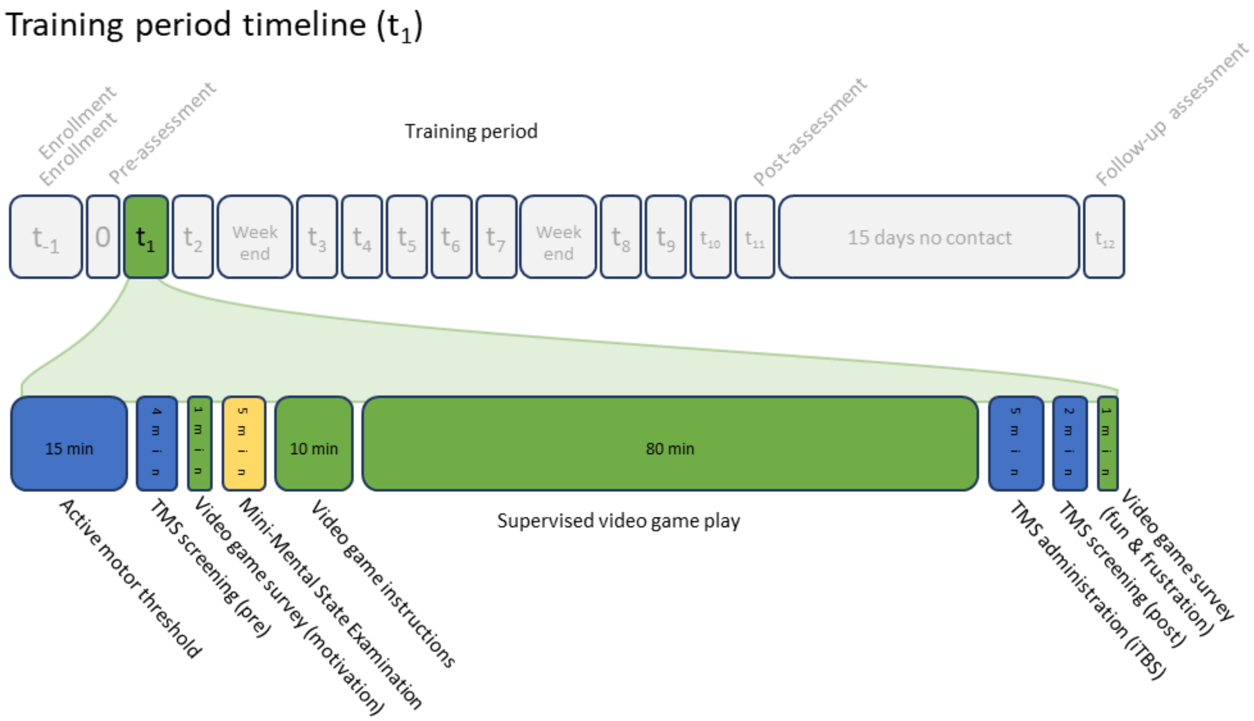


Figure 49. Timeline of the first session (t_1) of the training period. Elements in blue are TMS-related procedures, while elements in green are those related to video-games.

The remaining nine training sessions, which lasted approximately 110 minutes each, had a similar structure, but only featuring the video game training, the TMS stimulation and some additional procedures surrounding these events. A full account of the procedures carried out during the rest of the training sessions can be seen in Figure 50.

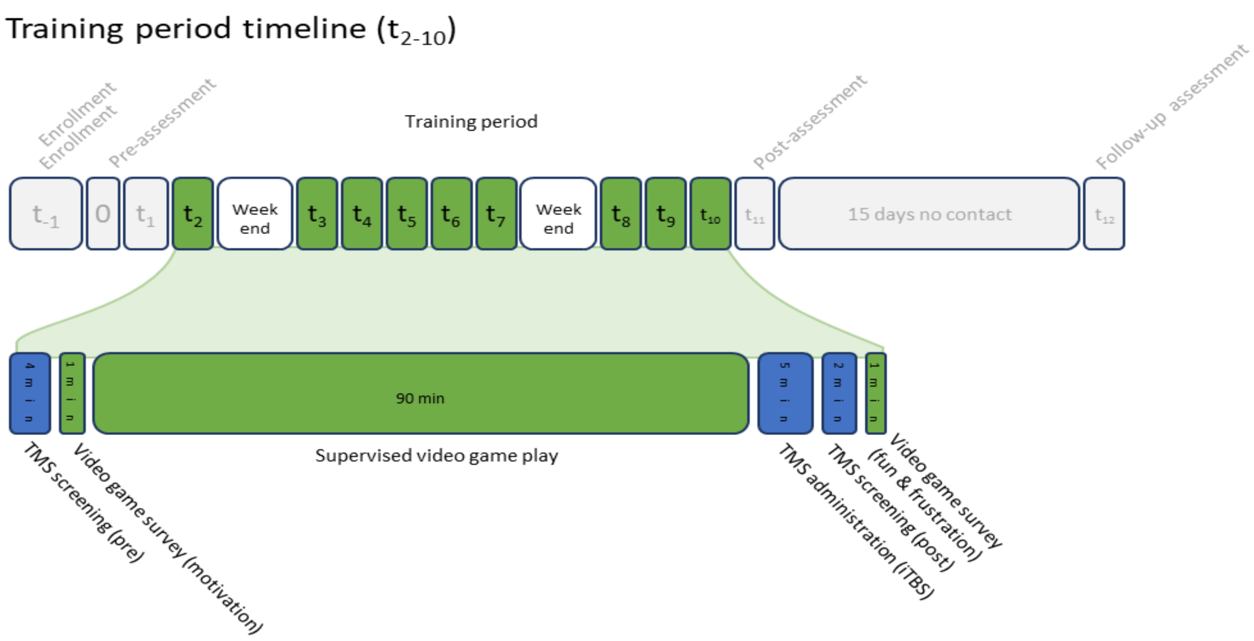


Figure 50. Time line of the second to tenth sessions (t_2-t_{10}) of the training period. The motor threshold and the participant's mood has already been measured, and most part of the session is dedicated to the video game training itself.

Active motor threshold

The stimulation intensity was defined by measuring each participant's active motor threshold before the pre-training assessment. Active motor threshold (AMT) is defined as the minimum output intensity needed to produce a motor evoked potential (MEP) in the first dorsal interossei muscle of the hand using a single magnetic pulse on five out of ten trials, while the participant maintained a voluntary contraction between their thumb and index finger. Following TMS guidelines for TBS stimulation, the intensity of the stimulation was set at the 80% of the AMT (Huang et al., 2005).

Video game survey

During the video game training routine, participants also needed to answer a short survey asking for the level of motivation, amusement, and frustration, organized in a 5-point Likert scale, relative to the video game experience. The motivation question was presented right before each video game session, and the levels of amusement and frustration were measured in the post-training questionnaire. These three variables were averaged for each participant at the end of their training period.

TMS screening

A set of data was collected from participants during each of the experimental training sessions in order to comply with the ethical and safety criteria and also to assess the participant's subjective experience with the video game task. A brief cognitive test was used to assess the possible effects of the TMS on the participant's cognition and physical status (see section 8.5 in the annex). Parts of the test were administered before the video game training, while others were completed at the end of the training session. This assessment was meant to be a quick screening test and took no longer than 5 minutes each time it was applied. The whole pre-post assessment was adapted to a computerized format, in order to standardize and better manage the answers, but the participant was always supervised by the experimenter during its application.

In the first place, the pre-stimulation assessment began with some general questions regarding physical well-being, sleep quality and consumption of psychoactive substances (alcohol, caffeine and other drugs) prior to the experiment. These questions were aimed at controlling the intake of any possible substance or any habit that would alter the normal cortical excitability since the stimulator output power was adjusted during the first session, and the level of excitability should remain stable unless some of the mentioned criteria were not met prior to the participation. Right after the stimulation, the participant answered a checklist consisting of several possible uncomfortable sensations. They also had the freedom to express any other discomforting or unexpected sensations they may have experienced during the stimulation.

Afterwards, the Spanish adapted version of the Mini-Mental State Examination (MMSE) questionnaire (Folstein, Folstein, & McHugh, 1975; Lobo, Saz, & Marcos, 2002) was applied, according to the safety and ethical guidelines, before and after the stimulation, in order to detect any possible effects of the stimulation respect the participant's baseline.

Video game training

All participants underwent a cognitive training period using a commercial video game, *Super Mario 64*, a 3D adventure-action platformer originally released in 1996 for the Nintendo 64 video game console.

This video game has a series of characteristics that make it suitable to be used as a cognitive task. First of all, as it is a commercial video game and not just a computerized cognitive task, it promotes the participants' engagement in the task and also provides more ecological validity when trying to extrapolate the results of the experiment to the effects of general video gaming. On the other hand, internal variables of the video game are hardly manipulable and we can only aim to control them among participants.

Unless other video games that were release at the end of the 90s, Super Mario 64 featured a non-linear 3D world in which players had some freedom on how to obtain the objectives of the game. As a platformer, a great deal of the action falls into trying to explore and get to unreachable areas through different kind of jumping abilities, all while avoiding traps and enemies. Although this game better fits in the 3D platformer genre, it also possesses some features, such as physical challenges and rapid hand-eye coordination and reaction times, which do not exclude it from being an action video game. However, these features are not as prominent as in other video game genres, especially first-person shooters and fighting games, in which reaction times need to be much more precise, quickly triggering the deployment of attentional resources. On the other hand, this particular game possesses elements of strategy that involve problem-solving that may not be present in other action VG. Therefore, it would be more precisely be categorized as a 3D adventure-action platformer.

Figure 51. Screen capture of the Super Mario 64 video game. The total number of "stars", the main indicator of game progress, can be observed in the top-right corner.

At the beginning of their first training session, participants were given the following instructions:

- *You can play freely.*
- *You will appear in a garden surrounding a castle. Inside, there are a series of doors where you can enter to select a game level. Some levels are not accessible from the beginning.*
- *The objective in each level is to obtain a star. You can get it through several ways. When you obtain a star, the level is completed.*
- *You can repeat the same level indefinitely since there are several ways of beating them. Each level, except for a few exceptions, contains six stars, which correspond to the different ways of beating them. Some stars should be obtained in a specific order while others can be obtained from the beginning. When you enter a level, a title screen will appear, hinting what to do next.*
- *Once you start getting stars, you will gain access to new levels. The number written on each door inside the castle is the number of stars required to enter that level.*
- *You need to register every time you start a level and you finish it, either because you have won a star or you lost a life. In order to do so, you must make a screen capture (using the Print screen key on the keyboard) on each level's title screen and when you finish it, showing that either you got a star or your character was killed. I will register the number of attempts for each session and the elapsed time. However, it is important that you play normally, without haste or excessive prudence.*
- *At the end of your participation, what I will take into account are the number of stars that you have achieved with the lesser number of attempts.*

Participants played while being supervised in our laboratory for ten consecutive 1h30m sessions, Monday to Friday, usually starting a Wednesday and ending on a Thursday two weeks later. Participants sat at a distance of ~70 cm from a 19-inch TFT monitor at full screen and played using a compatible N64 controller, which was designed around this specific video game in mind. The video game was run on a computer using an open-source Nintendo 64 emulator (Mupen64 0.5.0), not in the original console, because of its limited capabilities when dealing with multiple participants. Another reason was that the emulator also allowed to save and stop the game at the very specific moment the participant finished their training session, and resume at that point at the beginning of the next session.

Players were instructed on how to control the characters, but were not told any of the strategies of objectives on the game; they had to discover them by themselves. Participants were free to roam in the 3D scenarios of the game, and their gaming performance was supervised. The screen captures were automatized so they only had to press one button to register their progress. For each participant and each session, the number of stars achieved, the number of attempts and the start and ending time was recorded, and these variables were used as measures to compare performance between participants.

The video game consisted of 15 main courses containing 6 goals (stars) each, which were unlocked as the participant completed each course. It was always possible to obtain one of the stars by collecting eight red coins scattered around each course. Moreover, there was an additional 7th star in each stage that could be obtained by collecting 100 regular coins. There was also a number of secret stages and stars hidden throughout the game. It was not compulsory to complete all courses to finish the game, so the player could choose the best strategy to finish the game. The minimum number of stars required to do so was 70, although it was possible to collect up to 120 stars if all the secondary objectives were completed.

In the case that participants completed the game before the ten training sessions, they were told to continue playing with the game Super Mario Star Road, an unofficial sequel featuring 15 new levels and some secret areas, which retains the exact same gameplay with just a slightly higher level of difficulty. Three of the participants (11%) were able to finish the main game before the 10 training sessions and therefore continued playing with that sequel.

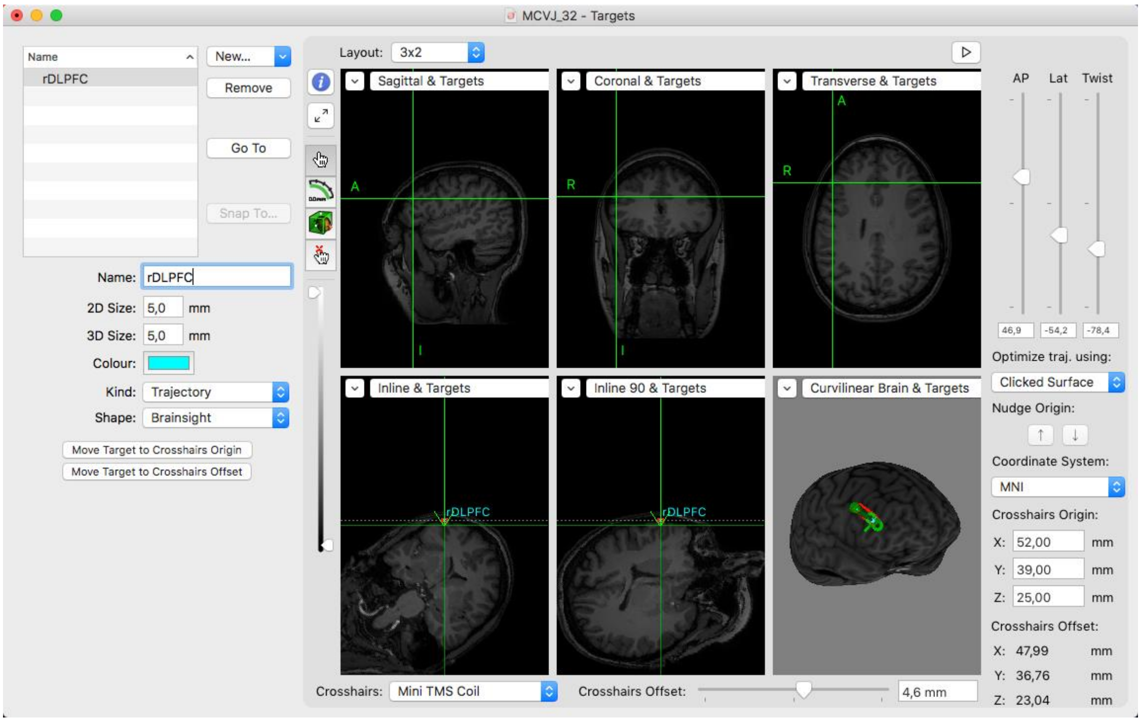
TMS administration

Right at the end of the video game training, the TMS stimulation was performed. Before starting the stimulation, a few instructions were given to participants, including a brief description of the stimulation and some safety recommendations, such as to remove any metallic object they may have been wearing (e.g. earrings, watches, hair clips) or clean eye makeup (see Redolar-Ripoll, Viejo-Sobera, Palaus, Valero-Cabré, & Marrón, 2015). Earplugs were provided to participants to muffle the noise of the magnetic stimulator.

TMS was delivered after each of the 10 sessions, right after finishing the 1.5h video game training period. To perform the stimulation, a Magstim Rapid 2 stimulator was employed in conjunction with the BrainSight 2 guided neuronavigation system. Magnetic stimulation was applied using a hand-held figure-of-eight coil (70mm standard coil, Magstim Co., Whitland, Dyfed, UK) placed tangentially to the scalp over the participant's right DLPFC with the handle pointing backward at 45º respective to the floor (see Figure 52).

The site for the stimulation was the right DLPFC, standardized across participants at the [x:52, y:39, z:25] Montreal Neurological Institute (MNI) coordinates. This area has been chosen due to the extensive research that has undergone and the number of relevant cognitive functions for which it is responsible (Kühn et al., 2013).

MNI coordinates were set individually for each participant and the stimulation was continuously guided by the neuronavigator during the time it took to complete the iTBS protocol.



Name: rDLPFC
2D Size: 5,0 mm
3D Size: 5,0 mm
Colour:
Kind: Trajectory
Shape: Brainsight
Layout: 3x2
AP 46,9 Lat -54,2 Twist -78,4
Optimize traj. using: Clicked Surface
Coordinate System: MNI
Crosshairs Origin:
X: 52,00 mm
Y: 39,00 mm
Z: 25,00 mm
Crosshairs Offset:
X: 47,99 mm
Y: 36,76 mm
Z: 23,04 mm
Crosshairs: Mini TMS Coil
Crosshairs Offset: 4,6 mm

Figure 52. Screenshot of the BrainSight 2 guided neuronavigation system, showing the coordinates of the stimulation site.

The specific iTBS protocol with excitatory effects over the cerebral cortex (Huang et al., 2005) was applied (see Figure 53) with the following parameters:

- 600 magnetic pulses.
- Distributed in twenty 2s periods, each separated from the following by 8 seconds.
- Each period will consist of groups of magnetic pulses applied at 5Hz.
- Each group of magnetic pulses will consist of trains of 3 pulses at 50Hz.
- The total time of the stimulation is 200 seconds.

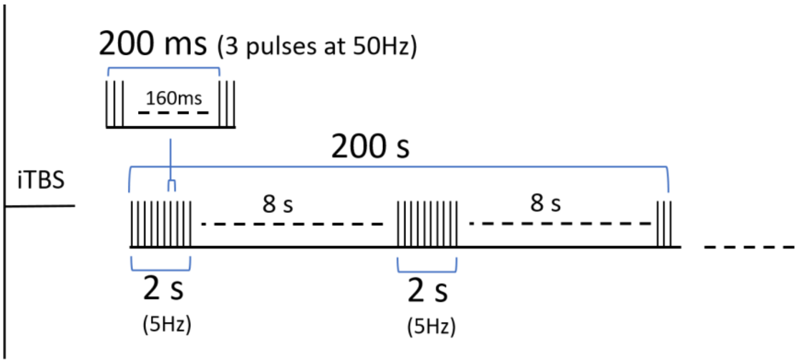


Figure 53. Schematic of the iTBS stimulation protocol used during the experiment.

3.2.4.4 Post-assessment

The two post-intervention assessments were similar to the pre-assessment, but were exclusively centered in the mood and cognitive aspects and no additional procedures were conducted. In the first post-assessment, carried out the day following the tenth training session, two additional cognitive measures were performed (Five-Point test and matchstick tasks) compared to pre-assessment, and it had an approximate total duration of 120 minutes. For a full account of the procedures carried out in the first post-assessment, see Figure 54.

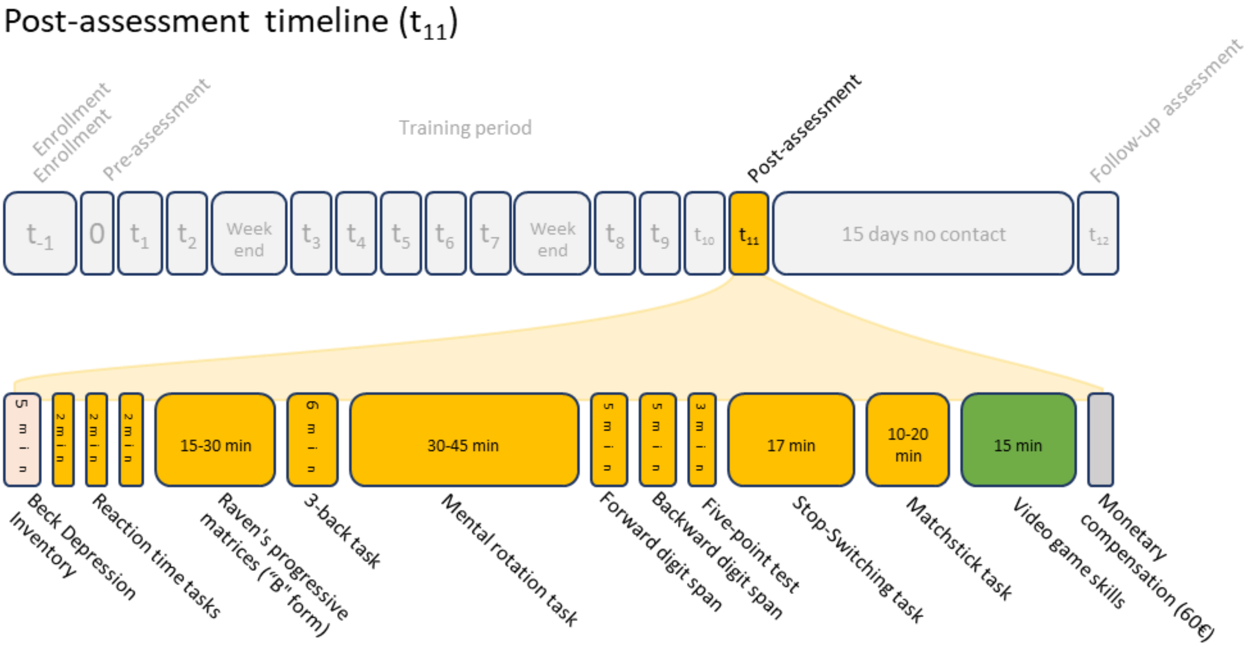


Figure 54. Timeline of the post-intervention assessment. Apart from the tasks from the pre-assessment, it includes the Five-Point Test and the matchstick task.

The follow-up assessment, two weeks after the end of the intervention, followed a similar structure, but was much shorter as fewer tasks were applied, having a total duration of 75 minutes. A detailed account of the procedures in the follow-up assessment can be seen in Figure 55.

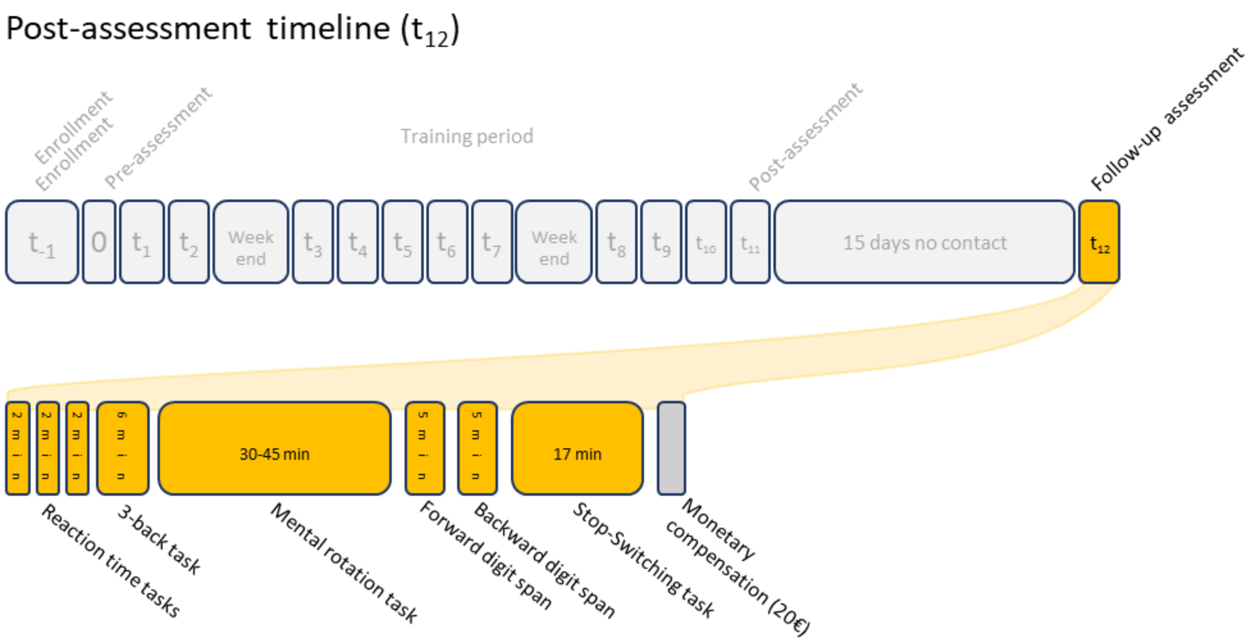


Figure 55. Timeline of the follow-up assessment. Raven's progressive matrices, the Five-Point Test, the matchstick task as well as the video game skills measure have been removed from the previous assessment.

Neuropsychological assessment

Compared to the pre-assessment, two additional tasks, the Five-Point test and the matchstick task, were added to the cognitive evaluation at the post-assessment.

During the follow-up assessment, neither Beck's depression inventory, Raven's progressive matrices, the matchstick task or the video game skills were assessed at this stage, resulting in a shorter session.

Five-point test

The Five-Point Test (5PT), a standardized version (Tucha, Aschenbrenner, Koerts, & Lange, 2012) of a design fluency task was used to measure an individual's ability to produce novel figures utilizing five different dot configurations, placed in a five-point domino-style pattern (see Figure 56). The participant was shown acceptable and unacceptable examples and the instructions place emphasis on the subject's making as many different drawings as possible during two minutes. Perseverative or repeated responses were subtracted from the total score. Rotations and mirror-imaging versions of a pattern were considered valid answers.

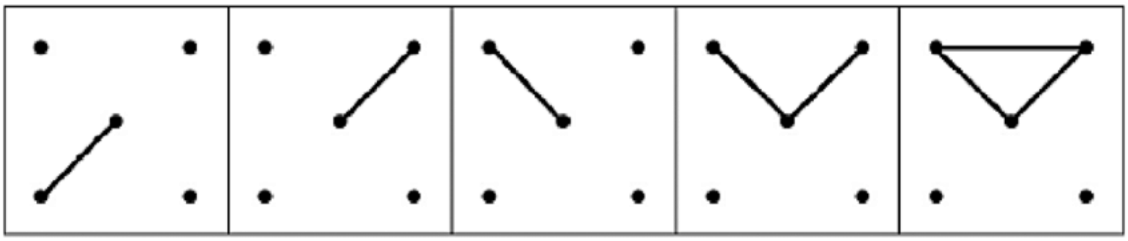


Figure 56. Response examples for the Five-Point Test (5PT). Adapted from: (Hansen et al., 2017).

This was the only non-computerized test in the whole battery. Participants had to manually draw the lines on a sheet of paper composed of 5 rows of 6 tiles. The way it was designed, the participant had the resource of checking the previous answers in order to avoid repetitions.

Considering there are 8 possible lines connecting the 5 dots, and participants could draw from 1 to 8 lines to provide valid answers, there is a total of 255 possible different patterns.

Matchstick task

The last cognitive domain to be assessed in the battery was the insight problem solving, a domain often overlooked during cognitive assessments. Problems that require insight to be solved feature a series of characteristics. They are often posed in a way that does not allow any straightforward sequence of action to solve it, so unless it is simple enough to provide a direct answer, an impasse is reached and no further advances are made until the solution comes as a sudden insight.

The presented task was an adaptation of the work by (Knoblich, Ohlsson, Haider, & Rhenius, 1999) in which a riddle in the form of arithmetic statements with roman numerals showed an incorrect equivalency and had to be solved. Each item was composed by the Roman numerals, the arithmetic operators, and equal signs, and all these elements were entirely composed of matchsticks (see Figure 57). Three rules have to be followed in order to solve each problem: 1) only one stick can be moved, 2) the stick cannot be discarded and has to be placed somewhere else in the equation and 3) the resulting equation has to be a correct arithmetic statement.

Figure 57. Matchstick task sample item, belonging to the first group of problems.

The authors discussed two hypothetical mechanisms by which one could find the solution: either by relaxing the self-imposed norms that guide how a similar problem, based on previous experiences, should be solved (constraint relaxation), and by decomposing the elements that form the problem which may be perceived as unitary in smaller units (chunk decomposition).

The task is composed of eight problems that can be grouped into four types depending on how the solution is achieved:

- Type A. Value constraint; loose chunks.
    - e.g.: VI = VII + I → VII = VI + I
- Type B Value and operator constraints; loose and intermediate chunks.
    - e.g.: I = II + II → I = III - II
- Type C Operator and tautology constraints; intermediate chunks.
    - e.g.: III = III + III → III = III = III
- Type D Value constraint; tight chunks.
    - e.g.: XI = III + III → VI = III + III

One item of each type, in a random order, was presented to the participant. Once the participant completed the four items, another group of four items, one of each type, were presented again in random order. Whether or not they solved each item, the time taken to solve it and the number of tries per item was recorded. There was a time limit of two minutes per item, so the maximum total time to complete the task was under 16 minutes, and most participants took around 10 minutes to go through the 8 items. Participants could not directly manipulate the elements of the items, so they had to mentally create the answer. Once they thought they knew a valid answer, they pressed the spacebar in order to stop the time and the experimenter indicated whether their answer vas correct or not. In the case of a wrong answer, the participant continued with the same item until the time was up, with no limit on the number of tries.

In the case the participant was not familiar with Roman numerals, a brief explanation and a test regarding how the numbers were represented was made before the start of the task to ensure that this specific knowledge was not a factor affecting the difficulty of the task.

According to the theory, items requiring to break easier constraints or to decompose looser chunks will be solved faster and more frequently, and the response time will be higher the first time an item of one specific type is presented compared to the second round.

3.2.5 Data analysis

3.2.5.1 Variables

Two main independent variables are used in this study: the TMS stimulation condition and the previous video game experience. In addition to that, there are other demographic and personal variables (age and gender) that acted as independent variables for some of the analysis (see Table 21).

Variable	Levels of measurement	Value range	Units	Assignment
TMS Condition	Categorical - Dichotomous	Active iTBS - Sham iTBS	-	Random
Video game Experience	Categorical - Ordinal	Exp - NoExp VGP	-	Demographic
Gender	Categorical - Dichotomous	[Man - Woman]	-	Demographic
Age	Quantitative - Ratio	18 - 40	years	Demographic

Table 21. List of the independent variables used in the experiment.

All the acquired information through neuropsychological testing, as well as data linked to video game use during the training or assessment sessions, fell into the category of dependent variables. Moreover, information about the participant's mood and cognitive integrity, primarily used as requirements for inclusion in the experiment, were also measured at different time points.

Dependent variables related to video game usage (see Table 35 in the annex) included measures of video gaming skills, measured before and after the 10 training sessions, and assessed through qualitative methods in a scale from 0 to 5. Performance in the video game during the training sessions was assessed through two variables: the *stars* collected during the video game, indicative of the goals accomplished in the video game (up to 120), and another measure of video game performance (*perf*) calculated as goals (*stars*) accomplished divided by the number of tries, therefore ranging from 0 to 1, and providing a measure of the efficiency of the participant in the game. Higher scores on these two variables are associated with better performance in the video game, but discrepant scores are indicative of different attitudes towards the challenges posed by the game.

Three other variables were collected for each of the 10 video gaming training sessions: the motivation (willingness to play) (*Mot*), the frustration (*Fru*) and the fun (*Fun*) experienced during the game. These three variables were self-assessed and were ranked from a 0 to 5 scale, the first one measured before starting the training session and the other two right at the end of the session. The values used for the analysis were built using the mean score of the ten sessions, therefore admitting decimal points and constituting continuous variables.

The bulk of the dependent variables (see Table 37 in the annex) was composed of the data extracted through the cognitive assessments at the three time points. All variables in this category are quantitative and measured on a ratio scale. Most are either a measure of response times, quantified in milliseconds, or the score of a task, usually assessing its accuracy or level of performance. In some cases (*3-back d'* and *stop-signal reaction time*), the variable contains an index created with the combination of several scores provided by the task. Indices offer more complex data, such as interactions between other variables, and often allow for negative values, where its interpretation is not as simple and can be attributed to different response styles, not necessarily linked to worse performance.

In addition to the variables representing the outcome of the neuropsychological assessment, a set of variables was created containing the differential scores and reaction times between the pre-training assessment and the post-training and follow-up assessments (see Table 38 in the annex). The reason behind these variables is to be able to make comparisons between groups using simpler statistical models. Since they are basically a subtraction of already existing variables, they were still measured in a quantitative ratio scale, and their range of values included positive and negative numbers.

3.2.5.2 Statistical analysis

Before the inferential analysis, the presence of significant differences in the demographic variables (gender and age) between the experimental groups was assessed. We compared differences between experimental groups, by age, gender, and by the combination of both. These differences were tested through the *Student's t-test* for the variables with two levels, and a *one-way analysis of variance (ANOVA)* for variables with more than two levels. Moreover, *Pearson's chi-square test* was calculated to compare the frequency of men and women in each experimental group.

In order to assess the normality of the distribution of the data, the *Shapiro-Wilk test* was used. The homogeneity of variances was contrasted through the *Levene's Test of Equality of Variances*. Lastly, in order to test sphericity, *Mauchly's test* was used in those cases where there were three levels of a repeated measure.

Variables related to the subjective experience during the video game training sessions (motivation, fun and frustration) were analyzed using *Pearson's r coefficient* in order to observe the existence of correlation among them. This coefficient was also used to link these values to the video game performance during the training sessions, to study the influence they could have had on video game play. Finally, *Student t-tests* were used to assess the differences in those variables among experimental groups.

To compare the performance between the two groups of participants (active and sham TMS conditions), and taking into account the three time points of the assessment, a *repeated measures general linear model* (GLM) was performed for each cognitive task. In those tests only used once, the differences between groups were analyzed (through the *Student t-test*, *Mann-Whitney's U*, *Kruskal-Wallis H test* and *Welch's ANOVA*, depending on the parametricity of the data). Significant interactions were followed up using *paired t-tests*, corrected for multiple comparisons using *Holm–Bonferroni* corrections. To assess the changes in the outcomes of all tests performed three times (pre, post and follow-up) the data in the three time points was analyzed thorough *one-way ANOVA*s, comparing the performance after the intervention in comparison with the baseline (Pre - Post) and two weeks after the end of the intervention (Pre - Follow-up).

After performing the main analyses, and based on previous literature about video game usage and its effects on brain structure and function (see Palaus et al., 2017), an additional analysis were performed, in order to observe the possible predictive power of personal variables (age, gender, and previous video game experience) on the cognitive enhancement. A logistic regression model including these three variables was performed for each dependent variable (see section 3.3.5). The results showed, that the previous video game experience was a variable that could potentially influence cognitive performance results. As a result, two more sets of analysis were performed: a *repeated-measures GLM* for variables related to the cognitive assessment for participants with and without previous video game experience (Exp, NoExp), and a *repeated-measures GLM* for the four experimental groups resulting for combining the TMS condition and the previous video game experience (iTBS+Exp, iTBS+NoExp, Sham+Exp, Sham+NoExp).

A special focus on gender differences was placed for some measures that were more likely to be affected by this variable. Therefore, the qualitative video game performance during the pre and post-assessments, as well as the performance in the mental rotation task were contrasted with the gender of the participants through *Student's t-test*.

For all those variables that did not comply the parametric adjustment, alternative statistics were employed. In order to compare means, the *Mann-Whitney U test* was used as a substitute of the Student's t-test. For more than two independent groups, the *Kruskal-Wallis H test* was used as a substitute for the one-way ANOVA and the GLM.

All the analyses have been performed using the IBM SPSS Statistics® software, version 23.

3.3 Results

The following section is devoted to describing all the results obtained from the variables collected during the cognitive assessments in its three time points: pre-intervention, post-intervention and follow-up, the intervention consisting in the ten video game training sessions. Moreover, those variables related to performance in the video game during the training sessions (e.g. goals achieved, number of attempts, goals per attempt, etc.) will be also described and analyzed.

This section has been structured as follows: first, personal variables are described and analyzed. This includes variables such as the age and gender of participants, the level of previous video game experience, their educational level and how they are divided between experimental groups. In addition, variables related to their subjective experience during the video game training sessions are also analyzed in this section, studying their trends during the training period and finding possible correlations among them.

Next, the results of the three cognitive assessments are provided, divided in three main blocks corresponding to the possible combinations of the independent variables, showing the results by TMS modality (active iTBS or sham), by previous video game experience (experienced or non-experienced), and by the interaction effect of these two independent variables. Within each one of these three blocks, the effects of the video game training and the eight main neuropsychological tasks (reaction times, digit span, Raven's test, Five-Point Test (5PT), n-back, mental rotation, stop-switching, and matchstick task) assessed at the three time points, in addition to variables related to video game performance, have been analyzed.

For each one of these blocks and the variables they contain, a series of standardized analysis has been performed. First, baseline measures are compared to identify differences between the experimental groups. Next, an account of descriptive statistics has been provided for each one of them (see tables in annex 8.7), followed by an analysis of parametricity (see tables in annex 8.8) in order to determine by which means these variables will be compared. For all those variables assessed in two or more time points that meet the parametricity assumptions, a repeated measures GLM (including the two and three time points, when available) has been used to study the possible effects of the training sessions and the repeated exposure to the task during the assessments, the interaction effect of these sessions with the experimental group (TMS, video game experience or both), and possible between-subject effects. Moreover, all variables are compared at their post-assessments values to determine possible differences between groups, especially relevant for those variables that were only measured during a post-intervention assessment with no previous baseline.

3.3.1 Summary

In order to facilitate the visualization and interpretation of the big volume of data, highlighting all the significant results found in the analysis that will be described in the following sections (see Table 22). The table shows the three main comparisons in which this section is structured (active vs. sham ITBS, experienced vs. non-experienced players, and the interaction between these two independent variables). For each independent variable, the between-subject and within-subject differences are provided first, followed by their simple effects, indicating the time points that were included in each analysis.

For a more exhaustive overview of every result and its level of signification for each dependent variable, as well as the statistic used for each analysis, tables summarizing the whole results section have been provided in the annex (see Table 87 in the annex).

		Active iTBS vs. Sham iTBS	Experienced vs. Non-Experienced players	TMS*Exp_VGP
Between-subject differences	**Pre (baseline)**	▲ Raven RT ▲ N-Back D'	▲ Mental rotation score	-
	Pre & Post 1	▲ Raven RT ▲ N-Back D'	-	▲ Raven RT
	Pre, Post 1 & Post 2	▲ N-Back D'	-	-
Within-subject differences	**Pre & Post 1**	▲ Video gaming skills ▲ Forward digits ▼ Stop-Switching SSRT ▲ Stop-Switching Switch score	▲ Forward digits ▲ Mental rotation RT ▼ Stop-Switching SSRT	▲ Video gaming skills ▼ Stop-Switching SSRT
	Pre, Post 1 & Post 2	▼ Simple reaction time ▲ N-Back RT ▼ Stop-Switching Go RT ▲ Stop-Switching Switch score ▲ Stop-Switching Switch RT	▼ Simple reaction time ▲ Forward digits ▲ Backward digits ▲ N-Back D' ▼ Stop-Switching Go RT	▼ Stop-Switching Go RT ▲ Stop-Switching Switch RT
Interaction effects	**Pre & Post 1**	-	▲ N-Back D' ▲ Stop-Switching SSRT	-
	Pre, Post 1 & Post 2	▼ Simple reaction time	▲ N-Back D' ▼ Mental rotation score	-

Table 22. Cognitive tasks that achieved significant differences when participants were divided by TMS group, previous video game experience or the combination of both. Results were grouped by between-subject differences, possible learning effects due to the repeated exposition to the cognitive task, or the interaction between the differences among groups and the effect of the video game training. Dependent variables which did not obtain statistically significant differences at $p<0.05$ were omitted. TMS: independent variable containing active iTBS and sham iTBS. Exp_VGP: independent variable containing experienced and non-experienced video game players. RT: response time. SSRT: stop-signal reaction time. An upward pointing triangle (▲) indicates a performance improvement (measured in response speed or accuracy) respective to the control group in each independent variable (sham iTBS or non-experienced players), whereas a downward pointing triangle (▼) indicates a worsening of the performance respective to the control group.

3.3.2 Demographic data

The 27 participants (14 women, 13 men) which completed all the stages of the experimental procedure had a mean age of 29.44±6.28 years. There were no significant age differences between genders (women: 29.43±5.53; men: 29.46±7.24; t-test p=0.495) (see Table 39 and Table 40 in the annex).

Measuring their level of expertise in video games, 12 participants were categorized as Experienced video game players (Exp) and 15 as Non-experienced video game players (NoExp). Players with low video game experience were slightly older (28.17±7.30) than the experienced player's group (30.47±5.38), but the age differences were not significant among them (t-test p=0.177).

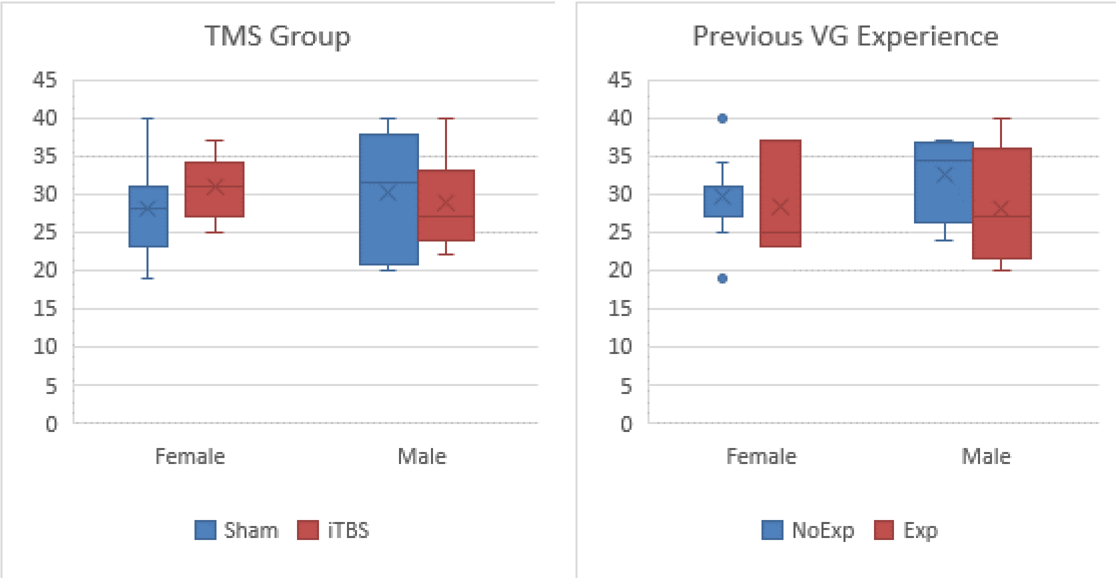


Figure 58. Age and gender distribution of the participants categorized among TMS and video game experience groups.

Overall, men were more likely to be experienced video game players than women (8 men, 3 women), while the opposite for low video game players was also true (4 men, 11 women, $\chi^2_{(1)}=6.238$, p=.013), and that inequality was mitigated in the composition of each one of the four subgroups ($\chi^2_{(3)}=6.591$, p=.086). The number of men and women in each stimulation condition was roughly equal (13 men, 14 women, $\chi^2_{(1)}=.039$, p=.841).

When the actual video game performance was measured, either during the pre-intervention assessment, during the training sessions or at the post-intervention assessment, gender differences became evident in this sample of participants. The qualitative video game performance measures showed that male participants performed significantly better at the baseline compared to their female counterparts, and that difference was still present at the end of the ten training sessions [Pre: $t_{(25)}=3.838$, p=.001; Post: $t_{(25)}=3.171$, p=.004] (see Figure 59).

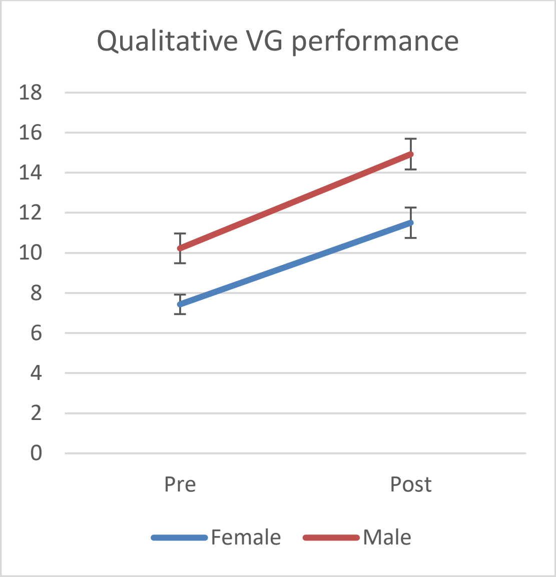


Figure 59. Gender differences in the qualitative video game performance assessment.
Error bars indicate one standard error.

Gender differences were also found in other video game performance measures. For instance, male participants achieved a larger number of goals during the training sessions [Men: 46.54±28.858; Women: 16.36±9.443; $t_{(25)}=3.710$, $p=.001$] and required less attempts for achieving each goal [Men: 21.745±11.445; Women: 9.77±7.143; $t_{(25)}=3.287$, $p=.003$], despite spending similar time in each attempt. Even accounting for previous video game experience, gender differences are visible between male and female participants in the number of goals achieved during the training sessions, although that difference was not significant [$F_{(1,23)}=.216$, $p=.646$].

Once randomly assigned to the experimental conditions, 14 participants were placed in the active iTBS and 13 in the sham iTBS condition. The active iTBS condition was composed by 6 experienced video game players (5 men, 1 woman) and 8 participants without video game experience (2 men, 6 women), whereas the sham iTBS condition included 6 players with high experience in video games (4 men, 2 women) and 7 with low experience (2 men, 5 women). All four groups were fairly even in terms of mean age (iTBS+Exp: 28.11±7.23; iTBS+NoExp: 32.50±3.70; Sham+Exp: 28.33±7.32; Sham+NoExp: 29.73±7.00), and did not show significant age differences among them (one-way ANOVA p=.46). Grouped by gender, age differences were not significant either for the stimulation group (one-way ANOVA p=.85) or by video game experience (one-way ANOVA p=.71).

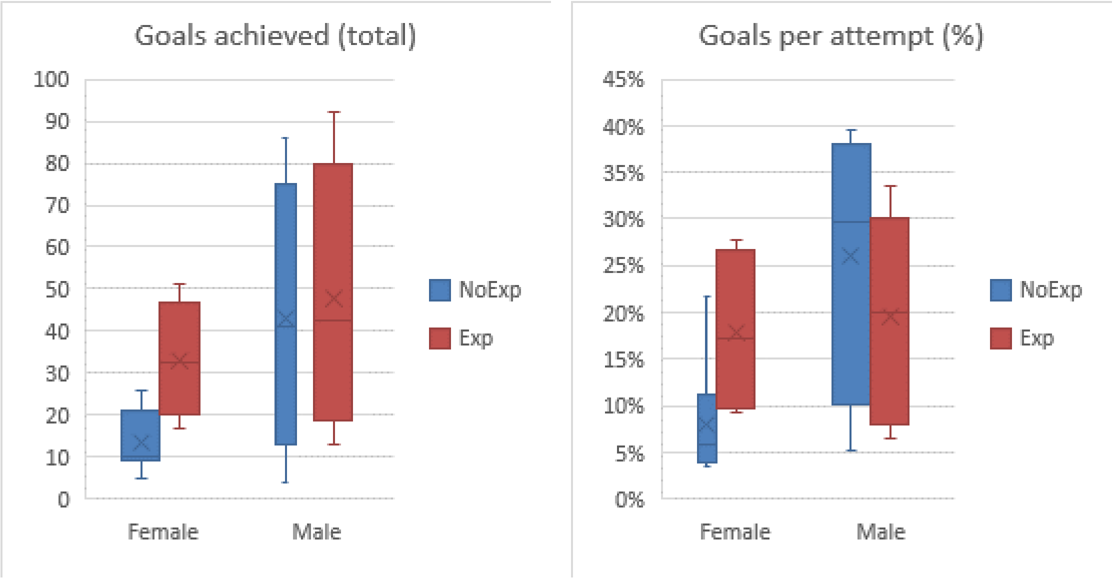


Figure 60. Gender differences in the total number of goals achieved (left) and goals per attempt (right) during the training sessions, by previous video game experience.
Exp: participants with previous video game experience; NoExp: Participants with low video game experience.

In terms of educational level, most participants had some degree of university education (n = 22), either finished or in progress, while a minority had just completed secondary education (n = 5) (see Table 41 in the annex). No participant in the study had less than secondary education. When examining how the level of education is spread among the groups, the active and sham stimulation conditions had approximately equivalent groups (iTBS: 11 university, 3 secondary; Sham: 11 university, 2 secondary), while the high and low video game players showed bigger differences (Experienced VGP: 8 university, 4 secondary; Non-experienced VGP: 14 university, 1 secondary).

When the two independent variables are combined, we can observe how the participants with only secondary studies are more prevalent in the experienced video game players conditions (see Table 42 in the annex).

3.3.3 Subjective experience during VG play

The three variables measured during each training session, the levels of motivation, fun, and frustration, provide information about the subjective experience towards the video game training sessions for each participant. Across the ten training sessions, values tend to remain stable, and *frustration* seems to act as the inverse of *motivation* and *Fun*, which in turn display very similar values for all the sessions. There is a slight increase in the *motivation* and *fun* levels (and decrease of *frustration*) from the first to the second training session that remained stable from that moment on. *Frustration* appears to rise slightly towards the last session, maybe indicating the impossibility of achieving a self-declared goal. In all cases, variability is high among participants and values overlap with each other, downplaying the small variations found between the mean values in each session (see Figure 61).

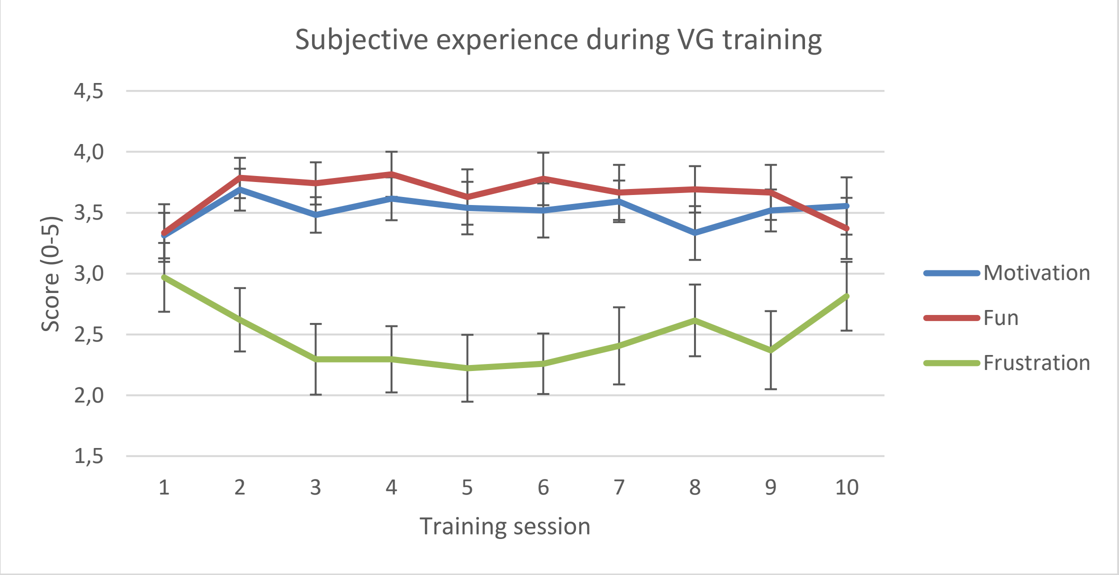


Figure 61. Evolution of the self-reported motivation, fun, and frustration across the ten training sessions. Errors bars indicate one standard error.

These variables display a moderate to strong significant correlations against each other. The strongest correlation is found between the level of motivation and fun, where a positive relationship is found. The levels of motivation before the training session also show a moderate negative correlation with the levels of frustration after playing. Finally, another strong and significant correlation appears between the level of frustration and the fun experienced during video game play (see Table 23).

		Motivation	Fun	Frustration
Motivation	Pearson Correlation	1	.880**	-.462*
	Sig. (2-tailed)		.000	.015
	N	27	27	27
Fun	Pearson Correlation	.880**	1	-.606**
	Sig. (2-tailed)	.000		.001
	N	27	27	27
Frustration	Pearson Correlation	-.462*	-.606**	1
	Sig. (2-tailed)	.015	.001	
	N	27	27	27

Table 23. Correlation table for the three self-reported variables (motivation, fun, and frustration) for each video game training session. **. Correlation is significant at the .01 level (2-tailed). *. Correlation is significant at the .05 level (2-tailed).

When correlating these three variables with other measures of video game performance, only a few variables achieved significant values, while most of them did not show any link. Only the *time per attempt* variable displayed moderate positive correlations with both the level of *motivation* and the *fun* experienced during the video game training sessions, whereas *frustration* was not linked to video game performance in any way. Other measures of video game performance, such as the number of achieved goals, the number of attempts or the ration between the two were not linked to the subjective experience during the training sessions. Finally, qualitative measures of video game performance as recorded before and after the training period, indicative of the baseline video game expertise and video game performance after the training period respectively, were not correlated to these three subjective variables in any way (see Table 24).

		Goals achieved (stars)	Attempts	Performance (goals/attempts)	Time per attempt	Video game expertise PRE	Video game expertise POST
Motivation	Pearson Correlation	-.183	-.270	-.098	.404*	-.073	.013
	Sig. (2-tailed)	.360	.173	.626	.037	.717	.950
	N	27	27	27	27	27	27
Fun	Pearson Correlation	-.312	-.359	-.196	.407*	-.191	-.068
	Sig. (2-tailed)	.113	.066	.326	.035	.341	.737
	N	27	27	27	27	27	27
Frustration	Pearson Correlation	.368	.310	.277	-.361	.305	.268
	Sig. (2-tailed)	.059	.115	.162	.064	.122	.177
	N	27	27	27	27	27	27

Table 24. Correlation table between the three self-reported variables (motivation, fun, and frustration) for each video game training session and video game performance measures (before, during and after the training period). *. Correlation is significant at the .05 level (2-tailed).

When the levels of motivation, fun, and frustration are examined among the experimental groups, no meaningful differences are present (see Table 25, Table 26 and Table 27). By TMS modality, participants report similar motivation [$F_{(1,25)}$=.143, p=.708], fun [$F_{(1,25)}$=.021, p=.885] and frustration [$F_{(1,25)}$=.255, p=.618] levels, and none of them reached significance, either comparing the means or for each individual session.

		N	Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Motivation	Sham	13	3.5600	.75375	3.1045	4.0155	2.50	5.00
	iTBS	14	3.4857	.83007	3.0064	3.9650	2.10	5.00
	Total	27	3.5215	.77984	3.2130	3.8300	2.10	5.00
Fun	Sham	13	3.6538	.79856	3.1713	4.1364	2.10	5.00
	iTBS	14	3.6543	.76361	3.2134	4.0952	2.30	4.90
	Total	27	3.6541	.76542	3.3513	3.9569	2.10	5.00
Frustration	Sham	13	2.6769	1.27093	1.9089	3.4449	0.00	4.50
	iTBS	14	2.3686	.97080	1.8081	2.9291	.30	3.90
	Total	27	2.5170	1.11417	2.0763	2.9578	0.00	4.50

Table 25. Descriptive statistics for motivation, fun, and frustration reported during the ten video game training sessions, by TMS group.

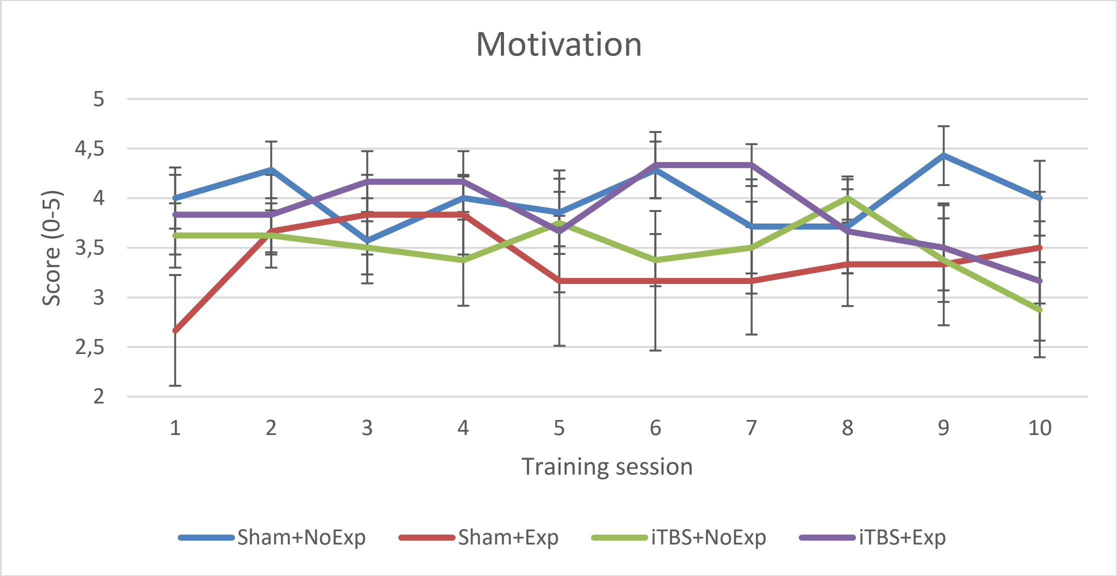


Figure 62. Evolution of participant's motivation across the ten training sessions, by TMS group and previous video game experience. Error bars indicate one standard error.

By previous video game experience, results were similar (see Table 26). Participants' motivation [$F_{(1,25)}$=.442, p=.512], fun [$F_{(1,25)}$=.139, p=.712], and frustration [$F_{(1,25)}$=.183, p=.673] did not show any significant differences between groups, either as a whole or for each separate training session.

		N	Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Motivation	No	15	3.4187	.82916	2.9595	3.8778	2.10	5.00
	Yes	12	3.6500	.72801	3.1874	4.1126	2.60	5.00
	Total	27	3.5215	.77984	3.2130	3.8300	2.10	5.00
Fun	No	15	3.6840	.78766	3.2478	4.1202	2.30	5.00

		N	Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
	Yes	12	3.6167	.76969	3.1276	4.1057	2.10	4.90
	Total	27	3.6541	.76542	3.3513	3.9569	2.10	5.00
Frustration	No	15	2.4707	1.00643	1.9133	3.0280	0.00	3.90
	Yes	12	2.5750	1.28000	1.7617	3.3883	.30	4.50
	Total	27	2.5170	1.11417	2.0763	2.9578	0.00	4.50

Table 26. Descriptive statistics for motivation, fun, and frustration reported during the ten video game training sessions, by previous video game experience.

When participants are grouped by TMS modality and previous video game experience (see Table 27), the lack of differences between the four groups was notorious, either for motivation [F$_{(3,23)}$=.880, p=.466], fun [F$_{(3,23)}$=1.022, p=401], or frustration [F$_{(3,23)}$=.516, p=.676].

		N	Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Motivation	Sham+NoExp	7	3.6400	.92261	2.7867	4.4933	2.50	5.00
	Sham+Exp	6	3.4667	.56804	2.8705	4.0628	2.90	4.40
	iTBS+NoExp	8	3.2250	.74402	2.6030	3.8470	2.10	4.20
	iTBS+Exp	6	3.8333	.87331	2.9169	4.7498	2.60	5.00
	Total	27	3.5215	.77984	3.2130	3.8300	2.10	5.00
Fun	Sham+NoExp	7	3.9000	.78740	3.1718	4.6282	2.80	5.00
	Sham+Exp	6	3.3667	.77632	2.5520	4.1814	2.10	4.40
	iTBS+NoExp	8	3.4950	.78862	2.8357	4.1543	2.30	4.60
	iTBS+Exp	6	3.8667	.74207	3.0879	4.6454	3.10	4.90
	Total	27	3.6541	.76542	3.3513	3.9569	2.10	5.00
Frustration	Sham+NoExp	7	2.4571	1.23539	1.3146	3.5997	0.00	3.90
	Sham+Exp	6	2.9333	1.37792	1.4873	4.3794	1.20	4.50
	iTBS+NoExp	8	2.4825	.84694	1.7744	3.1906	1.20	3.80
	iTBS+Exp	6	2.2167	1.18223	.9760	3.4573	.30	3.90
	Total	27	2.5170	1.11417	2.0763	2.9578	0.00	4.50

Table 27. Descriptive statistics for motivation, fun, and frustration reported during the ten video game training sessions, by TMS group and previous video game experience.

3.3.4 Effects of the TMS stimulation

For the first batch of analysis, participants were grouped by the first independent variable: the type of stimulation they received during the experiment, regardless of their previous video game experience. Considering a total valid sample of 27 participants, 14 of them were assigned to the active iTBS group and 13 of them received sham iTBS stimulation (see Table 28).

		Video game experience
		Experienced and Non-experienced VGP
Stimulation type	**Active iTBS**	14
	Sham iTBS	13

Table 28. Factorial matrix displaying group sizes for the active and sham iTBS groups.

3.3.4.1 Video game-related variables

Descriptive analysis

The several measures of video game performance do not seem to differ between TMS groups. For instance, qualitative video game performance during the pre-intervention assessment show similar scores for both groups, and the situation does not change when the same measures are shown at the end of the training sessions. Actual in-game performance variables, either in the form of achieved goals (stars), number of attempts, or goals/attempt seems to give similar results for both groups. Participants in the sham iTBS group, however, seem to spend more time per attempt during the gaming sessions (see Table 43 in the annex).

Determination of parametric adjustment

When divided by TMS group, some variables related to the performance during the video game training presented a non-normal distribution. That was specifically the case of the goals achieved during the training sessions, the goals per attempt, and the time per attempt (see Table 71 in the annex), whereas the homogeneity of variances was met in all but one variable: the time dedicated per attempt (see Table 73 in the annex).

Main results

No baseline differences were found for the qualitative measures of video game performance at during the assessment sessions for the two TMS groups (see Table 86 in the annex).

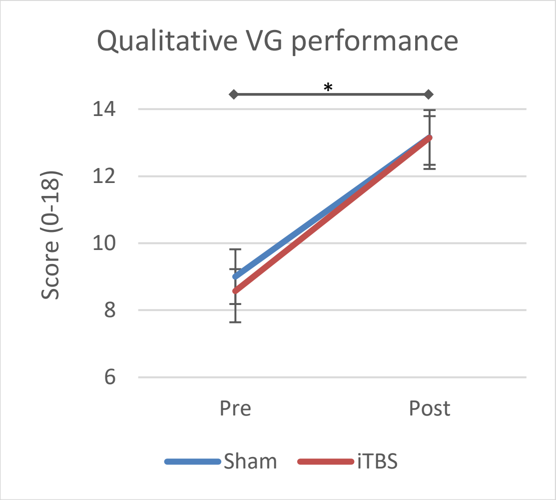


Figure 63. Mean qualitative scores for video game performance during the pre—and post-training assessments, by TMS group.
* Significant at the .05 probability level. Error bars indicate one standard error.

When analyzing this qualitative measure of performance using a repeated measures GLM including the pre- and post-intervention assessments, a highly significant effect of the training sessions can be observed [$F_{(1,25)}$=102.743, p=.000]. However, this effect did not interact with the stimulation group [$F_{(1,25)}$=.757, p=.393] and no between-subject differences appeared [$F_{(1,25)}$=.121, p=.731] (see Figure 63).

Performance variables during the video game training sessions did not show differences between the two groups. Neither the number of goals achieved [U=88.500, p=.903], the number of attempts [$t_{(25)}$=-.522, p=.606], the goals per attempt [U=86.500, p=.827], or the time per attempt [$F_{(1,15.606)}$=2.043, p=.173] resulted in significant differences.

3.3.4.2 Reaction times

Overall, reaction times show a clearly different pattern for each one of the three subtasks, where the *simple reaction time* task gets faster responses [61ms on average] compared to the *direction choice reaction time* task [at baseline: $t_{(26)}$=-10.782, p<.001], which in turn has even faster responses [128ms on average] compared to *choice reaction time* task [at baseline: $t_{(26)}$=-12.197, p<.001] (see Figure 64). These differences are found across all groups, regardless of the subdivision (TMS, previous video game experience, or both), and are present in the three time points.

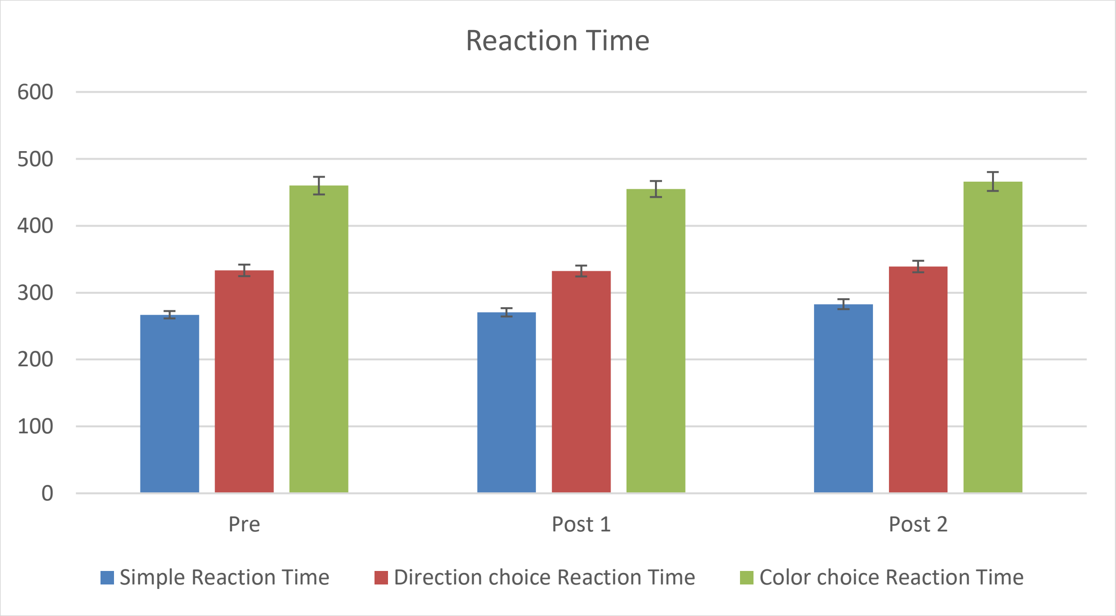


Figure 64. Mean values for the three reaction time tasks at each time point.
Error bars indicate one standard error.

Moreover, response times do not change from one session to the next, remaining stable for all three assessments [SRT: $t_{(26)}$=-.801, p=.43; DRT: $t_{(26)}$=.007, p=.94; CRT: $t_{(26)}$=.253, p=.80].

Descriptive analysis

As expected, baseline reaction times grouped by TMS modality were lower for the simple task compared to the direction and color choice tasks, and this effect is maintained for each of the post-intervention assessments. There is no degree of overlap among the response speed in the three tasks, indicative of the qualitatively different cognitive processing needed for each one (see Table 44).

Determination of parametric assumptions

The data obtained through the reaction time tasks in some cases did not fit a normally distributed curve, particularly the direction choice reaction time during the first assessment in the iTBS group, and direction choice reaction time during the third assessment. Moreover, the Color choice reaction time during the first assessment also failed to meet a normal distribution, all of them measured by the Shapiro-Wilk test (see Table 71 in the annex).

Differential variables measuring the change between the two assessments in reaction time tasks succeed in passing the normality test for the TMS group subdivision (see Table 72 in the annex).

All but one of the measures, the first post-assessment of the color choice reaction time, met the assumption of homogeneity of variance, according to Levene's test for equality of variances (see Table 73 and Table 74 in the annex).

For the repeated measures analysis, Mauchly's test indicated that the variances of all possible pairs of within-subject conditions for reaction time task were equal meeting the sphericity criteria (see Table 75 in the annex).

Main results

No significant differences were detected in the baseline measures of reaction times between the two stimulation groups (see Table 86 in annex).

Analyzing the results from the simple reaction time task, a GLM using the three assessments as repeated measures with TMS as the between-subjects factor showed a main effect of the assessment time point [$F_{(2,50)}$=5.947, p=.005] and of the interaction between the assessment time point and the stimulation type [$F_{(2,50)}$=4.453; p=.017].

When exploring a possible trend of the main effect when accounting for the effect of these three assessments we observe significance in the form of a linear relationship [$F_{(1,25)}$=7.531; p=.011], whereas the interaction effect of the assessment time point and the stimulation type showed significance when fitting a linear ($F_{(1,25)}$=4.405; p=.046) and a quadratic [$F_{(1,25)}$=4.571; p=.042] function. No between-subject effects of the TMS stimulation were found [$F_{(1,25)}$=.042; p=.839] when exploring the results of the simple reaction time task.

However, when only using the pre-intervention and first post-intervention assessments, the GLM did not show any significant effect of the number of assessment sessions [$F_{(1,25)}$=.609; p=.442] or for the interaction effects with the TMS stimulation type [$F_{(1,25)}$=.030; p=.864], which also did not show any between-subjects effects [$F_{(1,25)}$=.949; p=.339].

Exploring the differences between the baseline and the first post-assessment (Post-Pre) an ANOVA did not show significant differences [$F_{(1,25)}$=0.30, p=.864] according to the stimulation group, whereas reaching significance [Mann-Whitney, U=40.500, p=.014] when comparing the follow-up assessment with the baseline.

Figure 65. Simple, direction choice and color choice reaction time speeds (in ms) at the three measured time points, by TMS group.
* Significant at the .05 probability level. Error bars indicate one standard error.

Regarding the direction choice reaction time task, comparing the means of the post-assessments (Post, Follow-up) with the baseline (Pre) using a one-way ANOVA, no significant differences were found for neither the first post-assessment [$F_{(1,25)}$=.953, p=.338] nor the follow-up assessment [$F_{(1,25)}$=2.663, p=.115]. Differences between the two groups during the first post-assessment [$t_{(25)}$=1.028, p=.314] and the follow-up assessment [U=89.000, p=.923] were not significant either.

In the case of the color choice reaction time, comparing the post-assessments (Post, Follow-up) against the baseline (Pre) using an ANOVA, no significant differences were found for neither the post-intervention assessment [$F_{(1,25)}$=1.459, p=.238] nor the follow-up assessment [$F_{(1,25)}$=.927, p=.345]. Directly comparing the differences between groups, no significant results were found at the post-intervention assessment [Welch's ANOVA, $F_{(1,18.646)}$=.532, p=.475] or the follow-up assessment [Student's t-test, $t_{(25)}$=-.442, p=.662].

3.3.4.3 Digit Span

Descriptive analysis

Responses in the digit span task, measured as the number of correctly responded items, tend to get higher scores on the forward modality compared to the backward part of the task, indicative of the more complex cognitive processing required for the latter. Mean scores tend to gradually increase with each application of the test both for the forward and backward modalities. While the mean scores tend to be higher in the forward modality, the maximum scores were reached during the backward modality (see Table 45 in the annex).

Parametric determination

When testing the data obtained from the forward and backward digit task, a couple of measures did not adjust to normality (see Table 71 in the annex). The third assessment of forward digits for the active ITBS group and the first assessment of backward digits for the same group showed that the data was not normally distributed, according to the Shapiro-Wilk test.

In this case, the differential variables measuring the change in digit span performance between the baseline and the first post-intervention assessment fitted the normal curve when participants were divided according to TMS groups (see Table 72 in the annex).

Homogeneity of variances was present in all but one of the measures related to the digit span task. The follow-up assessment of the forward digits did not meet this criterion (see Table 73 and Table 74 in the annex).

Mauchly's test of sphericity indicated that the assumption of sphericity had not been violated for either forward or backward digits (see Table 75 in the annex).

Main results

No baseline differences could be appreciated on a significant level between the mean scores of the forward and backward digit tasks (see Table 86 in annex).

A repeated measures GLM including the pre-assessment and the first post-assessment for the forward digit span task indicated only a significant effect of the number of assessments [$F_{(1,25)}=6.156$, $p=.020$], but not when the interaction effect of the TMS modality is taken into account [$F_{(1,25)}=.008$, $p=.927$]. Similarly, the between-subjects effect of the TMS stimulation did not reach significance [$F_{(1,25)}=.015$, $p=.903$]. Comparing the first post-intervention assessment with the baseline, no differences were found [one-way ANOVA, $F_{(1,25)}=.008$, $p=.927$].

Taking into account the follow-up assessment of the forward digit span task, analyzing the Follow-up-Pre difference using a one-way ANOVA, no differences were found [$F_{(1,25)}=.037$, $p=.849$], as well as no between-subjects differences appeared at this time point [Welch’s ANOVA, $F_{(1,18.111)}=.003$, $p=.957$].

Regarding the backward digit span task, a one-way ANOVA indicates no significant differences between the pre-assessment and the post-intervention [$F_{(1,25)}=.028$, $p=.867$] and follow-up [$F_{(1,25)}=.048$, $p=.828$] assessments. Likewise, between subjects differences were not significant at any of these two time points [$t_{(25)}=-.950$, $p=.351$; $t_{(25)}=-.866$, $p=.394$].

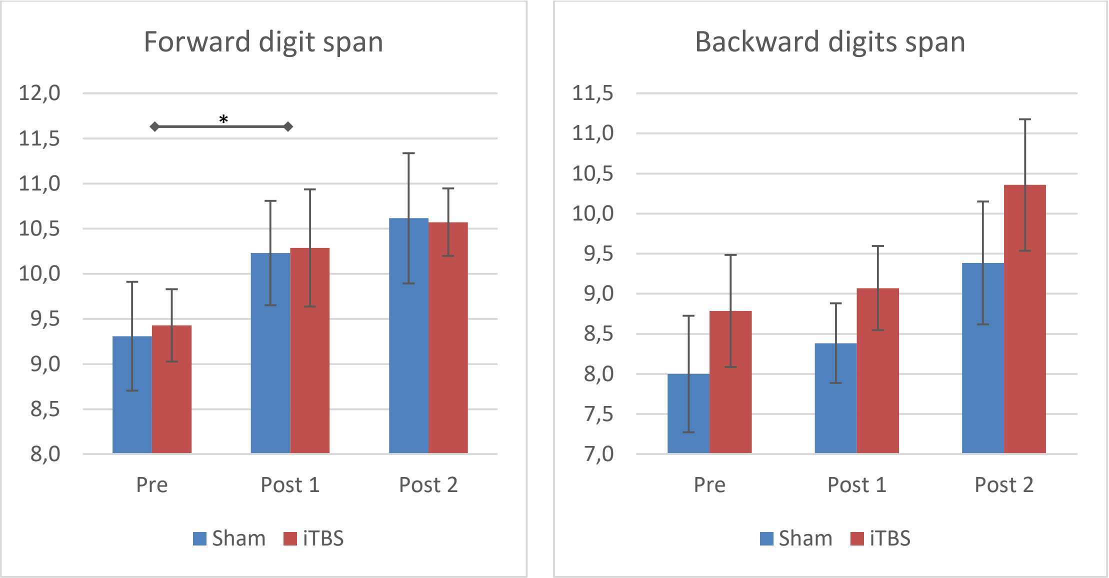


Figure 66. Digit span task scores (forward and backward) at the three measured time points, by TMS group. Higher values indicate a better performance. * Significant at the .05 probability level. Error bars indicate one standard error.

3.3.4.4 Raven's Progressive Matrices

Descriptive analysis

Scores on the Raven's Progressive Matrices are characterized by having similar means between the two groups before and after the intervention. Scores tend to be high, approaching the maximum possible value in that task, 31, for each assessment. The only marked difference appears in how the scores are distributed, the active iTBS group presenting a higher variability, particularly during the pre-intervention assessment.

Regarding the average time to complete each item, measured in milliseconds, differences can be observed between the two groups, where the active iTBS group needed less time per item in both the pre- and post-intervention assessments, but in both cases, there was a tendency to reduce the response time for the latter assessment.

Determination of parametric adjustment

In the Raven Progressive Matrices test, the scores during the first assessment when participants are divided by stimulation group do not follow a normal distribution as checked with the Shapiro-Wilk test. Reaction times in that test in both groups, however, do not violate the normality assumption (see Table 71 in the annex).

The differential data from the only post-intervention assessment against the baseline from Raven's test show that data fails to meet normality for the direct score measure, but is normally distributed when response times are taken into account (see Table 72 in the annex).

The scores of the Raven task in the post-assessment did not meet the homoscedasticity assumption according to Levene's test, but that criterion was met in the pre-intervention assessment. When examining the response times, both the pre- and post-intervention assessment data showed equal variances, as analyzed with the same test (see Table 73 and Table 74 in the annex).

Main results

Exploring the possibility of baseline differences, they were not present for the scores obtained in this task, but in the case of response times, the two TMS stimulation groups showed significantly different baselines, where the sham stimulation group was significantly slower in responding to the items (see Table 86 in the annex).

Comparing the median score differences between the pre-assessment and the first post-assessment using non-parametric analysis (Mann-Whitney's U), no significant differences were found [U=81.500, p=.638]. Directly comparing the scores during the post-intervention assessment did not return significant differences either [Welch's ANOVA, $F_{(1,22.183)}$=.661, p=.425].

In the case of the response times, a repeated measures GLM could not find either an effect of the number of sessions [$F_{(1,25)}$=2.096, p=.160] or an interaction effect of the number of sessions and the TMS stimulation [$F_{(1,25)}$=.592, p=.449]. However, a between-subject effect of just the TMS stimulation modality was found [$F_{(1,25)}$=7.412, p=.012], in agreement the already present baseline differences between the two groups.

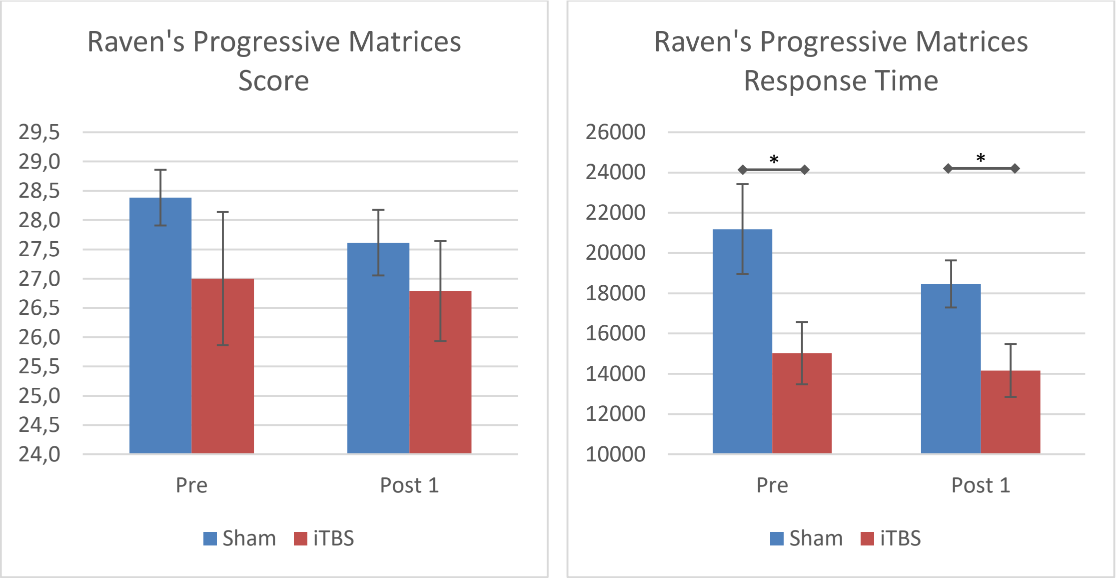


Figure 67. Raven's Progressive Matrices scores and response times per item in (ms) at the three measured time points, by TMS group. Higher values in the score (left) indicate a better performance, whereas lower response times (right) indicate faster correct responses. * Significant at the .05 probability level. Error bars indicate one standard error.

3.3.4.5 Five-Point Test (5PT)

Descriptive analysis

The scores from the Five-Point Test (5PT) averaged 31.56 completed items, where the TMS sham stimulation group had a slightly better performance and less variability compared to the iTBS group (see Table 47 in the annex).

Determination of parametric adjustment

The unique measure obtained from the Five-Point Test (5PT), in the form of a score, was observed to fit the normal distribution when participants were divided by stimulation group (see Table 71 in the annex). Likewise, Levene's test for equality of variances showed that this variable was homoscedastic (see Table 73 in the annex).

Main results

Since this variable was only measured during the first post-assessment, only a direct comparison of the scores (using the Student's t-test) will suffice to observe differences between the TMS groups. In this case, the test was unable to find a significant difference in the performance between the two groups [$t_{(25)}$=.936, p=.358].

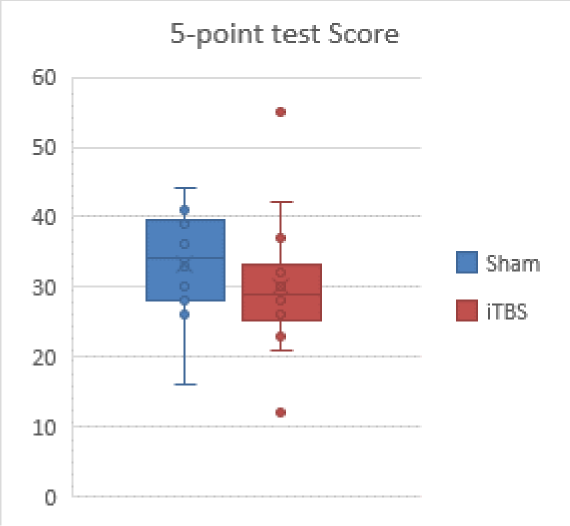


Figure 68. Scores on the Five-Point Test (5PT) as measured after the intervention, by TMS group.

3.3.4.6 N-Back

Descriptive analysis

Compared by TMS stimulation group, the three main variables obtained by the N-back task display similar tendencies. Scores on the N-back task tend to remain equal between the two groups, with a slight increase towards the last assessment. Likewise, response times follow an equivalent trend, remaining in similar values along the three assessments with a tendency to decrease. The *d'* value, which is based on the performance on the other two variables, summarizes the same effect, and perhaps accentuating a small difference between the groups, the active iTBS group obtaining better scores than the sham group in each of the three time points (see Table 48).

Determination of parametric adjustment

The measures of task score obtained during the three time points do not meet the normality criteria for the iTBS group, as measured by the Shapiro-Wilk test. The responses in all the other measures, including the response times and the d' index, were normally distributed (see Table 71 in the annex).

The variables containing the scores, the response times as well as the D' met the criterion of equality of variances, for both experimental groups (see Table 73 in the annex).

N-back differential data had also some problems adjusting to normality. That was the case for the reaction times for the TMS group subdivision and for the difference in direct scores for the game experience subdivision, whereas the rest of the measures in that task did adjust to normality (see Table 72 in the annex).

Mauchly's test indicated that the sphericity assumption was not met for the scores and response times of the n-back task, although the d' index was an exception, meeting all the parametricity criteria (see Table 75 in the annex).

Main results

The measures obtained for the N-back task did not show any baseline differences between the TMS groups when direct measures are contemplated. That is valid for the n-back score and the n-back response time. However, the n-back d' index, which takes into account both the accuracy and the response speed, did show baseline differences between the active iTBS and sham groups (See Table 86 in the annex).

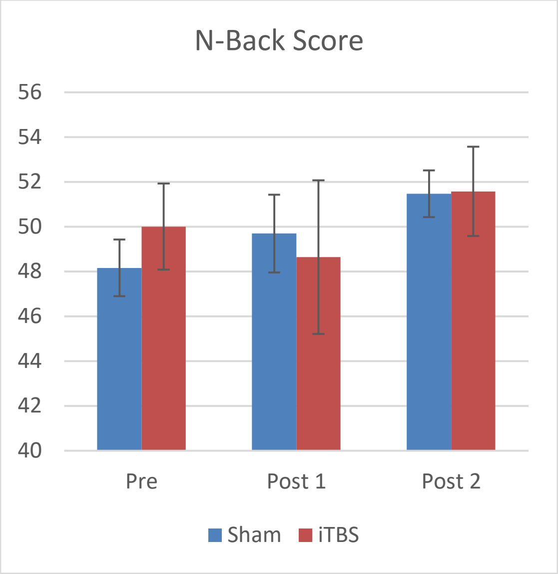


Figure 69. N-back scores across the three time points, by TMS group.
Error bars indicate one standard error.

Due to the non-normality of the data regarding the scores, the differences between the baseline and the two post-intervention assessments were used as a measure of the interaction effects between the video game training and the stimulation groups. No significant differences were found between the baseline and the first post-intervention assessment $F_{(1,25)}=.851$, $p=.365$), and the same result was obtained when comparing the data regarding the follow-up assessment [$F_{(1,25)}=.1.085$, $p=.308$]. Directly comparing the scores between groups at these time points, no significant differences appeared at the post-intervention [$U=76.000$, $p=.465$] or follow-up [$U=72.500$, $p=.367$] assessments.

A repeated measures GLM was used to assess the differences between the active iTBS and sham groups for the response times of the n-back task. The complete model, including the three time points, detected a significant effect of the number of assessments [$F_{(1.504,37.608)}=4.852$ $p=.021$], but not an interaction effect of the assessments by the stimulation type [$F_{(1.504,\ 37.608)}=.454$, $p=.583$]. Contrasting the effect of the number of assessments against a linear regression, a significant effect was found ($p=.042$), but the significance was even higher when fitted for a quadratic curve ($p=.024$). No between-subject effect was found [$F_{(1,25)}=.123$, $p=.729$] when exploring the differences among the TMS groups.

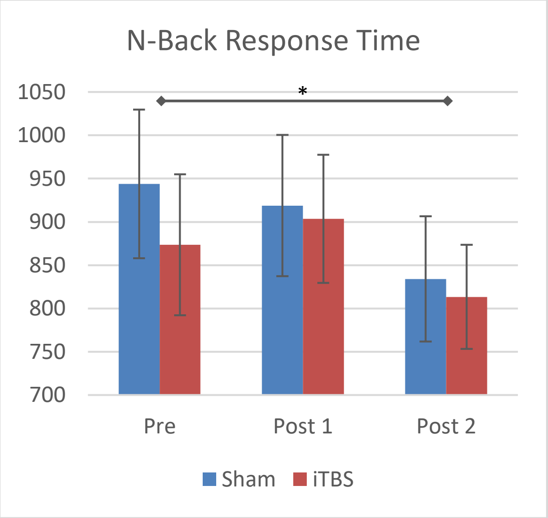


Figure 70. N-back response times across the three time points, by TMS group.
The effect of each assessment session is significant, but no effect of the stimulation group was found. * Significant at the .05 probability level. Error bars indicate one standard error.

When applying the repeated measures GLM to only the first post-intervention assessment, the effect of the number of assessments disappeared [$F_{(1,25)}=.013$, $p=.910$], probably due to the initial differences in the pre-assessment. The interaction effect of the number of assessments and the TMS group remained non-significant [$F_{(1,25)}$=.794, p=.381], as well as the fitness of the data to a linear or quadratic curve. Just like the complete model, no between-subject differences of the TMS groups were observed [$F_{(1,25)}$=.152, p=.700].

Comparing the two post-assessments against the baseline, no significant differences arise for either the first post-assessment [U=79.000, p=.560] or the follow-up assessment [U=88.000, p=.884].

A repeated measures GLM of the d’ index indicated that, when including the three time points, no significant differences between TMS groups can be observed regarding the effect of the consecutive assessment sessions [$F_{(2,50)}$=2.466, p=.095], or the interaction effect of the sessions and the stimulation type [$F_{(2,50)}$=.016, p=.984]. There is, however, a between-subject effect of the TMS stimulation group [$F_{(1,25)}$=5.526, p=.027]. Including just two time points (the baseline and the first post-intervention assessment), does not affect the results: neither the effect of the session number [$F_{(1,25)}$=.436, p=.515] or the interaction between the session number and the TMS group [$F_{(1,25)}$=.001, p=.974] is significant, whereas the between-subject effect of the TMS group is still present [$F_{(1,25)}$=5.436, p=.028].

Directly comparing the results on the d’ index from post-assessments with the baseline shows that neither for the first post-assessment [$F_{(1,25)}$=.001, p=.974] and the follow-up assessment [U=89.000, p=.923] showed significant differences.

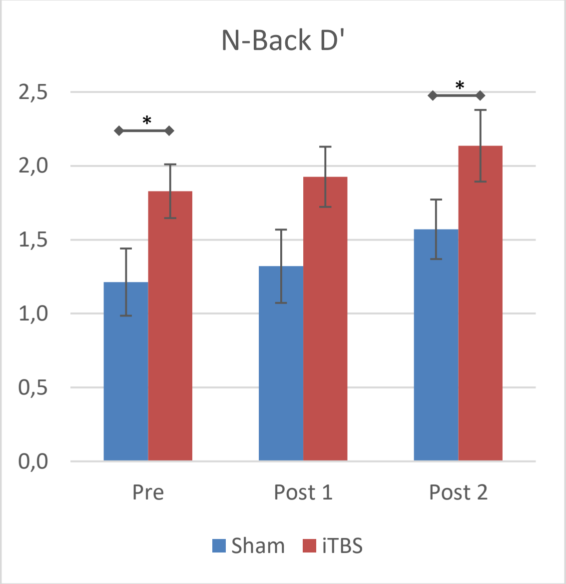


Figure 71. Values of the d’ index of the n-back task at the three measured time points, by TMS group. * Significant at the .05 probability level. Error bars indicate one standard error.

3.3.4.7 Mental Rotation

The analog effect in which visuospatial stimuli are processed is shown in this task, where greater degrees of rotation between two figures take longer times to process, as observed in the classic 1971 study (Shepard & Metzler, 1971). These results could have been replicated in this sample, where response times show an almost perfect increase for each 20º step, taking a longer time to process the more divergent each pair of stimuli was (see Figure 72). Comparing the three time points, a reduction of the time needed to process each stimulus is shown for each subsequent assessment, indicating that this ability is subject to training effects, unlike simpler reaction time tasks that show more invariable results.

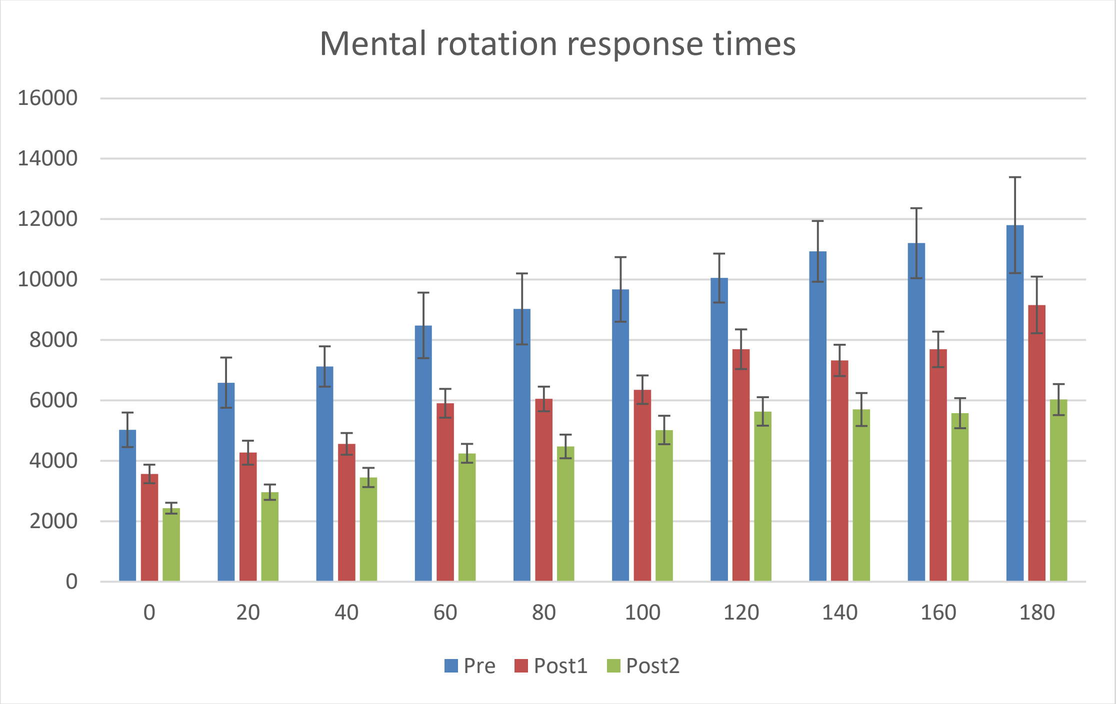


Figure 72. Mean response times in correct responses for each rotation degree in the mental rotation task across the three assessments.

The ratio of correct responses is inversely proportional to the rotation degrees for each item pair, indicating that greater differences in degrees no only increase the time needed to process the stimulus, but also increases the difficulty of the task. Some changes can be appreciated from the pre-intervention to the post-intervention assessments, where the latter show a higher number of correct responses, but mostly in the most difficult pairs of figures (see Figure 73).

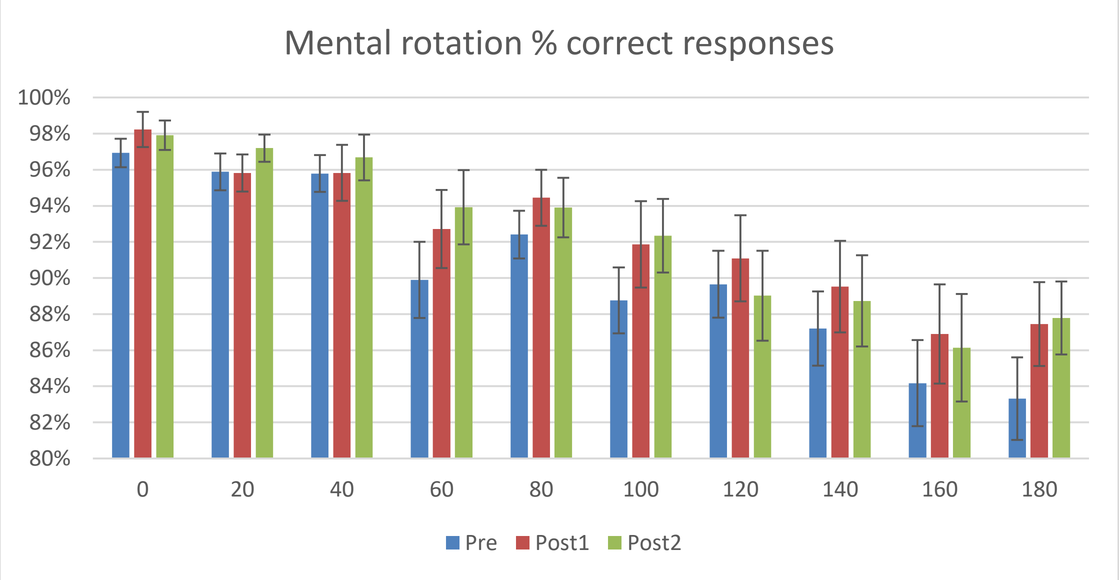


Figure 73. Proportion of correct responses in the mental rotation task depending on the figure's rotation degrees.

Exploring the possible gender differences in this task, as previous literature (Feng et al., 2007) has observed an initial decreased performance of female participants that tends to catch-up with further training, could not be replicated in this case. Male participants, overall, present slightly lower response times for correct items compared to females (see Figure 74), but these mean differences, although present during all three assessments, were not big enough to be significant [PRE: $t_{(25)}$=-1.156, p=.258; Post: $t_{(25)}$=-1.692, p=.103; Follow-up: $t_{(25)}$=-2.003, p=.056], and variability within each gender was greater than differences between genders. Comparing the percentage of correct items, there is a small but non-significant difference [Females: 88.4±5.3%, Males: 92.7±8.6%; $t_{(25)}$=-1.577, p=.128] between males and females, where the former obtain better scores overall. However in the assessment following the video game training period, scores were almost identical between genders [Females: 92.0±10.4%, Males: 93.3±10.4%; $t_{(25)}$=-0.348, p=.731], having leveled that initial difference in performance.

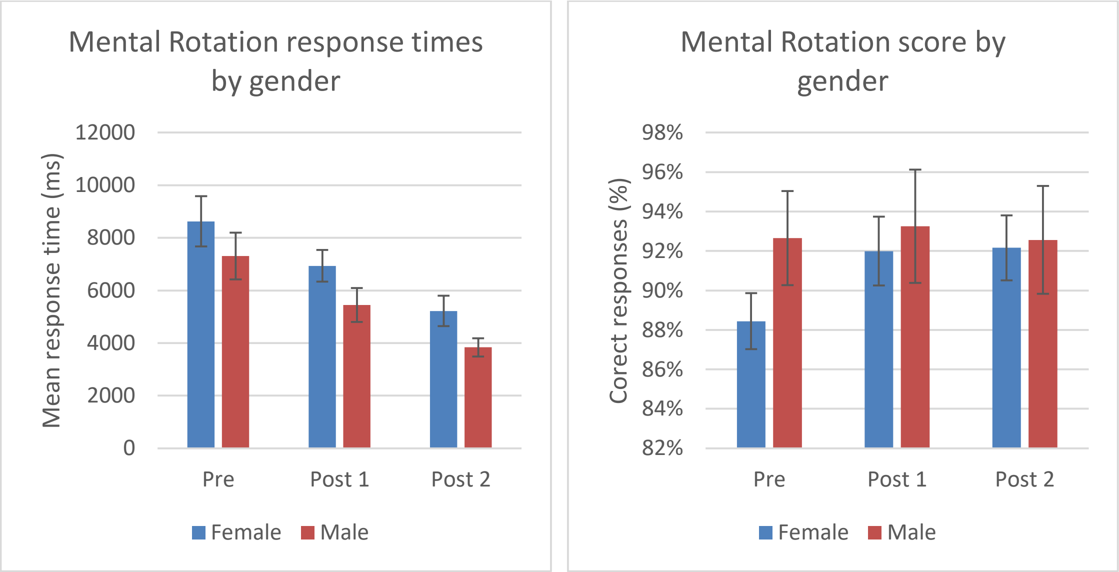


Figure 74. Mean response times (left) and scores (right) for female and male participants in the mental rotation task across the three assessments.
Error bars indicate one standard error.

Descriptive analysis

The scores on this task represent the proportion of correctly responded items, ranging from 0 to 1. The level of accuracy was similar between the two TMS groups, surpassing the 90% of correct responses in most cases, where the sham TMS group seems to have a slight advantage that is carried out to the two post-intervention assessments.

Response speeds by TMS group (in milliseconds) also show equivalent results among the two groups, with no big differences from one group to the other. Response speeds tend to follow a notable decreasing trend with each subsequent assessment regardless of the stimulation group (see Table 49).

Determination of parametric adjustment

When analyzing the data belonging to the mental rotation task, non-adjustment to normality is found in several measures as measured with the Shapiro-Wilk test. Separated by TMS group, the data from the direct scores, the post-intervention and follow-up assessment were not normally distributed, as were the baseline and follow-up assessments when reaction times are taken into account, all of them belonging to the active iTBS group (see Table 71 in the annex).

The differential scores for mental rotation showed the opposite effect. Whereas direct scores on mental rotation showed an adjustment to normality, the differential scores for the reaction times in that task failed to meet normality consistently across the two subgroups (see Table 72 in the annex).

Variances of the scores on this task between the two groups were not equal for the post-intervention and follow-up assessments, and response times also failed to meet this criterion for the baseline and follow-up assessments as measured by Levene's test (see Table 73 in the annex).

A violation of the sphericity assumption, as measured by Mauchly's test, was detected for the response time measure in the mental rotation task (see Table 75 in the annex).

Main results

The scores obtained in the mental rotation task at the baseline assessment did not differ between TMS stimulation groups. In the case of the response times, analyzed using the Kruskal-Wallis test due to their non-normality, no differences could be observed either at the baseline (see Table 86 in the annex).

Due to the lack of parametric adjustment, neither of the two measures (scores and response times) in the mental rotation task were analyzed using a GLM, and between-group comparisons were used instead.

Comparing the scores on this task from the baseline to the two post-intervention assessments, no significant differences were found between the groups in either the difference between the baseline and post-intervention [$F_{(1,25)}$=.830, p=.371] or follow-up [$F_{(1,25)}$=.011, p=.917] assessments, as compared using a one-way ANOVA. Directly compared the performance in the post-intervention [U=83.000, p=.679] and follow-up [U=67.000, p=.244] assessments, no differences were found either.

Comparing the response time differences between the baseline and the two post-intervention assessments, neither the first post-intervention [U=54.000, p=.073] or the follow-up [$F_{(1,21.832)}$=2.106, p=.161] assessments show significant changes as measured by a t-test. In only the differences in each time point are used instead of comparing them against the baseline, the lack of significant differences was still present [$t_{(25)}$=-.068, p=.946; U=85.000, p=.771].

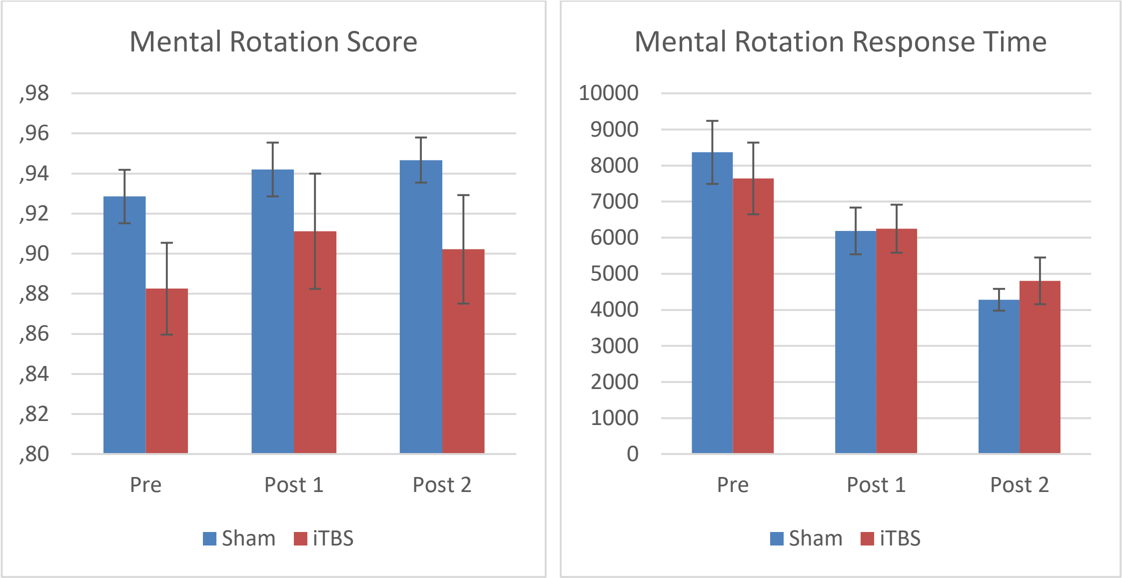


Figure 75. Scores (left) and response times (right) in the mental rotation task, by TMS group. Error bars indicate one standard error.

3.3.4.8 Stop-Switching task

Descriptive analysis

The stop-switching task provides a series of measures including the score and response times of the *go* trials, the score from the *stop* trials, the *stop-signal reaction time* index, and the score and response times from the *switching* trials.

The scores on *go* trials appear to be quite homogeneous across groups and each assessment, centering on the 286 mark out of a maximum of 288, which many participants reached regardless of the group. A better indicator of the performance in these trials are the response times. Whereas at baseline both groups seem to respond at the same rate, differences are more notable in the post-intervention assessments, and a tendency to increase response times across the assessments can also be observed (see Table 50 in the annex).

Stop trials, only measured directly in its accuracy, seem to be pretty equivalent in both experimental groups. The presence of a certain ceiling effect can be inferred, since some participants in all groups and assessments were able to reach the maximum score (72), although group means tend to remain a few points below that score. A slight tendency to improve the scores as the task is repeated in the subsequent assessments is present in both groups (see Table 50 in the annex).

The stop-signal reaction time measure presents a large difference between the pre-assessment and the first post-assessment, the latter being twice as slow, and keeping that tendency to the follow-up assessment. It also seems to be a slight advantage for the sham TMS group in the baseline and first post-assessment, but not in the follow-up (see Table 50 in the annex).

Scores on switching trials are characterized by homogeneity between the groups, and they usually not reach the maximum possible value. As it is common in this task, scores on the last assessments tend to be slightly bigger than at the baseline. Regarding the response times for switch trials, a difference between groups can be observed, where the active stimulation group has average faster response times in the three assessments. In addition to that, a trend to improve response times across each assessment is visible in this variable (see Table 50 in the annex).

Determination of parametric adjustment

The stop-signal reaction time task provided a large set of measures corresponding to its different subcomponents. Scores on *go* trials were generally not normally distributed in that task when subgroups are formed according to the stimulation modality. This result contrasts with measures of reaction times in the same trials that did fit the normality assumption, as measured by the Shapiro-Wilk test, in all their assessments and in both subgroups (see Table 71 in the annex).

Data from the *stop* scores on the stop-switching reaction time task on occasions displayed non-normality. That is the case of the post-intervention and follow-up assessments, in both subgroups, TMS modality and video game experience, where the Shapiro-Wilk test reached significance in data from the sham condition and low video game experience, respectively (see Table 71 in the annex). On the other hand, the stop-signal reaction time (SSRT) measure had a better fit to the normal distribution. Only during the third assessment, for the active iTBS group, data did not fit the distribution (see Table 71 in the annex).

Next, scores obtained from *switch* trials were analyzed. A general fit to normality was observed in this set of data, with no exceptions. When subgroups are formed according to the stimulation modality, all the data fitted the normal distribution within the required parameters. Finally, the reaction times in *switch* trials followed a similar pattern to scores on the same trials. In the active iTBS/sham division, all reaction times followed a normal distribution, with no normality test reaching significance (see Table 71 in the annex).

When analyzing the differential scores for the diverse stop-switching reaction time measurements, the only variable that does not adjust for normality was the score on *go* trials, for the sham TMS group subdivision. The rest of the data from this task meets all the requirements of normality for the TMS modality subdivision (see Table 72 in the annex).

Main results

None of the variables recorded during the execution of the stop-switching task, regarding the scores and response times of *go*, *stop* and *switch* trials presented baseline differences between the two TMS stimulation groups (see Table 86 in the annex).

Go trials

Go scores, due to their non-normality, were analyzed comparing the two post-intervention assessments against the baseline and comparing the scores on the post-intervention assessments between the two groups. Differences were not found for the difference between the first post-intervention assessment and the baseline [U=87.500, p=.864], and neither a between-subjects effect of the TMS group was found [U=90.000, p=.959] at that time point. Regarding the follow-up assessment, the situation is similar: no significant differences between groups [$F_{(1,25)}$=.014, p=.907] appeared when the difference against the baseline was contemplated, and neither when just that time point was compared between the two stimulation groups [U=88.500, p=.899].

Regarding the response times in *go* trials, the complete model including the three time points yields a significant effect of the number of assessments [$F_{(2,50)}$=3.346, p=.043], fitting a linear regression [F$_{(1,25)}$= 4.713, p=.040], but not when interacting with the TMS group [F$_{(2,50)}$=.603, p=.551], accompanied by a lack of between-subjects effects [F*(1,25)*=.175, p=.679]. If only the first post-assessment is included, the significant effect of the number of assessment disappears [F$_{(1,25)}$=.993, p=.329] and the interaction effect of the assessments and TMS group remains non-significant [F$_{(1,25)}$=.858, p=.363], just like the between-subject effect [F$_{(1,25)}$=.095, p=.761].

Comparing the Post-pre assessment difference, no significant differences per stimulation group were found, either for the first post-intervention assessment [F$_{(1,25)}$=.858, p=.363] or the follow-up [F$_{(1,25)}$=.676, p=.419].

Figure 76. Mean scores (left) and response times (right) for *Go* trials in the stop-switching task, by TMS group. * Significant at the .05 probability level. Error bars indicate one standard error.

Stop trials

Comparing the differences between scores on *stop* trials in the baseline and the subsequent assessments, no significant group differences for TMS stimulation are present for the first post-intervention [F$_{(1,25)}$=1.134, p=.297] or the follow-up [F$_{(1,25)}$=1.326, p=.260] assessments. Directly comparing the scores between the groups at these two time points does not result in significant differences either [U=86.500, p=.827; U=83.500, p=.715].

The stop-signal reaction time index, indicative of the reaction time needed to process *stop* trials, presented an effect of the number of assessments [F$_{(1,25)}$=4.298, p=.049], fitting a linear regression, in a repeated measures GLM including only the baseline and the first post-assessment, with no signs of a between-subjects effect [F$_{(1,25)}$=.089, p=.767] or an interaction effect between the two [F$_{(1,25)}$=.012, p=.913]. Likewise, when comparing the baseline with the follow-up assessment, the difference between groups was not significant [U=75.000, p=.438], and neither was the direct comparison between groups at that time point [U=80.000, p=.593].

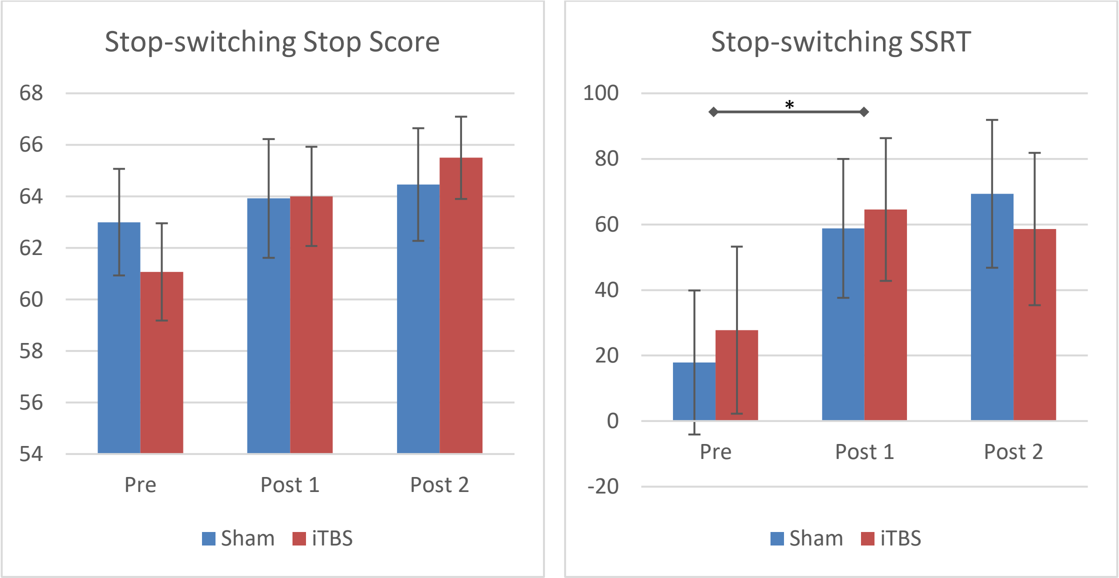


Figure 77. Mean scores (left) and stop-signal reaction time (right) for *Stop* trials in the Stop-switching task, by TMS group. * Significant at the .05 probability level. Error bars indicate one standard error.

Switch trials

A repeated measures GLM of the scores on *switch* trials, including the three time points yields a strong effect of the number of assessments [$F_{(2,50)}=5.880$, f=.005], fitting a linear regression [$F_{(1,25)}=8.574$, p=.007] but no interaction effect of the TMS stimulation [$F_{(2,50)}=.023$, f=.977] or a between-subjects effect of this factor [$F_{(1,25)}=.015$, p=.902]. Including only the first post-intervention assessment in that model, similar results are achieved. There is a significant although weaker effect of the number of sessions [$F_{(1,25)}=5.068$, p=.033], but the TMS group had no significance neither as an interaction effect [$F_{(1,25)}=.869$, p=.869] nor a between-subjects effect [$F_{(1,25)}=.022$, p=.883]. No significant differences between TMS groups appeared when comparing them at the post-intervention [$t_{(25)}=.075$, p=.941] or follow-up [$t_{(25)}=.055$, p=.956] assessments.

When considering the response times instead of the scores, results do not change much. Including the three time points, the trend caused by the number of assessments is still present [$F_{(2,50)}=3.819$, p=.029], with no interaction effects [$F_{(2,50)}=.213$, p=.809] or between-subjects effects [$F_{(1,25)}=1.015$, p=.321]. Results are similar when the follow-up assessment is not included in the model. Removing the last time point from the model, the effect of the number of assessments is no longer significant [$F_{(1,25)}=3.146$, p=.088], but the rest of the contrasts, like the interaction effect of the TMS group [$F_{(1,25)}=.338$, p=.566] and the between-subjects effect [$F_{(1,25)}=1.327$, p=.260], remain non-significant as well. The same situation is found when directly comparing the difference between the two groups at these two time points [Post: $t_{(25)}=1.191$, p=.245; Follow-up: $t_{(25)}=.645$, p=.525].

Figure 78. Mean scores (left) and response times (right) for switch trials in the Stop-switching task, by TMS group. * Significant at the .05 probability level. Error bars indicate one standard error.

3.3.4.9 Matchstick task

Performance in the matchstick task, which features a series of problems that must be solved by insight instead of by trial and error, should benefit from the repeated exposure to problems of the same kind since the possible solutions will be part of the participant's repertoire from that moment on. The task used in these assessments consisted of 8 items composed of 4 different problems, which are presented in a random order in the first half of the task, and again in the second half. As a result, performance in the second half, in the form of shorter response times, is expected to improve for those items that were answered correctly during the first half.

Overall, if problems presented during the 2nd block were to be facilitated for their previous exposure during the 1st block, the number of correct responses during the 2nd block should be, on average, higher. However, this is not what the data shows: correct responses during the 1st and 2nd blocks are very similar [1st: M=2.481±0.975; 2nd: M=2.630±1.182], display a high variability, and their differences are not significant [$t_{(26)}$=-.779, p=.443] (see Figure 79). When accounting for facilitated responses (that is, correct responses in the 2nd block for problems what were already solved during the 1st block), they should show a similar number to correct responses during the 1st block, but instead they only suppose slightly more than half the correct responses during the 1st block [1st: M=2.481±0.975; 2nd: M=1.481±0.975]. On the other side, non-facilitated responses (those that were correctly guessed in the 2nd block despite having failed the same type of problem during the 1st block) are a minority [M=0.222±0.506] and most participants did not have any of these.

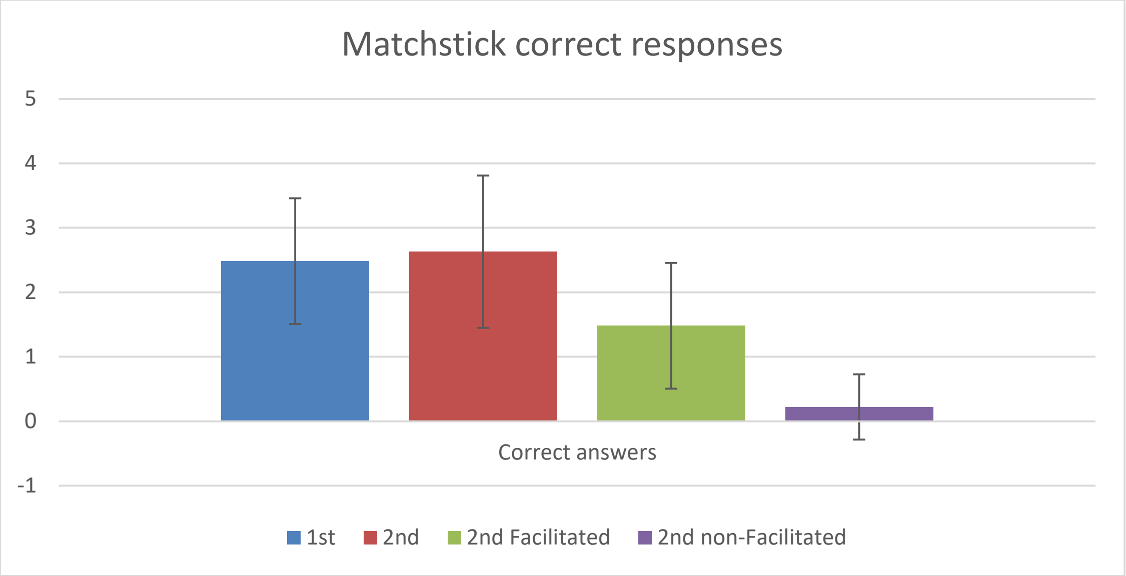


Figure 79. Mean number of correct responses during the matchstick task, for each presentation of the problems. Facilitated answers refer to those responded correctly during the 2nd presentation that were already correctly answered at the 1st presentation. Non-facilitated answers are those problems responded correctly at the 2nd presentation that were not correctly answered the 1st time. Error bars indicate one standard deviation.

When dealing with response times for correct responses, it is expected that problems during the 2nd block would feature lower response times than those in the 1st block, and that was the case for this sample of participants [1st: M=55879±28435; 2nd: M=40850±36999] (see Figure 80). However, when only accounting for facilitated responses in the 2nd block, they were not lower than general responses in the 2nd block [2nd: M=40850±36999; 2nd facilitated: M=42909±36999] as they were expected to be, and featured a much higher variability. Moreover, non-facilitated responses, which in turn should be slower than the facilitated ones, were virtually identical [2nd facilitated: M=42909±36999; 2nd non-facilitated: M=43083±46501], although they featured an even larger variability.

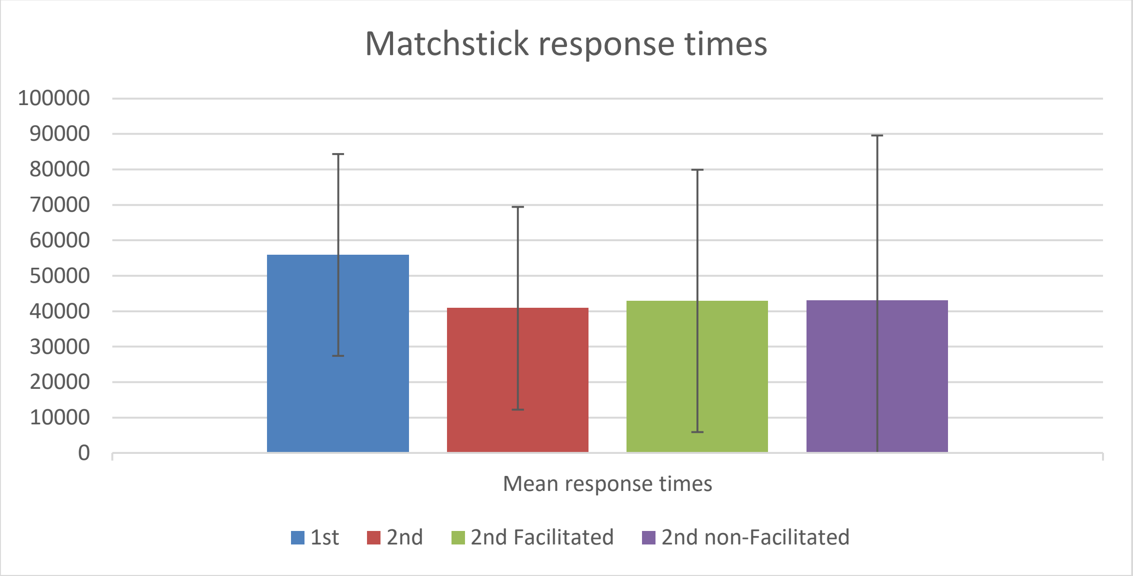


Figure 80. Mean response times (in ms) for correct responses for each presentation of the problems in the matchstick task. Facilitated answers refer to those responded correctly during the 2nd presentation that were already correctly answered at the 1st presentation. Non-facilitated answers are those problems responded correctly at the 2nd presentation that were not correctly answered the 1st time. Error bars indicate one standard deviation.

Overall, the facilitating effect of having guessed correctly a type of mental problem was not observed in this sample of participants, either in the form of more responses that are correct or faster response times.

Descriptive analysis

Out of a maximum score of 8 points, both TMS groups show similar scores on the task, which was only measured in the first post-intervention assessment. The mean response time per item was also similar; the iTBS showing slight faster response times when solving the items and lower variability (see Table 51 in the annex).

Determination of parametric adjustment

There were no violations of the normality assumption for both the total score and the response times when dividing the variable by TMS group. That was also the case for equality of variances, where the results for the two groups were homoscedastic (see Table 86 in the annex).

Main results

No significant differences in the score of this task were present between these two groups [$t_{(25)}$=.305, p=.763]. Likewise, response times for each item did not show a significant difference either [$t_{(25)}$=.177, p=.861]. When separating the performance of the task between the first and second exposure to the problems, scores [U=85.000, p=.755; U=80.500, p=.596] and response times [$t_{(25)}$.055, p=.956; U=68.000, p=.397] still do not differ between TMS groups. Finally, the percentage of facilitated responses by a previous exposure to the same kind of problem did not differ between groups either [U=36.000, p=.094], as happened with the response times of these facilitated answers [U=50.000, p=.491].

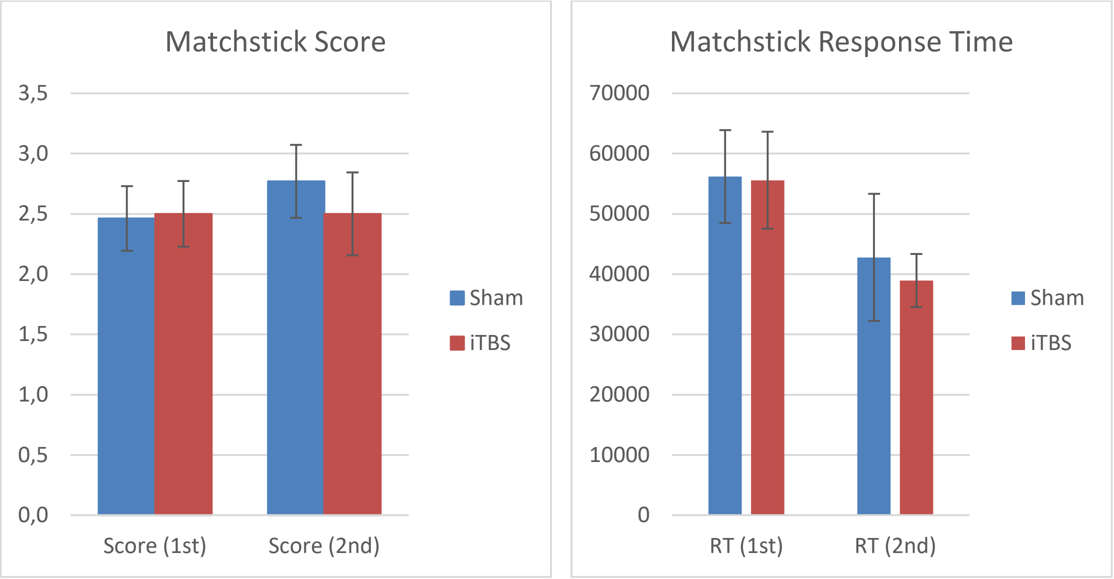


Figure 81. Scores (left) and response time (right) in the matchstick task, by TMS group.

3.3.5 Logistic regression of personal variables

Age, gender, and previous video game experience were explored, through a logistic regression analysis, in order to find out if these variables could work as predictors of cognitive enhancement after the training period.

Previous video game experience had an effect on the improvement of variables related to executive functioning, particularly in the N-back d' index (p=.002) (see Table 29 and Figure 82) and the stop-signal reaction time (p=.001) (see Table 30 and Figure 82). On the other hand, participant's genre had also an effect, albeit weaker, on the stop-signal reaction time (p=.004) (see Table 30), and in one of the processing speed tasks, the color choice reaction time (p=.024). Therefore, it is justified to explore this independent variable as a second factor the same way TMS modality was analyzed.

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	,637[a]	,405	,328	,64557

a. Predictors: (Constant), Experienced VGP, Age, Gender

Coefficients[a]

		Unstandardized Coefficients		Standardized Coefficients		
Model		B	Std. Error	Beta	t	Sig.
1	(Constant)	-,547	,703		-,772	,448
	Age	-,006	,021	,045	-,272	,788
	Gender	,048	,285	,031	,170	,867
	Experienced VGP	1,023	,292	-,658	3,507	,002

a. Dependent Variable: Post-Pre N-back d'

Table 29. Logistic regression model summary and coefficients on the performance enhancement of the n-back d' index for the three personal variables considered in this study: age, gender, and previous video game experience.

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	,648[a]	,420	,344	77,19278

a. Predictors: (Constant), Experienced VGP, Age, Gender

Coefficients[a]

		Unstandardized Coefficients		Standardized Coefficients		
Model		B	Std. Error	Beta	t	Sig.
1	(Constant)	188,684	84,057		2,245	,035
	Age	-1,205	2,466	-,079	-,489	,630
	Gender	-107,501	34,100	-,574	-3,153	,004

Experienced VGP	-132,045	34,893	-,701	-3,784	,001

a. Dependent Variable: Post-Pre Stop-signal Reaction Time

Table 30. Logistic regression model summary and coefficients on the performance enhancement of the stop-signal reaction time for the three personal variables considered in this study: age, gender, and previous video game experience.

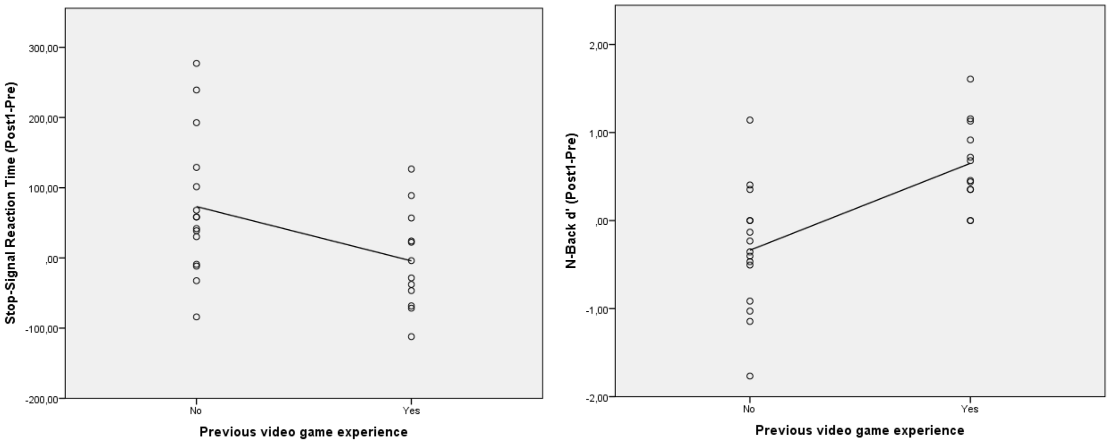


Figure 82. Effect of the previous video game experience on the performance enhancement of the stop-signal reaction time (left) and the N-back d’ index (right) after two weeks of video game training.

3.3.6 Effects of the video game experience

For the second part of the analysis, participants were grouped by their previous video game experience, into non-experienced players or experienced players, regardless of the modality of TMS they received. Considering a total valid sample of 27 participants, 15 of them were assigned to the non-experienced VGP group and 12 of them to the experienced VGP group (see Table 31).

		Video game experience	
		Non-Experienced	**Experienced**
Stimulation type	**Active and Sham TMS**	15	12

Table 31. Factorial matrix displaying the sample size for the video game experienced and non-experienced participants.

3.3.6.1 Video game-related variables

Descriptive analysis

Compared to groups divided by TMS modality, previous video game experience seems to have a greater effect on video game performance variables. The qualitative assessments at the start and end of the training period show similar scores, with the more experienced group having a slight advantage. Actual in-game performance shows greater differences: the number of goals achieved during the training sessions is twice as big for the experienced group, and also required fewer attempts and less time per attempt to achieve each goal (see Table 52).

Determination of parametric adjustment

Most video game-related variables, when participants are divided by previous video game experience, do not fit a normal distribution. That was the case for the number of achievements (stars) in the game, the achievements per attempt, and the time per attempt. Moreover, regarding the qualitative measures of video game performance during the assessments, the baseline measure did not meet the normality assumption either (see Table 76 in the annex). The homoscedasticity assumption was met in all cases (see Table 78 in the annex).

Main results

No significant differences between baseline qualitative measures of video gaming performance could be observed [U=58.500, p=.120] when groups were divided by previous video game experience (see Table 86 in the annex).

An ANOVA of the difference between the qualitative measure of video game performance in the pre- and post-intervention assessments shows that differences between groups are not big enough to be significant [$F_{(1,25)}$=2.362, p=.137] (see Figure 83). Nevertheless, comparing the scores at the post-assessment, a significant difference is present [$t_{(25)}$=-2.195, p=.038], where more experienced participants performed better.

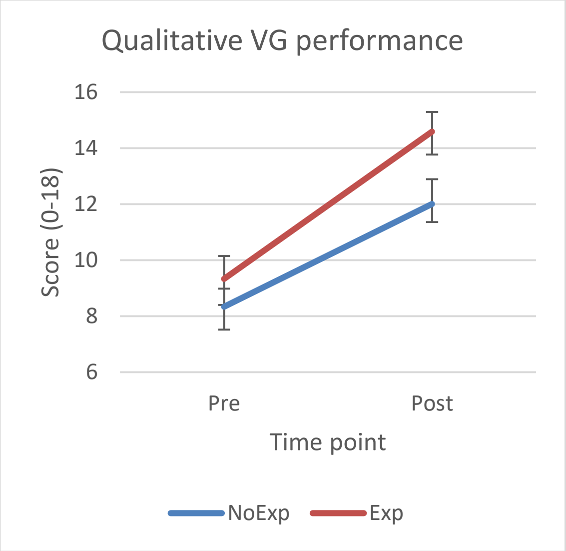


Figure 83. Mean qualitative scores for video game performance during the pre- and post-training assessments, by previous video game experience. Error bars indicate one standard error.

In this case, some of the variables registered during the video game training sessions achieved significant or near-significant differences between groups. That was the case for the number of goals achieved in the game [U=37.000, p=.010], the number of attempts [t(25)=-1.976, p=.059], and the goals per attempt [U=51.500, p=.060], whereas the time per attempt [U=55.000, p=.088] was further from significance.

3.3.6.2 Reaction times

Descriptive analysis

Just like what happened when examining the effects of the TMS stimulation, response times increase equally for the two video game experience groups as the task becomes more complex. Participants with low experience in video games had slower response times on average, difference that was maintained during the first post-intervention and follow-up assessments. It appears to be a trend towards slower response times for each new assessment, more notorious for the less video game-experienced group, which is counterintuitive to the expected practice effects found in neuropsychological tasks.

Determination of parametric adjustment

The data appears to be more normally distributed when the groups are classified according to their previous video game experience. In this case, the only non-normally distributed that were the results of the Direction choice reaction time during the first assessment, while all the rest adjust to normality according to Shapiro-Wilk's test (see Table 76 in the annex). No violations of the homoscedasticity assumptions were present these variables when grouped by video game experience (see Table 78 in the annex). The assumption of sphericity was met for the three time points in the simple and color choice reaction time tasks but failed to meet this criterion for the direction choice reaction time task, according to Mauchly's test (see Table 80 in the annex).

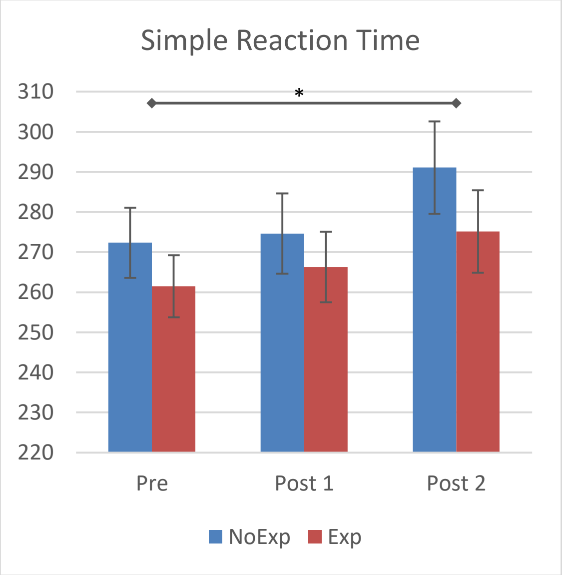


Figure 84. Mean response times in the simple reaction time task, by previous video game experience. Error bars indicate one standard error.

Main results

No significant baseline differences can be observed for any of the three measures of reaction times (see Table 86 in the annex).

Regarding the simple reaction time task, a repeated measures GLM including the three time points detected a strong effect of the number of assessment sessions [$F_{(2,50)}$=5.136, p=.009], fitting a linear trend [$F_{(1,25)}$=6.509, p=.017] but no interaction effects [$F_{(2,50)}$=.266, p=.767] and no between-subjects effects [$F_{(2,50)}$=1.006, p=.325] of the video game experience were found. Not accounting for the third assessment from the model, the effect of the assessment number is no longer significant [$F_{(1,25)}$=.610, p=.442], and the interaction effect [$F_{(1,25)}$=.080, p=.780], just like the between-subjects effects [$F_{(1,25)}$=.723, p=.403], remains non-significant. Comparing the post-intervention assessments between groups did not result in significant differences for either the first post-intervention [$t_{(25)}$=.650, p=.522] or the follow-up [$t_{(25)}$=1.053, p=.302] assessment.

The direction choice reaction time task was analyzed by non-parametric statistics, due to the non-normality of the baseline assessment. Comparing the baseline with the first post-intervention assessment could not find differences between experienced and less experienced video game players [U=87.000, p=.884], an effect that was also observed when compared with the last assessment [U=79.000, p=.591]. Observing the presence of between-subject differences in the two groups, they were not significant for neither the first post-intervention assessment [$t_{(25)}$=.651, p=521] nor the follow-up [$t_{(25)}$=.966, p=.343].

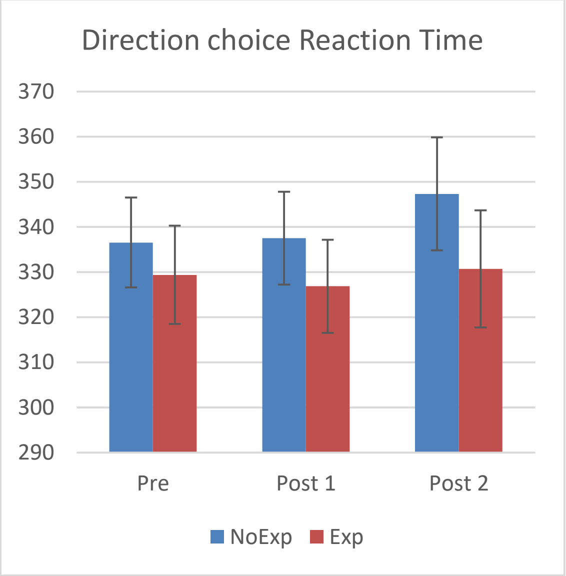


Figure 85. Mean response times in the direction choice reaction time task, by previous video game experience.
Error bars indicate one standard error.

The color choice reaction time task, using a repeated measures GLM with the three assessments, did not yield any significant effect of the session number [$F_{(2,50)}$=.358, p=.701] or interaction effect with the video game expertise level [$F_{(2,50)}$=.365, p=.696]. The between-subject effects, indicative of a possible pre-existing difference between experienced and non-experienced players, was more notorious, but still did not reach significance [$F_{(1,25)}$=3.495, p=.073]. The situation does not change if only the two first assessments are included; no effect of the number of assessments [$F_{(1,25)}$=.062, p=.806] or interaction effects with the video game experience [$F_{(1,25)}$=.695, p=.412] are present, whereas the between-subjects effects of the video game experience are even less significant [$F_{(1,25)}$=2.879, p=.102]. Between-subject differences at the first post-intervention assessment, however, were near-significant [$t_{(25)}$=2.052, p=.051], but those differences could not be appreciated at the last time point [$t_{(25)}$=1.590, p=.124].

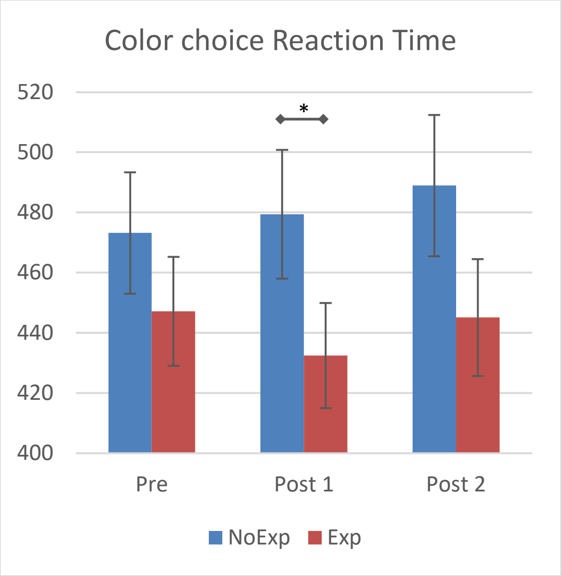


Figure 86. Mean response times in the color choice reaction time task, by previous video game experience. * Significant at the .05 probability level. Error bars indicate one standard error.

3.3.6.3 Digit Span

Descriptive analysis

When examining this task divided by the previous video game experience of the participants, an overall tendency to obtain better scores appears, an effect already observed when participants were divided by stimulation modality. Some differences appear between the two groups, but they are not consistent among trials. Again, average scores are higher in the forward part of the task, but more extreme scores appear during the backward digit task (see Table 54 in the annex).

Parametric determination

There were no violations of the normality and homoscedasticity assumptions when the groups are divided by previous video game experience. The sphericity assumption was also met in the two variables involved in the digit span task. (see Table 76, Table 78, and Table 80 in the annex).

However, differential variables measuring the change in digit span performance between the baseline and first post-intervention assessment in reaction time tasks failed to meet the normality assumption requirement if divided by game experience, for both direct and inverse digit span, and the assumption of equality of variances for forward digit span (see Table 77 and Table 79 in the annex).

Main results

There were no baseline differences in the execution of this task among groups, either for the forward or backward version (see Table 86 in the annex).

Examining the data with a repeated measures GLM including the three time points, the forward digits tests showed a significant effect of the number of assessments [$F_{(2,50)}$=4.994, p=.011], but no interaction effects with the video game experience [$F_{(2,50)}$=1.825, p=.172] or between subjects effects derived from the video game experience [F(1,25)=.330, p=.571]. When the last time point is removed from the analysis, the number of assessments remains significant [$F_{(1,25)}$=6.995, p=.014], the interaction effect with the video game experience becomes near-significant [$F_{(1,25)}$=3.415, p=.076], but between-subject effects are absent [$F_{(1,25)}$=.023, p=.881]. Overall, differences between subjects at these two post-intervention assessments were not big enough to be significant [$t_{(25)}$=-.845, p=.406; $t_{(25)}$=-1.133, p=.268].

Results in the backward digit task are similar. Apart from an increasing trend for higher scores on both groups [$F_{(2,50)}$=8.087, p=.001], there were no interaction [$F_{(2,50)}$=.476, p=.630] or between-subjects [$F_{(1,25)}$=2.973, p=.097] effects. However, the effects of the repeated exposition to the task are not visible unless the third intervention is included from the analysis [$F_{(1,25)}$=1.382, p=.251], and the interaction [$F_{(1,25)}$=1.728, p=.201] and the between-subject [$F_{(1,25)}$=3.284, p=.082] effects are also non-significant. Differences between subjects at the two post-intervention assessments are not significant [$t_{(25)}$=.-1.506, p=.145; $t_{(25)}$=-1.260, p=.219].

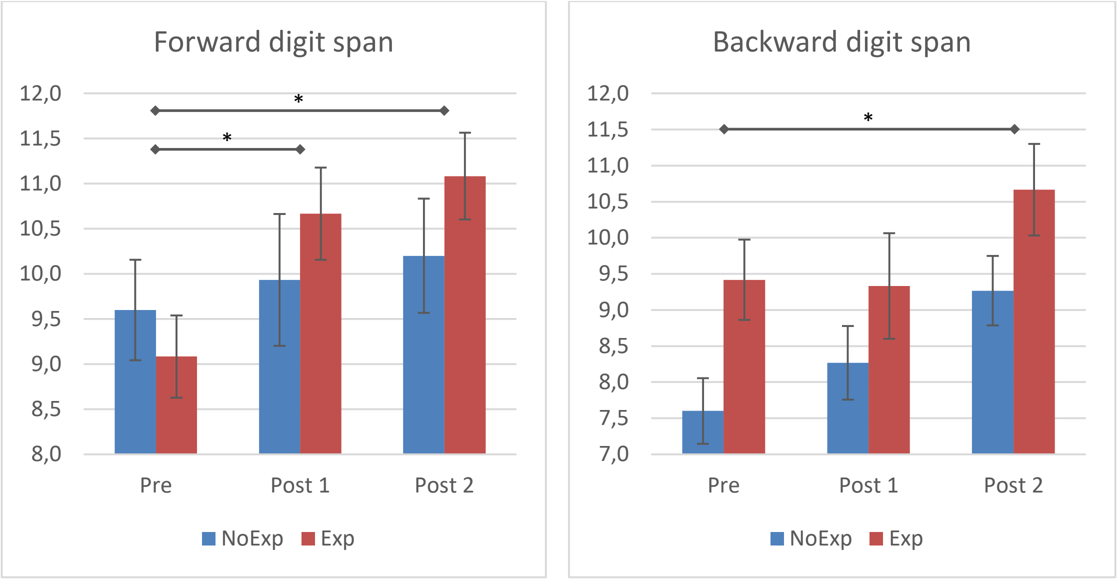


Figure 87. Mean scores for the forward (left) and backward (right) digit span test, by previous video game experience. * Significant at the .05 probability level. Error bars indicate one standard error.

3.3.6.4 Raven's Progressive Matrices

Descriptive analysis

Similar to when groups were divided by stimulation type, scores on the Raven's Progressive Matrices are similar between the two video game experience groups in the two time points where the task was used. Scores still tend to be high for both groups, approaching the ceiling.

Response times per item show a slight difference between groups. Less experienced video game players tend to spend more time resolving each item, a trend that is reduced, but still present, in the post-intervention assessment (see Table 55 in the annex).

Determination of parametric adjustment

More violations of the normality assumption are detected when the experimental groups are separated by video game experience. The scores on Raven's progressive matrices do not show normal distributions in any of the two assessments, and the reaction times from the first assessment do show a non-normal distribution too (see Table 76 in the annex).

Differential data from Raven's test show that it fails to meet normality for the direct score measure, but is normally distributed when the response time is taken into account. This effect is true for video game experience subdivisions as it was for the stimulation modality groups (see Table 77 in the annex).

No violation of equality of variance was detected for these two variables when examined for each video game experience group (see Table 78 in the annex).

Main results

There were no baseline differences between the two groups, neither for scores or for response times (see Table 86 in the annex).

Due to the violation of normality of the data, the differences between the baseline and the post-intervention assessment have been analyzed with non-parametric statistics. The analysis of the scores did not report any significant differences [U=65.000, p=.213] and neither did response times [U=87.000, p=.884]. Directly comparing these variables at the post-intervention assessment, statistics did not reach significant values either [scores: $F_{(1,22,113)}=.282$, p=.601; response times: $t_{(25)}=.680$, p=.503].

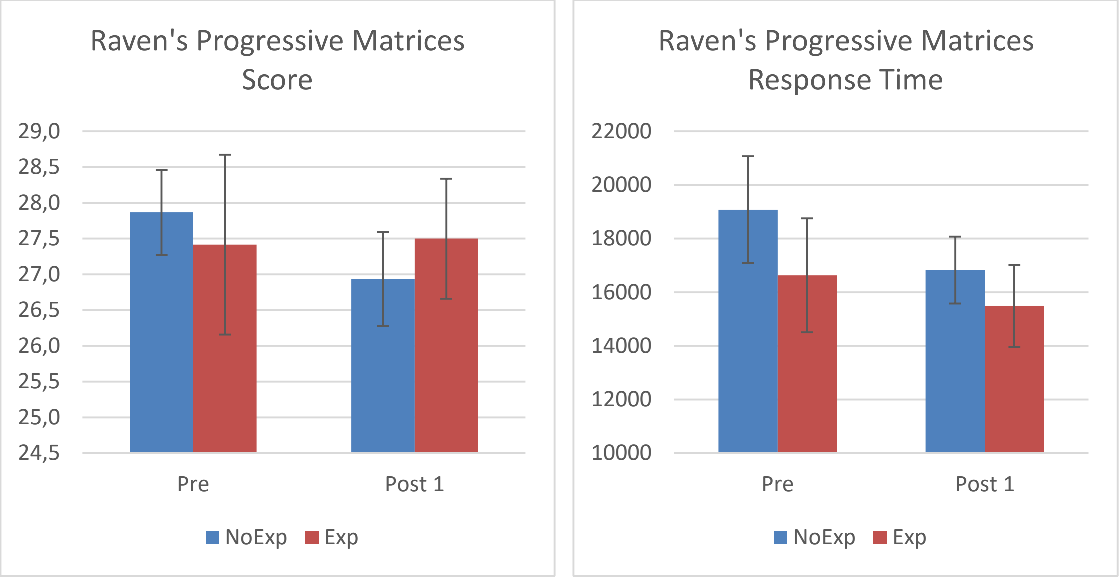


Figure 88. Mean scores (left) and response times (right) for the Raven's Progressive Matrices task by previous video game experience. Error bars indicate one standard error.

3.3.6.5 Five-Point Test (5PT)

Descriptive analysis

In the Five-Point Test (5PT), participants with low video game experience obtained overall higher scores, that is also reflected in higher minimum and maximum values (see Table 56 in the annex).

Determination of parametric adjustment

When separated by video game experience, responses were normally distributed (see Table 76 in the annex), although the data showed less robustness than when participants are divided by TMS modality. Variances are equal for both groups (see Table 78 in the annex). Overall, no violation of parametricity was detected for this variable when participants were divided by their previous video game experience.

Main results

The single assessment performed using this task indicates that the performance between participants based on previous video game experience is not different enough to be significant [$t_{(25)}=.455$, p=.653].

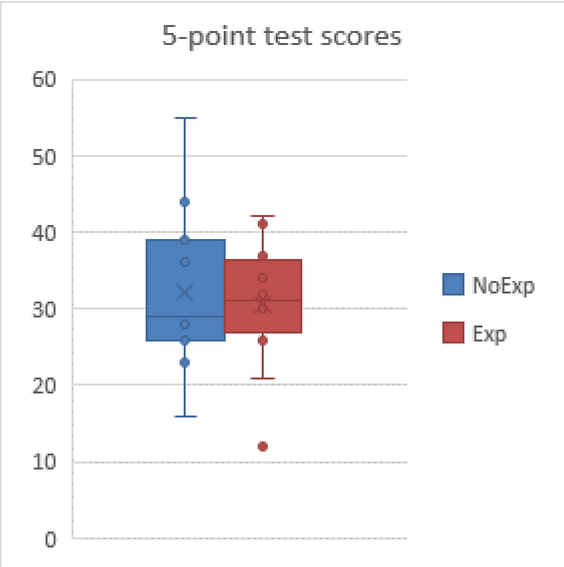


Table 32. Score distribution in the Five-Point Test (5PT), by previous video game experience.

3.3.6.6 N-back

Descriptive analysis

Scores on the n-back task among video game experienced and non-experienced participants, while virtually identical in the baseline assessment, appear to rise in the following post-assessment (especially the first) for the more experienced participants, but not for the others. Response times also tend to improve in the later assessments, reducing the differences between the two groups of participants that were more noticeable in the baseline. The d' index, combining both measures, shows a much clearer picture, where, departing from a common baseline, differences between groups accentuate and the participants with more video game experience obtain better scores on the two post-intervention assessments (see Table 57 in the annex).

Determination of parametric adjustment

Just like when groups were divided by stimulation modality, a similar effect regarding data parametricity is found when the groups are divided by video game experience. Direct scores on the task generally do not provide normally distributed data, and that is the case in the three assessments. In this case, one single measure of reaction times, the one belonging to the first assessment reaches significance in Shapiro-Wilk's test, invalidating the assumption of normality. The rest of the reaction time measures, as well as the d prime indices, seem to fit a normal distribution (see Table 76 in the annex).

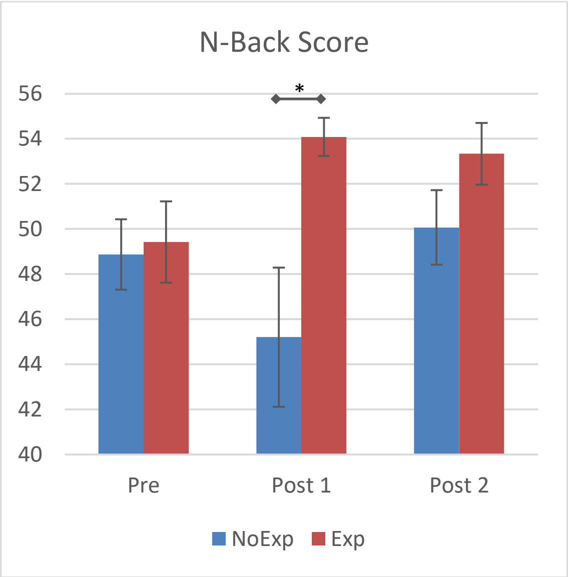


Figure 89. Mean scores on the N-back task for each assessment, by previous video game experience.
* Significant at the .05 probability level. Error bars indicate one standard error.

Scores on the n-back task, particularly during the first post-intervention assessment, did not possess homogeneity of variances, but response times and the d' index met this assumption (see Table 78 in the annex).

For the repeated measures analysis of the scores and response times, Mauchly's test pointed out that the variances of the differences between all possible pairs of within-subject conditions were only equal, meeting the assumption of sphericity, for the d' index. Scores and response times in the n-back task did not meet this criterion and therefore special corrections have been employed to analyze these two variables (see Table 80 in the annex).

Main results

No significant baseline differences between video game experience groups were present in the scores, response times or the d' index (see Table 86 in the annex).

Comparing the baseline scores with the first post-intervention assessment, strong significant differences [U=24.000, p=.001] arise between the low and high video game experience groups. When the two groups are compared at the first post-intervention assessment, without accounting for the effect of the number of assessments, differences are still significant [F$_{(1,16.040)}$=7.736, p=.013]. Comparing the scores between the third and first assessments, however, the strong signification disappears [F$_{(1,25)}$=2.800, p=.107], as does when groups are directly compared at this last assessment [t$_{(25)}$=-1.471, p=.154].

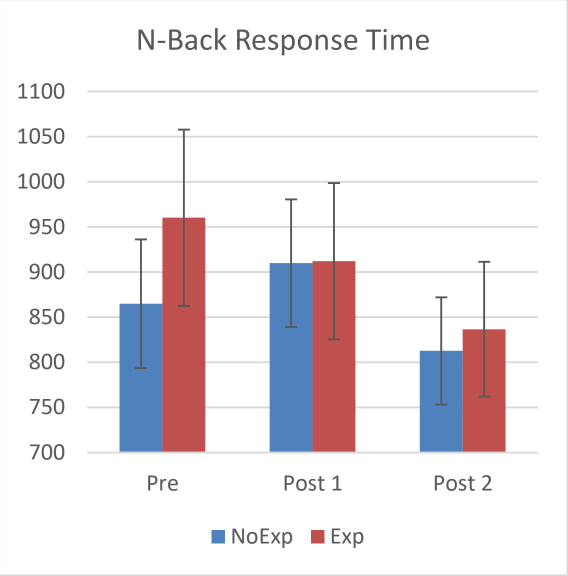


Figure 90. Response times in the N-back task for the three assessments, by previous video game experience.
Error bars indicate one standard error.

Response times, comparing the baseline with the two other time points, do not show any significant difference regarding the first post-intervention [U=60.000, p=.143] or follow-up [U=67.000, p=.262] assessments, and the direct comparison between the groups at these time points did not result in significant results either [Post 1: t$_{(25)}$=-.022, p=983; Post 2: U=80.000, p=.626].

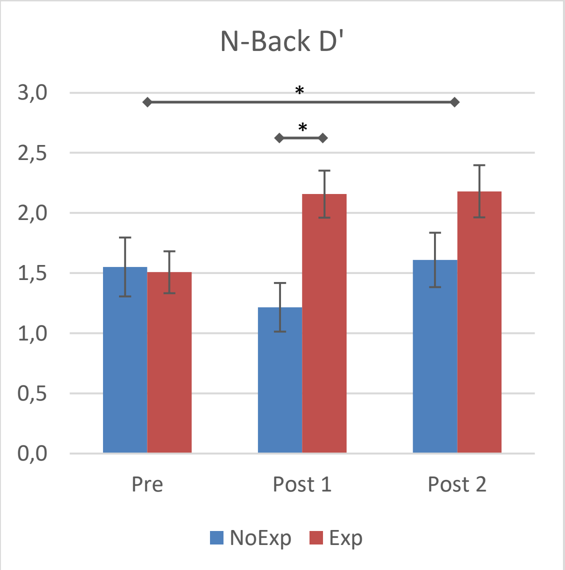


Figure 91. D' index in the N-back task for the three assessments, by previous video game experience.
* Significant at the .05 probability level. Error bars indicate one standard error.

The d' index, in a repeated measures GLM including the three time points, finds both a near significant effect of the number of assessments [F$_{(2,50)}$=3.121, p=.053] fitting a linear regression, and a significant interaction effect of the number of assessments and the previous video game experience of the participants [F$_{(2,50)}$=6.654, p=.003], without detecting a between-subjects effect of the previous video game experience [F$_{(1,25)}$=3.449, p=.075]. When only the baseline and the first post-assessment intervention are considered in the model, the effect of the repeated assessments disappears [F$_{(1,25)}$=.731, p=.401] but the interaction effect with the video game experience is even more robust [F$_{(1,25)}$=16.869, p=.000], while between-subjects effects are absent [F$_{(1,25)}$=2.647, p=.116].

Comparing the two post-intervention assessments between the groups, a Student’s t-test shows a strong signification of the first one [$t_{(25)}$=-3.298, p=.003], whereas the follow-up assessment, compared through Mann-Whitney’s U, does not reach the point of signification [U=60.000, p=.139].

3.3.6.7 Mental Rotation

Descriptive analysis

Mean scores between the two groups show a noticeable difference at baseline, where video game experienced participants obtained overall better scores, but in the following assessments that difference is reduced. An increase of the mean scores can be observed from the baseline to the first post-intervention assessment, although tends to stagnate towards the last assessment.

Response times follow a more linear trend, where participants in both groups improve their performance for each assessment. Nevertheless, a slight advantage of participants with more video game experience can be observed in this measure (see Table 58 in the annex).

Determination of parametric adjustment

When participants are divided by video game experience, both groups show similar results. None of the direct scores from mental rotation fitted a normal distribution, particularly in those subgroups with more game expertise. Generally, reaction times among these subgroups tended to distribute normally, with the exception of the third assessment, for the less experienced players (see Table 76 in the annex).

No violations of the principle of equality of variances were found for either the scores or the response times in this task (see Table 78 in the annex). Likewise, for the repeated measures analysis, Mauchly’s test found that all the variances of the differences between the pair of within-subject conditions were equal (see Table 80 in the annex).

Main results

Baseline significant differences were present for the mental rotation scores, where participants with more video game experience performed better in this task, although these differences mitigated in posterior assessments. Response times do not reflect that difference, and baselines do not differ (see Table 86 in the annex).

Score differences between the baseline and the first post-intervention assessment are not significant [$F_{(1,25)}$=1.231, p=.278], but they are if we compare them against the last assessment [$F_{(1,25)}$=4.564, p=.043]. Between-subject differences at these two time points show an almost significant difference during the first post-intervention assessment [U=53.000, p=.071], but that difference disappears during the follow-up assessment [U=63.000, p=.187].

Response times in the mental rotation task do not differ significantly from the baseline to the first post-intervention [U=83.000, p=.744] or follow-up [$F_{(1,25)}$=.346, p=.562] assessments. Including the baseline and first post-intervention assessment in a repeated measures GLM, a strong effect of the number of assessments is present [$F_{(1,25)}$=18.184, p=.000], but the level of previous video game experience did not interact with the TMS intervention [$F_{(1,25)}$=.451, p=.508]. Just like the baseline analysis indicated, a between-subjects effect of the previous video game experience was close to reaching significance [$F_{(1,25)}=3.497$, $p=.073$].

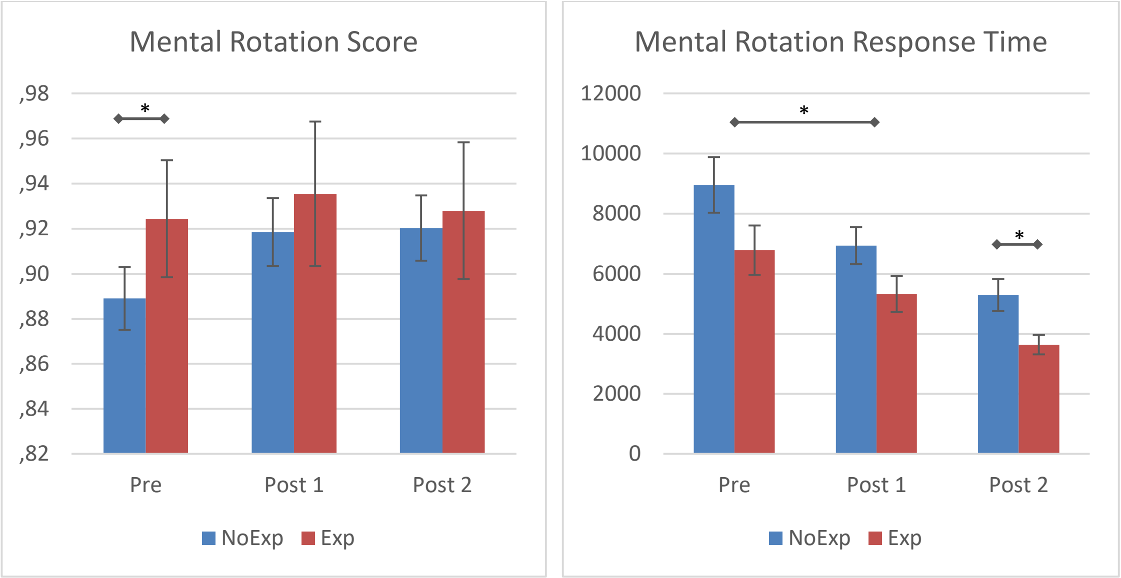


Figure 92. Mean scores (left) and response times (right) in the mental rotation, by previous video game experience. * Significant at the .05 probability level. Error bars indicate one standard error.

3.3.6.8 Stop-Switching task

Descriptive analysis

Scores on *go* trials are very similar between the two groups and alongside the three assessments. In all cases, for the two groups, maximum scores were reached, and variability was kept to the minimum, indicating that these trials were not a challenge for the participants, as opposed to *switch* and *stop* trials, which required more cognitive effort. Response times in *go* trials tend to increase for each assessment for both groups, possibly reflecting a change of strategy, and more experienced video game players show overall faster response times in the three time points.

Stop scores increased after each assessment for the two groups, and apparently less video game experienced participants obtained slightly better scores on these trials. Stop-signal reaction times do not present a clear pattern between groups, and differences between more and less experienced participants are quite notorious and reverse for one assessment to the next, until reaching equivalent scores at the follow-up assessment.

Scores on *switching* trials, similar between the two groups, show a trend towards higher scores for every new assessment. Likewise, response times tend to grow faster for each assessment, regardless of the participant's group (see Table 59 in the annex).

Determination of parametric adjustment

None of the measures of scores on *go* trials met the normality assumption, but no violations of parametric adjustment were present in the response times of *go* trials. More violations of normality appeared when analyzing the data for the first post-intervention and the follow-up assessments in the scores of *stop* trials. Regarding the measures taken during switching trials, scores did not distribute normally during the first post-intervention assessment, and response times did not adjust to that parameter during the (see Table 76 in the annex).

No violations of the homoscedasticity were detected in any of the measures when participants were divided by previous video game experience (see Table 78 in the annex). The sphericity requirement was met for all pairs of within-subject conditions except for the score on *stop* trials (see Table 80 in the annex).

Main results

No baseline differences were detected in any of the six measures of the stop-switching task, including *go*, *stop* and *switch* trials (see Table 86 in the annex).

Comparing the baseline *go* scores with the following assessments, no significant differences could be found against the first post-intervention [$F_{(1,25)}$=.512, p=.481] or the follow-up [$F_{(1,25)}$=.967, p=.335] assessments, proving that the increasing trend in the scores is not significant. Comparing the two groups of participants at the same time point, differences between them are not significant either for the first post-intervention [U=85.000, p=.795] or the follow-up [U=69.000, p=.286] assessment.

Response times in *go* trials, when the three time points are included in a repeated measures GLM, show a significant effect of the number of assessments [$F_{(2,50)}$=3.309, p=.045] but no interaction effects of the video game experience of the participants [$F_{(2,50)}$=.319, p=.728] or between-subjects effects [$F_{(1,25)}$=.314, p=.580]. Leaving the last assessment out of the analysis, the effect of the repeated assessments ceases to be significant [$F_{(1,25)}$=.975, p=.333] and the interaction effect [$F_{(1,25)}$=.393, p=.537] and between-subjects effects [$F_{(1,25)}$=.438, p=.514] of the video game experience remains non-significant. Comparing the groups at these two time points, no significances arise related to the video game experience level [Post 1: $t_{(25)}$=.769, p=.449; Post 2: $t_{(25)}$=.329, p=.745].

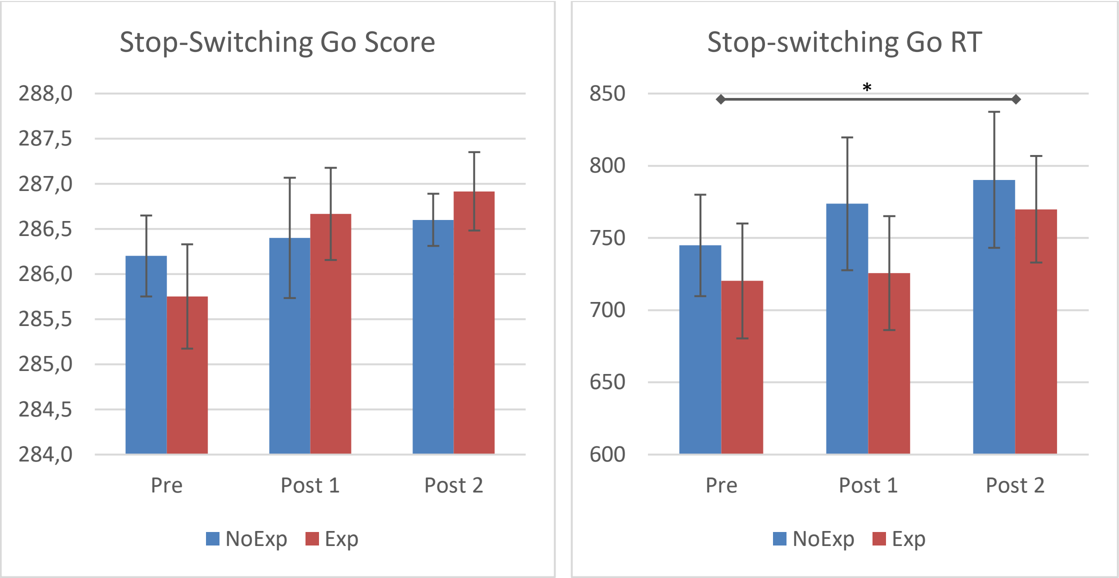


Figure 93. Scores (left) and response times (right) for Go trials in the Stop-switching task, by previous video game experience. * Significant at the .05 probability level. Error bars indicate one standard error.

Scores on *stop* trials do not differ significantly between the two groups in either the first post-intervention [U=78.500, p=.573] or follow-up [U=84.500, p=.788] assessments. Comparing the baseline with these two interventions, no significant changes could be [Post 1: $F_{(1,25)}$=.015, p=.905; Post 2: $F_{(1,25)}$=.080, p=.780].

Including the stop-signal reaction task measures in a repeated measures GLM with the three time points did not reach significance levels for the effect of the number of assessments [$F_{(2,50)}$=2.706, p=.077] or the interaction effects with the previous video game experience [$F_{(2,50)}$=1.951, p=.153], although these interaction effects reached significance when fitting a quadratic curve [$F_{(1,25)}$=4.258, p=.050]. In this case, between-subjects effects were not significant [$F_{(1,25)}$=.509, p=.482]. Including only the first post-intervention assessment in the model, significant results are reached for both the effect of the number of assessments [$F_{(1,25)}$=5.167, p=.032], fitting a linear regression, and the interaction effects with the previous video game experience [F(1,25)=5.072, p=.033], also fitting a linear regression, without the presence of between-subject effects [$F_{(1,25)}$=.196, p=.662].

By directly comparing the differences between groups at the post-assessment interventions, it can be observed that both groups did not differ significantly at these time points [Post 1: $t_{(25)}$=1.740, p=.094; Follow-up: $t_{(25)}$=.729, p=.473].

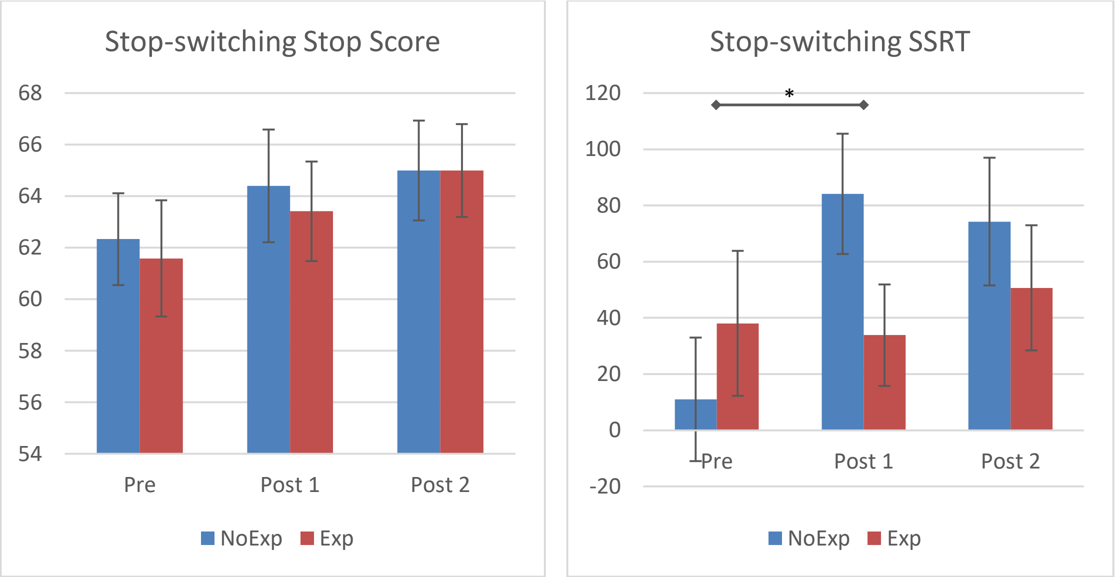


Figure 94. Scores for *stop* trials (left) and stop-signal reaction time (right) in the Stop-switching task, by previous video game experience. * Significant at the .05 probability level. Error bars indicate one standard error.

Scores on *switch* trials, when analyzed with a repeated measures GLM including the baseline and follow-up assessments (due to the non-parametricity of the first post-intervention assessment), a strong significance of the repeated assessments can be observed [$F_{(1,25)}$=8.567, p=.007], fitting a linear regression, but without any interaction effects with the video game experience [$F_{(1,25)}$=.010, p=.921]. Between-subjects effects in this variable were also absent [$F_{(1,25)}$=.009, p=.924]. Comparing the difference between the baseline and the following assessments did not yield any significant value either [Post 1: U=69.500, p=.315; Post 2: $F_{(1,25)}$=.010, p=.921]. Directly comparing the scores of the post-intervention assessments, no significant differences arose from any of them [Post 1: U=74.000, p=.434; Post 2: $t_{(25)}$=-.042, p=.967].

When response times in *switch* trials are considered, comparing the post-intervention assessment between groups did not show any significant difference, either for the first post-intervention [U=77.000, p=.526] or follow-up [U=78.000, p=.558] assessments. Comparing these measures against the baseline, again, no significant differences are found for the post-intervention [$F_{(1,25)}$=.012, p=.914] or follow-up [$F_{(1,25)}$=.011, p=.919] assessments.

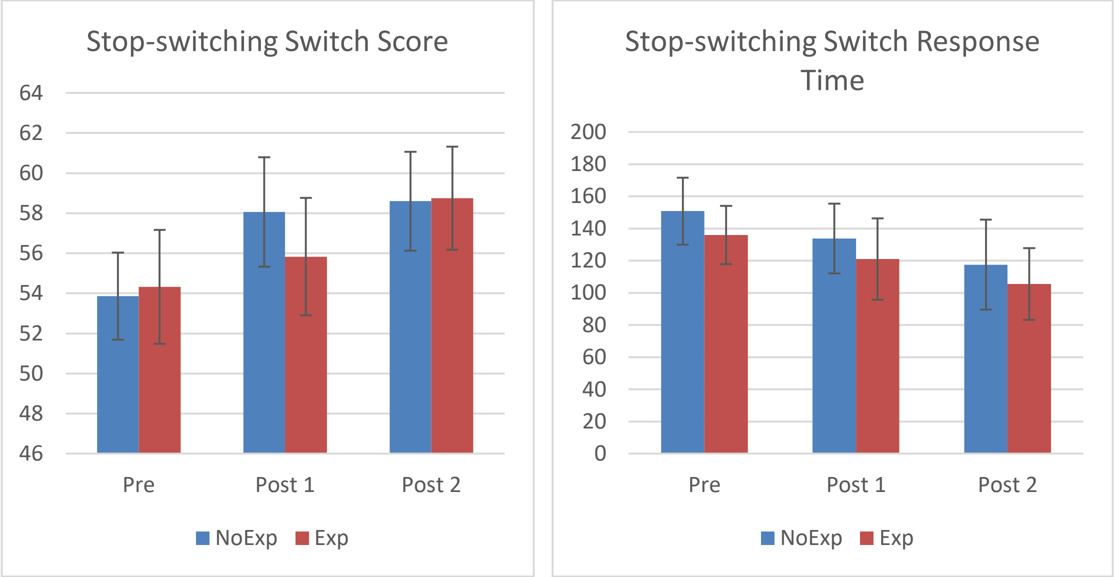


Figure 95. Scores (left) and response times (right) for switch trials in the Stop-Switching task, by previous video game experience. Error bars indicate one standard error.

3.3.6.9 Matchstick task

Descriptive analysis

Participants with more video game experience obtained slightly better scores on the matchstick task, although some participants from both groups were able to reach the maximum score on the task. The mean time needed to complete each item, however, was similar in the two groups, although non-experienced participants experimented higher variability in their responses (see Table 60 in the annex).

Determination of parametric adjustment

The normality assumption in the matchstick task when participants are divided by previous video game experience was met in all but three cases: the score during the first exposition to the problems, the response times during the second exposition, and in the number of facilitated responses (see Table 76 in the annex).

Equality of variances was generally present, with the only exception of the scores obtained during the first exposition to the problems (see Table 78 in the annex).

Main results

The difference in scores between the two experimental groups is significant [$t_{(25)}$=-2.059, p=.050], where participants with more experience obtained overall better scores. When dividing the scores by each exposition to the problems, these significant differences only appear during the first exposition [$F_{(1,23.871)}$=5.470, p=.028] but not during the second [$t_{(25)}$=-1.491, p=.149].

On the other hand, that was not the case for response times, as the difference between the two groups was not significant [$t_{(25)}$=-.048, p=.962], even when differences were studied by each exposition to the problem [1st: $t_{(25)}$=-1.162, p=.256; 2nd: U=69.000, p=.440].

The total number of solved problems during the second exposition being facilitated by a correct solution in the first exposition was significantly different between groups [U=48.500, p=.034], but that value was not significant if correct responses were counted as a proportion (%) of total possible facilitated answers [$t_{(20)}$=-.224, p=.825]. Finally, differences in response times for facilitated responses are near-significant between the two groups [$t_{(20)}$=.-2.047, p=.054].

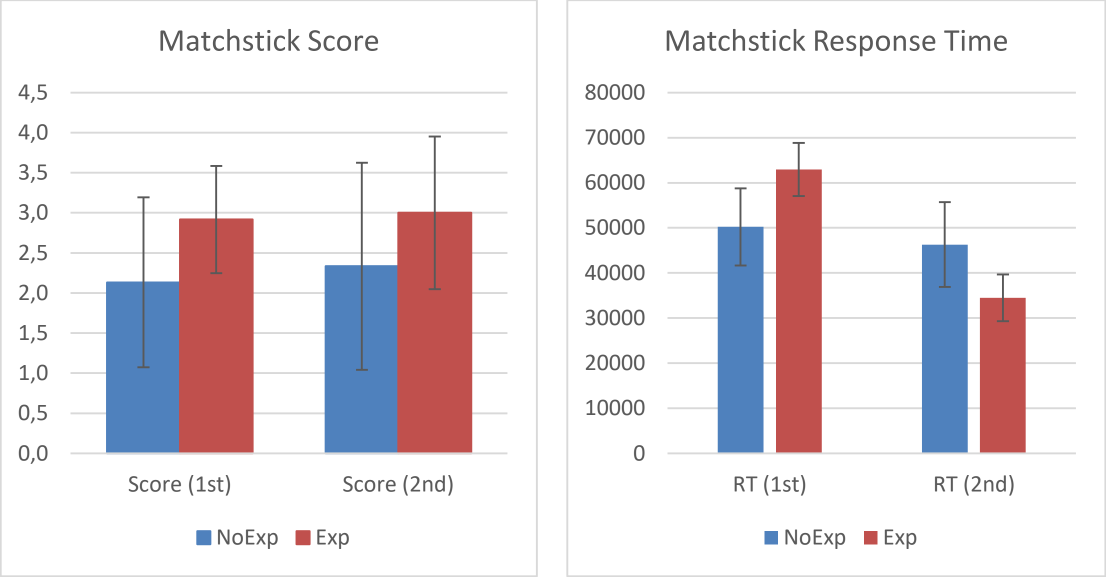


Figure 96. Score (left) and response time (right) distribution, by previous video game experience. Error bars indicate one standard error.

3.3.7 Combined effects of the TMS stimulation and previous video game experience

For the third and last section of the analysis, participants were divided into four groups, considering the TMS modality they received (sham or active iTBS) and their previous video game experience (experienced or non-experienced video game players). Considering a total valid sample of 27 participants, 8 of them were assigned to the non-experienced group and active iTBS stimulation (iTBS+NoExp), 7 of them to the non-experienced and sham iTBS stimulation (Sham+NoExp), 6 of them to the experienced group and active iTBS stimulation (iTBS+Exp) and the remaining 6 participants to the experienced and sham iTBS stimulation (Sham+Exp) (see Table 33).

		Video game experience	
		Non-experienced	**Experienced**
Stimulation type	**Active iTBS**	8	6
	Sham iTBS	7	6

Table 33. Factorial matrix displaying group sizes for the two independent variables compared in the study.

3.3.7.1 Video game-related variables

Descriptive analysis

There are a few observable differences between groups regarding video game performance. Overall, participants in the Sham+NoExp group seem to be the ones with a lower performance, either in the qualitative assessments before and after the training sessions, and in several in-game variables (goals achieved, goals per attempt, time spent per attempt, etc.). On the other hand, participants in the Sham+Exp group have a slight advantage over the rest, getting somewhat higher scores and especially achieving a greater number of goals during the training sessions. Both groups pertaining to the active iTBS stimulation appear to be on a middle ground, obtaining similar scores on most variables that would rank these two groups between the other two (see Table 61 in the annex).

Determination of parametric adjustment

All but two of the variables related to video game performance did not adjust to a normal distribution: the number of goals achieved during the training sessions and the goals per attempt. All the rest met the normality assumption (see Table 81 in the annex). No violations of the homoscedasticity assumption were found for these variables when divided in the four group (see Table 83 in the annex).

Main results

Baseline differences between the four experimental groups were non-existent for the qualitative video game performance assessment (see Table 86 in the annex).

A repeated measures GLM indicated that, while there was a solid effect of the training session [$F_{(1,23)}=110.555$, $p<.0001$], no interaction effects with the experimental groups were detected [$F_{(3,23)}=1.572$, $p=.223$], and between-subjects effects were not present either [$F_{(1,23)}=1.243$, $p=.317$].

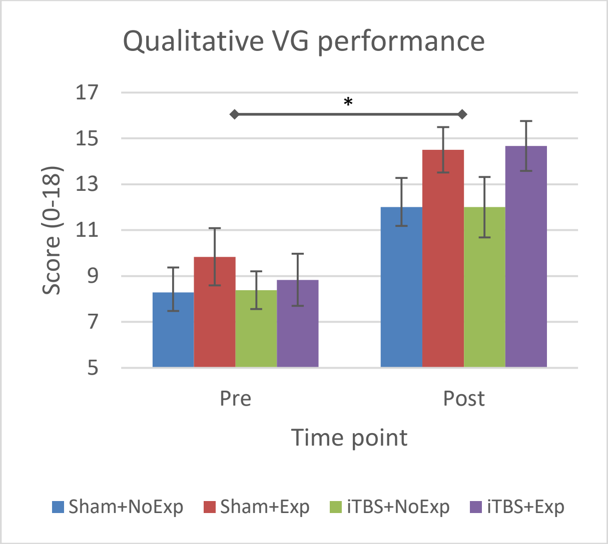


Figure 97. Mean qualitative scores for video game performance during the pre- and post-assessment, by TMS group and previous video game experience.
* Significant at the .05 probability level. Error bars indicate one standard error.

Variables related to video game performance during the training sessions showed that either the number of achievements during video game play [$X^2_{(3)}=7.263$, $p=.064$], the number of attempts [$F_{(3,23)}=1.819$, $p=.172$], the time per attempt [$F_{(3,23)}=2.775$, $p=.064$], and the achievements per attempt [$X^2_{(3)}=3.606$, $p=.307$] did not reach significant differences between the four experimental groups.

3.3.7.2 Reaction times

Descriptive analysis

Response times in the simple reaction time task show some differences among the four groups. The main difference can be observed in the last time point, where the two active TMS groups tend to develop slower reaction times compared to their baseline, whereas the response speeds for sham TMS participants tend to remain stable. The group with more video game experience and active TMS stimulation achieved faster response times overall, although a confluence with the other three groups can be seen at the last time point (see Table 62 in the annex).

Results in the direction choice reaction time task display the same trend to slower response times in those participants who received active TMS stimulation, and the video game experienced with active TMS group still obtained better response times. A different trend appears within the sham TMS groups: whereas the non-player participant performed equally in the three time points, more experienced players tended to improve their response times in each assessment.

Finally, response times in the color choice reaction time task do not follow the trend observed in the other two tasks. Overall, the group with more video game experience that received active TMS stimulation still performed better than the other three groups, while the non-player active stimulation group had the slowest response times, especially in the second and third time points.

Determination of parametric adjustment

No violations of the normality assumption were present in the three assessments of the simple reaction time task (see Table 81 in the annex). However, the post-intervention assessment of this task did not possess equal variances (see Table 83 in the annex).

Non-normal distributions of the data were found for the direction choice reaction time task at the baseline and the first post-intervention assessment (see Table 81 in the annex). However, homoscedasticity was met in all three assessments (see Table 83 in the annex).

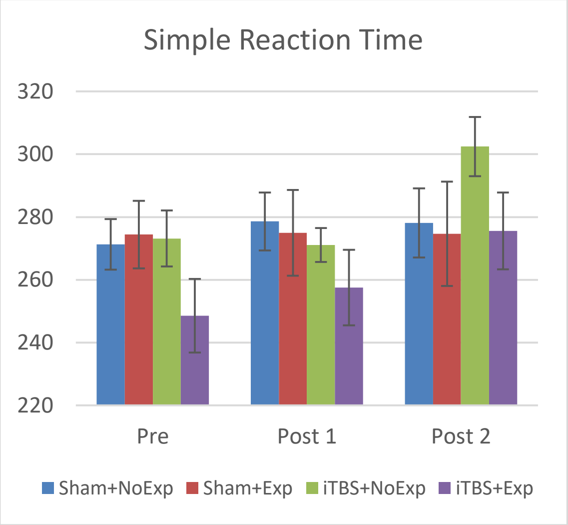


Figure 98. Mean reaction times for the simple reaction time task, by TMS group and previous video game experience.

Responses during the third task, the color choice reaction time, did not comply with the normality assumption during the baseline (see Table 81 in the annex), and the homogeneity of variances requirement was not met at the first post-intervention assessment (see Table 83 in the annex).

The variances of the differences between all possible pairs of within-subject conditions were equal, as measured with Mauchly's test (see Table 85 in the annex).

Main results

No baseline differences were found when examining the three reaction time tasks when divided by TMS modality and previous video game experience (see Table 86 in the annex).

In the simple reaction time task, examining the data with a repeated measures GLM including the baseline and follow-up assessments (due to the non-parametricity of the first post-intervention assessment), an effect of the number of assessments can be observed [$F_{(1,23)}$=7.386, p=.012] but there was no interaction [$F_{(3,23)}$=1.412, p=.265] or between-subject effects [$F_{(3,23)}$=.807, p=.503] of the group. Analyzing the differences between the baseline and the following assessments did not result in significant differences for either the first post-intervention [$X^2_{(3)}$=.530, p=.912] or follow-up [$X^2_{(3)}$=6.056, p=.109] assessments.

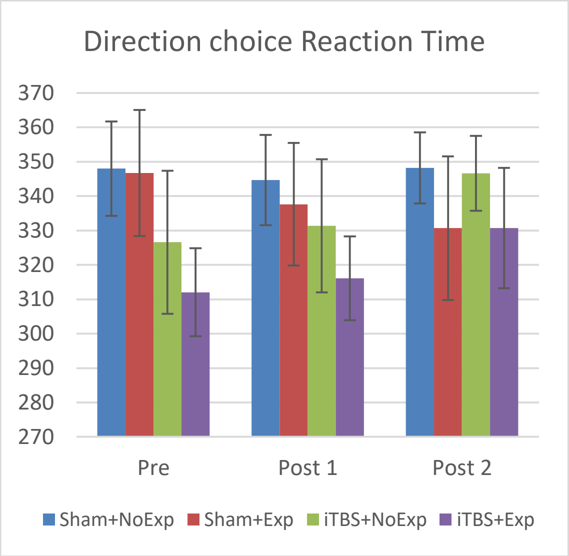


Figure 99. Mean reaction times for the direction choice reaction time task, by TMS group and previous video game experience.

Directly comparing the first post-intervention [$F_{(3,11.537)}$=.314, p=.815] and follow-up [$F_{(3,23)}$=.833, p=.489] assessments did not yield any significant difference between the four groups.

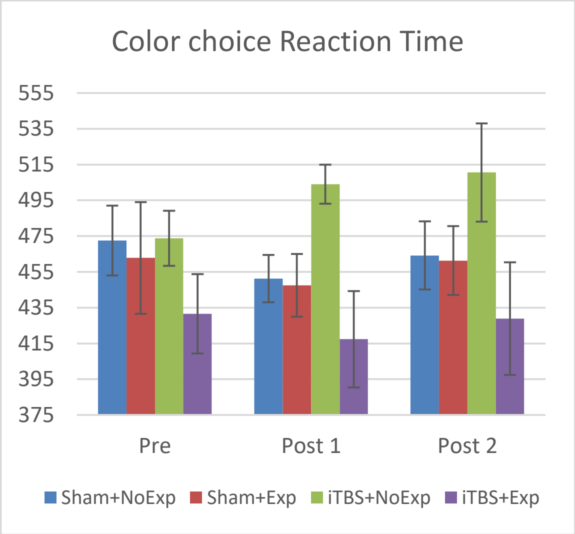


Figure 100. Mean reaction times for the color choice reaction time task, by TMS group and previous video game experience.

Participants' performance in the direction choice reaction time task did not differ between groups in either the first post-intervention [$X^2_{(3)}$=1.828, p=.609] or the follow-up [$F_{(3,23)}$=.287, p=.834] assessments. The differences between the baseline and the first post-intervention assessment were not significant [$X^2_{(3)}$=.708, p=.871], and the same was found for the follow-up [$X^2_{(3)}$=2.827, p=.419].

Comparing the differences between groups in the color choice reaction times yield non-significant results at the first post-intervention assessment [$F_{(3,12.159)}$=1.791, p=.202]. No significant differences were found either at the last time point [$F_{(3,23)}$=1.591, p=.219]. Comparing the results of these two post-intervention assessments with the baseline, no significant differences are found either for the first post-intervention [$X^2_{(3)}$=2.188, p=.534] or the follow-up [$X^2_{(3)}$=2.188, p=.534] assessments.

3.3.7.3 Digit Span

Descriptive analysis

Overall, the forward digits task presents a tendency to obtain higher scores for each new assessment, and all groups performed better in the last assessment compared to the first. For some groups (Sham+NoExp and iTBS+Exp) the highest scores were achieved in the first post-intervention assessment, whereas the rest continued to improve until the final assessment (see Table 63 in the annex).

The effect of the repeated exposure to the task seems clearer when examining the results from the backward digits. In this case, all four groups improved continuously until the last assessment. There appear to be some persistent differences between groups: those with more previous video game experience, particularly the group that received active TMS stimulation, had an overall better performance in this task.

Determination of parametric adjustment

Several violations of parametric adjustment were found in the digits task. Mainly, the data obtained from the first post-intervention assessment of the forward digits was neither normally distributed nor homoscedastic. The same assessment, for backward digits, also turned out to be non-normally distributed, although variances were equal in this case. The rest of the assessments met all the parametric criteria (see Table 81 and Table 83 in the annex).

There was equality in the variances of the differences between all possible pairs of within-subject conditions in the digit span task when the four groups were considered, meeting the assumption of sphericity (see Table 85 in the annex).

Main results

No baseline differences were detected for the forward and backward digit span task between the four groups (Table 86 in the annex).

Analyzing the forward digits using a repeated measures GLM with only the first and third assessment, a strong significant effect of the number of assessments was detected [$F_{(1,23)}$=9.414, p=.005], whereas the interaction effect with the TMS/VG group was not significant [$F_{(3,23)}$=2.033, p=.137], as neither appeared between-subjects effects of the group [$F_{(3,23)}$=.121, p=.947]. When comparing the differences between the baseline and the following assessments, results were not significant either for the first post-intervention [$F_{(3,11.269)}$=.886, p=.477] or the follow-up [$F_{(3,23)}$=2.033, p=.137] assessments. Directly comparing the differences between groups at the first post-intervention assessment, no differences were found [$F_{(3,11.456)}$=.345, p=.793]. Differences at the follow-up assessment did not yield different results either [$F_{(3,23)}$=1.008, p=.407].

Regarding the results in the backward digit task, the situation is similar. In a GLM including the first and last assessments, only an effect of the number of assessments was found [$F_{(1,23)}$=11.229, p=.003], without interaction [$F_{(3,23)}$=.086, p=.967] or between-subjects [$F_{(3,23)}$=1.376, p=.275] effects. The results in the two post-intervention assessments continue without being significantly different [Post 1: X2(3)=2.458, p=.483; Post 2: $F_{(3,23)}$=.872, p=.470], and comparisons of these two assessments against the baseline also show their lack of differences [Post 1: $X^2_{(3)}$=1.325, p=.723; Post 2: $F_{(3,23)}$=.086, p=.96].

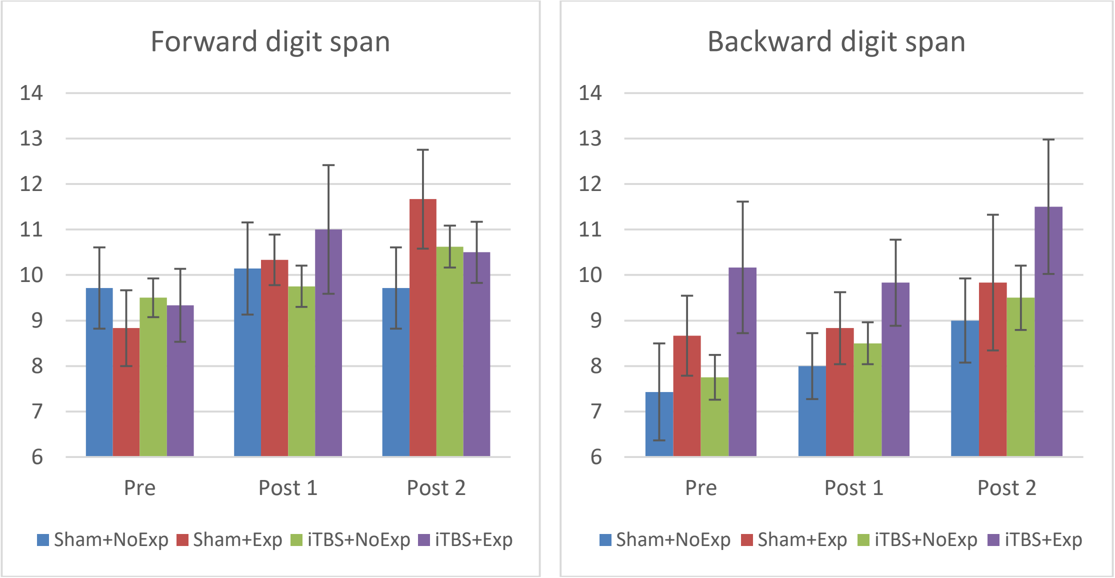


Figure 101. Mean scores for the forward (left) and backward (right) digits task, by TMS group and previous video game experience. Error bars indicate one standard error.

3.3.7.4 Raven's Progressive Matrices

Descriptive analysis

The main difference between the two assessments where this task was employed is the mean score decrease for two of the groups, the ones with less video game experience. Nevertheless, scores are very similar among the four groups. Response times also show similarities for all groups, with the exception of the slower responses in the sham and non-experienced group in the baseline assessment (see Table 64 in the annex).

Determination of parametric adjustment

Neither measure of scores on Raven's test did not fit a normal distribution, but that was not the case for response times per item, where they fit all parametric parameters (see Table 81 in the annex). Equality of variances was met in all cases, for both variables (see Table 83 in the annex).

Main results

No baseline differences could be appreciated for the scores between the four groups, although these differences reached near-significant values when comparing the response times, as a result of the distinct results for the sham and non-video game experienced group being slower than the other three groups (see Table 86 in the annex).

At the post-intervention assessment, no differences in the scores were observed [$X^2_{(3)}$=1.240, p=.743] and comparing the baseline against the post-intervention assessment, the difference is not significant either for the four groups [$X^2_{(3)}$=2.464, p=.482].

Response times in that task, when analyzed with a GLM, do not show any significant effect of the session [$F_{(1,23)}$=2.397, p=.135] or interaction effects with the group [$F_{(3,23)}$=2.089, p=.130], although near significant between-subjects effects ($F_{(3,23)}$=3.006, p=.051) are found. Directly comparing the response times in the post-intervention assessment, differences between groups are not significant [$F_{(3,23)}$=2.257, p=.109], and comparing these measures against their baseline, does not result in significant differences either [$F_{(3,23)}$=2.089, p=.130].

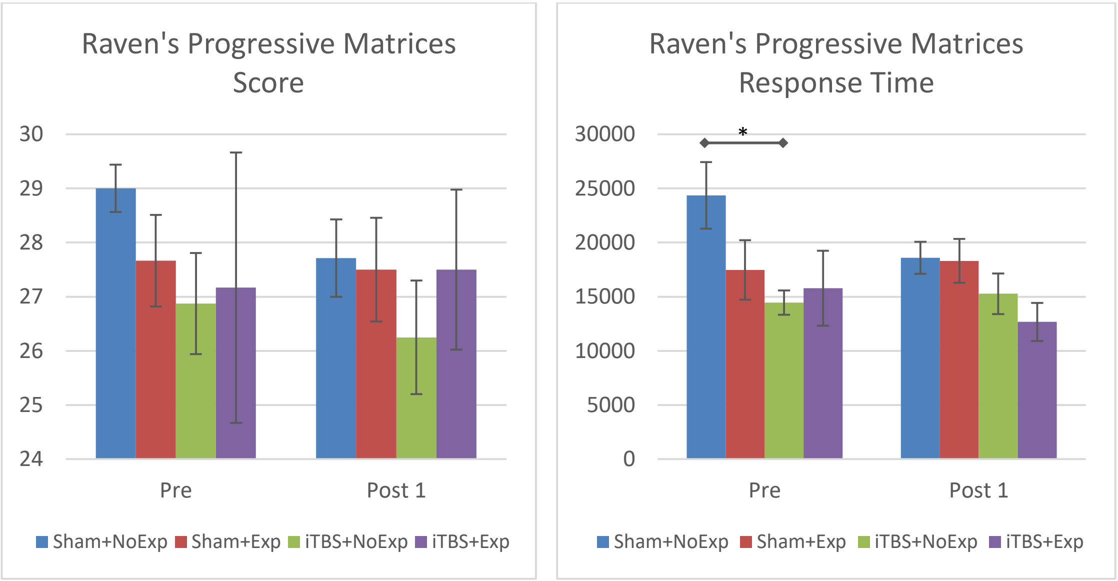


Figure 102. Mean scores (left) and response times (right) for Raven's progressive matrices, by TMS group and previous video game experience. * Significant at the .05 probability level. Error bars indicate one standard error.

3.3.7.5 Five-Point Test (5PT)

Descriptive analysis

No notable differences can be appreciated between the four groups. Only the group that received active TMS and had more video game experienced obtained lower scores overall, although the response variability is high in that group (see Table 65 in the annex).

Determination of parametric adjustment

Unlike the previous analyses of this task where the groups were separated by stimulation method and video game experience, when these two variables are combined to create the four groups, a lack of adjustment to normality appears, needing to use non-parametric tools to study the data (see Table 81 in the annex). Homoscedasticity, however, is not a problem and was met for this measure (see Table 83 in the annex).

Main results

Comparing the scores on the Five-Point Test (5PT) for the single time point where it was applied, no significant differences appeared between the four groups [$X^2_{(3)}$=1.830, p=.608].

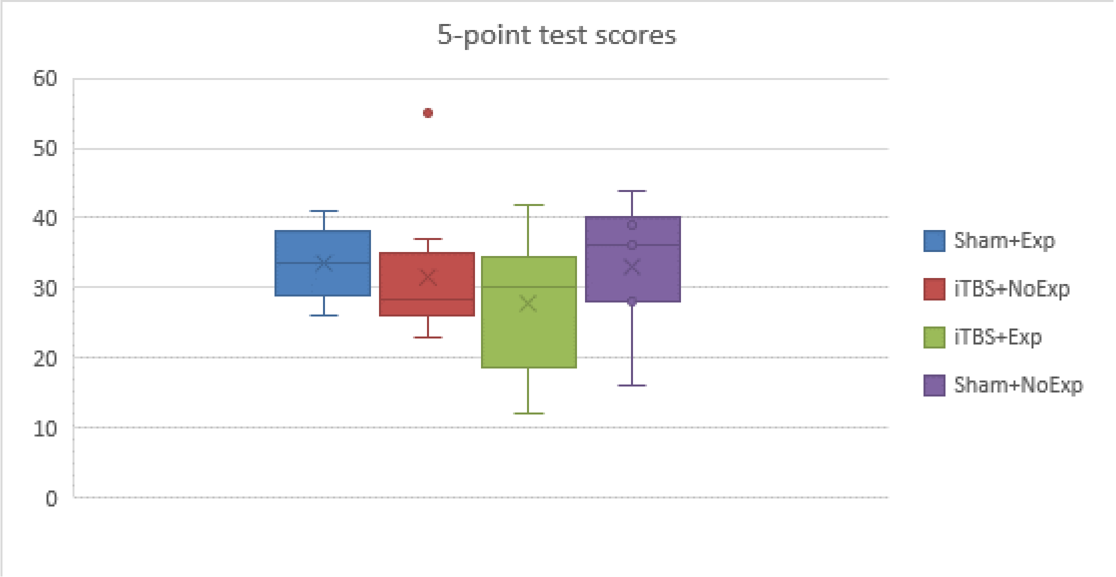


Figure 103. Mean scores on the Five-Point Test (5PT), by TMS group and previous video game experience.

3.3.7.6 N-back

Descriptive analysis

Direct scores on the N-back task show different patterns between groups. The two groups with less video game experience tended to obtain lower scores overall, and that trend was maintained for the three assessments. Positive changes from the baseline to the first post-intervention assessment are more notable for the groups including experienced players compared to the last assessment, but less experienced participants tended to first obtain stable or worse scores until they improved in the third assessment (see Table 66 in the annex).

Response times also showed their main differences between experienced and non-experienced players, where the latter tended to have slower responses, although improving towards the last assessment, without reaching the speeds of the more video game experience experienced participants. The more experienced groups, in turn, overall performed better in this task but did not show signs of improvement for each new assessment (see Table 66 in the annex).

The d' measure combined the two previous results. More experienced players increased their performance from the baseline to the first post-intervention assessment and remained stable towards the follow-up assessment, whereas less experienced participants experimented initially performed worse but recovered their scores to near-baseline values towards the follow-up assessment. Nevertheless, a difference can be appreciated between two extreme groups: the group that received active stimulation and was more experienced, which performed better, and the sham stimulation and low-video game experience group, which comparatively did worse in this task (Table 66 in the annex).

Determination of parametric adjustment

Several violations of parametric adjustment were detected on the data from the N-back task. Virtually all measures related to the scores and response times in the n-back task showed non-normal distributions. That was also the case for data of the d' index obtained during the first assessment (see Table 81 in the annex).

Moreover, one of the measures of the n-back, the scores obtained during the first post-intervention assessment, did not meet the assumption of homogeneity of variances (see Table 83 in the annex).

Mauchly's test pointed out some inequality of the variances of the differences between all the pairs of possible within-subject conditions for the n-back score and n-back response times, although these variances were equal when the d' index was considered (see Table 85 in the annex).

Main results

No baseline differences were found for either the scores, the response times, or the d' index, as examined with the Kruskal-Wallis test (see Table 86 in the annex).

Comparing the scores between groups at the first post-intervention assessment, significant differences were found [$F_{(3,12.411)}=3.635$, p=.044]. Pairwise comparisons show that this signification comes from the scores difference between the experienced and non-experienced participants that received active TMS stimulation. These differences we no longer significant during the last assessment [$X^2_{(3)}=4.051$, p=.256]. Compared with the baseline, the first post-assessment intervention resulted in a significant change [$X^2_{(3)}=11.640$, p=.009], as a result of the differences between the two groups mentioned above. Comparing the last assessment with the baseline, that signification disappeared [$F_{(3,23)}=1.790$, p=.117].

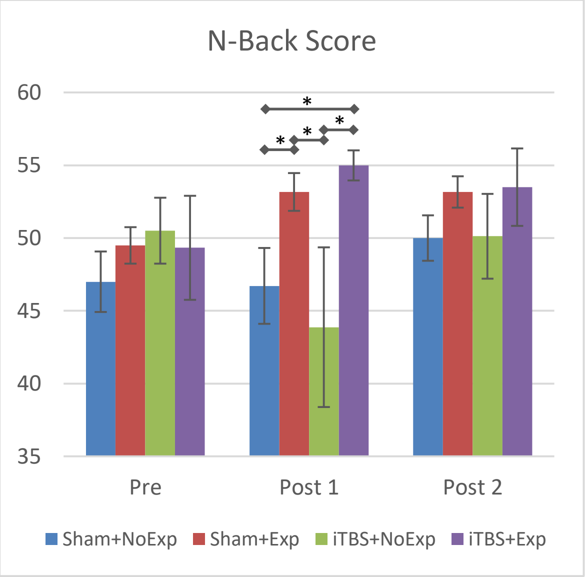


Figure 104. Mean score on the N-back task, by TMS group and previous video game experience.
* Significant at the .05 probability level. Error bars indicate one standard error.

Response times did not differ between groups in either the first post-intervention [$X^2_{(3)}=3.610$, p=.307] nor the follow-up [$X^2_{(3)}=2.767$, p=.429] assessments. Differences between the baseline and these two assessments were not significant either [Post 1: $X^2_{(3)}=2.428$, p=.488 Post 2: $X^2_{(3)}=1.675$, p=.642].

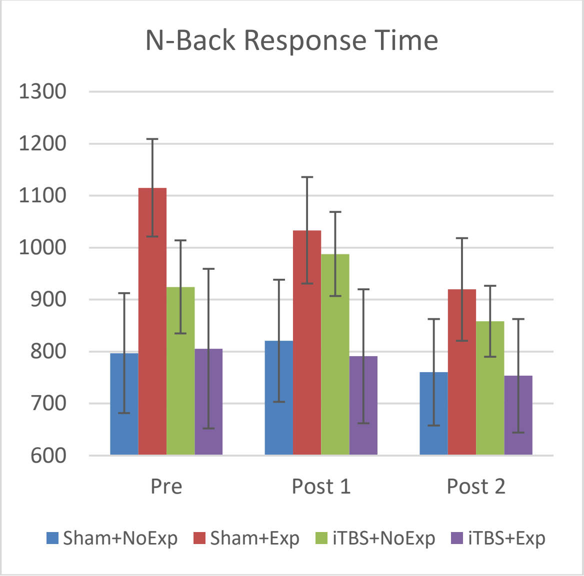


Figure 105. Mean response times in the N-back task, by TMS group and previous video game experience. Error bars indicate one standard error.

The d' index displays a significant difference between groups during the first post-intervention assessment [$F_{(3,23)}=6.095$, p=.003], where the greatest difference was found between the experienced and non-experienced players within the active TMS group. However, these differences are not maintained towards the last assessment [$F_{(3,23)}=2.337$, p=.100]. Contrasting the baseline with the first post-intervention assessment resulted in significant between-subject differences [$F_{(3,23)}=5.599$, p=.005], particularly between the two aforementioned groups, but that signification disappeared when the baseline was compared with the last assessment [$X^2_{(3)}=3.138$, p=.371].

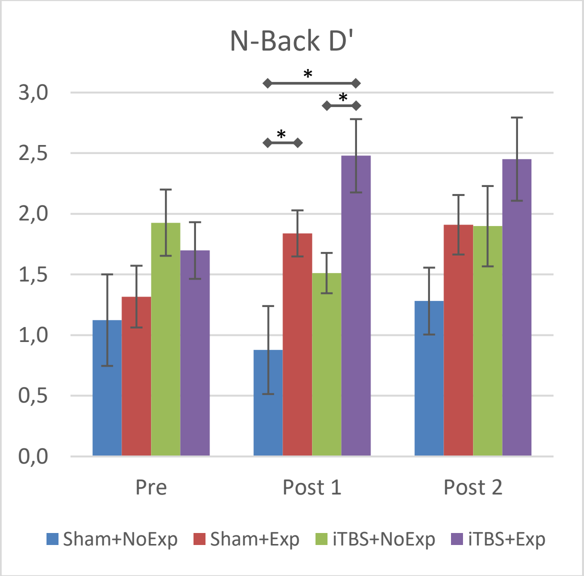


Figure 106. D' scores on the N-back task, by TMS group and previous video game experience

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* Significant at the .05 probability level. Error bars indicate one standard error.

3.3.7.7 Mental Rotation

Descriptive analysis

All four groups present some improvement from the baseline to the follow-up assessment, although from that point, scores tend to stabilize or even decline near baseline values. The two groups that received sham TMS stimulation obtained better scores overall, and carried that advantage up to the latest assessment. The greatest improvement from the baseline corresponds to the active TMS and no video game experience group, whereas that difference was much smaller for the other three groups (see Table 67 in the annex).

Response times, on the other hand, show a clear and linear tendency to become faster for each assessment. The four groups can be categorized based on their performance, where the two groups containing the most experienced players performed faster than the groups that were less experienced, and these two categories obtained virtually identical results in the two post-intervention assessments (see Table 67 in the annex).

Determination of parametric adjustment

There were serious violations of parametric assumptions in most of the measures of the mental rotation task. All three time points of the mental rotation score presented non-normal distributions, whereas the response times did not meet this criterion at the first and third assessment (see Table 81 in the annex). In addition, the response times during last assessment did also not comply with the homoscedasticity assumption (see Table 83 in the annex).

Sphericity was not a problem when mental rotation measures were divided into the four groups combining previous video game experience and TMS modality (see Table 85 in the annex).

Main results

Baseline scores did not show significant differences between the four groups, as neither did the baseline measures of response times (see Table 86 in the annex).

Comparing the differences in the scores for the two following time points did not result in significant differences between the groups. That was true for both the first post-intervention [$X^2_{(3)}=3.437$, p=.329] and follow-up [$X^2_{(3)}=3.100$, p=.376] assessments. When comparing the baselines against these two assessments, differences remained non-significant [Post 1: $F_{(3,23)}=1.191$, p=.335; Post 2: $X^2_{(3)}=4.098$, p=.251].

Response times in the mental rotation showed a somewhat different picture. Differences between subjects were not significant either in the first post-intervention assessment [$F_{(3,23)}=1.037$, p=.395] but were in the follow-up assessment [$F_{(3,11.598)}=4.432$, p=.027]. Respective to the baseline, the first post-intervention assessment did not show any significant differences [$X^2_{(3)}=3.841$, p=.279] as neither did the follow-up [$X^2_{(3)}=1.878$, p=.598].

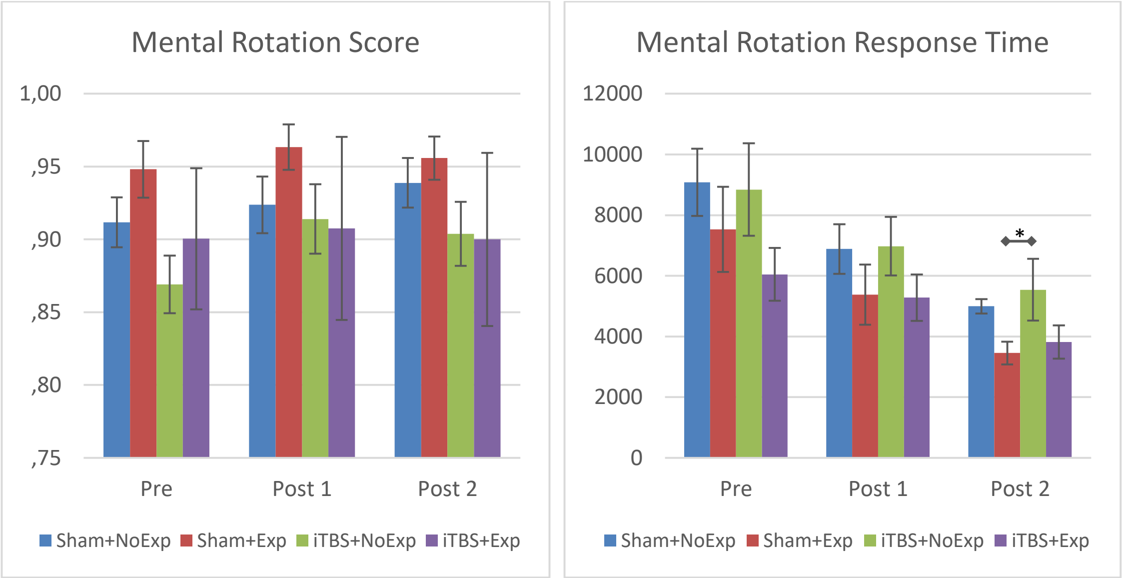

Figure 107. Mean scores (left) and response times (right) for the mental rotation, by TMS group and previous video game experience. * Significant at the .05 probability level. Error bars indicate one standard error.

3.3.7.8 Stop-Switching task

Descriptive analysis

Scores on *go* trials of the stop-switching task show similar results in all four groups. A tendency to obtain better scores can be observed in all four groups for each new assessment, but scores tend to be very close the maximum, experiencing a ceiling effect. Response times in *go* trials show the opposite effect. All four groups experience slower response times in each time point, although one of the groups, the active TMS with no video game experience, experienced average slower response times already in the baseline, whereas the rest performed very similarly (see Table 68 in the annex).

Scores on *stop* trials also show a progression towards better performance for the later assessments. Two groups, not sharing any condition (iTBS+NoExp and Sham+Exp) obtained better scores overall. SSRT values display a much different scenario. The two sham TMS groups started with low response times but slowed down in the two last assessments, whereas the two active TMS groups, even departing from different baselines, managed to retain faster response times. Nevertheless, the slowing of response times in these trials may indicate an adaptation to a more conservative strategy for this task (see Table 68 in the annex).

Scores on *switch* trials, just like in the other measures, show a positive progression for each new assessment. In this case, no big differences between groups can be perceived. When observing the response times in these trials, all groups improve their response times for each assessment, but one of them, Sham+NoExp, starts with slower baseline response times and carries that difference until the last assessment (see Table 68 in the annex).

Determination of parametric adjustment

Several violations of parametric assumptions occur during the score measurements in the three types of trials. The first post-intervention and follow-up assessments for the scores on *go* trials did not meet the normality assumption, and the same situation applied for scores on *stop* trials. For switch trials, only the scores on the first post-intervention assessment did not adjust to normality. Measures related to response times, on the other hand, met all the parametric adjustment parameters in all three measures (see Table 81 in the annex). No violations of the homoscedasticity assumption were detected in any of the measures (see Table 83 in the annex). The criterion of sphericity was not met for one of the measures: the scores on *stop* trials (see Table 85 in the annex).

Main results

No baseline differences were found for any of the six measures in the stop-switching task (see Table 86 in the annex).

Comparing the scores of *go* trials for the two post-intervention assessments, no significant differences between groups were found for either the first post-intervention [$X^2_{(3)}=.206$, $p=.977$] or follow-up [$X^2_{(3)}=2.899$, $p=.408$] assessments. If these two assessments are compared against the baseline, the situation does not change, as none of them display in significant changes [Post 1: $F_{(3,23)}=.197$, $p=.898$; Post 2: $F_{(3,23)}=.310$, $p=.818$].

Response times in *go* trials, when included in a repeated measures GLM with the three time points, show a near significant effect of the number of assessments [$F_{(2,46)}=3.146$, $p=.052$], which fitted a linear regression [$F_{(1,23)}=4.388$, $p=.047$], but no interaction effect with the experimental groups [$F_{(6,46)}=.357$, $p=.902$] or between-subjects effects [$F_{(3,23)}=.415$, $p=.744$]. Including only the first and second time points into the model only changed the effect of the number of assessments, which was now non-significant [$F_{(1,23)}=.928$, $p=.345$]. Neither the interaction effects [$F_{(3,23)}=.385$, $p=.765$] nor the between-subjects effects [$F_{(3,23)}=.519$, $p=.674$] were significant. Directly comparing the first post-intervention and the follow-up assessments did not result in significant differences either [Post 1: $F_{(3,23)}=.524$, $p=.670$; Post 2: $F_{(3,23)}=.242$, $p=.866$].

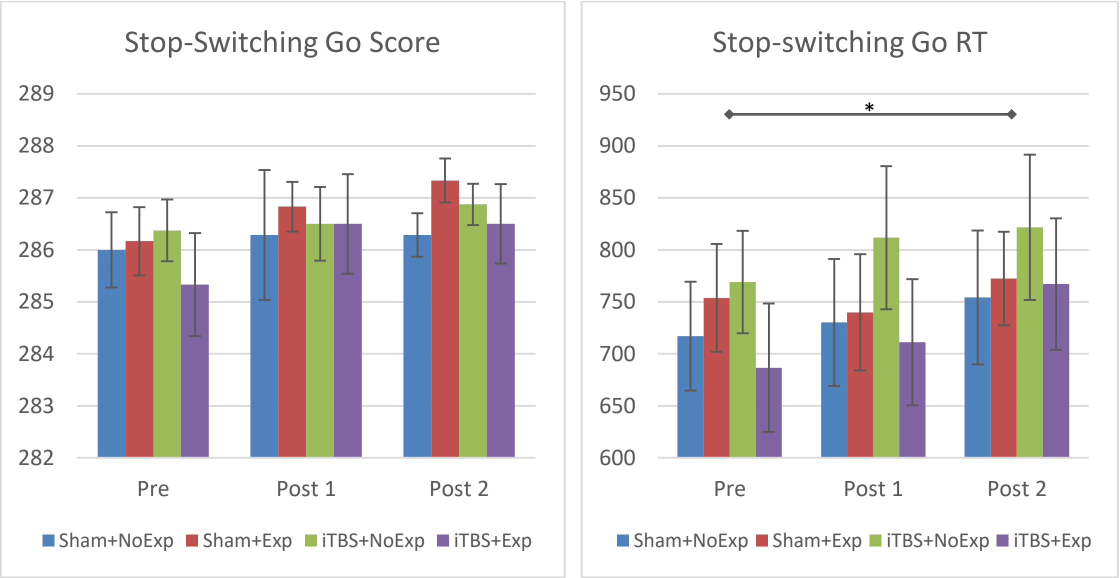

Figure 108. Mean scores (left) and response times (right) for the Go trials in the stop-switching task, by TMS group and previous video game experience. * Significant at the .05 probability level. Error bars indicate one standard error.

Stop scores do not show between-subjects differences during the first post-intervention [$X^2_{(3)}=.789$, $p=.852$] or the follow-up [$X^2_{(3)}=.607$, $p=.895$] assessments. Comparing these two assessments against their baseline scores failed to detect significant differences [$F_{(3,23)}=.383$, $p=.767$; $F_{(3,23)}=.452$, $p=.719$].

The stop-signal reaction time index, as examined with a repeated measures GLM with the three time points, did not show an effect of the number of sessions [$F_{(2,46)}=2.563$, $p=.088$] or interaction effects with the groups [$F_{(6,46)}=.842$, $p=.544$], and between-subjects effects were absent as well [$F_{(3,23)}=.238$, $p=.869$]. Removing the third time point from the model, the effect of the number of sessions became apparent [$F_{(1,23)}=5.057$, $p=.034$], but the interaction effect was not significant [$F_{(3,23)}=.2.143$, $p=.122$], just like the between-subjects effects [$F_{(3,23)}=.152$, $p=.927$]. Direct comparison at the two post-intervention assessments did not yield any significant difference either [Post 1: $F_{(3,23)}=.965$, $p=.426$; Post 2: $F_{(3,23)}=.227$, $p=.876$].

Figure 109. Mean scores (left) and stop-signal reaction time (right) for the *stop* trials in the stop-switching task, by TMS group and previous video game experience. * Significant at the .05 probability level. Error bars indicate one standard error.

Exploring *switching* scores with a repeated measures GLM composed by the baseline and follow-up assessments (due to the non-parametricity of the first post-intervention assessment), an effect of the number of assessments was found [$F_{(1,23)}=7.881$, $p=.010$] but the interaction effect with the experimental group was absent [$F_{(3,23)}=.110$, $p=.954$], and between-subjects effects were also non-significant [$F_{(3,23)}=.286$, $p=.835$]. When comparing the first post-intervention assessment between the four groups, no significant differences could be found [$X^2_{(3)}=1.036$, $p=.792$]. At the last time point, comparing the scores between groups also did not result in significant differences [$F_{(3,23)}=.106$, $p=.956$]. The differences from the baseline to the first post-intervention assessment did not achieve significance [$X^2_{(3)}=1.750$, $p=.626$], and neither did when comparing the baseline to the results in last assessment [$F_{(3,23)}=.110$, $p=.954$].

Response times in switch trials, explored with a repeated measures GLM with the three time points, achieved significant differences in the number of assessments [$F_{(2,46)}=.3.536$, $p=.037$], but no interaction [$F_{(6,46)}=.113$, $p=.994$] or between-subjects effects [$F_{(3,23)}=.489$, $p=.693$]. Removing the last time point from the model resulted in the lack of significance of the number of assessments [$F_{(1,23)}=2.901$, $p=.102$], while the interaction [$F_{(3,23)}=.122$, $p=.946$] and between-subject effects [$F_{(3,23)}=.655$, $p=.588$] remained non-significant. Differences between the four groups at the first post-intervention assessment did not reach significance [$F_{(3,23)}=.651$, $p=.590$], and neither did the follow-up [$X^2_{(3)}=.634$, $p=.889$].

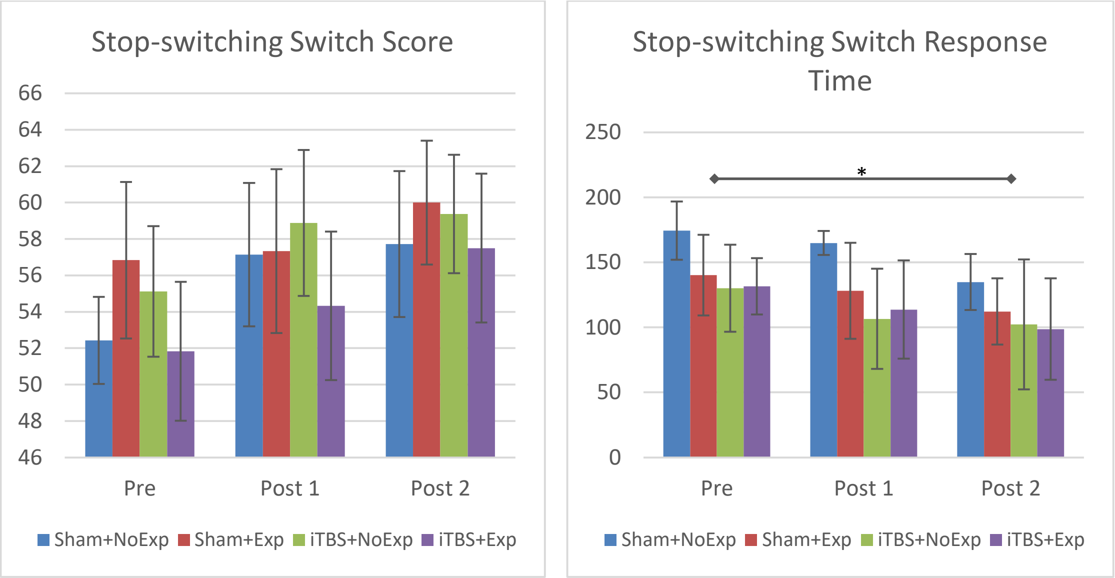

Figure 110. Mean scores (left) and response times (right) for the switch trials in the stop-switching task, by TMS group and previous video game experience. * Significant at the .05 probability level. Error bars indicate one standard error.

3.3.7.9 Matchstick task

Descriptive analysis

Scores on the matchstick task show some differences between groups but are also characterized by a high interindividual variability. Generally, the scores for the more video game experienced participants were slightly higher than those that were less experienced. In contrast, response times were not faster for more experienced players, and were similar between groups, while also featuring a high variability (see Table 69 in the annex).

Determination of parametric adjustment

Data from the two measures of the matchstick task, scores and response times, at a single time point met the requirements of normality and homoscedasticity (see Table 81 and Table 83 in the annex).

Main results

A one-way ANOVA indicated that scores did not significantly differ between groups [$F_{(3,23)}=1.609$, p=.215], and these differences are even smaller when we compare the response times [$F_{(3,23)}=.086$, p=.967].

Separating the performance on this task in the first and second exposition to each type of problem, it was found that scores for the first exposition were near-significant between groups [$F_{(3,12.005)}=3.229$, p=.061], but those on the second exposition were not [$X^2_{(3)}=2.142$, p=.543]. Differences in response times for these two expositions were, in both case, not big enough to be significant [1st: $F_{(3,23)}=1.013$, p=.405; 2nd: $F_{(3,11.776)}=.426$, p=.738].

Focusing on the facilitated responses by a previously correct type of problem, it can be observed that neither the absolute number [$X^2_{(3)}=5.609$, p=.132] nor the proportion [$F_{(3,18)}=1.104$, p=.373] of facilitated responses reached significant differences. Finally, response times in these facilitated responses did not differ between groups either [$F_{(3,18)}=1.262$, $p=.317$].

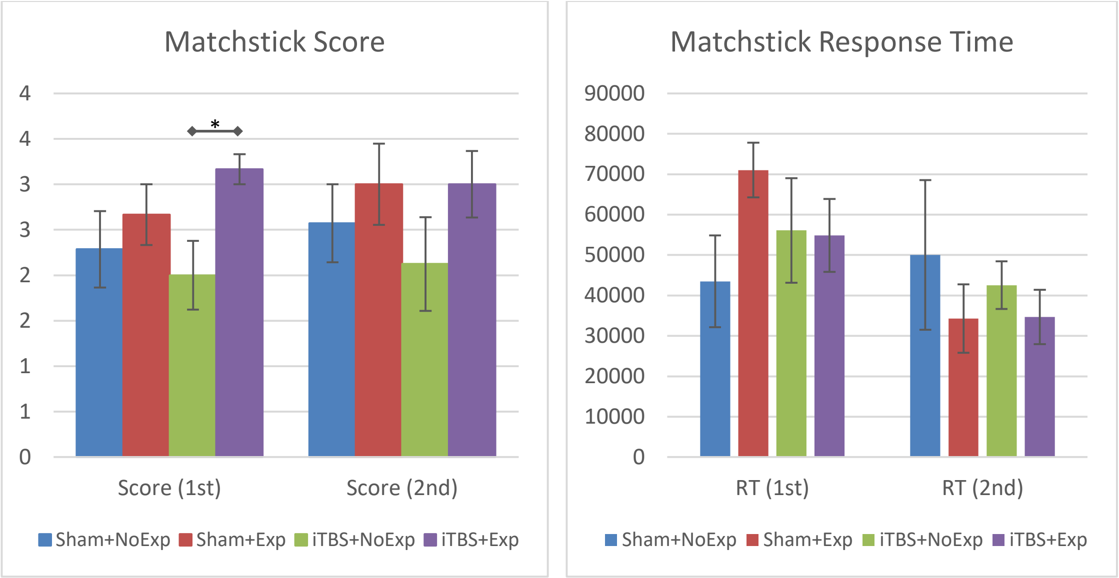

Figure 111. Score (left) and response time (right) distribution in the matchstick task, by TMS group and previous video game experience. * Significant at the .05 probability level. Error bars indicate one standard error.

3.4 Discussion

This section aims to delve into the results detailed in the previous section and their possible explanations, finding whether they match the hypothesis posed in this research. Since the key point lays on whether the independent variables had effects in cognitive enhancement, and in order to offer a comprehensive account of the results, the discussion is structured based on the explored cognitive domains: processing speed, attention, visuospatial skills, executive functions and general intelligence.

However, not all these cognitive domains have been trained directly during the training sessions, so positive results in these areas would represent the so-called *far-transfer effects*. Preceding the analysis of far-transfer effects, a section is dedicated to exploring the near-transfer effects, as measured with a task that is equivalent to the one used during the training sessions: a matching video game.

3.4.1 Near-transfer effects

The first step in assessing the success of the training period in video games is checking whether it had an impact on a similar task, what could be considered a near-transfer effect. In this case, the task in which the performance was assessed was a similar video game with exactly the same mechanics but set in a completely new environment, meeting all the requisites for detecting the possible transfer of learning on the same domain because of the training, what is often termed as *near-transfer*.

Broadly speaking, near-transfer effects are ubiquitous among all participants. All of them, without exception, improved their direct score on the video game respective the baseline score, regardless of their previous experience in video gaming or their actual performance. There is one possible confounding variable though, as part of the increase of performance may have happened as a result of the baseline assessment in which participants already played the game used for the assessment of near-transfer effects. However, that exposure to video game play involved only a small fraction of the total video game practice done in the study. It only took 15 minutes per participant, compared to the 15 hours (900 minutes) dedicated to training in the main video game, making the time spent playing during the assessment only a 1.67% of the total time spent playing video games in the study.

When analyzing the possible effect of the active TMS stimulation on the rate of improvement, we can observe that this variable did not really affect the performance, since both stimulation groups reached a near-identical performance increase in the game (see Figure 63), and there were no differences in baseline performance, either. This is already relevant, since a lack of effect of the active TMS stimulation in achieving cognitive improvement in near-transfer tasks may be indicative of the possible effect (or lack thereof) of the stimulation on the neuropsychological tasks that will be discussed in the far-transfer section. Therefore, it can be stated that active TMS stimulation did not have an effect on enhancing or decreasing participants' performance on a 3D platform video game, which otherwise would have been promising for the outcomes of this project since it would have been a first indicator of the potential beneficial effects of TMS.

Unfortunately, there are no records to date in the literature in which TMS has been used to potentiate the performance during video game play, although some recent successful attempts are carried out with transcranial current stimulation (tDCS) over the bilateral DLPFC (e.g. Looi et al., 2016), despite the differences in both the training program and the intervention protocol they used compared to ours. The differences between the two techniques also make the results hardly comparable, mainly due to their different approaches at stimulating a specific brain region; where TMS is extremely focal, tDCS affects a much larger area of the brain. Moreover, among the different brain structures that the chosen video game seems to activate (DLPFC, right hippocampus and cerebellum, Kühn et al., 2013), only the DLPFC was actively stimulated in this project, with the intention of potentiating the processing of strategy elements in the game, while the other regions, responsible for spatial memory and fine motor skills, were omitted, possibly being one of the reasons why TMS did not have a direct effect on video game performance.

Studying the effect of the previous video game experience yielded some results worth commenting. First, experienced and non-experienced groups performed similarly on the baseline, although it has to be noted that experienced gamers had a slight, but non-significant, advantage. Nevertheless, it is in the post-intervention assessment that more interesting results appear: those participants who had been regular video game players in the past, despite not currently playing, had higher performance rates when being assessed with the 3D video game (see Figure 83). Indeed, experienced participants, after a long period without playing actively, seemed to lose their advantage to their non-experienced counterparts, reaching similar baseline scores, but after a short training period, their previous exposure to video games was visible again in the form of a superior performance and higher learning rates. This leads us to some conclusions on the effects of the previous video game experience: after some time (probably years) without playing regularly, the possible benefits of being a regular video game player tend to fade away and apparently disappear, at least when assessed with another video game. These benefits appear again after being trained, in the form of faster learning rates, surpassing the performance of those who were not as experienced. It is likely that a lifetime of learning, after a period of inactivity in which that procedural knowledge has not been used, has been left in a dormant state in which its effects are not apparently visible, but only a brief period of exposition to that task is needed in order to be active again and regain the latent abilities.

The lack of interaction effects between TMS and previous video game experienced showed no surprises here. While the effect of the training sessions is evident in each of the four groups, none of them showed any effects that differed from what was previously inferred: the two groups belonging to the more experienced video game players showed a greater improvement (agreeing with what has been commented on the previous paragraph) than the two non-experienced participants, regardless of the type of TMS stimulation. A possible explanation for the lack of significance in these differences may be the low sample size as a result of dividing participants into the four groups.

Regarding which cognitive domains correlate with higher near-transfer effects, participants with better performance in the mental rotation task tended to display a larger improvement in the video game performance after training. This is consistent with the fact that these effects were more notable in participants with previous video game experience, and that initial advantage in

3D visual skills may be attributed to that previous experience. Coincidentally, those same participants had also better baseline response times in Raven's progressive matrices, which is considered a test of fluid intelligence, but may also share a visual component together with the problem-solving factor. In fact, skills related to visuospatial cognition, in which mental rotation is found, are one of the cognitive domains most sensible to change, with medium effect sizes as a result of action video game play, without noticeable accuracy/speed tradeoffs (see section 2.2.2.1). This effect is more pronounced in those individuals who had a lifetime video game experience compared to those who underwent video game training without previous video game experience (Bediou et al., 2017). While this is not a proof of the predictive power of visuospatial skills on video game performance, it helps to establish a link between them.

Since there is a significant leap between the tasks used for near and far-transfer assessment (from a near-identical video game to a more reductionist computerized task) it would have been interesting to explore transfer effects in a more gradual way, not only using a near/far division. An ideal approach would be assessing all the spectrum by using a range of video games and computerized tasks from more similar (like the one used in this project) to more distantly related, sharing only some of the features with the video game used during the training (e.g. 3D navigation, fast reaction times, use of gamepad, strategy elements, time constraints).

For instance, after the near-transfer assessment (which used exactly the same video game mechanics but in a new environment), another 3D platformer game could have been used where the 3D exploration and strategy elements are equally present, but different psychomotor skills are needed. A first-person shooter game would follow (placing more importance on the precision and timing of the actions), then a fighting game (similar, but without the 3D exploration feature), continuing with real-time and turn-based strategy games (that do not feature fast action at the same extent and do not require manual precision, but are more reliant on planning capacity), and ending with puzzle games (featuring pure executive and general intelligence skills).

Each genre of video gaming, to which *Super Mario 64* only shares part of its features, would tell us if there are some cognitive skills that are more prone to be transferred, or which of these skills the video game was actually training. This variety of video games would also show us if training in just one video game would be enough to achieve generalization of common features in a diversity of video games.

3.4.2 Far-transfer effects

In this study, cognitive enhancement has been assessed by a neuropsychological battery applied after the training period. Since these tasks do not feature elements that were directly trained in the video game, an improvement in any of these tasks could be a sign of far-transfer effects, where the specific skills and knowledge acquired during the training phase had an impact on non-trained abilities, as measured in the different cognitive domains of the neuropsychological battery.

3.4.2.1 Processing speed

Simple processing speed, understood as the time needed to perform simple cognitive tasks, is one of the cognitive functions that shows more resistance to change, although it tends to decline with age, as it is closely related to white matter physiological properties (Penke et al., 2012; Tuch et al., 2005) and measures of general fluid intelligence (Deary, Liewald, & Nissan, 2011).

In the tasks measuring reaction times, the results are affected not only by the cognitive latency itself but also by motor speed and general alertness. Three reaction time tasks were used in this study: a simple task, a direction choice task, and a color choice task. While the first one is the purest of the three, only requiring visual perception to provide a motor response through the keyboard, the other two featured a more complex level of processing that was shown on the higher reaction times needed to respond correctly. Moreover, the fact that all three tasks used stimuli with a visual (instead of e.g. auditory or somatosensory) component must be also taken into consideration when interpreting the results.

This is consistent with Hick's Law, where the time to make a decision will depend on the number of choices, increasing reaction times logarithmically (Hick, 1952). Despite the two choice reaction time tasks only having two possible choices, the one involving color feature showed, in all cases, higher response times. This is likely due to the fact that in the direction choice task, the spatial position of the stimuli had a direct correspondence with the position of the keys that the participant must press, while in the color choice task participants had to rely on their short-term memory to remember the rule (red-left, blue-right) and apply it correctly. Whereas simple reaction times averaged 260ms, trials in the color choice reaction time task took around 460ms to complete, and direction choice reaction time trials around 330ms, being consistent among all experimental groups (see Figure 64). Furthermore, the two choice reaction time tasks were simple enough that, even under time pressure, participants rarely failed any trial, so there was virtually no accuracy/speed tradeoff.

Processing speed has a crucial role in the rest of cognitive processes, so an enhancement or impairment in this domain will have an impact on the remainder of the cognitive measures. Most of the other cognitive tasks used during the assessment also provide values of reaction time, but these different constructs, while related, must not be confused. Here processing speed is used in a reductionist way, measuring only the response latency in very simple tasks with little cognitive load, whereas in the rest of the cognitive assessment is referred to the total time required to complete a cognitive trial in a given task.

In the sample that has been studied, processing speed was not influenced in a relevant way by either the video game training sessions, the TMS stimulation or the previous video game experience. Nevertheless, some significant, albeit small, differences between groups arose that is worth commenting.

When dividing the participants by stimulation condition, those who received active iTBS over the DLPFC suffered a decline in the simple reaction time task during the third assessment (two weeks later) compared to the baseline and the first post-intervention assessment, whereas response times in the sham group did not change at all during the course of the experiment (see Figure 65). This decline had a small magnitude, being around 25ms slower, which would be equivalent to a ~9% change in reaction speed. The counterintuitive nature of this data, where active iTBS had the opposite effect that would be expected, together with the fact that the change appeared during a follow-up period (two weeks after the end of the training) indicate that it is most likely a result of a statistical artifact. Interestingly enough, participants in the active iTBS group also suffered a slight (but non-significant) decline of performance in the direction choice reaction time task whereas those in the sham group tended to improve, eliminating the performance gap found in the baseline. A possible explanation for that phenomenon is that the stimulation over the DLPFC had a positive effect on participant's capacity to reflect, reducing impulsivity, taking longer to respond to each item.

Having previous video game experience had some slight effect over reaction times. There was an initial gap between experienced and non-experienced participants that tended to be larger in each subsequent assessment. This tendency that can be appreciated in all three tasks (see Figure 84, Figure 85 and Figure 86) but becomes more apparent as the task becomes more cognitively demanding, finally reaching significance in the color choice reaction time task. In this case, the correlation indicates that having been a regular video game player at some point has a beneficial effect on processing speed. However, a causal link between the two cannot be established with just the data available from this experiment, as it might as well be the case that participants with faster processing speed had a marked natural tendency to like playing video games, and not vice versa.

No interaction effect between TMS and previous video game experience has been found in processing speed, although some of the tendencies that were found in these two classifications in isolation can also be observed when looking at their interaction. Again, it is in the color choice reaction time were groups displayed more differences, especially between active iTBS participants with and without video game experience (see Figure 100). Actually, non-experienced iTBS participants showed the worst performance among the four groups, being around 60ms slower than the average. This result can be explained by the same phenomenon found when groups were categorized by TMS condition and by previous video game experience separately, as commented above.

There is another measure in the cognitive assessment which is worth commenting here, and that is the *go* trials in the stop-switching task. Differences were found between assessments, showing that participants of all groups had a progressive slowdown in performance. Despite the apparent worsening effect, it does not actually correspond to a decline in performance; even if *go* trials in that task are very similar to those in the direction choice reaction time task, the fact that they were mixed with *stop* and *switch* trials could made participants distrust the stimuli and elaborate strategies to maximize their accuracy, at the cost of the response speed. This is seen in how participants responded during the baseline versus the two following expositions to the stop-switching task, becoming more cautious in case the initial stimuli turned into a *stop* or *switch* trial.

Overall, processing speed did not show big differences between the experimental groups, but it is possible that these small differences become more accentuated as the neuropsychological tasks become more demanding, as has been observed between the three reaction time tasks.

3.4.2.2 Attention

Only one task in the assessment used in this project can be considered to obtain an attentional measure: the forward digit span task. It actually combines measures of closely related attentional and memory aspects: attentional span and rote recall. Its backward modality requires the use of the same attentional resources plus a working memory component, so it is going to be discussed deeply in the working memory section.

Other tasks used during the assessment also make extensive use of the participant's attentional resources. For instance, the n-back task and stop-switching task have an emphasis in selected and sustained attention, but these attentional components are shadowed by other neuropsychological measures (executive functions in this specific case), making the extraction of purely attentional values unreliable. The two choice reaction time tasks (direction and color) commented above also rely on an attentional component, as selective and sustained attention is also necessary to avoid committing errors or omissions. Nevertheless, due to the short duration and the low difficulty of the reaction time task, the overwhelming majority of items were responded correctly, thus not being optimal for measuring possible attentional changes.

Results in the forward digit span task are characterized by an effect of the successive assessments, especially between the pre and post-intervention, indicative that this task is strongly affected by practice (see Figure 66 in the annex). It is worth mentioning that this learning effect was also present in the backward modality. Nevertheless, neither the TMS stimulation condition or the previous video game experience (see Figure 87) seemed to have a significant effect on the performance of this task, although experienced participants achieved near-significant differences respective to their non-experienced counterparts after training, having an overall somewhat superior performance on the post-assessments that was not evident at the baseline.

Moreover, there is an unexpected effect on the digit span task when observing the scores obtained in the forward and backward modalities. Despite the backward modality needing extra cognitive processing to provide a valid response (holding the information in the short-term memory, mentally reversing it, and enunciating the response), scores on both tasks did not differ by much, especially towards the follow-up assessment. What is more, in some cases, participants that obtained overall above-average scores in the digit-span task tended to perform better in the backward modality rather than the forward task. Some explanations are possible for this phenomenon. First of all, the fact that the forward task always immediately preceded the backward modality favors the latter, as the former could have acted as a training. Secondly, participants might acknowledge the increase in difficulty in the second modality and consciously dedicate more efforts to that task, resulting in fewer errors. Finally, participants informally reported the use of different strategies towards the backward digit span task, such as not responding immediately, actively rehearsing the whole digit sequence before responding, trying to remember the complete sequence at once, clustering digits in groups of two or three, and predicting the length of the number sequence for a more efficient clustering.

Having a look at the literature, the possible improvement of attentional processes using TMS seems plausible, although most studies focus on the assessment and improvement of visuo-spatial selective attention rather than sustained attention (e.g. Cooper, Humphreys, Hulleman, Praamstra, & Georgeson, 2004; Galea, Albert, Ditye, & Miall, 2010; M. F. Rushworth, Ellison, & Walsh, 2001; M. F. S. Rushworth, Johansen-Berg, Göbel, & Devlin, 2003), where attentional resources are required to select a specific spatial location in the visual field, which is an aspect that was not directly assessed in this project. Moreover, most of these studies failed to achieve long-lasting effects, partly due to their design and partly to their aim. In any case, no study used a multiple-session paradigm like the one applied in this project. For instance, a group of participants in the study by Galea et al. (2010) improved their performance in a spatial emotional memory task (a task that requires short-term memory, spatial memory, spatial attention and emotional components) after one session of 1Hz rTMS stimulation over the left DLPFC, a counterintuitive effect considering the location and the type of stimulation. In a similar fashion, Thut et al. (2006), who also used an offline 1Hz rTMS paradigm over the right dorsal PPC, measured the participant's performance using a Posner cueing task, assessing spatial attention shifting. Attentional gains were achieved but depended on the laterality of the stimuli. In these two cases, it seems that the cognitive benefits of the stimulation work under the addition-by-subtraction mechanism, where competing processes are inhibited (Luber & Lisanby, 2014), and are hardly comparable with this project's approach where the stimulated region, the right DLPFC, neither the PPC nor the left DLPFC, is directly potentiated and measured with a sustained attention task. Therefore, the literature lacks directly comparable studies, using similar tasks and stimulation protocols, to corroborate the results obtained in this project.

Literature regarding the possible augmentation of attentional resources using video games is more common, but again we find the problem that the cognitive tasks employed in these studies usually assess different forms of visuospatial attention (e.g. alternating and divided attention), not sustained attention. Actually, attention appears to be the cognitive domain which is most easily improved by using video game training, particularly if fast-paced and visually complex games are used (J. E. Cohen et al., 2008). In this regard, cognitive improvements after video game training have been found in an attentional blink task and in a multiple object tracking task (J. E. Cohen et al., 2008; C. Shawn Green & Bavelier, 2006b), and in a visual selective attention task (Cassavaugh & Kramer, 2009), although failed to detect cognitive improvement using tasks such as the flanker task or the trail making test (Boot et al., 2013). In some cases, alleged attentional increases can be likely attributed to an augmentation of visual perception or processing speed rather than pure attentional process (Wang et al., 2016). The most comparable study is the one conducted by Stern et al. (2011) that assessed performance after 21.5 hours of video game training using a neuropsychological battery including Letter-Number Sequencing of WAIS-III (Wechsler, 1999), finding positive results. In this task, the participant listens to a sequence of numbers and letters and he/she has to recall the numbers in ascending order and, later, the letters in alphabetical order. Thus, this task would be more appropriately compared to the backward digit span, not forward, due to the mix of attentional and working memory processes.

The component of attention measured in this project differs from the common visual attentional tasks found in the literature, because the forward digit span task was a first measure of attentional span, preceding the backward digit span task which is used as a more general measure of working memory, given the emphasis of this project in executive functions. The improvement of attentional processing was therefore not a priority, as neither the stimulated region nor the video game genre used in this project were chosen for this purpose.

The effects of the TMS stimulation and the previous video game experience proved non-significant for improving the performance in the forward digit task. If some kind of attentional enhancement were present, the effects were so small that the task was not sensitive enough to measure the changes, due to its scoring system that excludes the time taken to complete each item. Nevertheless, the attentional domain was not a primary aim in this study, so there was no particular reason to use a more complete cognitive battery including measures of visual perception, spatial, selective, alternating, and divided attention.

3.4.2.3 Visuospatial skills

Due to the nature of chosen video game for the training period, visuospatial skills are, together with executive functions, one of the components that has been given more emphasis in this research. *Super Mario 64* features open 3D environments in which participants must navigate and interact with different objects and characters in specific ways, often requiring high-precision movements, in order to achieve the goals in the game. Navigation in the 3D environment is a defining feature of platform video games, requiring a high level of visuospatial accuracy, especially the ability to execute actions chosen among a large number of possible jumps and other movements to reach new areas in the game. Therefore, since playing this video game entailed a continuous exposure to visual and spatial stimuli that the participant had to keep processing, it was considered that 3D visuospatial skills were an adequate candidate for detecting the presence of far-transfer effects in this study.

The chosen task to assess the possible improvement in visuospatial skills after the training period was a modern adaptation of the classic Mental Rotation task (Shepard & Metzler, 1971). As can be observed in the results, the general mental rotation effect (where larger angular differences took longer times to process) was clearly present in all groups in the baseline assessment, thus giving validity to the test. It is worth mentioning that this exact paradigm, video game training and visuospatial skills measured with the mental rotation task, has been used in the literature to explore possible gender differences regarding this ability. These gender differences will be commented in more detail in section 3.4.3.

Regarding the results, overall, it can be observed that the time needed to process each item decreased in each assessment in all participants (see Figure 72), indicative of a performance improvement, possibly as a result of both the video game training and the learning effects from being repeatedly exposed to the assessment task. The improvement from one assessment session to the next is quite remarkable, reducing the average time to process and respond to each stimulus by 22.18% (-1773ms) from the baseline to the first post-assessment, and by 43.03% (-3439ms) to the follow-up assessment. These changes indicate that 3D visuospatial skills, as measured with the mental rotation task, are sensitive to training, and these improvements were still present two weeks later.

Nevertheless, this effect was not present when observing the accuracy in this task, since scores stayed stable throughout all the assessments in all groups (see Figure 73 in the annex). It makes sense, considering that participants were instructed to prioritize accuracy over speed for this task. As response times increased as items became more difficult, the accuracy level also was inversely associated with item difficulty. However, the learning effect observed in response times was not present in accuracy, except perhaps for the most difficult items (those rotated 160º and 180º), where a slight, but non-significant, improvement can be observed in the post-assessment and the follow-up.

Exploring the effects of the TMS stimulation over visuospatial skills, it can be observed that the time needed for processing the stimuli did not differ between groups (see Figure 75). Participants assigned to the sham iTBS group had a significantly better accuracy at the baseline compared to the active iTBS group, a difference that tended to disappear towards the post and follow-up assessments, and no changes derived from the stimulation could be observed.

Mental rotation recruits two cortical regions: the intraparietal sulcus and surrounding areas, that contain spatially mapped analog representations of mental rotation, and the medial superior precentral cortex, indicative of the processing of motor simulations. While mostly bilateral, parietal activity is more focused on the right hemisphere, whereas frontal activity prevails in the left hemisphere (Zacks, 2008). The TMS stimulation site used in this research, the DLPFC, was not optimal for directly affecting areas related to mental rotation, but it was hoped that stimulating that area, which constitutes a major hub interconnecting many other cortical regions, together with the video game training as a form of visuospatial training, it would be enough to achieve an improvement in mental rotation. However, our results did not support that idea, since TMS did not have a significant effect in improving visuospatial skills, neither in accuracy nor in speed of processing (see Figure 75). There are examples in the literature where successful cognitive enhancement in mental rotation skills was reached through TMS, by directly stimulating the intraparietal sulcus at 1Hz (but neither at 3Hz nor 20Hz) (Klimesch et al., 2003). This study demonstrates the potential of the technique to improve this domain, but it seems that a more direct approach is required when choosing target area for that function.

The effects of previous video game experience yielded more interesting results. Those participants which were more experienced had, on average, a near-significant higher baseline visuospatial performance (both in accuracy and response times) than non-experienced participants (see Figure 92). Interestingly enough, this initial difference tends to disappear in the following assessments, where the performance is virtually identical in both groups. To this effect, we must add the significant improvement in accuracy between the baseline and the follow-up assessments in both groups. However, that was not the case for response times, that despite the strong progressive improvement across groups, it was not mediated by previous video game experience.

The interaction between TMS stimulation and prior video game experience was non-existent (see Figure 107). While all four groups improved significantly respective to the baseline, in particular the *TMS+NoExp* group, the only differences were those between groups containing experienced and non-experienced participants (regardless of the TMS condition), since the effects of TMS could not be perceived in this task.

From these results, we can infer that lifelong video game experience can have a beneficial effect on visuospatial skills since more experienced participants had better performance on this task. It is likely that this transfer effect is not limited to neuropsychological tasks, and video game players have an advantage in other contexts that require visuospatial processing, like better driving skills (as tested in a simulator) (Cassavaugh & Kramer, 2009) or piloting skills (Gopher et al., 1994). Nevertheless, there is evidence that the effects of video games on visuospatial skills can have limited far-transfer effects constrained by the characteristics of the stimuli trained in the game.

For instance, after being trained in *Tetris* (a puzzle video game) participants had a better mental rotation performance when the stimuli resembled those of the game itself (Sims & Mayer, 2002).

In addition to that, video game training had a leveling effect on visuospatial skills, where non-experienced participants improved enough to reach the level of their more experienced counterparts that, despite maintaining a slight advantage towards the last assessments, had a negligible difference in performance. If the initial difference in performance can be attributed to the previous video game experience (as Feng et al., 2007 stated), it is impressive how a 15h video game training intervention was enough for the non-experienced participants to catch-up with the rest. This is not the first case where a quick leveling effect in visuospatial skills has been reported in the literature (e.g. Cherney, 2008), although most of the time these changes have been attributed to gender differences, an aspect that is confounded in our sample since more experienced players tended to be men.

3.4.2.4 Executive functions

Compared to the cognitive domains mentioned previously, executive functions belong to higher-order cognitive processes to which more emphasis has been given during the evaluations, because of the importance that finding improvements in this area would require. Due to the nature of the tasks used for the assessments, executive functions are being discussed separately in three subdomains: cognitive inhibition, task switching, and working memory. While the first two were covered by the stop-switching task, elements of working memory were evaluated by the n-back task and the backward digit span test.

Inhibition

Stop trials in the stop-switching task was the variable used for measuring cognitive inhibition in this study.

A change in strategy when answering the task can be observed from the baseline to the post-assessment and in the follow-up. Despite the pressure to answer quickly, participants became more cautious when responding in order to be more accurate and avoid errors by confusing *go* and *stop* trials. Therefore, maintaining high accuracy rates, but with slower reaction times (SSRT; see section 2.1.2.1) that could be more likely attributed to an active waiting period after each trial, in which participants become more cautious as they wait to see if the stimulus changes its nature (from a *go* to *stop* item), than a true worsening in performance.

Exploring the effects of the TMS on cognitive inhibition, we observe that both groups (active and sham TMS) obtained similar accuracy scores on all assessments, without noticeable differences. In fact, there is the presence of a ceiling effect, where most participants get close to the maximum possible score, indicating the low difficulty of the task. Therefore, focus on the response times, calculated as the SSRT (see section 2.1.2.1), seems to be more adequate to measures performance in cognitive inhibition, but, again, no significant differences were present among TMS conditions and no interaction effects appeared. However, as commented above, a change of strategy between the baseline and the post-intervention assessments significantly slowed down the SSRT, and participants took more than twice the time to respond without affecting the accuracy, compared to the baseline.

Regarding previous video game experience, scores on *stop* trials were not affected by it, and these results remained stable for all assessments. Reaction times, however, show big differences between the baseline and the first post-intervention assessment: participants with prior video game experience had much lower SSRTs compared to non-experienced participants. Actually, non-experienced participants start with faster baseline response times compared to the post-assessment, where their reaction times became seven times slower (see Figure 94). Consequently, it seems that the change in strategy discussed previously was not present in experimented players, but was particularly noticeable for those who had no gaming experience. Observing the follow-up, this difference tended to fade, not being significant anymore. Whether the video game training interacted with the previous video game experience, inducing somehow the change of strategy in responding, although possible, is not clear.

No relevant interaction effects between the TMS condition and the previous video game experience appeared in cognitive inhibition. Scores remained unchanged among groups and assessments, response times did not present any significant differences among the four groups, and presenting a much higher variability than when separate in two groups likely due to the low number of participants assigned to each group. There are, however, examples in the literature that achieved improvements in processes related to inhibition. That is the case of the study conducted by Evers et al. (2001), in which participants achieved faster response times in evoked response potentials (ERP) in a visual oddball task after applying rTMS at 20Hz in three 5Hz trains over the left prefrontal cortex (F3 according to the 10-20 EEG system). Although this is not a measure that is accompanied by motor inhibition, it sheds some light on the possibility of improving cognitive inhibition.

In the present research, only previous video game experience seemed to have an effect on cognitive inhibition, whereas the TMS condition did not. The effects did not appear in the form of an obvious improvement of the scores (which remained stable across assessments) or a reduction of the SSRT, but on how participants faced the task. The change in strategy, where participants became more cautious before responding, was exclusive of non-experienced participants. It is possible that experienced participants had another approach to this kind of tasks as a result of their experience, avoiding cognitive and behavioral changes that would effectively impact their performance.

These results partially match the lack of change in cognitive inhibition that other studies have found on experienced players, compared to their non-experienced counterparts. A study focused on the influence of using first-person shooter video games, found that SSRT were immutable, despite changes were actually found in working memory (Colzato, van den Wildenberg, Zmigrod, & Hommel, 2013). Inhibition, as measured with the Stroop task, also failed to achieve far-transfer to untrained abilities (Whitlock et al., 2012). Likewise, using a related inhibition task (stop-change), Steenbergen et al. (2015) reached a similar conclusion: experienced gamers did not benefit from improved inhibitory control, despite having superior performance in other abilities related to cognitive control, such as task switching.

There are some exceptions, though. Van Muijden et al. (2012) found far-transfer effects in a stop-signal task after a brain training video game training in older adults, although improvements in working memory or task switching were absent. Also, enhancements were detected in a Stroop task after a 15h video game training period, also in older adults with a *brain training* game (Sosa, 2012).

Task switching

Task switching was the second executive component that was assessed in this study. Again, the stop-switching task, particularly *switch* trials, was the primary source for examining changes in this process.

Performance in this task can be described as homogeneous among all groups at baseline, without an apparent ceiling effect, since its difficulty was notable compared to *stop* trials, as evidenced by the number of errors. Overall, task switching is a capacity that can be subject to improvement since there is an apparent learning effect both in scores and response times, as they tend to increase for each new assessment in a linear way.

Unfortunately, neither the TMS condition or the previous video game experience (or the combination of both) seemed to have an effect on task switching performance, not even when comparing the groups at a single time point. Only a strong and significant effect of the number of assessment sessions, attributed to practice effects, is observed in our sample regardless of how participants were divided. A literature search was not helpful when trying to find precedents of task switching improvement using TMS stimulation, more than being used as a tool to identify brain networks related to this function, where the pre-SMA played a key role (Obeso et al., 2013; M. F. S. Rushworth, Hadland, Paus, & Sipila, 2002).

Some empirical evidence supports the possible improvement of task switching as a result of video game play (Anguera et al., 2013; Basak et al., 2008; C. Shawn Green et al., 2012), that we have been unable to replicate in this study. A possible explanation could be that the genre of video game is determinant, being first-person shooters more suitable for training this executive component. The meta-analysis by Bediou et al. (2017) found that, indeed, previous experience in action video games had a moderate impact on task switching, but a video game training intervention had a non-significant effect on this domain, possibly due to the short duration of these training programs compared to a lifetime of video game play.

There is the possibility that some interference was present between the answers to *stop* and *switch* trials, as both types of trials were presented in a combined way and the participants had to be prepared to execute one or another. If each subdomain had been presented separately in two different tasks, the result would have possibly been different. Nevertheless, using them in combination, a greater cognitive load was required, improving its ecological validity.

As the meta-analysis suggested, task switching can be trained and is plastic enough to change as a result of lifetime video game experience; but it is also one of the domains which is most resistant to change (only surpassed by reasoning/problem solving), with moderate to low effect sizes. It appears that, as a cognitive domain belongs to a higher-order level of processing, there are more difficulties in inducing changes in it, overall in healthy subjects.

Working memory

Two tasks in our neuropsychological battery were responsible for providing values of working memory performance. On one hand, the 3-back task was used as a working memory task and it provides data about more complex working memory components. On the other hand, the backward subtest of the digit span task also provides a supplementary verbal working memory measure that, contrary to the n-back task, did not rely on precise and fast-paced timings but had a higher short-term memory involvement.

With the aim of obtaining a global improvement in cognition, it is a key aspect to determine whether executive functioning, including working memory, can be trained and improved, and those improvements transfer to general intelligence. Indeed, empirical evidence shows that cognitive training in n-back tasks for a few weeks not only enhances working memory but is also able to achieve small but positive far-transfer effects over general intelligence, as has been determined by a recent meta-analysis (Au et al., 2015). However, another meta-analysis showed that, when accounting for a wider range of working memory tasks for cognitive training, near-transfer effects to other verbal and visuospatial working memory tasks were present, but far-transfer effects (to nonverbal abilities and verbal abilities) were not present in a reliable way. Moreover, the level of near-transfer to other working memory tasks did not correlate with the amount of far-transfer (Melby-Lervåg, Redick, & Hulme, 2016). Altogether, these inconsistencies call into question the effectivity of many cognitive training programs, which are often focused on the direct training of working memory.

The n-back task, one of the measures of working memory used in this study, is likely affected by other cognitive domains, as it depends on selective and sustained attention to process the information that is presented at a constant rate for a relatively long period of time.

Our results showed that this task is affected by practice effects, as can be observed from the improvement after each subsequent assessment, regardless of the experimental group. It is not known if those improvements are a result of a direct enhancement of the cognitive functions required for the execution of the task, or participants developed strategies in order to better cope with the task.

The effects of the TMS stimulation were not visible as measured with the n-back task. Scores and response times did not present any differences, except for a slight (but significant) baseline difference in the d' index, a measure of discriminability, where the sham iTBS group performed worse than active iTBS group. This difference was mitigated, although did not disappear completely, towards the two latter assessments (see Figure 69 and Figure 70). Several studies have been able to achieve working memory improvements with TMS. By using repetitive TMS, Luber et al. (2007) were able to improve working memory reaction times, as measured by a delayed match-to-sample task. They achieve these results by stimulating the left DLPFC with rTMS at 5Hz, but not when the stimulation was applied at the corresponding region in the right hemisphere or at frequencies of 1 or 20Hz in both hemispheres. Another research team (Yamanaka et al., 2010) was able to enhance reaction times in spatial working memory by applying 5Hz rTMS over the right parietal cortex (P4 location in the EEG 10-20 system), but failed to do so when applied over the left hemisphere (P3) or over the frontal cortex of both hemispheres (F3, F4).

Improved accuracies have been also achieved in working memory tasks through TMS, notably through the addition-by-subtraction effect. Kirschen et al. (2006) improved both accuracy and response speeds in a verbal working memory task based on the delayed match-to-sample paradigm by applying single-pulse TMS over the left inferior parietal cortex during the task. Similarly, also using a delayed match-to-sample paradigm, Sauseng et al. (2009) improved accuracy by stimulating both left and right PPC (P3 and P4) at 10Hz. The differences between these stimulation protocols and the tasks used for the assessment makes it difficult to compare these studies to the results obtained in the present research. The use of TBS stimulation was non-existent absent in the literature, and there were no instances of the utilization of the n-back task as a working memory paradigm.

Compared to TMS stimulation, previous video game experience yielded more interesting outcomes. Despite no baseline differences in either score, response times or in the d' index, experimented participants improved their scores and their d' index substantially towards the post-intervention assessment, whereas non-experienced participants did not show that change (see Figure 91). In the follow-up assessment, this difference fades away when non-experimented participants improve to the point of reaching their more experimented counterparts. This is an interesting effect since it implies that previous video game experience affected how participants adapted to that task after the initial presentation, improving at a much faster rate than participants that lack it, that did not reach that level of performance until the follow-up. On the other side, far-transfer effects on visual working memory tasks as a result of video game play are not common. Blacker et al. (2014) achieved that effect after a video game training period, enhancing working memory performance measured with a change-detection paradigm. However, Boot et al. (2011) failed to observe significant changes in the n-back task (and other measures of task switching and stop-signal) after a video game training period in the *Space Fortress* video game.

Although less sensitive to changes than the n-back task, the other measure of working memory used during the assessment was the backward digit span. Overall, scores on this task seem to be affected by an obvious practice effect, where participants improved after each assessment. Mean scores were inferior to those of the forward digit span, but paradoxically, maximum scores were achieved in this sub-task.

The TMS stimulation condition did not seem to affect performance in this task. Both groups performed equally well, and only the effect of the practice was notable towards the later assessments (see Figure 66). Previous video game experience suffered the same fate, although there is a tendency where more experimented participants obtained better scores, without reaching the point of significance, a difference which is more notable at the baseline (see Figure 87). Exploring the interaction between TMS condition and video game experience did not yield any promising results.

There are instances where improvements in the backward digit span and similar tasks were achieved after a video game training period. McDougall & House (2012) improved the backward digit span in a sample of older adults using a brain training game. Likewise, Stern et al. (2011)

improved performance in letter-number sequencing (WAIS-III) after 36h of training through the *Space Fortress* game in an old adult sample.

Overall, the effects of the TMS stimulation could not be observed on working memory; both measures (n-back and backward digit span tasks) remained stable through the post-intervention and follow-up assessments. Some previous studies achieved a performance improvement after TMS in working memory tasks, although always with different stimulation protocols from the one used in the present study. Previous video game experience was, indeed, linked to faster improvement rates in the n-back task, although this effect was not present in the backward digit span, possibly reflecting different cognitive components of these two different working memory tasks.

3.4.2.5 General intelligence

Achieving positive changes in general intelligence would represent the ultimate goal in cognitive improvement, since it would mean that the far-transfer effects linked to a cognitive enhancement program had a profound impact on a person's mental capacities, enough to affect all spheres of cognition. Since the concept of general intelligence often means that all cognitive domains are linked together, positively correlating with each other, transfer effects from a cognitive training to general intelligence not only represents that far-transfer has been achieved to untrained tasks related to the same cognitive domain, but that those effects also integrated with the rest of the cognitive processes, achieving an inter-domain transfer noticeable enough to be detected through regular intelligence tests, and possibly in everyday life.

This premise is, of course, the most ambitious goal one could attain in the field of cognitive improvement, and it is as important as elusive, especially if we are working with healthy individuals without cognitive impairments.

Raven's Progressive Matrices is commonly used as a measure of fluid general intelligence. If any global changes in intelligence were produced as a consequence of the video game training and TMS intervention, it was expected that this test would be able to detect it.

The first outcome that was observed in the results was a noticeable ceiling effect in all instances of this test. Participants tended to get very close to the maximum score allowed in the task, often failing just one or two items in each assessment, which entails an accuracy rate above 90% (see Figure 67 and Figure 88). The Standard Progressive Matrices version that was used for the assessments was the original form of the matrices test developed by John C. Raven as an attempt to measure intelligence and, theoretically, it should be suited for the general population. Nevertheless, the high scores obtained in the study's sample lead us to think that this version was not challenging enough for our sample, and that using the Advanced Progressive Matrices version, or a combination of the two, could have avoided the ceiling effect and return more meaningful results.

Since scores on this task were not useful to measure cognitive change due to the reasons explained above, response times could be a more practical measure for this purpose due to their higher sensitivity to changes, although, like it was the case in the mental rotation task, participants were told to prioritize solving the items correctly, regardless of the time it took to answer.

Overall, results indicate that neither the TMS condition nor the prior video game experience had an effect on general intelligence as measured by this task. Also, no learning effects were present from the baseline to the post-assessment. Baseline differences by TMS condition appeared in response speed, but these still persisted in the post-intervention assessment, confirming the lack of effect of the stimulation. Practice effects in response times, if present, were small and non-significant. Previous video game experience did not have any impact on scores or response times, and no changes could be appreciated from one assessment to the next. Likewise, when dividing the sample between four groups, interaction effects were absent.

The Five-Point Test (5PT), a figure fluency test which emphasizes the capacity of generating alternative solutions to a problem relying on planning, reasoning, and cognitive flexibility, suffered a similar fate. In this case, the task was only administered once after the intervention, in order to avoid practice effects. No significant differences between groups could be observed as a result of the TMS condition or the previous video game experience. All of them showed a similar performance, also contributing to the idea that higher-order executive functions are quite resistant to change.

The last task whose results can be linked to general intelligence is the matchstick task. This task should provide us a measure of insight problem solving, an aspect which is often neglected in the assessment of intelligence. Results showed that one of the premises of insight problem solving was not met in this experiment. This premise assumes that the correct solution to one specific type of problem should greatly facilitate answers of previously unknown problems of the same type, but that was not the case in this task, neither for scores or for response times, although the response variability increased.

The TMS condition did not affect the outcome of this task. Both groups performed equally well in the first and second blocks of the task, with no noticeable group differences. However, when divided by previous video game experience, some interesting effects can be observed: experienced participants obtained significantly better scores overall. Response times were not faster for that group, though, except for the case of facilitated responses (see section 3.2.4.4 for a description of the task), that almost reached significance. It is hard to ascertain whether this slight advantage comes from video game experience or not. Just like the other two tasks commented in this section, the low number of problems that were presented to each participant (due to the time needed to complete each item) affected the sensibility of the measure, and the fact that it was only applied at one time point (due to the nature of insight problem-solving tasks) does not provide us with a baseline to compare. Overall, this task was included to cover a more exploratory aspect of problem-solving that is seldom discussed in the literature, but its results are not entirely convincing.

In the literature, the use of TMS for cognitive enhancement is a frequent topic, although most studies focus on the improvement of many cognitive domains separately and, to date, there are no publications that tried to improve “intelligence” as a unitary concept, as measured with general intelligence task of some sort. Video games are at the moment a popular option for improving intelligence, but when general intelligence is addressed, it is rarely done in a unitary way, since separating cognition in its components is more common. In the few cases where general intelligence is measured using Raven's Progressive matrices before and after a video game training period, the lack of effect is often the most usual scenario. This is the case in several video game genres, such as *brain training* games (Colom et al., 2012), multiplayer role-playing games (Whitlock et al., 2012), 2D arcade shooters (Boot et al., 2010; Lee et al., 2012), action, real-time strategy, and puzzle games (Boot, 2007). Nevertheless, enhancement in the Raven's Progressive Matrices is sometimes found, like in the study conducted by Basak et al. (2008), which trained older adults during 23.5h in a real-time strategy game, also finding improvements in working memory and task switching.

Other studies tried to operationalize general intelligence as the results of several neuropsychological tests including spatial ability, numerical ability, and short-term memory. These measures correlated with performance in a brain training video game, that improved in each training session (Quiroga et al., 2009). In a later study, the same research group (Quiroga et al., 2011), also using brain training video games, assessed the effect of training in reasoning ability tests (PMA-R [Thurstone, 1938] and D48 [Gough & Domino, 1963]). When correlating the scores with video game performance, they observed that general intelligence requirements really depend on the type of game, as the abilities required to play some games cannot be automated as easily.

A recent meta-analysis conducted by Bediou et al. (2017), examines which cognitive domains are more likely to be affected by the use of action video games, being a problem-solving category (assessed by Raven's Progressive Matrices) one of these cognitive domains, and concluding that problem solving was the only one where no significant effects were found.

To sum up, general intelligence remained unaffected by our intervention. The low sensibility of the employed tasks, together with the change-resistant nature of general intelligence made this the most predictable outcome. Only in insight problem solving certain indications have been found that video game experience may positively affect intelligence, but this is a rather limited scope, and the nature of the assessment makes it difficult to attribute changes to our intervention.

3.4.3 Gender differences

Men in our sample had generally more previous video game experience compared to women (69.23% of men in our sample, compared to 21.43% of women), that is likely a reflection of a more general trend in the general population. Despite the difference in the number of men and women who report playing video games is not huge (59% of men and 41% of women) (Entertainment Software Association, 2016), it is in the genre of video games that each gender plays where the main differences are found. For instance, some genders were almost exclusive (>90%) to male players, such as sports, shooters, racing, strategy, and multiplayer online arena games (see Table 34), whereas women only surpassed men in match-3 (e.g. *Candy Crush*) and family/farming casual games (Yee, 2017).

Moreover, even if roughly half of the population plays regularly, more than 75% of the games could be included in the *casual game* category, since they are played on either mobile phones or tablet computers. So, in reality, less than one-quarter of players actually play what we would traditionally consider a video game. As a result, when numbers are self-reported, the actual ratio between men/women playing video games would be closer to 81.5/18.5% (Yee, 2017).

There are gender differences in the age of players too. Female gamers are on average older than men (44 vs. 35 years old, respectively), and there are almost twice as much adult female players (over 18 years old) than men.

These gender imbalances are factors that can act as a confound when we are trying to study the gender effects in this kind of experiments. The quasi-experimental nature of this variable complicates discerning whether the observed differences are due purely to gender effects or are influenced by prior video game experience or other personality variables linked to sex, such as the gender differences observed in mental rotation tasks, as commented previously.

Gender differences in our sample have been clearly reflected in the pre-assessment, where men performed significantly better than women in mental rotation tasks. Moreover, this difference was still evident in the post-intervention assessment, although both genres improved substantially, and in a proportional way. During the training period, men also achieved statistically more goals and in a more efficient way in the video game, needing fewer attempts for each goal. Similarly, there were gender differences in cognitive inhibition performance, as measured through the SSRT. After a baseline difference where men were notably faster than women in inhibition trials, both genders slowed down their response times and reached equal performance. However, this decrease in performance should not be interpreted as a worsening sign, as it reflects a change of strategy rather than a change in performance, as was discussed in section 3.4.2.4.

Genre	Women	Men
Match-3	69%	31%
Family or farming simulator	69%	31%
Casual puzzle	42%	58%
Atmospheric exploration	41%	59%
Interactive drama	37%	63%
High fantasy MMO	36%	64%
Japanese RPG	33%	66%
Western RPG	26%	74%
Survival roguelike	25%	75%
Platformer	25%	75%
City-building	22%	78%
Action RPG	20%	80%
Sandbox	18%	82%
Action-adventure	18%	82%
Sci-fi MMO	16%	84%
Open world	14%	86%
Turn-based strategy	11%	89%
MOBA	10%	90%
Grand strategy	7%	93%
First-person shooter	7%	93%
Racing	6%	94%
Tactical shooter	4%	96%
Sports	2%	98%

Table 34. Women/men ratio of video game players for each genre.
Source: Quantic Foundry (2017). MMO: Massive Multiplayer Online game. RPG: Role-Playing Game. MOBA: Multiplayer Online Battle Arena.

Controlling by previous video game experience, non-experienced men also managed to achieve more goals (despite the higher inter-individual variability) than non-experienced women did, and the same effect appears when observing the goal per attempt ratio. In fact, performance in men, regardless of their previous experience, is quite similar, while women display more accused differences depending on whether they have prior experience or not. It is difficult to draw conclusions even when controlling by previous experience because this is a highly qualitative factor and the great diversity in video games that our sample played makes these comparisons more difficult.

Previous video game experience should have been controlled for other 3D platform video games or using other relevant criteria related to the video game genre, even though during the sample acquisition, those volunteers that had played the game used during the experiment were directly excluded from participating. Actually, only three of the participants classified as "experienced" mentioned having played games that would be included in the 3D platform genre (e.g. *Tomb Raider*, *Ratchet & Clank*, *Crash Bandicoot*), while the rest preferred other genres (racing, role-playing games, football and 2D platformers).

Visuospatial tasks are considered adequate and sensitive enough for exploring gender differences, men having often a slightly higher performance. In this research, these skills were assessed through the Mental Rotation task, and that is the reason why the possible presence of gender differences in the performance of this task was examined. In this case, no meaningful differences (in response times) were observed between genders, although men tended to respond faster on average. These results contrast with the studies by Feng et al. (2007) and Chernet et al. (2008) where they observed that, faced with initial differences in performance, after a video game training period with a first-person shooter they managed to balance the performance between male and female participants in the mental rotation task. However, this effect has been explored in other studies (e.g. De Lisi & Cammarano, 1996; Okagaki & Frensch, 1994; Subrahmanyam & Greenfield, 1994) with mixed results, and the recent meta-analysis by Powers et al. (2013) failed to observe overall gender differences in the effects of cognitive training with video games.

3.4.4 Limitations

There are some limitations that may have prevented obtaining the expected results in this study. Some of these limitations are intrinsic to the TMS technique, whereas others could be due to how the experiment was designed and to other external limitations. A detailed account of all the identified limitations of this research will be discussed in this section.

TMS is a relatively modern technique, and the iTBS protocol, despite its promising outcomes in prolonging the effects of the stimulation, is still not widely used in research or in clinical settings. The lack of literature using this protocol on cognitive domains also contributes to the difficulty on comparing data and to deepen knowledge about the physiological mechanisms of this protocol. Therefore, using the iTBS protocol was highly innovative and, hence, exploratory.

Initially, the TBS protocol was developed on its evidence to prolong activation or deactivation over the motor cortex, but it is possible that its effects on other cortical regions are not the same, or not as remarkable, as in the motor areas. One recent study (Viejo-Sobera et al., 2017) that used cTBS and iTBS protocols to study its effects on executive functions, assessed through classical neuropsychological tests, found that its immediate effects were not as promising as initially expected. In order to learn more about the effects of TMS, and specifically of the TBS protocol, in non-motor cortical areas, it is necessary to compare the cortical activation patterns right after the stimulation using a functional neurophysiological or neuroimaging technique, such as EEG or fMRI, and study and correlate the participant's performance over a wide range of neuropsychological tasks. Collecting all that information, although representing a very complex feat, would be of great interest in order to determine the effect of non-invasive brain stimulation in different brain regions and in diverse cognitive domains.

The limited efficacy of the iTBS protocol in our study could be linked to the different excitability and connectivity patterns in the motor cortex respective to the DLPFC (Farzan et al., 2009). Moreover, iTBS does not only affect the stimulation site, but can also have an effect on other regions that are structurally or functionally connected to it (Gratton, Lee, Nomura, & D'Esposito, 2013; Reithler, Peters, & Sack, 2011). This is a particularly relevant fact when dealing with the DLPFC, a cortical hub responsible for the transmission and integration of information between widespread functional networks (van den Heuvel, Van Gorsel, Veltman, & Van Der Werf, 2013), so excitability changes in this region can lead to complex effects on cortical activity and cognition. Evidence of actual excitability changes through the iTBS protocol on the DLPFC is still scarce. The few existing electrophysiological studies have found conflicting results (Grossheinrich et al., 2009; Wischnewski & Schutter, 2015), indicative of the complexity and the lack of knowledge over the precise effects of iTBS stimulation on the cortical activity of the DLPFC (Viejo-Sobera et al., 2017).

The DLPFC is a relatively large structure for the focality that a figure-of-eight coil provides. We stimulated a very specific area in a region which spans centimeters in the prefrontal cortex. Despite stimulating the hotspot of maximum activation during the video game training, as determined by previous functional studies, it is possible that a more diffuse stimulation (with a round coil, for instance) covering a larger fraction of the DLPFC could have improved its efficacy. This is relevant since even an offset of a fraction of a millimeter on a cortical region is enough to lose the desired effect (as can be clearly observed during the determination of the motor threshold). Different areas of the DLPFC and their structural and functional connectivity should be taken into consideration for each participant when choosing to use such a precise method.

The experimental design used in this research required a notable investment in resources, both economically and in terms of time and human resources. The large number of training sessions in which participants were guided and supervised, and finally stimulated greatly increased the time spent in the experimental stage of this research, especially due to the limited number of concurrent participants that the lab could accommodate. In addition to that, in order to perform the stimulation, two researchers were always required in the lab. Another resource were the MRI scans that were needed for each participant, that added up quickly to the cost of the project, limiting the sample size of the study.

From the volunteer's side, the participation also required a notable degree of involvement, and there were a series of factors which could compromise their participation. The longer the experimental stages, the higher the possibility of participants dropping off the experiment, or just not enrolling in it. Participation required a high level of availability that not all the interested volunteers had, and the economic compensation for their participation was deemed insufficient by some, factors that affected the recruitment and retention of the sample. The TMS stimulation itself was another factor that compromised the participation of some individuals because of its novelty. In addition, the stimulation produced an uncomfortable sensation to a minority of participants, likely due to interindividual differences the location of peripheral facial nerves, that was enough to interrupt their participation in some cases.

Based on previous scientific studies the duration of the training period was adjusted as to be the minimum time necessary for achieving cognitive changes. The longer the training period, the higher the probability of inducing cognitive improvements, but longer training times exacerbate many of the problems mentioned above.

As mentioned in previous sections, when studying near-transfer effects, a more gradual approach could have been used. The transition from near-transfer to far-transfer effects is quite an abrupt leap in our assessments. In the presence of near-transfer, but not far-transfer effects, as a result of TMS, the extent of the generalization of the effects of the video game training would have been difficult to ascertain.

Comparing the experimental procedure followed in this study with other video game-related literature, it could have made sense to add another experimental group to act as the control for the video game training group. Actually, that option was considered in the planning stages of this project, but was not deemed imperative at that point and was left as a possible extension of the current research. In that case, that design would allow us to compare the effects of the video game training independently from the TMS stimulation in an experimental way.

Actually, a recently published study (West et al., 2017) complements the results obtained in this research, using the same video game to train participants and comparing it with an active (learning to play the piano) and a passive no-contact control group, but without using a non-invasive brain stimulation technique. With a sample of older adults instead of a young population, they compare cognitive enhancement through Super Mario 64 against piano lessons and, lastly, a no-contact group during a 6-month training period. Their cognitive assessment was more limited, only including a screening battery and a measure of short-term memory, but the study included measures of structural neuroimaging. They found out that the video game group, not the music or the passive control group, improved their performance in these measures that also correlated with a hippocampal grey matter increase.

The addition of a second control group would have had a positive impact on one of the most important limitations of this project: the small sample size. A larger number of participants would have helped to obtain more significant results, especially in those cases where near-significant outcomes were observed. It would have also mitigated the variability between participants regarding the effects of the TMS stimulation, possibly detecting subtler effects.

As mentioned above, the length of the video game training period is another of the variables that could have affected the effectiveness of the intervention. In this case, the number of sessions was limited by the fact that participants had to be present in the lab during their video game play, as the TMS stimulation was applied immediately after playing. Most studies let participants play from home, allowing for longer training periods; this approach maximizes the exposure to the training video game while reducing the resources needed to carry out the experiment, but compromising the degree of control over the experimental conditions, as participants could not be supervised during their participation. There is a higher degree of control in the present experiment, as participants were supervised and guided during the experiment, but at the cost of a fewer number of sessions, reducing the chances that the video game exposure had an impact on cognition.

The fact that our participants had to be physically at the laboratory for the intervention implied some temporal discontinuities since experiments were only carried away during weekdays. In practice, that meant that volunteers needed to dedicate almost three weeks of their time to their participation, when including both the training period and the assessments. The effects of stopping the experiments during weekends was mitigated by always starting the assessments and the video game training on the same day of the week, and always performing the post-intervention assessment on the day consecutive to the last training session.

The empirical evidence from the reviewed neuroimaging studies seems to indicate that functional and structural changes in the brain predate cognitive changes, both when dealing with the effects of non-invasive brain stimulation and for video game exposure (Richlan, Schubert, Mayer, Hutzler, & Kronbichler, 2018). That was also the case in the study by West et al. (2017), where gray matter changes in the DLPFC were detected, with no detectable cognitive correlation. A post-intervention structural MRI was planned for this research with that idea in mind, and participants were scanned a second time. Unfortunately, due to unforeseen circumstances (relocation of the laboratory), different MRI protocols had to be used throughout the experiment and neuroimaging data could not be compared, thus structural analyses were finally omitted.

Another reason that can have influenced the results is the profile of the participants. In neuropsychology, it is harder to achieve cognitive improvement in young, healthy individuals that already perform near the top of their potential. On the other hand, in populations that are more prone to suffer cognitive deficits, such as older adults, patients with mild cognitive impairment, or psychiatric patients, cognitive rehabilitation programs show a greater efficacy. Agreeing with this fact, the magnitude of the effects of the TMS stimulation also seem to be related to the participant's baseline performance, where low levels of baseline performance were linked to cognitive facilitation after TMS and high-baseline performance was associated with an impaired performance. Therefore, the modulation neural excitability underlying has a non-linear outcome on the effect of TMS on cognition (Silvanto, Bona, & Cattaneo, 2018).

The use of video games as training tools also exhibit a similar effect. Compared to this study, West et al. (2017) chose an older adult sample (55 to 75 years old) and were able to observe cognitive improvement using a less sensitive assessment, the Montreal Cognitive Assessment, a 10-minute test more suitable for detecting mild cognitive dysfunctions than subtle cognitive changes. It is not the only case; other teams also showed success in detecting cognitive changes as a result of video game training by using older adult samples (Anguera et al., 2013; McDougall & House, 2012; Nouchi et al., 2012) in a wide range of game genres.

Finally, this study aimed at reporting not only the short-term benefits of the cognitive intervention but also included a follow-up assessment to examine medium-term effects two weeks after the end of the participation. However, an additional measure taken with a greater temporal spacing, such as six months or one year, could have been useful to have a more global picture of the duration of the effects of the stimulation. Nevertheless, the potential loss of participants, together with the additional resources needed for conducting such a longitudinal experimental design made this option unfeasible.

3.5 Final conclusions and future research

After discussing the results obtained in this research, it is the moment to extract some general conclusions from all the analyzed data.

Globally, the effects of TMS were not the expected ones. In most cases, iTBS stimulation did not reach the predicted effect on cognitive performance, or changes could not be detected in the post-intervention assessments.

We first observed that near-transfer effects were almost ubiquitous. Performance in the video game, assessed through a parallel version of the game, improved as a result of 15 hours of video game training. Moreover, this improvement correlated with baseline performance in visuospatial skills, being indicative of the type of cognitive domain that could be more closely linked to the game chosen for the training. However, the impact of our intervention on these improvements was limited: the TMS stimulation did not have a significant effect on near-transfer, as both experimental groups showed similar improvements at the end of the training period.

Some effects of the non-invasive stimulation on far-transfer could be noticed, but they were not consistent. Processing speed was only affected as tasks became more demanding, but the stimulation seemed to produce counterintuitive effects, slowing down responses in the active stimulation group, maybe reducing impulsiveness. In any case, these were slight differences that were not necessarily meaningful.

Attentional performance did not change as a result of the TMS stimulation, although this is a domain that was not thoroughly assessed, as it diverged from the main aim of this study. The low sensitivity to change of the forward digit task may have prevented the detection of subtle improvements. Our results are hardly comparable with those observed in the literature, due to the different type of tasks that are commonly used, assessing different attentional components.

Visuospatial skills suffered a similar fate. Despite using a well-established task and observing improvements as a result of the training, these changes were independent of the type of the stimulation applied to the participants being, thus, a result of the training in the video game and reflecting some kind of near-transfer effect.

Despite the focus on executive functions and directly stimulating the right DLPFC, none of the three executive measures ended up supporting the hypothesis that our intervention will improve this cognitive domain. Neither inhibition, nor task switching, nor working memory were affected by the TMS intervention.

Finally, general intelligence, as was expected from the results obtained in executive tasks, also remained immutable after the intervention. Not only TMS did not affect fluid intelligence, but neither practice effects were found, supporting the idea that general intelligence is quite resistant to change, outside of natural processes like aging or external factors like brain injury.

Overall, the effects of the TMS were not the expected when planning this study, and there was a lack of detectable cognitive effects of the TMS intervention as have been discussed in the limitations section.

Considering the previous video game experience as a second independent variable allowed us to assess the impact of lifetime video game exposure on cognition. This data has proven very valuable and actually led to some interesting results, that have been contrasted against current evidence in the literature.

With near-transfer effects in mind, it appears that having been exposed to video games in the past, even if there has not been a continuous use of that entertainment option, can have a positive effect on some domains of cognition. In this case, these benefits were observed in the form of slightly better baseline performance and faster learning rates in some tasks. This was a promising first step towards validating video games as cognitive facilitators, but it remains to see if these effects would also be present when dealing with far-transfer.

The presence of far-transfer effects really depended on the cognitive domain which was assessed. In most cases, having past experience with video games appeared to be beneficial for the execution of cognitive tasks, where participants either showed better baseline performances, faster learning rates, or better adoption of strategies. For instance, processing speed improvements are more notable in experienced participants, especially for more demanding tasks, even when starting from equivalent baselines.

Visuospatial skills showed initial differences between experienced and non-experienced participants, with those with more exposition to video games having better performance, but those differences were mitigated after the training period. This result is consistent with the findings of other studies dealing with visuospatial effects of video gaming, where a brief video game training period was enough to achieve a leveling effect by improving visuospatial performance in those participants that had initially performed worse, regardless of the previous video game experience.

Regarding executive functions, outcomes are complex. Both cognitive inhibition and task switching seem to be quite resistant to change, a phenomenon that has also been described in the literature. In cognitive inhibition, a difference was observed where non-experienced participants ended up using a non-optimal strategy to obtain better accuracy in comparison to the experienced group, leading to an overall worse performance. On the contrary, no differences in performance could be found in task switching among experienced and non-experienced participants, despite the strong practice effects. Working memory was more sensible to this variable since a link was found between previous video game experience and performance improvements in the n-back task, an effect that was not present in non-experienced participants.

Other domains seemed to be unaffected by the previous experience. Our measure of attention was unable to detect any changes between participants with or without experience, although it can be partly attributed to the lack of sensitivity of the task. Likewise, general intelligence remained unaffected, despite having achieved improvements in working memory, considering the close link between the two.

Finally, no significant interaction between TMS and previous video game experience could be observed in this research. Furthermore, some studies highlighted the importance of motivation as a determinant factor in order to achieve far-transfer, but this effect was not found in this study. Neither the effects of TMS nor previous video game experience were modulated by the level of motivation for each training sessions, that did not differ between among groups. It is also worth noting that, in some studies, motivation was operationalized in a different way, understanding it as a personality trait rather than a temporary state towards the participation in the experiment.

Overall, the outcomes of using active iTBS stimulation repeatedly for a period of two weeks, applied right after a video game training, were not as satisfactory as initially expected. As the results showed, it is possible that the video game training period alone had a stronger impact on cognition during these two weeks than the effects of the brain stimulation, and the coupling of the two techniques did not result in a meaningful synergic effect. By also studying the effects of previous video game exposure, it allowed us to observe several changes on cognition that were not initially expected, as the sample consisted entirely on non-gamers, and the effects of previous exposure to video games were not thought relevant at the time.

This project has been useful at providing some evidence of the effects of the TMS stimulation combined with a video game training on cognition, although further research is needed in order to find an optimal stimulation protocol capable of inducing longer-lasting cognitive enhancements.

From a theoretical perspective, and based on previous evidence, directly inducing excitatory changes to the DLPFC seemed to be a good way to achieve these effects, but there are some factors at play that can have prevented this from happening. It is not clear whether the low impact on cognition is due to an ineffective excitation of that cortical region by the iTBS, or due to the choice of a non-optimal stimulation target.

There was previous evidence of the ability to up- or down-regulate cortical excitability on the motor cortex as a result of a iTBS protocol, but its use on predominantly cognitive cortical regions is scarce and its effects are still largely unknown. The use of high-frequency repetitive TMS is more commonly used in the literature, and apparently more successful at achieving cognitive changes, just based on the volume of evidence that supports it. Efforts should be made to directly compare the effectiveness of these two protocols side by side, over a common cortical region, and study the presence of cognitive changes, the size, and the duration of these effects.

The presence of non-specific effects of iTBS stimulation on non-motor areas have been suggested in some studies, possibly improving the balance between the excitatory and inhibitory inputs, facilitating information transmission (Viejo-Sobera et al., 2017). These effects, a result of the peripheral sensations that accompany the stimulation, can explain why both cTBS and iTBS elicit similar outcomes.

The results obtained from this research are especially relevant in the field of cognitive neuroscience, but can also be targeted for being applied to a more clinical setting. One of the aims of this project was to validate the iTBS protocol as one of the optimal TMS configurations for inducing cognitive improvement, due to its long-lasting effects with a very short time of stimulation.

Anyhow, this project contributes to the pool of knowledge of the TMS technique on cognition, since iTBS is a promising, but still relatively new protocol, that has barely been tested before in this context. More efforts are needed in order to find the optimum stimulation techniques and parameters for the effective use of non-invasive brain stimulation and the achievement of long-term neural changes.

The combined use of neurophysiological and neuroimaging techniques and non-invasive brain stimulation, even if requiring more resources, constitutes a more interesting approach, since each technique compensates each other's limitations. In this particular case, it could not be determined with certainty whether iTBS is really a successful way to increase cortical excitability in the DLPFC. Pairing TMS with EEG or MRI would eliminate this ambiguity. The cortical activity could be measured with EEG or MRI before and after the stimulation, allowing to know the effects of TMS on brain activity and measuring the time until it returns to baseline levels, comparing both excitability levels within and between stimulation sessions.

On the other hand, this research has been focused on the use of TMS technique, but there are other non-invasive stimulation techniques that are gaining traction in the field of cognitive improvement. Particularly, tDCS seems to show promising results and has already been used in combination with video games for inducing cognitive enhancement, although not for the achievement of long-term changes. One of the strongest point of TMS, and at the same time one of its weaknesses, is the very high spatial resolution of the technique. It is possible that when trying to target an area such as the DLPFC, stimulating just a small subarea does not produce an optimal outcome, and inducing changes over a larger area might actually be beneficial. tDCS, in its high definition or multisite modality, meets this requisite. Moreover, the lower cost of this technique, compared to TMS, must be taken into account as well.

A large number of cognitive domains have been targeted in this study, although the body of evidence already shows that some areas are more prone to be improved than others more resistant to change. In addition, not all areas contribute equally to the detectable improvement of cognition, keeping in mind the final goal of obtaining cognitive enhancements that translate to everyday situations. Therefore, the improvement of cognitive aspects closely linked to the execution of daily activities should be prioritized. In this case, domains like attention and working memory, which are cognitive functions capable of being improved, seem to be a good choice, having chances of producing a more global impact on cognition and inducing generalization of the enhanced skills.

Regarding the potential clinical use of the technique, it must be noted that cognitive changes had not been remarkable enough in this research so that a therapeutic use based on this protocol can be effectively implemented. It is likely that the weak effects of TMS in this research are partly due to the use of healthy individuals in the sample instead of a clinical population with more room for improvement. The therapeutic use of TMS is undoubtedly one long-term goal of this kind of projects, but it would be premature to develop treatment plans for cognitive dysfunction based on the current protocols without first fully understanding the inner workings of the technique on a more basic level.

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5. Glossary of acronyms

5PT	Five-Point Test
ACC	Anterior cingulate cortex
AMT	Active motor threshold
ANOVA	Analysis of variance
cTBS	Continuous theta burst stimulation
DLPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalography
ERN	Error-related negativity
FEF	Frontal eye fields
fMRI	Functional magnetic resonance imaging
FP	Frontal polar region
GLM	General linear model
IFG	Inferior frontal gyrus
iTBS	Intermittent theta burst stimulation
LTD	Long-term depression
LTP	Long-term potentiation
MEP	Motor Evoked Potential
MNI	Montreal Neurological Institute
nAcc	Nucleus accumbens
OFC	Orbitofrontal cortex
PFC	Prefrontal cortex
PPC	Posterior parietal cortex
Pre-SMA	Pre-supplementary motor area
RT	Response time

rTMS	Repetitive transcranial magnetic stimulation
SEF	Supplementary eye field
SMA	Supplementary motor area
SSD	Stop-signal delay
SSRT	Stop-signal reaction time
tACS	Transcranial alternating current stimulation
TBS	Theta burst stimulation
tDCS	Transcranial direct current stimulation
tES	Transcranial electrical stimulation
TMS	Transcranial magnetic stimulation
tRNS	Transcranial random noise stimulation
VGP	Video game player
VLPFC	Ventrolateral prefrontal cortex
VMPFC	Ventromedial prefrontal cortex
VTA	Ventral tegmental area

6. List of tables

7. List of figures

8. Annex

8.1 MRI exclusion criteria

Any participant who met any of the following exclusion criteria, as checked before the MRI scan, was not eligible to participate in the experiment:

- Wearers of:
    - Pacemakers.
    - Prosthetic heart valves.
    - Middle ear hearing prosthesis.
    - Dental implants.
    - Joint prosthesis or artificial limbs.
    - Surgical clips, pins, plates, screws, metal sutures, or wire mesh.
- Previous aneurysm surgery or intracranial bypass.
- Having worked in the metal industry.
- Metal fragments in the head (e.g. pellets, bullets, or shrapnel).
- Pregnancy or the possibility of pregnancy.
- Tattoos or permanent makeup (indicating location and date of completion). Most tattoos are safe in an MRI scanner, but some inks may contain ferromagnetic pigments.
- Claustrophobia.

8.2 TMS exclusion criteria

Any participant who met any of the following exclusion criteria was not eligible to participate in the experiment:

- Progressive neurological disorders, including signs of increased intracranial pressure or intracranial lesions.
- Previous medical history of concussion.
- Current or past psychiatric illnesses (e.g.: major depression, bipolar affective disorder, schizophrenia, obsessive-compulsive disorder, post-traumatic stress disorder, anxiety, etc.).
- Unstable medical conditions, regardless of its cause.
- Medical conditions that can cause uncontrolled medical emergencies if they result in convulsions (e.g.: cardiac malformations, cardiac arrhythmias, asthma, etc.)
- History of fainting or loss of consciousness of unknown etiology or by traumatic origin.
- Hearing problems or tinnitus.
- History of seizures, previous diagnosis of epilepsy, prior abnormal EEG records (epileptiform) or family history of epilepsy.
- Drugs affecting the central nervous system.
- Possible pregnancy.
- Substance abuse or dependency.
- Implants or metal pieces in the head (excluding dental fillings).
- Any of the following medical devices: pacemakers, implanted medication pumps, vagal nerve stimulators, deep brain stimulators, transcutaneous electrical stimulation units, ventriculoperitoneal shunts, titanium plates, cochlear implants, aneurysm clips, etc.

8.3 Informed consent form

COGNITIVE NEURO-LAB
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FORMULARIO DE CONSENTIMIENTO INFORMADO PARA COLABORAR EN UNA INVESTIGACIÓN

Nombre y apellidos: ____

Teléfono y mail de contacto: ____

Identificación del sujeto (Iniciales): ____

Fecha de nacimiento: _______ /_______ /________

Género: ______________________________

Título del proyecto de investigación: __Mejora Cognitiva y Videojuegos__________________________

Investigador principal: ______________Marc Palaus Gallego________________________________

INTRODUCCIÓN

Ha sido invitado a participar en una investigación centrada en el estudio de las funciones cognitivas mediante el uso de la técnica de estimulación magnética transcraneal (TMS). La TMS es un procedimiento no invasivo que utiliza un campo magnético que es capaz de modificar levemente la actividad del cerebro durante un tiempo limitado (entre segundos y minutos).

Se le propone participar en este estudio como voluntario sano, por lo que su colaboración depende únicamente de su decisión de participar, y podrá abandonar el experimento en el momento que lo desee. Por favor, lea cuidadosamente este documento y pregunte a los investigadores o al personal del estudio cualquier palabra o información que no entienda con claridad.

Importante

- Su participación es voluntaria.
- Usted podrá o no beneficiarse de esta investigación. Sin embargo, su participación puede ayudar a otros en el futuro como resultado de los conocimientos obtenidos a partir del estudio.
- Puede abandonar el estudio cuando lo desee.

Una vez leído el presente formulario de consentimiento y entendida lo que implica su participación, se le pedirá que firme el consentimiento si desea tomar parte en el estudio. Se le dará una copia del consentimiento para que la guarde.

DECLARACIÓN DE INTERESES DEL IN3 Y LOS INVESTIGADORES

El investigador principal de este estudio es Marc Palaus Gallego y será llevado a cabo en el Cognitive Neuro-Lab, situado dentro de las instalaciones de la UOC. La UOC y Marc Palaus Gallego no tienen ningún interés personal o económico en este proyecto de investigación.

POR QUÉ SE REALIZA ESTE ESTUDIO

El control ejecutivo del procesamiento de la información y el mantenimiento temporal de la información recién percibida o recuperada de la memoria a largo plazo cuando ya no se encuentra disponible en nuestro entorno, depende de una red neural que engloba a diferentes regiones del cerebro. Dentro de esta red, la corteza prefrontal dorsolateral parece desempeñar un papel cardinal en la memoria de trabajo y en la organización y en el control ejecutivo de la conducta. El papel de la corteza prefrontal dorsolateral en estas funciones cognitivas ha sido escasamente explorado mediante la TMS, por lo que resulta necesario una investigación más extensa y exhaustiva para alcanzar resultados concluyentes y poder, así, sentar las bases para la aplicación de la TMS como herramienta para la mejora de la memoria de trabajo y de las funciones ejecutivas. El principal objetivo de este estudio es analizar la implicación de la corteza prefrontal dorsolateral en el funcionamiento ejecutivo y la memoria de trabajo, analizando su implicación temporal y qué papel tiene en la mediación de las interferencias cognitivas por distracción emocional.

La TMS se utilizará para modificar la excitabilidad de la corteza prefrontal dorsolateral, para analizar su posible implicación sobre la memoria de trabajo. El estudio únicamente incluye sujetos sanos. Todos los participantes pasarán por condiciones experimentales en las que podrán recibir diferentes parámetros de estimulación con TMS. En ningún caso el participante sabrá cuáles son los parámetros de la condición en la que se encuentra. Sólo finalizado el estudio se le podrá proporcionar dicha información.

Los parámetros de la TMS utilizados en este estudio son propios de la investigación llevada a cabo con dicha técnica, y cumplen todos los criterios de seguridad establecidos por consenso en el año 2009 por el “Safety of TMS Consensus Group” y otros investigadores de prestigio internacional (Rossi et al., 2009).

QUIÉN PARTICIPA EN EL ESTUDIO

Aproximadamente 70 sujetos voluntarios sanos participarán en el estudio en las instalaciones del Cognitive Neuro-Lab. Dependiendo de los objetivos de los protocolos experimentales, todos ellos pasarán por una o por varias de las condiciones experimentales.

PROCEDIMIENTO TMS

Usted permanecerá sentado en una silla mientras el investigador, o alguien de su equipo, colocará la bobina de estimulación sobre su cabeza, apoyándola de forma cómoda para usted sobre su cuero cabelludo. La bobina produce un campo magnético que puede modificar brevemente la actividad de su cerebro. Cada vez que se genera un pulso magnético se oirá un *clic*, y puede sentir una breve contracción en el músculo del cuero cabelludo. Lo sentirá como si fuera un golpecito o un pellizco en el cuero cabelludo. No se aplicará corriente eléctrica en su cabeza y no habrá contacto eléctrico entre la bobina y usted.

Para encontrar la intensidad de la estimulación magnética necesaria para usted, los investigadores primero medirán los pulsos de TMS sobre una parte de su cerebro que controla el movimiento de los dedos. Su movimiento muscular será registrado por unos electrodos colocados en su mano. El investigador comprobará cual es la intensidad mínima de la estimulación magnética necesaria para crean un pequeño movimiento muscular en su dedo. Este número es diferente en cada persona y servirá para fijar la intensidad de estimulación de la TMS que se empleará durante el estudio.

El estudio se llevará a cabo a lo largo de varias semanas, comprendiendo 10 sesiones de 1:45h de entrenamiento más 3 sesiones de evaluación.

Ninguno de los procedimientos de este experimento es doloroso o dañinos para usted.

EVALUACIÓN COGNITIVA

Antes y después de aplicar la TMS se le administrará un breve examen del estado mental, un cuestionario de efectos secundarios y un cuestionario sobre su estado emocional. En algunos casos, se le podrán aplicar antes de las sesiones con TMS algunos test neuropsicológicos para evaluar el proceso cognitivo que se estudia en la investigación.

POSIBLES RIESGOS, EFECTOS SECUNDARIOS Y MALESTARES

La TMS ha sido utilizada en investigación desde hace más de 20 años, y se han desarrollado guías de seguridad. Hay diferentes tipos de TMS y en este estudio los investigadores seguirán todas las recomendaciones de seguridad para el tipo de TMS que se utilizará. Aún siguiendo las recomendaciones de seguridad pueden aparecer los siguientes efectos secundarios.

Efectos secundarios más comunes

- Dolor de cabeza y cuello: puede sufrir dolor de cabeza o de cuello después de la TMS. Se debe a la tensión muscular por mantener erguida de la cabeza y el cuello durante la TMS. Entre el 20 y el 40% de los sujetos que se han sometido a TMS sufre dolor de cabeza. Si le aparece dolor de cabeza le ofreceremos paracetamol o aspirina que le aliviará del dolor de cabeza producido por la TMS. En algunos casos, la TMS causa malestar facial en el lado de la cara en el que se ha administrado la TMS.
- Molestias auditivas: el chasquido que produce la TMS puede provocar un zumbido en los oídos o cambios temporales en su capacidad para oír los sonidos de frecuencias más bajas. El uso de tapones o auriculares puede prevenir de forma efectiva la presencia de molestias auditivas posteriores, por lo que se le proporcionaran tapones durante el experimento. Si durante el experimento su tapón se afloja o se cae avise al investigador. No podrá participar en el estudio si tiene historial de problemas auditivos.

Efectos secundarios poco frecuentes

- Convulsiones: la TMS puede causar convulsiones en muy raras ocasiones. Si se cumplen los parámetros de seguridad es un hecho altamente improbable. Los investigadores utilizarán las preguntas del cribado para reducir el riesgo de que ningún participante tenga historia de riesgo de sufrir convulsiones. Si las convulsiones aparecen, hay disponible un protocolo de actuación de emergencia y posteriormente recibirá atención médica.
- Experimentar convulsiones causadas por la TMS no quiere decir que vaya a sufrir más convulsiones. No significa que tenga epilepsia. No significa que deba tomar medicación para prevenir futuras convulsiones. Los sujetos que han tenido convulsiones debidas a la TMS no tienen porqué continuar teniendo problemas de salud relacionados con las convulsiones.

- Síncope (desvanecimiento): es posible que pueda desvanecerse durante la TMS. Es muy infrecuente, pero puede suceder si está ansioso, nervioso o si no ha comido. Deberá informar inmediatamente al equipo si siente vértigo, mareo o siente que va a perder el conocimiento. La TMS se interrumpirá y será monitorizado hasta que se sienta mejor.

- Memoria: la TMS puede ocasionar cambios en la memoria, la atención y otras funciones cognitivas. Sin embargo, no se ha documentado que ninguno de estos efectos sea duradero, son muy leves y son extremadamente poco frecuentes.

Aunque la TMS ha sido utilizada mundialmente desde 1984, puede haber complicaciones que todavía no se conozcan.

SI DECIDE NO PARTICIPAR EN EL ESTUDIO

La participación en el estudio es voluntaria. Tiene el derecho de decidir no participar. Si escoger participar, tiene el derecho de abandonar el estudio cuando desee. Si decide no participar o abandonar el experimento sin haberlo concluido, su decisión no afectará a su relación con grupo de investigación ni con el IN3. Su decisión de no participar no supondrá penalizaciones ni pérdida de beneficios para usted. Los investigadores le comentarán cualquier nueva información que pueda afectar su voluntad de permanecer en el estudio.

DERECHOS DE LOS INVESTIGADORES DEL ESTUDIO

Los investigadores tienen el derecho de interrumpir su participación en el estudio si determinan que no adecuado que continúe en él, si pudiera ser peligroso para usted continuar o si no sigue los procedimientos del estudio como le indican los investigadores.

CONFIDENCIALIDAD Y PROTECCIÓN DE DATOS DE CARÁCTER PERSONAL

La mayor parte de los datos de este estudio serán guardados en archivos electrónicos. Cualquier dato recogido de los participantes del estudio será tratado con estricta confidencialidad. Se utilizará un identificador (ID) codificado de números secuenciales y de combinación de letras para todos los resultados y datos adquiridos. La única identificación nominal será la del consentimiento informado, así como la de otros formularios que el sujeto tenga que rellenar. Dichos formularios serán almacenados y guardados bajo llave en el laboratorio de investigación. Este laboratorio está localizado en las instalaciones del Hospital de Sant Pau, pabellón 18, que es un edificio seguro con accesos electrónicos en todas las entradas.

La información resultante de este estudio y de sus registros sólo podrá ser utilizada con un fin científico y puede ser publicada. Sin embargo, usted no será identificado por su nombre en las publicaciones en ningún caso. Ningún tipo de información relacionada con los datos específicos del estudio será proporcionada a terceros fuera del equipo de investigación, excepto en el caso de que el comité de ética de la universidad, el gobierno o la ley lo requieran.

Los datos se guardarán durante un período total de 7 años. Pasado este tiempo serán eliminados a través de un servicio profesional de eliminación de documentos. El acceso a cualquiera de los datos digitales del estudio requiere una contraseña que sólo es conocida por el equipo de investigación. Todos los miembros del equipo de investigación han sido formados en métodos para proteger la confidencialidad de los datos del estudio.

De conformidad con la Ley Orgánica 15/1999 de Protección de Datos de Carácter Personal, le informamos que los datos personales proporcionados en virtud de la participación en este estudio formarán parte de un fichero de Investigación debidamente registrado en la Autoridad Catalana de Protección de Datos responsabilidad de la FUNDACIÓ PER LA UNIVERSITAT OBERTA DE CATALUNYA (UOC). El interesado en cualquier momento podrá ejercer sus derechos de acceso, rectificación, cancelación y oposición dirigiéndose a: **FUNDACIÓ PER LA UNIVERSITAT OBERTA DE CATALUNYA** –Asesoría Jurídica- Av. Tibidabo, número 39-41, 08035 de Barcelona, o en el siguiente correo electrónico: fuoc_pd@uoc.edu.

A QUIEN LLAMAR SI TIENE DUDAS O PROBLEMAS

Si tiene alguna duda sobre esta investigación o sufre algún problema debe contactar con Marc Palaus Gallego, en el teléfono 678681612, o en la dirección *mpalausg@uoc.edu*.

CNIT. PROGRAMA DE INVESTIGACIÓN EN NEUROCIENCIA COGNITIVA
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FORMULARIO DE CONSENTIMIENTO INFORMADO PARA COLABORAR EN UNA INVESTIGACIÓN

He leído las páginas anteriores del consentimiento informado y el investigador me ha explicado los detalles del estudio. He entendido que puedo pedir información adicional y realizar cuantas preguntas considere oportunas.

Estoy avisado de que es un proyecto de investigación y de que pueden aparecer efectos secundarios imprevistos.

Entiendo que la participación en este estudio es voluntaria y puedo rechazar participar o discontinuar mi participación en cualquier momento sin ninguna consecuencia.

Tengo una copia del presente documento que será firmada por mi parte, por parte del investigador principal y por un testigo.

Consiento en participar en este estudio y para que conste a los efectos oportunos firmo el presente documento.

Nombre y firma del participante En Barcelona a _____ de _____ de 20_____

Nombre y firma investigador principal En Barcelona a _____ de _____ de 20_____

Nombre y firma testigo En Barcelona a _____ de _____ de 20_____

8.4 Dependent variables

Variable	Code	Levels of measurement	Value range	Units	Measurements
Motivation	Mot	Quantitative - Interval	0 - 5	(index)	Before each video game training session
Frustration	Fru	Quantitative - Interval	0 - 5	(index)	End of each video game training session
Fun	Fun	Quantitative - Interval	0 - 5	(index)	End of each video game training session
Video game performance	Perf	Quantitative - Ratio	0 - 1	(index)	Pre - Post
In-game "stars"	Stars	Quantitative - Ratio	0 - 120	(game score)	End of 10th video game training session
Attempts	Attempts	Quantitative – Ratio	0 - ∞	(in-game tries)	End of 10th video game training session
Time per attempt	Time_Attempt	Quantitative - Ratio		(seconds)	End of 10th video game training session
Video gaming skills (Pre)	VGskill_1	Quantitative - Ordinal	0 - 18	(index)	Pre
Video gaming skills (Post)	VGskill_2	Quantitative-Ordinal	0 – 18	(index)	Post

Table 35. Video gaming-related dependent variables.

Variable	Code	Levels of measurement	Value range	Units	Measurements
Mini-Mental State Examination	MMSE	Quantitative - Ratio	0 - ∞	milliseconds	Before each video game training session
Beck Depression Inventory (BDI-II)	Beck	Quantitative - Ratio	0 - 63	milliseconds	Pre - Post

Table 36. Dependent variables related to mood and cognitive integrity, used as requisites for the participation.

Variable	Code	Levels of measurement	Value range	Units	Measurements
Simple Reaction Time	SRT	Quantitative - Ratio	0 - ∞	milliseconds	Pre - Post - Follow-up
Direction Choice Reaction Time	DRT	Quantitative - Ratio	0 - ∞	milliseconds	Pre - Post - Follow-up
Color Choice Reaction time	CRT	Quantitative - Ratio	0 - ∞	milliseconds	Pre - Post - Follow-up
Digit Span (direct)	DigD	Quantitative - Ratio	0 - ∞	(task score)	Pre - Post - Follow-up
Digit Span (reverse)	DigI	Quantitative - Ratio	0 - ∞	(task score)	Pre - Post- Follow-up
Raven's Progressive Matrices (Score)	RavSc	Quantitative - Ratio	0 - 31	(task score)	Pre – Post
Raven's Progressive Matrices (Total response time)	RavRT	Quantitative - Ratio	0 - ∞	milliseconds	Pre – Post
5-Point test (Score)	5point	Quantitative - Ratio	0 - ∞	(task score)	Post
3-Back (Score)	nbSc	Quantitative - Ratio	0 - 60	(task score)	Pre - Post - Follow-up
3-Back (Reaction time)	nbRT	Quantitative - Ratio	0 - 3000	milliseconds	Pre - Post - Follow-up
3-Back (d')	nbDp	Quantitative - Ratio	-∞ - ∞	(index)	Pre - Post - Follow-up

Variable	Code	Levels of measurement	Value range	Units	Measurements
Mental Rotation (Score)	MRSc	Quantitative - Ratio	0 - 1	(task score)	Pre - Post - Follow-up
Mental Rotation (Response time)	MRRT	Quantitative - Ratio	0 - ∞	milliseconds	Pre - Post - Follow-up
Stop-Switching. Go Trials (Score)	goSc	Quantitative - Ratio	0 - 288	(task score)	Pre - Post - Follow-up
Stop-Switching. Go Trials (Response time)	goRT	Quantitative - Ratio	0 - ∞	milliseconds	Pre - Post - Follow-up
Stop-Switching. Stop Trials (Score)	SpSc	Quantitative - Ratio	0 - 72	(task score)	Pre - Post - Follow-up
Stop-Switching. Stop-signal Reaction Time	SSRT	Quantitative - Ratio	-∞ - ∞	(index)	Pre - Post - Follow-up
Stop-Switching. Switching Trials (Score)	SwSc	Quantitative - Ratio	0 - 72	(task score)	Pre - Post - Follow-up
Stop-Switching. Switching Trials (Response Time)	SwRT	Quantitative - Ratio	-∞ - ∞	milliseconds (index)	Pre - Post - Follow-up
Matchstick 1st block (Score)	Match1_Sc	Quantitative - Ratio	0 - 4	(task score)	Post
Matchstick 2nd block (Score)	Match2_Sc	Quantitative - Ratio	0 - 4	(task score)	Post
Matchstick 1st block (response time)	Match1_RT	Quantitative - Ratio	0 – 120000	milliseconds	Post
Matchstick 2nd block (response time)	Match2_RT	Quantitative - Ratio	0 – 120000	milliseconds	Post

Table 37. Comprehensive list of the dependent variables related to neuropsychological assessment. Units in parenthesis indicate that the variable does not have an established unit, and its value reflects the performance of the task in either a direct score or an index of several factors.

Variable	Code	Levels of measurement	Value range	Units
Simple Reaction Time (change Post-Pre)	DIFF_SRT	Quantitative - Ratio	-∞ - ∞	milliseconds
Simple Reaction Time (change Follow-up-Pre)	DIFF2_SRT	Quantitative - Ratio	-∞ - ∞	milliseconds
Direction Choice Reaction Time (change Post-Pre)	DIFF_DRT	Quantitative - Ratio	-∞ - ∞	milliseconds
Direction Choice Reaction Time (change Follow-up-Pre)	DIFF2_DRT	Quantitative - Ratio	-∞ - ∞	milliseconds
Color Choice Reaction time (change Post-Pre)	DIFF_CRT	Quantitative - Ratio	-∞ - ∞	milliseconds
Color Choice Reaction time (change Follow-up-Pre)	DIFF2_CRT	Quantitative - Ratio	-∞ - ∞	milliseconds
Digit Span (direct, change Post-Pre)	DIFF_DigD	Quantitative - Ratio	-∞ - ∞	(task score)
Digit Span (direct, change Follow-up-Pre)	DIFF2_DigD	Quantitative - Ratio	-∞ - ∞	(task score)
Digit Span (reverse, change Post-Pre)	DIFF_DigI	Quantitative - Ratio	-∞ - ∞	(task score)
Digit Span (reverse, change Follow-up-Pre)	DIFF2_DigI	Quantitative - Ratio	-∞ - ∞	(task score)
Raven’s Progressive Matrices (Score, change Post-Pre)	DIFF_RavSc	Quantitative - Ratio	-∞ - ∞	(task score)

Variable	Code	Levels of measurement	Value range	Units
Raven's Progressive Matrices (Total response time, change Post-Pre)	DIFF_RavRT	Quantitative - Ratio	-∞ - ∞	milliseconds
3-Back (Score, change Post-Pre)	DIFF_nbSc	Quantitative - Ratio	-∞ - ∞	(task score)
3-Back (Score, change Follow-up-Pre)	DIFF2_nbSc	Quantitative - Ratio	-∞ - ∞	(task score)
3-Back (Reaction time, change Post-Pre)	DIFF_nbRT	Quantitative - Ratio	-∞ - ∞	milliseconds
3-Back (Reaction time, change Follow-up-Pre)	DIFF2_nbRT	Quantitative - Ratio	-∞ - ∞	milliseconds
3-Back (d', change Post-Pre)	DIFF_nbDp	Quantitative - Ratio	-∞ - ∞	(index)
3-Back (d', change Follow-up-Pre)	DIFF2_nbDp	Quantitative - Ratio	-∞ - ∞	(index)
Mental Rotation (Score, change Post-Pre)	DIFF_MRSc	Quantitative - Ratio	-∞ - ∞	(task score)
Mental Rotation (Score, change Follow-up-Pre)	DIFF2_MRSc	Quantitative - Ratio	-∞ - ∞	(task score)
Mental Rotation (Response time, change Post-Pre)	DIFF_MRRT	Quantitative - Ratio	-∞ - ∞	milliseconds
Mental Rotation (Response time, change Follow-up-Pre)	DIFF2_MRRT	Quantitative - Ratio	-∞ - ∞	milliseconds
Stop-Switching. Go Trials (Score, change Post-Pre)	DIFF_goSc	Quantitative - Ratio	-∞ - ∞	(task score)
Stop-Switching. Go Trials (Score, change Follow-up-Pre)	DIFF2_goSc	Quantitative - Ratio	-∞ - ∞	(task score)
Stop-Switching. Go Trials (Response time, change Post-Pre)	DIFF_goRT	Quantitative - Ratio	-∞ - ∞	milliseconds
Stop-Switching. Go Trials (Response time, change Follow-up-Pre)	DIFF2_goRT	Quantitative - Ratio	-∞ - ∞	milliseconds
Stop-Switching. Stop Trials (Score, change Post-Pre)	DIFF_SpSc	Quantitative - Ratio	-∞ - ∞	(task score)
Stop-Switching. Stop Trials (Score, change Follow-up-Pre)	DIFF2_SpSc	Quantitative - Ratio	-∞ - ∞	(task score)
Stop-Switching. Stop-signal Reaction Time (change Post-Pre)	DIFF_SSRT	Quantitative - Ratio	-∞ - ∞	(index)
Stop-Switching. Stop-signal Reaction Time (change Follow-up-Pre)	DIFF2_SSRT	Quantitative - Ratio	-∞ - ∞	(index)
Stop-Switching. Switching Trials (Score, change Post-Pre)	DIFF_SwSc	Quantitative - Ratio	-∞ - ∞	(task score)
Stop-Switching. Switching Trials (Score, change Follow-up-Pre)	DIFF2_SwSc	Quantitative - Ratio	-∞ - ∞	(task score)
Stop-Switching. Switching Trials (Response Time, change Post-Pre)	DIFF_SwRT	Quantitative - Ratio	-∞ - ∞	milliseconds
Stop-Switching. Switching Trials	DIFF2_SwRT	Quantitative - Ratio	-∞ - ∞	milliseconds

Variable	Code	Levels of measurement	Value range	Units
(Response Time, change Follow-up-Pre)				

Table 38. Differential variables, calculated through the subtraction of neuropsychological variables at different time points. Variables with the prefix DIFF_ were created by subtracting the first Post-intervention assessment (Post) from the Pre-intervention assessment (Pre), and variables containing the prefix DIFF2_ were created by subtracting the second Post-intervention assessment (Follow-up) from the Pre-intervention assessment (Pre).

8.5 Pre-Post screening assessment

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PRE

Nombre y apellidos: ____

Teléfono y mail de contacto: ____

Identificación del sujeto (Iniciales): ____

Fecha de nacimiento: ______ /______ /_______ Género: __________________

Protocolo aplicado:

TMS pulso único ☐

rTMS ☐ Frecuencia ________ Hz

Fecha:

______ /______ / 20___
Día Mes Año

Hora:

MT:

1. CRITERIOS DE INCLUSIÓN PARA PARTICIPANTES VOLUNTARIOS SANOS

(Marcar con una X la casilla que corresponda)

	Sí	No
Edad comprendida entre 18-65 años		
Sin historia de conmoción cerebral		

2. CRITERIOS DE EXCLUSIÓN PARA PARTICIPANTES VOLUNTARIOS SANOS

(Marcar con una X la casilla que corresponda)

	Sí	No
Trastornos neurológicos progresivos, incluyendo signos de aumento de la presión intracraneal o lesiones intracraneales, incluidos los hallazgos fortuitos en la RM.		
Enfermedad psiquiátrica actual o pasada (p.e.: depresión, trastorno afectivo bipolar, esquizofrenia, trastorno obsesivo compulsivo, trastorno de estrés post-traumático, trastorno de ansiedad, etc.).		
Condición médica inestable sea cual sea su causa.		
Condiciones médicas no controladas que puedan causar emergencias médicas en caso de que provoquen convulsiones (p.e: malformaciones cardíacas, arritmias cardíacas, asma, etc.).		
Antecedentes de desmayos o pérdida de conciencia de etiología desconocida o por golpes.		
Problemas auditivos o zumbido en los oídos (tinitus)		
Antecedentes de convulsiones, diagnóstico previo de epilepsia, registros previos de EEG anormales (epileptiformes) o historia familiar de epilepsia.		
Medicación con actividad en el SNC u otra medicación.		
Posible embarazo. (*Cualquier mujer con sospecha de embarazo debe someterse a un test de embarazo*).		
Abuso o dependencia de sustancias (p.e: alcohol, anfetaminas, cocaína, MDMA, PCP, polvo de ángel, etc.) durante los seis meses anteriores al estudio.		

	Sí	No
Implantes o piezas de metal en la cabeza (excluyendo los empastes dentales).		
Cualquiera de los siguientes dispositivos médicos: marcapasos, bombas de medicación implantadas, estimuladores del nervio vagal, estimuladores cerebrales profundos, unidades de estimulación eléctrica transcutánea, derivaciones ventrículo-peritoneales, placas de titanio, implantes cocleares, clips aneurisma, etc.		

Si ya te aplicaron estimulación magnética transcraneal en alguna ocasión, ¿Hubo algún problema?		
Si ya te han realizado una resonancia magnética en el pasado, ¿Hubo algún problema?		

3. SITUACIÓN ACTUAL

- ¿Se encuentra bien? ( ) Sí ( ) No
- ¿Le duele la cabeza? ( ) Sí ( ) No
- ¿Ha bebido alcohol ayer u hoy? ( ) Sí ( ) No
- ¿Ha consumido drogas ayer u hoy? ( ) Sí ( ) No
- ¿Has tomado café, té o chocolate en las últimas 5 horas? ( ) Sí ( ) No
- ¿Ha dormido bien esta noche? ( ) Sí ( ) No
- ¿Cuándo ha sido la última vez que ha comido? *(p.e: horas)* ____________________________

4. EXPERIENCIA DEL JUEGO

- Evalúe sus ganas de jugar. (0 – ningunas ganas; 5 – muchas ganas): _____

5. INSTRUCCIONES

- Quítese los objetos de metal que lleve (p.e: joyas, reloj, gafas, cinturón, llaves, etc.).
- Ahora le facilitaremos unos tapones de los oídos para que el sonido de la máquina no le resulte molesto, puede colocárselos usted mismo.
- Si en cualquier momento se marea, se encuentra mal, necesita levantarse o no puede continuar con el experimento, por favor, avísenos.

6. COMENTARIOS

____
____
____
____

7. Aplicación del MINI MENTAL y la Escala de depresión de Beck.

Investigador,
(Nombre y Firma)

Barcelona, a ____ de _________ de 20____

CNIT. PROGRAMA DE INVESTIGACIÓN EN NEUROCIENCIA COGNITIVA
IN3. UNIVERSITAT OBERTA DE CATALUNYA
Institut d'Investigació Biomèdica
Hospital de Sant Pau
C/ Sant Antoni Maria Claret, 167. 08025 Barcelona
Pabellón 18. Planta baja, laboratorio 37
TEL: 93 326 35 51 / 93 326 38 90 • FAX: 93 356 88 22

Nombre y apellidos:
Identificación del sujeto (Iniciales):

POST

Fecha:

Hora:

______ /______ / 20___
Día Mes Año

1. SITUACIÓN ACTUAL

- ¿Se encuentra bien?	( ) Sí	( ) No
- ¿Le duele la cabeza?	( ) Sí	( ) No
- ¿Se siente mareado/a?	( ) Sí	( ) No
- ¿Siente alguna molestia en los oídos?	( ) Sí	( ) No
- ¿Siente alguna molestia en el cuello?	( ) Sí	( ) No

- Algún comentario o molestia que tengas:

____
____
____
____

2. EXPERIENCIA DEL JUEGO

Valore de 0 a 5 qué le ha parecido el juego:

- ¿Ha sido divertido? (0 – nada divertido; 5 – muy divertido): _____
- ¿Ha resultado frustrante? (0 – nada frustrante; 5 – muy frustrante): _____

3. Aplicación del MINI MENTAL y la Escala de depresión de Beck.

4. Que el sujeto permanezca en las instalaciones durante un tiempo para controlar que no haya ningún efecto secundario.

Investigador,
(Nombre y Firma)

Barcelona, a ____ de _________ de 20___

8.6 Demographic data

Ages	n	Mean	Std. deviation	95% Confidence Interval for Mean		ANOVA
				Lower	Upper	
Male+iTBS	7	28.86	6.44	24.09	33.63	
Female+iTBS	7	30.86	4.02	27.88	33.83	
Male+Sham	6	30.17	8.66	23.24	37.09	
Female+Sham	7	28.00	6.73	23.01	32.99	p = .850
Male+Experienced	9	28.11	7.67	23.10	33.12	
Female+Experienced	3	28.33	7.57	19.77	36.90	
Male+Non-experienced	4	32.50	5.92	26.70	38.30	
Female+Non-experienced	11	29.73	5.27	26.61	32.84	p = .714

Table 39. Age distribution of the participants according to gender, TMS group, and previous video game experience.

Ages	**n**	**Mean**	**Std. deviation**	**95% Confidence Interval for Mean**		**t-test / ANOVA**
				Lower bound	Upper bound	
All	27	29.44	6.28	27.07	31.81	
iTBS	14	29.86	5.26	27.10	32.61	
Sham	13	29.00	7.43	24.96	33.04	p = .365
Exp	12	28.17	7.30	24.04	32.30	
NoExp	15	30.47	5.38	27.74	33.19	p = .177
iTBS+Exp	6	28.11	7.23	22.33	33.90	
iTBS+NoExp	8	32.50	3.70	29.93	35.07	
Sham+Exp	6	28.33	7.32	22.48	34.19	
Sham+NoExp	7	29.73	7.00	24.54	34.91	p = .457

Table 40. Age distribution of the participants among the main groups and subgroups in the experiment.

	Total	**iTBS**	**Sham**	**Exp**	**NoExp**
No studies	0	0	0	0	0
Primary	0	0	0	0	0
Secondary	5	3	2	4	1
University	22	11	11	8	14

Table 41. Distribution of the participants according to their level of education in the main independent variables.

	Total	iTBS + Exp	Sham + Exp	iTBS + NoExp	Sham + NoExp
No studies	0	0	0	0	0
Primary	0	0	0	0	0
Secondary	5	2	2	1	0
University	22	4	4	7	7

Table 42. Distribution of the level of education among the four experimental conditions.

8.7 Descriptive statistics

8.7.1 By TMS group

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Stars achieved SuperMario64	Sham	13	29.92	24.63	15.04	44.81	4	85
	iTBS	14	31.79	27.72	15.78	47.79	5	92
	Total	27	30.89	25.79	20.69	41.09	4	92
Number of attempts (started levels) during the game	Sham	13	191.92	94.54	134.79	249.05	78	369
	iTBS	14	208.64	71.14	167.57	249.72	102	368
	Total	27	200.59	82.02	168.14	233.04	78	369
Goals (stars) accomplished divided by the number of tries	Sham	13	15.27	10.02	9.22	21.33	4.91	33.51
	iTBS	14	15.78	12.39	8.63	22.94	3.42	39.45
	Total	27	15.54	11.10	11.15	19.93	3.42	39.45
Time (seconds) for each attempt	Sham	13	391.77	249.16	241.20	542.34	148	1032
	iTBS	14	285.71	101.00	227.40	344.03	150	534
	Total	27	336.78	191.49	261.03	412.53	148	1032
Questionnaire analysis of video game expertise PRE	Sham	13	9.31	2.810	7.61	11.01	6	15
	iTBS	14	8.57	2.441	7.16	9.98	4	12
	Total	27	8.93	2.601	7.90	9.95	4	15
Questionnaire analysis of video game expertise POST	Sham	13	13.15	3.132	11.26	15.05	8	18
	iTBS	14	13.14	3.483	11.13	15.15	5	18
	Total	27	13.15	3.255	11.86	14.44	5	18

Table 43. Descriptive statistics for variables related to video game performance, by TMS group.

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Simple reaction time PRE (ms)	Sham	13	272.76	24.66	257.85	287.66	241.09	319.52
	iTBS	14	262.65	32.74	243.75	281.55	222.26	331.61
	Total	27	267.52	29.04	256.03	279.00	222.26	331.61
Simple reaction time POST (ms)	Sham	13	276.93	27.01	260.61	293.25	231.57	318.48
	iTBS	14	265.32	37.47	243.68	286.95	203.26	332.57
	Total	27	270.91	32.77	257.95	283.87	203.26	332.57
Simple reaction time FOLLOW-UP (ms)	Sham	13	276.53	34.44	255.71	297.34	234.13	357.05
	iTBS	14	290.95	43.18	266.02	315.88	217.35	350.57
	Total	27	284.00	39.16	268.51	299.50	217.35	357.05
Direction choice reaction time PRE (ms)	Sham	13	347.40	47.46	318.72	376.07	290.73	423.32
	iTBS	14	320.34	37.29	298.81	341.88	270.04	411.43
	Total	27	333.37	43.87	316.01	350.72	270.04	423.32
Direction choice reaction time POST (ms)	Sham	13	341.40	45.38	313.97	368.82	290.48	427.85
	iTBS	14	324.79	38.45	302.59	346.99	269.70	387.87
	Total	27	332.79	41.97	316.18	349.39	269.70	427.85

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Direction choice reaction time FOLLOW-UP (ms)	Sham	13	340.11	43.65	313.73	366.48	295.57	453.91
	iTBS	14	339.78	46.85	312.73	366.83	263.74	412.52
	Total	27	339.94	44.46	322.35	357.53	263.74	453.91
Colour choice reaction time PRE (ms)	Sham	13	468.03	63.53	429.64	506.42	400.59	644.22
	iTBS	14	455.70	75.49	412.11	499.29	345.14	597.14
	Total	27	461.64	68.93	434.37	488.91	345.14	644.22
Colour choice reaction time POST (ms)	Sham	13	449.57	37.13	427.13	472.01	388.04	504.35
	iTBS	14	466.87	79.98	420.70	513.05	351.67	625.46
	Total	27	458.54	62.54	433.80	483.28	351.67	625.46
Colour choice reaction time FOLLOW-UP (ms)	Sham	13	462.88	56.43	428.77	496.98	378.55	575.23
	iTBS	14	475.56	87.87	424.82	526.29	339.68	672.70
	Total	27	469.45	73.29	440.46	498.44	339.68	672.70

Table 44. Descriptive statistics summary for reaction time tasks, by TMS group.

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Forward digits PRE	Sham	13	9.31	2.18	7.99	10.62	6.00	12.00
	iTBS	14	9.43	1.50	8.56	10.30	7.00	12.00
	Total	27	9.37	1.82	8.65	10.09	6.00	12.00
Forward digits POST	Sham	13	10.23	2.09	8.97	11.49	7.00	14.00
	iTBS	14	10.29	2.43	8.88	11.69	6.00	16.00
	Total	27	10.26	2.23	9.38	11.14	6.00	16.00
Forward digits FOLLOW-UP	Sham	13	10.62	2.60	9.04	12.19	7.00	15.00
	iTBS	14	10.57	1.40	9.76	11.38	8.00	12.00
	Total	27	10.59	2.02	9.79	11.39	7.00	15.00
Backward digits PRE	Sham	13	8.00	2.52	6.48	9.52	4.00	12.00
	iTBS	14	8.79	2.72	7.21	10.36	6.00	16.00
	Total	27	8.41	2.61	7.38	9.44	4.00	16.00
Backward digits POST	Sham	13	8.38	1.89	7.24	9.53	6.00	11.00
	iTBS	14	9.07	1.86	8.00	10.14	7.00	13.00
	Total	27	8.74	1.87	8.00	9.48	6.00	13.00
Backward digits FOLLOW-UP	Sham	13	9.38	2.96	7.60	11.17	5.00	16.00
	iTBS	14	10.36	2.87	8.70	12.02	7.00	17.00
	Total	27	9.89	2.90	8.74	11.04	5.00	17.00

Table 45. Descriptive statistics for variables related to the Digit span task, by TMS group.

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Raven Score PRE	Sham	13	28.38	1.71	27.35	29.42	24	31

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
	iTBS	14	27.00	4.26	24.54	29.46	15	31
	Total	27	27.67	3.31	26.36	28.97	15	31
Raven Score POST	Sham	13	27.62	2.02	26.39	28.84	23	30
	iTBS	14	26.79	3.19	24.94	28.63	21	31
	Total	27	27.19	2.68	26.13	28.24	21	31
Raven RT PRE	Sham	13	21184	8045	16322	26046	8644	40837
	iTBS	14	15022	5796	11675	18368	4189	28022
	Total	27	17989	7518	15015	20963	4189	40837
Raven RT POST	Sham	13	18460	4215	15913	21007	11062	25200
	iTBS	14	14165	4907	11332	16998	8069	23033
	Total	27	16233	5002	14254	18211	8069	25200

Table 46. Descriptive statistics for the Raven's Progressive Matrices task, by TMS group.

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Five-Point Test	Sham	13	33.23	7.596	28.64	37.82	16	44
	iTBS	14	30.00	10.054	24.20	35.80	12	55
	Total	27	31.56	8.937	28.02	35.09	12	55

Table 47. Descriptive statistics for the Five-Point Test (5PT), by TMS group.

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
n-back score PRE	Sham	13	48.15	4.562	45.40	50.91	39	55
	iTBS	14	50.00	7.190	45.85	54.15	33	57
	Total	27	49.11	6.028	46.73	51.50	33	57
n-back score POST	Sham	13	49.69	6.250	45.92	53.47	36	56
	iTBS	14	48.64	12.822	41.24	56.05	15	58
	Total	27	49.15	10.026	45.18	53.11	15	58
n-back score FOLLOW-UP	Sham	13	51.46	3.755	49.19	53.73	44	57
	iTBS	14	51.57	7.460	47.26	55.88	31	59
	Total	27	51.52	5.860	49.20	53.84	31	59
n-back RT right answer PRE (ms)	Sham	13	943.85	309.28	756.96	1130.74	455.07	1312.75
	iTBS	14	873.47	304.79	697.49	1049.45	412.09	1237.21
	Total	27	907.36	303.12	787.45	1027.27	412.09	1312.75
n-back RT right answer POST (ms)	Sham	13	918.80	294.40	740.90	1096.70	492.31	1435.67
	iTBS	14	903.50	276.82	743.67	1063.33	405.07	1231.16
	Total	27	910.87	279.96	800.12	1021.62	405.07	1435.67
n-back RT right answer FOLLOW-UP (ms)	Sham	13	833.99	260.80	676.39	991.59	473.02	1333.12
	iTBS	14	813.32	225.11	683.35	943.29	431.40	1085.02

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
	Total	27	823.27	238.41	728.96	917.59	431.40	1333.12
n-back d' PRE (ms)	Sham	13	1.21	0.82	0.72	1.71	-.356	2.123
	iTBS	14	1.83	0.68	1.44	2.22	.630	2.681
	Total	27	1.53	0.80	1.22	1.85	-.356	2.681
n-back d' POST	Sham	13	1.32	0.89	0.78	1.86	-.588	2.476
	iTBS	14	1.93	0.76	1.49	2.36	.915	3.605
	Total	27	1.63	0.87	1.29	1.98	-.588	3.605
n-back d' FOLLOW-UP	Sham	13	1.57	0.72	1.13	2.01	.271	2.476
	iTBS	14	2.13	0.91	1.61	2.66	.068	3.605
	Total	27	1.86	0.86	1.52	2.20	.068	3.605

Table 48. Descriptive statistics for variables related to the N-Back task, by TMS group.

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Mental rotation score PRE	Sham	13	.929	.048	.899	.958	.859	.995
	iTBS	14	.883	.086	.833	.932	.665	.979
	Total	27	.905	.073	.876	.934	.665	.995
Mental rotation score POST	Sham	13	.942	.049	.913	.971	.838	1.000
	iTBS	14	.911	.108	.849	.973	.595	.995
	Total	27	.926	.084	.893	.959	.595	1.000
Mental rotation score FOLLOW-UP	Sham	13	.947	.041	.922	.971	.859	1.000
	iTBS	14	.902	.101	.844	.961	.611	.985
	Total	27	.924	.080	.892	.955	.611	1.000
Mental rotation RT PRE (ms)	Sham	13	8366	3139	6469	10263	3244	13680
	iTBS	14	7644	3716	5498	9790	2670	16227
	Total	27	7992	3404	6645	9338	2670	16227
Mental rotation RT POST (ms)	Sham	13	6186	2325	4781	7591	2660	11384
	iTBS	14	6250	2478	4819	7680	2557	12457
	Total	27	6219	2359	5286	7153	2557	12457
Mental rotation RT FOLLOW-UP (ms)	Sham	13	4284	1088	3626	4941	2534	6307
	iTBS	14	4803	2436	3396	6210	1588	11743
	Total	27	4553	1893	3804	5302	1588	11743

Table 49. Descriptive statistics for the mental rotation task, by TMS group.

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Stop-switching GO Score PRE	Sham	13	286.08	1.706	285.05	287.11	283	288
	iTBS	14	285.93	2.018	284.76	287.09	282	288
	Total	27	286.00	1.840	285.27	286.73	282	288
Stop-switching GO Score POST	Sham	13	286.54	2.470	285.05	288.03	279	288
	iTBS	14	286.50	2.066	285.31	287.69	282	288
	Total	27	286.52	2.225	285.64	287.40	279	288
Stop-switching GO Score FOLLOW-UP	Sham	13	286.77	1.166	286.06	287.47	285	288
	iTBS	14	286.71	1.437	285.88	287.54	283	288
	Total	27	286.74	1.289	286.23	287.25	283	288
Stop-switching GO RT PRE (ms)	Sham	13	734.01	129.03	656.04	811.99	506.66	949.46
	iTBS	14	733.79	144.97	650.08	817.49	503.05	1047.65
	Total	27	733.90	134.88	680.54	787.25	503.05	1047.65
Stop-switching GO RT POST (ms)	Sham	13	734.67	144.54	647.32	822.01	402.28	916.61
	iTBS	14	768.67	177.31	666.30	871.05	535.37	1218.19
	Total	27	752.30	160.19	688.93	815.67	402.28	1218.19
Stop-switching GO RT FOLLOW-UP (ms)	Sham	13	762.70	140.16	678.00	847.40	435.19	937.38
	iTBS	14	798.31	176.25	696.55	900.07	529.38	1245.79
	Total	27	781.16	157.88	718.71	843.62	435.19	1245.79
Stop-switching STOP Score PRE	Sham	13	63.00	7.45	58.50	67.50	49	72
	iTBS	14	61.07	7.07	56.99	65.15	48	72
	Total	27	62.00	7.18	59.16	64.84	48	72
Stop-switching STOP Score POST	Sham	13	63.92	8.32	58.89	68.95	41	72
	iTBS	14	64.00	7.21	59.84	68.16	49	72
	Total	27	63.96	7.61	60.95	66.97	41	72
Stop-switching STOP Score FOLLOW-UP	Sham	13	64.46	7.89	59.69	69.23	43	72
	iTBS	14	65.50	5.96	62.06	68.94	51	72
	Total	27	65.00	6.84	62.29	67.71	43	72
Stop-signal Reaction Time PRE (ms)	Sham	13	17.89	79.27	-30.01	65.79	-108.00	140.53
	iTBS	14	27.79	95.37	-27.28	82.85	-170.50	167.33
	Total	27	23.02	86.45	-11.18	57.22	-170.50	167.33
Stop-signal Reaction Time POST (ms)	Sham	13	58.80	76.34	12.67	104.93	-51.11	209.33
	iTBS	14	64.58	81.31	17.63	111.52	-65.11	262.00
	Total	27	61.80	77.49	31.14	92.45	-65.11	262.00
Stop-signal Reaction Time FOLLOW-UP (ms)	Sham	13	69.34	81.34	20.19	118.50	-71.06	168.78
	iTBS	14	58.62	86.80	8.50	108.74	-35.00	283.00
	Total	27	63.78	82.77	31.04	96.52	-71.06	283.00
Stop-switching SWITCH Score PRE	Sham	13	54.46	8.452	49.35	59.57	42	70
	iTBS	14	53.71	9.587	48.18	59.25	41	71
	Total	27	54.07	8.892	50.56	57.59	41	71
Stop-switching SWITCH Score POST	Sham	13	57.23	10.248	51.04	63.42	37	69
	iTBS	14	56.93	10.637	50.79	63.07	38	72
	Total	27	57.07	10.250	53.02	61.13	37	72

Stop-switching SWITCH Score FOLLOW-UP	Sham	13	58.77	9.311	53.14	64.40	37	69
	iTBS	14	58.57	9.221	53.25	63.90	40	72
	Total	27	58.67	9.085	55.07	62.26	37	72
Stop-switching SWITCH RT PRE	Sham	13	158.61	66.88	118.20	199.02	38.11	272.59
	iTBS	14	130.83	76.96	86.39	175.26	-34.20	225.90
	Total	27	144.20	72.29	115.61	172.80	-34.20	272.59
Stop-switching SWITCH RT POST	Sham	13	148.00	63.80	109.44	186.55	7.45	249.87
	iTBS	14	109.67	98.35	52.88	166.46	-100.60	225.86
	Total	27	128.13	84.24	94.80	161.45	-100.60	249.87
Stop-switching SWITCH RT FOLLOW-UP	Sham	13	124.46	58.28	89.24	159.68	40.29	225.69
	iTBS	14	100.80	119.67	31.70	169.90	-182.20	247.61
	Total	27	112.19	94.20	74.93	149.46	-182.20	247.61

Table 50. Descriptive statistics for the Stop-switching task, including Go, *Stop* and Switch trials, by TMS group.

		N	**Mean**	**Std. Deviation**	**95% Confidence Interval for the Mean**		**Minimum**	**Maximum**
					Lower Bound	Upper Bound		
Matchstick total score (correct answers)	Sham	13	5.23	1.878	4.10	6.37	2	8
	iTBS	14	5.00	2.038	3.82	6.18	1	8
	Total	27	5.11	1.928	4.35	5.87	1	8
Matchstick total Response time (correct answers)	Sham	13	48986	21271	36132	61840	10846	86092
	iTBS	14	47647	17969	37272	58022	26450	85895
	Total	27	48292	19254	40675	55908	10846	86092
Matchstick Score (first exposition)	Sham	13	2.46	.967	1.88	3.05	1	4
	iTBS	14	2.50	1.019	1.91	3.09	1	4
	Total	27	2.48	.975	2.10	2.87	1	4
Matchstick Score (second exposition)	Sham	13	2.77	1.092	2.11	3.43	1	4
	iTBS	14	2.50	1.286	1.76	3.24	0	4
	Total	27	2.63	1.182	2.16	3.10	0	4
Matchstick Facilitated responses	Sham	13	1.62	.961	1.03	2.20	0	3
	iTBS	14	1.36	1.008	.78	1.94	0	3
	Total	27	1.48	.975	1.10	1.87	0	3
Matchstick Facilitated response percentage	Sham	11	78.789	18.012	66.687	90.890	50.00	100.00
	iTBS	11	61.363	25.352	44.331	78.395	33.33	100.00
	Total	22	70.076	23.240	59.772	80.380	33.33	100.00
Matchstick Facilitated response time (ms)	Sham	11	17269	55049.735	-19713.82	54252.01	-133926	67570
	iTBS	11	18696	63343	-23858	61250	-59052	119863
	Total	22	17982	57915	-7695	43661	-133926	119863

Table 51. Descriptive statistics for the matchstick task, by TMS group.

8.7.2 By previous video game experience

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Stars achieved SuperMario64	No	15	21.27	21.519	9.35	33.18	4	86
	Yes	12	42.92	26.432	26.12	59.71	13	92
	Total	27	30.89	25.790	20.69	41.09	4	92
Number of attempts (started levels) during the game	No	15	174.13	70.408	135.14	213.12	78	292
	Yes	12	233.67	86.286	178.84	288.49	108	369
	Total	27	200.59	82.025	168.14	233.04	78	369
Goals (stars) accomplished divided by the number of tries	No	15	12.8173	11.72871	6.3222	19.3125	3.42	39.45
	Yes	12	18.9392	9.65553	12.8043	25.0740	6.44	33.51
	Total	27	15.5381	11.09616	11.1487	19.9276	3.42	39.45
Time (seconds) for each attempt	No	15	390.67	227.015	264.95	516.38	173	1032
	Yes	12	269.42	110.328	199.32	339.52	148	511
	Total	27	336.78	191.493	261.03	412.53	148	1032
Questionnaire analysis of video game expertise PRE	No	15	8.33	2.498	6.95	9.72	6	14
	Yes	12	9.67	2.640	7.99	11.34	4	15
	Total	27	8.93	2.601	7.90	9.95	4	15
Questionnaire analysis of video game expertise POST	No	15	12.00	3.443	10.09	13.91	5	17
	Yes	12	14.58	2.429	13.04	16.13	10	18
	Total	27	13.15	3.255	11.86	14.44	5	18

Table 52. Descriptive statistics for variables related to video game performance, by previous video game experience.

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Simple reaction time PRE (ms)	NoExp	15	272.32	30.02	255.69	288.94	227.48	331.61
	Exp	12	261.51	27.84	243.83	279.20	222.26	305.04
	Total	27	267.52	29.04	256.03	279.00	222.26	331.61
Simple reaction time POST (ms)	NoExp	15	274.61	33.97	255.80	293.43	231.57	332.57
	Exp	12	266.28	32.04	245.92	286.63	203.26	314.43
	Total	27	270.91	32.77	257.95	283.87	203.26	332.57
Simple reaction time FOLLOW-UP (ms)	NoExp	15	291.09	39.78	269.06	313.12	238.52	357.05
	Exp	12	275.15	38.17	250.90	299.40	217.35	336.96
	Total	27	284.00	39.16	268.51	299.50	217.35	357.05
Direction choice reaction time PRE (ms)	NoExp	15	336.56	42.20	313.19	359.93	290.73	423.32
	Exp	12	329.38	47.45	299.23	359.53	270.04	413.91
	Total	27	333.37	43.87	316.01	350.72	270.04	423.32
Direction choice reaction time POST (ms)	NoExp	15	337.54	39.91	315.44	359.64	271.65	412.43
	Exp	12	326.85	45.46	297.96	355.73	269.70	427.85
	Total	27	332.79	41.97	316.18	349.39	269.70	427.85

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Direction choice reaction time FOLLOW-UP (ms)	NoExp	15	347.34	50.27	319.50	375.18	273.52	453.91
	Exp	12	330.69	35.87	307.90	353.48	263.74	385.61
	Total	27	339.94	44.46	322.35	357.53	263.74	453.91
Colour choice reaction time PRE (ms)	NoExp	15	473.20	70.03	434.42	511.98	364.10	644.22
	Exp	12	447.18	67.67	404.18	490.18	345.14	597.14
	Total	27	461.64	68.93	434.37	488.91	345.14	644.22
Colour choice reaction time POST (ms)	NoExp	15	479.38	67.59	441.95	516.81	388.04	625.46
	Exp	12	432.49	45.81	403.38	461.60	351.67	490.09
	Total	27	458.54	62.54	433.80	483.28	351.67	625.46
Colour choice reaction time FOLLOW-UP (ms)	NoExp	15	488.94	75.16	447.32	530.57	347.80	672.70
	Exp	12	445.09	65.89	403.22	486.95	339.68	575.23
	Total	27	469.45	73.29	440.46	498.44	339.68	672.70

Table 53. Descriptive statistics for reaction time measures, by previous video game experience.

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Forward digits PRE	NoExp	15	9.60	1.765	8.62	10.58	6	12
	Exp	12	9.08	1.929	7.86	10.31	6	12
	Total	27	9.37	1.822	8.65	10.09	6	12
Forward digits POST	NoExp	15	9.93	1.981	8.84	11.03	7	14
	Exp	12	10.67	2.535	9.06	12.28	6	16
	Total	27	10.26	2.229	9.38	11.14	6	16
Forward digits FOLLOW-UP	NoExp	15	10.20	1.859	9.17	11.23	7	14
	Exp	12	11.08	2.193	9.69	12.48	7	15
	Total	27	10.59	2.024	9.79	11.39	7	15
Backward digits PRE	NoExp	15	7.60	2.098	6.44	8.76	4	11
	Exp	12	9.42	2.906	7.57	11.26	6	16
	Total	27	8.41	2.606	7.38	9.44	4	16
Backward digits POST	NoExp	15	8.27	1.580	7.39	9.14	6	11
	Exp	12	9.33	2.103	8.00	10.67	6	13
	Total	27	8.74	1.873	8.00	9.48	6	13
Backward digits FOLLOW-UP	NoExp	15	9.27	2.154	8.07	10.46	6	13
	Exp	12	10.67	3.576	8.39	12.94	5	17
	Total	27	9.89	2.900	8.74	11.04	5	17

Table 54. Descriptive statistics for the forward and backward digits task, by TMS group.

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Raven Score PRE	NoExp	15	27.87	2.295	26.60	29.14	22	31

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
	Exp	12	27.42	4.358	24.65	30.19	15	31
	Total	27	27.67	3.305	26.36	28.97	15	31
Raven Score POST	NoExp	15	26.93	2.549	25.52	28.34	22	30
	Exp	12	27.50	2.908	25.65	29.35	21	31
	Total	27	27.19	2.675	26.13	28.24	21	31
Raven RT PRE	NoExp	15	19073	7718	1993	14799	23348	9994
	Exp	12	16633	7359	2124	11957	21308	4189
	Total	27	17989	7518	1447	15015	20963	4189
Raven RT POST	NoExp	15	16825	4847	1251	14141	19509	8069
	Exp	12	15493	5307	1532	12121	18864	8513
	Total	27	16233	5002	963	14254	18211	8069

Table 55. Descriptive statistics for scores and response times in Raven's Progressive Matrices, by previous video game experience.

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Five-Point Test	NoExp	15	32.27	9.640	26.93	37.60	16	55
	Exp	12	30.67	8.305	25.39	35.94	12	42
	Total	27	31.56	8.937	28.02	35.09	12	55

Table 56. Descriptive statistics for the Five-Point Test (5PT), by previous video game experience.

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
n-back score PRE	NoExp	15	48.87	6.06	1.56	45.51	52.22	39
	Exp	12	49.42	6.24	1.80	45.45	53.38	33
	Total	27	49.11	6.03	1.16	46.73	51.50	33
n-back score POST	NoExp	15	45.20	11.94	3.08	38.59	51.81	15
	Exp	12	54.08	2.91	0.84	52.24	55.93	48
	Total	27	49.15	10.03	1.93	45.18	53.11	15
n-back score FOLLOW-UP	NoExp	15	50.07	6.41	1.65	46.52	53.62	31
	Exp	12	53.33	4.74	1.37	50.32	56.34	41
	Total	27	51.52	5.86	1.13	49.20	53.84	31
n-back RT right answer PRE (ms)	NoExp	15	865.03	276.29	71.34	712.02	1018.03	455.07
	Exp	12	960.27	338.40	97.69	745.26	1175.28	412.09
	Total	27	907.36	303.12	58.33	787.45	1027.27	412.09
n-back RT right answer POST (ms)	NoExp	15	909.79	273.81	70.70	758.17	1061.42	492.31
	Exp	12	912.21	299.73	86.52	721.77	1102.65	405.07
	Total	27	910.87	279.96	53.88	800.12	1021.62	405.07
	NoExp	15	812.58	229.79	59.33	685.33	939.84	473.02

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
n-back RT right answer FOLLOW-UP (ms)	Exp	12	836.63	258.44	74.61	672.43	1000.84	431.40
	Total	27	823.27	238.41	45.88	728.96	917.59	431.40
n-back d' PRE	NoExp	15	1.55	0.95	0.24	1.03	2.08	-0.36
	Exp	12	1.51	0.60	0.17	1.12	1.89	0.84
	Total	27	1.53	0.80	0.15	1.22	1.85	-0.36
n-back d' POST	NoExp	15	1.22	0.78	0.20	0.78	1.65	-0.59
	Exp	12	2.16	0.68	0.20	1.73	2.59	1.32
	Total	27	1.63	0.87	0.17	1.29	1.98	-0.59
n-back d' FOLLOW-UP	NoExp	15	1.61	0.88	0.23	1.12	2.10	0.07
	Exp	12	2.18	0.75	0.22	1.70	2.66	0.88
	Total	27	1.86	0.86	0.16	1.52	2.20	0.07

Table 57. Descriptive statistics for the n-back task, by previous video game experience.

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Mental rotation score PRE	NoExp	15	.8890	.0541	.8591	.9189	.7600	.9850
	Exp	12	.9243	.0898	.8673	.9814	.6650	.9950
	Total	27	.9047	.0729	.8759	.9335	.6650	.9950
Mental rotation score POST	NoExp	15	.9185	.0585	.8861	.9509	.7840	1.0000
	Exp	12	.9354	.1109	.8649	1.0059	.5950	.9950
	Total	27	.9260	.0844	.8927	.9594	.5950	1.0000
Mental rotation score FOLLOW-UP	NoExp	15	.9202	.0561	.8891	.9512	.7828	1.0000
	Exp	12	.9279	.1052	.8611	.9948	.6110	.9950
	Total	27	.9236	.0799	.8920	.9552	.6110	1.0000
Mental rotation RT PRE (ms)	NoExp	15	8954.76	3599.99	6961.15	10948.36	4321.09	16226.89
	Exp	12	6787.43	2836.91	4984.95	8589.92	2670.29	11815.71
	Total	27	7991.50	3404.09	6644.89	9338.11	2670.29	16226.89
Mental rotation RT POST (ms)	NoExp	15	6932.73	2396.33	5605.68	8259.77	3318.09	12456.87
	Exp	12	5327.27	2070.41	4011.79	6642.75	2557.19	9204.24
	Total	27	6219.19	2359.35	5285.86	7152.52	2557.19	12456.87
Mental rotation RT FOLLOW-UP (ms)	NoExp	15	5286.36	2094.36	4126.54	6446.18	2701.92	11743.09
	Exp	12	3636.38	1113.78	2928.72	4344.04	1587.85	5203.47
	Total	27	4553.04	1893.35	3804.05	5302.02	1587.85	11743.09

Table 58. Descriptive statistics for the mental rotation task, by previous video game experience.

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Stop-switching GO Score PRE	NoExp	15	286.20	1.740	285.24	287.16	283	288
	Exp	12	285.75	2.006	284.48	287.02	282	288
	Total	27	286.00	1.840	285.27	286.73	282	288
Stop-switching GO Score POST	NoExp	15	286.40	2.586	284.97	287.83	279	288
	Exp	12	286.67	1.775	285.54	287.79	282	288
	Total	27	286.52	2.225	285.64	287.40	279	288
Stop-switching GO Score FOLLOW-UP	NoExp	15	286.60	1.121	285.98	287.22	285	288
	Exp	12	286.92	1.505	285.96	287.87	283	288
	Total	27	286.74	1.289	286.23	287.25	283	288
Stop-switching GO RT PRE (ms)	NoExp	15	744.82	136.32	669.33	820.31	506.66	1047.65
	Exp	12	720.24	137.78	632.70	807.78	503.05	930.74
	Total	27	733.90	134.88	680.54	787.25	503.05	1047.65
Stop-switching GO RT POST (ms)	NoExp	15	773.67	178.45	674.84	872.49	402.28	1218.19
	Exp	12	725.59	136.83	638.65	812.53	574.92	940.24
	Total	27	752.30	160.19	688.93	815.67	402.28	1218.19
Stop-switching GO RT FOLLOW-UP (ms)	NoExp	15	790.26	182.30	689.31	891.22	435.19	1245.79
	Exp	12	769.79	127.94	688.50	851.08	529.38	965.11
	Total	27	781.16	157.88	718.71	843.62	435.19	1245.79
Stop-switching STOP Score PRE	NoExp	15	62.33	6.89	58.52	66.15	49	72
	Exp	12	61.58	7.81	56.62	66.55	48	72
	Total	27	62.00	7.18	59.16	64.84	48	72
Stop-switching STOP Score POST	NoExp	15	64.40	8.48	59.70	69.10	41	72
	Exp	12	63.42	6.69	59.16	67.67	53	72
	Total	27	63.96	7.61	60.95	66.97	41	72
Stop-switching STOP Score FOLLOW-UP	NoExp	15	65.00	7.50	60.85	69.15	43	72
	Exp	12	65.00	6.24	61.04	68.96	51	72
	Total	27	65.00	6.84	62.29	67.71	43	72
Stop-signal Reaction Time PRE (ms)	NoExp	15	11.01	85.08	-36.10	58.12	-170.50	140.53
	Exp	12	38.04	89.49	-18.82	94.90	-108.00	167.33
	Total	27	23.02	86.45	-11.18	57.22	-170.50	167.33
Stop-signal Reaction Time POST (ms)	NoExp	15	84.15	82.87	38.25	130.04	-39.78	262.00
	Exp	12	33.86	62.60	-5.91	73.63	-65.11	129.22
	Total	27	61.80	77.49	31.14	92.45	-65.11	262.00
Stop-signal Reaction Time FOLLOW-UP (ms)	NoExp	15	74.26	88.14	25.46	123.07	-35.00	283.00
	Exp	12	50.68	77.26	1.59	99.77	-71.06	163.78
	Total	27	63.78	82.77	31.04	96.52	-71.06	283.00
Stop-switching SWITCH Score PRE	NoExp	15	53.87	8.400	49.22	58.52	42	71
	Exp	12	54.33	9.847	48.08	60.59	41	70
	Total	27	54.07	8.892	50.56	57.59	41	71
Stop-switching SWITCH Score POST	NoExp	15	58.07	10.566	52.22	63.92	37	72
	Exp	12	55.83	10.161	49.38	62.29	45	71
	Total	27	57.07	10.250	53.02	61.13	37	72

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Stop-switching SWITCH Score FOLLOW-UP	NoExp	15	58.60	9.553	53.31	63.89	37	72
	Exp	12	58.75	8.884	53.11	64.39	40	69
	Total	27	58.67	9.085	55.07	62.26	37	72
Stop-switching SWITCH RT PRE	NoExp	15	150.82	80.74	106.11	195.53	-34.20	272.59
	Exp	12	135.93	62.62	96.14	175.72	38.11	262.40
	Total	27	144.20	72.29	115.61	172.80	-34.20	272.59
Stop-switching SWITCH RT POST	NoExp	15	133.85	84.13	87.26	180.44	-100.60	225.86
	Exp	12	120.97	87.54	65.35	176.59	-59.84	249.87
	Total	27	128.13	84.24	94.80	161.45	-100.60	249.87
Stop-switching SWITCH RT FOLLOW-UP	NoExp	15	117.56	108.22	57.63	177.49	-182.20	247.61
	Exp	12	105.49	77.34	56.35	154.62	-31.63	225.69
	Total	27	112.19	94.20	74.93	149.46	-182.20	247.61

Table 59. Descriptive statistics for the Stop-switching task, including go, *stop* and switch trials, by TMS group and previous video game experience.

		N	Mean	Std. Deviation	95% Confidence Interval for the Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Matchstick total score (correct answers)	NoExp	15	4.47	2.066	3.32	5.61	1	8
	Exp	12	5.92	1.443	5.00	6.83	3	8
	Total	27	5.11	1.928	4.35	5.87	1	8
Matchstick total Response time (correct answers)	NoExp	15	48129.50	22576.148	35627.25	60631.75	10846	86092
	Exp	12	48495.25	15084.163	38911.23	58079.27	29382	76696
	Total	27	48292.06	19254.668	40675.16	55908.95	10846	86092
Matchstick Score (first exposition)	NoExp	15	2.13	1.060	1.55	2.72	1	4
	Exp	12	2.92	.669	2.49	3.34	2	4
	Total	27	2.48	.975	2.10	2.87	1	4
Matchstick Score (second exposition)	NoExp	15	2.33	1.291	1.62	3.05	0	4
	Exp	12	3.00	.953	2.39	3.61	1	4
	Total	27	2.63	1.182	2.16	3.10	0	4
Matchstick Facilitated responses	NoExp	15	1.13	.915	.63	1.64	0	3
	Exp	12	1.92	.900	1.34	2.49	0	3
	Total	27	1.48	.975	1.10	1.87	0	3
Matchstick Facilitated response percentage	NoExp	11	68.94	24.179	52.69	85.18	33.33	100.00
	Exp	11	71.21	23.382	55.50	86.92	33.33	100.00
	Total	22	70.07	23.240	59.77	80.38	33.33	100.00
Matchstick Facilitated response time (ms)	NoExp	11	-5562.98	65709.531	-49707.25	38581.28	-133926	113250
	Exp	11	41528.48	38813.772	15453.04	67603.93	-19696	119863
	Total	22	17982.75	57915.928	-7695.73	43661.23	-133926	119863

Table 60. Descriptive statistics for the matchstick task, by previous video game experience.

8.7.3 By TMS x Previous video game experience

		N	Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Stars achieved SuperMario64	Sham+NoExp	7	15.86	12.536	4.26	27.45	4	40
	Sham+Exp	6	46.33	25.828	19.23	73.44	13	85
	iTBS+NoExp	8	26.00	27.140	3.31	48.69	5	86
	iTBS+Exp	6	39.50	29.016	9.05	69.95	16	92
	Total	27	30.89	25.790	20.69	41.09	4	92
Number of attempts (started levels) during the game	Sham+NoExp	7	148.14	75.814	78.03	218.26	78	275
	Sham+Exp	6	243.00	93.484	144.89	341.11	108	369
	iTBS+NoExp	8	196.88	61.002	145.88	247.87	102	292
	iTBS+Exp	6	224.33	86.206	133.87	314.80	125	368
	Total	27	200.59	82.025	168.14	233.04	78	369
Goals (stars) accomplished divided by the number of tries	Sham+NoExp	7	11.13	8.463	3.30	18.96	4.91	25.00
	Sham+Exp	6	20.10	10.139	9.46	30.74	6.44	33.51
	iTBS+NoExp	8	14.28	14.436	2.21	26.35	3.42	39.45
	iTBS+Exp	6	17.77	9.952	7.33	28.22	6.58	31.93
	Total	27	15.53	11.096	11.14	19.92	3.42	39.45
Time (seconds) for each attempt	Sham+NoExp	7	499.43	283.993	236.78	762.08	193	1032
	Sham+Exp	6	266.17	130.593	129.12	403.22	148	511
	iTBS+NoExp	8	295.50	108.450	204.83	386.17	173	534
	iTBS+Exp	6	272.67	98.484	169.31	376.02	150	433
	Total	27	336.78	191.493	261.03	412.53	148	1032
Questionnaire analysis of video game expertise PRE	Sham+NoExp	7	8.29	2.870	5.63	10.94	6	14
	Sham+Exp	6	10.50	2.429	7.95	13.05	8	15
	iTBS+NoExp	8	8.38	2.326	6.43	10.32	6	12
	iTBS+Exp	6	8.83	2.787	5.91	11.76	4	11
	Total	27	8.93	2.601	7.90	9.95	4	15
Questionnaire analysis of video game expertise POST	Sham+NoExp	7	12.00	3.367	8.89	15.11	8	17
	Sham+Exp	6	14.50	2.429	11.95	17.05	12	18
	iTBS+NoExp	8	12.00	3.742	8.87	15.13	5	16
	iTBS+Exp	6	14.67	2.658	11.88	17.46	10	18
	Total	27	13.15	3.255	11.86	14.44	5	18

Table 61. Descriptive statistics for variables related to video game performance, by TMS group and previous video game experience.

		N	Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Simple reaction time PRE (ms)	Sham+NoExp	7	271.32	28.50	244.96	297.67	241.09	319.52
	Sham+Exp	6	274.43	21.88	251.47	297.40	253.57	305.04
	iTBS+NoExp	8	273.19	33.23	245.41	300.97	227.48	331.61

	iTBS+Exp	6	248.60	28.73	218.44	278.75	222.26	302.48
	Total	27	267.52	29.04	256.03	279.00	222.26	331.61
Simple reaction time POST (ms)	Sham+NoExp	7	278.61	36.15	245.18	312.04	231.57	318.48
	Sham+Exp	6	274.97	13.21	261.11	288.82	253.57	292.74
	iTBS+NoExp	8	271.11	34.04	242.66	299.57	238.65	332.57
	iTBS+Exp	6	257.59	43.62	211.81	303.36	203.26	314.43
	Total	27	270.91	32.77	257.95	283.87	203.26	332.57
Simple reaction time FOLLOW-UP (ms)	Sham+NoExp	7	278.11	43.86	237.54	318.67	238.52	357.05
	Sham+Exp	6	274.68	23.05	250.50	298.87	234.13	300.13
	iTBS+NoExp	8	302.45	34.65	273.48	331.41	261.13	350.57
	iTBS+Exp	6	275.62	51.70	221.36	329.87	217.35	336.96
	Total	27	284.00	39.16	268.51	299.50	217.35	357.05
Direction choice reaction time PRE (ms)	Sham+NoExp	7	347.98	48.45	303.17	392.79	290.73	423.32
	Sham+Exp	6	346.71	50.87	293.33	400.10	294.61	413.91
	iTBS+NoExp	8	326.57	36.12	296.37	356.76	299.86	411.43
	iTBS+Exp	6	312.05	40.56	269.49	354.61	270.04	386.82
	Total	27	333.37	43.87	316.01	350.72	270.04	423.32
Direction choice reaction time POST (ms)	Sham+NoExp	7	344.63	47.16	301.02	388.24	290.48	412.43
	Sham+Exp	6	337.62	47.35	287.93	387.32	302.09	427.85
	iTBS+NoExp	8	331.34	34.43	302.55	360.12	271.65	375.48
	iTBS+Exp	6	316.07	45.00	268.84	363.29	269.70	387.87
	Total	27	332.79	41.97	316.18	349.39	269.70	427.85
Direction choice reaction time FOLLOW-UP (ms)	Sham+NoExp	7	348.19	55.24	297.10	399.27	295.57	453.91
	Sham+Exp	6	330.68	26.69	302.67	358.69	296.48	363.48
	iTBS+NoExp	8	346.60	49.38	305.31	387.88	273.52	412.52
	iTBS+Exp	6	330.70	46.03	282.39	379.01	263.74	385.61
	Total	27	339.94	44.46	322.35	357.53	263.74	453.91
Colour choice reaction time PRE (ms)	Sham+NoExp	7	472.51	82.64	396.08	548.94	400.59	644.22
	Sham+Exp	6	462.80	37.83	423.10	502.50	413.91	515.14
	iTBS+NoExp	8	473.80	62.89	421.23	526.38	364.10	547.22
	iTBS+Exp	6	431.56	89.77	337.36	525.77	345.14	597.14
	Total	27	461.64	68.93	434.37	488.91	345.14	644.22
Colour choice reaction time POST (ms)	Sham+NoExp	7	451.28	46.41	408.36	494.21	388.04	504.35
	Sham+Exp	6	447.57	26.73	419.52	475.62	413.38	479.78
	iTBS+NoExp	8	503.97	76.23	440.24	567.70	408.42	625.46
	iTBS+Exp	6	417.41	57.94	356.61	478.22	351.67	490.09
	Total	27	458.54	62.54	433.80	483.28	351.67	625.46
Colour choice reaction time FOLLOW-UP (ms)	Sham+NoExp	7	464.22	50.98	417.07	511.37	378.55	531.30
	Sham+Exp	6	461.31	67.23	390.76	531.86	411.41	575.23
	iTBS+NoExp	8	510.57	89.03	436.15	585.00	347.80	672.70
	iTBS+Exp	6	428.86	66.33	359.26	498.47	339.68	529.55
	Total	27	469.45	73.29	440.46	498.44	339.68	672.70

Table 62. Descriptive statistics for the three reaction time tasks, by TMS group and previous video game experience.

		N	Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Forward digits PRE	Sham+NoExp	7	9.71	2.36	7.53	11.90	6	12
	Sham+Exp	6	8.83	2.04	6.69	10.98	6	12
	iTBS+NoExp	8	9.50	1.20	8.50	10.50	7	11
	iTBS+Exp	6	9.33	1.97	7.27	11.40	7	12
	Total	27	9.37	1.82	8.65	10.09	6	12
Forward digits POST	Sham+NoExp	7	10.14	2.67	7.67	12.61	7	14
	Sham+Exp	6	10.33	1.37	8.90	11.77	9	13
	iTBS+NoExp	8	9.75	1.28	8.68	10.82	8	12
	iTBS+Exp	6	11.00	3.46	7.36	14.64	6	16
	Total	27	10.26	2.23	9.38	11.14	6	16
Forward digits FOLLOW-UP	Sham+NoExp	7	9.71	2.36	7.53	11.90	7	14
	Sham+Exp	6	11.67	2.66	8.88	14.46	7	15
	iTBS+NoExp	8	10.63	1.30	9.54	11.71	8	12
	iTBS+Exp	6	10.50	1.64	8.78	12.22	8	12
	Total	27	10.59	2.02	9.79	11.39	7	15
Backward digits PRE	Sham+NoExp	7	7.43	2.82	4.82	10.04	4	11
	Sham+Exp	6	8.67	2.16	6.40	10.93	6	12
	iTBS+NoExp	8	7.75	1.39	6.59	8.91	6	10
	iTBS+Exp	6	10.17	3.54	6.45	13.89	6	16
	Total	27	8.41	2.61	7.38	9.44	4	16
Backward digits POST	Sham+NoExp	7	8.00	1.91	6.23	9.77	6	11
	Sham+Exp	6	8.83	1.94	6.80	10.87	6	11
	iTBS+NoExp	8	8.50	1.31	7.41	9.59	7	10
	iTBS+Exp	6	9.83	2.32	7.40	12.26	7	13
	Total	27	8.74	1.87	8.00	9.48	6	13
Backward digits FOLLOW-UP	Sham+NoExp	7	9.00	2.45	6.73	11.27	6	13
	Sham+Exp	6	9.83	3.66	6.00	13.67	5	16
	iTBS+NoExp	8	9.50	2.00	7.83	11.17	7	13
	iTBS+Exp	6	11.50	3.62	7.70	15.30	8	17
	Total	27	9.89	2.90	8.74	11.04	5	17

Table 63. Descriptive statistics for the forward and backward digits task, by TMS group and previous video game experience.

		N	Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Raven Score PRE	Sham+NoExp	7	29.00	1.15	27.93	30.07	28	31
	Sham+Exp	6	27.67	2.07	25.50	29.83	24	30
	iTBS+NoExp	8	26.88	2.64	24.67	29.08	22	30
	iTBS+Exp	6	27.17	6.11	20.75	33.58	15	31

	Total	27	27.67	3.31	26.36	28.97	15	31
Raven Score POST	Sham+NoExp	7	27.71	1.89	25.97	29.46	25	30
	Sham+Exp	6	27.50	2.35	25.04	29.96	23	29
	iTBS+NoExp	8	26.25	2.96	23.77	28.73	22	30
	iTBS+Exp	6	27.50	3.62	23.70	31.30	21	31
	Total	27	27.19	2.68	26.13	28.24	21	31
Raven RT PRE	Sham+NoExp	7	24357.60	8138.31	16830.92	31884.28	16468.35	40836.66
	Sham+Exp	6	17481.50	6732.00	10416.70	24546.29	8644.17	26747.52
	iTBS+NoExp	8	14449.78	3165.84	11803.07	17096.49	9994.29	21074.67
	iTBS+Exp	6	15784.04	8490.61	6873.69	24694.40	4189.20	28022.13
	Total	27	17988.69	7517.77	15014.76	20962.62	4189.20	40836.66
Raven RT POST	Sham+NoExp	7	18586.50	3890.99	14987.93	22185.07	13464.68	25200.19
	Sham+Exp	6	18311.82	4941.24	13126.31	23497.33	11061.86	23555.69
	iTBS+NoExp	8	15283.12	5309.37	10844.37	19721.86	8069.04	23033.17
	iTBS+Exp	6	12673.81	4296.72	8164.68	17182.94	8512.95	19812.17
	Total	27	16232.75	5001.85	14254.09	18211.41	8069.04	25200.19

Table 64. Descriptive statistics for the Raven's Progressive, by TMS group and previous video game experience.

		N	Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Five-Point Test	Sham+NoExp	7	33.00	9.61	24.11	41.89	16	44
	Sham+Exp	6	33.50	5.24	28.00	39.00	26	41
	iTBS+NoExp	8	31.63	10.28	23.03	40.22	23	55
	iTBS+Exp	6	27.83	10.25	17.08	38.59	12	42
	Total	27	31.56	8.94	28.02	35.09	12	55

Table 65. Descriptive statistics for the Five-Point Test (5PT), by TMS group and previous video game experience.

		N	Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
n-back score PRE	Sham+NoExp	7	47.00	5.51	41.91	52.09	39	53
	Sham+Exp	6	49.50	3.08	46.27	52.73	47	55
	iTBS+NoExp	8	50.50	6.39	45.16	55.84	40	57
	iTBS+Exp	6	49.33	8.73	40.17	58.50	33	56
	Total	27	49.11	6.03	46.73	51.50	33	57
n-back score POST	Sham+NoExp	7	46.71	6.87	40.36	53.07	36	55
	Sham+Exp	6	53.17	3.19	49.82	56.51	48	56
	iTBS+NoExp	8	43.88	15.50	30.92	56.83	15	57
	iTBS+Exp	6	55.00	2.53	52.35	57.65	52	58
	Total	27	49.15	10.03	45.18	53.11	15	58

n-back score FOLLOW-UP	Sham+NoExp	7	50.00	4.12	46.19	53.81	44	56
	Sham+Exp	6	53.17	2.64	50.40	55.94	50	57
	iTBS+NoExp	8	50.13	8.22	43.25	57.00	31	57
	iTBS+Exp	6	53.50	6.50	46.67	60.33	41	59
	Total	27	51.52	5.86	49.20	53.84	31	59
n-back RT right answer PRE (ms)	Sham+NoExp	7	797.11	304.67	515.34	1078.88	455.07	1225.33
	Sham+Exp	6	1115.05	229.91	873.78	1356.33	662.47	1312.75
	iTBS+NoExp	8	924.46	253.90	712.19	1136.72	524.41	1217.58
	iTBS+Exp	6	805.49	376.26	410.62	1200.35	412.09	1237.21
	Total	27	907.36	303.12	787.45	1027.27	412.09	1312.75
n-back RT right answer POST (ms)	Sham+NoExp	7	820.60	310.85	533.11	1108.09	492.31	1435.67
	Sham+Exp	6	1033.38	250.59	770.39	1296.36	634.60	1236.41
	iTBS+NoExp	8	987.84	228.47	796.84	1178.84	580.24	1231.16
	iTBS+Exp	6	791.04	315.61	459.83	1122.25	405.07	1168.78
	Total	27	910.87	279.96	800.12	1021.62	405.07	1435.67
n-back RT right answer FOLLOW-UP (ms)	Sham+NoExp	7	760.41	271.20	509.59	1011.23	473.02	1333.12
	Sham+Exp	6	919.83	242.00	665.87	1173.79	533.60	1144.35
	iTBS+NoExp	8	858.23	193.56	696.41	1020.05	521.47	1078.47
	iTBS+Exp	6	753.44	267.90	472.30	1034.58	431.40	1085.02
	Total	27	823.27	238.41	728.96	917.59	431.40	1333.12
n-back d' PRE (ms)	Sham+NoExp	7	1.124	1.000	0.199	2.049	-0.356	2.123
	Sham+Exp	6	1.317	0.626	0.660	1.974	0.842	2.123
	iTBS+NoExp	8	1.926	0.772	1.281	2.571	0.630	2.681
	iTBS+Exp	6	1.698	0.571	1.098	2.297	0.881	2.476
	Total	27	1.532	0.799	1.216	1.848	-0.356	2.681
n-back d' POST (ms)	Sham+NoExp	7	0.877	0.960	-0.010	1.765	-0.588	2.476
	Sham+Exp	6	1.838	0.466	1.348	2.327	1.320	2.476
	iTBS+NoExp	8	1.511	0.468	1.119	1.902	0.915	2.476
	iTBS+Exp	6	2.478	0.740	1.702	3.255	1.561	3.605
	Total	27	1.634	0.867	1.291	1.977	-0.588	3.605
n-back d' FOLLOW-UP (ms)	Sham+NoExp	7	1.281	0.731	0.605	1.957	0.271	2.123
	Sham+Exp	6	1.909	0.601	1.278	2.540	0.881	2.476
	iTBS+NoExp	8	1.898	0.935	1.116	2.680	0.068	2.926
	iTBS+Exp	6	2.450	0.837	1.572	3.329	1.095	3.605
	Total	27	1.863	0.857	1.524	2.202	0.068	3.605

Table 66. Descriptive statistics for the n-back task, by TMS group and previous video game experience.

		N	**Mean**	**Std. Deviation**	**95% Confidence Interval for Mean**		**Minimum**	**Maximum**
					Lower Bound	Upper Bound		
Mental rotation score PRE	Sham+NoExp	7	.912	.045	.870	.953	.874	.985
	Sham+Exp	6	.948	.048	.898	.998	.859	.995
	iTBS+NoExp	8	.869	.056	.822	.916	.760	.949
	iTBS+Exp	6	.901	.119	.776	1.025	.665	.979

	Total	27	.905	.073	.876	.934	.665	.995
Mental rotation score POST	Sham+NoExp	7	.924	.051	.876	.971	.838	1.000
	Sham+Exp	6	.963	.038	.923	1.004	.905	.995
	iTBS+NoExp	8	.914	.067	.858	.970	.784	.965
	iTBS+Exp	6	.908	.154	.746	1.069	.595	.995
	Total	27	.926	.084	.893	.959	.595	1.000
Mental rotation score FOLLOW-UP	Sham+NoExp	7	.939	.045	.897	.981	.859	1.000
	Sham+Exp	6	.956	.036	.918	.994	.895	.995
	iTBS+NoExp	8	.904	.062	.852	.956	.783	.975
	iTBS+Exp	6	.900	.145	.747	1.053	.611	.985
	Total	27	.924	.080	.892	.955	.611	1.000
Mental rotation RT PRE (ms)	Sham+NoExp	7	9084.11	2924.89	6379.04	11789.18	5636.07	13680.34
	Sham+Exp	6	7527.74	3437.89	3919.89	11135.58	3243.61	11815.71
	iTBS+NoExp	8	8841.57	4307.63	5240.31	12442.84	4321.09	16226.89
	iTBS+Exp	6	6047.13	2138.07	3803.36	8290.90	2670.29	8820.93
	Total	27	7991.50	3404.09	6644.89	9338.11	2670.29	16226.89
Mental rotation RT POST (ms)	Sham+NoExp	7	6882.97	2160.54	4884.81	8881.13	4583.60	11383.76
	Sham+Exp	6	5373.77	2429.07	2824.62	7922.92	2660.28	9204.24
	iTBS+NoExp	8	6976.26	2734.79	4689.92	9262.60	3318.09	12456.87
	iTBS+Exp	6	5280.77	1877.50	3310.45	7251.08	2557.19	8192.34
	Total	27	6219.19	2359.35	5285.86	7152.52	2557.19	12456.87
Mental rotation RT FOLLOW-UP (ms)	Sham+NoExp	7	4995.37	622.29	4419.85	5570.90	4408.16	6306.80
	Sham+Exp	6	3453.36	917.61	2490.39	4416.34	2533.87	4923.37
	iTBS+NoExp	8	5540.98	2877.85	3135.04	7946.92	2701.92	11743.09
	iTBS+Exp	6	3819.39	1344.14	2408.81	5229.98	1587.85	5203.47
	Total	27	4553.04	1893.35	3804.05	5302.02	1587.85	11743.09

Table 67. Descriptive statistics for variables related to the N-back, by TMS group and previous video game experience.

		N	**Mean**	**Std. Deviation**	**95% Confidence Interval for Mean**		**Minimum**	**Maximum**
					Lower Bound	Upper Bound		
Stop-switching GO Score PRE	Sham+NoExp	7	286.00	1.91	284.23	287.77	283	288
	Sham+Exp	6	286.17	1.60	284.49	287.85	284	288
	iTBS+NoExp	8	286.38	1.69	284.97	287.78	283	288
	iTBS+Exp	6	285.33	2.42	282.79	287.88	282	288
	Total	27	286.00	1.84	285.27	286.73	282	288
Stop-switching GO Score POST	Sham+NoExp	7	286.29	3.30	283.23	289.34	279	288
	Sham+Exp	6	286.83	1.17	285.61	288.06	285	288
	iTBS+NoExp	8	286.50	2.00	284.83	288.17	283	288
	iTBS+Exp	6	286.50	2.35	284.04	288.96	282	288
	Total	27	286.52	2.23	285.64	287.40	279	288
Stop-switching GO Score FOLLOW-UP	Sham+NoExp	7	286.29	1.11	285.26	287.31	285	288
	Sham+Exp	6	287.33	1.03	286.25	288.42	286	288

	iTBS+NoExp	8	286.88	1.13	285.93	287.82	285	288
	iTBS+Exp	6	286.50	1.87	284.54	288.46	283	288
	Total	27	286.74	1.29	286.23	287.25	283	288
Stop-switching GO RT PRE (ms)	Sham+NoExp	7	717.04	138.16	589.27	844.81	506.66	949.46
	Sham+Exp	6	753.82	127.19	620.34	887.30	592.82	930.74
	iTBS+NoExp	8	769.13	139.13	652.81	885.45	602.55	1047.65
	iTBS+Exp	6	686.67	151.25	527.94	845.40	503.05	856.77
	Total	27	733.90	134.88	680.54	787.25	503.05	1047.65
Stop-switching GO RT POST (ms)	Sham+NoExp	7	730.18	161.71	580.62	879.74	402.28	896.23
	Sham+Exp	6	739.90	136.74	596.40	883.40	614.90	916.61
	iTBS+NoExp	8	811.72	194.24	649.33	974.11	535.37	1218.19
	iTBS+Exp	6	711.28	148.32	555.63	866.93	574.92	940.24
	Total	27	752.30	160.19	688.93	815.67	402.28	1218.19
Stop-switching GO RT FOLLOW-UP (ms)	Sham+NoExp	7	754.34	170.43	596.72	911.97	435.19	937.38
	Sham+Exp	6	772.45	109.92	657.10	887.80	576.84	895.59
	iTBS+NoExp	8	821.70	197.86	656.28	987.11	577.85	1245.79
	iTBS+Exp	6	767.13	154.64	604.84	929.41	529.38	965.11
	Total	27	781.16	157.88	718.71	843.62	435.19	1245.79
Stop-switching STOP Score PRE	Sham+NoExp	7	62.00	7.92	54.68	69.32	49	69
	Sham+Exp	6	64.17	7.41	56.39	71.95	56	72
	iTBS+NoExp	8	62.63	6.41	57.26	67.99	55	72
	iTBS+Exp	6	59.00	7.95	50.66	67.34	48	68
	Total	27	62.00	7.18	59.16	64.84	48	72
Stop-switching STOP Score POST	Sham+NoExp	7	63.29	10.18	53.87	72.70	41	70
	Sham+Exp	6	64.67	6.38	57.97	71.36	58	72
	iTBS+NoExp	8	65.38	7.27	59.30	71.45	49	72
	iTBS+Exp	6	62.17	7.36	54.44	69.89	53	72
	Total	27	63.96	7.61	60.95	66.97	41	72
Stop-switching STOP Score FOLLOW-UP	Sham+NoExp	7	63.29	9.74	54.28	72.30	43	71
	Sham+Exp	6	65.83	5.60	59.96	71.71	56	72
	iTBS+NoExp	8	66.50	5.07	62.26	70.74	57	72
	iTBS+Exp	6	64.17	7.25	56.56	71.78	51	71
	Total	27	65.00	6.84	62.29	67.71	43	72
Stop-signal Reaction Time PRE (ms)	Sham+NoExp	7	20.92	78.82	-51.98	93.81	-53.28	140.53
	Sham+Exp	6	14.36	87.16	-77.12	105.83	-108.00	125.00
	iTBS+NoExp	8	2.34	94.69	-76.83	81.50	-170.50	92.83
	iTBS+Exp	6	61.72	93.14	-36.03	159.46	-72.78	167.33
	Total	27	23.02	86.45	-11.18	57.22	-170.50	167.33
Stop-signal Reaction Time POST (ms)	Sham+NoExp	7	77.89	82.97	1.16	154.63	-39.78	209.33
	Sham+Exp	6	36.54	67.97	-34.79	107.86	-51.11	125.53
	iTBS+NoExp	8	89.62	88.10	15.97	163.27	-29.81	262.00
	iTBS+Exp	6	31.19	63.12	-35.05	97.42	-65.11	129.22
	Total	27	61.80	77.49	31.14	92.45	-65.11	262.00
Stop-signal Reaction Time FOLLOW-UP (ms)	Sham+NoExp	7	84.64	75.80	14.54	154.74	-18.89	168.78
	Sham+Exp	6	51.50	90.97	-43.97	146.96	-71.06	152.92

	iTBS+NoExp	8	65.19	102.03	-20.11	150.49	-35.00	283.00
	iTBS+Exp	6	49.86	69.67	-23.26	122.98	-31.19	163.78
	Total	27	63.78	82.77	31.04	96.52	-71.06	283.00
Stop-switching SWITCH Score PRE	Sham+NoExp	7	52.43	6.32	46.58	58.27	42	61
	Sham+Exp	6	56.83	10.53	45.78	67.89	47	70
	iTBS+NoExp	8	55.13	10.15	46.64	63.61	46	71
	iTBS+Exp	6	51.83	9.35	42.02	61.64	41	62
	Total	27	54.07	8.89	50.56	57.59	41	71
Stop-switching SWITCH Score POST	Sham+NoExp	7	57.14	10.42	47.51	66.78	37	68
	Sham+Exp	6	57.33	11.04	45.75	68.92	46	69
	iTBS+NoExp	8	58.88	11.34	49.39	68.36	38	72
	iTBS+Exp	6	54.33	9.99	43.85	64.82	45	71
	Total	27	57.07	10.25	53.02	61.13	37	72
Stop-switching SWITCH Score FOLLOW-UP	Sham+NoExp	7	57.71	10.61	47.90	67.53	37	69
	Sham+Exp	6	60.00	8.34	51.24	68.76	45	69
	iTBS+NoExp	8	59.38	9.20	51.69	67.06	44	72
	iTBS+Exp	6	57.50	10.01	46.99	68.01	40	67
	Total	27	58.67	9.09	55.07	62.26	37	72
Stop-switching SWITCH RT PRE	Sham+NoExp	7	174.40	59.19	119.65	229.14	106.39	272.59
	Sham+Exp	6	140.19	75.98	60.45	219.92	38.11	262.40
	iTBS+NoExp	8	130.19	94.82	50.92	209.46	-34.20	225.90
	iTBS+Exp	6	131.68	53.02	76.03	187.32	62.36	181.62
	Total	27	144.20	72.29	115.61	172.80	-34.20	272.59
Stop-switching SWITCH RT POST	Sham+NoExp	7	164.97	24.48	142.32	187.61	135.97	193.54
	Sham+Exp	6	128.20	90.42	33.31	223.09	7.45	249.87
	iTBS+NoExp	8	106.62	108.75	15.70	197.54	-100.60	225.86
	iTBS+Exp	6	113.74	92.51	16.66	210.83	-59.84	184.45
	Total	27	128.13	84.24	94.80	161.45	-100.60	249.87
Stop-switching SWITCH RT FOLLOW-UP	Sham+NoExp	7	134.94	57.26	81.99	187.89	40.29	199.70
	Sham+Exp	6	112.24	62.33	46.83	177.66	53.94	225.69
	iTBS+NoExp	8	102.35	141.58	-16.01	220.72	-182.20	247.61
	iTBS+Exp	6	98.73	95.72	-1.72	199.19	-31.63	212.72
	Total	27	112.19	94.20	74.93	149.46	-182.20	247.61

Table 68. Descriptive statistics for the Stop-switching , by TMS group and previous video game experience (TMS x VG experience).

		N	**Mean**	**Std. Deviation**	**95% Confidence Interval for Mean**		**Minimum**	**Maximum**
					Lower Bound	Upper Bound		
Matchstick total score (correct answers)	Sham+NoExp	7	4.86	2.035	2.97	6.74	2	8
	Sham+Exp	6	5.67	1.751	3.83	7.50	3	8
	iTBS+NoExp	8	4.13	2.167	2.31	5.94	1	7
	iTBS+Exp	6	6.17	1.169	4.94	7.39	5	8
	Total	27	5.11	1.928	4.35	5.87	1	8

Matchstick total Response time (correct answers)	Sham+NoExp	7	47052	27360.429	21748.32	72356.68	10846	86092
	Sham+Exp	6	51242	13275.964	37310.06	65174.60	38200	72619
	iTBS+NoExp	8	49071	19378.824	32870.77	65272.98	26450	85895
	iTBS+Exp	6	45748	17498.788	27384.31	64112.02	29382	76696
	Total	27	48292	19254.668	40675.16	55908.95	10846	86092
Matchstick Score (first exposition)	Sham+NoExp	7	2.29	1.113	1.26	3.31	1	4
	Sham+Exp	6	2.67	.816	1.81	3.52	2	4
	iTBS+NoExp	8	2.00	1.069	1.11	2.89	1	3
	iTBS+Exp	6	3.17	.408	2.74	3.60	3	4
	Total	27	2.48	.975	2.10	2.87	1	4
Matchstick Score (second exposition)	Sham+NoExp	7	2.57	1.134	1.52	3.62	1	4
	Sham+Exp	6	3.00	1.095	1.85	4.15	1	4
	iTBS+NoExp	8	2.13	1.458	.91	3.34	0	4
	iTBS+Exp	6	3.00	.894	2.06	3.94	2	4
	Total	27	2.63	1.182	2.16	3.10	0	4
Matchstick Facilitated responses	Sham+NoExp	7	1.43	.976	.53	2.33	0	3
	Sham+Exp	6	1.83	.983	.80	2.87	0	3
	iTBS+NoExp	8	.88	.835	.18	1.57	0	2
	iTBS+Exp	6	2.00	.894	1.06	2.94	1	3
	Total	27	1.48	.975	1.10	1.87	0	3
Matchstick Facilitated response percentage	Sham+NoExp	6	76.39	20.011	55.39	97.39	50.00	100.00
	Sham+Exp	5	81.67	17.077	60.46	102.87	66.67	100.00
	iTBS+NoExp	5	60.00	27.891	25.37	94.63	33.33	100.00
	iTBS+Exp	6	62.50	25.687	35.54	89.46	33.33	100.00
	Total	22	70.08	23.240	59.77	80.38	33.33	100.00
Matchstick Facilitated response time (ms)	Sham+NoExp	6	-4182.39	68340.312	-75901.15	67536.37	-133926	67570
	Sham+Exp	5	43010.87	14820.179	24609.18	61412.55	19335	55025
	iTBS+NoExp	5	-7219.70	70356.722	-94579.11	80139.71	-59052	113250
	iTBS+Exp	6	40293.17	53228.553	-15566.77	96153.11	-19696	119863
	Total	22	17982.75	57915.928	-7695.73	43661.23	-133926	119863

Table 69. Descriptive statistics for the matchstick task, by TMS group and previous video game experience.

8.8 Parametric Adjustment

8.8.1 Summary

	TMS			Exp_VGP			TMS+Exp_VGP		
	Norm.	Homosc.	Sphe	Norm.	Homosc.	Sphe.	Norm.	Homosc.	Sphe.
Stars achieved SuperMario64	No	Yes	-	No	Yes	-	No	Yes	-
Attempts	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Performance	No	Yes	-	No	Yes	-	No	Yes	-
Time per attempt (s)	No	No	-	No	Yes	-	Yes	Yes	-
VG skill (questionnaire) PRE	Yes	Yes	-	No	Yes	-	Yes	Yes	-
VG skill (questionnaire) POST	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
VG skill (qualitative) PRE	Yes	Yes	-	No	Yes	-	Yes	Yes	-
VG skill (qualitative) POST	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Motivation (0-5)	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Fun (0-5)	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Frustration (0-5)	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Post-Pre VGskill (questionnaire)	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Post-Pre VGskill (qualitative)	Yes	Yes	-	Yes	Yes	-	No	Yes	-
Simple reaction time PRE (ms)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Simple reaction time POST (ms)	Yes	Yes		Yes	Yes		Yes	No	
Simple reaction time FOLLOW-UP (ms)	Yes	Yes		Yes	Yes		Yes	Yes	
Direction choice reaction time PRE (ms)	No	Yes	Yes	No	Yes	No	No	Yes	Yes
Direction choice reaction time POST (ms)	Yes	Yes		Yes	Yes		No	Yes	
Direction choice reaction time FOLLOW-UP (ms)	No	Yes		Yes	Yes		Yes	Yes	
Colour choice reaction time PRE (ms)	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Colour choice reaction time POST (ms)	Yes	No		Yes	Yes		Yes	No	
Colour choice reaction time FOLLOW-UP (ms)	Yes	Yes		Yes	Yes		Yes	Yes	
Post-Pre Simple reaction time	Yes	Yes	-	No	Yes	-	No	Yes	-
Post-Pre Direction choice reaction time	Yes	Yes	-	Yes	Yes	-	No	Yes	-
Post-Pre Color choice reaction time	Yes	Yes	-	Yes	Yes	-	No	Yes	-
Follow-up-Pre Simple reaction time	No	Yes	-	Yes	Yes	-	No	Yes	-
Follow-up-Pre Direction choice reaction time	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Follow-up-Pre Color choice reaction time	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Forward digits PRE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Forward digits POST	Yes	Yes		Yes	Yes		No	No	
Forward digits FOLLOW-UP	No	No		Yes	Yes		Yes	Yes	
Backward digits PRE	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Backward digits POST	Yes	Yes		Yes	Yes		No	Yes	
Backward digits FOLLOW-UP	Yes	Yes		Yes	Yes		Yes	Yes	
Post-Pre Forward digits	Yes	Yes	-	No	No	-	Yes	No	-
Post-Pre Backward digits	Yes	Yes	-	No	Yes	-	No	Yes	-
Follow-up-Pre Forward digits	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Follow-up-Pre Backward digits	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Raven Score PRE	No	Yes	-	No	Yes	-	No	Yes	-
Raven Score POST	Yes	No	-	No	Yes	-	No	Yes	-
Raven RT PRE	Yes	Yes	-	No	Yes	-	Yes	Yes	-
Raven RT POST	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Post-Pre Raven score	No	Yes	-	No	Yes	-	No	Yes	-
Post-Pre Raven response time	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Five-Point Test (5PT)	Yes	Yes	-	Yes	Yes	-	No	Yes	-
n-back score PRE	No	Yes	No	Yes	Yes	No	No	Yes	No
n-back score POST	No	Yes		No	No		No	No	
n-back score FOLLOW-UP	No	Yes		No	Yes		No	Yes	
n-back RT right answer PRE (ms)	Yes	Yes	No	No	Yes	No	No	Yes	No
n-back RT right answer POST (ms)	Yes	Yes		Yes	Yes		No	Yes	
n-back RT right answer FOLLOW-UP (ms)	Yes	Yes		Yes	Yes		No	Yes	
n-back d prime PRE (ms)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
n-back d prime POST (ms)	Yes	Yes		Yes	Yes		Yes	Yes	
n-back d prime FOLLOW-UP (ms)	Yes	Yes		Yes	Yes		Yes	Yes	
Post-Pre N-back score	Yes	Yes	-	No	Yes	-	No	Yes	-
Post-Pre N-back reaction time	No	Yes	-	Yes	Yes	-	No	Yes	-
Post-Pre N-back d'	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Follow-up-Pre N-back score	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Follow-up-Pre N-back reaction time	No	Yes	-	No	Yes	-	No	Yes	-
Follow-up-Pre N-back d'	No	Yes	-	No	Yes	-	No	Yes	-
Mental rotation score PRE	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Mental rotation score POST	No	Yes		No	Yes		No	Yes	

	TMS			Exp_VGP			TMS+Exp_VGP		
	Norm.	Homosc.	Sphe	Norm.	Homosc.	Sphe.	Norm.	Homosc.	Sphe.
Mental rotation score FOLLOW-UP	No	Yes		No	Yes		No	Yes	
Mental rotation RT PRE (ms)	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Mental rotation RT POST (ms)	Yes	Yes		Yes	Yes		Yes	Yes	
Mental rotation RT FOLLOW-UP (ms)	No	Yes		No	Yes		No	No	
Post-Pre Mental rotation score	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Post-Pre Mental rotation response time	No	Yes	-	No	Yes	-	No	Yes	-
Follow-up-Pre Mental rotation score	Yes	Yes	-	Yes	Yes	-	No	Yes	-
Follow-up-Pre Mental rotation response time	No	No	-	Yes	Yes	-	No	Yes	-
Stop-switching GO Score PRE	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Stop-switching GO Score POST	No	Yes		No	Yes		No	Yes	
Stop-switching GO Score FOLLOW-UP	No	Yes		No	Yes		No	Yes	
Stop-switching GO RT PRE (ms)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Stop-switching GO RT POST (ms)	Yes	Yes		Yes	Yes		Yes	Yes	
Stop-switching GO RT FOLLOW-UP (ms)	Yes	Yes		Yes	Yes		Yes	Yes	
Stop-switching STOP Score PRE	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No
Stop-switching STOP Score POST	No	Yes		No	Yes		No	Yes	
Stop-switching STOP Score FOLLOW-UP	No	Yes		No	Yes		No	Yes	
Stop-signal Reaction Time PRE (ms)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Stop-signal Reaction Time POST (ms)	Yes	Yes		Yes	Yes		Yes	Yes	
Stop-signal Reaction Time FOLLOW-UP (ms)	No	Yes		Yes	Yes		Yes	Yes	
Stop-switching SWITCH Score PRE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Stop-switching SWITCH Score POST	Yes	Yes		No	Yes		No	Yes	
Stop-switching SWITCH Score FOLLOW-UP	Yes	Yes		Yes	Yes		Yes	Yes	
Stop-switching SWITCH RT PRE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Stop-switching SWITCH RT POST	Yes	Yes		No	Yes		Yes	Yes	
Stop-switching SWITCH RT FOLLOW-UP	Yes	Yes		No	Yes		Yes	Yes	
Post-Pre Stop-switching GO score	No	Yes	-	Yes	Yes	-	Yes	Yes	-
Post-Pre Stop-switching GO response time	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Post-Pre Stop-switching STOP score	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Post-Pre Stop-signal Reaction Time	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Post-Pre Stop-switching SWITCH Score	Yes	Yes	-	Yes	Yes	-	No	Yes	-
Post-Pre Stop-switching SWITCH response time	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Follow-up-Pre Stop-switching GO score	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Follow-up-Pre Stop-switching GO response time	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Follow-up-Pre Stop-switching STOP score	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Follow-up-Pre Stop-signal Reaction Time	No	Yes	-	Yes	Yes	-	Yes	Yes	-
Follow-up-Pre Stop-switching SWITCH Score	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Follow-up-Pre Stop-switching SWITCH response time	Yes	Yes	-	Yes	Yes	-	No	Yes	-
Matchstick total score (correct answers)	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Matchstick total Response time (correct answers)	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Matchstick Score (first exposition)	No	Yes	-	No	No	-	No	No	-
Matchstick Score (second exposition)	No	Yes	-	Yes	Yes	-	No	Yes	-
Matchstick RT (first exposition)	Yes	Yes	-	Yes	Yes	-	Yes	Yes	-
Matchstick RT (second exposition)	No	Yes	-	No	Yes	-	Yes	No	-
Matchstick Facilitated responses	Yes	Yes	-	No	Yes	-	No	Yes	-
Matchstick Facilitated response percentage	No	Yes	-	Yes	Yes	-	Yes	Yes	-
Matchstick Facilitated response time (ms)	No	Yes	-	Yes	Yes	-	Yes	Yes	-

Table 70. Summary for the normality, homoscedasticity and sphericity tests for video game and cognitive variables used during the data analysis.

8.8.2 By TMS Group

8.8.2.1 Normality

		Shapiro-Wilk		
	Stimulation group	Statistic	df	Sig.
Stars achieved SuperMario64	Sham	.897	13	.123
	iTBS	.823	14	.010
Attempts	Sham	.933	13	.373
	iTBS	.965	14	.803
Performance	Sham	.875	13	.061
	iTBS	.869	14	.041
Time per attempt (s)	Sham	.849	13	.027
	iTBS	.908	14	.150
VG skill (questionnaire) PRE	Sham	.910	13	.185
	iTBS	.922	14	.234
VG skill (questionnaire) POST	Sham	.928	13	.323
	iTBS	.904	14	.127
VG skill (qualitative) PRE	Sham	.949	13	.587
	iTBS	.921	14	.227
VG skill (qualitative) POST	Sham	.919	13	.240
	iTBS	.901	14	.117
Motivation (0-5)	Sham	.902	13	.141
	iTBS	.987	14	.997
Fun (0-5)	Sham	.954	13	.659
	iTBS	.932	14	.328
Frustration (0-5)	Sham	.947	13	.556
	iTBS	.967	14	.836
Simple reaction time PRE (ms)	Sham	.892	13	.103
	iTBS	.934	14	.346
Simple reaction time POST (ms)	Sham	.960	13	.752
	iTBS	.928	14	.282
Simple reaction time FOLLOW-UP (ms)	Sham	.924	13	.282
	iTBS	.908	14	.147
Direction choice reaction time PRE (ms)	Sham	.901	13	.137
	iTBS	.836	14	.014
Direction choice reaction time POST (ms)	Sham	.894	13	.109
	iTBS	.944	14	.475
Direction choice reaction time FOLLOW-UP (ms)	Sham	.863	13	.042
	iTBS	.959	14	.712
Colour choice reaction time PRE (ms)	Sham	.816	13	.011
	iTBS	.965	14	.801
Colour choice reaction time POST (ms)	Sham	.958	13	.723
	iTBS	.955	14	.635
Colour choice reaction time FOLLOW-UP (ms)	Sham	.954	13	.667
	iTBS	.941	14	.432
Forward digits PRE	Sham	.882	13	.077
	iTBS	.936	14	.366
Forward digits POST	Sham	.926	13	.302
	iTBS	.942	14	.446
Forward digits FOLLOW-UP	Sham	.950	13	.601
	iTBS	.850	14	.022
Backward digits PRE	Sham	.959	13	.735
	iTBS	.864	14	.035
Backward digits POST	Sham	.893	13	.108
	iTBS	.894	14	.091
Backward digits FOLLOW-UP	Sham	.939	13	.443
	iTBS	.876	14	.051
Raven Score PRE	Sham	.883	13	.078
	iTBS	.782	14	.003
Raven Score POST	Sham	.914	13	.210
	iTBS	.922	14	.233
Raven RT PRE	Sham	.939	13	.450
	iTBS	.926	14	.270
Raven RT POST	Sham	.970	13	.897
	iTBS	.920	14	.218
Five-Point Test	Sham	.954	13	.655
	iTBS	.917	14	.198
n-back score PRE	Sham	.953	13	.650
	iTBS	.842	14	.017

		Shapiro-Wilk		
	Stimulation group	Statistic	df	Sig.
n-back score POST	Sham	.872	13	.055
	iTBS	.664	14	.000
n-back score FOLLOW-UP	Sham	.972	13	.913
	iTBS	.792	14	.004
n-back RT right answer PRE (ms)	Sham	.870	13	.052
	iTBS	.876	14	.051
n-back RT right answer POST (ms)	Sham	.941	13	.467
	iTBS	.908	14	.149
n-back RT right answer FOLLOW-UP (ms)	Sham	.939	13	.440
	iTBS	.911	14	.164
n-back d prime PRE (ms)	Sham	.902	13	.142
	iTBS	.925	14	.256
n-back d prime POST (ms)	Sham	.942	13	.478
	iTBS	.919	14	.216
n-back d prime FOLLOW-UP (ms)	Sham	.935	13	.398
	iTBS	.922	14	.234
Mental rotation score PRE	Sham	.903	13	.148
	iTBS	.879	14	.056
Mental rotation score POST	Sham	.918	13	.233
	iTBS	.680	14	.000
Mental rotation score FOLLOW-UP	Sham	.952	13	.628
	iTBS	.761	14	.002
Mental rotation RT PRE (ms)	Sham	.965	13	.835
	iTBS	.839	14	.016
Mental rotation RT POST (ms)	Sham	.945	13	.521
	iTBS	.931	14	.318
Mental rotation RT FOLLOW-UP (ms)	Sham	.933	13	.369
	iTBS	.816	14	.008
Stop-switching GO Score PRE	Sham	.897	13	.120
	iTBS	.853	14	.025
Stop-switching GO Score POST	Sham	.633	13	.000
	iTBS	.761	14	.002
Stop-switching GO Score FOLLOW-UP	Sham	.841	13	.022
	iTBS	.830	14	.012
Stop-switching GO RT PRE (ms)	Sham	.977	13	.960
	iTBS	.967	14	.835
Stop-switching GO RT POST (ms)	Sham	.924	13	.286
	iTBS	.917	14	.200
Stop-switching GO RT FOLLOW-UP (ms)	Sham	.923	13	.272
	iTBS	.920	14	.220
Stop-switching STOP Score PRE	Sham	.916	13	.224
	iTBS	.971	14	.890
Stop-switching STOP Score POST	Sham	.813	13	.010
	iTBS	.894	14	.092
Stop-switching STOP Score FOLLOW-UP	Sham	.811	13	.009
	iTBS	.892	14	.087
Stop-signal Reaction Time PRE (ms)	Sham	.943	13	.493
	iTBS	.950	14	.553
Stop-signal Reaction Time POST (ms)	Sham	.957	13	.713
	iTBS	.941	14	.427
Stop-signal Reaction Time FOLLOW-UP (ms)	Sham	.931	13	.354
	iTBS	.870	14	.043
Stop-switching SWITCH Score PRE	Sham	.921	13	.262
	iTBS	.934	14	.348
Stop-switching SWITCH Score POST	Sham	.914	13	.208
	iTBS	.952	14	.592
Stop-switching SWITCH Score FOLLOW-UP	Sham	.883	13	.077
	iTBS	.957	14	.668
Stop-switching SWITCH RT PRE	Sham	.946	13	.542
	iTBS	.911	14	.164
Stop-switching SWITCH RT POST	Sham	.916	13	.219
	iTBS	.906	14	.136
Stop-switching SWITCH RT FOLLOW-UP	Sham	.962	13	.781
	iTBS	.931	14	.313
Matchstick total score (correct answers)	Sham	.952	13	.634
	iTBS	.892	14	.086
Matchstick total Response time (correct answers)	Sham	.955	13	.676
	iTBS	.921	14	.224

		Shapiro-Wilk		
	Stimulation group	Statistic	df	Sig.
Matchstick Score (first exposition)	Sham	.901	13	.139
	iTBS	.708	14	.000
Matchstick Score (second exposition)	Sham	.774	13	.003
	iTBS	.906	14	.140
Matchstick Response time (first exposition)	Sham	.963	13	.798
	iTBS	.964	14	.780
Matchstick Response time (second exposition)	Sham	.772	13	.003
	iTBS	.958	13	.729
Matchstick Facilitated responses	Sham	.883	13	.078
	iTBS	.895	14	.096
Matchstick Facilitated response percentage	Sham	.831	11	.024
	iTBS	.844	11	.035
Matchstick Facilitated response time (ms)	Sham	.736	11	.001
	iTBS	.909	11	.235

Table 71. Normality data for video game and cognitive variables, by TMS group. Shaded variables indicate a violation of the normality assumption.

	Stimulation group	Shapiro-Wilk		
		Statistic	df	Sig.
Post-Pre VGskill (questionnaire)	Sham	0.917	13	0.225
	iTBS	0.923	14	0.240
Post-Pre VGskill (qualitative)	Sham	0.931	13	0.356
	iTBS	0.903	14	0.126
Post-Pre Simple reaction time	Sham	0.904	13	0.153
	iTBS	0.924	14	0.248
Post-Pre Direction choice reaction rime	Sham	0.914	13	0.205
	iTBS	0.953	14	0.609
Post-Pre Color choice reaction time	Sham	0.923	13	0.278
	iTBS	0.948	14	0.527
Post-Pre Forward digits	Sham	0.940	13	0.461
	iTBS	0.945	14	0.483
Post-Pre Backward digits	Sham	0.948	13	0.573
	iTBS	0.917	14	0.199
Post-Pre Raven score	Sham	0.918	13	0.239
	iTBS	0.833	14	0.013
Post-Pre Raven response time	Sham	0.957	13	0.704
	iTBS	0.876	14	0.052
Post-Pre N-back score	Sham	0.944	13	0.514
	iTBS	0.883	14	0.064
Post-Pre N-back reaction time	Sham	0.845	13	0.025
	iTBS	0.959	14	0.704
Post-Pre N-back d'	Sham	0.964	13	0.814
	iTBS	0.972	14	0.905
Post-Pre Mental rotation score	Sham	0.941	13	0.466
	iTBS	0.963	14	0.779
Post-Pre Mental rotation response time	Sham	0.946	13	0.541
	iTBS	0.682	14	0.000
Post-Pre Stop-switching GO score	Sham	0.850	13	0.028
	iTBS	0.977	14	0.950
Post-Pre Stop-switching GO response time	Sham	0.930	13	0.338
	iTBS	0.979	14	0.968
Post-Pre Stop-switching STOP score	Sham	0.959	13	0.732
	iTBS	0.956	14	0.662
Post-Pre Stop-signal Reaction Time	Sham	0.972	13	0.916
	iTBS	0.898	14	0.105
Post-Pre Stop-switching SWITCH Score	Sham	0.930	13	0.337
	iTBS	0.934	14	0.350
Post-Pre Stop-switching SWITCH response time	Sham	0.961	13	0.776
	iTBS	0.942	14	0.443
Follow-up-Pre Simple reaction time	Sham	0.815	13	0.010
	iTBS	0.895	14	0.097
Follow-up-Pre Direction choice reaction rime	Sham	0.986	13	0.997
	iTBS	0.951	14	0.572

		Shapiro-Wilk		
	Stimulation group	Statistic	df	Sig.
Follow-up-Pre Color choice reaction time	Sham	0.965	13	0.825
	iTBS	0.892	14	0.087
Follow-up-Pre Forward digits	Sham	0.908	13	0.174
	iTBS	0.892	14	0.087
Follow-up-Pre Backward digits	Sham	0.950	13	0.604
	iTBS	0.919	14	0.212
Follow-up-Pre N-back score	Sham	0.920	13	0.250
	iTBS	0.951	14	0.581
Follow-up-Pre N-back reaction time	Sham	0.859	13	0.037
	iTBS	0.969	14	0.870
Follow-up-Pre N-back d'	Sham	0.901	13	0.137
	iTBS	0.803	14	0.005
Follow-up-Pre Mental rotation score	Sham	0.940	13	0.458
	iTBS	0.892	14	0.085
Follow-up-Pre Mental rotation response time	Sham	0.920	13	0.251
	iTBS	0.711	14	0.000
Follow-up-Pre Stop-switching GO score	Sham	0.948	13	0.568
	iTBS	0.973	14	0.912
Follow-up-Pre Stop-switching GO response time	Sham	0.923	13	0.278
	iTBS	0.957	14	0.668
Follow-up-Pre Stop-switching STOP score	Sham	0.923	13	0.274
	iTBS	0.928	14	0.290
Follow-up-Pre Stop-signal Reaction Time	Sham	0.966	13	0.844
	iTBS	0.847	14	0.020
Follow-up-Pre Stop-switching SWITCH Score	Sham	0.947	13	0.560
	iTBS	0.933	14	0.334
Follow-up-Pre Stop-switching SWITCH response time	Sham	0.943	13	0.496
	iTBS	0.945	14	0.480

Table 72. Normality data for differential variables (difference between the first and second post-intervention assessments and the baseline), by TMS group. Shaded variables indicate a violation of the normality assumption.

8.8.2.2 Homoscedasticity

Levene Test for Equality of Variances	F	Sig.
Age	2.132	0.157
Stars achieved SuperMario64	0.065	0.800
Attempts	1.785	0.194
Performance	0.638	0.432
Time per attempt (s)	6.996	0.014
VG skill (questionnaire) PRE	0.004	0.948
VG skill (questionnaire) POST	0.440	0.513
VG skill (qualitative) PRE	0.010	0.923
VG skill (qualitative) POST	2.041	0.165
Motivation (0-5)	0.032	0.860
Fun (0-5)	0.016	0.901
Frustration (0-5)	0.948	0.339
Simple reaction time PRE (ms)	0.814	0.375
Simple reaction time POST (ms)	2.624	0.118
Simple reaction time FOLLOW-UP (ms)	2.031	0.166
Direction choice reaction time PRE (ms)	2.373	0.136
Direction choice reaction time POST (ms)	0.558	0.462
Direction choice reaction time FOLLOW-UP (ms)	0.575	0.455
Colour choice reaction time PRE (ms)	1.292	0.266
Colour choice reaction time POST (ms)	5.082	0.033
Colour choice reaction time FOLLOW-UP (ms)	1.314	0.263
Forward digits PRE	1.974	0.172
Forward digits POST	0.193	0.664
Forward digits FOLLOW-UP	5.234	0.031
Backward digits PRE	0.005	0.947
Backward digits POST	0.459	0.504
Backward digits FOLLOW-UP	0.001	0.974

Levene Test for Equality of Variances	F	Sig.
Raven Score PRE	3.406	0.077
Raven Score POST	4.241	0.050
Raven RT PRE	1.200	0.284
Raven RT POST	0.315	0.580
Five-Point Test	0.079	0.781
n-back score PRE	2.878	0.102
n-back score POST	1.730	0.200
n-back score FOLLOW-UP	1.773	0.195
n-back RT right answer PRE (ms)	0.000	0.989
n-back RT right answer POST (ms)	0.236	0.631
n-back RT right answer FOLLOW-UP (ms)	0.598	0.447
n-back d' PRE (ms)	0.701	0.410
n-back d' POST (ms)	0.036	0.851
n-back d' FOLLOW-UP (ms)	0.235	0.632
Mental rotation score PRE	1.027	0.321
Mental rotation score POST	2.393	0.134
Mental rotation score FOLLOW-UP	3.003	0.095
Mental rotation RT PRE (ms)	0.003	0.956
Mental rotation RT POST (ms)	0.074	0.788
Mental rotation RT FOLLOW-UP (ms)	1.409	0.246
Stop-switching GO Score PRE	0.732	0.400
Stop-switching GO Score POST	0.019	0.893
Stop-switching GO Score FOLLOW-UP	0.052	0.822
Stop-switching GO RT PRE (ms)	0.111	0.742
Stop-switching GO RT POST (ms)	0.202	0.657
Stop-switching GO RT FOLLOW-UP (ms)	0.387	0.540
Stop-switching STOP Score PRE	0.065	0.802
Stop-switching STOP Score POST	0.002	0.964
Stop-switching STOP Score FOLLOW-UP	0.403	0.531
Stop-signal Reaction Time PRE (ms)	0.319	0.577
Stop-signal Reaction Time POST (ms)	0.002	0.967
Stop-signal Reaction Time FOLLOW-UP (ms)	0.269	0.608
Stop-switching SWITCH Score PRE	1.056	0.314
Stop-switching SWITCH Score POST	0.018	0.896
Stop-switching SWITCH Score FOLLOW-UP	0.107	0.747
Stop-switching SWITCH RT PRE	0.965	0.335
Stop-switching SWITCH RT POST	1.883	0.182
Stop-switching SWITCH RT FOLLOW-UP	3.590	0.070
Matchstick total score (correct answers)	0.011	0.917
Matchstick total Response time (correct answers)	0.337	0.567
Matchstick Score (first exposition)	0.077	0.784
Matchstick Score (second exposition)	0.989	0.330
Matchstick Facilitated responses	0.080	0.780
Matchstick Facilitated response percentage	1.091	0.309
Matchstick Facilitated response time (ms)	0.951	0.341

Table 73. Homoscedasticity data for video game and cognitive variables, by TMS group. Shaded variables indicate a violation of the equality of variances assumption.

Levene Test for Equality of Variances	F	Sig.
Post-Pre VGskill (questionnaire)	0.207	0.653
Post-Pre VGskill (qualitative)	0.437	0.515
Post-Pre Simple reaction time	0.838	0.369
Post-Pre Direction choice reaction rime	0.055	0.816
Post-Pre Color choice reaction time	1.323	0.261
Post-Pre Forward digits	0.098	0.756
Post-Pre Backward digits	0.035	0.852
Post-Pre Raven score	0.703	0.410
Post-Pre Raven response time	2.838	0.105
Post-Pre N-back score	2.214	0.149
Post-Pre N-back reaction time	0.132	0.720

Levene Test for Equality of Variances	F	Sig.
Post-Pre N-back d'	2.291	0.143
Post-Pre Mental rotation score	4.201	0.051
Post-Pre Mental rotation response time	0.048	0.828
Post-Pre Stop-switching GO score	0.003	0.956
Post-Pre Stop-switching GO response time	3.234	0.084
Post-Pre Stop-switching STOP score	0.875	0.358
Post-Pre Stop-signal Reaction Time	0.738	0.398
Post-Pre Stop-switching SWITCH Score	0.000	0.993
Post-Pre Stop-switching SWITCH response time	3.227	0.085
Follow-up-Pre Simple reaction time	0.117	0.736
Follow-up-Pre Direction choice reaction rime	0.023	0.881
Follow-up-Pre Color choice reaction time	0.020	0.888
Follow-up-Pre Forward digits	2.702	0.113
Follow-up-Pre Backward digits	0.140	0.711
Follow-up-Pre N-back score	2.704	0.113
Follow-up-Pre N-back reaction time	0.930	0.344
Follow-up-Pre N-back d'	1.593	0.219
Follow-up-Pre Mental rotation score	0.024	0.879
Follow-up-Pre Mental rotation response time	5.055	0.034
Follow-up-Pre Stop-switching GO score	0.118	0.735
Follow-up-Pre Stop-switching GO response time	3.702	0.066
Follow-up-Pre Stop-switching STOP score	1.633	0.213
Follow-up-Pre Stop-signal Reaction Time	0.124	0.728
Follow-up-Pre Stop-switching SWITCH Score	2.778	0.108
Follow-up-Pre Stop-switching SWITCH response time	0.265	0.611

Table 74. Homoscedasticity data for differential variables (difference between the first and second post-intervention assessments and the baseline), by TMS group. Shaded variables indicate a violation of the normality assumption.

8.8.2.3 Sphericity

	Pre. Post. Follow-up			
	Mauchly's W	**Chi-squared**	**df**	**p**
Simple reaction time	0.821	4.741	2	0.093
Direction choice reaction time	0.796	5.490	2	0.064
Color choice reaction time	0.981	0.449	2	0.799
Digits (forward)	0.034	1.647	2	0.439
Digits (backward)	0.811	5.037	2	0.081
N-back score	0.597	12.363	2	0.002
N-back RT	0.670	9.594	2	0.008
N-back d'	0.900	2.528	2	0.283
Mental rotation score	0.800	5.366	2	0.068
Mental rotation RT	0.739	7.274	2	0.026
StopSwitching Go score	0.925	1.872	2	0.392
StopSwitching Go RT	0.787	5.750	2	0.056
StopSwitching Stop score	0.742	7.170	2	0.028
StopSwitching SSRT	0.824	4.642	2	0.098
StopSwitching Switch scores	0.870	3.334	2	0.189
StopSwitching Switch RT	0.801	5.312	2	0.070

Table 75. Sphericity data for cognitive variables, by TMS group across the three time points. Shaded variables indicate a violation of the sphericity assumption.

8.8.3 By previous video game experience

8.8.3.1 Normality

Previous video game experience		Shapiro-Wilk		
		Statistic	df	Sig.
Stars achieved SuperMario64	No	.743	15	.001
	Yes	.905	12	.182
Attempts	No	.931	15	.284
	Yes	.952	12	.671
Performance	No	.779	15	.002
	Yes	.929	12	.366
Time per attempt (s)	No	.817	15	.006

Previous video game experience		Shapiro-Wilk		
		Statistic	df	Sig.
	Yes	.895	12	.137
VG skill (questionnaire) PRE	No	.855	15	.020
	Yes	.915	12	.244
VG skill (questionnaire) POST	No	.944	15	.440
	Yes	.964	12	.845
VG skill (qualitative) PRE	No	.847	15	.016
	Yes	.973	12	.936
VG skill (qualitative) POST	No	.911	15	.140
	Yes	.938	12	.475
Motivation (0-5)	No	.968	15	.820
	Yes	.955	12	.714
Fun (0-5)	No	.951	15	.544
	Yes	.934	12	.421
Frustration (0-5)	No	.941	15	.398
	Yes	.966	12	.862
Simple reaction time PRE (ms)	No	.961	15	.703
	Yes	.914	12	.243
Simple reaction time POST (ms)	No	.899	15	.091
	Yes	.979	12	.979
Simple reaction time FOLLOW-UP (ms)	No	.918	15	.178
	Yes	.940	12	.492
Direction choice reaction time PRE (ms)	No	.840	15	.013
	Yes	.874	12	.074
Direction choice reaction time POST (ms)	No	.959	15	.669
	Yes	.900	12	.158
Direction choice reaction time FOLLOW-UP (ms)	No	.956	15	.628
	Yes	.959	12	.773
Colour choice reaction time PRE (ms)	No	.951	15	.540
	Yes	.958	12	.754
Colour choice reaction time POST (ms)	No	.937	15	.344
	Yes	.929	12	.370
Colour choice reaction time FOLLOW-UP (ms)	No	.928	15	.257
	Yes	.947	12	.592
Forward digits PRE	No	.934	15	.318
	Yes	.935	12	.432
Forward digits POST	No	.949	15	.514
	Yes	.919	12	.281
Forward digits FOLLOW-UP	No	.943	15	.418
	Yes	.933	12	.416
Backward digits PRE	No	.949	15	.504
	Yes	.923	12	.308
Backward digits POST	No	.930	15	.273
	Yes	.971	12	.919
Backward digits FOLLOW-UP	No	.924	15	.225
	Yes	.905	12	.183
Raven Score PRE	No	.861	15	.025
	Yes	.707	12	.001
Raven Score POST	No	.925	15	.231
	Yes	.861	12	.050
Raven RT PRE	No	.848	15	.016
	Yes	.967	12	.873
Raven RT POST	No	.982	15	.979
	Yes	.927	12	.352
Five-Point Test	No	.938	15	.356
	Yes	.935	12	.431
n-back score PRE	No	.915	15	.163
	Yes	.836	12	.025
n-back score POST	No	.807	15	.004
	Yes	.958	12	.748
n-back score FOLLOW-UP	No	.811	15	.005
	Yes	.860	12	.049
n-back RT right answer PRE (ms)	No	.908	15	.125
	Yes	.803	12	.010
n-back RT right answer POST (ms)	No	.967	15	.816
	Yes	.878	12	.082
n-back RT right answer FOLLOW-UP (ms)	No	.943	15	.426

	Previous video game experience	Shapiro-Wilk		
		Statistic	df	Sig.
	Yes	.897	12	.145
n-back d prime PRE (ms)	No	.929	15	.267
	Yes	.868	12	.061
n-back d prime POST (ms)	No	.941	15	.393
	Yes	.932	12	.404
n-back d prime FOLLOW-UP (ms)	No	.937	15	.343
	Yes	.958	12	.751
Mental rotation score PRE	No	.931	15	.281
	Yes	.688	12	.001
Mental rotation score POST	No	.893	15	.074
	Yes	.550	12	.000
Mental rotation score FOLLOW-UP	No	.928	15	.252
	Yes	.604	12	.000
Mental rotation RT PRE (ms)	No	.905	15	.114
	Yes	.969	12	.895
Mental rotation RT POST (ms)	No	.905	15	.113
	Yes	.960	12	.781
Mental rotation RT FOLLOW-UP (ms)	No	.736	15	.001
	Yes	.960	12	.791
Stop-switching GO Score PRE	No	.865	15	.028
	Yes	.922	12	.305
Stop-switching GO Score POST	No	.695	15	.000
	Yes	.769	12	.004
Stop-switching GO Score FOLLOW-UP	No	.876	15	.042
	Yes	.746	12	.002
Stop-switching GO RT PRE (ms)	No	.954	15	.593
	Yes	.944	12	.556
Stop-switching GO RT POST (ms)	No	.905	15	.112
	Yes	.875	12	.076
Stop-switching GO RT FOLLOW-UP (ms)	No	.939	15	.371
	Yes	.957	12	.733
Stop-switching STOP Score PRE	No	.955	15	.602
	Yes	.950	12	.634
Stop-switching STOP Score POST	No	.730	15	.001
	Yes	.910	12	.216
Stop-switching STOP Score FOLLOW-UP	No	.805	15	.004
	Yes	.888	12	.110
Stop-signal Reaction Time PRE (ms)	No	.967	15	.809
	Yes	.947	12	.589
Stop-signal Reaction Time POST (ms)	No	.954	15	.594
	Yes	.951	12	.655
Stop-signal Reaction Time FOLLOW-UP (ms)	No	.932	15	.291
	Yes	.952	12	.666
Stop-switching SWITCH Score PRE	No	.937	15	.343
	Yes	.936	12	.447
Stop-switching SWITCH Score POST	No	.911	15	.142
	Yes	.848	12	.034
Stop-switching SWITCH Score FOLLOW-UP	No	.946	15	.462
	Yes	.897	12	.145
Stop-switching SWITCH RT PRE	No	.956	15	.621
	Yes	.954	12	.698
Stop-switching SWITCH RT POST	No	.856	15	.021
	Yes	.932	12	.405
Stop-switching SWITCH RT FOLLOW-UP	No	.874	15	.038
	Yes	.972	12	.931
Matchstick total score (correct answers)	No	.942	15	.409
	Yes	.929	12	.370
Matchstick total Response time (correct answers)	No	.933	15	.303
	Yes	.921	12	.291
Matchstick Score (first exposition)	No	.811	15	.005
	Yes	.809	12	.012
Matchstick Score (second exposition)	No	.898	15	.089
	Yes	.862	12	.051
Matchstick Facilitated responses	No	.881	15	.050
	Yes	.865	12	.056
Matchstick Facilitated response percentage	No	.885	11	.120

	Previous video game experience	Shapiro-Wilk		
		Statistic	df	Sig.
	Yes	.864	11	.066
Matchstick Facilitated response time (ms)	No	.976	11	.939
	Yes	.963	11	.812

Table 76. Normality data for video game and cognitive variables, by previous video game experience. Shaded variables indicate a violation of the normality assumption.

	Previous video game experience	Shapiro-Wilk		
		Statistic	df	Sig.
Post-Pre VGskill (questionnaire)	No	.916	15	.166
	Yes	.911	12	.217
Post-Pre VGskill (qualitative)	No	.891	15	.070
	Yes	.900	12	.156
Post-Pre Simple reaction time	No	0.846	15	0.015
	Yes	0.952	12	0.671
Post-Pre Direction choice reaction rime	No	0.951	15	0.548
	Yes	0.937	12	0.463
Post-Pre Color choice reaction time	No	0.967	15	0.813
	Yes	0.915	12	0.245
Post-Pre Forward digits	No	0.839	15	0.012
	Yes	0.944	12	0.551
Post-Pre Backward digits	No	0.899	15	0.093
	Yes	0.844	12	0.031
Post-Pre Raven score	No	0.909	15	0.130
	Yes	0.730	12	0.002
Post-Pre Raven response time	No	0.914	15	0.155
	Yes	0.949	12	0.620
Post-Pre N-back score	No	0.777	15	0.002
	Yes	0.787	12	0.007
Post-Pre N-back reaction time	No	0.948	15	0.501
	Yes	0.914	12	0.237
Post-Pre N-back d'	No	0.982	15	0.982
	Yes	0.953	12	0.678
Post-Pre Mental rotation score	No	0.953	15	0.570
	Yes	0.939	12	0.482
Post-Pre Mental rotation response time	No	0.846	15	0.015
	Yes	0.880	12	0.089
Post-Pre Stop-switching GO score	No	0.922	15	0.208
	Yes	0.882	12	0.093
Post-Pre Stop-switching GO response time	No	0.977	15	0.945
	Yes	0.920	12	0.288
Post-Pre Stop-switching STOP score	No	0.953	15	0.569
	Yes	0.897	12	0.147
Post-Pre Stop-signal Reaction Time	No	0.944	15	0.431
	Yes	0.973	12	0.940
Post-Pre Stop-switching SWITCH Score	No	0.961	15	0.712
	Yes	0.934	12	0.422
Post-Pre Stop-switching SWITCH response time	No	0.946	15	0.462
	Yes	0.903	12	0.171
Follow-up-Pre Simple reaction time	No	0.895	15	0.081
	Yes	0.886	12	0.106
Follow-up-Pre Direction choice reaction rime	No	0.921	15	0.197
	Yes	0.945	12	0.566
Follow-up-Pre Color choice reaction time	No	0.948	15	0.493
	Yes	0.973	12	0.937
Follow-up-Pre Forward digits	No	0.917	15	0.171
	Yes	0.930	12	0.375
Follow-up-Pre Backward digits	No	0.952	15	0.564
	Yes	0.934	12	0.429
Follow-up-Pre N-back score	No	0.928	15	0.258
	Yes	0.956	12	0.724
Follow-up-Pre N-back reaction time	No	0.922	15	0.203
	Yes	0.823	12	0.017
Follow-up-Pre N-back d'	No	0.849	15	0.017
	Yes	0.913	12	0.232

	Previous video game experience	Shapiro-Wilk		
		Statistic	df	Sig.
Follow-up-Pre Mental rotation score	No	0.963	15	0.741
	Yes	0.939	12	0.491
Follow-up-Pre Mental rotation response time	No	0.907	15	0.121
	Yes	0.912	12	0.226
Follow-up-Pre Stop-switching GO score	No	0.931	15	0.278
	Yes	0.939	12	0.490
Follow-up-Pre Stop-switching GO response time	No	0.925	15	0.229
	Yes	0.943	12	0.540
Follow-up-Pre Stop-switching STOP score	No	0.896	15	0.082
	Yes	0.931	12	0.394
Follow-up-Pre Stop-signal Reaction Time	No	0.941	15	0.397
	Yes	0.949	12	0.622
Follow-up-Pre Stop-switching SWITCH Score	No	0.931	15	0.284
	Yes	0.961	12	0.795
Follow-up-Pre Stop-switching SWITCH response time	No	0.913	15	0.150
	Yes	0.930	12	0.379

Table 77. Normality data for differential variables (difference between the first and second post-intervention assessments and the baseline), by previous video game experience. Shaded variables indicate a violation of the normality assumption.

8.8.3.2 Homoscedasticity

Levene Test for Equality of Variances	F	Sig.
Age	2.297	0.142
Stars achieved SuperMario64	1.625	0.214
Attempts	0.434	0.616
Performance	0.224	0.640
Time per attempt (s)	3.586	0.070
VG skill (questionnaire) PRE	0.187	0.669
VG skill (questionnaire) POST	2.982	0.097
VG skill (qualitative) PRE	0.197	0.661
VG skill (qualitative) POST	3.305	0.081
Motivation (0-5)	0.178	0.676
Fun (0-5)	0.028	0.868
Frustration (0-5)	1.130	0.298
Simple reaction time PRE (ms)	0.009	0.924
Simple reaction time POST (ms)	0.562	0.460
Simple reaction time FOLLOW-UP (ms)	0.561	0.461
Direction choice reaction time PRE (ms)	0.250	0.622
Direction choice reaction time POST (ms)	0.040	0.843
Direction choice reaction time FOLLOW-UP (ms)	1.638	0.212
Colour choice reaction time PRE (ms)	0.001	0.982
Colour choice reaction time POST (ms)	1.312	0.263
Colour choice reaction time FOLLOW-UP (ms)	0.027	0.872
Forward digits PRE	0.359	0.555
Forward digits POST	0.434	0.516
Forward digits FOLLOW-UP	0.117	0.735
Backward digits PRE	1.053	0.315
Backward digits POST	0.725	0.403
Backward digits FOLLOW-UP	2.626	0.118
Raven Score PRE	1.677	0.207
Raven Score POST	0.020	0.889
Raven RT PRE	0.030	0.863
Raven RT POST	0.290	0.595
Five-Point Test	0.714	0.406
n-back score PRE	0.239	0.629
n-back score POST	8.975	0.006
n-back score FOLLOW-UP	0.230	0.635
n-back RT right answer PRE (ms)	1.308	0.264
n-back RT right answer POST (ms)	0.304	0.586
n-back RT right answer FOLLOW-UP (ms)	0.600	0.446
n-back d' PRE (ms)	1.768	0.196
n-back d' POST (ms)	0.005	0.946
n-back d' FOLLOW-UP (ms)	0.890	0.354

Levene Test for Equality of Variances	F	Sig.
Mental rotation score PRE	1.092	0.306
Mental rotation score POST	0.626	0.436
Mental rotation score FOLLOW-UP	0.914	0.348
Mental rotation RT PRE (ms)	0.881	0.357
Mental rotation RT POST (ms)	0.025	0.875
Mental rotation RT FOLLOW-UP (ms)	0.754	0.393
Stop-switching GO Score PRE	0.362	0.553
Stop-switching GO Score POST	1.025	0.321
Stop-switching GO Score FOLLOW-UP	0.274	0.605
Stop-switching GO RT PRE (ms)	0.291	0.594
Stop-switching GO RT POST (ms)	0.007	0.936
Stop-switching GO RT FOLLOW-UP (ms)	0.614	0.441
Stop-switching STOP Score PRE	0.466	0.501
Stop-switching STOP Score POST	0.010	0.923
Stop-switching STOP Score FOLLOW-UP	0.047	0.830
Stop-signal Reaction Time PRE (ms)	0.167	0.686
Stop-signal Reaction Time POST (ms)	0.664	0.423
Stop-signal Reaction Time FOLLOW-UP (ms)	0.127	0.724
Stop-switching SWITCH Score PRE	0.655	0.426
Stop-switching SWITCH Score POST	0.125	0.726
Stop-switching SWITCH Score FOLLOW-UP	0.077	0.784
Stop-switching SWITCH RT PRE	0.450	0.509
Stop-switching SWITCH RT POST	0.144	0.708
Stop-switching SWITCH RT FOLLOW-UP	0.739	0.398
Matchstick total score (correct answers)	2.525	0.125
Matchstick total Response time (correct answers)	1.396	0.248
Matchstick Score (first exposition)	8.109	0.009
Matchstick Score (second exposition)	3.472	0.074
Matchstick Facilitated responses	0.148	0.704
Matchstick Facilitated response percentage	0.023	0.882
Matchstick Facilitated response time (ms)	1.335	0.262

Table 78. Homoscedasticity data for video game and cognitive variables by previous video game experience. Shaded variables indicate a violation of the equality of variances assumption.

Levene Test for Equality of Variances	F	Sig.
Post-Pre VGskill (questionnaire)	0.375	0.546
Post-Pre VGskill (qualitative)	0.014	0.907
Post-Pre Simple reaction time	0.142	0.710
Post-Pre Direction choice reaction rime	0.070	0.794
Post-Pre Color choice reaction time	2.430	0.132
Post-Pre Forward digits	8.242	0.008
Post-Pre Backward digits	1.522	0.229
Post-Pre Raven score	0.010	0.922
Post-Pre Raven response time	0.074	0.788
Post-Pre N-back score	0.567	0.459
Post-Pre N-back reaction time	1.775	0.195
Post-Pre N-back d'	0.794	0.381
Post-Pre Mental rotation score	0.379	0.544
Post-Pre Mental rotation response time	1.021	0.322
Post-Pre Stop-switching GO score	0.926	0.345
Post-Pre Stop-switching GO response time	1.917	0.178
Post-Pre Stop-switching STOP score	0.543	0.468
Post-Pre Stop-signal Reaction Time	0.934	0.343
Post-Pre Stop-switching SWITCH Score	0.377	0.545
Post-Pre Stop-switching SWITCH response time	1.140	0.296
Follow-up-Pre Simple reaction time	0.105	0.748
Follow-up-Pre Direction choice reaction rime	1.343	0.258
Follow-up-Pre Color choice reaction time	0.210	0.651
Follow-up-Pre Forward digits	1.013	0.324
Follow-up-Pre Backward digits	3.148	0.088
Follow-up-Pre N-back score	0.626	0.436
Follow-up-Pre N-back reaction time	0.112	0.740
Follow-up-Pre N-back d'	0.361	0.553
Follow-up-Pre Mental rotation score	1.147	0.294

Levene Test for Equality of Variances	F	Sig.
Follow-up-Pre Mental rotation response time	0.227	0.638
Follow-up-Pre Stop-switching GO score	0.009	0.923
Follow-up-Pre Stop-switching GO response time	0.003	0.960
Follow-up-Pre Stop-switching STOP score	2.621	0.118
Follow-up-Pre Stop-signal Reaction Time	0.116	0.736
Follow-up-Pre Stop-switching SWITCH Score	1.243	0.276
Follow-up-Pre Stop-switching SWITCH response time	0.004	0.948

Table 79. Homoscedasticity data for differential variables (difference between the first and second post-intervention assessments and the baseline), by previous video game experience. Shaded variables indicate a violation of the equality of variances assumption.

8.8.3.3 Sphericity

	Pre. Post. Follow-up			
	Mauchly's W	**Chi-squared**	**df**	**p**
Simple reaction time	0.801	5.317	2	0.070
Direction choice reaction time	0.77	6.276	2	0.043
Color choice reaction time	0.986	0.345	2	0.842
Digits (forward)	0.897	2.606	2	0.272
Digits (backward)	0.786	5.788	2	0.055
N-back score	0.707	8.325	2	0.016
N-back RT	0.662	9.911	2	0.007
N-back d'	0.843	4.108	2	0.128
Mental rotation score	0.768	5.778	2	0.056
Mental rotation RT	0.728	7.606	2	0.022
StopSwitching Go score	0.921	1.985	2	0.371
StopSwitching Go RT	0.759	6.605	2	0.037
StopSwitching Stop score	0.72	7.887	2	0.019
StopSwitching SSRT	0.784	5.845	2	0.054
StopSwitching Switch scores	0.849	3.933	2	0.140
StopSwitching Switch RT	0.808	5.11	2	0.078

Table 80. Sphericity data for cognitive variables, by previous video game experience across the three time points. Shaded variables indicate a violation of the sphericity assumption.

8.8.4 By TMS x Previous video game experience

8.8.4.1 Normality

	TMS + Previous VG experience	Shapiro-Wilk		
		statistic	df	Sig.
Age	Sham+NoExp	0.945	7	0.683
	Sham+Exp	0.809	6	0.070
	iTBS+NoExp	0.897	8	0.273
	iTBS+Exp	0.939	6	0.650
Stars achieved SuperMario64	Sham+NoExp	0.873	7	0.197
	Sham+Exp	0.983	6	0.964
	iTBS+NoExp	0.771	8	0.014
	iTBS+Exp	0.839	6	0.127
Attempts	Sham+NoExp	.879	7	0.220
	Sham+Exp	.979	6	0.946
	iTBS+NoExp	.947	8	0.685
	iTBS+Exp	.950	6	0.737
Performance	Sham+NoExp	.743	7	0.011
	Sham+Exp	.979	6	0.945
	iTBS+NoExp	.763	8	0.011
	iTBS+Exp	.937	6	0.636
Time per attempt (s)	Sham+NoExp	.923	7	0.494
	Sham+Exp	.835	6	0.119
	iTBS+NoExp	.847	8	0.089
	iTBS+Exp	.963	6	0.844
VG skill (questionnaire) PRE	Sham+NoExp	0.813	7	0.055
	Sham+Exp	0.869	6	0.221
	iTBS+NoExp	0.886	8	0.216
	iTBS+Exp	0.814	6	0.079
VG skill (questionnaire) POST	Sham+NoExp	0.901	7	0.339

	TMS + Previous VG experience	Shapiro-Wilk		
		statistic	df	Sig.
	Sham+Exp	0.871	6	0.230
	iTBS+NoExp	0.906	8	0.328
	iTBS+Exp	0.921	6	0.514
VG skill (qualitative) PRE	Sham+NoExp	0.849	7	0.119
	Sham+Exp	0.857	6	0.178
	iTBS+NoExp	0.891	8	0.239
	iTBS+Exp	0.982	6	0.961
VG skill (qualitative) POST	Sham+NoExp	0.908	7	0.380
	Sham+Exp	0.827	6	0.101
	iTBS+NoExp	0.893	8	0.248
	iTBS+Exp	0.878	6	0.261
Motivation (0-5)	Sham+NoExp	0.907	7	0.378
	Sham+Exp	0.889	6	0.315
	iTBS+NoExp	0.965	8	0.856
	iTBS+Exp	0.981	6	0.958
Fun (0-5)	Sham+NoExp	0.894	7	0.294
	Sham+Exp	0.973	6	0.911
	iTBS+NoExp	0.959	8	0.802
	iTBS+Exp	0.811	6	0.073
Frustration (0-5)	Sham+NoExp	0.870	7	0.184
	Sham+Exp	0.872	6	0.233
	iTBS+NoExp	0.992	8	0.998
	iTBS+Exp	0.943	6	0.685
Simple reaction time PRE (ms)	Sham+NoExp	0.888	7	0.263
	Sham+Exp	0.855	6	0.171
	iTBS+NoExp	0.960	8	0.807
	iTBS+Exp	0.834	6	0.115
Simple reaction time POST (ms)	Sham+NoExp	0.880	7	0.227
	Sham+Exp	0.964	6	0.848
	iTBS+NoExp	0.880	8	0.189
	iTBS+Exp	0.904	6	0.399
Simple reaction time FOLLOW-UP (ms)	Sham+NoExp	0.872	7	0.195
	Sham+Exp	0.929	6	0.576
	iTBS+NoExp	0.888	8	0.225
	iTBS+Exp	0.878	6	0.261
Direction choice reaction time PRE (ms)	Sham+NoExp	0.942	7	0.657
	Sham+Exp	0.888	6	0.307
	iTBS+NoExp	0.697	8	0.002
	iTBS+Exp	0.855	6	0.174
Direction choice reaction time POST (ms)	Sham+NoExp	0.916	7	0.437
	Sham+Exp	0.791	6	0.049
	iTBS+NoExp	0.931	8	0.526
	iTBS+Exp	0.866	6	0.211
Direction choice reaction time FOLLOW-UP (ms)	Sham+NoExp	0.864	7	0.166
	Sham+Exp	0.930	6	0.582
	iTBS+NoExp	0.964	8	0.846
	iTBS+Exp	0.939	6	0.653
Colour choice reaction time PRE (ms)	Sham+NoExp	0.790	7	0.032
	Sham+Exp	0.951	6	0.746
	iTBS+NoExp	0.924	8	0.467
	iTBS+Exp	0.862	6	0.196
Colour choice reaction time POST (ms)	Sham+NoExp	0.913	7	0.414
	Sham+Exp	0.926	6	0.547
	iTBS+NoExp	0.932	8	0.530
	iTBS+Exp	0.919	6	0.498
Colour choice reaction time FOLLOW-UP (ms)	Sham+NoExp	0.968	7	0.883
	Sham+Exp	0.802	6	0.062
	iTBS+NoExp	0.868	8	0.144
	iTBS+Exp	0.944	6	0.694
Forward digits PRE	Sham+NoExp	0.864	7	0.164
	Sham+Exp	0.975	6	0.926
	iTBS+NoExp	0.848	8	0.090
	iTBS+Exp	0.927	6	0.557
Forward digits POST	Sham+NoExp	0.926	7	0.519
	Sham+Exp	0.709	6	0.008

	TMS + Previous VG experience	Shapiro-Wilk		
		statistic	df	Sig.
	iTBS+NoExp	0.938	8	0.592
	iTBS+Exp	0.996	6	0.998
Forward digits FOLLOW-UP	Sham+NoExp	0.922	7	0.489
	Sham+Exp	0.921	6	0.514
	iTBS+NoExp	0.877	8	0.178
	iTBS+Exp	0.863	6	0.201
Backward digits PRE	Sham+NoExp	0.914	7	0.423
	Sham+Exp	0.983	6	0.964
	iTBS+NoExp	0.931	8	0.521
	iTBS+Exp	0.929	6	0.574
Backward digits POST	Sham+NoExp	0.908	7	0.380
	Sham+Exp	0.912	6	0.452
	iTBS+NoExp	0.808	8	0.035
	iTBS+Exp	0.958	6	0.801
Backward digits FOLLOW-UP	Sham+NoExp	0.907	7	0.377
	Sham+Exp	0.958	6	0.807
	iTBS+NoExp	0.939	8	0.600
	iTBS+Exp	0.852	6	0.164
Raven Score PRE	Sham+NoExp	0.856	7	0.139
	Sham+Exp	0.915	6	0.473
	iTBS+NoExp	0.906	8	0.325
	iTBS+Exp	0.663	6	0.002
Raven Score POST	Sham+NoExp	0.932	7	0.567
	Sham+Exp	0.739	6	0.015
	iTBS+NoExp	0.927	8	0.492
	iTBS+Exp	0.891	6	0.325
Raven RT PRE	Sham+NoExp	0.855	7	0.135
	Sham+Exp	0.977	6	0.937
	iTBS+NoExp	0.861	8	0.123
	iTBS+Exp	0.978	6	0.942
Raven RT POST	Sham+NoExp	0.975	7	0.930
	Sham+Exp	0.917	6	0.482
	iTBS+NoExp	0.925	8	0.471
	iTBS+Exp	0.908	6	0.424
Five-Point Test	Sham+NoExp	0.925	7	0.508
	Sham+Exp	0.995	6	0.998
	iTBS+NoExp	0.742	8	0.007
	iTBS+Exp	0.954	6	0.773
n-back score PRE	Sham+NoExp	0.915	7	0.430
	Sham+Exp	0.850	6	0.158
	iTBS+NoExp	0.875	8	0.169
	iTBS+Exp	0.786	6	0.044
n-back score POST	Sham+NoExp	0.921	7	0.480
	Sham+Exp	0.889	6	0.315
	iTBS+NoExp	0.766	8	0.012
	iTBS+Exp	0.894	6	0.342
n-back score FOLLOW-UP	Sham+NoExp	0.985	7	0.979
	Sham+Exp	0.966	6	0.863
	iTBS+NoExp	0.724	8	0.004
	iTBS+Exp	0.794	6	0.052
n-back RT right answer PRE (ms)	Sham+NoExp	0.910	7	0.393
	Sham+Exp	0.741	6	0.016
	iTBS+NoExp	0.924	8	0.463
	iTBS+Exp	0.822	6	0.093
n-back RT right answer POST (ms)	Sham+NoExp	0.876	7	0.211
	Sham+Exp	0.789	6	0.047
	iTBS+NoExp	0.925	8	0.475
	iTBS+Exp	0.890	6	0.320
n-back RT right answer FOLLOW-UP (ms)	Sham+NoExp	0.790	7	0.032
	Sham+Exp	0.872	6	0.234
	iTBS+NoExp	0.925	8	0.469
	iTBS+Exp	0.897	6	0.356
n-back d prime PRE (ms)	Sham+NoExp	0.889	7	0.267
	Sham+Exp	0.701	6	0.006
	iTBS+NoExp	0.876	8	0.171

TMS + Previous VG experience		Shapiro-Wilk		
		statistic	df	Sig.
	iTBS+Exp	0.995	6	0.998
n-back d prime POST (ms)	Sham+NoExp	0.970	7	0.898
	Sham+Exp	0.901	6	0.377
	iTBS+NoExp	0.912	8	0.372
	iTBS+Exp	0.962	6	0.838
n-back d prime FOLLOW-UP (ms)	Sham+NoExp	0.923	7	0.490
	Sham+Exp	0.902	6	0.385
	iTBS+NoExp	0.876	8	0.174
	iTBS+Exp	0.965	6	0.859
Mental rotation score PRE	Sham+NoExp	0.810	7	0.051
	Sham+Exp	0.860	6	0.187
	iTBS+NoExp	0.935	8	0.562
	iTBS+Exp	0.709	6	0.008
Mental rotation score POST	Sham+NoExp	0.976	7	0.940
	Sham+Exp	0.799	6	0.058
	iTBS+NoExp	0.766	8	0.012
	iTBS+Exp	0.605	6	0.001
Mental rotation score FOLLOW-UP	Sham+NoExp	0.973	7	0.921
	Sham+Exp	0.921	6	0.516
	iTBS+NoExp	0.911	8	0.364
	iTBS+Exp	0.670	6	0.003
Mental rotation RT PRE (ms)	Sham+NoExp	0.919	7	0.465
	Sham+Exp	0.938	6	0.641
	iTBS+NoExp	0.815	8	0.041
	iTBS+Exp	0.938	6	0.641
Mental rotation RT POST (ms)	Sham+NoExp	0.812	7	0.054
	Sham+Exp	0.954	6	0.769
	iTBS+NoExp	0.933	8	0.540
	iTBS+Exp	0.980	6	0.951
Mental rotation RT FOLLOW-UP (ms)	Sham+NoExp	0.802	7	0.043
	Sham+Exp	0.909	6	0.429
	iTBS+NoExp	0.814	8	0.040
	iTBS+Exp	0.933	6	0.607
Stop-switching GO Score PRE	Sham+NoExp	0.908	7	0.380
	Sham+Exp	0.908	6	0.425
	iTBS+NoExp	0.866	8	0.139
	iTBS+Exp	0.907	6	0.415
Stop-switching GO Score POST	Sham+NoExp	0.617	7	0.000
	Sham+Exp	0.908	6	0.421
	iTBS+NoExp	0.788	8	0.021
	iTBS+Exp	0.739	6	0.015
Stop-switching GO Score FOLLOW-UP	Sham+NoExp	0.922	7	0.482
	Sham+Exp	0.640	6	0.001
	iTBS+NoExp	0.882	8	0.197
	iTBS+Exp	0.815	6	0.080
Stop-switching GO RT PRE (ms)	Sham+NoExp	0.970	7	0.901
	Sham+Exp	0.953	6	0.762
	iTBS+NoExp	0.901	8	0.297
	iTBS+Exp	0.875	6	0.247
Stop-switching GO RT POST (ms)	Sham+NoExp	0.841	7	0.101
	Sham+Exp	0.832	6	0.112
	iTBS+NoExp	0.890	8	0.232
	iTBS+Exp	0.887	6	0.305
Stop-switching GO RT FOLLOW-UP (ms)	Sham+NoExp	0.910	7	0.398
	Sham+Exp	0.914	6	0.466
	iTBS+NoExp	0.875	8	0.167
	iTBS+Exp	0.964	6	0.851
Stop-switching STOP Score PRE	Sham+NoExp	0.834	7	0.088
	Sham+Exp	0.841	6	0.133
	iTBS+NoExp	0.917	8	0.409
	iTBS+Exp	0.928	6	0.566
Stop-switching STOP Score POST	Sham+NoExp	0.682	7	0.002
	Sham+Exp	0.841	6	0.133
	iTBS+NoExp	0.776	8	0.016
	iTBS+Exp	0.959	6	0.811

	TMS + Previous VG experience	Shapiro-Wilk		
		statistic	df	Sig.
Stop-switching STOP Score FOLLOW-UP	Sham+NoExp	0.788	7	0.031
	Sham+Exp	0.872	6	0.232
	iTBS+NoExp	0.917	8	0.408
	iTBS+Exp	0.878	6	0.261
Stop-signal Reaction Time PRE (ms)	Sham+NoExp	0.848	7	0.118
	Sham+Exp	0.966	6	0.865
	iTBS+NoExp	0.890	8	0.236
	iTBS+Exp	0.922	6	0.522
Stop-signal Reaction Time POST (ms)	Sham+NoExp	0.978	7	0.947
	Sham+Exp	0.939	6	0.650
	iTBS+NoExp	0.938	8	0.587
	iTBS+Exp	0.950	6	0.743
Stop-signal Reaction Time FOLLOW-UP (ms)	Sham+NoExp	0.915	7	0.435
	Sham+Exp	0.908	6	0.426
	iTBS+NoExp	0.861	8	0.122
	iTBS+Exp	0.923	6	0.527
Stop-switching SWITCH Score PRE	Sham+NoExp	0.976	7	0.936
	Sham+Exp	0.804	6	0.064
	iTBS+NoExp	0.843	8	0.081
	iTBS+Exp	0.865	6	0.207
Stop-switching SWITCH Score POST	Sham+NoExp	0.891	7	0.280
	Sham+Exp	0.787	6	0.045
	iTBS+NoExp	0.932	8	0.535
	iTBS+Exp	0.899	6	0.371
Stop-switching SWITCH Score FOLLOW-UP	Sham+NoExp	0.895	7	0.301
	Sham+Exp	0.896	6	0.353
	iTBS+NoExp	0.978	8	0.955
	iTBS+Exp	0.885	6	0.292
Stop-switching SWITCH RT PRE	Sham+NoExp	0.904	7	0.356
	Sham+Exp	0.978	6	0.943
	iTBS+NoExp	0.891	8	0.237
	iTBS+Exp	0.830	6	0.108
Stop-switching SWITCH RT POST	Sham+NoExp	0.890	7	0.276
	Sham+Exp	0.964	6	0.849
	iTBS+NoExp	0.917	8	0.408
	iTBS+Exp	0.804	6	0.064
Stop-switching SWITCH RT FOLLOW-UP	Sham+NoExp	0.936	7	0.600
	Sham+Exp	0.880	6	0.269
	iTBS+NoExp	0.857	8	0.112
	iTBS+Exp	0.906	6	0.409
Matchstick total score (correct answers)	Sham+NoExp	.978	7	.948
	Sham+Exp	.974	6	.918
	iTBS+NoExp	.894	8	.254
	iTBS+Exp	.908	6	.421
Matchstick total Response time (correct answers)	Sham+NoExp	.911	7	.401
	Sham+Exp	.921	6	.514
	iTBS+NoExp	.936	8	.571
	iTBS+Exp	.881	6	.272
Matchstick Score (first exposition)	Sham+NoExp	.922	7	.482
	Sham+Exp	.822	6	.091
	iTBS+NoExp	.665	8	.001
	iTBS+Exp	.496	6	.000
Matchstick Score (second exposition)	Sham+NoExp	.794	7	.036
	Sham+Exp	.814	6	.078
	iTBS+NoExp	.930	8	.516
	iTBS+Exp	.853	6	.167
Matchstick Facilitated responses	Sham+NoExp	.937	7	.609
	Sham+Exp	.770	6	.031
	iTBS+NoExp	.835	8	.067
	iTBS+Exp	.853	6	.167
Matchstick Facilitated response percentage	Sham+NoExp	.891	6	.324
	Sham+Exp	.782	5	.057
	iTBS+NoExp	.881	5	.314
	iTBS+Exp	.902	6	.389
Matchstick Facilitated response time (ms)	Sham+NoExp	.822	6	.092

TMS + Previous VG experience		Shapiro-Wilk		
		statistic	df	Sig.
	Sham+Exp	.841	5	.168
	iTBS+NoExp	.793	5	.070
	iTBS+Exp	.920	6	.506

Table 81. Normality data for video game and cognitive variables, by TMS group and previous video game experience. Shaded variables indicate a violation of the normality assumption.

TMS + Previous VG experience		Shapiro-Wilk		
		Statistic	df	Sig.
Post-Pre VGskill (questionnaire)	Sham+NoExp	0.939	7	0.630
	Sham+Exp	0.814	6	0.078
	iTBS+NoExp	0.889	8	0.230
	iTBS+Exp	0.912	6	0.452
Post-Pre VGskill (qualitative)	Sham+NoExp	0.720	7	0.006
	Sham+Exp	0.814	6	0.078
	iTBS+NoExp	0.948	8	0.690
	iTBS+Exp	0.814	6	0.078
Post-Pre Simple reaction time	Sham+NoExp	0.772	7	0.021
	Sham+Exp	0.931	6	0.589
	iTBS+NoExp	0.936	8	0.576
	iTBS+Exp	0.915	6	0.469
Post-Pre Direction choice reaction rime	Sham+NoExp	0.874	7	0.203
	Sham+Exp	0.704	6	0.007
	iTBS+NoExp	0.893	8	0.247
	iTBS+Exp	0.937	6	0.636
Post-Pre Color choice reaction time	Sham+NoExp	0.915	7	0.431
	Sham+Exp	0.783	6	0.041
	iTBS+NoExp	0.935	8	0.567
	iTBS+Exp	0.924	6	0.538
Post-Pre Forward digits	Sham+NoExp	0.887	7	0.262
	Sham+Exp	0.948	6	0.721
	iTBS+NoExp	0.858	8	0.114
	iTBS+Exp	0.905	6	0.405
Post-Pre Backward digits	Sham+NoExp	0.820	7	0.064
	Sham+Exp	0.786	6	0.044
	iTBS+NoExp	0.931	8	0.521
	iTBS+Exp	0.822	6	0.091
Post-Pre Raven score	Sham+NoExp	0.893	7	0.292
	Sham+Exp	0.773	6	0.033
	iTBS+NoExp	0.873	8	0.162
	iTBS+Exp	0.751	6	0.020
Post-Pre Raven response time	Sham+NoExp	0.951	7	0.737
	Sham+Exp	0.966	6	0.864
	iTBS+NoExp	0.958	8	0.787
	iTBS+Exp	0.905	6	0.404
Post-Pre N-back score	Sham+NoExp	0.966	7	0.870
	Sham+Exp	0.930	6	0.582
	iTBS+NoExp	0.766	8	0.012
	iTBS+Exp	0.799	6	0.058
Post-Pre N-back reaction time	Sham+NoExp	0.976	7	0.941
	Sham+Exp	0.663	6	0.002
	iTBS+NoExp	0.890	8	0.236
	iTBS+Exp	0.994	6	0.996
Post-Pre N-back d'	Sham+NoExp	0.918	7	0.452
	Sham+Exp	0.953	6	0.768
	iTBS+NoExp	0.971	8	0.902
	iTBS+Exp	0.996	6	0.998
Post-Pre Mental rotation score	Sham+NoExp	0.899	7	0.327
	Sham+Exp	0.899	6	0.367
	iTBS+NoExp	0.940	8	0.610
	iTBS+Exp	0.957	6	0.795
Post-Pre Mental rotation response time	Sham+NoExp	0.981	7	0.965
	Sham+Exp	0.897	6	0.359
	iTBS+NoExp	0.703	8	0.002
	iTBS+Exp	0.894	6	0.339

	TMS + Previous VG experience	Shapiro-Wilk		
		Statistic	df	Sig.
Post-Pre Stop-switching GO score	Sham+NoExp	0.836	7	0.091
	Sham+Exp	0.920	6	0.505
	iTBS+NoExp	0.938	8	0.592
	iTBS+Exp	0.891	6	0.324
Post-Pre Stop-switching GO response time	Sham+NoExp	0.884	7	0.247
	Sham+Exp	0.957	6	0.794
	iTBS+NoExp	0.990	8	0.995
	iTBS+Exp	0.909	6	0.431
Post-Pre Stop-switching STOP score	Sham+NoExp	0.932	7	0.564
	Sham+Exp	0.875	6	0.247
	iTBS+NoExp	0.960	8	0.807
	iTBS+Exp	0.929	6	0.570
Post-Pre Stop-signal Reaction Time	Sham+NoExp	0.989	7	0.991
	Sham+Exp	0.977	6	0.935
	iTBS+NoExp	0.842	8	0.079
	iTBS+Exp	0.940	6	0.661
Post-Pre Stop-switching SWITCH Score	Sham+NoExp	0.973	7	0.921
	Sham+Exp	0.769	6	0.030
	iTBS+NoExp	0.903	8	0.309
	iTBS+Exp	0.915	6	0.471
Post-Pre Stop-switching SWITCH response time	Sham+NoExp	0.931	7	0.558
	Sham+Exp	0.952	6	0.759
	iTBS+NoExp	0.960	8	0.813
	iTBS+Exp	0.902	6	0.383
Follow-up-Pre Simple reaction time	Sham+NoExp	0.797	7	0.038
	Sham+Exp	0.928	6	0.567
	iTBS+NoExp	0.837	8	0.070
	iTBS+Exp	0.917	6	0.484
Follow-up-Pre Direction choice reaction rime	Sham+NoExp	0.910	7	0.397
	Sham+Exp	0.901	6	0.382
	iTBS+NoExp	0.933	8	0.541
	iTBS+Exp	0.890	6	0.318
Follow-up-Pre Color choice reaction time	Sham+NoExp	0.971	7	0.902
	Sham+Exp	0.988	6	0.984
	iTBS+NoExp	0.882	8	0.196
	iTBS+Exp	0.934	6	0.611
Follow-up-Pre Forward digits	Sham+NoExp	0.952	7	0.752
	Sham+Exp	0.966	6	0.866
	iTBS+NoExp	0.877	8	0.175
	iTBS+Exp	0.908	6	0.421
Follow-up-Pre Backward digits	Sham+NoExp	0.927	7	0.523
	Sham+Exp	0.908	6	0.423
	iTBS+NoExp	0.939	8	0.600
	iTBS+Exp	0.839	6	0.128
Follow-up-Pre N-back score	Sham+NoExp	0.922	7	0.483
	Sham+Exp	0.940	6	0.660
	iTBS+NoExp	0.915	8	0.394
	iTBS+Exp	0.891	6	0.326
Follow-up-Pre N-back reaction time	Sham+NoExp	0.945	7	0.688
	Sham+Exp	0.741	6	0.016
	iTBS+NoExp	0.827	8	0.055
	iTBS+Exp	0.925	6	0.545
Follow-up-Pre N-back d'	Sham+NoExp	0.841	7	0.101
	Sham+Exp	0.942	6	0.675
	iTBS+NoExp	0.864	8	0.132
	iTBS+Exp	0.788	6	0.046
Follow-up-Pre Mental rotation score	Sham+NoExp	0.932	7	0.569
	Sham+Exp	0.892	6	0.326
	iTBS+NoExp	0.777	8	0.016
	iTBS+Exp	0.938	6	0.646
Follow-up-Pre Mental rotation response time	Sham+NoExp	0.915	7	0.433
	Sham+Exp	0.968	6	0.876
	iTBS+NoExp	0.684	8	0.001
	iTBS+Exp	0.931	6	0.584
Follow-up-Pre Stop-switching GO score	Sham+NoExp	0.881	7	0.230

	TMS + Previous VG experience	Shapiro-Wilk		
		Statistic	df	Sig.
	Sham+Exp	0.847	6	0.149
	iTBS+NoExp	0.969	8	0.893
	iTBS+Exp	0.955	6	0.781
Follow-up-Pre Stop-switching GO response time	Sham+NoExp	0.905	7	0.359
	Sham+Exp	0.862	6	0.197
	iTBS+NoExp	0.939	8	0.600
	iTBS+Exp	0.928	6	0.567
Follow-up-Pre Stop-switching STOP score	Sham+NoExp	0.930	7	0.550
	Sham+Exp	0.949	6	0.729
	iTBS+NoExp	0.843	8	0.081
	iTBS+Exp	0.963	6	0.839
Follow-up-Pre Stop-signal Reaction Time	Sham+NoExp	0.942	7	0.655
	Sham+Exp	0.925	6	0.543
	iTBS+NoExp	0.849	8	0.093
	iTBS+Exp	0.952	6	0.754
Follow-up-Pre Stop-switching SWITCH Score	Sham+NoExp	0.878	7	0.220
	Sham+Exp	0.922	6	0.518
	iTBS+NoExp	0.873	8	0.162
	iTBS+Exp	0.933	6	0.605
Follow-up-Pre Stop-switching SWITCH response time	Sham+NoExp	0.892	7	0.285
	Sham+Exp	0.912	6	0.451
	iTBS+NoExp	0.801	8	0.030
	iTBS+Exp	0.913	6	0.456

Table 82. Normality data for differential variables (difference between the first and second post-intervention assessments and the baseline), by TMS group and previous video game experience. Shaded variables indicate a violation of the normality assumption.

8.8.4.2 Homoscedasticity

Variable	Levene Statistic	df1	df2	Sig.
Age	0.876	3	23	0.468
Stars achieved SuperMario64	1.021	3	23	0.402
Attempts	0.667	3	23	0.581
Performance	0.796	3	23	0.509
Time per attempt (s)	2.626	3	23	0.075
VG skill (questionnaire) PRE	0.176	3	23	0.911
VG skill (questionnaire) POST	0.979	3	23	0.420
VG skill (qualitative) PRE	0.435	3	23	0.730
VG skill (qualitative) POST	1.873	3	23	0.162
Motivation (0-5)	0.676	3	23	0.575
Fun (0-5)	0.034	3	23	0.991
Frustration (0-5)	0.548	3	23	0.655
Simple reaction time PRE (ms)	0.148	3	23	0.930
Simple reaction time POST (ms)	3.226	3	23	0.041
Simple reaction time FOLLOW-UP (ms)	1.311	3	23	0.295
Direction choice reaction time PRE (ms)	0.774	3	23	0.521
Direction choice reaction time POST (ms)	0.510	3	23	0.679
Direction choice reaction time FOLLOW-UP (ms)	1.160	3	23	0.346
Colour choice reaction time PRE (ms)	0.775	3	23	0.520
Colour choice reaction time POST (ms)	3.191	3	23	0.043
Colour choice reaction time FOLLOW-UP (ms)	0.147	3	23	0.930
Forward digits PRE	1.780	3	23	0.179
Forward digits POST	3.216	3	23	0.042
Forward digits FOLLOW-UP	0.697	3	23	0.563
Backward digits PRE	1.632	3	23	0.209
Backward digits POST	0.669	3	23	0.580
Backward digits FOLLOW-UP	1.127	3	23	0.359
Raven Score PRE	2.496	3	23	0.085
Raven Score POST	1.059	3	23	0.386
Raven RT PRE	1.497	3	23	0.242
Raven RT POST	0.266	3	23	0.849
Five-Point Test	0.692	3	23	0.566
n-back score PRE	1.712	3	23	0.192
n-back score POST	6.452	3	23	0.002
n-back score FOLLOW-UP	0.528	3	23	0.668

Variable	Levene Statistic	df1	df2	Sig.
n-back RT right answer PRE (ms)	2.354	3	23	0.098
n-back RT right answer POST (ms)	0.277	3	23	0.842
n-back RT right answer FOLLOW-UP (ms)	0.214	3	23	0.886
n-back d' PRE (ms)	2.001	3	23	0.142
n-back d' POST (ms)	1.180	3	23	0.339
n-back d' FOLLOW-UP (ms)	0.515	3	23	0.676
Mental rotation score PRE	1.271	3	23	0.308
Mental rotation score POST	2.180	3	23	0.118
Mental rotation score FOLLOW-UP	2.283	3	23	0.106
Mental rotation RT PRE (ms)	1.173	3	23	0.342
Mental rotation RT POST (ms)	0.425	3	23	0.737
Mental rotation RT FOLLOW-UP (ms)	3.161	3	23	0.044
Stop-switching GO Score PRE	0.762	3	23	0.527
Stop-switching GO Score POST	0.772	3	23	0.521
Stop-switching GO Score FOLLOW-UP	0.588	3	23	0.629
Stop-switching GO RT PRE (ms)	0.220	3	23	0.882
Stop-switching GO RT POST (ms)	0.055	3	23	0.982
Stop-switching GO RT FOLLOW-UP (ms)	0.416	3	23	0.743
Stop-switching STOP Score PRE	0.331	3	23	0.803
Stop-switching STOP Score POST	0.134	3	23	0.939
Stop-switching STOP Score FOLLOW-UP	0.414	3	23	0.744
Stop-signal Reaction Time PRE (ms)	0.029	3	23	0.993
Stop-signal Reaction Time POST (ms)	0.290	3	23	0.832
Stop-signal Reaction Time FOLLOW-UP (ms)	0.331	3	23	0.803
Stop-switching SWITCH Score PRE	1.807	3	23	0.174
Stop-switching SWITCH Score POST	0.250	3	23	0.861
Stop-switching SWITCH Score FOLLOW-UP	0.141	3	23	0.934
Stop-switching SWITCH RT PRE	1.366	3	23	0.278
Stop-switching SWITCH RT POST	1.995	3	23	0.143
Stop-switching SWITCH RT FOLLOW-UP	1.491	3	23	0.243
Matchstick total score (correct answers)	1.314	3	23	0.294
Matchstick total Response time (correct answers)	0.940	3	23	0.438
Matchstick Score (first exposition)	5.515	3	23	0.005
Matchstick Score (second exposition)	0.813	3	23	0.500
Matchstick Facilitated responses	0.109	3	23	0.954
Matchstick Facilitated response percentage	0.372	3	18	0.774
Matchstick Facilitated response time (ms)	1.127	3	18	0.365

Table 83. Homoscedasticity data for video game and cognitive variables, by TMS group and previous video game experience. Shaded variables indicate a violation of the equality of variances assumption.

Variable	Levene Statistic	gl1	gl2	Sig.
Post-Pre VGskill (questionnaire)	0.019	3	23	0.996
Post-Pre VGskill (qualitative)	0.363	3	23	0.780
Post-Pre Simple reaction time	0.975	3	23	0.422
Post-Pre Direction choice reaction rime	0.182	3	23	0.907
Post-Pre Color choice reaction time	0.685	3	23	0.570
Post-Pre Forward digits	3.023	3	23	0.050
Post-Pre Backward digits	0.409	3	23	0.748
Post-Pre Raven score	1.359	3	23	0.280
Post-Pre Raven response time	1.765	3	23	0.182
Post-Pre N-back score	2.064	3	23	0.133
Post-Pre N-back reaction time	1.384	3	23	0.273
Post-Pre N-back d'	1.451	3	23	0.254
Post-Pre Mental rotation score	0.891	3	23	0.460
Post-Pre Mental rotation response time	0.716	3	23	0.552
Post-Pre Stop-switching GO score	0.432	3	23	0.732
Post-Pre Stop-switching GO response time	1.951	3	23	0.150
Post-Pre Stop-switching STOP score	0.512	3	23	0.678
Post-Pre Stop-signal Reaction Time	0.885	3	23	0.464
Post-Pre Stop-switching SWITCH Score	0.344	3	23	0.794
Post-Pre Stop-switching SWITCH response time	1.309	3	23	0.295
Follow-up-Pre Simple reaction time	0.306	3	23	0.821
Follow-up-Pre Direction choice reaction rime	2.127	3	23	0.125
Follow-up-Pre Color choice reaction time	0.213	3	23	0.886
Follow-up-Pre Forward digits	2.244	3	23	0.110
Follow-up-Pre Backward digits	1.087	3	23	0.374

Variable	Levene Statistic	gl1	gl2	Sig.
Follow-up-Pre N-back score	0.374	3	23	0.773
Follow-up-Pre N-back reaction time	0.602	3	23	0.620
Follow-up-Pre N-back d'	1.263	3	23	0.310
Follow-up-Pre Mental rotation score	0.496	3	23	0.689
Follow-up-Pre Mental rotation response time	2.005	3	23	0.141
Follow-up-Pre Stop-switching GO score	0.183	3	23	0.907
Follow-up-Pre Stop-switching GO response time	0.841	3	23	0.485
Follow-up-Pre Stop-switching STOP score	1.213	3	23	0.327
Follow-up-Pre Stop-signal Reaction Time	2.847	3	23	0.060
Follow-up-Pre Stop-switching SWITCH Score	1.375	3	23	0.275
Follow-up-Pre Stop-switching SWITCH response time	1.989	3	23	0.144

Table 84. Homoscedasticity data for differential variables (difference between the first and second post-intervention assessments and the baseline) by TMS group and previous video game experience. Shaded variables indicate a violation of the equality of variances assumption.

8.8.4.3 Sphericity

	Pre. Post. Follow-up			
	Mauchly's W	**Chi-squared**	**df**	**p**
Simple reaction time	0.794	5.069	2	0.079
Direction choice reaction time	0.801	4.875	2	0.087
Color choice reaction time	0.968	0.705	2	0.703
Digits (forward)	0.935	1.486	2	0.476
Digits (backward)	0.782	5.41	2	0.067
N-back score	0.728	6.983	2	0.030
N-back RT	0.655	9.318	2	0.009
N-back d'	0.838	3.877	2	0.144
Mental rotation score	0.798	4.976	2	0.083
Mental rotation RT	0.753	6.243	2	0.044
StopSwitching Go score	0.921	1.799	2	0.407
StopSwitching Go RT	0.768	5.794	2	0.055
StopSwitching Stop score	0.739	6.659	2	0.036
StopSwitching SSRT	0.768	5.798	2	0.055
StopSwitching Switch scores	0.853	3.488	2	0.175
StopSwitching Switch RT	0.801	4.876	2	0.087

Table 85. Sphericity data for cognitive variables by TMS group and previous video game experience across the three assessments. Shaded variables indicate a violation of the sphericity assumption.

8.9 Baseline Differences

	TMS					Exp_VGP					TMS*Exp_VGP				
Variable	**Test**	**Statistic (t. X2. F)**	**df**	**Sig.**	**Equal?**	**Test**	**Statistic (t. X2. F)**	**df**	**Sig**	**Equal?**	**Test**	**Statistic (t. X2. F)**	**df**	**Sig**	**Equal?**
VG skill (questionnaire)	t-test	0.728	25	0.473	No	Mann-Whitney	58.500		0.120	No	ANOVA	0.996	3. 23	0.412	No
VG skill (qualitative)	t-test	0.497	25	0.623	No	Mann-Whitney	57.000		0.101	No	ANOVA	1.506	3. 23	0.240	No
Simple reaction time PRE (ms)	t-test	0.900	25	0.377	No	t-test	0.959	25	0.347	No	ANOVA	1.12	3. 23	0.361	No
Direction choice reaction time PRE (ms)	Mann-Whitney	61.000		0.145	No	Mann-Whitney	73.000		0.407	No	Kruskal Wallis	33.48	3	0.323	No
Colour choice reaction time PRE (ms)	Mann-Whitney	80.500		0.610	No	t-test	0.974	25	0.340	No	Kruskal Wallis	3.048	3	0.384	No
Forward digits PRE	t-test	-0.169	25	0.867	No	t-test	0.726	25	0.475	No	ANOVA	0.248	3. 23	0.862	No
Backward digits PRE	Mann-Whitney	82.000		0.659	No	t-test	-1.887	25	0.071	No	ANOVA	1.516	3. 23	0.237	No
Raven Score PRE	Mann-Whitney	79.000		0.553	No	Mann-Whitney	82.500		0.710	No	Kruskal Wallis	4.038	3	0.257	No
Raven RT PRE	t-test	2.296	25	0.030	Yes	Mann-Whitney	78.000		0.558	No	ANOVA	3.016	3. 23	0.051	No
n-back score PRE	Mann-Whitney	73.000		0.382	No	t-test	-0.231	25	0.819	No	Kruskal Wallis	2.689	3	0.442	No
n-back RT right answer PRE (ms)	t-test	0.595	25	0.557	No	Mann-Whitney	69.000		0.306	No	Kruskal Wallis	5.494	3	0.139	No
n-back d prime PRE (ms)	t-test	-2.129	25	0.043	Yes	t-test	0.141	25	0.889	No	Kruskal Wallis	3.817	3	0.282	No
Mental rotation score PRE	t-test	1.696	25	0.102	No	Mann-Whitney	46.000		0.032	Yes	Kruskal Wallis	6.261	3	0.100	No
Mental rotation RT PRE (ms)	Mann-Whitney	73.000		0.382	No	t-test	1.703	25	0.101	No	Kruskal Wallis	2.911	3	0.406	No
Stop-switching GO Score PRE	Mann-Whitney	89.500		0.941	No	Mann-Whitney	78.500		0.568	No	ANOVA	0.361	3. 23	0.782	No
Stop-switching GO RT PRE (ms)	t-test	0.004	25	0.997	No	t-test	0.463	25	0.647	No	ANOVA	0.477	3. 23	0.702	No
Stop-switching STOP Score PRE	t-test	0.690	25	0.496	No	t-test	0.265	25	0.793	No	ANOVA	0.521	3. 23	0.672	No
Stop-signal Reaction Time PRE (ms)	t-test	-0.292	25	0.773	No	t-test	-0.802	25	0.430	No	ANOVA	0.545	3. 23	0.675	No
Stop-switching SWITCH Score PRE	t-test	0.214	25	0.832	No	t-test	-0.133	25	0.895	No	ANOVA	0.407	3. 23	0.750	No
Stop-switching SWITCH RT PRE	t-test	0.998	25	0.328	No	t-test	0.524	25	0.605	No	ANOVA	0.543	3. 23	0.658	No

Table 86. Baseline differences among groups in the cognitive assessment.

8.10 Results Summary

Results where participants are divided by stimulation group are provided first. then by previous video game experience and. finally. by the interaction of these two independent variables. Results for data including the two (Pre & Post) and three (Pre. Post & Follow-up) assessments. in addition to direct comparisons between subjects at the post-intervention assessments. are provided. The color of each cell indicates the kind of statistic used for the analysis. Green corresponds to a repeated-measures general linear model (including two or three time points). blue refers to a univariate ANOVA. grey was used for Student's t-test. and. for non-parametric statistics. dark yellow corresponds to Mann-Whitney's U statistic. pale yellow to Kruskal-Wallis H test and. finally. salmon color for Welch's ANOVA. Results highlighted in **bold** refer to statistically significant and near-significant values. Shaded cells indicate that the current analysis was not applicable for that variable (e.g. variables measured at a single time point). and empty cells indicate a lack of parametric adjustment and that alternative statistics have been used. Analyses between the first and third assessments. even when reported in their corresponding section. have not been included in the table.

			Pre & Post				Post	Pre. Post & Follow-up				Follow-up
			Session	Session*Group	Between-subject	Post-Pre	Between-subject	Session	Session*Group	Between-subject	Follow-up-Pre	Between-subject
TMS	Video game performance	Stars achieved SuperMario64	-	-	-	-	U=88.500. p=.903	-	-	-	-	-
		Attempts	-	-	-	-	t(25)=-.522. p=.606	-	-	-	-	-
		Performance	-	-	-	-	U=86.500. p=.827	-	-	-	-	-
		Time per attempt (s)	-	-	-	-	F(1.15.606)=2.043 . p=.173	-	-	-	-	-
		VG skill (questionnaire)	**F(1.25)=102.743. p=.000**	F(1.25)=.757. p=.393	F(1.25)=.121. p=.731	F(1.25)=.757. p=.393	t(25)=.009. p=.993	-	-	-	-	-
	Reaction times	Simple Reaction time	F(1.25)=.609; p=.442	F(1.25)=.030; p=.864	F(1.25)=.949; p=.339	F(1.25)=0.30. p=.864	t(25)=.917. p=.368	**F(2.50)=5.947. p=.005**	**F(2.50)=4.453. p=.017**	F(1.25)=.042; p=.839	**U=40.500. p=.014**	t(25)=-.955. p=.349
		Direction Choice Reaction Time	-	-	-	F(1.25)=.953. p=.338	t(25)=1.028. p=.314	-	-	-	F(1.25)=2.663. p=.115	U=89.000. p=.923
		Color Choice Reaction time	-	-	-	F(1.25)=1.459. p=.238	F(1.18.646)=.532. p=.475	-	-	-	F(1.25)=.927. p=.345	t(25)=-.442. p=.662
	Digits	Forward Digits	**F(1.25)=6.156. p=.020**	F(1.25)=.008. p=.927	F(1.25)=.015. p=.903	F(1.25)=.008. p=.927	t(25)=-.063. p=.950	-	-	-	F(1.25)=.037. p=.849	F(1.18.111)=.003. p=.957
		Backward Digits	-	-	-	F(1.25)=.028. p=.867	t(25)=-.950. p=.351	-	-	-	F(1.25)=.048. p=.828	t(25)=-.866. p=.394
	Raven	Raven Score	-	-	-	U=81.500. p=.638	F(1.22.183)=.661. p=.425	-	-	-	-	-

		Pre & Post				**Post**	**Pre. Post & Follow-up**				**Follow-up**
		Session	Session*Group	Between-subject	Post-Pre	Between-subject	Session	Session*Group	Between-subject	Follow-up-Pre	Between-subject
	Raven RT	F(1.25)=2.096. p=.160	F(1.25)=.592. p=.449	**F(1.25)=7.412. p=.012**	F(1.25)=.592. p=.449	**t(25)=2.431. p=.023**	-	-	-	-	-
Five-Point	Five-Point Test (5PT)	-	-	-	-	t(25)=.936. p=.358	-	-	-	-	-
N-Back	N-back Score	-	-	-	F(1.25)=.851. p=.365	U=76.000. p=.465	-	-	-	F(1.25)=.1.085. p=.308	U=72.500. p=.367
	N-back RT	F(1.25)=.013. p=.910	F(1.25)=.794. p=.381	F(1.25)=.152. p=.700	U=79.000. p=.560	U=89.000. p=.923	**F(1.504.37.608)=4.852 p=.021**	F(1.504. 37.608)=.454. p=.583	F(1.25)=.123. p=.729	U=88.000. p=.884	U=89.000. p=.923
	N-back D'	F(1.25)=.436. p=.515	F(1.25)=.001. p=.974	**F(1.25)=5.436. p=.028**	F(1.25)=.001. p=.974	U=57.000. p=.097	F(2.50)=2.466. p=.095	F(2.50)=.016. p=.984	**F(1.25)=5.526. p=.027**	U=89.000. p=.923	**U=52.500. p=.059**
Mental Rotation	Mental Rotation Score	-	-	-	F(1.25)=.830. p=.371	U=83.000. p=.679	-	-	-	F(1.25)=.011. p=.917	U=67.000. p=.244
	Mental Rotation RT	-	-	-	U=54.000. p=.073	t(25)=-.068. p=.946	-	-	-	F(1.21.832)=2.106. p=.161	U=85.000. p=.771
Stop-Switching	Stop-switching Go Score	-	-	-	U=87.500. p=.864	U=90.000. p=.959	-	-	-	F(1.25)=.014. p=.907	U=88.500. p=.899
	Stop-switching Go RT	F(1.25)=.993. p=.329	F(1.25)=.858. p=.363	F(1.25)=.095. p=.761	F(1.25)=.858. p=.363	t(25)=-.926. p=.363	**F(2.50)=3.346. p=.043**	F(2.50)=.603. p=.551	F(1.25)=.175. p=.679	F(1.25)=.676. p=.419	t(25)=-.822. p=.419
	Stop-switching Stop Score	-	-	-	F(1.25)=1.134. p=.297	U=86.500. p=.827	-	-	-	F(1.25)=1.326. p=.260	U=83.500. p=.715
	Stop-switching SSRT	**F(1.25)=4.298. p=.049**	F(1.25)=.012. p=.913	F(1.25)=.089. p=.767	F(1.25)=.012. p=.913	t(25)=-.190. p=.851	-	-	-	U=75.000. p=.438	U=80.000. p=.593
	Stop-switching Switch Score	**F(1.25)=5.068. p=.033**	F(1.25)=.869. p=.869	F(1.25)=.022. p=.883	F(1.25)=.028. p=.869	t(25)=.075. p=.941	**F(2.50)=5.880. f=.005**	F(2.50)=.023. f=.977	F(1.25)=.015. p=.902	F(1.25)=.031. p=.862	t(25)=.055. p=.956
	Stop-switching Switch RT	F(1.25)=3.146. p=.088	F(1.25)=.338. p=.566	F(1.25)=1.327. p=.260	F(1.25)=.338. p=.566	t(25)=1.191. p=.245	**F(2.50)=3.819. p=.029**	F(2.50)=.213. p=.809	F(1.25)=1.015. p=.321	F(1.25)=.023. p=.881	t(25)=.645. p=.525
Matchstick	Matchstick Score	-	-	-	-	t(25)=.305. p=.763	-	-	-	-	-
	Matchstick RT	-	-	-	-	t(25)=.177. p=.861	-	-	-	-	-
	Matchstick Score 1st	-	-	-	-	U=85.000. p=.755	-	-	-	-	-
	Matchstick Score 2nd	-	-	-	-	U=80.500. p=.596	-	-	-	-	-
	Matchstick RT 1st	-	-	-	-	t(25).055. p=.956	-	-	-	-	-
	Matchstick RT 2nd	-	-	-	-	U=68.000. p=.397	-	-	-	-	-
	Matchstick Facilitated answers	-	-	-	-	t(25)=.680. p=.258	-	-	-	-	-
	Matchstick Facilitated %	-	-	-	-	U=36.000. p=.094	-	-	-	-	-

			Pre & Post				**Post**	**Pre. Post & Follow-up**				**Follow-up**
			Session	Session*Group	Between-subject	Post-Pre	Between-subject	Session	Session*Group	Between-subject	Follow-up-Pre	Between-subject
		Matchstick Facilitated RT	-	-	-	-	U=50.000. p=.491	-	-	-	-	-
Exp_VGP	Video game performance	Stars achieved SuperMario64	-	-	-	-	**U=37.000. p=.010**	-	-	-	-	-
		Attempts	-	-	-	-	**t(25)=-1.976. p=.059**	-	-	-	-	-
		Performance	-	-	-	-	U=51.500. p=.060	-	-	-	-	-
		Time per attempt (s)	-	-	-	-	U=55.000. p=.088	-	-	-	-	-
		VG skill (questionnaire)	-	-	-	F(1.25)=2.362. p=.137	**t(25)=-2.195. p=.038**	-	-	-	-	-
	Reaction times	Simple Reaction time	F(1.25)=.610. p=.442	F(1.25)=.080. p=.780	F(1.25)=.723. p=.403	F(1.25)=0.80. p=.780	t(25)=.650. p=.522	**F(2.50)=5.136. p=.009**	F(2.50)=.266. p=.767	F(2.50)=1.006. p=.325	F(1.25)=.164. p=.689	t(25)=1.053. p=.302
		Direction Choice Reaction Time	-	-	-	U=87.000. p=.884	t(25)=.651. p=521	-	-	-	U=79.000. p=.591	t(25)=.966. p=.343
		Color Choice Reaction time	F(1.25)=.062. p=.806	F(1.25)=.695. p=.412	F(1.25)=2.879. p=.102	F(1.25)=.695. p=.412	**t(25)=2.052. p=.051**	F(2.50)=.358. p=.701	F(2.50)=.365. p=.696	F(1.25)=3.495. p=.073	F(1.25)=.458. p=.505	t(25)=1.590. p=.124
	Digits	Forward Digits	**F(1.25)=6.995. p=.014**	F(1.25)=3.415. p=.076	F(1.25)=.023. p=.881	F(1.25)=3.415. p=.076	t(25)=-.845. p=.406	**F(2.50)=4.994. p=.011**	F(2.50)=1.825. p=.172	F(1.25)=.330. p=.571	F(1.25)=2.927. p=.099	t(25)=-1.133. p=.268
		Backward Digits	F(1.25)=1.382. p=.251	F(1.25)=1.728. p=.201	F(1.25)=3.284. p=.082	F(1.25)=1.728. p=.201	t(25)=.-1.506. p=.145	**F(2.50)=8.087. p=.001**	F(2.50)=.476. p=.630	F(1.25)=2.973. p=.097	F(1.25)=.238. p=.630	t(25)=-1.260. p=.219
	Raven	Raven Score	-	-	-	U=65.000. p=.213	F(1.22.113)=.282. p=.601	-	-	-	-	-
		Raven RT	-	-	-	U=87.000. p=.884	t(25)=.680. p=.503	-	-	-	-	-
	Five-Point	Five-Point Test (5PT)	-	-	-	-	t(25)=.455. p=.653	-	-	-	-	-
	N-Back	N-back Score	-	-	-	**U=24.000. p=.001**	**F(1.16.040)=7.736 . p=.013**	-	-	-	F(1.25)=2.800. p=.107	t(25)=-1.471. p=.154
		N-back RT	-	-	-	U=60.000. p=.143	t(25)=-.022. p=983	-	-	-	U=67.000. p=.262	U=80.000. p=.626
		N-back D'	F(1.25)=.731. p=.401	**F(1.25)=16.869. p=.000**	F(1.25)=2.647. p=.116	**F(1.25)=16.969. p=.000**	**t(25)=-3.298. p=.003**	**F(2.50)=3.121. p=.053**	**F(2.50)=6.654. p=.003**	F(1.25)=3.449. p=.075	**F(1.25)=3.620. p=.069**	U=60.000. p=.139
	Mental Rotation	Mental Rotation Score	-	-	-	F(1.25)=1.231. p=.278	**U=53.000. p=.071**	-	-	-	**F(1.25)=4.564. p=.043**	U=63.000. p=.187
		Mental Rotation RT	**F(1.25)=18.184. p=.000**	F(1.25)=.451. p=.508	F(1.25)=3.497. p=.073	U=83.000. p=.744	t(25)=1.835. p=.078	-	-	-	F(1.25)=.346. p=.562	**U=40.000. p=.015**
	Stop-Switching	Stop-switching Go Score	-	-	-	F(1.25)=.512. p=.481	U=85.000. p=.795	-	-	-	F(1.25)=.967. p=.335	U=69.000. p=.286
		Stop-switching Go RT	F(1.25)=.975. p=.333	F(1.25)=.393. p=.537	F(1.25)=.438. p=.514	F(1.25)=.393. p=.537	t(25)=.769. p=.449	**F(2.50)=3.309. p=.045**	F(2.50)=.319. p=.728	F(1.25)=.314. p=.580	F(1.25)=.009. p=.927	t(25)=.329. p=.745

			Pre & Post				Post	Pre. Post & Follow-up				Follow-up
			Session	Session*Group	Between-subject	Post-Pre	Between-subject	Session	Session*Group	Between-subject	Follow-up-Pre	Between-subject
		Stop-switching Stop Score	-	-	-	F(1.25)=.015. p=.905	U=78.500. p=.573	-	-	-	F(1.25)=.080. p=.780	U=84.500. p=.788
		Stop-switching SSRT	**F(1.25)=5.167. p=.032**	**F(1.25)=5.072. p=.033**	F(1.25)=.196. p=.662	**F(1.25)=5.072. p=.033**	t(25)=1.740. p=.094	F(2.50)=2.706. p=.077	F(2.50)=1.951. p=.153	F(1.25)=.509. p=.482	F(1.25)=1.107. p=.303	t(25)=.729. p=.473
		Stop-switching Switch Score	-	-	-	U=69.500. p=.315	U=74.000. p=.434	-	-	-	F(1.25)=.010. p=.921	t(25)=-.042. p=.967
		Stop-switching Switch RT	-	-	-	F(1.25)=.012. p=.914	U=77.000. p=.526	-	-	-	F(1.25)=.011. p=.919	U=78.000. p=.558
	Matchstick	Matchstick Score	-	-	-	-	**t(25)=-2.059. p=.050**	-	-	-	-	-
		Matchstick RT	-	-	-	-	t(25)=-.048. p=.962	-	-	-	-	-
		Matchstick Score 1st	-	-	-	-	**F(1.23.871)=5.470 . p=.028**	-	-	-	-	-
		Matchstick Score 2nd	-	-	-	-	t(25)=-1.491. p=.149	-	-	-	-	-
		Matchstick RT 1st	-	-	-	-	t(25)=-1.162. p=.256	-	-	-	-	-
		Matchstick RT 2nd	-	-	-	-	U=69.000. p=.440	-	-	-	-	-
		Matchstick Facilitated answers	-	-	-	-	**U=48.500. p=.034**	-	-	-	-	-
		Matchstick Facilitated %	-	-	-	-	t(20)=-.224. p=.825	-	-	-	-	-
		Matchstick Facilitated RT	-	-	-	-	**t(20)=.-2.047. p=.054**	-	-	-	-	-
TMS*Exp_VGP	Video game performance	Stars achieved SuperMario64	-	-	-	-	X2(3)=7.263. p=.064					
		Attempts	-	-	-	-	F(3.23)=1.819. p=.172					
		Performance	-	-	-	-	F(3.23)=2.775. p=.064					
		Time per attempt (s)	-	-	-	-	X2(3)=3.606. p=.307					
		VG skill (questionnaire)	**F(1.23)=110.555. p<.0001**	F(3.23)=1.572. p=.223	F(1.23)=1.243. p=.317	F(3.23)=1.572. p=.223	F(3.23)=1.480. p=.246					
	Reaction times	Simple Reaction time	-	-	-	X2(3)=.530. p=.912	F(3.11.537)=.314. p=.815	-	-	-	X2(3)=6.056. p=.109	F(3.23)=.833. p=.489
		Direction Choice Reaction Time	-	-	-	X2(3)=.708. p=.871	X2(3)=1.828. p=.609	-	-	-	X2(3)=2.827. p=.419	F(3.23)=.287. p=.834
		Color Choice Reaction time	-	-	-	X2(3)=2.188. p=.534	F(3.12.159)=1.791 . p=.202	-	-	-	F(3.23)=.688. p=.569	F(3.23)=1.591. p=.219

		Pre & Post				**Post**	**Pre. Post & Follow-up**				**Follow-up**
		Session	Session*Group	Between-subject	Post-Pre	Between-subject	Session	Session*Group	Between-subject	Follow-up-Pre	Between-subject
Digits	Forward Digits	-	-	-	F(3.11.269)=.886 . p=.477	F(3.11.456)=.345. p=.793	-	-	-	F(3.23)=2.033. p=.137	F(3.23)=1.008. p=.407
	Backward Digits	-	-	-	X2(3)=1.325. p=.723	X2(3)=2.458. p=.483	-	-	-	F(3.23)=.086. p=.967	F(3.23)=.872. p=.470
Raven	Raven Score	-	-	-	X2(3)=2.464. p=.482	X2(3)=1.240. p=.743	-	-	-	-	
	Raven RT	F(1.23)=2.397. p=.135	F(3.23)=2.089. p=.130	**F(3.23)=3.006. p=.051**	F(3.23)=2.089. p=.130	F(3.23)=2.257. p=.109	-	-	-	-	
Five-Point	Five-Point Test (5PT)	-	-	-	-	X2(3)=1.830. p=.608	-	-	-	-	
N-Back	N-back Score	-	-	-	**X2(3)=11.640. p=.009**	**F(3.12.411)=3.635 . p=.044**	-	-	-	F(3.23)=1.790. p=.117	X2(3)=4.051. p=.256
	N-back RT	-	-	-	X2(3)=2.428. p=.488	X2(3)=3.610. p=.307	-	-	-	X2(3)=1.675. p=.642	X2(3)=2.767. p=.429
	N-back D'	-	-	-	**F(3.23)=5.599. p=.005**	**F(3.23)=6.095. p=.003**	-	-	-	X2(3)=3.138. p=.371	F(3.23)=2.337. p=.100
Mental Rotation	Mental Rotation Score	-	-	-	F(3.23)=1.191. p=.335	X2(3)=3.437. p=.329	-	-	-	X2(3)=4.098. p=.251	X2(3)=3.100. p=.376
	Mental Rotation RT	-	-	-	X2(3)=3.841. p=.279	F(3.23)=1.037. p=.395	-	-	-	X2(3)=1.878. p=.598	**F(3.11.598)=4.432 . p=.027**
Stop-Switching	Stop-switching Go Score	-	-	-	F(3.23)=.197. p=.898	X2(3)=.206. p=.977	-	-	-	F(3.23)=.310. p=.818	X2(3)=2.899. p=.408
	Stop-switching Go RT	F(1.23)=.928. p=.345	F(3.23)=.385. p=.765	F(3.23)=.519. p=.674	F(3.23)=.385. p=.765	F(3.23)=.524. p=.670	**F(2.46)=3.146. p=.052**	F(6.46)=.357. p=.902	F(3.23)=.415. p=.744	F(3.23)=.302. p=.824	F(3.23)=.242. p=.866
	Stop-switching Stop Score	-	-	-	F(3.23)=.383. p=.767	X2(3)=.789. p=.852	-	-	-	F(3.23)=.452. p=.719	X2(3)=.607. p=.895
	Stop-switching SSRT	**F(1.23)=5.057. p=.034**	F(3.23)=.2.143. p=.122	F(3.23)=.152. p=.927	F(3.23)=2.143. p=.122	F(3.23)=.965. p=.426	F(2.46)=2.563. p=.088	F(6.46)=.842. p=.544	F(3.23)=.238. p=.869	F(3.23)=.492. p=.691	F(3.23)=.227. p=.876
	Stop-switching Switch Score	-	-	-	X2(3)=1.750. p=.626	X2(3)=1.036. p=.792	-	-	-	F(3.23)=.110. p=.954	F(3.23)=.106. p=.956
	Stop-switching Switch RT	F(1.23)=2.901. p=.102	F(3.23)=.122. p=.946	F(3.23)=.655. p=.588	F(3.23)=.122. p=.946	F(3.23)=.651. p=.590	**F(2.46)=.3.536. p=.037**	F(6.46)=.113. p=.994	F(3.23)=.489. p=.693	X2(3)=.634. p=.889	F(3.23)=.187. p=.904
Matchstick	Matchstick Score	-	-	-	-	F(3.23)=1.609. p=.215	-	-	-	-	-
	Matchstick RT	-	-	-	-	F(3.23)=.086. p=.967	-	-	-	-	-
	Matchstick Score 1st	-	-	-	-	**F(3.12.005)=3.229 . p=.061**	-	-	-	-	-
	Matchstick Score 2nd	-	-	-	-	X2(3)=2.142. p=.543	-	-	-	-	-
	Matchstick RT 1st	-	-	-	-	F(3.23)=1.013. p=.405	-	-	-	-	-

	Pre & Post				Post	Pre. Post & Follow-up				Follow-up
	Session	Session*Group	Between-subject	Post-Pre	Between-subject	Session	Session*Group	Between-subject	Follow-up-Pre	Between-subject
Matchstick RT 2nd	-	-	-	-	F(3.11.776)=.426. p=.738	-	-	-	-	-
Matchstick Facilitated answers	-	-	-	-	X2(3)=5.609. p=.132	-	-	-	-	-
Matchstick Facilitated %	-	-	-	-	F(3.18)=1.104. p=.373	-	-	-	-	-
Matchstick Facilitated RT	-	-	-	-	F(3.18)=1.262. p=.317	-	-	-	-	-

Table 87. Summarized results found for the two independent variables (TMS and previous video game experience) and the interaction between the two. Effects of the training sessions and exposure to the assessments. interaction effects of the sessions with the experimental groups and direct between-subject comparisons are provided. The color of the cells indicates the statistic used. Shaded cells indicate the statistic used for the analysis: Green: repeated-measures general linear model. blue: univariate ANOVA. grey: Student's t-test. dark yellow: Mann-Whitney's U. pale yellow: Kruskal-Wallis H test. and salmon: Welch's ANOVA. Results highlighted in **bold** indicate statistically significant and near-significant values.