The principles of advanced virtual reality-based neurorehabilitation

How the training in virtual reality and based on principles can support the recovery and diagnosis of disabilities after stroke

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To my family

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ABSTRACT

The increase in stroke survivors poses a global challenge for the current health care system. The way that standard therapy is provided today impacts long-term disability and dependency in ADL insufficiently. The associated need for long-term care and the increase in health-care costs hence demand for novel therapeutic approaches. For this reason, we need to obtain gain a better understanding of the manifold consequences and the recovery process after stroke. In this dissertation we will advance the idea that besides increasing the intensity other factors need to be considered. Rehabilitation must incorporate learning strategies that induce recovery by changing the impaired behaviour. The principles of learning can be obtained from animal and human learning neuroscientific literature. As symptoms are neurologically and behaviourally interrelated, they can be addressed by common learning methods. We argue that technology is an aptly medium to implement and test these methods. Technology-based rehabilitation systems are not only cost-efficient, scalable and accessible, but also allow us to induce virtual manipulations which enhances learning in a way that is not possible in reality. The main goal of this dissertation is to design, test and deliver advanced neuroscience-based therapies in virtual reality that exploit principles of learning. We first offer a synthesis of known principles of learning obtained from human and animal behaviour and show that VR-based systems that incorporate these principles can have a significant impact on recovery. We then explore in three studies how augmented sensorimotor performance, individualized challenges and goal-oriented embodied training in a VR-based rehabilitation system can modify behaviour to address physical, cognitive and social post-stroke consequences. Lastly, we offer two possibilities how the information gained through the VR-based training can help to understand deficits better and therefore complement diagnostics. The contribution of the scientific work presented in this dissertation is that a systematic principle-based approach that augments learning with the advantages of technology can address a variety of post-stroke deficits and advance the understanding of recovery.

RESUM

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Part I

Introduction

Chapter 1

INTRODUCTION

Globally, one out of four people will have a stroke in their lifetime. There are over 13.7 million strokes each year, out of which 5.5 million will result in death (World Stroke Organization, 2016). Moreover, recurrence after the first stroke incident is high. The pooled cumulative stroke recurrence risk is about 26.4% the first year and at 39.2% after ten years post-stroke (Benjamin et al., 2019). Although these numbers are staggering, there is a silver lining. On the one hand, 90.5% of these strokes could be prevented, which is why much effort has been put into prevention and control of the modifiable risk factors (Feigin et al., 2016), reducing the rates of new strokes. On the other hand, improved acute medical treatments and certified hospitals with dedicated stroke units reduced door-to-needle time and the death toll caused by stroke (Benjamin et al., 2019), enhancing the short-term outcomes. However, as the population ages, the number of people having a stroke, and consequently, the number of stroke survivors will continue to rise. Currently, 80 million people are living with the consequences of stroke (World Stroke Organization, 2016). Alone in Europe, the number of stroke survivors is projected to increase by 25%, from 3.7 million in 2015 to 4.6 million in 2035 (Stevens, Emmett, Wang, McKevitt, & Wolfe, 2017). This increased survival rate implies a burden for the individual, their families and the society.

The direct medical costs of stroke, which include inpatient and outpatient care, medication, and doctor visits, are currently estimated at 30 billion USD yearly. This number is foreseen to increase to 94.3 billion USD by 2035, due to an increasing number of citizens who are over 80 years old (Benjamin et al., 2019). Importantly, this number underestimates the total economic burden associated with stroke. In particular, it excludes the indirect non-health care costs such as informal support or loss of productivity, which are estimated at 15.9 billion EUR in Europe, that is 35% of the total estimated costs of stroke (Stevens et al., 2017). Hence, a large part of the financial burden will not be carried by the taxpayers and insurance companies, but by the stroke survivors and their families.

The numbers presented here, however, reflect only a part of the challenge of this disease. Stroke survivors are facing not only short-term complications such as seizures or infections but also long-term chronic sequelae (Benjamin et al., 2019). Stroke has a greater disability impact and a greater range of disabilities than other chronic diseases (Adamson, Beswick, & Ebrahim, 2004). According to the fact sheet of the National Institute of Neurological Disorders and Stroke, stroke survivors might be confronted with a combination of different disabilities: paralysis or problems related to movement control, sensory disturbances such as pain or neglect, loss of language skills (speech production or understanding), cognitive impairments in attention, memory, executive functioning and spatial awareness, and emotional disturbances such as depression (National Institute of Neurological Disorders and Stroke, 2019). These functional disabilities might impede patients from performing normal daily activities independently and reduce their quality of life. Due to the heterogeneity of the disorder, only a few studies can provide an overview of the long-term functional outcome after stroke. For example, a longitudinal observational study from Sweden reports that 33.2 % of the patients were functionally dependent one-year post-stroke (Sennfält, Norrving, Petersson, & Ullberg, 2019). Data from the population-based south London Stroke Register indicates that among those individuals who survived 15 years post-stroke, 33.8% had mild, 14.3% moderate and 15% severe disability, with 1 in 10 living with moderate-severe disability since their stroke. The prevalence of cognitive impairment was 30%, depression 39.1% and anxiety 34.9% (Crichton, Bray, McKevitt, Rudd, & Wolfe, 2016). Five-year post-stroke survivors with greater functional dependence and disability severity require significantly more paid (e.g. hospital stays) and unpaid (e.g. informal caregiver) health care services (Matchar, Bilger, Do, & Eom, 2015).

There is a common agreement that rehabilitation is the key to counteract long-term disability and dependence (Winstein, Stein, et al., 2016) and patients should have access to multidisciplinary stroke units, with specialists for physiotherapy, occupational and communication therapy, where their disabilities are accurately diagnosed, and a long-term treatment plan is established (Stevens et al., 2017). Rehabilitation could promote physical activity and lifestyle changes and hence aid in preventing recurrent strokes by addressing the modifiable risks (Kernan et al., 2014). Indeed, there is some evidence that a specialised stroke rehabilitation ward can reduce long-term disability and the financial burden, but the results are limited to individual countries and health care systems (Katan & Luft, 2018). However, in the latest guidelines of the European Stroke Organisation that summons recent stroke therapy research and provides recommendations on how to implement the experimental results into the clinical routine, do not include any advancement or action plan regarding the reduction of recurrence or long-term disability through rehabilitation (Ahmed et al., 2019). The Stroke Alliance For Europe recommends the following activities: 1) early rehabilitation including physiotherapy and communication therapy in a stroke unit during the first year after stroke, 2) early discharge if medically appropriate and suitable community rehabilitation is available, and 3) assessment of the needs early after discharge. The reality, however, shows a different picture. Access to stroke units and multidisciplinary care varies considerably between European countries (Stevens et al., 2017). Some European patients do not even receive occupational or psychological therapy. Typically, patients obtain only 22 (Veerbeek et al., 2014) to 60 minutes of training a day, with fewer minutes at later stages (Schaechter, 2004). During inpatient rehabilitation, patients are physically active 13 % and are socially inactive 60 % of the time (Bernhardt, Dewey, Thrift, & Donnan, 2004). The average length of hospital stay is 4.7 days, and the mean rehabilitation length of stay is estimated to be 14.6 days (Benjamin et al., 2019). The trend towards early discharge, which is only feasible for one-third of the patients, is in stark contrast to limited or absent follow-up community support, outpatient stroke rehabilitation programmes and disability status reviews (Stevens et al., 2017). Besides, austerity policies have led to cuts in funds for health and social care for the disabled, leading to poor access to services especially in rural and remote areas (Stevens et al., 2017).

Taken together, it appears that stroke care, rehabilitation and recovery attempts, as well as research thereof, focus primarily on the early stages after stroke, despite stroke being classified as a fundamentally chronic condition (Winstein, Stein, et al., 2016). There is no formal pathway between the different phases of care. Hence, very little is known about the mechanisms and effects of long-term rehabilitation: What does it obtain currently, and what should it obtain instead (Stevens et al., 2017). This lack of knowledge is contributing to the persisting unmet needs such as health-related quality of life, maintenance of activity, social reintegration and increase in self-efficacy (Winstein,

Stein, et al., 2016). More importantly, therapy at the acute phase might be in vain if it does not ensure a reduction in long-term disability, and recurrence or death of stroke survivors.

Consequently, stroke care needs to incorporate advanced approaches to address the challenges outlined above. For this, we need to understand how rehabilitation can influence recovery. We will hence start this introduction by providing an overview of the neuroscientific advances but as well the shortcomings in understanding the relationship between rehabilitation and recovery. In order to build on the advances and to address the shortcomings, we will then devise three proposals. First, a "one standard therapy fits all" will most probably not work. Stroke causes a myriad of direct and indirect physical, mental and social problems. We will comment on the physical and mental challenges caused by stroke, but also identify the interrelations between them, which could be an opportunity for creating holistic therapy approaches that are more efficient. Second, "therapy just needs to be intensive enough" will most probably not work either. Effective therapy needs to influence physical and mental states through learning. There are conditions or principles that promote learning, and we argue they are currently missing in standard care. We will elaborate on why the identification of these principles can aid in creating effective multidomain protocols. Third, we will advance the idea that technology is most probably the only tool that can address the stroke burden and long-term care by generating cost-effective, scalable and neuroscience grounded intervention protocols that can accommodate a variety of stroke survivors.

1.1. Post-stroke plasticity and proportional recovery rule

An important aspect in the recovery process is time – When should rehabilitation start, how much rehabilitation should be given at each time point, and for how long. Animal models suggest that there is a period of spontaneous biological recovery: an early post-stroke phase of heightened brain plasticity, where training leads to maximal recovery (N. S. Ward, 2017). First, cortical map changes occur in the contralesional hemisphere while peri-infarct cortex expresses hypoexcitability leading to a diminished response to afferent input. Within two weeks the peri-infarct region regains responsiveness to afferent input, which is remapped to new non-infarct areas, while new connections within the cortical circuit are formed, and axonal sprouting takes place. This change is triggered by a molecular program (Krakauer, Carmichael, Corbett, & Wittenberg, 2012), and markers suggest similar restorative processes in humans (N. S. Ward, 2017). Dendritic growth, spine formation and synaptogenesis can also be caused by behavioural experience, giving rise to the idea that with enhancing experience, the brain's natural way of repairing could be augmented (Livingston-Thomas et al., 2016). The animal models suggest that activity promoted immediately after stroke might have adverse effects on plastic changes and recovery, and rehabilitation should start early after five but no later than 30 days post-stroke (Krakauer et al., 2012; N. S. Ward, 2017).

It has been suggested that the recovery in humans might be proportional to initial impairment. Mild and moderate impaired patients appear to achieve about 70% of their maximal potential upper limb recovery, and this achievement could be predicted from the impairment status at 1-week post-stroke. Approximately half of the patients with severe impairments, however, did not recover from their impairment (e.g. do not show a proportional recovery) (Prabhakaran et al., 2008), which was argued to be due to less residual corticospinal tract integrity (Guggisberg, Nicolo, Cohen, Schnider, & Buch, 2017). The patients of the original study received standard physical and occupational therapy, however of unknown daily duration and length (Krakauer & Marshall, 2015). The replication of these results also in non-motor deficits has led to the assumption that this proportional recovery operates independently of the dose of rehabilitation provided and possibly represents the spontaneous biological recovery that unfolds due to heightened plasticity in the post-stroke brain in response to any type of behavioural training (Krakauer et al., 2012; Kwakkel, Kollen, & Lindeman, 2004; N. S. Ward, 2017). Moreover, the maximum recovery appears to be reached after roughly 3 months, leading to the notion of a critical window (Krakauer et al., 2012). However, severe patients have been observed to make significant gains up to 6 months post-stroke (Hendricks, Van Limbeek, Geurts, & Zwarts, 2002). Studies have pointed out that the statistical methods typically used to calculate the proportional recovery are inconsistently reported (Kundert, Goldsmith, Veerbeek, Krakauer, & Luft, 2019) and may inflate the effect sizes found (Hope et al., 2019); hence the existence of proportionality in the underlying data is not confirmed. They recommend that besides different statistical methods, better assessment tools are required. However, given that the mathematical coupling problem could be solved, and there is still a proportional recovery, what would it mean?

There are two possible answers to this question. First, rehabilitation does not matter; independent of what patients do, they will always recover in proportion to their initial impairment, because of spontaneous biological recovery. Second, current rehabilitation does not matter *enough*; the current treatment of patients is not adequate to facilitate recovery beyond proportionality and spontaneous biological recovery (Krakauer & Marshall, 2015). Studies in animals point to the later answer. The proportional recovery was also identified in animals (albeit in lower percentages as in humans) which was independent of whether rehabilitation was provided or not (Jeffers, Karthikeyan, & Corbett, 2018). However, when the intensity of rehabilitation was considered, it was shown that as infarct volume and impairment increase, more intensive rehabilitation is required to achieve a significant motor recovery, which was especially evident in severely impaired animals (Jeffers, Karthikeyan, Gomez-Smith, et al., 2018).

Moreover, animals appear to reach their recovery already by four weeks post-stroke. Besides biological differences, it might be that the earlier commencement of therapy and the unrestricted access to high-repetitive physical training advance the recovery in rats (Krakauer et al., 2012). Although studies agree that the therapy currently provided to stroke survivors in the acute to subacute phase (1 – 3 months post-stroke) is most probably too little and not intensive enough (N. S. Ward, 2017), an increase in repetition and duration did not show a conclusive effect on recovery (French et al., 2016; Hayward, Barker, Carson, & Brauer, 2014; Langhorne, Bernhardt, & Kwakkel, 2011; Thomas et al., 2017; Veerbeek et al., 2014). An alternative proposal is that current rehabilitation is not providing the right training elements that foster relearning and hence does not maximise the effect of spontaneous biological recovery independent of or in addition to repetition amounts and dosage (N. S. Ward, 2017). Animals have typically unlimited access to practice in enriched environments (Johansson & Ohlsson, 1996; Krakauer et al., 2012). This training not only encompasses high voluntary doses and repetitions but also challenges, goal-directed behaviour, cognitive activation, sensorimotor stimulation and social interaction (see Figure 1.1), elements that are currently missing in standard care (Janssen et al., 2014; Livingston-Thomas et al., 2016).

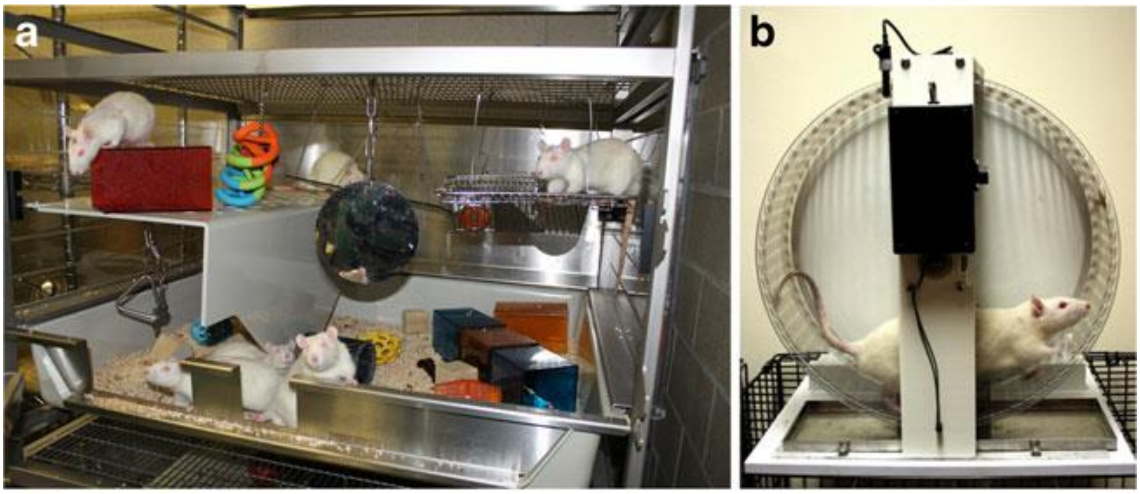

Figure 1.1. Rehabilitation setting for rats. A) A typical enriched environment cage containing a variety of objects, platforms and other animals encouraging exploration, sensorimotor stimulation and social interaction. B) Running wheels or treadmills for post-stroke exercise. Both pictures from (Livingston-Thomas et al., 2016)

Further, severe patients that would have been possibly deemed as non-responders according to the proportional rule at the acute stage were shown to make therapy-induced improvement at the chronic stage (Senesh & Reinkensmeyer, 2019). The authors argue that this population of initial nonfitters maybe had some small but undetected residual corticospinal tract integrity, that became functional later and needed especially large amounts of practice. Others have detected an extended sensitivity to treatment that extends beyond 12 months post-stroke, suggesting that there is a long-lasting period of enhanced neuroplasticity receptive to therapy in late chronic stages. This improvement in impairment was not seen when no treatment was provided (Ballester et al., 2019). Indeed, in a recent study, chronic stroke patients appeared to make a significant recovery by 6 months post-intervention (N. Ward, Brander, & Kelly, 2019).

Hence, the exact temporal evolution of the responsiveness to treatment, as well as the timing and minimal intensity, remain unclear. The proportional recovery rule, as well as the critical window for recovery, should be reassessed with better tools and early therapy should most probably be extended to patients in the chronic stages as well. Currently, the data on recovery at later chronic stages in human is inconclusive and sparse in animals (Krakauer et al., 2012). However, most importantly, we must rethink the kind of rehabilitation we provide today. In the following section, we will give an overview of the current standard rehabilitation methods and issues associated with it.

1.2. Limitations of current treatment and standard therapy

What is different between the standard rehabilitation of animals and the standard rehabilitation of humans? In humans, standard therapy is usually composed of physical therapy (PT) and occupation therapy (OT). Physical therapy aims at restoring and maintaining physical functionality and fitness of the body (e.g. gait, walking, arm-hand functioning) or body parts (e.g. muscles, joints, sensors, cardiovascular system) in order independently execute the activities of daily living (Veerbeek et al., 2014). The goal of occupational therapy (OT) is to facilitate task performance, either by improving the necessary skills or by teaching strategies to compensate for the lost skill. OT addresses the training of sensory-motor functions, cognitive functions, self-care activities, leisure activities, the use of assistive devices, splints or slings, and educates the family or primary caregiver (Case-Smith, 2003; Steultjens et al., 2003). There are overlaps in training elements between PT and OT, as both can address the activity of daily living. In addition, they appear not to be "pure" interventions. For instance, the meta-review on PT considers constraint-induced movement therapy (CIMT), mirror therapy, mental practice and VR-based interventions also as PT, although they are dissimilar therapeutic approaches with distinct training elements, which is possibly why no homogeneous effect on recovery was found, although they confirmed that higher doses of practice would be better (Veerbeek et al., 2014). Similarly, a meta-analysis on OT included leisure activities, home service, sitting in a rocking chair or intellectual function training. Although this meta-analysis found some pooled effects, it was for activities and social participation only (Steultjens et al., 2003).

Investing the effect of OT and PT is difficult, as comparing it to no therapy is not an option in the acute stage for humans. However, under the premise that a proportional recovery rule exists and given the current long-term outlook of patients, its current effect might be as good as absent. One might argue that it is the intensity that matters, and that the currently provided dose of OT and PT is just too little (N. S. Ward, 2017). Current research indicates that at least 16 hours of extra training (e.g., 71 minutes more per day for three months) within the first six months would be needed to influence recovery (Kwakkel, van Peppen, et al., 2004; Veerbeek et al., 2014). It is doubtful that the current health care system will be able to provide this amount of therapy for every present and future stroke patient. Further, it appears that we do not have a good understanding of standard care and its therapeutic elements that should be beneficial for recovery. Hence focussing only on increasing the repetitions and dosage of a diffuse therapy will not solve the problem. In addition, we need to be precise about what we want to achieve with therapy. In the next section, we will take a closer look at what we understand by recovery.

Figure 1.2. Occupational therapy in humans.

Occupational therapy in humans. US Navy occupational therapists are providing treatment to outpatients. By Grazioso2 - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=59183867

1.3. Compensation and true recovery

Recovery can be an ambiguous term. Whereas clinicians might use it to describe general improved behaviour following injury, research distinguishes whether recovery is due to the return to pre-stroke abilities and skills, also called true recovery, or compensatory behaviour (Hylin, Kerr, & Holden, 2017). It appears that standard therapy, such as OT and PT, in the acute or subacute stage, does not focus on the reduction of impairment (e.g. true recovery) but on training the patient to be independent in ADLs as soon as possible by using compensatory strategies (Hylin et al., 2017; Krakauer et al., 2012; Mindy F. Levin, Kleim, & Wolf, 2009). Although one could argue that being able to perform the ADL independently should be the goal of recovery, compensation might indeed not be the right strategy to achieve it. Some suggest that therapy and research should focus on changing impairment and not on modulating function, performance on ADL or quality of life because it reflects more likely true biological repair mechanism (Krakauer et al., 2012). The reason is that by teaching to compensate instead of repairing the impairments, they will continue to be present and could interfere with long-term functional outcome. Further silent motor and cognitive deficits might go unnoticed, because the patient appears to be fully functional in ADL (Hylin et al., 2017). The presence of anosognosia, e.g. lack of self-awareness of a sensory, perceptual, motor, affective or cognitive deficit, could further underestimate the undetected impairment (Orfei et al., 2007), and hence impede adequate therapy. However, clear evidence that compensation impedes a return to normal neurological functioning is missing (Kwakkel, Kollen, et al., 2004).

On the other hand, it could be argued that compensation is a natural learning strategy for an organism to adapt to changes. Animal research has shown that it is the most common behavioural response following brain damage that occurs in the absence of rehabilitation, and which is associated with ample neuronal changes to the structure (Kleim & Jones, 2008). However, by using behavioural strategies, for instance, limiting the use of the non-impaired limb, animals can learn as well to gradually use the impaired limb again to accomplish tasks. Similar behaviours can be observed in stroke patients (Kleim & Jones, 2008; Kwakkel, Veerbeek, van Wegen, & Wolf, 2015; Taub & Uswatte, 2003). These results imply that both compensation and reacquisition depend on learning. In turn, learning can cause differential changes in brain structures and function, depending on the experience (Nudo, 2011). The open question remains how post-stroke plasticity and experience-dependent plasticity interact (Kitago & Krakauer, 2013; Taub & Uswatte, 2003), and if that interaction can be exploited to indeed cause a reduction in impairment (Kitago & Krakauer, 2013).

Hence it is important to investigate the learning mechanism, that leads to compensation or reacquisition of pre-stroke abilities not only to use them effectively in therapy but as well to obtain data that can be used to study plastic changes in the post-stroke brain (Kitago & Krakauer, 2013). Currently, it appears to be difficult to distinguish whether a patient recovered due to compensation or shows indeed a reduction in impairment. The only accepted tool to measure impairment in the motor domain is the Fugl-Meyer Motor Assessment. (Kitago & Krakauer, 2013; Kwakkel et al., 2017). Therapies claiming to make any difference in impairment would need to show an improvement of at least 4.25 points on this scale to prove a clinically important difference as well (Page, Fulk, & Boyne, 2012). However, a better way of measuring improvement would be by obtaining unbiased physiological data, such as kinematics (Krakauer et al., 2012), spatiotemporal patterns (Latorre, Llorens, Colomer, & Alcañiz Raya, 2018), motor evoked potentials (Byblow, Stinear, Barber, Petoe, & Ackerley, 2015) or eye tracking (Delazer, Sojer, Ellmerer, Boehme, & Benke, 2018) that can be compared to clinical scales, animal data and human brain data. This would also aid in clarifying the contribution of the two mechanisms to changes in observed in behaviour and in the post-stroke brain. For this, we also need to understand better the deficits that we aim to recover.

1.4. Post-stroke deficits, differences and interrelations

Stroke is associated with a long list of complications (Benjamin et al., 2019) and most survivors suffer severe disabilities (Adamson et al., 2004) and comorbidities. Traditionally it has been thought that the lesion location is the main factor explaining the symptoms observed. Whereas motor and language deficits appear indeed to depend more on lesions in specific brain areas, lesion location was less indicative for cognitive functioning such as deficits in memory or attention. In fact, it appears that a specific deficit can be caused by damage in many different regions and that there are some regions where a neuronal loss is leading to five to six different deficits. Lesion volume, on the other hand, appears not to be indicative of the deficits observed (Corbetta et al., 2015). It appears that stroke leads to a disruption in neuronal networks which sustain sensorimotor and cognitive functioning (Guggisberg, Koch, Hummel, & Buetefisch, 2019). Consequently, stroke cohort studies show that most stroke patients are presenting deficits in various domains. Of 1259 stroke survivors only 6 % presented 1 or 2 symptoms, whereas 31.1 % had 3 to 5, 50.6 % had 6 to 10, and 10.6 % had more than ten symptoms at three months post-stroke. The most common impairments were limb weakness and cognitive impairment, amongst others (Lawrence et al., 2001). This presence of heterogeneity in deficits is not well reflected in RCTs investigating clinical interventions since often strict inclusion and exclusion criteria are applied to obtain a homogeneous sample with specific deficits and low variability. Further, the focus on specific deficits when investigating the effectiveness of interventions might not address the behavioural and neuronal interrelations between deficits. Many activities of daily living require not only motor functions but as well as various cognitive abilities to accomplish them (Hofgren, Björkdahl, Esbjörnsson, & Stibrant-Sunnerhagen, 2007). Therefore, treating deficits in isolation might not lead to the desired improvement, as various abilities that require each other are impaired. Also, the diagnosis of deficits could be enhanced if co-occurring impairments would be taken more into account. It is known that depression is frequent in stroke patients, however, it often remains undiagnosed (Hackett & Pickles, 2014; Srivastava, Taly, Gupta, & Murali, 2010). There is evidence that depression influences cognitive functioning (Kauhanen et al., 1999). It could therefore be, that patients score low on cognitive tests, not because of a cognitive deficit, but because of undiagnosed depression.

In summary, it is not only important to understand the individual impairments well, but also crucial to investigate their interrelations and address the neuronal and symptom network perspective in treatment (Borsboom & Cramer, 2013; Cumming, Marshall, & Lazar, 2013; Guggisberg et al., 2019). This might also lead to novel approaches on how to treat more heterogeneous groups of stroke patients. In the following sections, we will highlight some characteristics of and mechanisms underlying impairments specifically addressed in this thesis and point out some interrelations between them.

1.4.1. Motor impairments

With a prevalence rate up to 90%, motor deficits are the most common impairments after stroke, and upper limb deficits appear to be more frequent than lower limb deficits (Lawrence et al., 2001). It is often observed that stroke patients under-utilize their paretic limb in response to hemiparesis. Whereas compensation with the healthy limb in the acute phase might be caused by the biological recovery process that leads to reduced responsiveness, a prolonged period of non-use of the affected limb can lead to an increased loss of neuronal and behavioural function (Krakauer, 2006; Taub, Uswatte, Mark, & Morris, 2006). However, the reason for not using the paretic limb might not be based on actual capacity. The learned non-use phenomenon is given, when there is a discrepancy between a retained motor capacity, which can be retrieved by the patient when requested, and the spontaneous use of this motor capacity in daily life. This discrepancy may arise due to the experience of inept or non-productive perceived attempts to use that capacity (Hirsch et al., 2020). CIMT has been used to limit compensation with the less affected limb and to promote the use of the paretic limb. Albeit there is evidence that CIMT is effective, it is only suitable for a certain type of patients. In addition, the constraint and the intensity can compromise acceptance and adherence to CIMT (Page, Levine, Sisto, Bond, & Johnston, 2002; Sterr, O’Neill, Dean, & Herron, 2014). Hence alternative methods that build on similar principles, preferably with less intensity and no restraint should be sought. Taking a closer look at possible motor learning mechanisms that lead to learned non-use might help in this quest.

How an organism effectively accomplishes motor control is not known yet. It is thought that motor planning of voluntary action evokes predictions of expected sensory consequences and motor commands based on learned sensorimotor contingencies that are sent to the end effectors for execution. At the same time, sensory inputs must be integrated to allow the organism not only to decide whether movement outcome matches the prediction, but also to correct online when sudden disturbances require adaptation in movement to achieve a goal (Azim & Alstermark, 2015; Bolognini, Russo, Edwards, & Plains, 2016; Maffei, Herreros, Sanchez-Fibla, Friston, & Verschure, 2017). Predictions are constantly updated through new sensorimotor experiences and are not only biased by successful outcomes and the history of rewards (Marcos, Pani, et al., 2013; Sutton & Barto, 1998) but as well by the expected costs or effort associated with a given action (Marcos, Cos, Cisek, Girard, & Verschure, 2013), which in turn influence future action selection (Lisman, 2015). The prediction error can aid the system in learning how to maximise success or reward and minimise cost or effort and reinforce those motor models that optimise both (C. E. Han, Arbib, & Schweighofer, 2008). Learned non-use might be a result of repeated exposure to failures with the paretic limb (Ballester, Nirme, et al., 2015): post-stroke deficits violate existing sensorimotor contingencies and the actions with the affected arm become associated with high costs and unsuccessful outcomes. As a result, the action selection process is biased towards the healthy limb, which became associated with successful outcomes at low costs. Once this negative bias is acquired, it might persist even if the paretic limb recovers functionality, as the patient enters a vicious loop of non-use, that might be supported by the normal adaptive processes the brain possess (Ballester, Maier, et al., 2015; C. E. Han et al., 2008). Therefore, the selection process needs to be challenged by exposing the patient to new positive motor learning experiences with the paretic arm. Instead of “forcing” novel experiences, however, the patient could be instead reinforced to use the paretic limb. By manipulating the perceived prediction error, desired movement patterns can be given more reward and associated with less cost or error (Ballester, Nirme, et al., 2015; Ballester, Oliva, Duff, & Verschure, 2015).

Besides, simple repetition of identical movements might be not effective in creating long-lasting sensorimotor contingencies. A learner must be exposed to variability and novelty because after prolonged simple repetition, performance as well neuronal changes seem to plateau, and no further gains can be made. Setting goals that require various movements and steps to fulfil might be the proper setting for rehabilitation training (Nielsen, Willerslev-Olsen, Christiansen, Lundbye-Jensen, & Lorentzen, 2015). However, it appears that humans are sensitive to the magnitude of variation experienced. Adaptation to novel movements might only be enhanced if the experienced variance is within the task-relevant error values (Ballester, Oliva, et al., 2015). In very severely impaired patients where no voluntary muscle contraction is possible, alternative methods could be motor imagery or action observation. Sensorimotor contingencies might be restored through mental coactivation of the sensorimotor system (Nielsen et al., 2015).

1.4.2. Cognitive impairments

Stroke patients do not only face physical limitations. Poststroke cognitive impairment ten years after the stroke was found to be as high as 61%, pointing to a persistent cognitive decline after an initial period of recovery (Benjamin et al., 2019). Typically, cognitive deficits and physical deficits are treated and studied separately from each other (Mullick, Subramanian, & Levin, 2015), and the focus in standard care often relies on physical improvement only (Verstraeten & Mark, 2016). However, cognitive and physical impairments have interactions, that could aid in understanding post-stroke recovery and be exploited for rehabilitation purposes. With increasing age and sensorimotor deficits, the maintenance of postural control, which is typically an automatic process, appears to require more cognitive resources. Limitations in executive ability have shown to contribute to falls and gait disturbances in the elderly (Pichierri, Wolf, Murer, & de Bruin, 2011) and in stroke patients (Påhlman, Gutiérrez-pérez, Sävborg, Knopp, & Tarkowski, 2011). Many daily activities require both physical and cognitive skills, which often have to be flexibly combined on the spot to accomplish the tasks (Hofgren et al., 2007; Pichierri et al., 2011). It is therefore not surprising that a higher cognitive status at the acute phase seems to predict better motor outcome (Verstraeten & Mark, 2016). The presence of hemineglect, in addition to physical impairment, may lead to poorer functional outcome both in the ADL and mobility, independent of therapy intensity (Paolucci et al., 1996). A meta-analysis investigating the relationship between cognitive and motor improvement found that only executive function was moderately strong related to motor improvement, whereas attention showed only a weak correlation and memory did not correlate at all (Mullick et al., 2015). However, these results are based on six studies only, which demonstrates that the inclusion of cognitive and motor outcome measurements is rare in clinical trials. Also, the training protocols included varied highly in terms of type and intensity, which is why the results might conflict with the findings of other studies (Verstraeten & Mark, 2016). Hence it is difficult to make conclusions about the causality of these correlations (Mullick et al., 2015; Verstraeten & Mark, 2016).

Numerous dedicated cognitive therapies have been proposed. However, there is no strong evidence for their effectiveness. Patients appear to improve in the cognitive assessments after the treatment, but these gains do not persist nor improve everyday function (Gillespie et al., 2015). One reason for the absence of conclusive effects could be the narrow focus on patients that express a very specific syndrome or with similar lesion locations even though stroke patients typically express deficits in various cognitive domains (Leśniak, Bak, Wojciech, Seniów, & Członkowska, 2008) and the lesion location is not predictive of specific cognitive deficits (Corbetta et al., 2015). Importantly studies identified behavioural and neuronal interdependencies between cognitive domains. For instance, spatial neglect is now considered to arise from several component deficits. Besides the core deficit, the visual attention bias, patients also present spatial working memory problems, impairments in nonspatial sustained attention and motor deficits (Malhotra, Mannan, Driver, & Husain, 2004). This cooccurrence of deficits is thought to be due to an abnormal interaction between brain networks that are responsible for attention: the dorsal frontal-parietal network that controls attention and eye movements and encodes stimulus saliency, and the ventral frontal-parietal network that underlies reorienting and detection of novel behaviourally relevant events (Corbetta & Shulman, 2011). There is evidence that parietal regions are involved in episodic memory retrieval, which has given rise to the “attention to memory” model. According to this model, top-down attention is required in strategic memory retrieval, as attentional distraction impairs the ability to strategically retrieve memory items (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008). This top-down attentional modulation is thought to be involved as well in all working memory operations (expectation, encoding, maintenance and retrieval) and to regulate neuronal excitability to optimise performance through the involvement of frontal and parietal areas (Gazzaley & Nobre, 2012). However, it is not established how the frontal-parietal network achieves attention and working memory operations and interactions in cognitive tasks. This becomes apparent when looking at studies investigating executive control. There is no commonly acknowledged list of executive functions, and executive control is generally used as the umbrella term for all abilities that flexibly enable complex goal-oriented behaviour (D’Esposito & Gazzaley, 2006; Elliott, 2003; Zinn, Bosworth, Hoenig, & Swartzwelder, 2007) and that are thought to rely on both attention and working memory (Cicerone, Levin, Malec, Stuss, & Whyte, 2006), such as initiation/preservation of behaviour, cognitive persistence and flexibility, self-monitoring, and abstract thinking (including planning). Whereas some studies found evidence for a general neural basis where the prefrontal cortex drives the allocation of attention (Osaka et al., 2004), others found the allocation of attention to be located in the superior parietal cortex and to be accompanied by several separable mechanisms (Sylvester et al., 2003), depending on the working memory task used.

Together these studies might indicate that spatial neglect and executive function disabilities are a collection of symptoms that are characterised by behavioural deficits in cognitive tests and tasks that require goal-oriented behaviour, for which a disturbance in the frontal-parietal network that underlies attentional and memory processes is responsible. This notion fits well with the sensorimotor contingency theory, where cognitive processes are intertwined with perception and action and allow an agent to interact purposefully with the environment (P. F. M. J. Verschure, 2016). Hence training cognitive symptoms in isolation and also apart from physical disability might be suboptimal, neither from the behaviour or from the neuronal network perspective. Moreover, the accounts mentioned before neglect the co-occurrence of depression.

1.4.3. Depression

The presence of depression is associated with twice the chance to suffer from stroke, and one-third of stroke survivors develop depression in the first year after the incident, which worsens functional outcome and increases the risk of mortality (Benjamin et al., 2019; Hackett & Pickles, 2014). It is unclear whether post-stroke-depression is a psychological reaction to the stroke and its consequences, or is caused by biological mechanisms related to the damage in the brain (Robinson & Jorge, 2016). Besides being linked to higher dependence in ADL and more severe impairments, post-stroke depression is associated with poorer cognitive functioning (Hackett & Anderson, 2005), affecting in specific nonverbal problem solving, verbal and visual memory and attention and psychomotor speed (Kauhanen et al., 1999). Depression has as well been characterised as a cognitive deficit state, as it has been associated with a reduced capacity to direct attention and with impaired inhibitory mechanisms. Consequently, depressed individuals ruminate; they direct their attention to negative information that matches established negative memories, fail to inhibit the processing of irrelevant negative information in working memory and have difficulties to disengage from negative information, leading to attentional fatigue. According to the attention restoration theory, these negative patterns might be alleviated if the patient can gain distance from routine thoughts and can interact with a stimuli-rich environment that captures the attention in a non-effortful way (Gonzalez, Hartig, Patil, Martinsen, & Kirkevold, 2009).

It appears that the presence of post-stroke depression, but not the cognitive impairment reduces the effectiveness and progress of rehabilitation. It is hypothesised that this is due to the decreased motivation and reduced outcome exceptions that affect active participation in rehabilitation (Gillen, Tennen, McKee, Gernert-Dott, & Affleck, 2001). Besides sadness and anhedonia, depressive individuals also experience hopelessness and worthlessness, or in other words, low self-efficacy (Mukherjee, Levin, & Heller, 2006). Contrarily, higher self-efficacy has been linked to a higher quality of life, lower mood distress and depression (Robinson-Smith, Johnston, & Allen, 2000). Self-efficacy is the belief in one's capability to act in order to achieve a goal (A. Bandura, 1977), and it can be increased or reduced through experiences of success or failure. Strengthening self-efficacy appears to be the first step to develop self-management skills that allow patients to cope with their disabilities and deal with the consequences of stroke and hence improving health-related behaviours (Jones, 2006). Indeed, there is evidence that cognitive therapies that combine motor exercises and with self-assertiveness training, relaxation techniques and stress management can improve depressive moods in individuals with mild cognitive impairment. However, the reduction in depression was not related to improvements in ADL and memory ability (Kurz, Pohl, Ramsenthaler, & Sorg, 2009).

The issues brought forward here, highlight two important aspects. First, the level of depression should be clarified in clinical trials, especially when cognitive symptoms and training methods are investigated. Lower scoring in neuropsychological tests and cognitive task, as well as the absence of effects of cognitive interventions, might be due to the confounding factor of depression not due to the cognitive deficit per se. Currently, post-stroke depression often remains undiagnosed (Srivastava et al., 2010). Diagnosing depression more systematically would not only aid in interpreting clinical outcomes but also clarifying the relationship between cognitive rehabilitation, depression and cognitive functioning (Mukherjee et al., 2006). Second, interventions aiming at alleviating post-stroke depression might consider using an enriched training environment. Also, mechanisms to enhance self-efficacy, for instance, by enabling the patient to experience successful outcomes following self-generated actions, should be considered. For this reason, also the social environment needs to be involved, as self-efficacy can be modulated by the appraisal from others.

1.4.4. Social interaction and social isolation

Social interactions are important for physical and mental well-being whereas social isolation can cause serious health-related issues such as high blood pressure, increased inflammation, development of cardiovascular disorders, infections, and cognitive decline (Oddone, Hybels, McQuoid, & Steffens, 2011; Venna, Xu, Doran, Patrizz, & McCullough, 2014). The social situation after stroke (living alone, the place of residence, the presence of social support and social isolation) is a factor that has been associated with post-stroke depression (Hackett & Anderson, 2005). The prospected increase in stroke survivors, paired with earlier discharges and a prolonged life expectancy, will also increase the burden for the social environment of the patients. Some European countries have re-emphasised that the family is mainly responsible for providing post-acute stroke care (Stevens et al., 2017). Informal caregivers must deal with the patients' difficulties in mobility, self-care, communication, cognitive impairment, depression and personality changes (B. Han & Haley, 1999). This burden can have a toll on those caring for the survivors. 40% of caregivers show depressive symptoms and 21% expressed symptoms of anxiety (Benjamin et al., 2019). This can lead to a vicious cycle; The presence of depression in caregivers worsens the patient's depressive symptoms and response to rehabilitation (B. Han & Haley, 1999).

Moreover, not every stroke patient can count on a social network that will partake in the care. There has been a notable increase in the number of people living alone (Khan, Hafford-Letchfield, & Lambert, 2018). Also, difficulties in cognitive, communicative and emotional functions, changes in the social role as well as lack of mobility or employment can lead to a decline in social interactions after stroke (Mukherjee et al., 2006; Northcott, Moss, Harrison, & Hilari, 2016). The lack of support and isolation can increase the risk for recurrent strokes, lead to poorer recovery, increased functional decline and greater mortality (Venna et al., 2014). Studies in mice have shown that socially isolated animals displayed greater infarct volumes and no recovery, as compared to mice that were housed with partners post-stroke. Isolated mice also showed signs of depressive behaviour (Figure 1.3). However, animals housed with a healthy partner showed a lower mortality rate and better functional outcome than animals housed with a partner that had a stroke too (Venna et al., 2014).

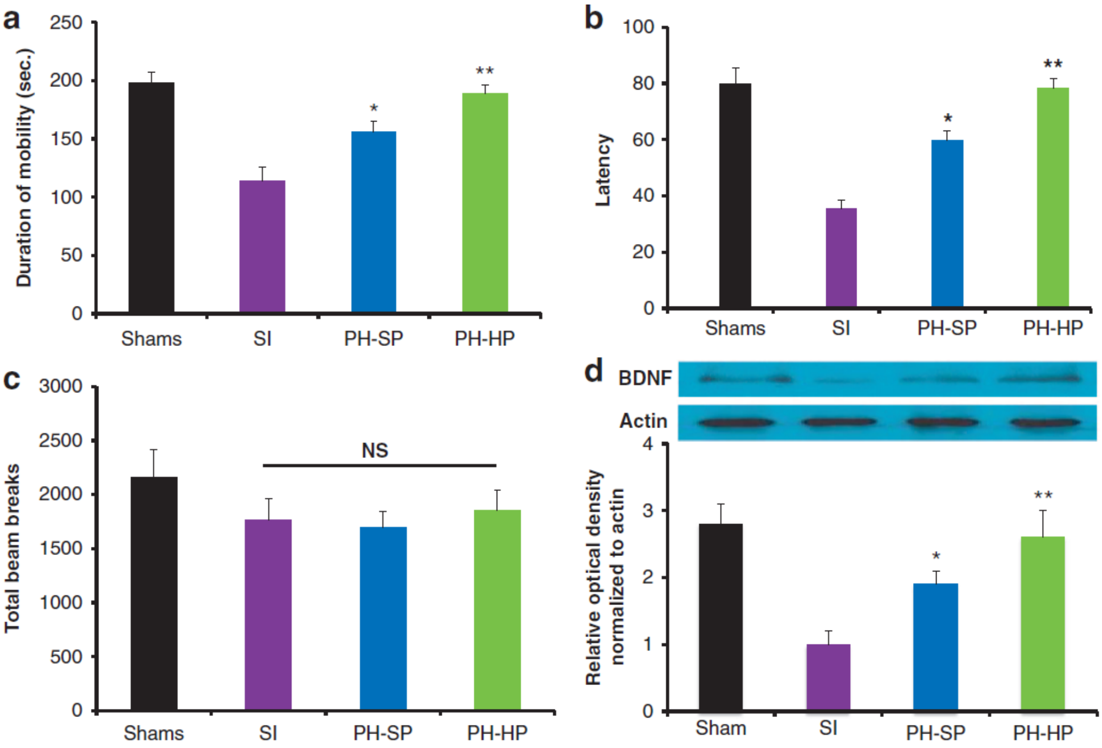

Figure 1.3. Housing with a healthy partner significantly improves long-term behaviour and enhanced BDNF compared with isolated mice or mice housed with a stroke partner.
A) SI mice showed a depression-like phenotype expressing less mobility when tested at 90 days post-stroke using the tail suspension test compare with PH-HP and shams. B) SI mice also expressed a reduced latency to the first bout of immobility compared with PH-HP and shams. C) All stroke mice expressed similar spontaneous locomotor activity when tested prior to TST. D) BDNF levels were significantly reduced at day 90 in whole brain homogenates of SI mice. β-actin was used as loading control and densitometry data are presented as normalized ratio. *p < .05 compared with PH-SP. Error bars denote standard error of the mean. Abbreviations: HP, healthy partner; PH, pair housed; SI, social isolation; SP, stroke partner. Reprinted from "Social interaction plays a critical role in neurogenesis and recovery after stroke", V. R. Venna et al., 2014, *Translational Psychiatry*, 4, 5. Copyright (2014) by Macmillan Publishers Limited.

Hence, inpatient rehabilitation is challenged to reduce disability and its associated dependency in ADL in order to relieve caregivers. Also, it is suggested that the caregiver should be included in the rehabilitation process in order to prevent health issues caused by the care burden (Pellerin, Rochette, & Racine, 2011). However, given the limitations of current rehabilitation care, alternative approaches that support the patient and their social network after discharge must be sought as well. This is even more important as the patients are required to continue with their rehabilitation programmes at home, but often fail to do so, mainly because of lack of motivation (Jurkiewicz, Marzolini, & Oh, 2011). However, including the caregivers into the home-based rehabilitation process might be beneficial for patient and caregiver alike. First, joint activities might aid adherence to home-based programmes (Jurkiewicz et al., 2011), which increases training intensity for the patient and might have a preventive effect on the caregiver's health (Oddone et al., 2011). Second, it might aid the patient's self-efficacy as well as the mutual perception between caregiver and patient, the acceptance of new social roles and the reduction of the stigma. The appraisal and acceptance from others also shape the perception of one's capability, and a caregiver might hold limiting beliefs on the capacities of the patient, which influences their social interaction (Mukherjee et al., 2006). Therefore, demonstrating one’s capabilities could have a positive effect on social interaction, self-determination and mental health. This consideration is particularly important for those that cannot count on a network for social interaction.

Common in all deficits is the notion that learning of previous or new behaviours can be fostered through a combination of sensory and cognitive experiences. However, these experiences need to be clearly defined and operationalized before they can be incorporated into rehabilitation approaches. In the following section, we will propose that this can be achieved by identifying core principles that have been shown to be beneficial for human and animal learning. By studying their behavioural and neuronal mechanisms, we can create testable hypotheses about which principles are beneficial for recovering specific post-stroke symptoms.

1.5. Challenges of the principles of learning

It has been shown in healthy animals and humans that learning can remodel the brain’s circuitry and create functionally appropriate connections (Kleim & Jones, 2008). Identifying relationships between impairments, neuronal changes and altered behavioural outcomes is challenging, as many factors that that cannot be controlled through an experiment can potentially contribute to each of these variables (Dobkin, 2005). In addition, it is assumed that the post-stroke brain could profit from experience-dependent plasticity, too (Kleim & Jones, 2008). However, it is not a given that a stroke patient’s brain will learn the same way as a healthy brain. The damaged brain undergoes many molecular and neural changes, some of which can positively or negatively influence learning behaviour (Kleim & Jones, 2008).

It is therefore important to identify and operationalize principles that have shown to govern learning in the healthy so that they can be tested in animal models and in human individuals alike. CIMT was one of the first approaches that build on insights from neuroscience studies on animal behaviour and learning. It includes a clear set of principles that should promote recovery by fostering experience-dependent plasticity (Taub, Uswatte, & Pidikiti, 1999): 1) Shaping, which is an intensive task-specific practice for the paretic limb during 6 hours a day for two weeks and that progressively increases in difficulty, 2) Constraint, restriction the use of the less affected limb in order to force the use of the impaired limb during 90% of the waking time, 3) Transfer package, which are adherence-enhancing behavioural methods that aim to transfer the outcomes from the clinic or laboratory to the patients real-world environment (Kwakkel et al., 2015). CIMT has shown to have a positive effect on body function (as measured by FM-UE) and activity (as measured by the action research-arm test, and Barthel Index) at the acute, sub-acute and chronic phase after stroke (Liu, Huai, Gao, Zhang, & Yue, 2017; McIntyre et al., 2012). CIMT is however only suitable for patients with a mild to moderate paresis and a favourable chance for dexterity early after stroke, which appears to be around 10 % of the patients that were screened for the trials included in the most comprehensive review (Kwakkel et al., 2015). Further, there is no clear evidence yet how the improvement in motor performance after CIMT related to the observed cortical changes and whether this is presenting true recovery or compensation (Kwakkel et al., 2015).

Apart from these limitations, CIMT has demonstrated that by incorporating principles as therapeutic elements into rehabilitation methods, the evidence for effectiveness for reducing impairment can be investigated systematically through many randomized controlled trials (RCT) (Nielsen et al., 2015). Grounding RCT's on explicit principles derived from existing scientific evidence for learning not only makes the outcomes comparable across studies but also aids in the decision process when conflicting outcomes are achieved. The respective likelihood of one outcome over the other could be obtained from the neurological evidence supporting them (Nielsen et al., 2015). Further, as stroke is a heterogeneous disease, operationalized principles can be combined to accommodate related symptoms through one therapy approach. Hence a synthesis of core principles that could guide novel rehabilitation could be of great value. There have been several attempts to synthesize currently known principles of learning across studies (Dobkin, 2004; Kleim & Jones, 2008; Kwakkel, 2009; M. F. Levin, Weiss, & Keshner, 2015; Thomas et al., 2017). However, they offer little concrete applicability, remain too vague, or only focused on a subset of currently known learning principles.

How can we address the challenges pointed out so far? We first need to identify the core principles of learning potentially beneficial for therapeutic approaches. In order to address the burden after stroke sustainably, overcome the pressing issues with standard care, and exploit maximally principles of learning to foster recovery, we must then explore alternative training methods. Ideally, these novel methods should generate kinematic and other detailed physiological data that can aid in understanding the emergence of proportional recovery and mechanisms of compensation and true recovery. In the last section, we will advocate that technology might be a suitable tool to overcome current limitations in rehabilitation, foster learning to promote recovery and provide scientifically valuable data.

1.6. Novel rehabilitation methods in virtual reality

As pointed out in previous sections, the amount of training, be it repetitions or time, that patients typically receive either as inpatients or in clinical studies is magnitudes lower than in studies investigating recovery in animals (Lang, MacDonald, & Gnip, 2007; Nielsen et al., 2015) and there is evidence that more training could be beneficial (Krakauer et al., 2012; Kwakkel, van Peppen, et al., 2004). Although studies appear to confirm that the largest gains in recovery are made in the earlier post-stroke phase (Kwakkel, Kollen, et al., 2004), it has been shown that reduction in impairment can be still achieved in the chronic phase, questioning the boundaries of the critical window (Ballester et al., 2019). However, it is unlikely that current rehabilitation settings will be able to answer the increased demand for long-term rehabilitation, as the resources in terms of personal and costs are limited. The only way that the therapy amount can be increased and sustained at the level needed is by using non-invasive and cost-effective methods based on technology. The patients could be familiarised to and start training with automated systems and computer programs in the acute phase alongside the rehabilitation sessions with the therapists. After discharge, the patient can continue the therapy at home using the same program as mobile versions, for instance, in the form of wearables or 3D glasses. Hence technology might accompany the patients across different phases of post-stroke, aiding in establishing a formal pathway. Also, mobile systems might support patients in their early discharge, not only because continuous therapy can be assured at the patients' residence, but also because doctors and therapists can follow-up on the patient's long-term progress and health status through telecommunication technologies and automated data reporting. This approach is especially suitable for patients in remote and non-urban areas. Technology can assist in lowering the costs of long-term stroke care. According to the road map for quality stroke care, it would be essential that stroke survivors have access to an interdisciplinary team that consists of physicians with stroke expertise, stroke nurses, nursing assistants, pharmacists, social workers or case managers, palliative care team, physiotherapists, occupational therapists and a speech-language pathologists (Lindsay et al., 2012). Technology can support these health care professional in exchanging information, covering times of great demand, and occupy patient during waiting times (Clarke et al., 2018).

Besides, automated data reporting can support the research of the recovery process (Proffitt & Lange, 2015). In order to check whether an improvement in end-point measurements was due to an actual reduction in impairment (which reflects true biological repair mechanisms), compensation or both, the kinematics of movement patterns need to be analysed. In animal models, pre-stroke and post-stroke kinematic analyses of reaching besides end-point measurement could be obtained, which could be compared to human post-stroke results (Krakauer et al., 2012). With technology, such as motion capture techniques or wearables, and algorithms that automate the process, this approach becomes feasible even in smaller proof of concept studies. Digital kinematic data can be easily compared and exchanged across studies and can provide a detailed reconstruction of motor recovery across all stages after stroke (Proffitt & Lange, 2015). Although Kinematic data is increasingly generated, it currently misses standardization and clinimetric evidence (Schwarz, Kanzler, Lambercy, Luft, & Veerbeek, 2019). Digital physiological data is also viable for assessment and diagnostics of cognitive or mental problems (Chicchi Giglioli, Bermejo Vidal, & Alcañiz Raya, 2019). For instance, memory and attentional deficits, as well as depression, can be assessed with eye tracking (S. Levin, Holzman, Rothenberg, & Lipton, 1981; Urgolites, Smith, & Squire, 2018).

Technology can allow patients to train in safe but ecologically valid environments, enriched with sensory stimuli, which provide a more controlled learning situation than real-world training set-ups (Mainetti, Sedda, Ronchetti, Bottini, & Borghese, 2013). However, in order to be effective for long-term recovery, technology-based rehabilitation methods have to incorporate evidence-based neurorehabilitation strategies and neuroscience principles (Perez-Marcos, Bieler-Aeschlimann, & Serino, 2018). We will present in the following section a well-established VR-based rehabilitation system which incorporates critical neuroscientific learning principles, which was used to develop the clinical interventions presented here.

1.6.1. The Rehabilitation Gaming System

The Rehabilitation Gaming System (RGS) is a VR-based rehabilitation tool, which combines theoretical neuroscience grounded intervention protocols with adaptation algorithms for post-stroke recovery. RGS has shown to be a valid approach to provide augmented multimodal feedback, effective sensorimotor training and aphasia training in clinical set-ups (Ballester, Nirme, et al., 2015; Cameirão, Bermúdez i Badia, Duarte Oller, Frisoli, & Verschure, 2012; Cameirão, Bermúdez i Badia, Duarte Oller, & Verschure, 2009, 2011; Cameirao, Bermudez i Badia, Duarte Oller, & Verschure, 2010; Grechuta et al., 2019).

The typical clinical set-up of RGS consists of a desktop computer with an integrated CPU that displays training scenarios to the patients and a Microsoft Kinect motion capture system (Microsoft, US). The Kinect detects the patient's upper-limb movements by tracking markers attached to the patient's arm and maps the movements to the virtual arms of an avatar. The computer and the Kinect are placed in front of the patient on top of a table. The training scenarios are played by the patient from the avatar's perspective (first-person view). The patients typically perform horizontal movements, supported by the table's surface (Figure 4.1).

Figure 1.4. Typical RGS set-up in the clinic.
RGS consists of a table, above which a desktop computer and the Kinect are placed. The patient's arms are tracked by the Kinect by detecting the markers on the forearms, and the movement is mapped to a virtual avatar displayed in the training scenarios on the screen.

The core theoretical neuroscience-based principles of learning that are beneficial for addressing the challenges of the deficits presented in the previous sections have been systematically investigated in the context of this dissertation, and the results are presented in Chapter 2 (Maier, Ballester, & Verschure, 2019). Specifically, we will provide a synthesis of all principles that we have identified in literature through a computerized search. The advantage of using a VR-based system is that certain principles can be exploited more effectively in the virtual than in the real world. In the following paragraphs, we will explain those principles that we have specifically exploited by using the technology behind RGS for the studies presented in this thesis.

RGS incorporates the neuroscientific paradigm that action execution and observation of the same action might activate the functional reorganisation of the motor and pre-motor systems that are affected by a stroke (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Small, Buccino, & Solodkin, 2012), potentially by recruiting undamaged primary or secondary motor areas through alternative sensorimotor pathways (Prochnow et al., 2013). This can be achieved as the patient controls with his movements a virtual body (avatar) on a computer screen and observes the digital movement from the first-person perspective. Execution of embodied goal-directed movement is thus coordinated with the observation of the same movement. This provision exploits in specific the principle of goal-oriented (Section 2.3.5) and action observation/embodied practice (Section 2.3.13). The sense of body-ownership, self-location and presence is augmented in the first-person perspective as compared to a third-person perspective in healthy individuals and patients is (Borrego, Latorre, Alcañiz Raya, & Llorens, 2019). fMRI studies with healthy participants showed that a first-person observation of a virtual hand is linked to contralateral praecuneus, bilateral angular gyri and contralateral extrastriate body area, which are related to sensorimotor integration, space perception to guide motor actions, as well as observation of moving body parts (Adamovich, August, Merians, & Tunik, 2009). This link between perception and action, when combined with methods to drive neuronal plasticity, creates optimal conditions for functional recovery after stroke by restoring sensorimotor contingencies (P. F. M. J. Verschure, 2011) and constitutes the core mechanisms of the studies presented in this dissertation.

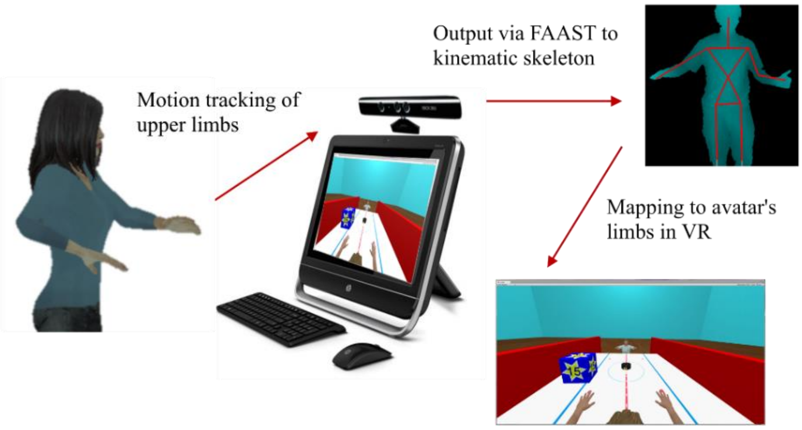

Figure 1.5. Set-up and functionality of the RGS-system.
The user's motion is tracked by a motion capture system (Kinect, Microsoft, Seattle) and mapped via the Flexible Action and Articulated Skeleton Toolkit (FAAST) on the virtual limbs of the avatar. By adapting the mapping, the user performs different tasks viewing the avatar from a first-person perspective.

One of the advantages of RGS is that the mapping between the real and the virtual arm can be modulated in order to improve recovery (Ballester et al., 2016). In specific, we can amplify the actual movement trajectory of the user in extent and accuracy towards a goal which matches the user's intention but facilitates the achievement of the goal. Hemiparetic stroke patients are often unable to perform a full extension of the arm, thus limiting their physical range of motion. By applying goal-oriented virtual movement amplification to the paretic limb, the visuomotor feedback is altered, e.g. the subject is exposed to diminished reaching errors. Importantly the manipulation is not disclosed to and cannot be perceived by the participant. This visual manipulation might be beneficial for promoting the use of the paretic limb and counteract learned non-use. As the patient is repeatedly exposed to less error feedback while performing active movements and embodied training, and hence perceives more successful reaching attempts, the increased use of the paretic arm is reinforced. Since the training scenarios within RGS are performed through a virtual body, the tasks include bi-manual training, hence equilibrize the usage of both limbs. This hypothesis is explored in detail in the clinical study presented in Chapter 4 (Ballester, Nirme, et al., 2015) and effectively links the principles of enhancing effector selection (Section 2.3.12), by providing implicit feedback (Section 2.3.11) during goal-oriented practice (Section 2.3.5) and action observation / embodied practice (Section 2.3.13). Successful movements are rewarded with points, reinforcing those actions by addressing the principle of providing explicit feedback (see Section 2.3.10). Further, this visual amplification can diminish the difference in performance between two players. Hence, a patient can compete on eye level with a healthy subject within the same training scenario. Being able to compete on the same level, allows for meaningful social interaction with a caregiver and might enhance self-efficacy as well as change mutual perception. In Chapter 6, (Maier, Ballester, Duarte Oller, Duff, & Verschure, 2014) we present the results of a pilot study that investigated this hypothesis that addresses the principle of providing social interaction (Section 2.3.15).

In addition, the training in RGS can be individualised. The difficulty of the tasks can be automatically adjusted to the patient's capacity. An algorithm can optimise specific elements of the training (for instance the speed of an object that must be intercepted) based on the ongoing performance in the task in order enable the patient to obtain a stable success rate. This has two advantages. First, it provides training at an optimal challenge level, as the task is never perceived too difficult nor too easy (Guadagnoli & Lee, 2004; Marteniuk, 1976). Second, a wide range of patients can be included in the same training paradigm. In Chapter 5 (Maier, Ballester, Bañuelos, Duarte Oller, & Verschure, 2020) we present the results of a clinical trial where we exploited this mechanism to simultaneously train various cognitive deficits in an individualised manner and which addresses the principle of providing increasing difficulty during practice (Section 2.3.7).

Moreover, the RGS training scenarios presented in this dissertation incorporate rich visual and auditory feedback addressing the principles of multisensory stimulation (Section 2.3.8), as well as a variety of tasks and target arrangements that foster variable proximal and distal movements addressing the principle of variable practice (Section 2.3.6). Further, they adhere to the principle of spaced practice (Section 2.3.2) as they allow for breaks within a session and across intervention time. This framework of RGS allows to flexibly deploy scenarios addressing specific needs (Cameirao et al., 2010). Lastly, detailed kinematic and behavioural data can be obtained through RGS (Proffitt & Lange, 2015). In Chapter 7 (Maier, Ballester, San Segundo Mozo, Duff, & Verschure, 2015a) and 8, (Maier et al., 2018) we demonstrate how this data can deliver valuable insights into behaviour and can be potentially used as diagnostics.

Although novel technology-based rehabilitation methods like RGS have increasingly been used in the last years, and some systems have proven to be beneficial for a variety of neurological conditions (Lucca, 2009), there has not been a consensus on the effectiveness of VR-based therapies (Laver et al., 2017; Saposnik et al., 2016). However, this contradiction might not be that surprising given that VR is intrinsically neutral to its use, which means that interventions are effective because they can mobilise recovery mechanisms, not because they use a certain type of technology. Hence technology-based therapeutic tools like RGS that incorporate principles of neurorehabilitation that foster learning and recovery might be more effective than those systems that do not. In Chapter 3, (Maier, Ballester, Duff, Duarte Oller, & Verschure, 2019a) we present the results of a meta-analysis that investigated this hypothesis.

1.7. Thesis outline

As outlined in the introduction, stroke is a societal burden that requires a change in how rehabilitation is provided in order to address the increasing demand for long-term care. In this vein, current standard rehabilitation methods must be revised. They are not only unsuitable to accommodate the number of stroke survivors in need for therapy but also show limited effect on recovery. In order to be able to find novel rehabilitation methods, a better understanding of the post-stroke consequences and the recovery processes must be obtained. One approach brought forward in this dissertation is to consider the behavioural and neuronal interrelation of symptoms and hence adopt a more holistic view on recovery. Once we identified concrete factors that appear common or unique between symptoms, we can revert to the neuroscientific knowledge obtained from human and animal learning to select methods that could be beneficial to induce recovery through behavioural changes. We propose that VR-technology is the most suitable medium to test and deliver these methods. Technology-based systems are not only cost-effective, scalable and widely accessible but also offer several methodological advantages when realising rehabilitation protocols. In specific, they allow us to alter sensorimotor perception, provide highly individualised training, obtain insight into behavioural mechanisms for treatment protocols and diagnosis, beyond real-world applications. Accordingly, this dissertation elaborates in its core how to design, test and deliver neuroscience-based protocols that incorporate principles of learning, by using the advantages of technology. In order to accommodate this goal, this work is divided into three parts. In the first part (Chapter 2 and 3), we synthesise the core principles of learning and demonstrate that the application of these principles in VR-based rehabilitation methods leads to effective recovery. In the second part (Chapter 4, 5 and 6), we present the results of three studies that tested the application of principled-based therapy methods in RGS to address physical, cognitive and social deficits post-stroke. In the last part (Chapter 7 and 8), we discuss two possible methods of how digital data obtained from a VR-based training of stroke patients can aid in understanding cognitive and mental deficits and, importantly, serve as diagnostics. The chapters are arranged as follows:

Part I – Principles of neurorehabilitation

What are the principles underlying effective neurorehabilitation? We first aim to unify the neuroscientific literature on human and animal learning that is potentially relevant to the recovery process and rehabilitation practice. Hence we provide in **Chapter 2** (Maier, Ballester, & Verschure, 2019) a synthesis of the principles that could constitute an effective neurorehabilitation approach. We conducted a computerised search and identified 15 principles of learning based on existing literature. We comment on trials that successfully implemented these principles, and report evidence from experimental and clinical work.

Are principle-based neurorehabilitation approaches more effective? Next, we explore if the principles of neurorehabilitation are used in current VR-based systems and whether their incorporation influences recovery. No consensus has been reached on whether rehabilitation in VR is effective or not. In **Chapter 3** (Maier, Ballester, Duff, et al., 2019a) we argue that it is not the technology that determines effectiveness, but the ability of the technologically implemented intervention to mobilise recovery mechanisms. We hypothesise that VR-based systems that were specifically built for rehabilitation might capitalise on the advantages of technology to implement neuroscientific grounded protocols. Hence, they might be more effective in recovering upper-limb function and activity than systems that were designed primarily for recreational gaming. We tested this hypothesis by conducting a meta-analysis over 30 randomised controlled trials, comparing the recovery effect of specifically build and non-specific VR-systems to conventional therapy outcomes. The results show that specifically build VR-systems have a significant impact on body function and activity measures, which was not present in non-specific systems. Also, we identified six principles of neurorehabilitation that are present in specific VR-systems and that are possibly responsible for the positive effect found.

Part II – Approaches for rehabilitation

How can we use principle-based technology to reverse learned non-use? In the first clinical evaluation presented in **Chapter 4** (Ballester et al., 2016) we aim to explore if the motor function of the paretic arm can be restored by maximising its use. We introduce a novel rehabilitation approach called Reinforcement-Induced Movement Therapy in RGS that exposes the patients to amplified goal-oriented movements which match their intended actions but reduce the error feedback. This approach promotes the principle of enhancing effector selection by providing implicit and explicit feedback during goal-oriented embodied practice. We hypothesise that this method reverses learned non-use and induces motor improvements because it reinforces paretic arm use. We conducted a randomised, double-blind clinical trial with 18 stroke patients, that lasted for six weeks. Whereas the experimental group was exposed to goal-oriented movement amplification, the control group followed the same training but without the amplification. The results show that both groups made significant motor gains after treatment, but only the experimental group continued to exhibit further significant gains at 12-weeks follow-up.

How can we use principle-based technology to train various cognitive domains together? To address the heterogeneity in stroke patients, we extend the physical training of RGS with cognitive rehabilitation. In the second clinical evaluation presented in **Chapter 5** (Maier et al., 2020) we aim to explore the effect on improvement if various cognitive deficits are trained together. The novel method called Adaptive Conjunctive Cognitive Training adapts training elements automatically to each patient's ability, providing training at the optimal challenge point. This approach addresses in specific the principle of increasing difficulty. We hypothesise that this approach can equalise performance and has a positive effect on the patient's impairment level in the four cognitive domains. We also investigate the influence of depression on the outcomes. We conducted a randomised controlled pilot trial with 30 stroke patients, that lasted for six weeks. The experimental group followed the adaptive conjunctive cognitive training in the hospital, whereas the control group solved standard cognitive tasks at home. The results indicate that the experimental group improved over time in three out of five cognitive measures. We further identify changes in depression levels that differed between the two groups.

How can we use principle-based technology to incorporate social interaction? Psychosocial aspects influence both physical and cognitive recovery. Hence, a holistic training approach must account for psychosocial factors as well. In the study presented in **Chapter 6** (Maier et al., 2014) we aim to explore the patient's social environment and the psychosocial dynamics between patient and caregiver. We extend RGS with a multiplayer game that uses the goal-oriented movement amplification to compensate for the patients' the motor impairment and enable them to compete with healthy participants on the same performance level. This approach capitalises on the principles explicit and implicit feedback, action observation and social interaction. We hypothesise that this method influences the psychosocial dynamics of patient and caregiver, as it increases self-efficacy and mutual perception. We conducted a psychosocial study and tested the method in two at-home case studies. The results suggest that this approach can equalise the performance between a healthy and a disabled player and benefit social interaction.

Part III – Approaches for diagnostics

What can we learn about spatial neglect from applying principle-based technology? In **Chapter 7** (Maier, Ballester, San Segundo Mozo, Duff, & Verschure, 2015b) we explore the possibility to use the data obtained in the study presented in Chapter 4 to diagnose the extent of spatial neglect. Neglect patients are often not aware of their impairment, which makes diagnosis difficult and current methods therefore not reliable. In addition, we assume that the training with RGS could be beneficial to counteract neglect as it might restore the perception of the neglected side as it capitalised on the principle of goal-oriented practice, paired with action observation and implicit feedback. In a case study, we were not only able to visualise the neglected area but as well show an improvement in the neglected space.

What can we learn about depression from applying principle-based technology? In **Chapter 8** (Maier et al., 2018) we use the data we obtained in the study presented in Chapter 5 to examine the relationship between depression and cognitive functioning. Analysing the data of a psychophysical task, which was one of the evaluation tasks, reveals that depression influences top-down conscious processing of stimuli but not bottom-up subconscious processing. Further evaluation reveals an interaction with visuoperceptual speed and working memory capacity. It appears that depression might act like a cognitive load impairing proper conscious processing. Using this psychophysical task within RGS could be a diagnostic extension to reveal undetected depressive moods.

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Part II

Principles of Neurorehabilitation

Chapter 2

PRINCIPLES OF NEUROREHABILITATION AFTER STROKE BASED ON MOTOR LEARNING AND BRAIN PLASTICITY MECHANISMS

This chapter is based on the following published work:

Maier, M., Ballester, B. R., & Verschure, P. F. M. J. (2019). Principles of neurorehabilitation after stroke based on motor learning and brain plasticity mechanisms. *Frontiers in Systems Neuroscience, 13, 74.*

What are the principles underlying effective neurorehabilitation? The aim of neurorehabilitation research is to identify interventions that improve the patient's health status. In this vain, the active ingredients responsible for the observed improvement need to be determined and clearly defined. A sharp definition of principles that govern the rehabilitation process also enables the community to compare the outcomes across studies. This is particularly important if neuroscientific studies intend to infer from behavioural changes to neurological changes in the post-stroke brain. In this chapter, we aim to unify the neuroscientific literature on human and animal learning that is potentially relevant to the recovery process and rehabilitation practice. It can serve clinicians and researchers as a synthesis of the principles that could constitute an effective neurorehabilitation approach. We conducted a computerised search and identified 15 principles of learning based on existing literature: massed practice, spaced practice, dosage, task-specific practice, goal-oriented practice, variable practice, increasing difficulty, multisensory stimulation, rhythmic cueing, explicit feedback/knowledge of results, implicit feedback/knowledge of performance, modulate effector selection, action observation/embodied practice, motor imagery, and social interaction. We comment on trials that successfully implemented these principles and reported evidence from experimental and clinical work. Most of these principles have been successfully applied and tested within the framework of RGS, and we will present some of the resulting methods in the second part of this dissertation. Hence, the principles identified here are not only relevant for real-world interventions but should also guide the development of new technology-based rehabilitation methods.

2.1. Background

So far, there is no clear understanding of the principles underlying effective neurorehabilitation approaches. Therapeutic protocols can be readily described by the following aspects: the body part trained (e.g., the legs), the tools or machines used for the training (e.g., a treadmill), the activity performed (e.g., walking), and when the therapy commences (e.g., during the acute phase after a stroke). However, an intervention includes more elements. For instance, the use of the less affected limb can be restricted, and the therapist can encourage the patient to spend more time exercising or give feedback about task performance. While some interventions, like constraint-induced movement therapy (CIMT), clearly define their active ingredients (Carter, Connor, & Dromerick, 2010; Proffitt & Lange, 2015) that should lead to effective recovery (Kwakkel et al., 2015), most others do not. Neurorehabilitation research aims to find interventions that promote recovery and to establish whether the presence or absence of improvement can be explained by any neuronal changes that occur in the post-stroke brain (Dobkin, 2005). Neuroscience can help us to create interventions that lead to changes in the brain; however, with no clear understanding of what an intervention does, attributing causality remains difficult. One way to formalize an intervention is by breaking it into parts, studying the behavioural and neural effects of these parts, and deriving principles from them–in the case of stroke neurorehabilitation, these would be principles that optimize acquisition, retention, and generalization of skills.

While there are plenty of meta-analyses that look at training effectiveness in terms of individual body parts/functions, tools, or machines and activities (Langhorne, Coupar, & Pollock, 2009; Veerbeek et al., 2014), the effect of experience remains much less clear in spite of attempts to formalize and identify the principles of neurorehabilitation. A review of the principles of experience-dependent neural plasticity by Kleim and Jones, 2008 explains why training is crucial for recovery. According to their work, neurorehabilitation presumes that exposure to specific training experiences leads to improvement of impairment by activating neural plasticity mechanisms. Consequently, most of the work in the field focuses on the identification of scientifically grounded principles that should guide the design of these training experiences. In this vein, Kleim and Jones elaborated on five main principles of effective training experience — specificity, repetition, intensity, time, and salience — but offered little concrete applicability (Kleim & Jones, 2008). Another synthesis addressed further principles (forced use, massed practice, spaced practice, task-oriented functional training, randomized training); however, the main focus of the review was on individual body functions, methods, or tools, providing a global view on rehabilitation strategies (Dobkin, 2004). Two meta-analyses investigated specific principles. One looked only at the principle of intensity and found that more therapy time did enhance functional recovery (Kwakkel, 2009). Another determined that repetition does improve upper and lower limb function (Thomas et al., 2017). However, both studies did not investigate the mechanisms that would lead to the effects observed. Similarly, a review that analysed CIMT, which combines several principles in one method, gained interesting insights in its efficacy but did not explain the results from a neuroscientific, mechanistic point of view (Kwakkel et al., 2015). The work by Levin et al., 2015, on the other hand, tried to link the principles of motor learning to the application of these principles in novel rehabilitation methods while offering some neuroscientific reasoning for doing so. Their review addresses the difficulty of the task, the organization of movement, movements to the contralateral workspace, visual cues and objects and the interaction with them, sensory feedback, feedback about performance and results, repetitions, variability, and motivation. However, the included motor control and motor learning principles were not well defined and therefore leave room for interpretation (M. F. Levin et al., 2015).

For the meta-analysis presented in the next chapter (see Chapter 2), we started to compile a list of principles for neurorehabilitation based on literature on motor learning and recovery: massed practice, dosage, structured practice, task-specific practice, variable practice, multisensory stimulation, increasing difficulty, explicit feedback/knowledge of results, implicit feedback/knowledge of performance, movement representation, and promotion of the use of the affected limb. We then performed a content analysis to determine whether these principles were present in the clinical studies included in the review, but we did not provide an analysis of the principles identified. In this chapter, we present the complete list of principles we have identified so far. For each principle we unify the neuroscientific literature from human or animal studies on motor learning and comment on the observed neuronal effects. We also include evidence from clinical studies to show its effect in recovering functionality after stroke. Some principles already serve as building blocks of effective rehabilitation programs, e.g. CIMT (Kwakkel et al., 2015), Bobath (Kollen et al., 2009), enriched rehabilitation (Livingston-Thomas et al., 2016), virtual reality (VR)-based rehabilitation (Laver et al., 2017), and exogenous or robotic interventions (Langhorne et al., 2011). However, transferring these principles into clinical practice faces the challenge of operationalizing them. We comment on these difficulties and the gaps between theory, evidence, and operationalization that we encountered. Consequently, this work can serve clinicians and researchers as a practical guide of principles to investigate further effective neurorehabilitation approaches.

2.2. Methods

In this conceptual analysis, the rehabilitation experience is broken down into individual parts that are termed principles of neurorehabilitation. They are principles because they are evidenced by experimental data, and together, they could form the foundation of a higher-order theoretical framework. As a first attempt, a list of 11 principles was compiled for the meta-analysis presented in the next chapter (see Chapter 2). The list has been revised, and additional principles have been identified through a computerized search in PubMed Central using the keywords “principles of motor learning,” “principles of recovery,” “principles of experience-dependent learning” and “principles of neurorehabilitation.” We restricted the search to the last five years to obtain currently used principles. We focused on reviews, perspectives, and debates around rehabilitation methods and interventions for stroke recovery and excluded articles that explained study protocols or clinical trials, prevention methods, pharmaceutical or medical interventions, or stroke taxonomies. The principles mentioned in each paper were compared with the original list and added if they were not present. Afterwards, we summarized for each principle the historical background based on learning literature and its contribution to motor learning based on human or animal studies. Further, where available, neurological effects and clinical outcomes were included as well.

2.2.1. Identification of principles of neurorehabilitation

Our computerized search yielded 548 records, of which 74 were deemed adequate for further screening after we examined if their titles either contained any of the search terms or appeared to discuss post-stroke rehabilitation strategies. After analysis of their abstracts and full texts, the principles mentioned in 17 articles were extracted. We excluded papers if their title or abstract reported or compared surgical or pharmaceutical interventions as well as if they discussed stroke taxonomies, proposed study protocols or clinical trials, covered principles unrelated to stroke and/or stroke rehabilitation itself (e.g., principles for disease prevention, pre- and post-operative care, care facilities, patient management, therapist education, nursing practice, dietary recommendation, veterinary etc.), or looked into patient or caregiver perception. The articles and reviews selected spawned various research fields in neurorehabilitation: Motor learning (Winstein, Lewthwaite, Blanton, Wolf, & Wishart, 2014), therapies (physical therapy (Veerbeek et al., 2014), upper limb immobilization (Furlan, Conforto, Cohen, & Sterr, 2016), environmental enrichment (Livingston-Thomas et al., 2016), aerobic training (Billinger, 2015; Hasan, Rancourt, Austin, & Ploughman, 2016), CIMT (Kwakkel et al., 2015; J. Zhang et al., 2017), cognitive rehabilitation (Middleton & Schwartz, 2012), music therapy (Y. Zhang et al., 2016)), tools and methods (hand robotics (Yue, Zhang, & Wang, 2017), VR (Darekar, McFadyen, Lamontagne, & Fung, 2015; Fu, Knutson, & Chae, 2015), neurofeedback (Renton, Tibbles, & Topolovec-Vranic, 2017) and principles (dose and timing (Basso & Lang, 2017)). Together with previously collated literature, we identified 15 principles.

The identified principles that were included in the meta-analysis as well are as follows:

- Massed practice/repetitive practice (Fu et al., 2015; Furlan et al., 2016; Kwakkel et al., 2015; Middleton & Schwartz, 2012; Veerbeek et al., 2014; Y. Zhang et al., 2016)

- Spaced practice (Billinger, 2015; Hasan et al., 2016; Livingston-Thomas et al., 2016; Middleton & Schwartz, 2012)

- Dosage/duration (Basso & Lang, 2017; Billinger, 2015; Darekar et al., 2015; Hasan et al., 2016; Kwakkel et al., 2015; Livingston-Thomas et al., 2016; Veerbeek et al., 2014; Winstein et al., 2014; J. Zhang et al., 2017)

- Task-specific practice (Fu et al., 2015; Furlan et al., 2016; Kwakkel et al., 2015; Livingston-Thomas et al., 2016; Veerbeek et al., 2014; Winstein et al., 2014; Yue et al., 2017)

- Variable practice (Darekar et al., 2015; Fu et al., 2015; Livingston-Thomas et al., 2016)

- Increasing difficulty (Fu et al., 2015; Furlan et al., 2016; Hasan et al., 2016; Kwakkel et al., 2015; Livingston-Thomas et al., 2016; Winstein et al., 2014; J. Zhang et al., 2017)

- Multisensory stimulation (Livingston-Thomas et al., 2016; Veerbeek et al., 2014; Yue et al., 2017)

- Explicit feedback/knowledge of results (Darekar et al., 2015; Fu et al., 2015; Middleton & Schwartz, 2012; Renton et al., 2017; Veerbeek et al., 2014)

- Implicit feedback/knowledge of performance (Darekar et al., 2015; Fu et al., 2015; Renton et al., 2017; Veerbeek et al., 2014; Yue et al., 2017; Y. Zhang et al., 2016)

- Modulate effector selection (Furlan et al., 2016; Kwakkel et al., 2015; Veerbeek et al., 2014; Winstein et al., 2014; J. Zhang et al., 2017)

- Action observation/embodied practice (Fu et al., 2015; Veerbeek et al., 2014; Yue et al., 2017)

Additional principles encountered through the search:

- Goal-oriented practice (Fu et al., 2015; Winstein et al., 2014; Yue et al., 2017)
- Rhythmic cueing (Middleton & Schwartz, 2012; Veerbeek et al., 2014; Y. Zhang et al., 2016)
- Motor imagery/mental practice (Veerbeek et al., 2014)
- Social interaction (Fu et al., 2015; Livingston-Thomas et al., 2016; Winstein et al., 2014; J. Zhang et al., 2017)

In the following sections, we summarize for each principle the theoretical background, the evidence for motor learning, and the clinical effectiveness. We also added studies that comment on the neurological changes observed after applying the principles in motor learning tasks. The detailed neurological changes reported by these studies can be found in Table 2.1.

2.3. Results

2.3.1. Massed practice/repetitive practice

Massed practice was defined as work episodes with very brief to no rest periods (Schmidt & Lee, 2011). Within a work episode, a skill can be trained repeatedly in a *constant* or *blocked* fashion (Robert B. Ammons, 1947; Mulligan, Guess, Holvoet, & Brown, 1980). In the field of rehabilitation, the term describes the prolonged and repeated use of the more affected limb (Taub et al., 1999). Theoretically, learning through repetitions can speed-up the shaping of priors, which, together with likelihoods based on sensory input, aid in making an optimal estimate for action selection (Körding & Wolpert, 2006). Animal studies have shown that repeating skilled movements leads to localized changes in the area responsible for the movement, whereas the pure repetition of unskilled movement does not (Plautz, Milliken, & Nudo, 2000). In humans, early studies have shown that blocked practice leads to faster acquisition, but poorer retention and less transfer than variable practice (J. B. Shea & Morgan, 1979) and that massed practice without breaks seems less effective for motor performance (R. B. Ammons & Willig, 1956; Robert B. Ammons, 1947).

In standard therapies or clinical studies, the amount of repetition is typically not quantified but was observed to be an order of magnitude lower than in studies investigating recovery in rats and monkeys (Lang et al., 2007). Instead, the evidence for massed practice relies typically on the number of sessions or duration (French et al., 2016). A study looking into the feasibility of translating repetition amounts of animals to humans found improved motor functioning after training with high-repetition doses. However, no “pure” repetition training was provided, as the protocol included a variety of tasks that increased in difficulty (Birkenmeier, Prager, & Lang, 2010). On the contrary, a study comparing four groups with different repetition amounts did not find significant differences based on the number of repetitions (Basso & Lang, 2017). This intervention included other principles as well. Meta-analyses confirm the mixed effects of repetitive training on improvement (French et al., 2016; Langhorne et al., 2011; Thomas et al., 2017; Veerbeek et al., 2014). Hence, massed practice appears to be a commonly used ingredient, but its clinical operationalization is often confounded with other principles. In order to investigate its true effects on recovery and compare across studies, the repetitions within a training session and across therapy duration should be measured and quantified.

2.3.2. Spaced practice

Spaced practice implies that training should be structured in time to include rest periods between repetitions or sessions (T. D. Lee & Genovese, 1988; Schmidt & Lee, 2011). Instead of spaced practice, the term *distributed practice* is often used in literature. However, some authors use the term distributed practice as a combination of spaced and massed practice (Cepeda, Pashler, Vul, Wixted, & Rohrer, 2006). Research on human skill acquisition suggests that increasing the time spacing between learning periods improves final test performance (Cepeda et al., 2006). However, when these learning periods are too long, learning and retention rates drop (Savion-Lemieux & Penhune, 2005). The mechanisms behind the effects of distributed practice remain unclear. It has been hypothesized that the first exposure to a stimulus pre-activates its representation in memory, requiring no further activation in a subsequent repetition trial, leading to a poorer internal representation of that stimulus, which has been termed as the repetition suppression effect (Gerbier & Toppino, 2015). Animal and fMRI studies support this hypothesis, showing that neuronal activation decreases after stimulus repetition where the magnitude is modulated by the delay between the first and second presentation, with larger delays leading to greater decreases (Brown, Wilson, & Riches, 1987; R. N. A. Henson, 2003; R. N. Henson, Rylands, Ross, Vuilleumeir, & Rugg, 2004; R. Henson, Shallice, & Dolan, 2000). Spaced practice might counteract the repetition suppression effect by cancelling stimulus priming (Gerbier & Toppino, 2015). Transcranial magnetic stimulation (TMS) revealed that primary and supplementary motor areas are involved in motor memory consolidation (Censor & Cohen, 2011), which might be facilitated by spaced practice. Further, learning and physical activity have been linked to hippocampal neurogenesis (Praag, Kempermann, & Gage, 1999). Animal studies also suggest that spaced practice facilitates long-term memory formation (Okamoto, Endo, Shirao, & Nagao, 2011; Yamazaki, Nagao, Lennon, & Tanaka, 2015) by fostering the survival of cells in the dentate gyrus that are important for learning and memory (Sisti, Glass, & Shors, 2007). Also, in vivo spacing of electrical stimulation facilitates the recruitment of protein-synthesis-dependent processes, which facilitates late long-term potentiation (LTP) effects (Gerbier & Toppino, 2015; Scharf et al., 2002).

In the clinical field, only a few studies have investigated the effect of spacing on post-stroke recovery. A clinical study that investigated whether a CIMT protocol could be distributed over more days with less therapy time per day showed improvement in motor outcomes that were similar to previous CIMT protocols and superior outcomes in long-term quality of life (Dettmers et al., 2005).

2.3.3. Dosage

Unlike in pharmacology, dosage is an ill-defined term in rehabilitation (Dobkin, 2005; Kwakkel, 2009). Generally, it is operationalized as the number of hours spent in therapy (Basso & Lang, 2017; Birkenmeier et al., 2010; Kwakkel, 2009; Veerbeek et al., 2014), the frequency of training sessions and the duration of a session (Dobkin, 2005), or the training amount required to stimulate learning (Wadden et al., 2017). High dosages are often equated with high intensity of training (Kwakkel et al., 2015). However, the intensity of training could also be operationalized as the metabolic cost, work rate, or perceived intensity through exertion (Billinger, 2015; Hasan et al., 2016), which are rarely measured in standard therapies except in fitness and aerobic protocols (Kwakkel, 2009).

Typically, inpatients receive only 22 (Veerbeek et al., 2014) to 60 minutes of training a day, with fewer minutes at later stages (Schaechter, 2004). There is some evidence that increasing therapy hours would be beneficial to speeding up functional recovery (Lohse, Lang, & Boyd, 2014; Veerbeek et al., 2014). At least 16 hours of extra training (e.g., 71 more minutes per day for three months) within the first six months seem to be required for functional gains (Kwakkel, van Peppen, et al., 2004; Veerbeek et al., 2014). However, there is some controversy over the benefits of increased training early after stroke (Dromerick et al., 2009; Kwakkel, 2009; Schaechter, 2004), and a pooled analysis revealed no evidence of an effect of additional doses (Hayward et al., 2014). Hence, the exact dose-response for different therapies at different stages post-stroke needs to be determined (Basso & Lang, 2017; Kwakkel, 2009). Also, it seems that motor performance needs to reach an asymptotic level in the first session to facilitate delayed performance gains across sessions or days. Therefore, delayed performance gains seem not to depend on repetition or over-night consolidation, but on the amount of training that induces asymptote in the individual’s performance (Hauptmann, Reinhart, Brandt, & Karni, 2005). Neurologically, high-dose rehabilitation protocols with extended training hours possibly induce structural plastic changes as well as a reorganization of neural networks (summarized by (Kwakkel et al., 2015), increase cortical excitability and improve motor function and use (Liepert, Bauder, Miltner, Taub, & Weiller, 2000; Veerbeek et al., 2014). Several studies observed a normalization in ipsilesional cortex activity, which could underlie the functional gains (Schaechter, 2004).

2.3.4. Task-specific practice

Task-specific practice postulates that changing the conditions of a task might require a change in the abilities needed to execute it; conditions during training should match the conditions during testing (Schmidt & Lee, 2011). Thus, the specific conditions of practice shape the internal sensorimotor representation of the skill learned (Nudo, Milliken, Jenkins, & Merzenich, 1996; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004), leading potentially to highly specialized skills (Keetch, Lee, Schmidt, & Young, 2005) whose performance is superior in transfer tasks that meet the training conditions (Schmidt & Lee, 2011). Grounded in this principle, conventional rehabilitation protocols focus their training on the execution of activities of daily living (ADL), as they are deemed meaningful to the patient (Hubbard, Parsons, Neilson, & Carey, 2009). Since the main target of rehabilitation is to enable the patient to perform ADL independently (Winstein et al., 2014), therapy might not prioritize the restoration of pre-stroke movement patterns but allows the patient to acquire compensatory movement skills.

One study with a large sample size found that task-specific practice appears to be similar to standard therapy in improving motor functionality (Winstein, Wolf, et al., 2016). On the other hand, smaller fMRI studies found that task-specific training facilitated motor learning and retention (Boyd, Vidoni, & Wessel, 2010) and induced a change in the laterality index, which was confirmed in other studies as well (Jang, Cho, Lee, & Park, 2003; Wilkins et al., 2017). However, while two studies found reduced activity in the contralesional cortex, one (Jang et al., 2003) found changes in neuronal activity patterns in both hemispheres. A study with TMS demonstrated a trend towards reduced interhemispheric inhibition following task-specific training (Singer, Vallence, Cleary, Cooper, & Loftus, 2013).

2.3.5. Goal-oriented practice

Since a given goal (e.g., throwing a ball into the basket) could be accomplished by many different motor synergies, it is assumed that movement control is achieved through the coupling of goal-specific functional movements. Goal-oriented practice, therefore, does not emphasize primarily individual muscles or movement patterns involved in execution but requires the patient to explore the couplings that are suitable to achieve the task (Horak, 1991). In general, motor skill performance and learning are enhanced if attention is directed to the effect of movement instead to the movement itself (Wulf & Prinz, 2001). Goal-oriented movements appear to produce a better reaching performance than the same movements without a goal (Wu, Trombly, Lin, & Tickle-Degnen, 2000), and setting specific, difficult goals leads to higher motor learning performance than non-specific goals (Gauggel & Fischer, 2001). It appears that probing a skill in a goal-directed fashion after overnight consolidation promotes better performance than probing the skill by drawing attention to finger movements (Cohen, Pascual-Leone, Press, & Robertson, 2005). Evidence from studies looking into tool-use in animals and humans suggest that, neurologically, action goals are represented as effector-dependent in the anterior intraparietal sulcus and primary motor areas, and as effector-independent in the ventral intraparietal sulcus and premotor cortex (Gallivan & Culham, 2015). Goal-oriented movements produce higher activity in sensorimotor areas (Nathan, Prost, Guastello, Jeutter And, & Reynolds, 2012).

There is some evidence that goal-oriented practice is beneficial for recovery (Bosch, O’Donnell, Barreca, Thabane, & Wishart, 2014). However, the described interventions seem to be confounded by other principles that are sometimes ascribed to goal-oriented training (Harvey, 2009).

2.3.6. Variable practice

Variable practice can be achieved in two ways: 1) by providing variability within a training sequence, a method termed as *variability of practice* (Schmidt, 1975), or 2) by randomizing the presentation of individual training sequences, a method termed as *random practice* or *contextual interference* (Battig, 1966; J. B. Shea & Morgan, 1979). Both methods have been shown to lead to better retention (C. H. Shea & Kohl, 1991) and enhanced generalization to similar but untrained tasks (McCracken & Stelmach, 1977) or movements (Theo Mulder & Hochstenbach, 2001; H. Park, Kim, Winstein, Gordon, & Schweighofer, 2016; J. B. Shea & Morgan, 1979), despite hampering initial performance (J. B. Shea & Morgan, 1979). However, a random presentation of information might be detrimental to motor learning (Theo Mulder & Hochstenbach, 2001). Imaging studies have shed some light on the mechanisms supporting these effects. fMRI and TMS studies in humans indicate that improved performance due to variable practice correlates with increased neuronal activity and connectivity in the areas of the motor learning network during acquisition, which is associated with better performance at retention stages (Lage et al., 2015). Also, the motor cortex showed greater excitability during retention. These results point to more efficient retrieval of motor memory due to variable practice (Lin et al., 2011). More complex bimanual visuomotor tasks that were practiced randomly have shown modality-specific activation patterns that led to the recruitment of areas related to visual processing (Pauwels et al., 2018). The effect of variable practice might be related to the strong link between the neuromodulatory systems that control neuronal plasticity and novelty, for instance, the dopaminergic (Redgrave & Gurney, 2006), cholinergic (Hasselmo, Wyble, & Wallenstein, 1996) and noradrenergic systems (Vankov, Hervé-Minvielle, & Sara, 1995), which are used by the brainstem activation system for controlling the global state of arousal (Gur et al., 2007).

In the clinical context, one study that investigated random versus blocked practice failed to find an effect (Hayward et al., 2014). It seems that this principle is rarely studied explicitly in clinical studies (Darekar et al., 2015; Nielsen et al., 2015), but instead applied in conjunction with other principles to overcome boredom (Birkenmeier et al., 2010).

2.3.7. Increasing difficulty

According to Guadagnoli and Lee, 2004 and based on the ideas from Marteniuk, 1976, task difficulty can be described by the training requirements and conditions that are pertinent to the task, called the nominal task difficulty, and by how challenging the training is relative to the skill of the performer, called the functional task difficulty. Practice leads to fewer prediction errors and less need to process error information. Increasing the nominal task difficulty hence increases prediction errors and error processing demands. The optimal challenge point lies where functional task difficulty leads to a balance between information processing demands and performance, which is optimal for learning (Guadagnoli & Lee, 2004; Marteniuk, 1976). It has been shown that training with difficulty levels personalized to the learner’s capabilities leads to superior learning outcomes than when increases in difficulty are fixed (C. D. Wickens, Hutchins, Carolan, & Cumming, 2013). Further, if subjects can control the task difficulty by themselves, their motor performance during acquisition and retention is significantly better (Andrieux, Danna, & Thon, 2012). However, if difficulty surpasses one’s perceived ability to succeed, it might lead to detrimental effects on performance (Gendolla, 1999). Brain imaging studies showed increased activity in lateralized pre-motor and sensorimotor areas, but with an even more pronounced increase in parietal areas, pointing to a specialization of that area for task complexity (Wexler et al., 1997; Winstein, Grafton, & Pohl, 1997). Potentially, noradrenergic neurons keep track of high or low task performance due to difficulty by switching their activity pattern preceding behaviour (Aston-Jones & Cohen, 2005; Rajkowski, Majczynski, Clayton, & Aston-Jones, 2004).

In stroke rehabilitation, task difficulty has been partly investigated through *shaping* or *graded practice*. Shaping is a concept that was initially used by behaviourists studying operant conditioning in animals and that was successfully transferred from animals to humans by making it part of CIMT (Taub, 1976; Taub & Uswatte, 2003): The use of the impaired limb is augmented by progressively increasing the complexity of the required movement (Kwakkel et al., 2015; Taub et al., 1994). Although shaping appears to be one of the essential components of CIMT, its particular effect on motor recovery has not been studied on its own (Kwakkel et al., 2015). Increasing difficulty has been successfully used in standard care studies (Woldag, Stupka, & Hummelsheim, 2010), robot-assisted therapy (Lucca, 2009), and VR-based systems (Ballester et al., 2016; Cameirão et al., 2012), all of which showed beneficial effects on motor recovery. Task difficulty appears to be implicitly present in many tasks that investigate motor learning without being explicitly operationalized.

2.3.8. Multisensory stimulation

The perception and integration of multiple senses are fundamental abilities of the brain. Because sensory information is noisy, the integration of various modalities requires probabilistic estimations to enhance perception (Knill & Pouget, 2004). Studies in the cat superior colliculus showed that a single neuron could be responsive to several sensory modalities (Meredith & Stein, 1986; Wallace & Stein, 1996). In primates, the classic areas associated with multisensory processing are the superior temporal sulcus, the intraparietal cortex, and the frontal cortex, with newer studies confirming multisensory processing also in areas that were previously thought to be mainly unisensory (Ghazanfar & Schroeder, 2006). One sensory input (e.g., touch) can influence how another sensory modality is perceived (e.g., vision) (Driver & Noesselt, 2008); therefore, exposure to multisensory feedback can enhance the ability to detect, discriminate and recognize sensory information (Driver & Noesselt, 2008; G. Gentile, Petkova, & Ehrsson, 2011; Shams & Seitz, 2008). For instance, active physical exploration of multisensory stimuli led to greater accuracy in an associative recognition task showing enhanced connectivity between sensory and motor cortices (Butler, James, & James, 2011). Animal studies demonstrated that sensory feedback is crucial in motor learning. Monkeys with an ablated primary sensory hand area had no problems in executing a previously known task but were unable to learn new skills (Pavlides, Miyashita, & Asanuma, 1993). Providing multisensory stimulation during goal-oriented action execution might help to establish sensorimotor contingencies (McGann, 2010). Muscle vibrations appear to influence the sensorimotor organization, whereas paired associative stimulation with TMS increases motor-evoked-potentials (Rosenkranz & Rothwell, 2006).

Of specific interest for rehabilitation is the integration of visual and proprioceptive information to perform movements. It has been shown that vision and proprioception are weighted differently at various stages during motor planning (Sober & Sabes, 2003), suggesting a target for multisensory manipulations. Concurrent haptic feedback during motor imagery appears to enhance the classification accuracy of brain-computer interfaces when decoding movement intention, indicating that it can aid in closing the sensorimotor loop (Gomez-Rodriguez et al., 2011). Multisensory stimulation training might help patients to recover from unimodal deficits, for instance, visual deficits or auditory localization deficits (Làdavas, 2008).

2.3.9. Rhythmic cueing

Neuroentrainment encompasses the study of the temporal relationship between the body’s movements and the rhythmic stimulation emerging from the environment. Any sensory modality (auditory, visual, tactile, or vestibular) can be used for entrainment

(Ross & Balasubramaniam, 2014). To date, there is not much literature about visual entrainment, possibly because the auditory-motor synchronization appears to be mainly driving internal rhythmic movement control (Ross & Balasubramaniam, 2014). Hence, mainly auditory cues are used to synchronize movements to rhythmic patterns (Rossignol & Jones, 1976; Schaefer, 2014). Rhythmic patterns act like a template whose sequence can be anticipated (Nombela, Hughes, Owen, & Grahn, 2013). The regularity detection and tempo tracking of rhythmic patterns increases the activity in motor network areas and cerebellum (Schaefer, 2014) and creates a mental representation of the rhythm, the so-called auditory model, which enables motor movements to anticipate the rhythmic pattern. The pooled evidence provided in the reviews by Grahn, 2012 and Nombela et al., 2013 suggests that there are neuronal interactions between auditory and motor systems (Grahn, 2012; Nombela et al., 2013), and auditory-cued motor training can change their mutual structural connectivity (E. Moore, Schaefer, Bastin, Roberts, & Overy, 2017). The auditory-motor action coupling relies on a subcortico-thalamic-cortical circuitry that can be activated through extrinsic cueing (Grahn, 2012; Nombela et al., 2013). Cerebellar patients cannot consciously perceive rhythm changes and show high variable motor responses. However, rhythmic synchronization, respectively, motor entrainment remains intact (Molinari, Leggio, De Martin, Cerasa, & Thaut, 2003), suggesting that the cerebellum might control the rhythmic auditory-motor synchronization by monitoring rhythmic patterns. Even without cueing, repetitive movements become periodic over time, as observed when analysing gait patterns. The gait impairment observed in Parkinson’s disease (PD) is ascribed to a deficiency of the internal timing ability that disturbs coordinated rhythmic locomotion, and which can be improved with rhythmical auditory stimulation (M. H. Thaut et al., 1996). Besides, rhythmic somatosensory cueing of stride frequency through vibrotactile stimulation at the wrist could improve qualitative walking performance in PD (van Wegen et al., 2006).

There is evidence that auditorily paced treadmill walking can improve gait coordination in stroke patients as well (Michael H. Thaut & Abiru, 2010). Further, bilateral arm training with rhythmic auditory cueing enhances functional motor performance, which is maintained long-term (Whitall, Waller, Silver, & Macko, 2000) and induces cortical and cerebellar changes (Luft et al., 2004). Meta-analyses found large effects that rhythmic auditory cueing improves walking velocity, cadence, and stride length (Yoo & Kim, 2016) and beneficial effects on improving upper limb impairment and function (Ghai, 2018) after stroke.

2.3.10. Explicit feedback/knowledge of results

Knowledge of results (KR) has been defined as verbal, terminal and augmented feedback about goal achievement (Salmoni, Schmidt, & Walter, 1984). Although the finding that extrinsic feedback can effectively create simple stimulus-response associations was brought forward by animal research in reinforcement learning, KR signifies more than just extrinsic rewards (Schmidt & Lee, 2011; Winstein, 1991). KR contributes to learning through cognitive processing, not through conditioning (Salmoni et al., 1984). KR is provided through explicit feedback. Explicit feedback is given on quantitative or qualitative task outcomes, e.g., correctness, exactness, success, or failure (Mazzoni & Krakauer, 2006; Schmidt & Lee, 2011; Subramanian, Massie, Malcolm, & Levin, 2010). This feedback does not have to be verbal. For instance, when failing to reach for a target, the subject can hear unpleasant tones or see that the failed targets change colour (Taylor, Krakauer, & Ivry, 2014). Also, explicit feedback about kinematic outcomes can be KR, e.g., playing back a recorded movement after execution. However, this feedback supports learning only if the movement features that led to the outcome are pointed out to the subject (Salmoni et al., 1984). Explicit feedback seems to activate explicit learning mechanisms and shows only subtle effects on implicit learning mechanisms (Taylor et al., 2014). While implicit learning appears to increase the cortical motor output maps of the involved movement initially, they return to baseline topography once the learned content can be explicitly declared. Possibly through explicit feedback a global motor plan is learned that is represented by higher-order neuronal networks, which influence the cortical sensorimotor representations differently (Pascual-Leone, Grafman, & Hallett, 1994). Rewarding or punishing feedbacks appear to have dissociative effects on skilled motor learning. Punishment can speed up motor learning, whereas rewards ensure long-term retention (Abe et al., 2011; Galea, Mallia, Rothwell, & Diedrichsen, 2015). The reinforcement of positive outcomes appears to foster a success-driven learning system, which limits decay after learning, possibly by mobilizing the dopaminergic system (J. R. Wickens, Reynolds, & Hyland, 2003). Reward expectations modulate the activity of caudate neurons (striatal projection neurons), which receive reward-related information through the dopaminergic input from substantia nigra and spatial information through the cortico-striatal connection. Consequently, they modulate the inhibitory output of the basal ganglia, biasing attention to rewarded items. Either reward-driven activity of caudate neurons is a result of cerebral plasticity, or activity in the cerebral cortex is influenced by caudate neurons through the output nuclei of basal ganglia (Kawagoe, Takikawa, & Hikosaka, 1998). Dopamine has a gradual build-up and can persist for longer time courses; it might support long-term memory formation of motor actions (Abe et al., 2011).

KR has been used to reinforce adherence to CIMT (Taub et al., 1994). Meta-analyses often analyse KR together with knowledge of performance under the umbrella term augmented feedback (Hayward et al., 2014; van Dijk, Jannink, & Hermens, 2005). A meta-analysis analysing different feedback types reported positive effects on motor function for KR (Molier, Van Asseldonk, Hermens, & Jannink, 2010). However, this evidence is based on one study (Eckhouse, Morash, & Maulucci, 1990), whose intervention included other principles as well. It can, therefore, not be established whether KR is effective for motor recovery.

2.3.11. Implicit feedback/knowledge of performance

Knowledge of performance (KP) was defined as feedback given about movement execution in the form of verbal descriptions, demonstrations, or replays of recordings (A. M. Gentile, 1972). Advances in technology made it possible that KP can be delivered online, in an implicit manner and concurrent during movement execution, providing verbal or non-verbal feedback about ongoing intrinsic somatic processes and movement kinematics (Salmoni et al., 1984; Winstein, 1991). For instance, feedback in the form of sounds and colours can be given while trunk displacements surpass a threshold (Subramanian et al., 2007). Biofeedback uses physiological sources like electromyograms to provide patients with real-time visual or auditory signals about their motor activity (Huang, Wolf, & He, 2006). Ultimately arm movements can be visualized and augmented using VR representations (Ballester, Oliva, et al., 2015; Ferreira dos Santos et al., 2016).

Implicit sensory feedback enhances learning from sensorimotor prediction errors, which for instance can aid the adaptation to unexpected perturbations (Shadmehr, Smith, & Krakauer, 2010), possibly by contributing to implicit learning mechanisms (Taylor et al., 2014). Concurrent implicit feedback leads to lasting adaptations to visuomotor rotations, which are not (Hinder, Tresilian, Riek, & Carson, 2008) or less observed (Taylor et al., 2014) when feedback about movement outcome, e.g., KR is given. Although KP appears to be beneficial during training, there is evidence that subjects can become dependent on it, showing inferior performance when feedback is removed (Ronsse et al., 2011). Ronsse et al., 2011 compared the effects of providing concurrent visual to concurrent auditory feedback during the acquisition of a bimanual movement pattern. The authors found that subjects that had obtained visual KP showed poorer performance during retention testing than subjects that were given auditory KP. During acquisition, the visual feedback increased the activity in vision/sensorimotor-specific areas, which was maintained during retention testing even in the absence of feedback. On the contrary, the concurrent auditory feedback reduced the activity in temporo-parieto-frontal areas and deactivated task-specific sensory areas during retention testing without feedback. These results suggest that subjects can become dependent on concurrent visual feedback, but not on concurrent auditory feedback because they rely on sensory processing areas that have become tuned to visual information during practice. The auditory feedback, on the other hand, might foster the formation of an internal controller, evidenced by the stronger activation of prefrontal areas. Alternatively, auditory feedback might promote reliance on proprioception and is consequently ignored during training (Ronsse et al., 2011). Results from cerebellar patients that were exposed to force-field learning tasks propose that the cerebellum may play an important role in using implicit information to correct and adapt motor commands to changed limb dynamics, and in forming internal controllers (Nezafat, Shadmehr, & Holcomb, 2001; Smith & Shadmehr, 2005; Tseng, Diedrichsen, Krakauer, Shadmehr, & Bastian, 2007). In contrast to explicit error signals mediated through midbrain dopamine neurons in basal ganglia, implicit sensorimotor errors are possibly encoded by cerebellar climbing fibres and manifest in complex spikes in Purkinje cells during reaching tasks (Kitazawa, Kimura, & Yin, 1998). Computational modelling of adaptation to visuomotor rotations following concurrent visual feedback points to narrowly tuned neurons in the cortex that are driven by a prediction error that is computed by the cerebellum (Tanaka, Sejnowski, & Krakauer, 2009).

Stroke patients experienced a significant recovery in motor function and showed increased activation in the ipsilesional primary sensorimotor cortex after four weeks of training with a VR system that provided them with implicit feedback about their upper-limb movement (Jang et al., 2005). However, the system also included several other principles. In addition, the provision of KP has been shown to recover impaired movement patterns (Cirstea & Levin, 2007), to reduce learned non-use (Ballester, Oliva, et al., 2015), and to lead to longer-lasting recovery effects (Subramanian et al., 2010). A meta-analysis found a beneficial effect for KP on motor function (Molier et al., 2010); however, the effect was based on two studies only.

2.3.12. Modulate effector selection

In the acute stage after stroke, patients typically suppress the use of the affected limb due to pain, weakness, or malfunctioning (Taub & Uswatte, 2003). As a consequence, they are prone to overuse the non-paretic limb, and the resulting under-usage of the impaired limb can cause a loss of behavioural and neuronal function (Andrews & Stewart, 1979; Taub et al., 2006). Some authors argue that this compensation strategy, called learned non-use, emerges because the spontaneous use of the paretic limb does not cross a threshold level (C. E. Han et al., 2008). Although standard therapy focuses on improving the functionality of the impaired limb, the improvement does not transfer to increased use of the arm for ADLs (Kwakkel et al., 2015; Smania et al., 2012).

Of those therapeutic approaches that were successful in counteracting learned non-use CIMT is the most common and most successful one (Kwakkel et al., 2015). An fMRI study revealed changes in brain activity patterns due to paretic arm use in patients that underwent a two weeks CIMT program at home where the non-affected arm was constrained for 90 % of the waking time. Increased grip strength in the affected limb correlated significantly with increased fMRI signal change in ipsilesional cortico-cerebellar areas (Johansen-Berg et al., 2002). However, a meta-analysis did not find a pooled effect that forcing the use of the paretic arm alone is effective (Hayward et al., 2014). Other approaches aimed at promoting paretic arm-use through positive reinforcement during bilateral arm training (Ballester et al., 2016) or through wearable devices (e.g., bracelets) that provide feedback about performance of ADLs (Ballester, Lathe, Duarte, Duff, & Verschure, 2015).

2.3.13. Action observation/embodied practice

Action observation (Martens, Burwitz, & Zuckerman, 1976) gained increased attention after the discovery of mirror neurons (Rizzolatti & Sinigaglia, 2010): in monkeys, some neurons discharged not only when the animal executed a motor command but also when it observed another individual executing it. In humans, subjects who first observed other individuals performing a novel task performed better in the same task than control subjects that did not observe other individuals or observed a slightly different task (Mattar & Gribble, 2005). It is thought that in monkeys, as in humans, action observation relies on the frontoparietal network (Rizzolatti & Sinigaglia, 2010). Indeed, a meta-analysis showed that in humans, movement observation, as well as movement execution, recruits mainly the premotor and parietal areas. Movement observation, however, exclusively activated the visual cortex, whereas execution activated the primary motor cortex (Hardwick, Caspers, Eickhoff, & Swinnen, 2018). Therefore, action observation might facilitate movement execution and motor learning by facilitating the excitability of the motor system (Th Mulder, 2007). Indeed, TMS during action observation elicited increased muscle activation patterns (Fadiga, Fogassi, Pavesi, & Rizzolatti, 1995). For practical reasons, action observation could be especially beneficial for stroke patients with severe hemiparesis or complete paralysis. There is some clinical evidence that action observation therapy can reduce impairment and increase brain activation in the frontoparietal network and bilateral cerebellum (Ertelt et al., 2007).

Besides internalizing someone else’s movement, humans can also ascribe ownership and agency to body parts that do not pertain to them (Botvinick & Cohen, 1998). The discovery of rubber hand illusions (Botvinick & Cohen, 1998) led to insights about the mechanisms underlying agency. Both the sense of agency (Sato & Yasuda, 2005) and ownership are susceptible to manipulations (Slater, Spanlang, Sanchez-Vives, & Blanke, 2010), that have been used for therapeutic purposes, for instance, in mirror therapy (Ramachandran & Rogers-Ramachandran, 1996). Similar to action observation, mirror therapy appears to rely on the frontoparietal circuit (Harmsen, Bussmann, Selles, Hurkmans, & Ribbers, 2015), which is why its motor learning effects are partly explained by the same mechanisms (Hamzei et al., 2012). However, contrary to movement observation, mirror therapy robustly activates the primary motor cortex and visual processing areas ipsilateral to the mirrored movement. Also, mirror therapy seems to increase functional connectivity between cortical motor areas and to excite the neural connection between the two hemispheres (Arya, 2016; Hamzei et al., 2012). A meta-analysis attests mirror therapy a significant long-term effect on motor function, the ADLs, the reduction of pain and the reduction of visuospatial neglect (Thieme, Mehrholz, Pohl, Behrens, & Dohle, 2012).

If the impairment of the limb impedes active movement, visual illusions could be presented to the patients to simulate movements with the paretic arm. The error-prediction mechanism driven by the cerebellum could be equally activated through the alternative representation (Fiorio et al., 2014). Possibly, the stronger the visual illusion, the more agency is ascribed to it, which could explain the difference in brain activation patterns between action observation and mirror therapy. The sense of agency seems to be important when learning from sensorimotor prediction errors (Tsakiris, Schütz-Bosbach, & Gallagher, 2007), respectively agency is reduced when prediction and outcome do not match (Sato & Yasuda, 2005). However, there is no consensus on the definition of ownership and agency, which makes their operationalization in clinical practice difficult.

2.3.14. Mental practice/motor imagery

Mental practice and motor imagery rely on the ability to simulate actions mentally without overt behaviour, as summarized by the simulation theory (Jeannerod, 2001). Motor imagery can be seen as a mental rehearsal of future movements and motor plans (Naito et al., 2002; Schmidt & Lee, 2011), that can be beneficial for motor learning (Di Rienzo et al., 2016). However, actual physical practice shows superior effects on learning (Hird, Landers, Thomas, & Horan, 1991). A meta-analysis compared the brain areas that are active during mental imagery and movement execution. Both seem to recruit premotor areas, somatosensory cortex, and subcortical areas. Also, activation in the mid-cingulate cortex was found, with motor imagery activating more the anterior region that is linked to the cognitive aspects of motor control, whereas motor execution recruiting more the posterior region that is associated with basic motor functions. While motor imagery appears to activate more the parietal cortex, movement execution appears to recruit more classic sensorimotor regions like the primary motor cortex and cingulate motor areas (Hardwick et al., 2018). These findings are in line with studies showing that lesions in the frontoparietal system can diminish the ability of motor imagery (Danckert et al., 2002; Johnson, 2000). Motor imagery and physical practice also appear to induce similar learning-dependent brain changes (Di Rienzo et al., 2016). Not surprisingly, the activation pattern of motor imagery appears to be similar to the one identified in action observation and mirror therapy.

The learning effects of motor imagery and mental practice have been extensively studied in sports, whereas research regarding their clinical efficacy and efficiency is sparse and relatively recent (Th Mulder, 2007). However, motor imagery is thought to be advantageous for stroke recovery, especially for severely impaired patients (Th Mulder, 2007). Since patients retain the ability to imagine movements with the paretic limb, mental motor practice might facilitate functional reorganization (Johnson, 2000). A meta-analysis looking into the effectiveness of mental practice also found some trends for positive outcomes. However, pooled effects could not be estimated because only a few Class I studies exist, and their protocols, measurements, and interventions vary widely (Braun, Beurskens, Borm, Schack, & Wade, 2006).

2.3.15. Social interaction

Social interaction has been defined as a behaviour in which the participants' actions are both a response to and a stimulus for the counterpart's behaviour (Rubin, Bukowski, & Parker, 2006). Many ADL implicate social interaction, and a failure to perform them might lead to an undesired dependence on others (Lilja, Bergh, Johansson, & Nygård, 2003). The level of self-efficacy influences motor skill performance and learning, and in turn, is influenced by the appraisal or discouragement from others (Wulf, Chiviacowsky, & Lewthwaite, 2012). fMRI recordings of a subject experiencing a live social interaction revealed activations in areas commonly identified in the perception of social cues besides other regions involved in goal-directed and visual attention as well as reward processing (Redcay et al., 2010).

Animals that are allowed social interaction when recovering from an artery occlusion show higher functional improvement (Johansson & Ohlsson, 1996), increased recovery of behaviour, and lower mortality, especially if the interaction partner was healthy (Venna et al., 2014). Including and investigating the impact of social interaction as part of the rehabilitation experience seems an important but missed opportunity. We found no study that was evaluating this specific aspect in a randomized controlled trial. One study evaluating enriched environments that included social interaction found positive results in terms of activity (Janssen et al., 2014).

Table 2.1. Overview of the neuronal changes due to exposure to principles of neurorehabilitation.

Experience-dependent changes	Principles	Brain areas	References
Cellular/neuronal level			
Increased neuronal activity	Spaced practice	Task/stimulus-dependent	Gerbier and Toppino, 2015
Increased cell survival and improved LTP	Spaced practice	Hippocampus	Scharf et al., 2002; Sisti et al., 2007
Upregulation of growth factors (protein 43, synaptophysin)	Dosage	Intact corticospinal tract	Zhao et al., 2013
Inhibition of upregulation of growth-inhibiting factors (NogoA, Nogo receptors and RhoA)	Dosage	Peri-infarct cortex	Zhao et al., 2013
Dopamine-dependent synaptic plasticity	Explicit feedback	Striatum	Kawagoe et al., 1998
Complex spikes in Purkinje cells	Implicit feedback	Cerebellum	Kitazawa et al., 1998
Cortical motor areas			
Expansion or change of effector representation / cortical map, dependent on effector trained	Massed practice	Motor cortex	Plautz et al., 2000
Increased excitability	- Dosage - Variable practice	- Motor cortex - Motor cortex	- Liepert et al., 2000; Veerbeek et al., 2014 - Lage et al., 2015; Lin et al., 2011
Normalization of activation in ipsilesional cortex	Dosage	Motor cortex	Schaechter, 2004
Change in sensorimotor organization	Multisensory stimulation	Motor cortex	Rosenkranz and Rothwell, 2006
Increased neuronal recruitment during acquisition, decreased activity during retention	Variable practice	Prefrontal areas, PMA, inferior frontal areas	Lage et al., 2015; Lin et al., 2011

Increased cortical activation in lesioned hemisphere during paretic movement	- Task-specific practice	- SMC, PMC - SMC	- (Jang et al., 2003) - Wilkins et al., 2017
	- Modulate effector selection	- SSC/SMA, dorsal PMC	- Johansen-Berg et al., 2002
Increased cortical activation in contralesional hemisphere during paretic movement	Rhythmic cueing	SMC	Luft et al., 2004
Decreased activation in contralesional hemisphere during paretic movement	Task-specific practice	- SMC, PMC, SMA - Motor cortex - SMA, PMA	- (Jang et al., 2003) - (Boyd et al., 2010) - Wilkins et al., 2017
Increased laterality index during paretic movement	Task-specific practice	- SMC - Motor cortex - SMC, SMA, PMA	- (Jang et al., 2003) - (Boyd et al., 2010) - Wilkins et al., 2017
Increased power spectra	Multisensory stimulation	SMC, SSC	Gomez-Rodriguez et al., 2011
Fronto-parietal network			
Increased activation of contralateral fronto-parietal network	Goal-oriented practice	Motor cortex, SMA, SSC, parietal areas	Nathan et al., 2012
Increased activation of bilateral parietal areas, together with lateralized pre-motor areas and sensorimotor areas	Increasing difficulty	PMC, SMA, SMC, SPA, IPA	Wexler et al., 1997; Winstein et al., 1997
Increased activation of bilateral parietal, premotor and visual areas	Action observation	Dorsal and ventral PMC, pre-SMA, SPA, IPA, visual cortex	(Hardwick et al., 2018)
Increased activation of lateralized parietal areas, together with pre-motor areas	Motor imagery	Bilateral dorsal PMC, left ventral PMC, Bilateral pre-SMA, left IPA, left SPA,	Hardwick et al., 2018
Increased activation and functional connectivity	Mirror therapy	- Ipsilateral motor cortex, visual processing areas	- Arya, 2016

		- Bilateral PMA, contralateral SMA and SMC, parietal cortex	- Hardwick et al., 2018
Cerebellum			
Increased activation	- Rhythmic cueing	- Cerebellum (ipsilesional)	- Luft et al., 2004
	- Modulate effector selection	- Cerebellum (bilateral)	- Johansen-Berg et al., 2002
Somatosensory Cortex			
Reversal of SEP to pre-infarct	Dosage	Somatosensory cortex	Joo et al., 2012
Extended networks			
Auditory feedback lead to reduced activity during acquisition	Implicit feedback	SMC, SMA, opercular, temporal and parietal areas	Ronsse et al., 2011
Visual feedback lead to increased activity during acquisition	Implicit feedback	Occipital gyri, cerebellar lobules and vermis	Ronsse et al., 2011
Visual feedback preserved activation, when no feedback was given during testing	Implicit feedback	Occipitotemporal cortex	Ronsse et al., 2011
Auditory feedback suppressed activity when no feedback was given during testing	Implicit feedback	Auditory cortex	Ronsse et al., 2011
Increased fractional anisotropy	Rhythmic cueing	Arcuate fasciculus (white matter tract connecting auditory and motor regions)	Moore et al., 2017
Activity in social cue network	Social interaction	Right posterior STS, right anterior STS, right TPJ	Redcay et al., 2010

LTP, long-term potentiation; PMC, premotor cortex; SPA, superior parietal area; IPA, inferior parietal area; SEP, somatosensory-evoked potentials; SMC, sensorimotor cortex; SMA, supplementary motor area; SSC, somatosensory cortex; STS superior temporal sulcus; TPJ, temporoparietal junction

2.4. Discussion

This synthesis aimed at identifying a set of principles that should guide the design of effective neurorehabilitation protocols for post-stroke recovery. We identified 15 principles based on existing work on motor learning and recovery: massed practice/repetitive practice, spaced practice, dosage/duration, task-specific practice, task-oriented practice, variable practice, increasing difficulty, multisensory information, rhythmic cueing, explicit feedback/knowledge of results, implicit feedback/knowledge of performance, modulate effector selection, action observation/embodied practice, mental practice, and social interaction. Where possible, we identified the therapeutic and neurological effects of these principles from experimental work and clinical studies and commented on their limitations.

Our motivation for this analysis is twofold. Firstly, we are confident that the quality of evidence from clinical work and its interpretation would be enhanced if interventions are described along with the included principles. Reviews or meta-analyses with ambiguous effects often state that the included protocols remained vague on the exact experience provided to the patients, which makes the comparison and interpretation difficult (Renton et al., 2017; Veerbeek et al., 2014). By focusing solely on the ingredients of therapeutic interventions and compiling their current neuroscientific evidence, we aim to raise awareness of their importance. Also, this work might serve as a guide for clinicians and researchers to construct or identify the active ingredients in their interventions and to discover evidence currently missing. Secondly, we believe that there is a need to create a link between the principles of motor learning and their current operationalization in clinical studies and practice. We have identified several difficulties and shortcomings that do not aid in obtaining a common understanding of these principles and hence complicate the clinical investigation.

It seems that many principles are poorly operationalized in clinical trials. For instance, when massed practice is investigated, the repetitions performed within a session and during the treatment duration are rarely quantified (Lang et al., 2007) such that recovery effects due exclusively to repetition cannot be singled out. Also, the clinical research of spaced practice and dosage/duration would benefit if the parameters were quantified in a standardized way. Particularly dosage should be explicitly described in treatment minutes per session in order to be able to establish a dose-response due to training (Dobkin, 2005). Furthermore, dosage/duration should not be equated with intensity since the intensiveness of training cannot be estimated through treatment minutes only (Billinger, 2015). Intensity should be an independent principle that needs to be investigated separately. Task-specific and goal-oriented practice appear to be often used interchangeably (Fu et al., 2015; Winstein et al., 2014; Yue et al., 2017) although their training target is different. While task-specific practice focuses on the acquisition of a specific skill (Keetch et al., 2005) for ADL, goal-oriented practice permits the use of any movement or skill that is deemed suitable to achieve the goal (Horak, 1991), fostering the exploration of alternative movement patterns. Variability appears to be included inherently in many protocols (Darekar et al., 2015), possibly because it renders the training less repetitive and, therefore, less boring (Birkenmeier et al., 2010), which could counteract low adherence. However, this link has not been explicitly studied. Increasing the difficulty during practice is part of many intervention protocols as well; however, personalizing the difficulty level in order to provide training at the optimal challenge point seems to be rarely addressed. Concerning multisensory integration, it would be interesting to explore whether the presence of more than two sensory stimulations could enhance learning (Sánchez, Millán-Calenti, Lorenzo-López, & Maseda, 2013). Similarly, rhythmic entrainment could be extended with protocols exploring if visual or haptic entrainment might aid recovery of impaired movements (Penhune, Zatorre, & Evans, 1998). Explicit feedback and implicit feedback are often investigated together under the umbrella term of augmented feedback, as evidenced by the sourced meta-analysis and clinical studies (Molier et al., 2010). However, their aim and the neuronal mechanisms that they appear to stimulate are different. While explicit feedback provides terminal feedback about movement outcome, implicit feedback provides concurrent error-signals during movement execution fostering possibly different learning mechanisms. Meta-analyses also appear to interpret the sensory modality of the feedback, e.g. if it is visual, auditory or haptic as a feedback type. However, the sensory modality is a separate layer that is added to feedback. Explicit feedback, as well as implicit feedback, can be unisensory or multisensory. Action observation and mirror-therapy appear to be well studied therapeutic ingredients, whereas mental practice is only addressed in a few studies, and social interaction remains unexplored territory so far. If the principles would be better operationalized it would not only help to identify their contribution to the recovery of motor functions but as well to other learning outcomes such as cognitive or language improvements.

The neuronal changes found within each principle allow us to draw some general conclusions for the advancement of neurorehabilitation. While some principles appear to modulate more specific brain areas (massed practice, dosage, variable practice, task-specific practice, modulate effector selection, multisensory stimulation) within the motor areas of the cortex others appear to recruit or rely more on networks of brain regions (goal-oriented practice, increasing difficulty, action observation, motor imagery, mirror therapy, rhythmic cueing, implicit feedback/knowledge of results, social interaction). An effective rehabilitation approach should thus incorporate principles of both types in order to counteract neuronal degradation and promote improvement. Firstly, a training that addresses only a limited subset of the neuronal circuitry underlying a general function might limit transfer to other behaviours that depend on the same circuitry (Kleim & Jones, 2008). Secondly, not all principles are equally applicable to all patients. Some principles might be more beneficial early after stroke, whereas others benefit patients with less severe damage. Spontaneous biological recovery and activity-dependent plasticity appear to interact differently at different stages after stroke, which, aside from other factors like severity, predicts recovery (Hylin et al., 2017; Reinkensmeyer et al., 2016). It seems that in acute patients the sensorimotor cortex activity is highly abnormal, and the normalization in activity patterns is linked to better recovery (Schaechter, 2004). Principles like task-oriented practice that promote localized changes, might therefore be more beneficial at the acute stage after stroke (Schaechter, 2004), whereas therapies like CIMT, where the forced use of the impaired limb is paired with increasing difficulty and further principles, have been shown to be more suitable at later stages after stroke and for less impaired patients (Dromerick et al., 2009). More severely impaired patients, on the other hand, might benefit from action observation, mirror therapy and motor imagery (Dohle et al., 2009; Sun et al., 2013). Future studies will show the optimal combinations of principles that stimulate plasticity in a way that learning of pre-existing or novel functions is enhanced.

We are aware that the view proposed here is strongly influenced by knowledge mainly derived from clinical work with hemiparetic stroke patients. However, the literature indicates that other diseases, for instance, PD (Rossiter, Boudrias, & Ward, 2014) or Alzheimer's disease (Kalaria, 2002), show similar cognitive, functional, and neuronal alterations even though they may have different pathologies. Therefore, these principles of neurorehabilitation could be potentially applied beyond the field of stroke. As our main goal was to provide a synthesis that is informative and practical, in-depth analysis of each principle and its neurological underpinnings lie outside of the scope of this work. In future work, we will unify the principles addressed here in a theoretical framework to show how each of them contributes to the restoration of sensorimotor contingencies (P. F. M. J. Verschure, 2011). In summary, this chapter provides a synthesis of effective therapeutic ingredients that could be beneficial in aiding recovery after stroke. We hope that future work will extend the evidence presented here by implementing and investigating the principles of neurorehabilitation in novel rehabilitation protocols for stroke and other patient populations.

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Chapter 3

EFFECT OF SPECIFIC OVER NONSPECIFIC VR-BASED REHABILITATION ON POSTSTROKE MOTOR RECOVERY: A SYSTEMATIC META-ANALYSIS

This chapter is based on:
Maier, M., Ballester, B. R, Duff, A., Duarte Oller, E., & Verschure, P. F. M. J. (2019). Effect of Specific Over Nonspecific VR-Based Rehabilitation on Poststroke Motor Recovery: A Systematic Meta-analysis. *Neurorehabilitation and Neural Repair, 33(2), pages 112-129.*

Are principle-based neurorehabilitation approaches more effective? VR-based rehabilitation systems have been around for a decade. However, current studies and meta-analyses do not agree on whether they are effective for recovery or not. We argue that this controversy is not surprising; an intervention is not effective solely because it uses a certain technology, but because it incorporates principles of learning that are beneficial for recovery. It is therefore necessary to differentiate between VR-based interventions. In this chapter we present a meta-analysis where we compare VR-based systems that have been specifically built for rehabilitation and systems that were designed for recreational purposes against conventional therapy. We hypothesize that specifically built systems capitalize on the principles of neurorehabilitation and therefore show a recovery effect on upper-limb function, unlike non-specific systems. A computerized search yielded 30 randomized controlled trials, including 1473 patients. The results show that specific VR systems have significant impact on body function and activity, whereas non-specific VR-systems do not. We suggest that specific VR systems are more beneficial than CT and non-specific systems, since they all include a set of 6 principles of neurorehabilitation.

3.1. Background

Novel technologies have sought to meet the increased rehabilitation demand and to potentially allow patients to continue rehabilitation at home after they leave the hospital (Piron et al., 2009). Several studies and meta-analyses have evaluated the effectiveness of technologies that use virtual reality (VR) in stroke rehabilitation. In a first review, Crosbie et al. analysed six studies that used VR to provide upper limb rehabilitation (Crosbie, Lennon, Basford, & Mcdonough, 2007). Although they found a positive effect, they concluded that the evidence was only weak to moderate given the low quality of the research. A later meta-analysis analysing five randomized controlled trials (RCTs) and seven observational studies suggested a positive effect on a patient's upper limb function after training (Saposnik & Levin, 2011). Another meta-analysis of 26 studies by Lohse et al. which compared specific VR (SVR) systems with commercial VR games, found a significant benefit for SVR systems as compared to conventional therapy (CT) in both body function and activity but not between the two types of systems (Lohse, Hilderman, Cheung, Tatla, & Van Der Loos, 2014). This study, however, included a variety of systems that would treat upper limb, lower limb, and cognitive deficits. Saywell et al. analysed 30 "play-based" interventions, such as VR systems including commercial gaming consoles, rehabilitation tools, and robot-assisted systems. They found a significant effect of play-based versus control interventions in dose-matched studies in the Fugl-Meyer Assessment of the Upper Extremity (FM-UE) (Saywell, Taylor, Rodgers, Skinner, & Boocock, 2016). In contrast, a more recent large-scale analysis of a study with Nintendo Wii-based video games, including 121 patients concluded that recreational activities are as effective as VR (Saposnik et al., 2016). A later review evaluated 22 randomized and quasi-randomized controlled studies and concluded that there is no evidence that the use of VR and interactive video gaming is more beneficial in improving arm function than CT (Laver et al., 2017). In all, 31% of the included studies tested nonspecific VR (NSVR) systems (Nintendo Wii, Microsoft Xbox Kinect, Sony PlayStation EyeToy). Hence, although VR-based interventions have been in use for almost two decades, their benefit for functional recovery, especially for the upper limb, remains unknown. Possibly, these contradictory results indicate that, at present, studies are too few, too small, and/or the recruited participants too variable to be conclusive (Shrier, Platt, & Steele, 2007).

However alternative conclusions can be drawn. First, VR is an umbrella term. Studies comparing its impact often include heterogeneous systems or technologies, customized or non-customized for stroke treatment, addressing a broad range of disabilities. However, effectiveness can only be investigated if similar systems that rehabilitate the same impairment are contrasted. This has been achieved by meta-analyses that investigated VR-based interventions for the lower limb, concluding that VR systems are more effective in improving balance or gait than CT (de Rooij, van de Port, & Meijer, 2016). Second, a clear understanding of the "active ingredients" (Proffitt & Lange, 2015) that make should make VR interventions effective in promoting recovery is missing. Therapeutic advantages of VR identified in current meta-analyses are that it might apply principles relevant to neuroplasticity (Laver et al., 2017; Saposnik & Levin, 2011), like providing goal-oriented tasks (Laver et al., 2017; Saposnik & Levin, 2011), increasing repetition and dosage (Laver et al., 2017; Saposnik & Levin, 2011), providing therapists and patients with additional feedback (Laver et al., 2017; Lohse, Hilderman, et al., 2014; Saposnik & Levin, 2011), and allowing to adjust task difficulty (Lohse, Hilderman, et al., 2014). In addition, it has been suggested that the use of VR increases patient motivation (Lohse, Hilderman, et al., 2014), enjoyment (Laver et al., 2017; Saposnik et al., 2016), and engagement (Saywell et al., 2016), makes intensive task-relevant training more interesting (Crosbie et al., 2007; Saywell et al., 2016), and offers enriched environments (Laver et al., 2017). Although motivational aspects are important in the rehabilitation process as they possibly increase adherence (Proffitt & Lange, 2015), their contribution to recovery is difficult to quantify as it relies on the patients' subjective evaluation (Jack et al., 2001) (Jack et al., 2001; Kizony, Katz, & Weiss, 2003; M F Levin, Snir, Liebermann, Weingarden, & Weiss, 2012; Saywell et al., 2016; Zondervan et al., 2016). Rehabilitation methods, whether VR or not, however, need to be objectively beneficial in increasing the patient's functional ability. Hence, an enormous effort has been expended to identify principles of neurorehabilitation that enhance motor learning and recovery (Christ & Reiner, 2014; Cirstea & Levin, 2007; Dobkin, 2004; Hanlon, 1996; Kleim & Jones, 2008; Kwakkel, 2009; Kwakkel et al., 2015; M. F. Levin et al., 2015; Thomas et al., 2017). In the previous chapter (Chapter 2) we have intended to compile a synthesis of these principles that may underly effective rehabilitation approaches. Consequently, an effective VR system should besides be motivating, also augment CT by applying these principles in their design (M. F. Levin et al., 2015).

Following this argument, we advance the hypothesis that custom-made VR rehabilitation systems might have incorporated these principles, unlike off-the-shelf VR tools that were created for recreational purposes. Combining the effects of both approaches in one analysis might thus mask their real impact on recovery. Again, in the rehabilitation of the lower limb, this effect has been observed. Two meta-analyses investigating the effect of using commercial VR systems for gait and balance training did not find a superior effect, which contradicts the conclusions of the other systematic reviews (de Rooij et al., 2016). In upper limb rehabilitation, this question has not been properly addressed until the most recent review by Aminov et al. (Aminov, Rogers, Middleton, Caeyenberghs, & Wilson, 2018). However, there are several flaws in the method applied that could invalidate the results they found. Specifically, studies were included regardless of their quality and it is not clear which outcome measurements were taken for the analysis according to the World Health Organization's International Classification of Function, Disability, and Health (ICF-WHO) ("World Health Organization. International classification of functioning disability and health: ICF," 2017). In addition, a specifically designed rehabilitation system (Interactive Rehabilitation Exercise, IREX)(GestureTek, n.d.) was misclassified as an off-the-shelf VR tool. As their search was concluded in June 2017, the more recent evidence is missing.

We decided to address these issues by conducting a well-controlled meta-analysis that focuses only on randomized controlled trials that use VR technologies for the recovery of the upper limb after stroke. We analyse the effect of VR systems specifically built for rehabilitation (i.e. SVR systems) and off-the-shelf systems (i.e. NSVR systems) against CT according to the ICF-WHO categories. Also, we extracted 11 principles of motor learning and recovery from established literature that could act as "active ingredients" in the protocols of effective VR systems. Through a content analysis, we identified which principles are present in the included studies and compared their presence between SVR and NSVR systems. We hypothesized, first, that SVR systems might be more effective than NSVR systems as compared with CT in the recovery of the upper-limb movement and, second, that this superior effect might be a result of the specific principles included in SVR systems.

3.2. Methods

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher, Liberati, Tetzlaff, Altman, & Group, 2009).

3.2.1. Identification of RCTs

We define VR as a computer-based technology that provides the user with a sense of presence in a virtual environment (Lombard & Ditton, 2006), which is induced by exposing the user to computer-generated sources of sensory stimulation that satisfy their perceptual predictions and expected sensorimotor contingencies (Steuer et al., 1992). The studies included aimed at training the upper extremity of stroke patients through active participation, without assistive robotic devices (e.g. exoskeleton, end-effector devices) or exogenous stimulation. We compared the impact on body function and activity of two kinds of VR systems to CT: SVR and NSVR systems. SVR systems were developed exclusively for neurorehabilitation purposes. NSVR systems, on the other hand, are recreational and/or off-the-shelf video games (e.g. Nintendo Wii, Microsoft Xbox Kinect). As CT, we considered occupational therapy and physical therapy. To identify all RCTs in these two categories, we performed a computerized search in the bibliographic databases MEDLINE (OVID), Cochrane Library Plus (including EMBASE), CINAHL, APA PsycNET, DARE, and PEDro for studies that were published in English from inception until August 7, 2018, the day of the conclusion of the search. The search strategy (Table 3.1) included only RCTs that tested the efficacy of SVR or NSVR systems in recovering the upper limbs of stroke patients who were either in the acute (up to 21 days post-stroke), subacute (between 3 weeks to 3 months post-stroke) or chronic (after 3 months post-stroke) stage. We combined the effects of various chronicity bands, as the current literature suggests that principles of motor learning interact constantly with the biological processes of recovery (Zeiler et al., 2015), therefore, no differential effect between SVR and NSVR systems due to chronicity should be expected. This notion has also been confirmed by the latest meta-analysis (Aminov et al., 2018). In addition, splitting the identified literature into VR type, ICF-WHO category and chronicity reduces statistical power due to a small number of studies remaining in each band. Two reviewers (BR and MM) assessed the studies for eligibility. We excluded studies that were not carried out on humans, lacked a control group, included less than five subjects per experimental condition, did not target upper extremity rehabilitation, used exoskeletons as interfaces, used exogenous stimulation (such as transcranial stimulation), or did not provide information on standard clinical scales (Figure 3.1). Exoskeletons and exogenous stimulation protocol were excluded for the passive or active support provided in the rehabilitation process that might lead to different outcomes.

Table 3.1. Search strategy.
The search was organized by MeSH headings [MeSH] and searches in titles, abstracts, and keywords [tiab].

Nº	Headings and keywords
#1	Stroke[MeSH] OR eva*[tiab] OR post-stroke*[tiab] OR stroke*[tiab] OR apoplexy*[tiab]
#2	Hemiplegia[MeSH] OR Paresis[MeSH] OR hemipleg*[tiab] OR hemipar*[tiab] OR paresis[tiab] OR paretic[tiab] OR upper-extremit*[tiab] OR upper-arm*[tiab]
#3	“Occupational Therapy” [MeSH] OR “Physical Therapy” [MeSH] OR “Rehabilitation” [MeSH] OR “Virtual Reality” [MeSH] OR “Serious games” [MeSH]
#4	#1 AND #2 AND #3

3.2.2. Outcome measurements

Two reviewers (BR and MM) cross-analysed the content of the included studies and extracted the relevant data into a separate database. In general, published articles were used. If information in the articles was missing, the respective authors were contacted by mail. To classify the impact of VR on upper extremity function and activity at the end of therapy according to the ICF-WHO framework, we followed the recommendations given by the Stroke Rehabilitation Evidence-Based Review (Salter et al., 2013) and considered the following outcome measurements in the respective order. For body function, we considered the FM-UE (Fugl-Meyer, Jääskö, Leyman, Olsson, & Steglind, 1975), Modified Ashworth Scale, Motricity Index (MI) (Collin & Wade, 1990), Brunnstrom Motor Recovery Stage (BS) (Brunnstrom, 1966) and Stroke Impact Scale (SIS, only hand items) (Duncan et al., 1999). For activity we considered the (Modified) Barthel Index (BI) (Mahoney & Barthel, 1965), the Functional Independence Measure (FIM) (Keith, Granger, Hamilton, & Sherwin, 1987), the Action Research Arm Test (ARAT) (Carroll, 1965), the Box and Block Test (BBT) (Mathiowetz, Volland, Kashman, & Weber, 1985) and the Wolf Motor Function Test (WMFT) (Wolf et al., 2001). We did not conduct a comparison for the ICF-WHO category participation, because of the four studies (da Silva Ribeiro et al., 2015; Duff et al., 2012; Saposnik et al., 2016, 2010) that had a corresponding outcome measurement (SIS and Medical Outcomes Study Short Form 36, SF-36 (Ware Jr & Sherbourne, 1992)), only one classified as SVR intervention (Duff et al., 2012). For each study, we identified one measurement in each category and took the absolute score (mean and SD) at the end of the treatment for intervention and control group. When the SD of the mean was not available (Saposnik et al., 2010; Zondervan et al., 2016), we requested it from the corresponding authors. When only the median and first/third quartile (Duff et al., 2012; Yin, Sien, Ying, Chung, & Leng, 2014; Zucconi et al., 2011) or minimum/maximum (Aşkın, Atar, Koçyiğit, & Tosun, 2018; Standen et al., 2016) was reported, we estimated the mean and the SD using the method proposed by Wan et al. (Wan, Wang, Liu, & Tong, 2014).

3.2.3. Quality appraisal and risk-of-bias assessment

We used the established PEDro checklist to assess the quality of the RCTs (Maher, Sherrington, Herbert, Moseley, & Elkins, 2003). In this review, we only included RCTs with a PEDro score of 5 or greater, which we considered to be high-quality studies. We then used The Cochrane Collaboration's "Risk of bias" tool to evaluate the methodological quality of the included studies.

3.2.4. Content analysis of included principles of neurorehabilitation

To see whether SVR and NSVR systems are different according to their therapeutic specifications, two reviewers (MM and BR) reviewed existing literature on principles of motor learning and recovery for neurorehabilitation. We extracted a list of 11 principles that have been shown to be effective for motor recovery as they enhance neural plasticity and therefore optimize acquisition, retention, and generalization of motor skills: massed practice (training that is repetitive) (Dobkin, 2004; Kleim & Jones, 2008; Kwakkel et al., 2015; M. F. Levin et al., 2015; Thomas et al., 2017), dosage (training that is intensive) (Dobkin, 2004; Kleim & Jones, 2008; Kwakkel, 2009; Kwakkel et al., 2015), structured practice (training that is spaced in time) (Dobkin, 2004; Kleim & Jones, 2008; Yamazaki et al., 2015), task-specific practice (skill training that is relevant for activities of daily living [ADL]) (Dobkin, 2004; Kleim & Jones, 2008; M. F. Levin et al., 2015), variable practice (training that is randomized and variable) (Hanlon, 1996; M. F. Levin et al., 2015), multisensory stimulation (training that provides not only visual feedback) (Kleim & Jones, 2008; M. F. Levin et al., 2015), increasing difficulty (training that is individualized) (Kwakkel et al., 2015; M. F. Levin et al., 2015), explicit feedback (training that provides knowledge about results) (Cirstea & Levin, 2007; M. F. Levin et al., 2015), implicit feedback (training that delivers implicit task-relevant cues) (Cirstea & Levin, 2007; M. F. Levin et al., 2015), avatar representation (training that is embodied and immersive) (Christ & Reiner, 2014; M. F. Levin et al., 2015), and promoting the use of the paretic limb (training that counteracts compensation and learned non-use) (Dobkin, 2004; Kleim & Jones, 2008; Kwakkel et al., 2015). Each principle was then assigned key descriptors. One of us (MM) then performed a qualitative content analysis in the included studies using the key descriptors as an indicator of whether a given principle was present or not (deductive category application). Only if the key descriptors were explicitly explained or mentioned in the text, the principle was defined to be present in the study. In Table 3.2 we present the 11 principles that were extracted from the literature together with their definitions, their ascribed effect on recovery and the assigned key descriptors for encoding. We performed a pure content analysis without following up with the authors to examine the reporting pattern of the principles they thought were relevant for their results. Lastly, we calculated for each principle the presence as a percentage, separately for SVR and NSVR studies. Description, Definition, and Effect of Identified Principles and Their Key Descriptors.

Table 3.2. Qualitative content analysis.
Description, definition, and effect of identified principles and their key descriptors.

Name	Definition	Effect	Key descriptors
Massed practice	The number of repetitions performed	Small effects on improvement and retention (Dobkin, 2004; Kleim & Jones, 2008; Kwakkel et al., 2015; Thomas et al., 2017)	- Number of repetitions was counted - Tasks were aimed at increasing number of repetitions of a movement
Dosage	Training of more than 5 hours a week	Can speed up functional recovery (Dobkin, 2004; Kleim & Jones, 2008; Kwakkel, 2009; Kwakkel et al., 2015)	- Training is more than 60 mins of therapy per session and weekday
Structured practice	Training schedule with frequent and longer breaks	Better retention than massed protocols (Dobkin, 2004; Kleim & Jones, 2008; Yamazaki et al., 2015)	- Rests were given during the session
Task-specific practice	Movements performed are relevant for ADL and goal-oriented	Learning is maximal if the task trained is specific (Dobkin, 2004; Kleim & Jones, 2008)	- Tasks incorporated movements that are functionally meaningful (reaching, lifting, grasping, pronation, supination, pinching, etc.) and were goal-oriented
Variable practice	Several tasks that require different movements	Better retention and enhances generalization (Hanlon, 1996)	- Training included various tasks that require a variety of movements
Multisensory stimulation	Providing feedback through multiple senses	Restoration of sensorimotor contingencies (Kleim & Jones, 2008)	- Besides visual, other types of feedback were provided (auditory, tactile, etc.)

Increasing difficulty	Progressively increasing the difficulty of the task or the involved movements	Augment task-specific use of the impaired limb (Kwakkel et al., 2015)	- Difficulty or complexity of tasks or movements is changing depending on ability, performance, or item
Explicit feedback	Knowledge about results (task success or failure, or movement outcome)	Retain and adapted movement better (Cirstea & Levin, 2007)	- Providing cues on task completion with regard to success or failure, or movement outcome (trajectory errors, average completion time, or exactness) - Feedback can also be provided through a therapist
Implicit feedback	Knowledge about performance that is obtained from tracking, analysing, and visualizing kinematic movement data	Reduce the sensorimotor prediction error and promote learning (Cirstea & Levin, 2007)	- Real-time visualization of arm/hand movement and other kinematic properties (speed, rotations, synergy compensations) - Display of correct trajectory to follow
Avatar representation	Active execution and observation of movement through an avatar	Degree of agency aids learning from sensorimotor prediction error (Christ & Reiner, 2014)	- Virtual movement is represented as human- or body part-like avatar (whole body, arm, or hand)
Promote use of affected limb	Tasks that are forcing or reinforcing the use of the affected arm	Counteracting learned non-use (Dobkin, 2004; Kleim & Jones, 2008; Kwakkel et al., 2015)	- Tasks were designed or required to be performed with the paretic limb - Tasks cannot be accomplished by the healthy arm only

3.2.5. Statistical analysis

We performed a subgroup analysis using RevMan 5.1. Outcome measures were included in absolute terms as provided by the authors or estimated from raw data. Heterogeneity was assessed using X^2 test and I^2 and was considered significant when the probability value of X^2 was < 0.05 or when I^2 was > 40% (Higgins & Thompson, 2002). The pooled treatment effect (Inverse Variance) was evaluated using random-effect models in order to avoid a heterogeneity bias (Higgins & Thompson, 2002). Since a direct comparison between the effects of SVR and NSVR on outcomes for body function and activity is not possible, we conducted an indirect comparison in which each VR type was compared to CT at each ICF level through a subgroup analysis. Since SVR and NSVR studies reported the continuous outcomes in different psychometric scales, the standardized mean difference (SMD) and 95% CI to represent the magnitude of the reported improvement was used. It should be noted that the SMD method does not correct for differences in the direction of the scale. As WMFT is measured in seconds to complete the task (and, therefore, decreases with better performance) its mean value was multiplied by –1 to ensure that all the scales point in the same direction. For all analyses, the statistical significance level was set at $p < 0.05$. Risk of publication bias across studies was estimated visually by inspecting the funnel plots. We used GRADEpro to assess the overall quality of the evidence found.

3.3. Results

We wanted to assess whether VR-based systems that are purposefully designed for stroke rehabilitation (SVR), render rehabilitation outcomes different from systems that are NSVR. Our prediction is that SVR studies should outperform NSVR studies because the former are designed around distinct principles for neurorehabilitation while the latter are not.

3.3.1. Study identification

We identified 1751 articles that matched the search strategy (Figure 3.1). Ten additional studies were identified through other sources (e.g. meta-analyses). Of the 1164 records screened, 30 articles that were published between January 2002 and August 2018 satisfied the inclusion criteria and were included in this review. The study's characteristics can be found in Table 3.4; the aim, the selected outcome measurements per ICF-WHO category and the main finding are reported in Table 3.5. A total of 1137 records and articles were removed, of which 22 after qualitative full-text analysis (Table 3.3). One of the articles included three experimental subgroups (Turolla et al., 2013), which were considered as separate trials resulting in a total of 32 outcomes that were included in the analysis. A total of 22 RCTs qualified as SVR systems (Aşkın et al., 2018; Brunner et al., 2017; Cameirão et al., 2011; Crosbie, Lennon, McGoldrick, McNeill, & McDonough, 2012; Duff et al., 2012; Jang et al., 2005; Jo, Jung, & Yu, 2012; Kiper, Agostini, Luque-Moreno, Tonin, & Turolla, 2014; Kiper, Piron, Turolla, Stozek, & Tonin, 2011; Kiper et al., 2018; Kottink, Prange, Krabben, Rietman, & Buurke, 2014; Kwon, Park, Yoon, & Park, 2012; S. Lee, Kim, & Lee, 2016; M F Levin et al., 2012; Piron et al., 2009, 2010; Shin, Ryu, & Jang, 2014; Standen et al., 2016; Turolla et al., 2013; Yin et al., 2014; Zondervan et al., 2016; Zucconi et al., 2011) and 8 as NSVR systems (da Silva Ribeiro et al., 2015; Kong et al., 2016; Rand et al., 2017; Saposnik et al., 2016, 2010; Sin & Lee, 2013; Türkbey, Kutlay, & Gök, 2017; Yavuzer, Senel, Atay, & Stam, 2008). Of the 30 articles included, 13 evaluated motor function at follow-up after a period of no treatment. Interventions were delivered from 2 to 12 weeks (mean SVR = 4.4 weeks, mean NSVR = 4.3 weeks) across all studies. The duration of the rehabilitation sessions varied in SVR studies from 20 to 158.3 mins (mean 23.9 hours total intervention time), and in the NSVR studies from 60 mins to 135 mins (mean 21.9 hours total intervention time). Overall, the most frequently used outcome measure was the FM-UE (SVR = 16, NSVR = 3).

Table 3.3. Excluded studies after full-text analysis.

Reference	Exclusion criteria
(Adie et al., 2017)	No after treatment measurement for MAL QOM reported
(Broeren, Claesson, Goude, Rydmark, & Sunnerhagen, 2008)	PEDro score below 5

(Carregosa et al., 2018)	Follow-up of already published study
(Chen et al., 2015)	Baseline not balanced
(Choi & Paik, 2018)	No endpoint measurements, baseline age not equal
(Fan et al., 2014)	Only Jebsen-Taylor hand test used
(N. Friedman et al., 2014)	Only changes reported
(Housman, Scott, & Reinkensmeyer, 2009)	No endpoint measurements reported
(In, Jung, Lee, & Song, 2012)	PEDro score below 5, no VR intervention
(B. R. Kim, Chun, Kim, & Park, 2011)	Control group did not do CT/PT/OC
(E. K. Kim, Kang, Park, & Jung, 2012)	Passive control, no clinical scales, electrical stimulation, PEDro score below 5
(W.-S. Kim et al., 2018)	Control group did not do CT/PT/OC
(G. Lee, 2013)	No clinical scales
(D. Lee, Lee, Lee, & Song, 2014)	No VR environment
(McNulty et al., 2015)	Control group did mCIMT
(H. Park et al., 2016)	Control group did not do CT/PT/OC
(Piron et al., 2007)	PEDro score below 5
(Rand, Weiss, & Katz, 2009)	Only 4 patients, no control group
(Shin, Bog Park, & Ho Jang, 2015)	Median and interquartile range is reported
(Shin et al., 2016)	RAPAEL smart glove, a hand exoskeleton, is used
(Subramanian, Lourenço, Chilingaryan, Sveistrup, & Levin, 2013)	No endpoint measurement reported
(Sucar, Leder, Hern, Israel, & Azc, 2009)	No endpoint measurement reported

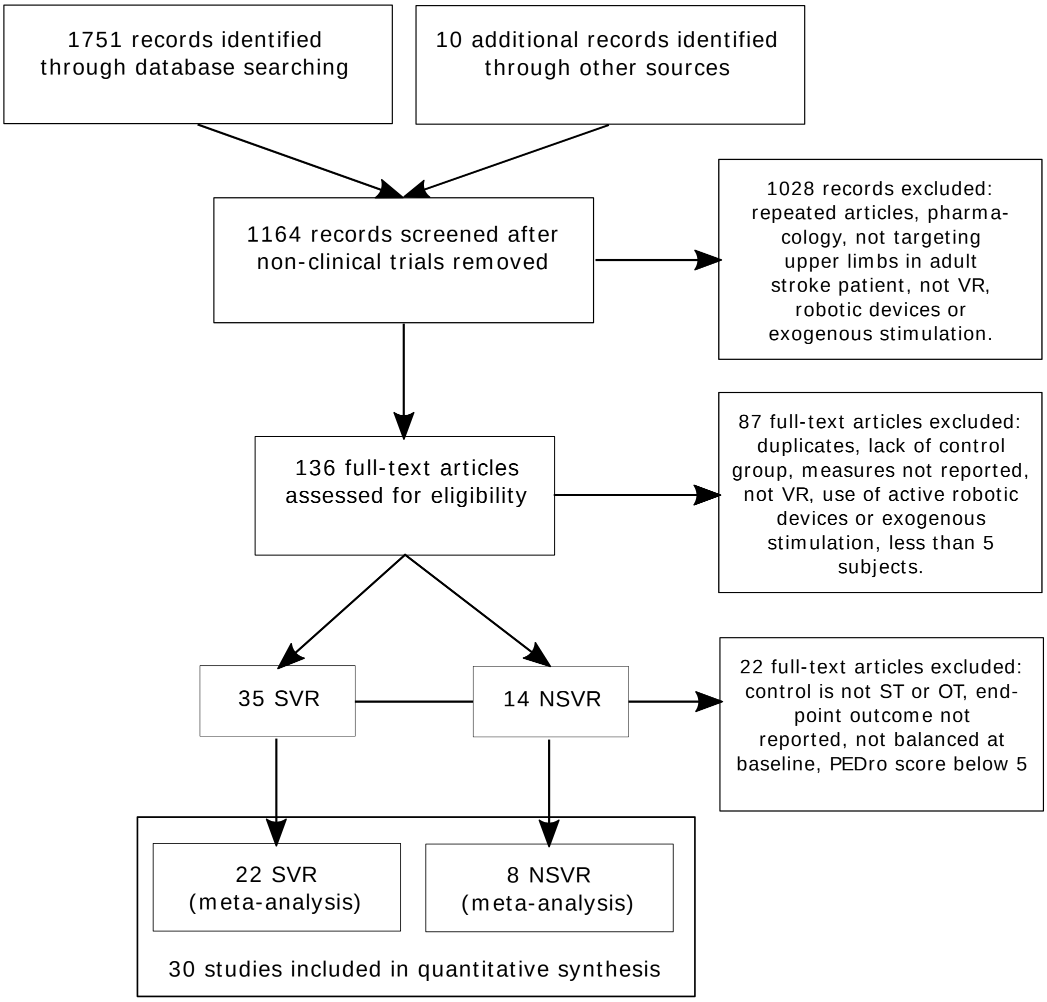


Figure 3.1. Study flow diagram (PRISMA).
The selection process of identified randomized controlled trials. Abbreviations: NSVR, nonspecific VR; SVR, specific VR; VR, virtual reality

Table 3.4. Characteristics of included studies.

Author	Intervention	n	Age	DSS	Phase	Type of VR	PEDro
SVR studies							
Aşkin et al. 2018	VR + CT vs CT; 4 × 5 × 60 (60) = 40 hours	18/38	55 (10.4)	603.33 (151.33)	Chronic	VR environment on TV and motion tracking through Microsoft Kinect	6
Brunner et al. 2017	VR + CT vs CT + CT; 4 × 4.1 × 51.1 (107.2) = 43.7 hours[b]	57/12	62 (32 - 88)	34.5 (20)	Subacute	VR environment on computer and motion tracking tracking through data gloves	9
da Silva Cameirão et al. 2011	VR + OT vs intensive OT; 12 × 3 × 20 = 12 hours[b]	10/19	61.4 (11.6)	13.2 (5.2)	Acute	VR environment on computer and motion tracking through computer vision and data gloves	7
Crosbie et al. 2012	VR vs CT; 3 × 3 × 30-45 = 4.5-6.8 hours[b]	9/18	60.3 (10.9)	329 (216)	Chronic	VR environment in head-mounted display and motion tracking through sensors	9
Duff et al. 2012	VR vs PT; 4 × 3 × 60 = 12 hours[b]	11/21	68.8 (8.2)	392 (316)	Chronic	Mixed VR environment and motion tracking through computer vision	6
Jang et al. 2005	VR vs passive control; 4 × 5 × 60 = 20 hours	5/10	57.1 (4.5)	414 (88)	Chronic	VR environment on screen and motion tracking through a video camera	5
Jo et al. 2012	VR + CT vs CT; 4 × 5 × 60 (18) = 26 hours	15/29	63.85 (7.95)	NA	NA	VR environment on screen and motion tracking through a video camera	6
Kiper et al. 2011	VR + CT vs CT; 4 × 5 × 60 (60) = 40 hours[b]	40/80	64.0 (16.4)	173.4 (106.5)	Chronic	VR environment on screen and motion tracking through video camera	6
Kiper et al. 2014	VR + CT vs CT; 4 × 5 × 60 (60) = 40 hours[b]	23/44	64.3 (12.6)	127.8 (94.3)	Chronic	VR environment on screen and motion tracking through video camera	7
Kiper et al. 2018	VR + CT vs CT; 4 × 5 × 60 (60) = 40 hours[b]	68/136	63.9 (14.1)	127.75 (91.25)	Chronic	VR environment on screen and motion tracking through video camera	6
Kottink et al. 2014	VR vs CT; 6 × 3 × 30 = 9 hours[b]	8/18	61.85 (10.65)	1196.9 (743.69)	Chronic	VR environment on horizontal screen and motion tracking through webcam	6
Kwon et al. 2012	VR + CT vs CT; 4 × 5 × 30 (70) = 33 hours	13/26	57.5 (13.7)	24.3 (18.1)	Subacute	VR environment on screen and motion tracking through video camera	9
Lee et al. 2016	VR + OT vs TV + OT; 6 × 3 × 30 (50) = 24 hours[b]	10/18	71.2 (7.2)	504.9 (196.4)	Chronic	Mixed VR environment on computer and motion tracking through video camera	8
Levin et al. 2012	VR vs OT; 3 × 3 × 45 = 6.75[b]	6/12	58.95 (14.85)	1168 (383.25)	Chronic	VR environment on screen and motion tracking through video camera	6
Piron et al. 2009	VR vs CT; 4 × 5 × 60 = 20 hours[b]	18/36	65.2 (7.8)	405 (158)	Chronic	VR environment on computer and motion tracking through sensors	7

Piron et al. 2010	VR vs CT; 4 × 5 × 60 = 20 hours[b]	27/47	60.5 (9)	464 (374)	Chronic	VR environment on screen and motion tracking through sensors	8
Shin et al. 2014	VR + OT vs OT; 2 × 5 × 20 (20) = 6.6 hours	9/16	49.3 (8.9)	71.9 (36.9)	Subacute	VR environment on screen and motion tracking trough depth sensor	8
Standen et al. 2016	VR vs passive control; 8 × 5 × 60 = 40 hours (maximum), actual ~7 hours	9/18	61 (13.1)	119 (83-279)	Subacute	VR environment on screen and motion tracking trough light-emitting diodes	5
Turolla et al. 2013	VR + CT vs CT; 4 × 5 × 60 (60) = 40 hours[b]	68/100	62.8 (13.4)	<91	Subacute	VR environment on screen and motion tracking through sensors	5
Turolla et al. 2013	VR + CT vs CT; 4 × 5 × 60 (60) = 40 hours[b]	113/170	62.8 (13.4)	91-365	Subacute	VR environment on screen and motion tracking through sensors	5
Turolla et al. 2013	VR + CT vs CT; 4 × 5 × 60 (60) = 40 hours[b]	82/106	62.8 (13.4)	>365	Chronic	VR environment on screen and motion tracking through sensors	5
Yin et al. 2014	VR + PT/OT vs PT/OT; 2 × 4.5 × 30 (90) = 18 hours	11/23	58.3 (13.5)	16.3 (7.4)	Acute	VR environment on screen and motion tracking through hand-held sensors	6
Zondervan et al. 2016	VR vs standard at home training; 3 × 3 × 60 = 9 hours[b]	9/17	59.5 (40-74)	1551.3 (1058.5)	Chronic	VR environment on laptop and motion tracking through sensors	8
Zucconi et al. 2011	VR vs PT; 4 × 5 × 60 = 20 hours[b]	11/22	62.25 (56-73)	236.5 (88 - 544)	Chronic	VR environment on screen and motion tracking through sensors	8
Mean	**4.4 × 4.4 × 49.7 (55) = 23.9 hours**	**27.1/43.6**	**61.4**	**370.4**			**6.7**
NSVR studies							
da Silva Ribeiro et al. 2015	VR vs PT; 2 × 2 × 60 = 4 hours[b]	15/30	53.3 (7.4)	1559 (1080)	Chronic	Nintendo Wii	5
Kong et al. 2016	VR + PT/OT vs CT + PT/OT; 3 × 4 × 60 (75) = 27 hours[b]	33/67	57.5 (9.8)	13.7 (8.9)	Acute	Nintendo Wii	9
Rand et al. 2016	VR vs standard at home therapy; 5 × 6 × 37.6 = 18.8 hours[b]	13/24	62 (8.7)	495.8 (263.1)	Chronic	Microsoft Xbox Kinect or Sony PlayStation EyeToy	7
Saposnik et al. 2010	VR + CT vs recreational therapy + CT; 2 × 4 × 60 (60) = 16 hours[b]	9/18	61.3 (13)	24.7 (12.5)	Subacute	Nintendo Wii	5
Saposnik et al. 2016	VR + CT vs recreational therapy + CT; 2 × 5 × 60 (37.3) = 16 hours[b]	59/121	62 (12.5)	25.8 (9.5 – 46.75)	Subacute	Nintendo Wii	6

Sin and Lee, 2013	VR + OT vs OT; 6 × 3 × 30 (30) = 18 hours	18/35	73.7 (7.5)	239 (64)	Chronic	Microsoft Xbox Kinect	6
Türkbey et al. 2017	VR + CT vs CT; 4 × 5 × 60 (60) = 40 hours	10/19	62 (38 - 79)	47 (13 - 125)	Subacute	Microsoft Xbox Kinect	9
Yavuzer et al. 2008	VR + CT vs CT + watching VR; 4 × 5 × 30 (60) = 30 hours	10/20	61.1 (8)	118.7 (70)	Subacute	Sony PlayStation EyeToy	8
Mean	**3.5 × 4.3 × 52.5 (57) = 21.9 hours**	**20.9/41.8**	**61.6**	**315.4**			**6.9**

Abbreviations: CT, conventional therapy; DSS, days since stroke; NSVR, nonspecific VR; OT, occupational therapy; PT, physical therapy; SVR, specific VR; VR, virtual reality. Intervention: intervention (VR) versus control group (CT, OT, PT), Weeks × Sessions per week × Minutes (if additional CT was given) = Total amount of intervention in hours; n = Number of patients in intervention/Total number of patients. Age: mean years (SD or range). DSS: mean days (SD or range). Phase: acute, 1 day to 3 weeks; subacute, 3 weeks to 3 months; chronic, more than 3 months after stroke. [b]Dose matched between groups.

Table 3.5. Aim, outcome measurements, main finding, and assigned principles of included studies.

		ICF-WHO category						
Author	**Aim**	**BF**	**AC**	**PP**	**Other scales**	**Follow-up**	**Main Finding**	**Principles**
SVR studies								
Aşkın et al. 2018	Effect of VR on upper-limb recovery	FM-UE	BBT		MAS, BS, MI	No	FM-UE significantly higher for VR than control after treatment	- Dosage - Task-specific practice - Variable practice - Multisensory stimulation
Brunner et al. 2017	Compare effectiveness of VR to CT		FIM		BBT, ARAT, Abilhand, PGIC	3 months	No significant difference after treatment, both groups improved	- Dosage - Task-specific practice - Variable practice - Increasing difficulty - Implicit feedback

Da Silva Cameirão et al. 2011	Clinical impact of VR on recovery time course	FM-UE	BI		MRC, MI, CAHAI	24 weeks	FM-UE significantly higher for VR than control after treatment	- Task-specific practice - Variable practice - Avatar representation - Increasing difficulty - Implicit feedback - Promote use of affected limb
Crosbie et al. 2012	Effectiveness of VR to CT on motor rehabilitation	MI	ARAT			6 weeks	VR maintained improvement in MI at follow-up	- Variable practice - Multisensory stimulation - Explicit feedback - Implicit feedback - Promote use of affected limb
Duff et al. 2012	Compare VR and PT	FM-UE	WMFT	SIS	MAL QOM/AOU	No	FM-UE significantly higher for control than VR after treatment	- Variable practice - Multisensory stimulation - Explicit feedback - Implicit feedback - Promote use of affected limb
Jang et al. 2005	Effect of VR on cortical reorganization and motor recovery	FM-UE	BBT		MAL QOM/AOU, MFT	No	FM-UE significantly higher for VR than control after treatment	- Task-specific practice - Variable practice - Increasing difficulty - Avatar representation - Implicit feedback - Promote use of affected limb
Jo et al. 2005	Changes in upper-extremity function and visual perception using VR		WMFT		MVPT	No	No significant difference after treatment, both groups improved significant in WMFT	- Dosage - Structured practice - Variable practice - Increasing difficulty - Explicit feedback - Promote use of affected limb

Kiper et al. 2011	Impact of VR versus CT on treatment of upper extremity	FM-UE	FIM	MAS	No	FM-UE significantly higher for VR than control after treatment	- Dosage - Task-specific practice - Variable practice - Increasing difficulty - Implicit feedback - Promote use of affected limb
Kiper et al. 2014	Is VR more effective than CT on treatment of upper-limb motor function	FM-UE	FIM		No	FM-UE significantly higher for VR than control after treatment	- Dosage - Variable practice - Increasing difficulty - Implicit feedback - Promote use of affected limb
Kiper et al. 2018	Effectiveness of reinforced feedback in VR vs CT	FM-UE	FIM	NIHSS, ESAS	No	FM-UE significantly higher for VR than control after treatment	- Dosage - Task-specific practice - Variable practice - Multisensory stimulation - Explicit feedback - Implicit feedback - Promote use of affected limb
Kottink et al. 2014	Compare effect of VR to CT on arm function	FM-UE			1 month	No significant difference after treatment, both groups improved significantly in FM-UE	- Task-specific practice - Increasing difficulty - Explicit feedback - Promote use of affected limb
Kwon et al. 2012	Impact of VR with CT on upper-extremity function and ADL in acute stage	FM-UE	BI	MFT	No	No significant difference after treatment, both groups improved significantly in FM_UE	- Dosage - Task-specific practice - Variable practice - Avatar representation
Lee et al. 2016	Effect of VR on upper-limb function and muscle strength		BBT	JTHFT, GPT	No	BBT significantly higher for VR than control after treatment	- Structure practice - Variable practice - Implicit feedback - Promote use of affected limb

Levin et al. 2012	Potential of VR to improve upper-limb motor ability	FM-UE	BBT	CSI, RPSS, WMFT, MAL QOM/AOU	1 month	More patients improved in FM-UE in VR than control	- Task-specific practice - Variable practice - Avatar representation - Increasing difficulty - Explicit feedback - Promote use of affected limb
Piron et al. 2009	Impact of VR on treating motor deficits	FM-UE		Abilhand, MAS	2 and 3 months	FM-UE significantly higher for VR than control after treatment	- Variable practice - Explicit feedback - Implicit feedback - Promote use of affected limb
Piron et al. 2010	Impact of VR versus CT	FM-UE	FIM		No	FM-UE was systematically lower in control than VR	- Variable practice - Increasing difficulty - Explicit feedback - Implicit feedback
Shin et al. 2014	Assessment of usability and clinical efficacy of VR	FM-UE	BI	MRC	No	FM-UE higher after treatment but not significant for VR	- Task-specific practice - Variable practice - Avatar representation - Increasing difficulty - Explicit feedback - Implicit feedback - Promote use of affected limb
Standen et al. 2016	Feasibility of home-based VR for arm rehabilitation		WMFT	9 peg hole, MAL QOM/AOU	No	WMFT grip strength at midpoint significantly higher improvement for VR	- Massed practice - Task-specific practice - Variable practice - Increasing difficulty - Explicit feedback - Promote use of affected limb

Turolla et al. 2013	Effectiveness of VR on restoration of upper-limb function and ADL	FM-UE	FIM			No	FM-UE significantly higher for VR than control after treatment	- Dosage - Task-specific practice - Variable practice - Increasing difficulty - Explicit feedback - Implicit feedback
Yin et al. 2014	Effect of VR on rehabilitation of upper-limb motor performance	FM-UE	FIM		ARAT, MAL QOM/AOU	1 month	No significant difference between groups in FM-UE	- Dosage - Structured practice - Task-specific practice - Multisensory stimulation - Avatar representation - Explicit feedback - Implicit feedback - Promote use of affected limb
Zondervan et al. 2016	Feasibility and efficacy of VR at patient's home		ARAT		BBT, MAL QOM/AOU, 9 Peg Hole	1 month	MAL QOM change from baseline significant for VR	- Massed practice - Task-specific practice - Multisensory stimulation - Explicit feedback - Promote use of affected limb
Zucconi et al. 2011	Effect of VR on motor impairment	FM-UE	FIM		MAS, RPS	No	Only VR improved significantly after treatment in FM-UE	- Variable practice - Increasing difficulty - Implicit feedback - Promote use of affected limb
NSVR studies								
da Silva Ribeiro et al. 2015	Effect of VR vs CT on sensorimotor function and quality of life	FM-UE		SF-36		No	No significant difference after treatment, both groups improved significantly in FM-UE	- Structured practice - Variable practice - Increasing difficulty

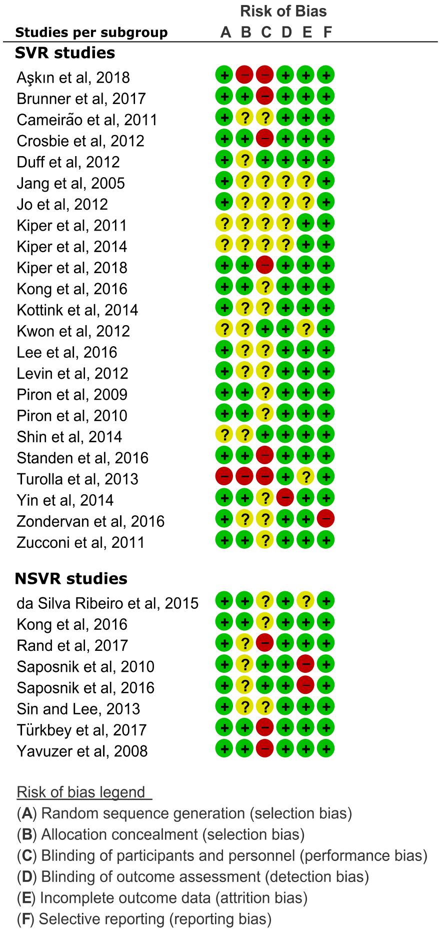
Kong et al. 2016	Efficacy of VR with CT on upper-limb recovery	FM-UE	FIM		ARAT, SIS-UL, VAS	7 and 15 weeks	No significant difference after treatment, both groups improved significantly in FM-UE	- Dosage - Variable practice - Explicit feedback - Promote use of affected limb
Rand et al. 2017	Effectiveness of self-training programs on upper-limb function		ARAT		MAL QOM/AOU, BBT	4 weeks	No significant difference or improvement in MAL QOM after treatment	- Variable practice - Promote use of affected limb
Saposnik et al. 2010	Efficacy of VR for stroke rehabilitation	SIS grip strength	WMFT	SIS	BBT	4 weeks	VR had significant improvement in WMFT, but only at follow-up	- Dosage - Variable practice - Multisensory stimulation - Avatar representation - Implicit feedback
Saposnik et al. 2016	Compare safety and efficacy of VR with recreational therapy on motor recovery	SIS grip strength	BI	SIS	WMFT, BBT, FIM, MRS	4 weeks	No significant difference after treatment, both groups significantly improved in WMFT	- Dosage - Task-specific practice - Variable practice - Promote use of affected limb
Sin and Lee, 2013	Effects of additional VR on upper-extremity function	FM-UE	BBT			No	FM-UE significantly higher for VR than control after treatment	- Task-specific practice - Variable practice - Multisensory stimulation - Explicit feedback - Implicit feedback - Promote use of affected limb
Türkbey et al. 2017	Feasibility and safety of VR on upper-limb recovery	BS	BBT		WMFT, FIM	No	No significant difference after treatment, both groups significantly improved in WMFT	- Dosage - Task-specific practice - Variable practice - Multisensory stimulation - Avatar representation - Promote use of affected limb

Yavuzer et al. 2008	Effect of VR on upper-limb motor recovery	BS	FIM		3 months	BS UE significantly higher in VR than control after treatment	- Dosage - Task-specific practice - Variable practice - Increasing difficulty - Promote use of affected limb

Abbreviations: AC, Activity; ADL, activities of daily living; AOU, amount of use; ARAT, Action Research Arm Test; BBT, Box and Block Test; BF, body function; BI, Barthel Index; BS, Brunnstrom Motor Recovery Stage; CAHAI, Chedoke Arm and Hand Inventory; CSI, Composite Spasticity Index; CT, conventional therapy; ESAS, Edmonton Symptom Assessment Scale; FIM, Functional Independence Measure; FM-UE, Fugl-Meyer Assessment Upper Extremity; GPT, Grooved Pegboard Test; ICF-WHO, World Health Organization's International Classification of Function, Disability, and Health; JTHFT, Jepsen-Taylor Hand Function Test; MAL, Motor Activity Log; MAS, Modified Ashworth Scale; MFT, Manual Function Test; MI, Motricity Index; MRC, Medical Research Council Grade; MVPT, Motor-Free Visual Perception Test; NIHSS, National Institutes of Health Stroke Scale; NSVR, nonspecific VR; PGIC, Patient Global Impression; PP, Participation; PT, physical therapy; QOM, quality of movement; RPSS, Performance Reaching Scale for Stroke; SF-36, Short-Form Health Survey; SIS, Stroke Impact Scale; SIS-UL, SIS upper limb items; SVR, specific VR; VAS, Visual Analogue Scale; VR, virtual reality; WMFT, Wolf Motor Function Test. BF, AC and PP are the ICF-WHO categories.

3.3.2. Assessment of risk of bias

We assessed the methodological quality of the included studies, by analysing each dimension in the risk of bias analysis. The detailed analysis per study and the summary plot can be found in Figure 3.2 and Figure 3.3, respectively.



	Risk of Bias					
Studies per subgroup	A	B	C	D	E	F
SVR studies						
Aşkın et al, 2018	+	−	−	+	+	+
Brunner et al, 2017	+	+	−	+	+	+
Cameirão et al, 2011	+	?	?	+	+	+
Crosbie et al, 2012	+	+	−	+	+	+
Duff et al, 2012	+	?	+	+	+	+
Jang et al, 2005	+	?	?	?	?	+
Jo et al, 2012	+	?	?	?	?	+
Kiper et al, 2011	?	?	?	?	+	+
Kiper et al, 2014	?	?	?	?	+	+
Kiper et al, 2018	+	+	−	+	+	+
Kong et al, 2016	+	+	?	+	+	+
Kottink et al, 2014	+	?	?	+	+	+
Kwon et al, 2012	?	?	+	+	?	+
Lee et al, 2016	+	?	?	+	+	+
Levin et al, 2012	+	?	?	+	+	+
Piron et al, 2009	+	+	?	+	+	+
Piron et al, 2010	+	+	?	+	+	+
Shin et al, 2014	?	?	+	+	+	+
Standen et al, 2016	+	+	−	+	+	+
Turolla et al, 2013	−	−	−	+	?	+
Yin et al, 2014	+	+	?	−	+	+
Zondervan et al, 2016	+	?	?	+	+	−
Zucconi et al, 2011	+	+	?	+	+	+
NSVR studies						
da Silva Ribeiro et al, 2015	+	+	?	+	?	+
Kong et al, 2016	+	+	?	+	+	+
Rand et al, 2017	+	?	−	+	+	+
Saposnik et al, 2010	+	?	+	+	−	+
Saposnik et al, 2016	+	?	+	+	−	+
Sin and Lee, 2013	+	?	?	+	+	+
Türkbey et al, 2017	+	+	−	+	+	+
Yavuzer et al, 2008	+	+	−	+	+	+

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)

Figure 3.2. Risk of bias per study.
Reviewers' judgement about each risk of bias item for all the included studies. Abbreviations: SVR, nonspecific VR; SVR, specific VR; VR, virtual reality.

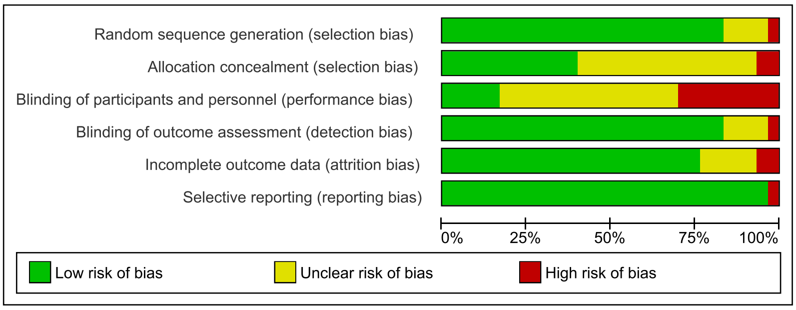


Figure 3.3. Risk of bias summary.
Review authors' judgments about each risk of bias item presented as percentages across all included studies. According to the assessment executed above, both study groups seem to be balanced with regards to their risk of bias.

3.3.2.1. Allocation

Random sequence generation was adequately reported by 18 SVR and all NSVR studies. One SVR study (Turolla et al., 2013) stated that no random allocation was performed, and therefore, also no allocation concealment was applied. In the other studies, allocation concealment was adequately reported by 9 SVR and 4 NSVR studies.

3.3.2.2. Blinding

A total of 18 SVR and all NSVR studies adequately reported that the outcome assessor was blinded. Because of the nature of the interventions, only a few studies could blind participants and therapists. We evaluated studies at a low risk if either of the two groups was blind or if they tried to limit the impact of non-blindness (3 SVR and 2 NSVR). Therefore, the nonblinding of personnel and patients could be a high risk of bias.

3.3.2.3. Incomplete Outcome Data

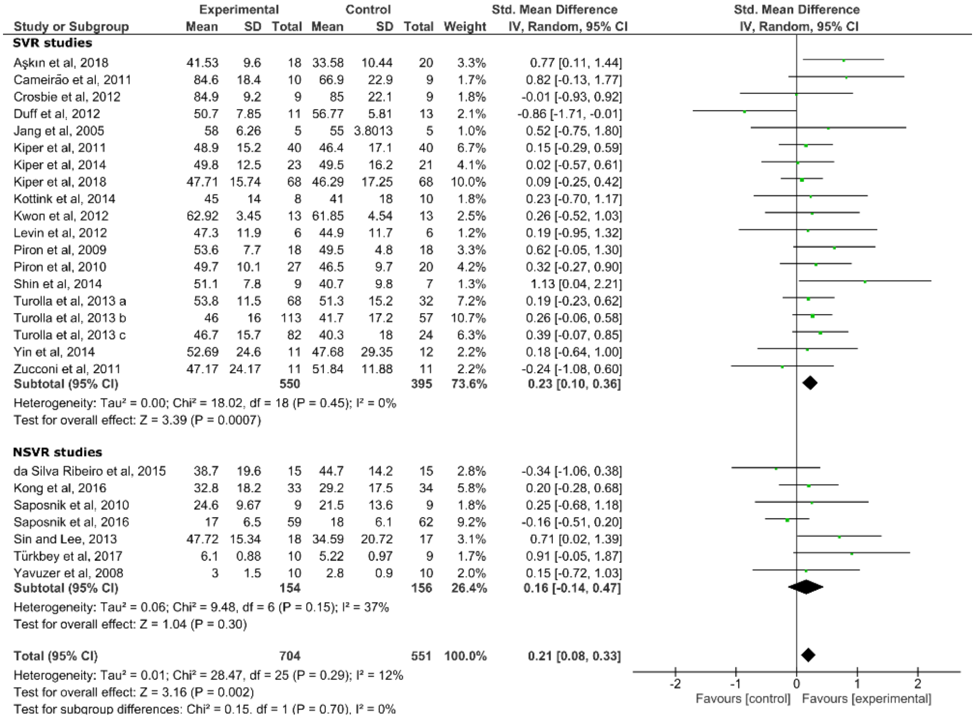
In all, 19 SVR and 5 NSVR studies adequately reported how missing data points were handled. Two NSVR studies reported inconsistent information about how the missing data was handled.

3.3.2.4. Selective Reporting

Except for 1 SVR study, all included studies reported the outcomes for all measurements taken.

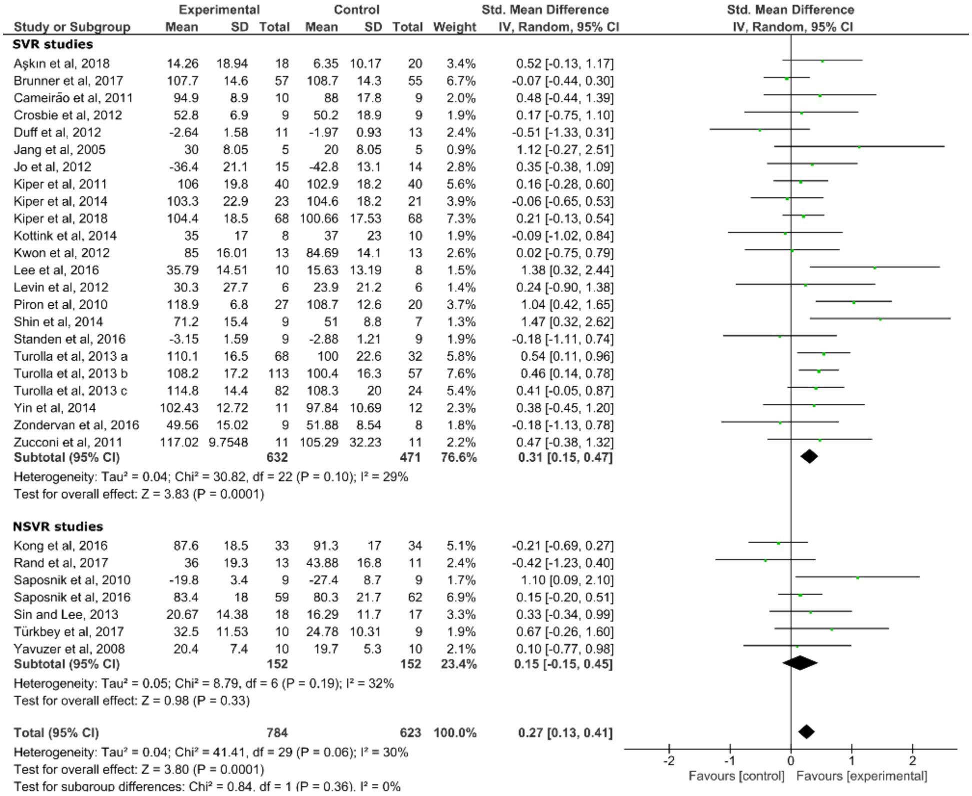
3.3.3. Effects of SVR and NSVR interventions

When analysing the outcome of the subgroup analysis, SVR studies showed a significant impact on the recovery of the upper limb function (SMD = 0.23, 95% CI 0.10 to 0.36, *p* = .0007) and activity (SMD = 0.31, 95% CI 0.15 to 0.47, *p* = .0001) that is superior in comparison to CT; see Figure 3.4 and Figure 3.5, upper panel. NSVR studies showed no significant effect, neither on body function (SMD = 0.16, 95% CI -0.14 to 0.47, *p* = .30) nor on activity (SMD = 0.15, 95% CI -0.15 to 0.45, *p* = .33); see Figure 3.4 and Figure 3.5, lower panel. No significant heterogeneity was present in any comparison. Also, there were no significant differences between the subgroups, neither in body function (*p* = .70) nor in activity (*p* = .36), as the CIs overlapped substantially. According to GRADE (Figure 3.6), there is moderate confidence in the effect estimates for the results found in SVR studies.



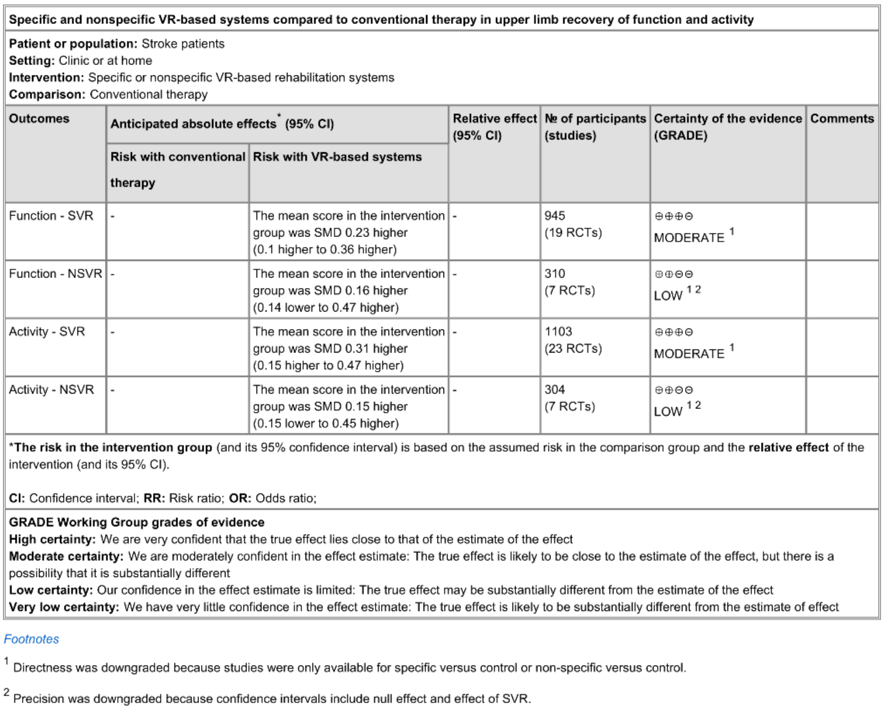
	Experimental			Control				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
SVR studies								
Aşkın et al, 2018	41.53	9.6	18	33.58	10.44	20	3.3%	0.77 [0.11, 1.44]
Cameirão et al, 2011	84.6	18.4	10	66.9	22.9	9	1.7%	0.82 [-0.13, 1.77]
Crosbie et al, 2012	84.9	9.2	9	85	22.1	9	1.8%	-0.01 [-0.93, 0.92]
Duff et al, 2012	50.7	7.85	11	56.77	5.81	13	2.1%	-0.86 [-1.71, -0.01]
Jang et al, 2005	58	6.26	5	55	3.8013	5	1.0%	0.52 [-0.75, 1.80]
Kiper et al, 2011	48.9	15.2	40	46.4	17.1	40	6.7%	0.15 [-0.29, 0.59]
Kiper et al, 2014	49.8	12.5	23	49.5	16.2	21	4.1%	0.02 [-0.57, 0.61]
Kiper et al, 2018	47.71	15.74	68	46.29	17.25	68	10.0%	0.09 [-0.25, 0.42]
Kottink et al, 2014	45	14	8	41	18	10	1.8%	0.23 [-0.70, 1.17]
Kwon et al, 2012	62.92	3.45	13	61.85	4.54	13	2.5%	0.26 [-0.52, 1.03]
Levin et al, 2012	47.3	11.9	6	44.9	11.7	6	1.2%	0.19 [-0.95, 1.32]
Piron et al, 2009	53.6	7.7	18	49.5	4.8	18	3.3%	0.62 [-0.05, 1.30]
Piron et al, 2010	49.7	10.1	27	46.5	9.7	20	4.2%	0.32 [-0.27, 0.90]
Shin et al, 2014	51.1	7.8	9	40.7	9.8	7	1.3%	1.13 [0.04, 2.21]
Turolla et al, 2013 a	53.8	11.5	68	51.3	15.2	32	7.2%	0.19 [-0.23, 0.62]
Turolla et al, 2013 b	46	16	113	41.7	17.2	57	10.7%	0.26 [-0.06, 0.58]
Turolla et al, 2013 c	46.7	15.7	82	40.3	18	24	6.3%	0.39 [-0.07, 0.85]
Yin et al, 2014	52.69	24.6	11	47.68	29.35	12	2.2%	0.18 [-0.64, 1.00]
Zucconi et al, 2011	47.17	24.17	11	51.84	11.88	11	2.2%	-0.24 [-1.08, 0.60]
Subtotal (95% CI)			**550**			**395**	**73.6%**	**0.23 [0.10, 0.36]**
Heterogeneity: Tau² = 0.00; Chi² = 18.02, df = 18 (P = 0.45); I² = 0%								
Test for overall effect: Z = 3.39 (P = 0.0007)								
NSVR studies								
da Silva Ribeiro et al, 2015	38.7	19.6	15	44.7	14.2	15	2.8%	-0.34 [-1.06, 0.38]
Kong et al, 2016	32.8	18.2	33	29.2	17.5	34	5.8%	0.20 [-0.28, 0.68]
Saposnik et al, 2010	24.6	9.67	9	21.5	13.6	9	1.8%	0.25 [-0.68, 1.18]
Saposnik et al, 2016	17	6.5	59	18	6.1	62	9.2%	-0.16 [-0.51, 0.20]
Sin and Lee, 2013	47.72	15.34	18	34.59	20.72	17	3.1%	0.71 [0.02, 1.39]
Türkbey et al, 2017	6.1	0.88	10	5.22	0.97	9	1.7%	0.91 [-0.05, 1.87]
Yavuzer et al, 2008	3	1.5	10	2.8	0.9	10	2.0%	0.15 [-0.72, 1.03]
Subtotal (95% CI)			**154**			**156**	**26.4%**	**0.16 [-0.14, 0.47]**
Heterogeneity: Tau² = 0.06; Chi² = 9.48, df = 6 (P = 0.15); I² = 37%								
Test for overall effect: Z = 1.04 (P = 0.30)								
Total (95% CI)			**704**			**551**	**100.0%**	**0.21 [0.08, 0.33]**
Heterogeneity: Tau² = 0.01; Chi² = 28.47, df = 25 (P = 0.29); I² = 12%								
Test for overall effect: Z = 3.16 (P = 0.002)								
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.70), I² = 0%								

Figure 3.4. Forest plot of functional outcomes.
SVR versus NSVR studies on upper limb function as measured by the selected outcome. Abbreviations: SVR, specific VR; NSVR, nonspecific VR; VR, virtual reality.



	Experimental			Control				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
SVR studies								
Aşkın et al, 2018	14.26	18.94	18	6.35	10.17	20	3.4%	0.52 [-0.13, 1.17]
Brunner et al, 2017	107.7	14.6	57	108.7	14.3	55	6.7%	-0.07 [-0.44, 0.30]
Cameirão et al, 2011	94.9	8.9	10	88	17.8	9	2.0%	0.48 [-0.44, 1.39]
Crosbie et al, 2012	52.8	6.9	9	50.2	18.9	9	1.9%	0.17 [-0.75, 1.10]
Duff et al, 2012	-2.64	1.58	11	-1.97	0.93	13	2.4%	-0.51 [-1.33, 0.31]
Jang et al, 2005	30	8.05	5	20	8.05	5	0.9%	1.12 [-0.27, 2.51]
Jo et al, 2012	-36.4	21.1	15	-42.8	13.1	14	2.8%	0.35 [-0.38, 1.09]
Kiper et al, 2011	106	19.8	40	102.9	18.2	40	5.6%	0.16 [-0.28, 0.60]
Kiper et al, 2014	103.3	22.9	23	104.6	18.2	21	3.9%	-0.06 [-0.65, 0.53]
Kiper et al, 2018	104.4	18.5	68	100.66	17.53	68	7.3%	0.21 [-0.13, 0.54]
Kottink et al, 2014	35	17	8	37	23	10	1.9%	-0.09 [-1.02, 0.84]
Kwon et al, 2012	85	16.01	13	84.69	14.1	13	2.6%	0.02 [-0.75, 0.79]
Lee et al, 2016	35.79	14.51	10	15.63	13.19	8	1.5%	1.38 [0.32, 2.44]
Levin et al, 2012	30.3	27.7	6	23.9	21.2	6	1.4%	0.24 [-0.90, 1.38]
Piron et al, 2010	118.9	6.8	27	108.7	12.6	20	3.7%	1.04 [0.42, 1.65]
Shin et al, 2014	71.2	15.4	9	51	8.8	7	1.3%	1.47 [0.32, 2.62]
Standen et al, 2016	-3.15	1.59	9	-2.88	1.21	9	1.9%	-0.18 [-1.11, 0.74]
Turolla et al, 2013 a	110.1	16.5	68	100	22.6	32	5.8%	0.54 [0.11, 0.96]
Turolla et al, 2013 b	108.2	17.2	113	100.4	16.3	57	7.6%	0.46 [0.14, 0.78]
Turolla et al, 2013 c	114.8	14.4	82	108.3	20	24	5.4%	0.41 [-0.05, 0.87]
Yin et al, 2014	102.43	12.72	11	97.84	10.69	12	2.3%	0.38 [-0.45, 1.20]
Zondervan et al, 2016	49.56	15.02	9	51.88	8.54	8	1.8%	-0.18 [-1.13, 0.78]
Zucconi et al, 2011	117.02	9.7548	11	105.29	32.23	11	2.2%	0.47 [-0.38, 1.32]
Subtotal (95% CI)			**632**			**471**	**76.6%**	**0.31 [0.15, 0.47]**
Heterogeneity: Tau² = 0.04; Chi² = 30.82, df = 22 (P = 0.10); I² = 29%								
Test for overall effect: Z = 3.83 (P = 0.0001)								
NSVR studies								
Kong et al, 2016	87.6	18.5	33	91.3	17	34	5.1%	-0.21 [-0.69, 0.27]
Rand et al, 2017	36	19.3	13	43.88	16.8	11	2.4%	-0.42 [-1.23, 0.40]
Saposnik et al, 2010	-19.8	3.4	9	-27.4	8.7	9	1.7%	1.10 [0.09, 2.10]
Saposnik et al, 2016	83.4	18	59	80.3	21.7	62	6.9%	0.15 [-0.20, 0.51]
Sin and Lee, 2013	20.67	14.38	18	16.29	11.7	17	3.3%	0.33 [-0.34, 0.99]
Türkbey et al, 2017	32.5	11.53	10	24.78	10.31	9	1.9%	0.67 [-0.26, 1.60]
Yavuzer et al, 2008	20.4	7.4	10	19.7	5.3	10	2.1%	0.10 [-0.77, 0.98]
Subtotal (95% CI)			**152**			**152**	**23.4%**	**0.15 [-0.15, 0.45]**
Heterogeneity: Tau² = 0.05; Chi² = 8.79, df = 6 (P = 0.19); I² = 32%								
Test for overall effect: Z = 0.98 (P = 0.33)								
Total (95% CI)			**784**			**623**	**100.0%**	**0.27 [0.13, 0.41]**
Heterogeneity: Tau² = 0.04; Chi² = 41.41, df = 29 (P = 0.06); I² = 30%								
Test for overall effect: Z = 3.80 (P = 0.0001)								
Test for subgroup differences: Chi² = 0.84, df = 1 (P = 0.36), I² = 0%								

Figure 3.5. Forest plot of activity outcomes.
SVR versus NSVR studies on upper limb activity as measured by the selected outcome. Abbreviations: SVR, specific VR; NSVR, nonspecific VR; VR, virtual reality.



Specific and nonspecific VR-based systems compared to conventional therapy in upper limb recovery of function and activity

Patient or population: Stroke patients
Setting: Clinic or at home
Intervention: Specific or nonspecific VR-based rehabilitation systems
Comparison: Conventional therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with conventional therapy	Risk with VR-based systems				
Function - SVR	-	The mean score in the intervention group was SMD 0.23 higher (0.1 higher to 0.36 higher)	-	945 (19 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
Function - NSVR	-	The mean score in the intervention group was SMD 0.16 higher (0.14 lower to 0.47 higher)	-	310 (7 RCTs)	⊕⊕⊖⊖ LOW [1 2]	
Activity - SVR	-	The mean score in the intervention group was SMD 0.31 higher (0.15 higher to 0.47 higher)	-	1103 (23 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
Activity - NSVR	-	The mean score in the intervention group was SMD 0.15 higher (0.15 lower to 0.45 higher)	-	304 (7 RCTs)	⊕⊕⊖⊖ LOW [1 2]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes

[1] Directness was downgraded because studies were only available for specific versus control or non-specific versus control.

[2] Precision was downgraded because confidence intervals include null effect and effect of SVR.

Figure 3.6. Summary of findings for the main comparisons.
The quality of evidence for this review was evaluated using GRADEpro, finding a moderate certainty of the effects observed in the SVR studies. Abbreviations: SVR, specific VR; NSVR, nonspecific VR; VR, virtual reality.

3.3.4. Assessment of reporting bias

Funnel plot asymmetry might point to a possible publication bias because of a lack of small studies with non-significant or unfavourable results (Figure 3.7 A and B). Because of our exclusion criteria, only one study had a small sample size (Jang et al., 2005) (n = 10). Together with other smaller studies, it skews the plot slightly to the right. However, other explanations are possible. Many SVR systems have become commercially available to clinics after the treatment effect was confirmed through experiments. It, therefore, cannot be ruled out that the confounding factor of conflict of interest could have biased the result described above. Within the included SVR studies we identified 3 groups of systems called IREX (Jang et al., 2005; Jo et al., 2012; Kwon et al., 2012), Virtual Reality Rehabilitation System (VRRS) (Kiper et al., 2014, 2011, 2018; Piron et al., 2009, 2010; Turolla et al., 2013; Zucconi et al., 2011) and other commercial systems (Brunner et al., 2017; Cameirão et al., 2011; Kottink et al., 2014; M F Levin et al., 2012; Zondervan et al., 2016) that qualified as commercially available devices for clinics. We then separated the funnel plots by these groups and contrasted them with systems that remained experimental set-ups only (Figure 3.7 C and D) (Aşkın et al., 2018; Crosbie et al., 2012; Duff et al., 2012; Kottink et al., 2014; S. Lee et al., 2016; Shin et al., 2014; Standen et al., 2016; Yin et al., 2014). The studies using VRRS are large-sized, and therefore, cluster at the top of the effect, both in body function outcomes (SMD = 0.21, 95% CI 0.06 to 0.36, $p = .007$) and activity outcomes (SMD = 0.38, 95% CI 0.19 to 0.56, $p < .0001$). Neither of the other groups reached significance. Therefore, the presence of a bias due to commercialization cannot be confirmed.

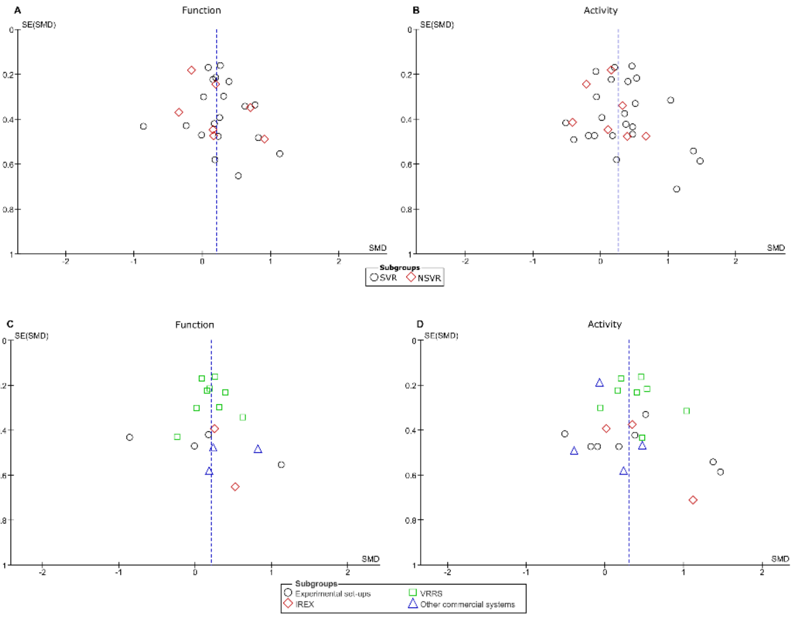


Figure 3.7. Funnel plots.
Upper panel (A and B) shows the evaluation of a possible publication bias in included studies. Black refers to SVR and red to NSVR studies. Lower panel (C and D) shows the funnel plots split by commercial systems that are available to clinics. Circles are experimental set-ups, squares represent VRRS studies, rhombi represent IREX studies, and triangles other commercial systems. A and C show the funnel plot for function outcomes, B and D show the funnel plot for activity outcomes. Abbreviations: NSVR, nonspecific VR; SMD, standardized mean difference; SE(SMD), standard error of SMD; SVR, specific VR; VR, virtual reality.

3.3.5. Evaluation of included principles of neurorehabilitation

We identified relevant differences between SVR and NSVR studies (Figure 3.8) with respect to the included principles. In Table 3.5, the assigned principles for each study can be found and the full data set used for the analysis is published online (Maier, Ballester, Duff, Duarte Oller, & Verschure, 2019b). First, the spectrum of the principles that are mentioned in more than 50% of the studies is broader in SVR than NSVR interventions. NSVR studies focused on three principles—variable practice (da Silva Ribeiro et al., 2015; Kong et al., 2016; Rand et al., 2017; Saposnik et al., 2016, 2010; Sin & Lee, 2013; Türkbey et al., 2017; Yavuzer et al., 2008), promoting the use of the paretic limb (Kong et al., 2016; Rand et al., 2017; Saposnik et al., 2016; Sin & Lee, 2013; Türkbey et al., 2017; Yavuzer et al., 2008), and dosage (Kong et al., 2016; Saposnik et al., 2016, 2010; Türkbey et al., 2017; Yavuzer et al., 2008)—that were present in 100%, 75% and 63% of the studies respectively. SVR studies did not share one specific principle in common, but more than 50% of the studies in this category included the same six principles: variable practice (86%) (Aşkın et al., 2018; Brunner et al., 2017; Cameirão et al., 2011; Crosbie et al., 2012; Duff et al., 2012; Jang et al., 2005; Jo et al., 2012; Kiper et al., 2014, 2011, 2018; Kwon et al., 2012; S. Lee et al., 2016; M F Levin et al., 2012; Piron et al., 2009, 2010; Shin et al., 2014; Standen et al., 2016; Turolla et al., 2013; Zucconi et al., 2011), promoting the use of the paretic limb (86%) (Aşkın et al., 2018; Cameirão et al., 2011; Crosbie et al., 2012; Duff et al., 2012; Jang et al., 2005; Jo et al., 2012; Kiper et al., 2014, 2011, 2018; Kottink et al., 2014; S. Lee et al., 2016; M F Levin et al., 2012; Piron et al., 2009, 2010; Shin et al., 2014; Standen et al., 2016; Yin et al., 2014; Zondervan et al., 2016; Zucconi et al., 2011) implicit feedback (64%) (Brunner et al., 2017; Cameirão et al., 2011; Duff et al., 2012; Jang et al., 2005; Kiper et al., 2014, 2011, 2018; S. Lee et al., 2016; Piron et al., 2009, 2010; Shin et al., 2014; Turolla et al., 2013; Yin et al., 2014; Zucconi et al., 2011), increasing difficulty (64%) (Brunner et al., 2017; Cameirão et al., 2011; Crosbie et al., 2012; Jang et al., 2005; Jo et al., 2012; Kiper et al., 2014, 2011; Kottink et al., 2014; M F Levin et al., 2012; Piron et al., 2010; Shin et al., 2014; Standen et al., 2016; Turolla et al., 2013; Zucconi et al., 2011), task-specific practice (64%) (Aşkın et al., 2018; Brunner et al., 2017; Cameirão et al., 2011; Jang et al., 2005; Kiper et al., 2011, 2018; Kottink et al., 2014; Kwon et al., 2012; M F Levin et al., 2012; Shin et al., 2014; Standen et al., 2016; Turolla et al., 2013; Yin et al., 2014; Zondervan et al., 2016), and explicit feedback (59%) (Aşkın et al., 2018; Duff et al., 2012; Jo et al., 2012; Kiper et al., 2018; Kottink et al., 2014; M F Levin et al., 2012; Piron et al., 2009, 2010; Shin et al., 2014; Standen et al., 2016; Turolla et al., 2013; Yin et al., 2014; Zondervan et al., 2016).

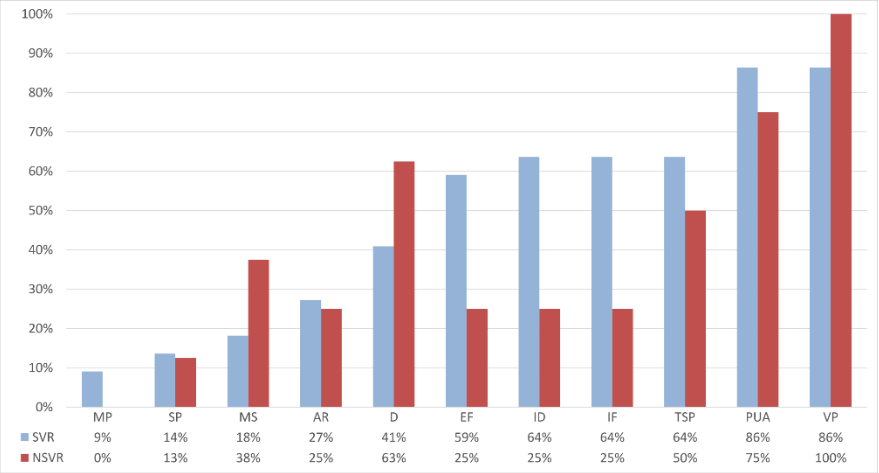


Figure 3.8. Distribution of included principles in SVR versus NSVR studies.
Blue indicates SVR and red NSVR studies. Abbreviations: AR, avatar representation; D, dosage; EF, explicit feedback; ID, increasing difficulty; IF, implicit feedback; MP, massed practice; MS, multisensory stimulation; NSVR, nonspecific VR; PUA, promote the use of the affected limb; SP, structured practice; SVR, specific VR; TSP, task-specific practice; VP, variable practice; VR, virtual reality.

We conducted a follow-up analysis to evaluate the effect of dosage as NSVR studies seem to have more intense intervention regimes. We compared the outcomes of those studies that provided more than 60 minutes of therapy per session per weekday. We identified 14 studies, 9 SVR (Aşkın et al., 2018; Brunner et al., 2017; Jo et al., 2012; Kiper et al., 2014, 2011, 2018; Kwon et al., 2012; Turolla et al., 2013; Yin et al., 2014) and 5 NSVR (Kong et al., 2016; Saposnik et al., 2016, 2010; Türkbey et al., 2017; Yavuzer et al., 2008), that fulfil this criterion. Comparing this subset of SVR and NSVR studies with their respective control, we still observe a significant superior impact of SVR studies on body function (SMD = 0.23, 95% CI 0.07 to 0.38, *p* = .004, see Figure 3.9, upper panel) and activity (SMD = 0.27, 95% CI 0.13 to 0.41, *p* = .0002, see Figure 3.10, upper panel), whereas the total number of hours of intervention (SVR: mean [SD] 35.6 [8] hours, NSVR: mean [SD] 25.8 [9.1] hours) and the number of weeks (SVR: mean [SD] 3.8 [0.6] weeks, NSVR: mean [SD] 3 [0.9] weeks) were not significantly different.

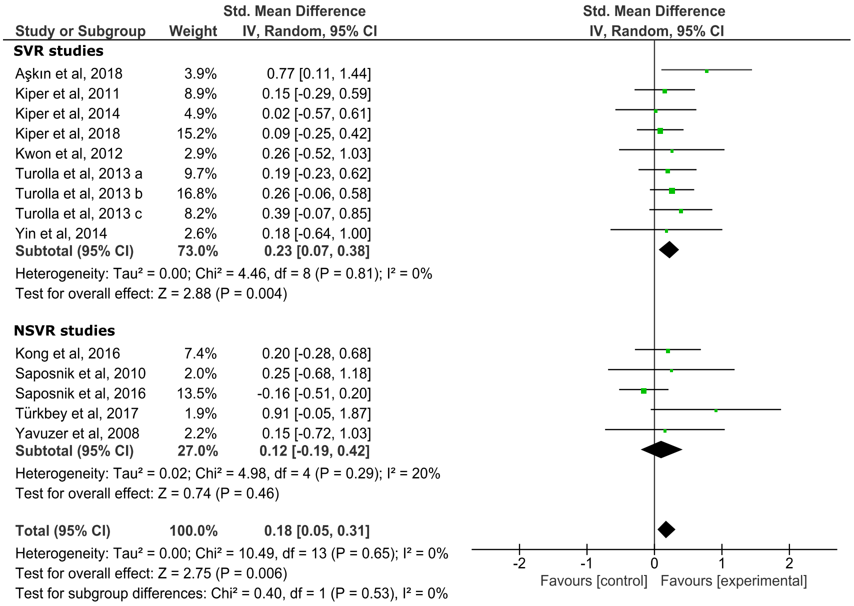


Figure 3.9. Forest plot of dosage in body function outcomes.
Comparison of SVR and NSVR studies with control group regarding intensive practice. Abbreviations: NSVR, nonspecific VR; SVR, specific VR; VR, virtual reality.

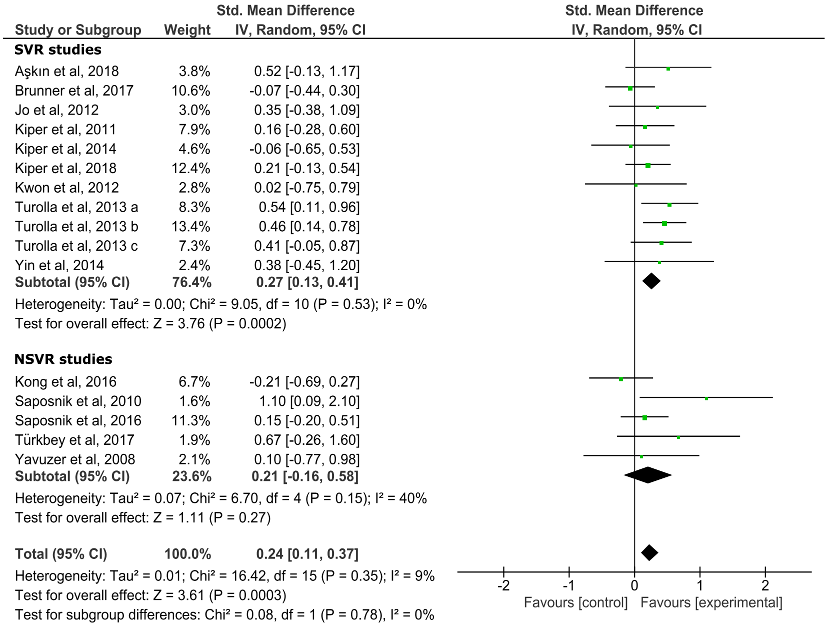


Figure 3.10. Forest plot of dosage in activity outcomes.
Comparison of SVR and NSVR studies with control group regarding intensive practice. Abbreviations: NSVR, nonspecific VR; SVR, specific VR; VR, virtual reality.

3.4. Discussion

The use of VR is increasing in neurorehabilitation. However, so far, it is unclear whether VR is effective in enhancing recovery after stroke. We proposed to distinguish between VR systems specifically built for rehabilitation (SVR) and off-the-shelf recreational VR systems (NSVR), based on the assumption that SVR systems incorporate principles of neurorehabilitation that potentially enhance learning and recovery, whereas NSVR systems do not. Our results demonstrate that SVR systems show a higher impact on recovery, both on body function as well on activity, than CT while NSVR systems do not. This is in line with evidence found for the use of VR interventions to train balance and gait (de Rooij et al., 2016) and the most recent meta-analysis on VR-based interventions (Aminov et al., 2018) The difference of our results with previous analyses is our focus on rehabilitation tools in VR for enhancing upper limb function and activity only. Hence, the re-categorization in SVR and NSVR systems provides a valid basis for the reinterpretation of effects reported in previous reviews.

We propose that the overall positive effect of SVR protocols is a result of the incorporation of principles of neurorehabilitation that enhance motor learning and recovery. Of the 11 principles identified through literature, we found 6 to be present in more than 50% of the SVR studies. In NSVR interventions, however, only three principles surpassed this level. Variable practice ranked high in both SVR and NSVR studies. In VR systems, variable practice can be easily achieved by including a variety of tasks with different goals, movement requirements and stimuli (M. F. Levin et al., 2015) in order to enhance learning (Hanlon, 1996) and retention (Krakauer, 2006). In addition, the variety can make repetitive training more engaging and enjoyable for the patient and counteract boredom which has been associated with low adherence to standard training protocols (Proffitt & Lange, 2015; Saywell et al., 2016). However, variable practice alone is possibly not sufficient to lead to a noticeable effect on recovery. If applied, the five additional principles that were present in SVR systems would generate a VR training that challenges the patient optimally through adaptive difficulty (Kwakkel et al., 2015; M. F. Levin et al., 2015) while providing information on success (results) (Cirstea & Levin, 2007; M. F. Levin et al., 2015) and optimizing implicit error-based learning (performance) (Cirstea & Levin, 2007; M. F. Levin et al., 2015) through tasks that are relevant for ADL (task-specific) (Dobkin, 2004; Kleim & Jones, 2008; M. F. Levin et al., 2015) besides promoting the use of the paretic arm (Dobkin, 2004; Kleim & Jones, 2008; Kwakkel et al., 2015). Only one SVR study included all six principles (Shin et al., 2014), and showed a large positive effect for the experimental group in recovery of body function (SMD = 1.13, 95% CI 0.04 to 2.21) and activity (SMD = 1.47, 95% CI 0.32 to 2.62).

However, besides known methodological issues (Laver et al., 2017), we note that many protocols relied on the therapists to individualize the practice to the patient's needs by selecting the training task, movement requirements or adjusting the difficulty parameters (Brunner et al., 2017; Crosbie et al., 2012; Jang et al., 2005; Jo et al., 2012; Kiper et al., 2014, 2018; Kong et al., 2016; Piron et al., 2010; Shin et al., 2014; Turolla et al., 2013). This might have biased the outcomes and could compromise the internal and external validity of these studies. Computerized systems have the advantage that every principle could be customized to the patient's individual ability and necessity automatically (Nirme, Duff, & Verschure, 2011). Whereas NSVR systems are typically not similarly adaptive and accessible for modification, this is a unique opportunity for SVR systems.

The results presented in this study do require further investigation for several reasons. First, it must be noted that the included studies may not have published all the details of their intervention. We can therefore not exclude that VR systems in this analysis might incorporate principles that were not detected and reported. To conclusively identify the "active ingredients" (Proffitt & Lange, 2015) of effective VR systems, a structured interview with the study authors might be the best approach. We see our analysis, however, as a first attempt to shift awareness from form (VR) to content (principles). Second, we recognize that the content analysis could gain validity if it was performed by an independent rater. However, given the relatively small set of indicators and the availability of the full data set with this article we believe this risk is sufficiently mitigated. Furthermore, the number of studies included in the NSVR category is relatively small and therefore the non-significant effect may be due to low statistical power. However, individual studies do report sufficient sample sizes. In addition, besides the exclusion of small studies, a source of reporting bias may relate to SVR systems that are commercially available to clinics. However, the system with the largest populations clustered well around the mean effect magnitude and the slight skewness is a result of commercial and non-commercial systems. Hence, a bias due to financial interest cannot be confirmed. Another potential limitation of our meta-analysis is the high heterogeneity across studies in terms of intervention protocols (e.g. training intensity, type of task, movement patterns addressed etc.) and the measurement tools used (e.g. the clinical scales). This also made it impossible to provide proof for the clinical relevance of our finding. Values of clinically important differences are not available for all clinical scales and chronicity bands established. For instance, for FM-UE, values to estimate the clinically important difference are available for the subacute (Narayan Arya, Verma, & Garg, 2011) and chronic (Page et al., 2012) but not for the acute phase. Despite these limitations, we are confident about the higher impact of SVR systems on motor recovery, as the groups were narrowly defined. Our results may also aid researchers in selecting the appropriate principles that drive the desired outcome and then identify the technology that can best implement and deliver these principles. This could be VR alone or coupled with other technologies (e.g. robotics or exogenous stimulation), potentially further enhancing recovery.

Overall, our findings suggest that tailor-made VR systems for neurorehabilitation may be valid tools to deliver effective motor rehabilitation post-stroke. Future studies should, therefore, not ask if VR should be used or not. Instead, they should investigate which technology, including VR, is most appropriate to facilitate the implementation of principles of neurorehabilitation in a more effective way than CT. We believe that VR is well suited for rehabilitation because it allows the patient to interact in a safe and ecologically valid environment, where the exposure to sensorimotor contingencies can be controlled and modulated in a goal-oriented and autonomous fashion. In our analysis, the superiority of specific VR systems is associated with the following combination of principles that might possibly lead to a greater effect on recovery: task-specific practice, explicit feedback, increasing difficulty, implicit feedback, variable practice and mechanisms to promote the use of the paretic limb. We are confident that dedicated VR-based systems are well suited for exploiting these principles and we expect that future technologies will contribute to an even more advantageous implementation of this set of principles underlying recovery and brain repair.

In the next part we will describe three studies that used the specific VR-based system RGS to deliver therapy for physical, cognitive and psychosocial problems by capitalizing on various principles for neurorehabilitation.

Part III

VR-based Approaches for Rehabilitation

Chapter 4

COUNTERACTING LEARNED NON-USE IN CHRONIC STROKE PATIENTS WITH REINFORCEMENT-INDUCED MOVEMENT THERAPY

This chapter is based on:
Ballester, B. R., Maier, M., San Segundo Mozo, R. M., Castañeda, V., Duff, A., & Verschure, P. F. M. J. (2016). Counteracting learned non-use in chronic stroke patients with reinforcement-induced movement therapy. *Journal of NeuroEngineering and Rehabilitation*.

How can we use principle-based technology to reverse learned non-use? Acquired non-use of the paretic limb paired with no training might lead to progressive deterioration of motor function. Although Constraint-Induced Movement Therapy has shown to be effective in treating this condition, it presents several limitations. In this chapter we present a novel method to counteract learned non-use. Reinforcement-Induced Movement Therapy aims to promote the use of the paretic limb through reinforcement and hence restore motor function, by exploiting primarily the principles implicit and explicit feedback during goal-oriented embodied practice. The patients are exposed to amplified goal-oriented movement in VR that match their intended actions, thereby reducing error feedback and increasing reward. We conduct a randomized, double-blind, longitudinal clinical study with 18 chronic stroke patients. Training lasted for six weeks of 30 minutes per weekday. While the experimental group was exposed to goal-oriented movement amplifications, the control group accomplished the same tasks but without the amplification. The results indicate that both groups improved significantly after the intervention, however only the experimental group continued to make further gains at 12-weeks follow-up. Their improvement was accompanied by a significant increase in arm-use during the training. We propose that implicitly reinforcing arm-use by augmenting visuomotor feedback tackles the patients' self-limiting beliefs and low self-efficacy to execute movements with the paretic arm. The regained confidence might encourage use and hence improve motor function in chronic stroke patients.

4.1. Background

After stroke, a neural shock leads to a learning process in which the brain progressively suppresses the use of the affected extremity (Taub & Uswatte, 2003). This phenomenon is commonly referred to as learned non-use (Andrews & Stewart, 1979; Taub et al., 2006). Constraint-Induced Movement Therapy (CIMT) (Taub & Uswatte, 2003) implements a technique that aims to re-integrate the affected arm in the performance of Activities of Daily Living (ADLs) and reduce learned non-use. In order to achieve this goal, CIMT restricts the movement of the patient's less-affected arm for about 90% of the patient's waking hours, which physically forces the use of the affected arm during performance of ADLs. As discussed in the introduction, CIMT has proved to be effective (Wolf, Blanton, Baer, Breshears, & Butler, 2002), it's therapy has several limitations. Hence, there is a need for developing alternative methods that build on CIMT principles to foster the usage of the paretic limb, while mitigate its limitations. A better understanding of the different factors determining hand selection could provide valuable insights for the development of new treatments that effectively counteract learned non-use and promote functional recovery. Previous studies have shown that the history of rewards may strongly bias action selection and habit learning (Daw, Kakade, & Dayan, 2002; C. E. Han et al., 2008; Marcos, Pani, et al., 2013; Sutton & Barto, 1998). Indeed, perceived self-efficacy, i.e. one's own belief in his or her capabilities to successfully execute actions that are required for a desired outcome (A. Bandura, 1977), appears to be an important driver for health behaviour improvements (Jones, 2006). In addition, the minimization of the expected cost/effort associated to a given action may as well regulate the decision-making process (Marcos, Cos, et al., 2013). The strong influence of these two factors on hand selection (i.e. expected cost and expected reward) may be sufficient to approximate the prediction of hand selection patterns and may provide a direct explanation of our general preference for the execution of ipsilateral movements (Stins, Kadar, & Costall, 2001).

Following this line of research, we have shown in previous studies that hemiparetic stroke patients may be highly sensitive to failure when using the affected limb, therefore exposure to goal-oriented movement amplification in VR when using the affected extremity may serve as implicit reinforcement and promote arm use (Ballester, Maier, et al., 2015). The resulting bias in hand selection patterns may rapidly emerge via action selection mechanisms, both reducing the expected cost and increasing the expected outcome associated to those movements executed with the paretic limb. It is generally known that motor learning is driven by motor error, and the high redundancy of the human motor system allows for the optimization of performance through decision-making processes (i.e. effector selection). Thus, by virtually reducing sensorimotor error, these decision-making processes can be modulated through intrinsic evaluation mechanisms (Ballester, Nirme, et al., 2015; Ballester, Oliva, et al., 2015). Previous studies have further proposed that a successful action-outcome might reinforce not only the intended action but also any movement that drives the ideomotor system during the course of its execution (Arbib & Bonaiuto, 2008; Bonaiuto & Arbib, 2010; P. F. M. J. Verschure, Voegtlin, & Douglas, 2003). This theory suggests that accidental success after action selection may be an effective mechanism for the spontaneous emergence of compensatory movements (Illert, Lundberg, & Tanaka, 1976). On this basis, by reducing sensorimotor feedback of those goal-oriented movements performed with the paretic limb, we may reinforce the future selection of the executed action. Indeed, a fMRI study on one stroke patient suggests that activations in the sensorimotor cortex of the affected hemisphere (the "inactive" cortex) were significantly increased simply by providing feedback of the contralateral hand (Adamovich, Fluet, Tunik, & Merians, 2009). This effect was also observed in healthy subjects (Adamovich, Fluet, et al., 2009). In more recent studies, the effect of visuomotor modulations in motor adaptation has been also explored, showing that diminished error feedback and goal-oriented movement amplification does not necessarily compromise error-based learning (Ballester, Oliva, et al., 2015; Herzfeld, Vaswani, Marko, & Shadmehr, 2014).

Building on these findings and grounding them on the Distributed Adaptive Control (DAC) theory of mind and brain, which proposes that restoring impaired sensorimotor contingencies is the key for promoting recovery (P. F. M. J. Verschure, 2012), we propose a new motor rehabilitation technique that we term Reinforcement-Induced Movement

Therapy (RIMT) (Ballester, Maier, et al., 2015). This strategy is a combination of the following methods: 1) Shaping through training, while increasing the task difficulty according the patient's performance; 2) limiting the use of the non-affected arm by introducing contextual restrictions in VR (i.e. restricted and symmetrically matched workspace for each arm); 3) providing explicit feedback about performance to the patient; and 4) augmenting goal-directed movements of the paretic limb in virtual reality (VR), in such a way that the patient executing the movement is exposed to diminished visuomotor errors, both in terms of distance and directional accuracy, thus increasing the expected action-outcome (i.e. expected success) and decreasing the expected action cost (i.e. expected effort) (Ballester, Nirme, et al., 2015). While principles one to three of RIMT are similarly present in CIMT and Occupational Therapy protocols, the novelty of RIMT resides in its fourth principle: the provision of implicit reinforcement through the reduction of sensorimotor errors. This unique component of RIMT is the only variable that will be manipulated in the present study. We hypothesize that by reducing visuomotor error within RIMT protocols, we may be able to boost the patients' perceived performance of the paretic limb, leading to an increased use over time. Consequently, the increased spontaneous use of the paretic limb may facilitate intense practice and induce use-dependent plastic changes, therefore establishing a closed-loop of recovery in which arm use and motor recovery reinforce each other. In this vein, a recent computational model of motor recovery suggested that there may be a functional threshold that predicts the use of the paretic limb after therapy (C. E. Han et al., 2008; Schweighofer, Han, Wolf, Arbib, & Winstein, 2009). According to this model, only therapies that enable the patient to exceed a given functional threshold will recursively increase the spontaneous use of the paretic limb and induce functional improvement, leading to a complete motor recovery. This principle of use it or lose it can as well predict the effectiveness of RIMT. Furthermore, based on simulations from a computational model (Ballester, Maier, et al., 2015), we propose that reinforcement-based and constraint-based protocols can be combined to maximally promote the use of the paretic limb and induce functional gains in the chronic phase after the stroke. To test our hypothesis we conduct a randomized, double-blind, longitudinal clinical study with chronic stroke patients, and we analyse the effects of RIMT intervention on counteracting learned non-use and inducing motor recovery.

4.2. Methods

4.2.1. Study design and patients

From January 2014 until May 2015, 23 hemiparetic stroke patients from Hospital Universitari Joan XXIII in Tarragona, Spain, were recruited according to the following inclusion criteria: a) patients with upper-limb hemiparesis due to a first-ever ischemic or haemorrhagic stroke (at least > four weeks post-stroke); b) between 25 and 75 years old; c) demonstrating an upper limb motor deficit superior to two points as measured by the Medical Research Council Scale for proximal muscle strength; d) a spasticity in the affected upper limb of less than three points as measured through the Modified Ashworth Scale; e) sufficient cognitive capacity to be able to follow the instruction of the intervention training as measured through the Mini Mental State Evaluation (superior than 24 on the scale). Exclusion criteria were defined as: a) severe cognitive deficits that impede the correct execution or understanding of the intervention training; b) severe impairments in vision or visual perception abilities (such as vision loss or spatial neglect), in spasticity, in communication abilities (such as aphasia or apraxia), severe pain as well as other neuromuscular or orthopaedic changes that impede the correct execution of the intervention training; d) mental dysfunctions during the acute or subacute phase after the stroke. All patients were right-handed. The study was approved by the local Ethical Committee at Hospital Universitari Joan XXIII, and the written consent to participate in the experiment was obtained from all patients involved. The 23 patients were recruited through the administrative staff of the rehabilitation centre of the Hospital Universitari Joan XXIII and then randomly assigned to two groups, an Experimental Group (EC) or a Control Group (CG), by the experimenter who ensured a balanced allocation in the two groups. Patients' demographics and characteristics are shown in Table 4.1. Clinicians, that were blinded regarding the group allocation, conducted the clinical assessments at the beginning of the experiment (baseline, T0), after six weeks at the end of the treatment (T1) and at follow-up after 12 weeks (T2). The experiment concluded in August 2015. Patients were instructed not to follow any specific therapy during the participation period. From the 23 patients recruited, five were excluded due to the following reasons: a) two patients presented spatial neglect; b) two patients that were assigned to EG, failed to complete the intervention training of six weeks; and c) one patient dropped out after the recruitment. The final analysis was therefore performed on a total of 18 patients (n=18), nine in each group.

Table 4.1. Patient's characteristics at baseline (n=18)

Characteristics	**EG**	**CG**	***p*-values**
	n (%)		
Subjects	12 (52 %)	11 (48 %)	
Dropouts	3 (13 %)	2 (9 %)	
Compliants	9 (39 %)	9 (39 %)	
Gender			*.578*
Female	2 (11 %)	1 (6 %)	
Male	7 (39 %)	8 (44 %)	
Aetiology			*1.00*
Haemorrhagic	1 (6 %)	3 (17 %)	
Ischemic	8 (44 %)	6 (33 %)	
Lesion side			1.00
Right	5 (28 %)	4 (22 %)	
Left	4 (22 %)	5 (28 %)	
	Mean (SD) – Median [25th-75th percentile]		
Age, years	63.40 (9.40) – 63 [57.80–68.50]	54.80 (12.00) – 57 [50.80–63.30]	.154
Days poststroke	1298.44 (1968.48) – 400 [269.25–1373.00]	1387.33 (1455.12) – 735 [493.50 – 1826.00]	.232
Clinical scales			

Total UE-FM	32.33 (16.09) – 38 [25.50–40.75]	36.89 (12.29) – 40 [50.80–63.30]	.651
UE-FM-Proximal	17.00 (7.40) – 17 [12.50–21.50]	18.89 (6.01) – 19 [16.88–21.13]	.88
UE-FM-Wrist	5.78 (3.60) – 8 [5.75–10.25]	4.78 (3.31) – 5 [2.25–7.75]	.49
UE-FM-Hand	7.44 (4.69) – 8 [4.63–11.38]	11.44 (4.72) – 12 [8.50–15.50]	.15
UE-FM-Coordination	2.56 (1.67) – 3 [1.75–4.25]	2.78 (1.30) – 3 [2.00–4.00]	.99
CAHAI	32.56 (14.47) – 36 [25.50–42.25]	36.89 (12.29) – 40 [16.00–45.00]	.475
BI	85.33 (10.82) – 88 [80.00–91.00]	90.56 (7.32) – 90 [84.00–96.25]	.445
Hamilton	14.44 (9.61) – 8 [6.75–24.75]	12.44 (9.10) – 10 [5.50–19.50	.649

Statistical test used for p-value: Wilcoxon rank-sum test.

4.2.2. Set-up

In this study we slightly modified the typical clinical set-up of RGS (Section 1.6.1). We used an acrylic table, on which a metallic frame was placed on top of the table, where a second Kinect and an overhead projector facing the table were mounted. This additional set-up was needed for one of the evaluation scenarios that are described after the following section (Figure 4.1 A).

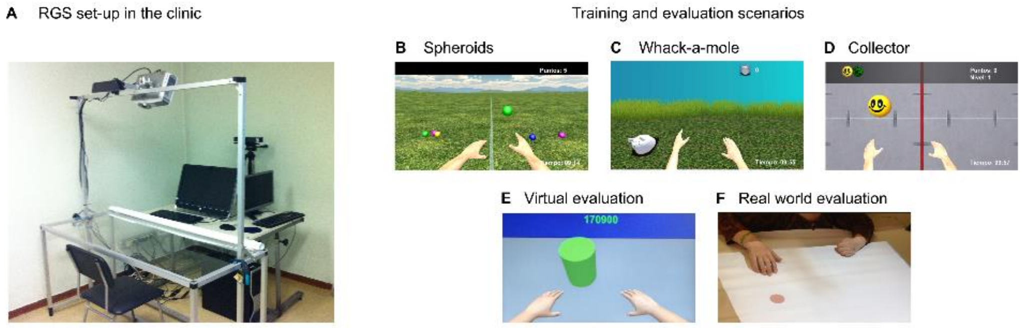


Figure 4.1 Set-up and scenario.
(A) RGS set-up in the hospital showing the transparent acrylic table in front of which the desktop computer with the Kinect (on a tadpole that elevates it above the screen) is placed. A white cover can be placed over the acrylic surface, in order to use the second Kinect and the overhead projector on the scaffold for displaying the real-world evaluation scenario. During a training session, the user sits in a chair facing the screen while resting the arms on the table. (B) Spheroids scenario, where sets of coloured spheres are launched towards the player who has to intercept them. (C) Whack-a-mole scenario, where the user freely chooses which limb to use in order to reach towards an appearing mole. (D) Collector scenario, where a set of patterned spheroids as indicated in the upper-left corner of the screen need to be collected. (E) Virtual evaluation scenario, an abstract version of the Whack-a-mole scenario, where the patient must reach towards an appearing cylinder. (F) Real-world scenario, where the user must reach towards randomly appearing dots that are projected from above on the table surface in front of him or her.

4.2.3. Training scenarios

The three training scenarios used in this study (Figure 4.1 B-D) which are called Spheroids, Whack-a-mole and Collector were game-like intervention protocols that incorporated various features that aimed to promote the usage of the paretic limb, either forced or voluntarily. In the Spheroids and Collector scenarios the patients were required to intercept coloured or patterned spheres by performing horizontal lateral arm movement. A bar in the middle of the scenery split the virtual workspace in two sides, herewith forcing the patient to perform ipsilateral movements only; targets that appeared in the paretic side of the screen had to be intercepted with the paretic limb, whereas the less-affected limb could only be used for the targets that appeared in the workspace ipsilateral to the less-affected side. As targets could occasionally appear simultaneously in both workspaces, the patient was prompted to do bimanual training. Since the avatar's arm movement was controlled by the patient's joints of the upper extremities and the avatar's arm length was fixed, the distance from the avatar's hand to the target was equal across patients. For every successfully intercepted sphere the patient was rewarded with a point. Within the Collector scenario the spheres fell from the upper part of the screen to the bottom, where the patients could intercept them. In contrast to Spheroids (Cameirao et al., 2010), did the Collector scenario possess an additional cognitive component. In the third scenario themed Whack-a-mole, patients executed a horizontal reaching movement to eliminate targets (moles) that appeared sequentially on a planar surface. The location of the target did not determine which hand had to be used, the patients were free in choosing one or the other limb for any given target, therefore applying ispi-and contralateral movements. In contrast to the other scenarios the hands had to be placed on start positions, that were indicated by two red cylinders of 7.5 cm in diameter and that were located 48 cm apart from each other, to initiate the appearance of a target respectively a trial. The hands had to be maintained on the start positions for a variable time of 1 ±0.5 seconds, after which the start positions disappeared, and a target was generated. The target could be located at any of nine possible positions that were defined in angles from the body mid-line (0, ±4, ±8, ±6 and ±32 degrees), forming a hemicircle on the planar surface, that was 65 cm away from the avatars body. In this scenario the maximal visibility of the target was set to 1.75 seconds, therefore setting a time limit for reaching, while the pace in Spheroids and Collector was only given by the speed of the approaching spheres. If the patient successfully reached for the target within this time limit, the target disappeared, and the patients was rewarded with a score that incremented by 30 points for each tenth of a second as the virtual hand was held over the target's position. In all training scenarios the movements to be performed were planar and were executed over a surface providing antigravity support. The task difficulty was adjusted automatically to the performance level of the patients in order to provide a customized and balanced rehabilitation experience that posed an optimal challenge level to the patients. A detailed explanation of the automated difficulty mechanisms can be found elsewhere (Nirme et al., 2011). The parameters that adjusted automatically within the Spheroids scenario were the speed, the size and the range of the appearing sphere. Within the Collector scenario only the speed parameter and within the Whack-a-mole only the size parameter of the targets was adjusted automatically. Common in all scenarios was that success and failure were indicated with a respective sound as well that points were displayed during the game in the upper right corner of the screen and were reset after each daily session. Besides that, all scenarios provided motor training, Spheroids and Collector forced the patients to use their paretic limb for targets in the given workspace, whereas Whack-a-mole served as a tool to evaluate hand selection patterns.

Together, these three training scenarios adhere to the principle of modulate effector selection (Section 2.3.12) by forcing the use of the paretic limb, the principle of explicit feedback (Section 2.3.10) and multisensory stimulation (Section 2.3.8) by providing visual and auditory feedback upon outcome, the principle of variable practice (Section 2.3.6) by arranging the targets at variable position requiring different types of movements, and the principle of increasing difficulty (Section 2.3.7) by adapting training elements to the performance of the patients and goal-oriented practice (Section 2.3.5) by putting the focus of the accomplishment of a goal.

4.2.4. Evaluation scenarios

Before the start of the training sessions and at the end of every week, the groups completed two additional evaluation scenarios (Figure 4.1 E and F). The first virtual evaluation scenario was an abstract version of the Whack-a-mole scenario, but where no movement amplification was applied in any group, and the trials were fixed to a given number of targets per angle in the semicircle array. The second evaluation scenario tested the hand selection pattern of both groups in a real-world scenario. This evaluation scenario was used to assess whether acquired hand selection patterns translated from the virtual space into a real-world set-up. The data of the real-world evaluation scenario to was used for the results presented in Part III Diagnostics, Chapter 7.

4.2.5. Experimental intervention

Both groups EG and CG were asked to perform 30 training sessions over the course of six weeks (one session a day, for five days a week, Figure 4.2 A). One session consisted of playing every scenario once for 10 min (30 min in total per training session). However, in the EG group we modified the visuomotor feedback that the patients received while training. Undisclosed to the EG subjects, we applied a movement amplification on the virtual representation of the paretic limb that led to a reduced exposure to visuomotor error feedback (Figure 4.2 B), whereas no such modulation was applied in the CG. The movement amplification took the patient’s movement with the paretic limb and instead of mapping it one to one on the virtual limb of the avatar, augmented it both in accuracy and extent before it was applied to the digital representation (Figure 4.2 C). This augmentation of visuomotor feedback builds on the principles of implicit feedback (Section 2.3.11) and action observation (Section 2.3.13). At each frame, while the patient progressed in the scenario, we obtained from the Kinect a vector (m) of the currently executed movement with the paretic limb and multiplied it by a constant gain factor G. The resulting vector (m_e) was projected towards the vector of the target (t), from which we obtained the direction vector (m_p). Finally, the exact amount of augmentation in the current time frame was calculated:

$$m_a = \alpha \cdot m_p + (1 - \alpha) m_e \tag{1}$$

$$where\ \alpha = \frac{|m_p|}{|t|} \cdot H$$

where H was a constant help factor. Notice that the movement amplification vector $m_a$was a weighted combination of two terms: an accuracy amplification vector and an extent amplification vector. The amount of contribution of each of these two components was determined by the alpha ratio. After computing the movement amplification vector m_a, the theoretical hand position in the virtual space could be extracted. By applying an inverse kinematics technique (Cyclic Coordinate Descent) the corresponding elbow and shoulder joint could be determined. As a last step these estimates were mapped on the virtual representation of the paretic limb. The constant factor G was set to 1.4 and H was fixed to 0.7.

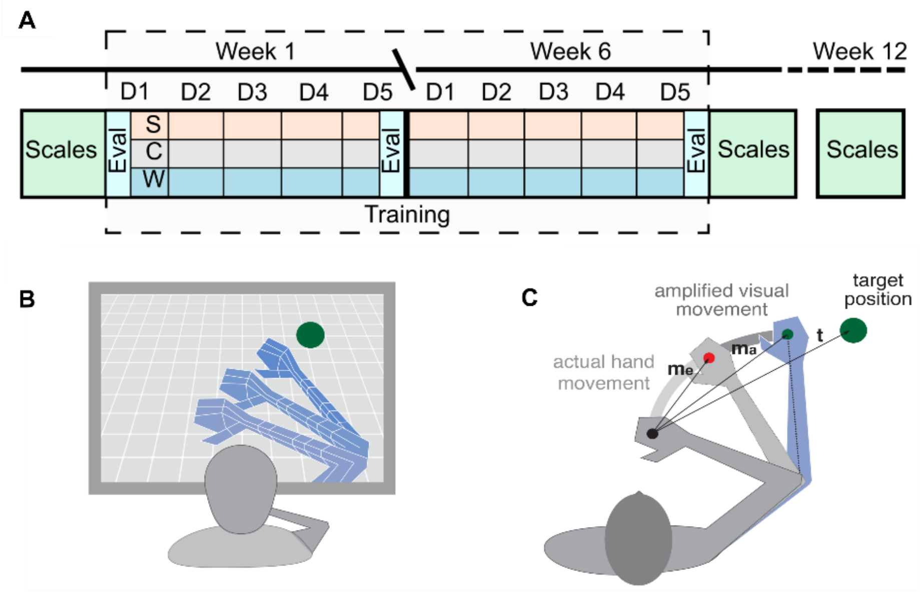


Figure 4.2. Experimental protocol.
(A) The clinical assessments (light green) are performed before the training, at the end of the training and at 12 weeks follow-up. The virtual and the real-world evaluation (dark green) are performed at the beginning of the treatment and at the end of every training week. Every workday for six weeks all patients completed a session containing the three training scenarios in the following order: Spheroids (S), Whack-a-mole (W) and Collector (C). (B) Experimental condition: during training the participant visualizes augmented goal-oriented movements that match his/her intended actions. (C) Diagram showing the methodology for the amplification of goal-oriented reaching movements in VR. At each time step, the executed movement vector is attracted towards the target, both in terms of extent and direction.

4.2.6. Outcome measures

Outcome measurements were taken from four standard clinical scales, that were assessed before (T0) and at the end of the treatment (T1) as well as at 12-weeks follow-up (i.e. 6 weeks after the end of the treatment) (T2). Additional measurements regarding arm use were extracted from the scenarios. The primary outcome measurement consisted of the upper extremity Fugl-Meyer Assessment (UE-FM) (Sanford, Moreland, Swanson, Stratford, & Gowland, 1993) and its subscales for Proximal, Wrist, Hand and Coordination function. Secondary outcome measurements were the outcomes of the remaining clinical scales: Chedoke Arm and Hand Activity Inventory to evaluate changes in bi-manual motor function (CAHAI-7) (Barreca, Stratford, Lambert, Masters, & Streiner, 2005), Barthel Index to assess effects in functional independence (BI) (Collin, Wade, Davies, & Horne, 1988), Hamilton to assess changes in mood disorders (Knesevich, Biggs, Clayton, & Ziegler, 1977), and the calculation of the change in hand selection patterns in the training and evaluation scenarios.

4.2.7. Statistical analysis

The homogeneity of the two groups at baseline with regards to demographic measures, stroke characteristics and clinical scales was assessed using the Wilcoxon rank-sum test. Homogeneity between groups at baseline was confirmed for all measurements (Table 4.1).

In order to verify that the movement amplification mechanism indeed reduced visuomotor error, we first quantified the mean error per session and subject, both in the training and evaluation scenarios. Error was defined as the minimum distance from the avatar’s hand to the target location along each trial. Next, we performed a within-subject analysis comparing mean errors in the training scenario (i.e. with movement amplification) and the evaluation scenario (i.e. without movement amplification) by applying a Wilcoxon rank-sum test. Our analysis revealed that the method we used for the amplification of goal-oriented movements reduced significantly the magnitude of the error experienced by the EG during training (median −0.07, MAD 0.037, $p < .01$, $r = -.62$, Figure 4.3).

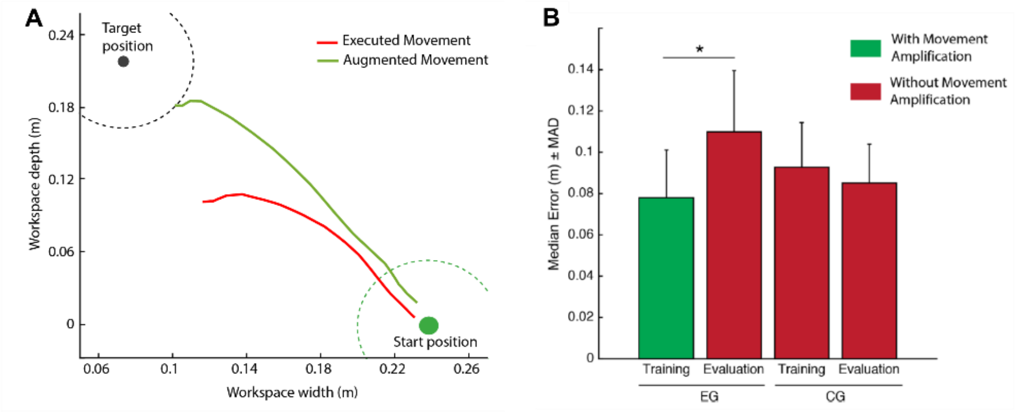


Figure 4.3. Validation of the movement amplification mechanism.
(A) Example trajectory of the patient’s real arm movement (red curve) and the amplified movement in VR (green curve). (B) Median of reaching errors (i.e. distance from the centre of the avatar’s hand to the target) of the virtual movement by group and scenario. Error bars indicate median absolute deviations for each group.

In order to analyse the clinical impact of the intervention (independent variable: augmented goal-directed movement or absence of augmentation) on the clinical measurements (dependent variable: primary and secondary outcome measurements) over time, we calculated for each patient the change from the baseline measurements (T0) to the measurements at the end of training (change at T1: T1-T0) and to the measurements at 12- weeks follow-up (change at T2: T2-T0). The descriptive data for each scale can be found in Table 4.2. In order to test for significant within-group effects at each time step, a Wilcoxon signed-rank test was used. In order to compare the changes at T1 and at T2 between groups, a Wilcoxon rank-sum test was applied. As normality tests (Lilliefors test) revealed that only the changes in UE-FM followed a normal distribution, non-parametric-tests were used. For the subscales of UE-FM the same statistical procedure was applied.

In order to determine a change in hand selection patterns we first fitted the probabilities of selecting the paretic limb to a psychometric function for discrimination. Calculating the 50% intersection point of the function provided us with the point of subjective equality (PSE). PSE represents an angle in space at which the patient demonstrates an equal probability to reach with one or the other limb (Figure 4.4). We extracted the PSE and the slope of the psychometric function for every patient within the Whack-a-mole, the virtual evaluation and the real-world scenario for every session. A change in PSE would reflect a change in hand selection bias, whereas a change in the slope indicates a shift in sensitivity for certain target locations (Figure 4.4 A and B).

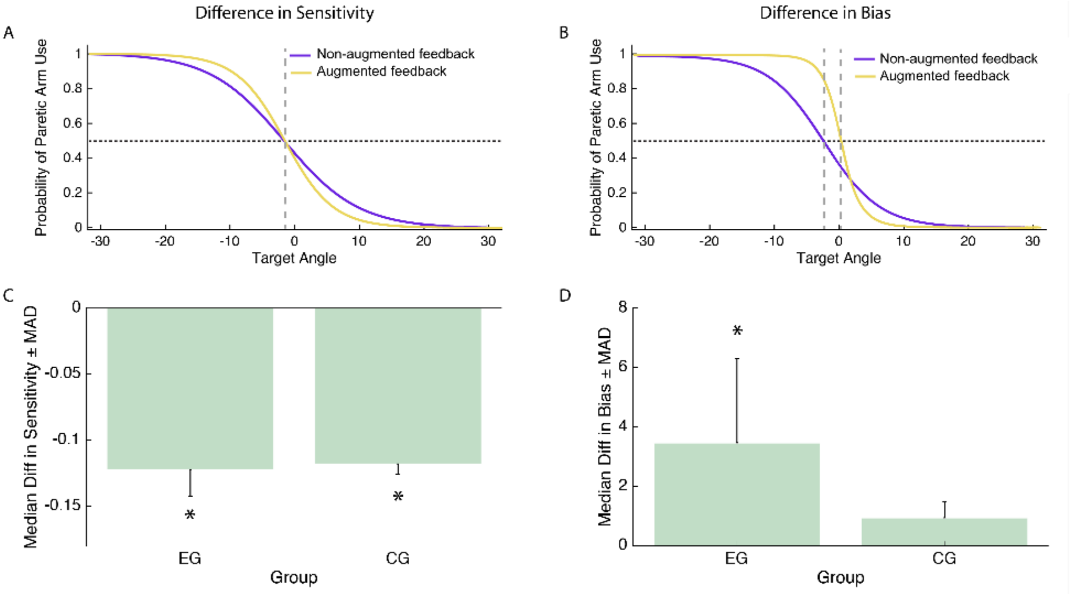


Figure 4.4. Influence of the augmented sensorimotor feedback on hand selection.
(A and B) Psychometric functions describing hand selection patterns of two representative patients in the EG group. The yellow line describes the probability of using the paretic limb in the Whack-a-Mole training scenario. The purple line refers to arm use during the virtual evaluation scenario, when no augmented sensorimotor feedback was provided. (C) indicates a difference in the sensitivity to the target position between scenarios (i.e. different slopes). (D) presents a difference in bias (i.e. change in the Point of Subjective Equality between scenarios).

In order to explore whether the patient’s reinforcement history could influence arm use, we performed a sequential analysis of hand bias. We computed the patient’s probability to select the paretic limb in each trial in respect to either the outcome (success or failure), effector selected (paretic or non-paretic) or a combination of the two factors in the previous trial. We then compared the probabilities of the individual factors or their combinations within and across group. These two categorical values were obtained for each patient in the Whack-a-mole and virtual evaluation scenario for each session. If normality was confirmed by the Lilliefors test, a dependent or independent t-test was performed to compare the factors within or across group, otherwise a Wilcoxon signed-rank or Wilcoxon rank-sum test was applied.

Effect sizes (Pearson’s r) for each for non-parametric test were calculated as follows:

$$r = \frac{Z}{\sqrt{N}}$$

where Z is the z-score of the non-parametric statistic performed and N is the total number of observations. The effect sizes for each parametric test (t-tests) were calculated as follows:

$$r = \sqrt{\frac{t^2}{t^2 + df}}$$

Statistical analysis was performed with MATLAB R2015b and IBM SPSS Statistics Data Editor (Version 19).

4.3. Results

4.3.1. Clinical impact

In order to explore the efficacy of RIMT on motor recovery, the clinical outcomes before and after the intervention were compared and analysed. The within-group analysis indicated a significant change from baseline in our primary outcome UE-FM at T1 and T2 for EC ($p = .008$, $r = -.595$ and $p = .004$, $r = -.628$ respectively) and CG ($p = .008$, $r = -.596$ and $p = .016$, $r = -.560$ respectively) as shown in Figure 4.5 and Table 4.2. The between-group analysis revealed in addition a significant difference in UE-FM change at T2 ($p = .037$, $r = .479$). This suggests that EG achieved significant higher UE-FM scores at T2, whereas the measurement at T1 and baseline was not significantly different between the groups. No further significant within- or between-group changes were found in the other clinical measurements.

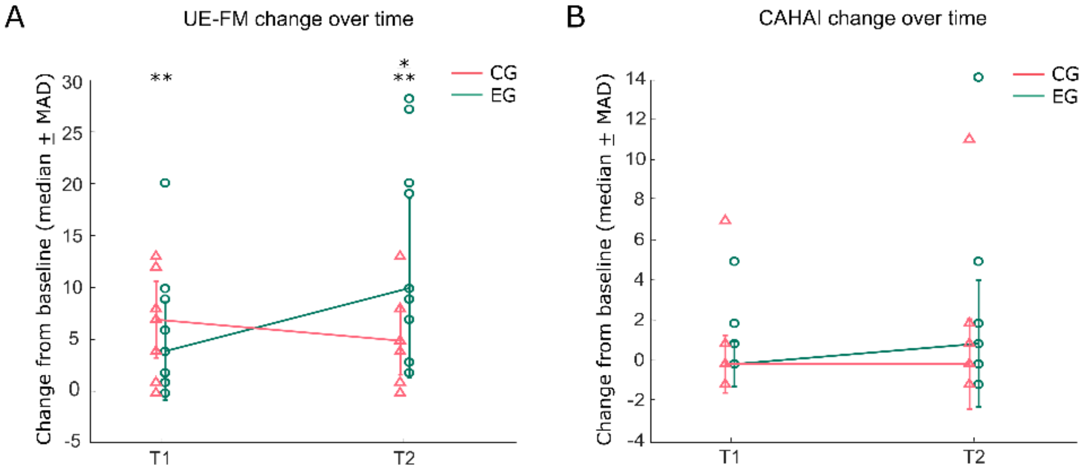


Figure 4.5. Clinical measurements main result.
Change in UE-FM (A) and CAHAI (B) from baseline to the end of treatment at week 6 (T1) and to follow-up at week 12 (T2) (i.e. 6 weeks after the end of the treatment) for the experimental (EG, green) and the control group (CG, red). Error bars indicate median absolute deviations for each group. The individual data for each subject is indicated with triangles for CG and with circles for EG.

Table 4.2. Clinical outcome measure at the end of treatment and at follow-up.

	Within-group analysis						Between-group analysis	
	Mean (SD) – Median 95 % confidence interval for the mean [lower and upper bound]						*p*-values	
	End of treatment T1	Change from baseline to T1	*p*-values	Follow-up T2	Change from baseline to T2	*p*-values	Change from baseline to T1	Change from baseline to T2
UE-FM								
EG	38.33 (17.30) – 39 [25.04–51.63]	6.00 (6.31) – 4 [1.15–10.85]	**.008**	46.22 (14.96) – 52 [34.72–57.73]	13.89 (9.88) – 10 [6.29–21.48]	**.004**	.715	**.037**
CG	43.22 (12.62) – 44 [33.52–52.92]	6.33 (4.50) – 7 [2.87–9.79	**.008**	41.78 (12.47) – 40 [32.19–51.36]	4.89 (4.31) – 5 [1.57–8.20]	**.016**		
CAHAI								
EG	33.56 (15.08) – 36 [21.96–45.15]	1.00 (1.66) – 0 [-0.27–2.27]	.125	25.11 (16.04) – 42 [22.78 – 47.44]	2.56 (4.64) – 1 [-1.01–6.12]	.094	.553	.552
CG	34.22 (14.71) – 43 [22.91–45.53]	0.89 (2.37) – 0 [-0.93–2.71]	.500	34.89 (14.34) – 43 [23.87–45.91]	1.56 (3.64) – 0 [-1.25–4.36]	.250		
BI								
EG	85.56 (10.90) – 88 [77.18–93.93]	0.22 (0.67) – 0 [-0.29–0.73]	1.000	87.78 (8.27) – 90 [81.42–94.14]	2.44 (5.18) – 0 [-1.53–6.42]	.125	1.000	.241
CG	91 (6.69) – 90 [85.86–96.14]	0.44 (1.33) – 0 [-0.58–1.47]	1.000	91 (6.69) – 90 [85.86–96.14]	0.44 (1.33) – 0 [-0.58–1.47]	1.000		
Hamilton								
EG	13.89 (9.61) – 8 [6.50–21.28]	-0.56 (1.13) – 0 [-1.42–0.31]	.500	13.67 (9.85) – 8 [6.10–21.24]	-0.78 (1.39) – 0 [-1.85–0.29]	.250		

							.506	.776
CG	10.78 (10.15) – 5 [2.98–18.58]	-1.67 (2.83) – 0 [-3.84–0.51]	.250	11.67 (11.87) – 5 [2.54–20.79]	-0.78 (3.93) – 0 [-3.80–2.24]	.688		

Bold values indicate significant values (*p* < .05), p-values for within-group analysis were obtained with Wilcoxon signed-rank test, p-values for between-group analysis were obtained with Wilcoxon rank-sum test.

Table 4.3. UE-FM subscales outcome measure at the end of treatment and at follow-up

	Within-group analysis						Between-group analysis	
	Mean (SD) – Median 95 % confidence interval for the mean [lower and upper bound]						*p*-values	
	End of treatment T1	Change from baseline to T1	*p*-values	Follow-up T2	Change from baseline to T2	*p*-values	Change from baseline to T1	Change from baseline to T2
UE-FM								
EG	38.33 (17.30) – 39 [25.04–51.63]	6.00 (6.31) – 4 [1.15–10.85]	**.008**	46.22 (14.96) – 52 [34.72–57.73]	13.89 (9.88) – 10 [6.29–21.48]	**.004**		
							.715	**.037**
CG	43.22 (12.62) – 44 [33.52–52.92]	6.33 (4.50) – 7 [2.87–9.79	**.008**	41.78 (12.47) – 40 [32.19–51.36]	4.89 (4.31) – 5 [1.57–8.20]	**.016**		
UE-FM Proximal								
EG	21.00 (8.90) – 18 [10.25–25.75]	4.00 (3.57) – 4 [-0.38–7.63]	**.016**	24.11 (7.67) – 27 [[21.38–32.63]	7.11 (4.65) – 8 [-1.01–6.12]	**.004**		
							.619	.420
CG	24.22 (6.50) – 24 [18.13–29.88]	5.33 (4.80) – 4 [-0.75–8.75]	**.016**	24.33 (7.23) – 24 [17.62–30.38]	5.44 (5.30) – 4 [4.63–11.38]	**.016**		
UE-FM-Wrist								
EG	7.22 (3.31) – 9 [6.89–11.13]	1.44 (2.07) – 1 [0.0–2.0]	.063	8.33 (2.00) – 9 [7.63–10.38]	2.56 (2.35) – 1 [-1.13–3.13]	**.016**		

CG	5.44 (2.92) – 5 [3.38–6.63]	0.67 (1.94) – 0 [-0.63–0.63]	.500	6.22 (2.77) – 5 [2.88–7.13]	1.44 (2.40) – 1 [-0.75–2.75]	.156	.375	.350
UE-FM-Hand								
EG	8.44 (5.36) – 9 [5.13–12.88]	1.00 (2.29) – 0 [-0.50–0.50]	.250	9.33 (4.64) – 10 [7.38–12.63]	1.89 (4.01) – 1 [-0.25–2.25]	.250	.116	.055
CG	10.22 (2.63) – 11 [8.50–13.50]	-1.22 (3.46) – 0 [-0.63–0.63]	.500	9.89 (3.79) – 12 [9.50–14.50]	-1.56 (3.94) – 0 [-1.37–1.37]	.313		
UE-FM-Coordination								
EG	2.89 (1.83) – 4 [2.75–5.25]	0.33 (1.00) – 0 [0.00–0.00]	1.000	3.00 (1.94) – 4 [2.63–5.38]	0.44 (1.01) – 0 [-1.25–1.25]	.500	.294	.587
CG	3.22 (1.48) – 3 [2.38–3.63]	0.44 (0.53) – 0 [-0.50–0.50]	.125	3.44 (1.81) – 3 [1.88–4.13]	0.67 (1.00) – 0 [-0.50–0.50]	.125		

Bold values indicate significant values ($p < .05$), p-values for within-group analysis were obtained with Wilcoxon signed-rank test, p-values for between-group analysis were obtained with Wilcoxon rank-sum test.

The analysis of the subscales of UE-FM revealed significant effects at within-group level. UE-FM-Proximal change was significant at T1 and at T2 for EC (*p* = .016, *r* = −.560 and *p* = .004, *r* = −.629 respectively) and CG (*p* = .016, *r* = −.558 and *p* = .016, *r* = −.558 respectively), as shown in Table 4.3. Further the improvement for UE-FM-Wrist was significant for EG at T2 (*p* = .016, *r* = −.572). The remaining subscales changes revealed no significant within- or between-group improvements.

4.3.2. Hand selection patterns and effects in arm use

In order to analyse which factors of the training might have contributed to the significant improvement in UE- FM for EG, we extracted and analysed the factors that influenced hand selection patterns in the intervention scenarios. We observed a strong correlation (*p* < .05, Spearman *r* > .4) between the PSEs measured in the three scenarios (Whack-a-mole, virtual evaluation and real-world evaluation) indicating a similar change in arm selection patterns. In addition, sensitivity to target location, as indicated by the slope of the psychometric fit, was significantly lower (median −.12, MAD .041, *p* < .01, Wilcoxon signed-rank test, *r* = −.88) during the Whack-a-mole scenario for both groups, where feedback augmentation was given to EG, as compared to the virtual evaluation or the real-world evaluation scenario where no feedback augmentation was given. Interestingly when the augmented visual feedback was present (i.e. Whack-a-mole scenario), arm use increased significantly, reflected by a positive change in PSE values (median 3.45, MAD 8.53, *p* < .05, Wilcoxon signed-rank test, *r* = .77, Figure 4.4. Influence of the augmented sensorimotor feedback on hand selection.C). CG, who did not experience the feedback augmentation, did not show this effect (median 0.93, MAD 1.67, *p* > .05, Wilcoxon signed-rank test, *r* = .61, Figure 4.4. Influence of the augmented sensorimotor feedback on hand selection.D). Hand choice and reinforcement history may influence hand selection patterns as well. We therefore investigated the contribution of these factors to arm use and assessed the probability to select the paretic hand in trial t, dependent if in the previous trial t-1 a) the paretic or non-paretic limb was selected, b) the outcome was successful or a failure, or c) combinations of these two events occurred. The sequential analysis revealed that in the virtual evaluation scenario the factors outcome or selection alone did not seem to influence decision making in the next trial, but the combination of the two factors led to significant effects. When the patients used their paretic limb and succeeded to reach for the target, the probability to select the paretic limb again in the next trial was higher than in the case of failure. Moreover this effect was more pronounced for CG than for EG (for EG *p* = .044, *r* = .721, paretic/success mean [SD] 0.529 [0.163], paretic/failure mean [SD] 0.380 [0.257]; for CG *p* = .006, *r* = .795, paretic/success mean [SD] 0.489 [0.155], paretic/failure mean [SD] 0.406 [0.178], Figure 4.6 A). In contrast was this sensitivity for movement outcome not present when EG experienced the augmentation of goal-oriented movement, e.g. in the Whack-a-mole scenario, (for EG *p* = .349, *r* = .332, paretic/success mean [SD] 0.431 [0.118], paretic/failure mean [SD] 0.390 [0.234], Figure 4.6 B), whereas the sensitivity of the control group slightly failed to be significant (for CG *p* = .057, *r* = .618, paretic/success mean [SD] 0.466 [0.114], paretic/failure mean [SD] 0.380 [0.195], Figure 4.6 B). Both groups showed no sensitivity when using the non-paretic arm. As the reported results did not violate the assumption of normality, t-tests were applied.

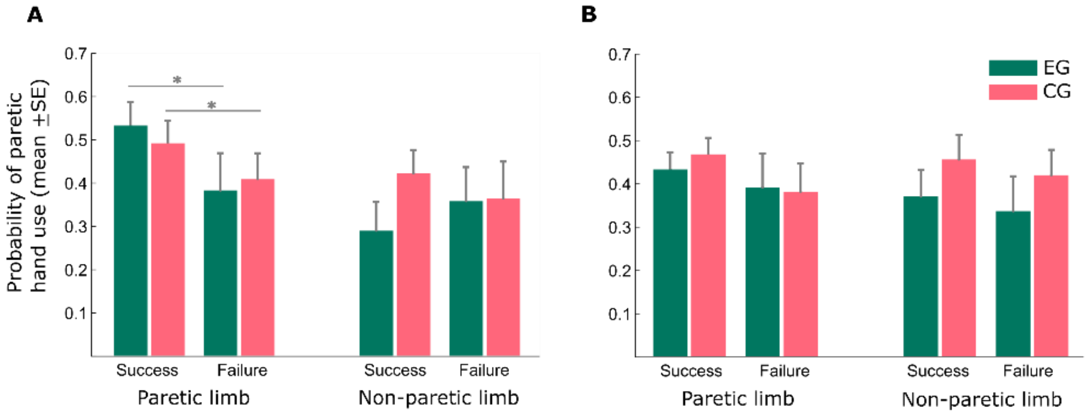


Figure 4.6. Sequential analysis of hand choice.
Influence of hand choice and reinforcement history on arm use. Probability of using the affected arm in the virtual evaluation (no augmentation, A) and the Whack-a-mole scenario (augmented sensory feedback for EG, B) given the movement outcome (i.e. success or failure) and the hand used (i.e. paretic or non-paretic) in the previous trials (t-1). Error bars indicate standard error of the mean.

4.4. Discussion

In this study we examined the effects of providing augmented sensorimotor feedback of goal-oriented arm movements on motor recovery and arm use after stroke. We named this combined treatment “Reinforced Induced- Movement Therapy” (RIMT). Simulations from a model of recovery after stroke support that reinforcement-based therapies can be combined with mild-restriction of the less-affected arm use to maximize recovery. We tested this assumption by conducting a double-blind randomized controlled trial on chronic stroke patients. Although both groups of patients showed motor recovery at the end of the treatment, only patients who underwent RIMT rehabilitation protocols experienced further functional gains during the follow-up period. Interestingly, these gains in the RIMT group were accompanied by an increased arm use during training. These results emphasize the benefits of providing augmented implicit reinforcement on motor recovery and arm use.

Psychosocial factors are often neglected in the study of rehabilitation, however they might be critical ingredients in successful recovery (Donnellan, 1968; Ownsworth & Clare, 2006; Rath, Simon, Langenbahn, Sherr, & Diller, 2003; Rutterford & Wood, 2006; Yates, 2003). A model of recovery proposed by Folkman and Lazarus et al. hypothesizes that suboptimal outcomes may worsen due to self-limiting cognitive beliefs, leading to poor coping strategies and initiating a vicious loop of recovery in which adaptive responses, stress, and function degrade recursively (Folkman & Lazarus, 1988). For instance, adaptive levels of challenge and feedback of progress may result in reduced stress, enhanced self-esteem, and increased self-efficacy (Jones, 2006; Timmermans, Seelen, Willmann, & Kingma, 2009). Similarly, previous work suggested that learned helplessness affects self-efficacy in a way that the patient overgeneralizes the effect that the injury has to the ADLs. As a consequence, the patients fails to test and update his self-limiting believes as he or she thinks of not being able to perform day-to-day activities (A. D. Moore & Stambrook, 1995). In Chapter 6 we will investigate whether self-efficacy can be modulated by providing the augmented sensory feedback presented here. Our results revealed that hemiparetic stroke patients exhibit a pronounced sensitivity to success and failure when using the affected arm, which strongly biases arm use. Similar findings have been reported in previous experiments (Ballester, Nirme, et al., 2015). Surprisingly, we also found that when we provided visuomotor feedback of goal-oriented arm movements, this sensitivity disappeared. The combination of explicit and implicit reinforcement in RIMT protocols may be the key factor for changing the patient's perceived competence, leading to sustained improvements in arm use and rising the intensity of the training. Furthermore, we speculate that frequent and sustained exposure to RIMT goal-oriented movement augmentation may be able to condition the patient to incorporate the affected limb into performance of ADLs. Future experiments will validate this hypothesis and evaluate the impact and the retention of these effects in domiciliary setups.

It has to be noted that previous studies investigating VR-based rehabilitation protocols do not examine whether the observed effects continue to persist during follow-up periods after the intervention ends (Lucca, 2009), which could be one of the reasons why the efficacy of VR-based clinical intervention is still debated and meta-analyses that determine a clearly proven effectiveness of these interventions are basically non-existent (Laver et al., 2011; Saposnik & Levin, 2011). Our results showed that, three months after the therapy ended, both groups retained the therapy-induced motor gains. Surprisingly, the EG group exhibited a significant improvement in motor function during the follow-up period. We find this result encouraging as it might indicate that the benefits of RIMT, if driven by behavioural changes, may be sustained in time. It has been previously shown that a 10-point change in UE-FM corresponds to a 1.5-point change in measurements of functional independence (FIM) (Shelton, Volpe, & Reding, 2001), which constitutes the Minimally Clinically Important Difference. FIM is a standardized assessment of the patient's ability in performing the activities of daily living independently. The EG in our study showed a mean improvement in UE- FM at follow-up of almost 14 points, which might possibly correspond to a functional gain in the performance of ADLs.

This study faces several limitations that have to be considered. The sample size used in the clinical evaluation was small and contained a considerably high individual variability, therefore reducing the overall statistical power of our results. In this regard, we also were not able to answer yet the question, whether RIMT would be suitable for patients with severe hemiparesis as the selection criteria was stringent in order to minimize inter-subjects' variability. However, since RIMT does not necessarily include distal movements in its training protocols, it is also suitable for those patients who do not present sufficient range of movement in the metacarpophalangeal and interphalangeal joints to benefit from CIMT (Page et al., 2002; Smania et al., 2012). Moreover, the total exposure to training in RIMT is remarkably inferior to the exposure time delivered by Reduced-intensity mCIMT (Smania et al., 2012), to the best of our knowledge the most reduced form of CIMT found in literature. In respect thereof future clinical trials with larger sample sizes are required to validate our results and determine which type of patients could benefit the most from RIMT protocols. We further propose that prospective studies should consider testing our findings directly against fully incorporated CIMT trials, as we investigated specifically the effect of augmented visuomotor feedback of goal-oriented arm movements against a control group without augmentation, prioritizing minimization of confounding variables and to guarantee a double-blinded experimental design.

In this chapter we propose and validate a novel technique for motor recovery: “Reinforced Induced-Movement Therapy” (RIMT). This therapy exposes the patient to augmented goal-oriented arm movements in VR and combines customized intensity training with implicit and explicit feedback to boost arm use and motor improvement. Our results show that after six weeks of daily training with RIMT, patients continue to experience further gains until week 12 follow-up, a period in which patients did not receive any specific training. The control group did not show this effect. We also found a significant increase in the paretic arm use during RIMT sessions. By incorporating psychosocial attributes into the rehabilitation approach, RIMT may be a powerful mechanism to shape the patient’s perceived competence, reinforce non-compensatory behaviour, and overcome learned non-use. Inspired by these results we will in the next chapter explore whether the physical training in RGS can be extended to address cognitive deficits. Instead of augmenting goal-oriented movements we will however exploit the principle of increasing difficulty to achieve our goal.

Chapter 5

ADAPTIVE CONJUNCTIVE COGNITIVE TRAINING (ACCT) IN VIRTUAL REALITY FOR CHRONIC STROKE PATIENTS: A RANDOMIZED CONTROLLED PILOT TRIAL

This chapter is based on:

Maier, M., Ballester, B. R., Leiva Bañuelos, N., Duarte Oller, E., & Verschure, P. F. M. J. (2019) Adaptive conjunctive cognitive training (ACCT) in virtual reality for chronic stroke patients: A randomized controlled pilot trial. (*accepted)*

How can we use principle-based technology to train various cognitive domains together? Inspired by the results that a complex phenomenon like learned non-use can be addressed by using specific principles of neurorehabilitation, we wanted to see if a similar approach can be used to address post-stroke cognitive deficits. We argue that one of the main issues in cognitive rehabilitation is the isolated treatment of specific deficits although patient typically express issues in various domains. In this chapter we investigate whether the we can train several cognitive deficits in conjunction, by using an algorithm that adjusts the difficulty to the capacity of each patient and that exploits the principle of increasing difficulty. It equalises success performance across patients, hence providing treatment at the optimal challenge level. We test this novel method called Adaptive Conjunctive Cognitive Training in a randomized controlled pilot trial with 30 chronic stroke patients. We expect to see that the training positively influences the patient's cognitive impairment. In addition, we investigate the influence of depression on the outcomes as depression is equally common but rarely diagnosed among stroke patients. The experimental groups followed the novel training method for six weeks in the hospital whereas the control group solved standard cognitive tasks at home for the same amount of time. The results show that the experimental group improves over time in attention, spatial awareness and generalized cognitive functioning, which as not observed in the control group. The control group worsened in depression level after treatment, whereas the experimental group displayed a lower level of depression until to follow-up. We are among the first to demonstrate that a heterogeneous group of stroke patients can be adequately trained through the same paradigm, resulting in positive effects on cognitive and mental well-being.

5.1. Background

Cognitive impairments are common after stroke, with incident rates up to 78% (Leśniak et al., 2008). Patients with mild cognitive impairment are at risk for developing dementia (Sascha M.C. Rasquin et al., 2004). Cognitive deficits correlate with poor functional outcomes and increased risk of dependence (Paolucci et al., 1996), have negative effects on the patient's quality of life (J. H. Park et al., 2013), and alter the patient's ability to socialize (Mukherjee et al., 2006). However, the current clinical practice seems to lack methods that specifically address cognitive sequelae. According to a meta-analysis that aimed at proposing recommendations for new clinical standards, currently available treatments that are used as control conditions are conventional therapies like physical therapy or occupational therapy, pseudo treatments like mental or social stimulation without therapeutic intent, as well as psychosocial interventions like psychotherapy or emotional support for individuals or groups (Cicerone et al., 2005). Besides, it has been shown that cognitively impaired patients participate less in rehabilitation activities, which potentially contributes to the poorer functional outcome they display (Skidmore et al., 2010). Finding effective cognitive rehabilitation methods that can be incorporated in clinical practice is therefore crucial.

Numerous methods to improve cognitive deficits, for instance, specifically attention (Barker-Collo et al., 2009), memory (Lundqvist, Grundström, Samuelsson, & Rönnberg, 2010), executive function (Chung, Pollock, Campbell, Durward, & Hagen, 2013), or spatial abilities (Bowen & Lincoln, 2007), have been proposed. However, the results show mixed efficacies. A meta-analysis on the impact of attentional treatments showed an effect on divided attention in the short term, but found no evidence for persisting effects on other attentional domains, global attention, or functional outcomes (Loetscher & Lincoln, 2013). Similarly, a meta-review that investigated the effect of memory rehabilitation found that training might benefit subjective reports of memory in the short term, but shows no effect in the long term, on objective memory measures, mood, functional abilities or quality of life (Roshan das Nair, Cogger, Worthington, & Lincoln, 2017). Ultimately, a meta-analysis over six Cochrane reviews shows insufficient research evidence or evidence of insufficient quality to support any recommendation for cognitive stroke rehabilitation (Gillespie et al., 2015).

Besides methodological issues, one limitation of existing methods could be that they focus on one deficit only, ignoring that patients typically express deficits in multiple cognitive domains (Leśniak et al., 2008; Sascha M.C. Rasquin et al., 2004). A study on a large sample of heterogeneous stroke patients which aimed at linking lesions to cognitive deficits found that a given lesion location leads to cognitive impairments in several domains (Corbetta et al., 2015). This emphasizes that cognitive functions rely on a network of brain regions. A lesion in one of those regions might cause a disturbance to the network, which leads to a multitude of symptoms. This is further supported by studies that revealed that pathological changes in brain structures are related to the occurrence of various cognitive deficits and symptoms for instance, in Alzheimer’s disease (Perry & Hodges, 1999) or spatial neglect (Malhotra et al., 2004). Moreover, the presence of multiple cognitive deficits seems to be a marker in patients that are at risk of developing Alzheimer’s disease later in life (Bäckman, Jones, Berger, Laukka, & Small, 2004). To what extent rehabilitation could potentially drive structural or functional changes to alleviate the symptoms of stroke is still under debate (Berlucchi, 2011; Robertson, 1999).

Nevertheless, rehabilitation methods must aid the patient in obtaining enough functionality to independently perform instrumental activities of daily living, be it through restoration of function or compensation. With this in mind, focusing the training on a single cognitive skill might not be efficient because many daily tasks or jobs require several cognitive abilities for their execution (Hofgren et al., 2007). For instance, most patients would like to be mobile and drive a car again after their stroke. Driving requires the individual to use selective attention to deal with the traffic, traffic signs and distractions, to be cognitively flexible to react to changing situations on the road, to visually scan the mirrors at the front, at the side, and in the back, to have a visual field that includes the sidewalks and to perform all of this while steering the car effectively in real-time (De Raedt & Ponjaert-Kristoffersen, 2000). Consequently, rehabilitation methods that address one specific cognitive ability only do not address the requirements of performing the activities of daily living and might not stimulate and train the underlying brain processes adequately. If a stroke leads to impairments in various cognitive domains, then these domains should be treated together to benefit a patient's performance in everyday life.

To address the challenge of simultaneously training various cognitive abilities in an individualized manner, we revert to interactive technologies, in particular to the coupling of motion capture technology with virtual reality (VR). VR-based systems have shown to be at least as effective as conventional therapies for physical rehabilitation, such as for the recovery of upper limb movements as demonstrated in Chapter 3 and by other recent studies (Aminov et al., 2018; Laver et al., 2017) or gait and balance (de Rooij et al., 2016). Contrarily, meta-analyses investigating the use of VR for stroke rehabilitation were either not able to analyse the effect of training on cognitive function (Laver et al., 2017) or only found a preliminary positive effect (Aminov et al., 2018) due to insufficient randomized controlled trials. Besides, computer-based interventions for cognitive rehabilitation are currently only recommended as a practice option when supervised by a therapist (Cicerone et al., 2011).

As elaborated in Chapter 3 the positive effect of VR for physical recovery, is only confirmed for those systems that incorporate distinct neuroscientific and psychological principles that underlie learning and recovery, which we have outlined in Chapter 2. It appears that existing cognitive rehabilitation methods also can also include principles of learning, like repetitive practice, increasing difficulty or complexity and providing feedback through auditory or verbal cues (Chung et al., 2013; Pedroli, Serino, Cipresso, Pallavicini, & Riva, 2015). However, it seems that these principles are either not explicitly declared in the interventions, or the field still needs to evaluate the exact mechanisms behind cognitive rehabilitation that would positively alter cognitive function and behaviour (Gillespie et al., 2015). This leads to the paradoxical situation, that although many cognitive rehabilitation protocols rely on technology (18 out of 44 studies in the meta-analyses mentioned here (Bowen & Lincoln, 2007; Chung et al., 2013; Loetscher & Lincoln, 2013; R Nair, Cogger, Worthington, & Lincoln, 2016)), VR appears to be rarely used in cognitive rehabilitation (4 studies in (Pedroli et al., 2015)). More specifically, certain principles of neurorehabilitation can be better implemented in virtual than in physical reality. As we have shown in the previous chapter (see Chapter 4) the intention compatible enhancement of movement is beneficial in counteracting learned non-use. This enhancement is only possible when the properties of visual feedback are manipulated beyond the properties of the physical world.

There are indications that such enhanced feedback can be used in cognitive rehabilitation too. Some rehabilitation methods for reducing spatial neglect use VR to recreate realistic scenarios (e.g., crossroads) that allow the patients to train attentional abilities in an ecologically valid but safe environment (Pedroli et al., 2015). Augmented visual or auditory feedback provides them with a more enriched and controlled learning situation than reality would be able to offer (Mainetti et al., 2013). The method we present in this chapter combines specifically two principles of neurorehabilitation: increasing and individualizing difficulty (Section 2.3.7) as well as embodied first-person practice (Section 2.3.13). The principle of increasing difficulty is grounded on the finding that learning is maximal if a task is individualized to the subject and provides training at an optimal challenge level (Guadagnoli & Lee, 2004; Marteniuk, 1976). This principle was also advanced as being beneficial for cognitive rehabilitation (Cicerone et al., 2000). A study that provided computerized working memory training which increased the difficulty level of each training task automatically to the patient’s working memory capacity found a significant improvement in trained and untrained working memory tasks (Lundqvist et al., 2010), which is similar to another study where the difficulty adapted as a function of individual performance and where feedback was provided through scores and verbal encouragement (Westerberg et al., 2007). Indeed, in VR, we can create tasks that require the patient to use abilities from various cognitive domains to achieve a given goal (Faria, Andrade, Soares, & Bermúdez i Badia, 2016). Algorithms can learn from the patient’s performance and adapt the difficulty of the task gradually and automatically to identify the current ability level of the patient and to challenge it appropriately (Cameirão, Bermúdez i Badia, Duarte Oller, & Verschure, 2008), potentially allowing a heterogeneous group of cognitively impaired individuals to train in a consistent rehabilitation regime. The principle of embodied practice relies on the insights gained from the studies of action observation (Martens et al., 1976), which is also the primary rational behind RGS. The embodied training of RGS could benefit cognitive rehabilitation too, as motor and cognitive skills training contributes to activity changes in common brain regions (Patel, Spreng, & Turner, 2013). Indeed, earlier theoretical work has shown that we can also think of the motor system as forming an integral part of cognitive control systems (P. Verschure, 2003; Wyss, König, & Verschure, 2004). Besides delivering individualized, embodied and immersive training, using a VR-based system might also promote motivation through presenting complex goal-oriented tasks combined with gamification (Katz, Jaeggi, Buschkuehl, Stegman, & Shah, 2014). Patients identified the lack of motivation as one of the factors preventing them from completing post-stroke exercise programs (Jurkiewicz et al., 2011). Lack of adherence appears to be a known issue in cognitive rehabilitation as well (Barrett et al., 2006). However, the exact relationship between adherence and motivation as well as the factors which in turn define and affect internal states need to be investigated. Ultimately VR-based systems are apt to increase training time and intensity and can extend the training to the patient’s home even after discharge from the hospital (Ballester et al., 2017), as they operate in an automated fashion, require less personnel, and are more cost-effective than traditional rehabilitation methods (Piron et al., 2009). It is, therefore, worthwhile to investigate the effectiveness of science and evidence-based VR systems for cognitive recovery as they can overcome current limitations in cognitive rehabilitation, such as labour-intensiveness, isolated treatment of cognitive deficits and missing knowledge of the active ingredients in treatments (Gillespie et al., 2015).

Another issue in cognitive rehabilitation is that co-occurring post-stroke depression is often not detected (Srivastava et al., 2010). However, depression is common after stroke—although incident rates can vary substantially between studies, pooled frequency is estimated to be at 31% (Hackett & Pickles, 2014). Patients with post-stroke depression show lower cognitive functioning as well as a higher dependency in activities of daily living, more severe impairments, and handicap than non-depressed patients (Kauhanen et al., 1999). Poor performance in neuropsychological tests, therefore, can be attributed not only to stroke, age (McDermott & Ebmeier, 2009) and the inefficacy of cognitive training but also mood disorders. On the other hand, cognitive rehabilitation can influence depressive mood positively, as shown in patients with mild cognitive impairment (Kurz et al., 2009). Thus, the presence of depression should be measured in cognitively impaired patients, and its interaction with cognitive functioning and cognitive rehabilitation should be investigated when patients with cognitive deficits are treated.

In this chapter, we propose and test a novel method for the conjunctive training of cognitive abilities from multiple cognitive domains in RGS. We developed integrated cognitive rehabilitation scenarios in VR to address deficits in memory, attention, spatial awareness, and executive function in combination and in a task- and goal-oriented manner. This proposal reflects the fundamental consideration that specific cognitive abilities are constituent aspects of cognition rather than isolated domains or, in other words, processes that are critically linked in the overall architecture of the brain (P. F. M. J. Verschure, 2012). The implementation of these scenarios includes a mechanism that adapts the difficulty automatically to the patient's capabilities using machine learning techniques (Nirme et al., 2011), thereby addressing unique profiles of impairments and skills in a heterogeneous group of stroke patients. The algorithm adapts several task parameters, which reflect cognitive abilities, to the performance of the patient and hence adjusts the task's difficulty automatically. The task parameters fitting the user's performance provide a user-specific model. The development of the adaptive conjunctive cognitive training (ACCT) program studied here is embedded and delivered through RGS. This explorative pilot study aims to identify potential effects and challenges in anticipation of a larger trial. We compare the ACCT program against a control group that performs a standard at-home cognitive rehabilitation program. We hypothesize that the training scenarios can adapt the difficulty to the individual cognitive impairment level of each patient, equalizing performance differences. Further, we expect to see that the ACCT intervention positively influences the patient's impairment level in the four cognitive domains addressed. Knowing that observed effects could be potentially modulated by post-stroke depression, we also analyse in a subgroup whether depression negatively influences cognitive functioning and can be positively modulated by the ACCT intervention.

5.2. Methods

5.2.1. Study design and patients

We conducted a randomized controlled pilot trial with an intended allocation ratio of 1:1, which was approved by the local Ethical Committee at Parc de Salut Mar and registered at ClinicalTrials.gov (NCT02816008). Recruitment and screening took place from August 2016 until August 2017 by the physicians from the neurological rehabilitation unit at Hospital d'Esperança in Barcelona. Potential participants were recruited and screened among the outpatients that visited the physicians for the yearly control at the hospital. This convenience sampling ensured a representative sample of community-dwelling chronic stroke patients. The inclusion criteria were as follows: a) cognitive impairment due to a first-ever stroke (Montreal Cognitive Assessment (Nasreddine et al., 2005), MoCA < 26), b) no severe upper limb motor disability (Medical Research Council Scale for stroke assessment (Guarantors of Brain, 1989), MRC > 2), c) age between 45 and 75 years old and d) chronic state (more than six months after stroke but less than ten years). The exclusion criteria were as follows: a) severe cognitive incapacity that prohibits the execution of the experiment, b) severe impairments like spasticity, communication disabilities (aphasia or apraxia) and perceptual or physical impairments that would interfere with the correct execution or understanding of the experiment, c) history of severe mental health problems that were present in the acute or subacute phase and d) presence of hemianopia. The reason for including patients with first-ever stroke only is that current literature is inconclusive whether a recurrent stroke enhances existing cognitive deficits or not (Pendlebury & Rothwell, 2009; Rist et al., 2013). Inclusion and exclusion criteria, as well as stroke aetiology, were checked by the physicians using standard clinical tools, the clinical history of the patient, and clinical appraisal. As there is no existing study from which estimations for our primary outcome measurements could have been obtained, the sample size had to be predicted instead of calculated through a power analysis. Based on our previous experiments that proved to be achievable with the resources and time available (Ballester, Nirme, et al., 2015; Cameirão et al., 2012), other trials with similar interventions (Faria et al., 2016, 2018) and the doctor's estimation of recruitment pace, a sample size of 30 participants was deemed adequate. The trial concluded when the sample size for a complete case analysis was reached. The Consolidated Standards of Reporting Trials (CONSORT) statement was used to report the trial.

Eligible patients that gave their written consent to participate were assessed by a neuropsychologist using the following tests: a neuropsychological test battery, additional clinical outcome scales and two VR assessments — at baseline (T0), after the intervention (T1) and at three months follow-up (T2). All assessments were conducted in the aforementioned order in one session, in the median four days before and three days after the intervention period. At baseline, the patients were randomized by the experimenter either into an experimental group (EG) or a control group (CG) using a custom-made computerized minimization procedure based on the open-source software OxMAR (O'Callaghan, 2014) to ensure balanced groups across the baseline characteristics (gender, age, days after stroke, MoCA, Mini-Mental State Examination (MMSE), Barthel Index (BI) and Fugl-Meyer Assessment for the upper extremity (FM-UE)) and all the scores of the neuropsychological test battery (see section Outcome Measurements). Specifically, the measurements were stratified (dummy-coded) as follows: For the neuropsychological test battery and as well as the MoCA, MMSE, BI and FM-UE established cut-offs for the categories "no impairment", "mild impairment", "moderate impairment" or "severe impairment" were taken from normative data [see Table A.1 in Appendix A], for age, the cut-off was set at 65, for days after stroke at 590 days and gender was categorized in male and female. First, a new patient would be stratified (dummy-coded with 0's and 1's) according to these cut-offs. Then the sums of the strati between the groups with the new patient added are compared. The patient is then either allocated to the group with the lower sum or if the sums are equal randomly allocated with a 50% chance for either group. The first four recruited patients were assigned using a computer-generated list of random numbers only known to the experimenter. Due to the nature of the intervention and personal resources, participants and the experimenter were not blind to the group allocation. The neuropsychologist was not informed about group allocation. However, since the assessments and the intervention took place in the same hospital it could not be prevented that some patients would cross path with the assessor. All patients underwent a six-weeks long, daily training of 30 minutes, five times per week (Figure 5.1 A).

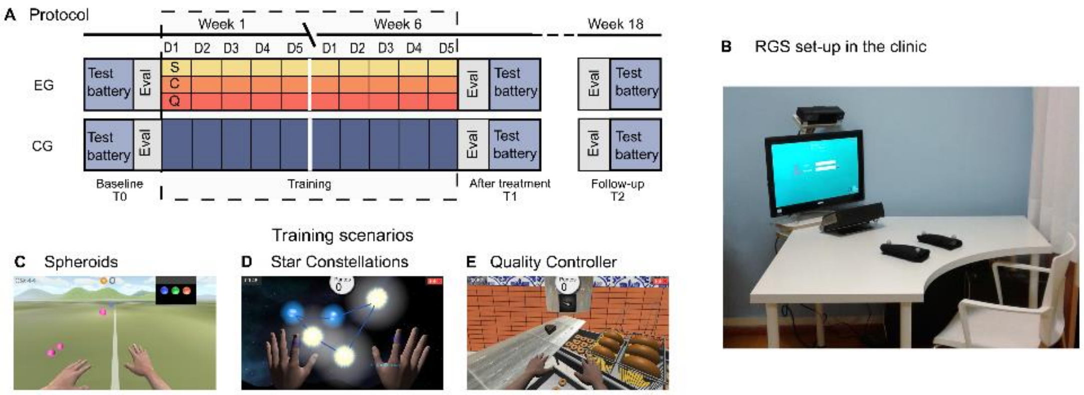


Figure 5.1. Experimental protocol and set-up.
(A) The protocol lasted 18 weeks in total, six weeks of training, and 3-months follow-up period. (B) The clinical set-up of RGS for the EG was extended with a Tobii EyeTracker T120 tracked the eye movement of the patient during the training. The training included three training scenarios ((C) Complex Spheroids, (D) Star Constellations, and (E) Quality Controller). C, Star Constellations; CG, control group; D, day; EG, experimental group; Eval, VR evaluation; Q, Quality Controller; RGS, Rehabilitation Gaming System; S, Complex Spheroids.

5.2.2. Experimental intervention

The EG played each day three cognitive training scenarios of 10 minutes each. The dose of training was estimated to be adequate based on the results from our previous studies in the motor domain (Ballester, Nirme, et al., 2015) and the currently reported average intervention time (Loetscher & Lincoln, 2013). The training was provided through the RGS set-up (Figure 5.1. Experimental protocol and set-up. B). After an initial introduction and explanation of the scenarios on the first day, the patients interacted independently with RGS. Every day the therapist on duty would place the patient in front of the motion capture sensor and the screen, log in to the system, and commence the intervention. Only a few patients required help with putting on and taking off the markers and to change between the training protocols. Apart from this, the therapist did neither assist during the intervention, check adherence to the goal of the task, nor provide any feedback to the patient. The therapist was, however, allowed to help when technical issues or computer problems arose. The data generated through the interaction with the system was automatically stored in a remote secured database at the experimenter's institution. With this pilot study, we extended the RGS framework of embodied training, where the patient controls a virtual avatar on a computer screen, with conjunctive cognitive training scenarios which we call ACCT. Besides, we exploit in specific the principle of increasing difficulty (Section 2.3.7) by using an automated mechanism that adapts the difficulty of the training to each patient's ability (Nirme et al., 2011). It is thought that training efficiency and engagement is maximal if the challenge level is optimal regarding performance, perceived difficulty and fatigue, e.g., a person learns maximally if the experienced difficulty is neither too low nor too high (Gendolla, 1999). To maintain the perceived challenge within a scenario at a consistent level, the algorithm used here adapts task parameters (for instance the speed of moving objects, or the number of items that need to be memorized) which influence the actual difficulty based on the patient's ongoing performance in the task (Nirme et al., 2011). Thus, when the patient is reaching a high level of performance, the algorithm makes the task more difficult, while when the patient’s performance drops, the algorithm makes the task easier. The task parameters were selected to train skills that underlie the cognitive domains investigated here and based on existing literature on recommendations for effective cognitive rehabilitation. The skills and task parameters were combined into two training scenarios in order to provide the patients with multidomain exercises. The training scenarios and their task parameters are explained hereinafter. Performance is calculated as the relative success rate, e.g. the number of successful attempts over a given number of trials and the algorithm's objective is to maintain it around 70 – 80%. In this study, we assume that the levels of the task parameters reflect the individual cognitive impairment levels.

The Complex Spheroids scenario aims at training basic attention and memory ability without an automated adaptation of difficulty (Figure 5.1 C). It requires the patient to intercept approaching coloured spheres by following a predefined sequence indicated at the top right corner of the screen. The patient must keep the current position of the colour sequence in memory. The spheres can either approach on the left, on the right or on both sides of the workspace that is divided by a white line. It prompts the patient to either focus his attention on one side or divide it to both sides of the screen. Errors in the sequence are indicated with a tone. When the patient completes the sequence correctly three times in a row, he is rewarded with a point, and the sequence changes to a new one.

The Star Constellations scenario (Figure 5.1 D) is a visuospatial short-term memory task (Westerberg et al., 2007). In a given trial, a star constellation is shown to the patient, and a subset of the stars light up in a sequence. The sequence must be kept in memory and after a delay period reproduced by touching the stars accordingly. Correctly reproducing the sequence rewards the patient with one point for each star in the sequence and lights up the whole constellation. If the patient committed a mistake, the wrongly touched stars are coloured in red. All actions are accompanied by distinct sounds. The difficulty level of four task parameters is adapted in this scenario: 1) The complexity and spatial extension of the constellations (seven levels from simple four-star constellations to complex 13-star ones) aim to train spatial attention and spatial memory. This parameter addresses the recommendation to offer a unique sequence of stimuli in each trial during working memory training (Westerberg et al., 2007), to progress from simpler to more complex tasks in executive function training (Chung et al., 2013) and to train the ability to detect and deploy attention to all sides of space (Loetscher & Lincoln, 2013). 2) and 3) The number of stars in a subset (from 3 to all) and the time interval between their appearance (ranging from 4 to 2 seconds) should aid the training of working memory (Westerberg et al., 2007). 4) The length of the delay period (1 to 5 seconds) progressively challenges memory delayed recall. This parameter aids the training of internal strategies (visual imagery) which are recommended for memory training (Cicerone et al., 2005). The countdown of the delay period serves as a non-spatial alerting intervention to train sustained attention (Robertson, 1999).

In the Quality Controller scenario (Figure 5.1 E), patients are presented with two tasks concurrently. In the right workspace, doughnuts must be taken out of a fryer when their cooking time ends as indicated by the sound of an alarm clock. If the patient moves his arm over the fryer at the right time, he is rewarded with one point. If he reacts too late or too early, he is penalized with a minus point. In the left workspace, a machine produces candies, that move over a conveyor belt. The type of candy currently produced is indicated in a display on the machine. The patient must spot candies on the conveyor belt that do not match the indicated sample and push them away. For every correctly spotted defective candy, the patient is rewarded with a point. If a non-defective candy is touched, the patient loses a point, and the touched candy lights up red. The difficulty level of five task parameters is adapted in this scenario: 1) and 2) The speed of the conveyor belt (from 2 meters per second to 5 meters per second), and the interval between appearing candies (4 to 2 seconds) aim to train alertness. These parameters address speed-of-processing training that fosters visual search skills to identify and locate visual information quickly and in a divided-attention format (Ball et al., 2002). 3) The ratio between defective and good candies is thought to promote selective and sustained attention and can change from 8 out of 24 to 1 out of 3. This parameter addresses the ability to focus on specific stimuli while ignoring irrelevant ones in attention training (Loetscher & Lincoln, 2013). 4) The baking time of the doughnuts (from 30 to 5 seconds) should train the ability to inhibit prepotent responses in executive function training (Chung et al., 2013). 5) The time given to take the doughnuts out of the fryer (from 6 seconds to 3 seconds) should aid the training of initiation of behaviours in executive function training (Chung et al., 2013). The alarm clock that signals when the doughnuts are ready should foster readiness to respond and, therefore, alertness and arousal (Loetscher & Lincoln, 2013). The patient has to take care of the two spatially distributed tasks simultaneously; therefore, training divided attention ability, which is essential for multitasking and spatial attention (Loetscher & Lincoln, 2013). The scenario should address bottom-up stimulus-driven alerting in spatial neglect (Barrett et al., 2006) by promoting visual search, which improves voluntary exploration of the contralesional space (Pedroli et al., 2015). It further addresses problem-solving and strategy formation techniques required in executive function (Chung et al., 2013; Cicerone et al., 2005).

Besides the automated adaptive difficulty mechanism and the embodied goal-oriented practice provided through RGS, these three training scenarios adhere to the following principles: multisensory stimulation (Section 2.3.8) by providing rich visual and auditory stimuli, explicit feedback (Section 2.3.10) by providing feedback on outcome of action, variable practice (Section 2.3.6) by providing various scenes and movement requirements, as well as promoting the use of the paretic limb (Section 2.3.12) by dividing the workspace.

5.2.3. Control intervention

The CG received from the experimenter at the hospital a folder with 30 individual cognitive tasks that had to be completed at home (e.g., crosswords, spot the ten differences, draw complex figures reversed, or complete sentences) during 30 minutes at each workday. The tasks were selected by the neuropsychologist to overlap with the cognitive abilities essential in the experimental tasks (spatial awareness, attention, memory, executive ability) and to be representative of what would be generally suggested to community-dwelling patients for at-home training. The adherence to the control intervention was not monitored during the experiment. The patients were asked to write down the date and the time spent on each task and return the folder after six weeks. After the treatment, the patient would return the folder to the experimenter, who checked that the exercises were completed and asked the patients whether they had any difficulties fulfilling the task.

5.2.4. Outcome measures

The primary outcome measurements were four averaged standardized composite scores (ASCS) for attention, memory, executive function, and spatial awareness calculated from the neuropsychological test battery. The neuropsychological test battery was compiled by the neuropsychologist and covered the four cognitive domains. For attention, we chose the Corsi Block Tapping Test Forward (Corsi F) (Corsi, 1973), the Trail Making Test A (TMT A) (Reitan, 1958), and the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS) (Wechsler, 2008) Digit Span Forward (WAIS F). For memory, we selected the Corsi Block Tapping Test Backward (Corsi B) (Corsi, 1973), the Rey Auditory Verbal Learning Test Immediate (RAVLT I) and Delayed Recall (RAVLT D) (Rey, 1941), and the WAIS Digit Span Backward (WAIS B). Executive function was covered by the TMT B, WAIS Digit Symbol Coding (WAIS C) and the Frontal Assessment Battery (FAB) (Dubois, Slachevsky, Litvan, & Pillon, 2000), and lastly, spatial awareness consisted of the Star Cancellation Test (Star) (Wilson, Cockburn, & Halligan, 1987). The standard scoring and Spanish test versions were used. Secondary outcomes were clinical scales that allowed us to check for additional effects of the treatment and consisted of the MoCA (Nasreddine et al., 2005), the BI (Collin et al., 1988), the FM-UE (Fugl-Meyer et al., 1975), the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) and the MMSE (Folstein, Folstein, & McHugh, 1975). The HAM-D outcome is only available for 21 subjects, as it was added after the first analysis of data (Maier, Banuelos, Ballester, Duarte, & Verschure, 2017). Although patients with a history of severe mental health problems should have been excluded by our exclusion criteria, we suspected that mood might influence the results. In addition, the protocol included two VR assessments that will be analysed in separate reports.

5.2.5. Statistical procedure

Since normality testing (Lilliefors test of normality) pointed out that most of our data except HAM-D were not normally distributed, we used non-parametric testing. Baseline characteristics and outcome measures were compared between groups using Wilcoxon's rank-sum test (W_s) for interval and ordinal variables, and Pearson's chi-square test (χ_2) for nominal variables. Spearman's correlation was used to assess how well the task parameters of each training scenario (the median over maximum difficulty level achieved of all successful trials after one week of training) correlated with the neuropsychological test battery at baseline. For the primary outcomes, the individual test scores for each cognitive assessment were converted into standardized z-scores, using the mean and standard deviation (SD) of normative age-adjusted data, following the procedure of similar studies in the field (Desmond, Moroney, Sano, & Stern, 1996; S. M C Rasquin, Verhey, Lousberg, Winkens, & Lodder, 2002). The following scores of each test and corresponding normative data were taken to compute the standardized z-score: Corsi F longest span achieved, age range for norms 62-72 (Pena-Casanova et al., 2009), TMT A seconds to complete, age range for norms 62-72 (Pena-Casanova et al., 2009), WAIS F max digit range achieved, age range for norms 62-72 years (Pena-Casanova et al., 2009), Corsi B longest span achieved, age range for norms 62-72 (Pena-Casanova et al., 2009), RAVLT I total recall, age 65 years, male (Van der Elst, van Boxtel, van Breukelen, & Jolles, 2005), RAVLT D number of recalled words, age 65 years, male (Van der Elst et al., 2005), WAIS B max range achieved, age range for norms 62-72 (Pena-Casanova et al., 2009), TMT B seconds to complete, age range for norms 62-72 (Pena-Casanova et al., 2009), WAIS C number of correct substitutions age range for norms 62-72 (Pena-Casanova et al., 2009), FAB mean scores, age 60-69, education 6-8 years (Appollonio et al., 2005) and Star items detected, patient no cognitive impairment BIT (Raspelli et al., 2012). By averaging the z-scores, the ASCS for each domain were obtained. To obtain a measurement of generalized cognitive functioning, we took the median of the patient's ASCS within each domain. Each patient's ASCS per domain was stratified according to its SD from the normative mean to obtain the impairment levels in each domain: 'no impairment' (higher than normative data), 'mild' (within -1 SD from normative data), 'moderate' (between -1 and -2 SD from normative data) and 'severe' (more than -2 SD from normative data). We adopted a finer gradient of impairment level as classically reported (O. L. Lopez et al., 2006; van Zandvoort, Kessels, Nys, de Haan, & Kappelle, 2005). The correlation within ASCS was evaluated using Spearman's correlation. First, a within-group analysis was performed, evaluating the changes of ASCS scores and secondary outcomes over time across the three assessment points of the study (baseline T0, after treatment T1 and follow-up T2) using the Friedman's ANOVA test statistic (χ_F^2). Then a post hoc analysis was performed using the Wilcoxon's sign rank test (T) comparing the scores after treatment and at follow-up with baseline. For the between-group analysis, the improvement after treatment (T1 – T0) and at follow-up (T2 – T0) was compared between EG and CG using Wilcoxon's rank-sum test (W_s). A complete case analysis and a last observation carried forward analysis were performed to deal with missing data. Significant results were only accepted when confirmed by both analyses. Lastly, we analysed the ASCS of those participants for which the HAM-D was obtained (EG=11, CG=10). For this depression subgroup analysis, the improvement in ASCS was evaluated with a linear regression, in addition to the within- and between-group analysis. We used MATLAB R2017b for all statistical analysis, except for the regression where we used the lm-package in R version 3.5.0. The minimization procedure was processed through a custom-made MATLAB-script which was based on the open-source software OxMaR (O'Callaghan, 2014).

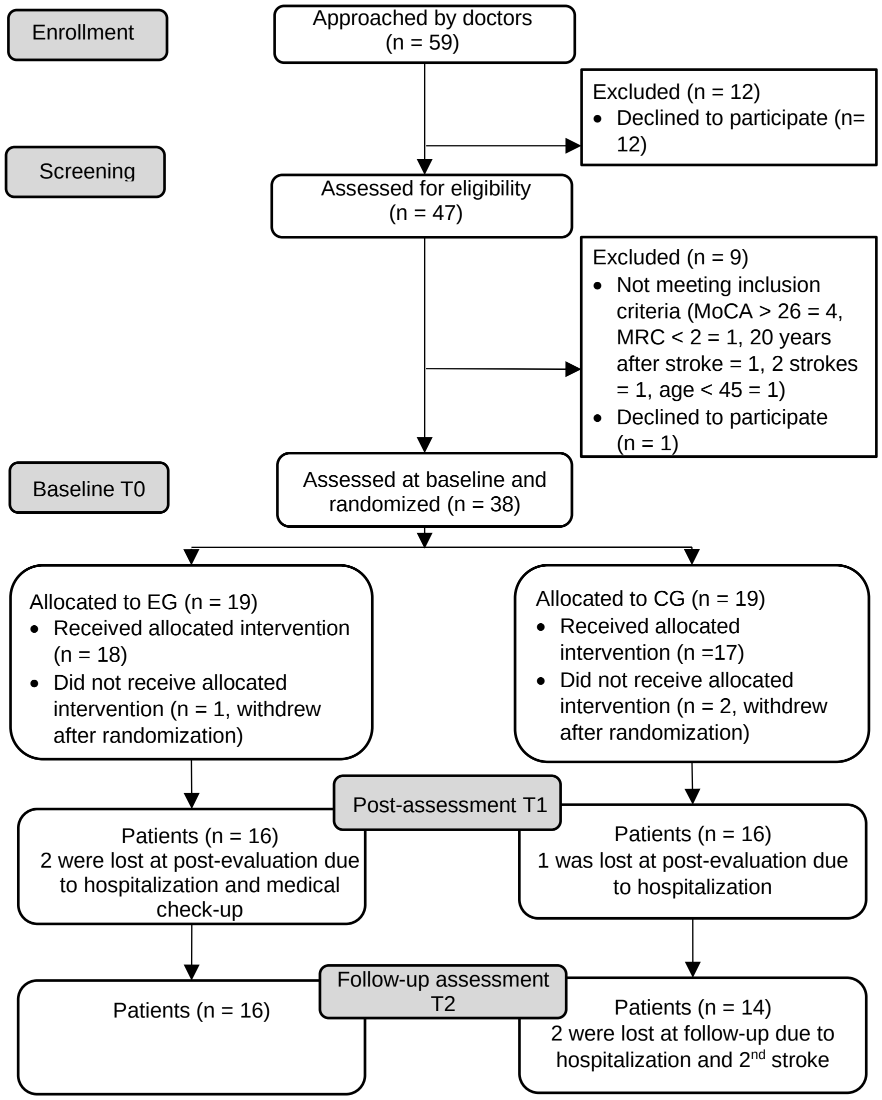


Figure 5.2. CONSORT flow diagram.
Abbreviations: CG, control group; EG, experimental group; MoCA: Montreal Cognitive Assessment; MRC: Medical Research Council Scale for stroke assessment.

5.3. Results

We approached 59 chronic stroke patients, of which 47 agreed to participate and were assessed for eligibility (CONSORT flow diagram Figure 5.2). Thirty-eight eligible individuals were assessed at baseline and randomized into EG (n = 19) and CG (n = 19). Their baseline characteristics can be found in Table 5.1. There were no differences between the groups in their baseline characteristics or in any of their baseline primary or secondary outcome measures. Three patients (CG = 2, EG = 1) withdrew after randomization. 35 patients (EG = 18, CG = 17) completed the six weeks intervention program. In the CG, one patient was lost at post-assessment and two at follow-up. In EG, two patients were lost at post-assessment, resulting in 30 valid cases (EG = 16, CG = 14).

Except for one patient that was able to complete only nine tasks, all the patients in the CG did complete all the paper and pencil tasks. However, only two patients noted down the time they spent on each task. Based on their reports, they spent between 20 to 30 minutes on each task, except for a few tasks they were able to finish in five minutes, and that should be replaced in the larger trial.

Table 5.1. Patient characteristics and secondary outcome measurements at baseline

Characteristics	**EG (n = 19)**	**CG (n = 19)**	*p*
	n (%)		χ^2
Gender, female	8 (42.11%)	7 (36.84%)	.33
Impaired limb, right	8 (42.11%)	5 (26.32%)	.62
Etiology			.39
Ischemic	10 (52.63%)	14 (73.68%)	
Hemorrhagic	7 (36.84 %)	5 (26.32%)	
Capsulo lenticular	1 (5.26%)	--	
Undefined	1 (5.26%)	--	
	Mean (SD) – Median [2.5th – 97.5th percentile]		W_s
Age, years	63.63 (6.73) – 63 [53.00 – 76.00]	67.21 (6.45) – 68 [57.00 – 76.00]	.15
Days after stroke	851.16 (805.26) – 620 [192.00 – 3211.00]	12625.9 (1376.1) – 625 [190.00 – 5805.00]	.32
MoCA	20.32 (3.92) – 21 [12.00 – 25.00]	20.05 (3.79) – 20 [12.00 – 25.00]	.76
MMSE	27 (2.08) – 27 [23.00 – 30.00]	26.68 (2.31) – 27 [22.00 – 29.00]	.79
MRC	3.79 (0.71) – 4 [3.00 – 4.00]	3.26 (1.28) – 4 [3.00 – 4.00]	.36
FM-UE	53.79 (14.36) – 60 [15.00 – 66.00]	50.44 (19.45) – 62 [5.00 – 66.00]	.74
BI	95 (7.63) – 100 [80.00 – 100.00]	86.11 (20.04) – 95 [20.00 – 100.00]	.15

BI, Barthel Index; CG, control group; EG, experimental group; FM-UE, Fugl-Meyer Assessment for the upper limb; SD, standard deviation; MoCA, Montreal Cognitive Assessment; MRC, Medical Research Council Scale; MMSE, Mini-Mental State Examination; X^2, Pearson Chi-square statistic; W_s, Wilcoxon's rank-sum test.

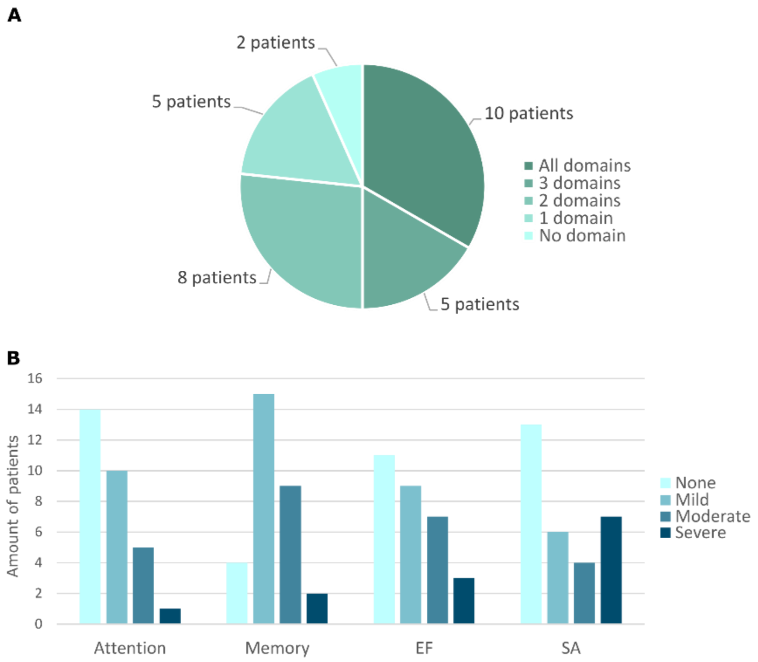


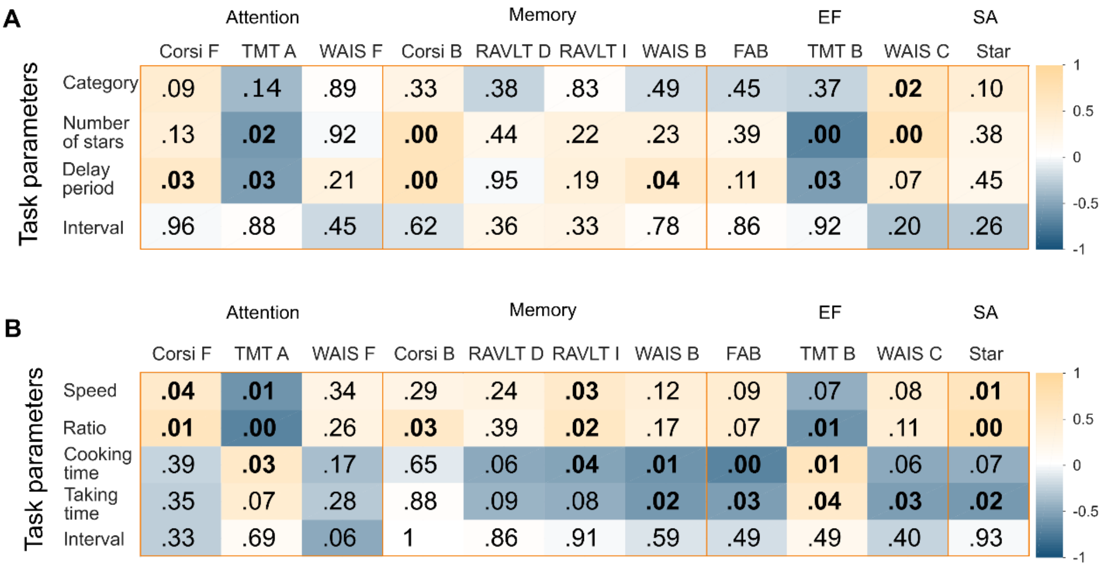
Figure 5.3. Impairment distribution and correlation at baseline.
(A) Distribution of the number of domains impaired. (B) Distribution of severity per domain.

SAB	**		*	*		*	**	**	**	**	***
.50	SAT			*				*	*	*	
.24	.33	SAF	*	**	*		*				
.40	.29	.41	EFB	***	***	***	***	***	***	***	***
.44	.38	.47	.88	EFT	***	***	***	***	***	***	***
.33	.28	.38	.86	.92	EFF	***	***	***	***	***	***
.40	.31	.29	.81	.81	.74	ATT	***	***	***	***	***
.49	.33	.39	.85	.82	.77	.84	ATB	***	***	***	***
.53	.39	.31	.82	.87	.86	.84	.89	ATF	***	***	***
.49	.39	.34	.72	.61	.60	.58	.60	.58	MEB	***	***
.57	.37	.34	.74	.76	.71	.67	.64	.72	.81	MET	***
.61	.27	.30	.76	.76	.76	.61	.67	.79	.68	.89	MEF

Figure 5.4. Correlation between ASCS for attention, memory, and executive function.
Significant p-values are indicated as * p < .05, ** p < .01, *** p < .001 and the colour scale represents the correlation coefficient (Spearman's r). Abbreviations: ASCS, averaged standardized composite score; ATB, attention ASCS at baseline; ATF, attention ASCS at follow-up; ATT, attention ASCS after treatment; EF, executive function; EFB, executive function ASCS at baseline; EFF, executive function ASCS at follow-up; EFT, executive function ASCS after treatment; MEB, memory ASCS at baseline; MEF, memory ASCS at follow-up; MET, memory ASCS after treatment; SA, spatial awareness; SAB, spatial awareness ASCS at baseline; SAF, spatial awareness after follow-up; SAT, spatial awareness at follow-up.

Most of the patients showed an impairment in all four domains at baseline (Figure 5.3 A). Only five patients showed an impairment in a single domain, whereas two patients were better as the normative mean in all domains. Every domain contains a spread across all impairment levels (Figure 5.3 B). The Spearman's correlation revealed that the ASCS of attention, memory and executive function, but not spatial awareness, of all patients together correlate significantly at baseline, after treatment, and at follow-up (Figure 5.4 C).

5.3.1. System evaluation



A

	Attention			Memory				EF			SA
	Corsi F	TMT A	WAIS F	Corsi B	RAVLT D	RAVLT I	WAIS B	FAB	TMT B	WAIS C	Star
Category	.09	.14	.89	.33	.38	.83	.49	.45	.37	**.02**	.10
Number of stars	.13	**.02**	.92	**.00**	.44	.22	.23	.39	**.00**	**.00**	.38
Delay period	**.03**	**.03**	.21	**.00**	.95	.19	**.04**	.11	**.03**	.07	.45
Interval	.96	.88	.45	.62	.36	.33	.78	.86	.92	.20	.26

B

	Attention			Memory				EF			SA
	Corsi F	TMT A	WAIS F	Corsi B	RAVLT D	RAVLT I	WAIS B	FAB	TMT B	WAIS C	Star
Speed	**.04**	**.01**	.34	.29	.24	**.03**	.12	.09	.07	.08	**.01**
Ratio	**.01**	**.00**	.26	**.03**	.39	**.02**	.17	.07	**.01**	.11	**.00**
Cooking time	.39	**.03**	.17	.65	.06	**.04**	**.01**	**.00**	**.01**	.06	.07
Taking time	.35	.07	.28	.88	.09	.08	**.02**	**.03**	**.04**	**.03**	**.02**
Interval	.33	.69	.06	1	.86	.91	.59	.49	.49	.40	.93

Figure 5.5. Correlations between the task parameter of the training scenarios and the neuropsychological test battery.
(A) The task parameters of the Star Constellations scenario are the constellation complexity level (category), the number of stars in the subset (number of stars), time interval between their appearance (interval) and the length of the delay period (delay period). (B) The task parameters of the Quality Controller scenario are the speed of the conveyor belt (speed), the time interval between the appearance of the candies (interval), the ratio between defective and good candies (ratio), the baking time of the doughnuts (baking time) and the time given to take the doughnuts out of the fryer (taking time). The number represents the p-value, with significant values in bold, and the colour scale represents the correlation coefficient (Spearman's r).

In Figure 5.5, we show the correlations between the median task parameters of each scenario, which regulate the difficulty of the training, after the first week of intervention, and the neuropsychological test battery at baseline in EG (n = 16). The analysis revealed that in the Star Constellations scenario (Figure 5.5 A) the median number of stars that a patient was able to remember correlated well with the scores in TMT A (r_s = -.57, p < .05), Corsi B (r_s = .67, p < .01), TMT B (r_s = -.69, p < .01) and WAIS C (r_s = .69, p < .01). Similarly, the median delay period achieved correlated well with the scores in TMT A (r_s = -.56, p < .05) and Corsi B (r_s = .68, p < .01), and moderately with WAIS C (r_s = .46, p = .07). In addition, it correlated with Corsi F (r_s = .54, p < .05) and WAIS B (r_s = -.56, p < .05). Moreover, there was a correlation between the median constellation complexity level and WAIS C (r_s = .59, p < .05). For the Quality Controller scenario

(Figure 5.5 B) several correlations between task parameters and neuropsychological test battery scores have been found as well. The median speed of the conveyor belt and the ratio between good and defective candy correlated well with Corsi F ($r_s = .53$, $p < .05$ and $r_s = .65$, $p < .01$) , TMT A ($r_s = -.61$, $p < .05$ and $r_s = -.69$, $p < .01$), RAVLT I ($r_s = .53$, $p < .05$ and $r_s = .57$, $p < .05$), TMT B ($r_s = -.46$, $p = .07$ and $r_s = -.62$, $p < .05$) and Star ($r_s = .65$, $p < .01$ and $r_s = .75$, $p < .001$). On the other hand, the median baking time and the median time to take out the doughnuts correlated with TMT A ($r_s = .54$, $p < .05$ and $r_s = .46$, $p = .07$), RAVLT I ($r_s = -.53$, $p < .05$ and $r_s = -.45$, $p = .08$), WAIS B ($r_s = -.60$, $p < .05$ and $r_s = -.58$, $p < .05$), FAB ($r_s = -.70$, $p < .01$ and $r_s = -.53$, $p < .05$), TMT B ($r_s = .65$, $p < .01$ and $r_s = .53$, $p < .05$), WAIS C ($r_s = -.47$, $p = .06$, and $r_s = -.53$, $p < .05$) and Star ($r_s = -.47$, $p = .07$ and $r_s = -.58$, $p < .05$).

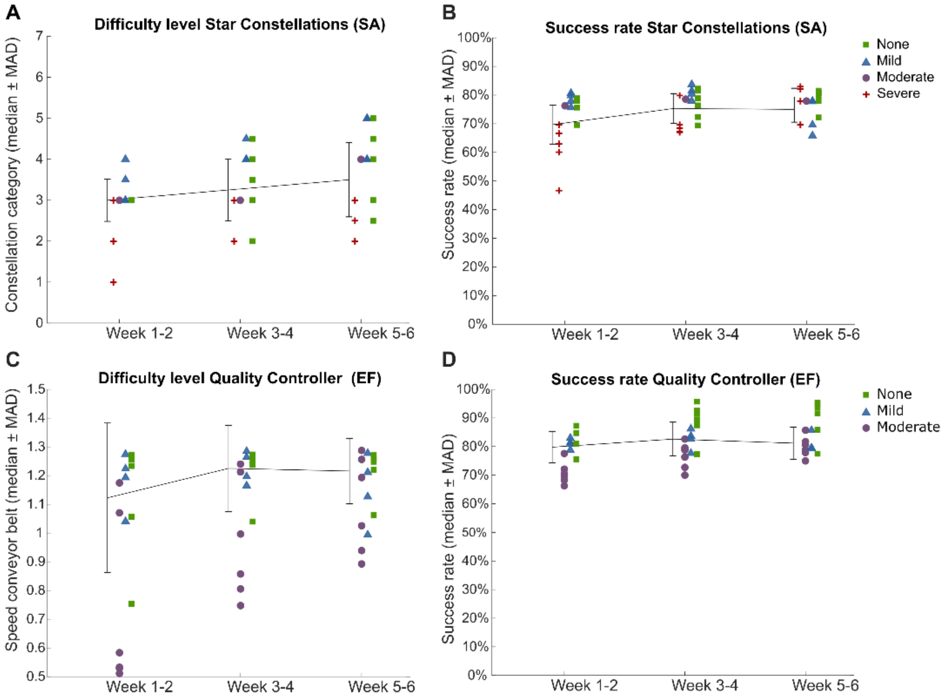


Figure 5.6. The relationship between impairment level, difficulty achievement, and performance (success rate) within training scenarios.
(A) Difficulty achievement in the Star Constellations scenario and (C) in the Quality Controller scenario. The task parameter in Star Constellations is the constellation complexity level, and in Quality Controller the speed of the conveyor belt. Success rate (number of successful attempts over all possible trials in percentage) for Star Constellations (B) and Quality Controller (D). Possible trials in Star Constellations are the total number of constellations shown in a session. In Quality Controller success rate represents the true positives of all defective candies in a session. Solid line and error bars represent median and median absolute deviation per 10 sessions (two weeks), data points represent individual patients stratified according to their impairment level in spatial awareness domain for Star Constellations and executive function domain for Quality Controller at baseline: severe (red cross), moderate (violet circle), mild (blue triangle) and no impairment (green square). EF, executive function domain; MAD, median absolute deviation; SA, spatial awareness domain.

The algorithm adapted the task parameters well to the individual impairment level in EG (n = 16), ensuring a stable success rate while training (Figure 5.6). For instance, in the Star Constellations scenario, stratifying patients according to their impairment level in the spatial awareness domain at baseline revealed that more severe patients achieved lower difficulty levels than less impaired ones (Figure 5.6 A). Throughout the training, however, the achieved difficulty level seemed to increase across all severity levels. Although the task parameter levels differed for each patient, the success rate remained stable at around 70% (Figure 5.6 B). The same pattern can be observed in the Quality Controller scenario (Figure 5.6 C and Figure 5.6 D). Here, however, the achieved task parameter might not have been challenging enough for non-impaired patients as their performance was around 90% (Figure 5.6 D).

5.3.2. Clinical impact

In Table 5.2, we show the descriptive data of the ASCS for every domain at baseline (T0), after treatment (T1) and at follow-up (T2) as well as the *p*-values of the within-group analysis for the complete cases (EG = 16, CG = 14). The data for the last observation carried forward analysis (EG = 19, CG = 19) can be found in Appendix A Table A.2. We found a significant change in ASCS over time for the EG in the attention domain (χ_F^2 (2) = 9.57, $p < .01$), in the spatial awareness domain (χ_F^2 (2) = 11.23, $p < .01$) and in the generalized cognitive functioning (χ_F^2 (2) = 14.00, $p < .001$) in the complete case analysis (Figure 5.7 A-C), which was confirmed by the last observation carried forward analysis. In the attention domain, the post hoc analysis revealed significantly higher scores at T2 (T = 84.5, r = .48, $p < .01$) as compared to baseline. In the spatial awareness domain, the post hoc analysis revealed significant higher scores at T1 (T = 47, r = .35, $p < .05$) and at T2 (T = 63, r = .47, $p < .01$) as compared to baseline. In the generalized cognitive functioning, the post hoc analysis indicated significant higher scores at T1 (T = 130, r = .59, $p < .01$) and at T2 (T = 123, r = .52, $p < .01$) as compared to baseline. For the CG, no significant change over time was found, although the memory domain yielded significantly higher scores at T1 (T = 86, r = .56, $p < .05$) that was confirmed by the last observation carried forward analysis. No significant results for either group were found in the executive function domain. Neither we found significant differences between the groups in the complete case analysis that would have been confirmed in the last observation carried forward analysis (Table 5.3). The descriptive statistics for every test in the neuropsychological test battery can be found in Appendix A Table A.3.

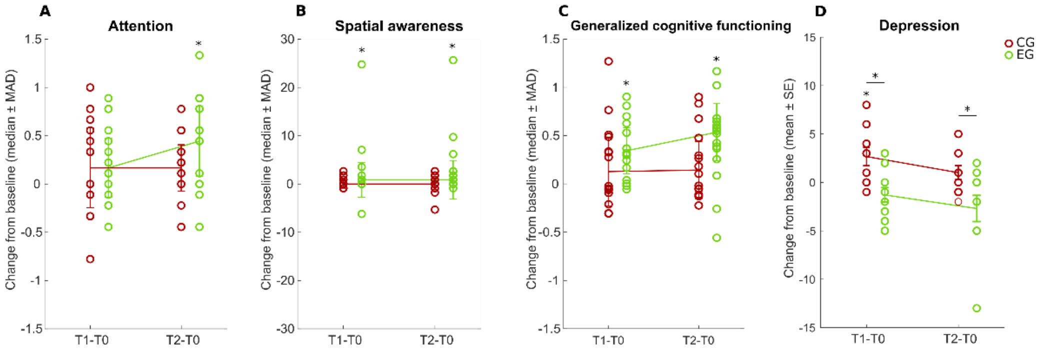


Figure 5.7. Main findings in ASCS scores and subgroup analysis.
Change in (A) attention ASCS, (B) spatial awareness ASCS, (C) generalized cognitive functioning ASCS, and (D) depression (HAM-D) from baseline to after treatment (T1-T0) and to follow-up (T2-T0) for the experimental group (EG, green) and control group (CG, red). The individual data for each subject is indicated with dots. Negative numbers in HAM-D mean improvement (less depression). MAD, median absolute deviation; SE, standard error of the mean.

Table 5.2. ASCS at baseline (T0), after treatment (T1) and follow-up (T2) and the p-values for the within-group analysis of the change over time for complete case analysis.

ASCS	**EG (n = 16)**				**CG (n= 14)**			
	Mean (SD) – Median [2.5th – 97.5th percentile]			*p*	Mean (SD) – Median [2.5th – 97.5th percentile]			*p*
	T0	**T1**	**T2**	$\chi_F^2(2)$	**T0**	**T1**	**T2**	$\chi_F^2(2)$
Attention	-0.35 (0.88) – -0.28 [-2.11 – 1.22]	-0.13 (0.94) – -0.17 [-1.67 – 1.33]	**0.06 (0.92) – 0.17** **[-1.44 – 1.67]****	**.01**	-0.16 (0.83) – 0.11 [-1.78 – 0.89]	0.02 (0.80) – 0.28 [-1.78 – 1.00]	0.03 (0.92) – 0.22 [-1.67 – 1.67]	.25
Memory	-0.76 (0.69) – -0.57 [-2.27 – 0.05]	-0.54 (0.91) – -0.31 [-2.17 – 0.76]	-0.43 (0.91) – -0.30 [-2.19 – 0.89]	.30	-0.72 (0.82) – -0.54 [-2.38 – 0.40]	**-0.52 (0.73) – -0.44** **[-1.78 – 0.56]***	-0.37 (0.83) – -0.52 [-1.37 – 1.52]	.42
EF	-0.34 (1.01) – -0.34 [-1.64 – 1.32]	-0.29 (1.18) – -0.38 [-2.09 – 2.02]	-0.15 (1.19) – 0.15 [-1.97 – 1.68]	.43	-0.45 (1.38) – -0.27 [-2.67 – 1.79]	-0.28 (1.33) – -0.02 [-2.60 – 2.02]	-0.28 (1.40) – -0.21 [-2.60 – 1.91]	.47
SA	-2.88 (6.57) – -0.39 [-25.17 – 0.50]	**-0.67 (3.95) – 0.50** **[-15.43 – 0.50]***	**0.33 (0.36) – 0.50** **[-0.39 – 0.50]***	**.00**	-0.58 (1.44) – 0.05 [-3.93 – 0.50]	-0.20 (1.44) – 0.50 [-4.81 - 50]	-0.52 (1.90) – 0.50 [-6.68 – 0.50]	.53
GCF	-0.56 (0.79) – -0.44 [-1.92 – 0.39]	**-0.20 (0.80) – -0.10** **[-1.64 – 0.91]****	**-0.12 (0.83) – 0.25** **[-1.56 – 0.99]****	**.00**	-0.38 (0.90) – 0.00 [-2.00 – 0.69]	-0.17 (0.81) – 0.10 [-1.93 – 0.75]	-0.16 (0.94) – 0.06 [-1.98 – 1.59]	.93

The change over time within each group was evaluated using Friedman's ANOVA test statistic χ_F^2 (degrees of freedom). The table shows the *p*-values (*p*) with values below .05 highlighted in bold. For the post hoc analysis the Wilcoxon's sign rank test *T* was used, and significant comparisons with respect to baseline are indicated with * for *p*-values < .05 and ** for *p*-values < .01. Abbreviations: ASCS, average standardized composite score; CG, control group; GCF, generalized cognitive functioning; EF, executive functioning; EG, experimental group; SA, spatial awareness.

Table 5.3. Between-group analysis of baseline ASCS (T0) as well as improvement in ASCS after treatment (T1 - T0) and at follow-up (T2 - T0).

ASCS	EG (n=16)	CG (n=14)	p
	Mean (SD) – Median [2.5th – 97.5th percentile]		W_s
Attention			
T0	-0.35 (0.88) – -0.28 [-2.11 – 1.22]	-0.16 (0.83) – 0.11 [-1.78 – 0.89]	.39
T1 – T0	0.22 (0.39) – 0.17 [-0.44 – 0.89]	0.17 (0.50) – 0.17 [-0.78 – 1.00]	.80
T2 – T0	0.41 (0.46) – 0.44 [-0.44 – 1.33]	0.19 (0.32) – 0.17 [-0.44 – 0.78]	.21
Memory			
T0	-0.76 (0.69) – -0.57 [-2.27 – 0.05]	-0.72 (0.82) – -0.54 [-2.38 – 0.40]	.85
T1 – T0	0.21 (0.50) – 0.23 [-0.70 – 1.22]	0.20 (0.31) – 0.10 [-0.30 – 0.76]	.82
T2 – T0	0.33 (0.65) – 0.47 [-0.73 – 1.71]	0.34 (0.51) – 0.34 [-0.47 – 1.29]	.79
EF			
T0	-0.34 (1.01) – -0.335 [-1.64 – 1.32]	-0.45 (1.38) – -0.27 [-2.67 – 1.79]	.92
T1 – T0	0.05 (0.61) – 0.04 [-1.55 – 0.96]	0.17 (0.54) – 0.17 [-0.30 – 0.76]	.57
T2 – T0	0.19 (0.62) – 0.22 [-0.85 – 1.55]	0.17 (0.56) – 0.18 [-1.25 – 1.00]	.79
SA			
T0	-2.88 (6.57) – -0.39 [-25.17 – 0.50]	-0.58 (1.44) – 0.05 [-3.93 – 0.50]	.45
T1 – T0	2.21 (6.55) – 0.88 [-6.19 – 24.78]	0.38 (1.08) – 0.00 [-0.88 – 2.65]	.24
T2 – T0	3.21 (6.57) – 0.88 [-0.88 – 25.66]	0.06 (1.95) – 0.00 [-5.31 – 2.65]	.10
GCF			
T0	-0.56 (0.79) – -0.44 [-1.92 – 0.39]	-0.38 (0.90) – 0.00 [-2.00 – 0.69]	.49
T1 – T0	0.36 (0.36) – 0.34 [-0.06 – 0.90]	0.21 (0.45) – 0.13 [-0.31 – 1.27]	.12
T2 – T0	0.44 (0.42) – 0.54 [-0.56 – 1.17]	0.22 (0.37) – 0.14 [-0.22 – 0.90]	.12

The differences at baseline and in improvement from baseline at T1 and T2 between groups were evaluated using the Wilcoxon rank-sum test Ws. The table shows the p-values (p) of the comparisons. ASCS, average standardized composite score; CG, control group; GCF, generalized cognitive functioning; EF, executive functioning; EG, experimental group; LOCF, last observation carried forward; SA, spatial awareness.

Appendix A Table A.4 shows the results for the secondary outcomes. We found a significant change over time only in MMSE for CG (χ^2_F (2) = 7.14, $p < .05$). Post hoc analysis revealed a significant difference between T0 and T2 ($T = 62.5$, $r = .72$, $p < .01$). For the EG we found that FM-UE after treatment was significant different from baseline ($T = 43$, $r = .61$, $p < .05$) and that this improvement was also significant different from the improvement of the CG ($W_s = 288.5$, $z = 2.22$, $r = .40$, $p < .05$). No other significant results in the secondary outcomes were found [see Table A.4 Appendix A].

5.3.3. Depression subgroup analysis

In Table 5.4, we report the results of the within-group analysis for the depression subgroup analysis (EGD = 11, CGD = 10). The CGD shows a significant worsening in the HAM-D at T1 ($T = 45$, $r = .72$, $p < .01$) as compared to baseline. At T1, the depression level of the CGD was significantly higher in comparison to the EGD ($W_s = 81.5$, $z = -2.76$, $r = -.60$, $p < .01$) and this difference remained significant at T2 ($W_s = 92$, $z = -2.03$, $r = -.44$, $p < .05$), see Table 5.5 and Figure 5.7 D. We observed a significant effect of time for EGD in the attention domain (χ_F^2 (2) = 10.82, $p < .01$) and in the generalized cognitive functioning domain (χ_F^2 (2) = 9.8, $p < .01$). Post hoc analysis in the attention domain revealed a significant difference between T0 and T2 ($T = 43.5$, $r = .53$, $p < .05$) and between T1 and T2 ($T = 40.5$, $r = .46$, $p < .05$). Post hoc analysis in the generalized cognitive functioning domain showed a significant difference from T0 to T1 ($T = 53$, $r = .57$, $p < .01$) and from T0 to T2 ($T = 53$, $r = .57$, $p < .01$). In addition, we found a difference between the two groups improvement at T1 in generalized cognitive functioning ($W_s = 151$, $r = .45$, $p < .05$). For CGD, no change over time was found. These results are similar to what was found in the analysis of the whole study sample. On the other hand, we could only confirm a reduced influence of the level of depression on the performance on the neuropsychological test battery. Of the eleven tests included in our battery, three correlated with the HAM-D at baseline (Corsi F: $r = -.69$, $p < .05$, TMT A: $r = .45$, $p < .05$, TMT B: $r = .47$, $p < .05$). These correlations disappeared after the treatment and at follow-up.

One patient in EGD showed a particularly large improvement of 13 points in HAM-D from T0 to T1. To check if this improvement influenced the results found, we performed the subgroup analysis without this patient. After excluding the patient, we observed that the difference between the groups at T2 loses significance as the p-value changes from .04 to .07. However, the EGD group continues to express lower depression levels at T2 (mean of 4.40) than the CGD (mean 6.30). The same patient also showed improvements in attention, memory, and spatial awareness. The exclusion of the patient in the analysis of the cognitive domains did not alter the results found, whether in the subgroup analysis nor in the analysis of the whole sample. We, therefore, did not deem this patient as an outlier that had to be excluded from the analysis.

Table 5.4. Depression subgroup analysis. HAM-D and ASCS at baseline (T0), after treatment (T1) and follow-up (T2) and the p-values for the within-group analysis of the change over time.

Measures	**EGD (n = 11)**				**CGD (n = 10)**			
	Mean (SD) – Median [2.5th – 97.5th percentile]			*p*	Mean (SD) – Median [2.5th – 97.5th percentile]			*p*
	T0	**T1**	**T2**	$\chi^2_F(2)$	**T0**	**T1**	**T2**	$\chi^2_F(2)$
HAM-D	6.64 (5.46) – 5.00 [0.00 – 15.00]	5.45 (4.89) – 3.00 [0.00 – 13.00]	4.18 (3.34) – 3.00 [0.00 – 12.00]	.22	5.20 (4.78) – 4.00 [0.00 – 13.00]	**7.8 (5.98) – 7.50** **[0.00 – 19.00]***	6.30 (6.20) – 4.00 [0.00 – 18.00]	.06
Attention	-0.27 (0.95) – -0.22 [-2.11 – 1.22]	**-0.10 (0.96) – -0.11** **[-1.67 – 0.76]***	**0.20 (0.89) – 0.11** **[-1.33 – 1.67]***	**.00**	0.01 (0.72) – 0.22 [-1.78 – 0.78]	0.03 (0.78) – 0.28 [-1.78 – 0.89]	0.10 (0.76) – 0.22 [-1.67 – 1.11]	.57
Memory	-0.65 (0.57) – -0.44 [-1.72 – 0.05]	-0.35 (0.85) – -0.09 [-1.97 – 0.76]	-0.18 (0.89) – 0.14 [-1.72 – 0.89]	.27	-0.61 (0.62) – -0.54 [-1.78 – 0.78]	-0.46 (0.62) – -0.29 [-1.78 – 0.48]	-0.36 (0.52) – -0.39 [-1.03 – 0.46]	.72
EF	-0.26 (0.88) – -0.32 [-1.64 – 1.13]	-0.34 (1.08) – -0.53 [-2.09 – 1.13]	-0.04 (0.98) – 0.09 [-1.57 – 1.57]	.11	-0.09 (0.67) – -0.11 [-1.13 – 1.13]	-0.14 (0.78) – 0.02 [-2.09 – 0.76]	-0.11 (0.81) – 0.00 [-1.90 – 1.02]	.61
SA	-1.60 (3.34) – -0.39 [-9.24 – 0.50]	-1.03 (4.78) – 0.50 [-15.43 – 0.50]	0.17 (0.45) – 0.50 [-0.39 – 0.50]	.16	-0.21 (1.43) – 0.50 [-3.93 – 0.50]	-0.21 (1.66) – 0.50 [-4.81 – 0.50]	0.05 (0.75) – 0.50 [-1.27 – 0.50]	.95
GCF	-0.41 (0.73) – -0.30 [-1.80 – 0.39]	**-0.11 (0.77) – 0.12** **[-1.64 – 0.88]****	**0.01 (0.73) – 0.24** **[-1.16 – 0.99]****	**.01**	-0.11 (0.61) – 0.06 [-1.63 – 0.53]	-0.07 (0.70) – 0.11 [-1.93 – 0.49]	0.00 (0.53) – 0.09 [-1.15 – 0.64]	.58

The change over time within each group was evaluated using Friedman's ANOVA test statistic χ^2_F (degrees of freedom). The table shows the p-values (p) with values below .05 highlighted in bold. For the post hoc analysis the Wilcoxon's sign rank test *T* was used, and significant comparisons with respect to baseline are indicated with * for p < .05 and ** for p < .01. ASCS, average standardized composite score; CGD, control group; EF, executive functioning; EGD, experimental group; GCF, generalized cognitive functioning; HAM-D, Hamilton Depression Rating Scale; SA, spatial awareness.

Table 5.5. Between-group analysis in depression subgroup of baseline HAM-D and ASCS (T0) as well as improvement in HAM-D and ASCS after treatment (T1 - T0) and follow-up (T2 - T0).

Measures	EGD (n = 11)	CGD (n = 10)	*p*
	Mean (SD) – Median [2.5th – 97.5th percentile]		W_s
HAM-D			
T0	6.64 (5.46) – 5.00 [0.00 – 15.00]	5.20 (4.78) – 4.00 [0.00 – 13.00]	.72
T1 – T0	-1.18 (2.40) – -1.00 [-5.00 – 3.00]	2.60 (2.84) – 2.50 [-1.00 – 8.00]	**.01**
T2 – T0	-2.45 (4.32) – 0.00 [-13.00 – 2.00]	1.10 (2.18) – 1.00 [-2.00 – 5.00]	**.04**
Attention			
T0	-0.27 (0.95) – -0.22 [-2.11 – 1.22]	0.01 (0.72) – 0.22 [-1.78 – 0.78]	.26
T1 – T0	0.17 (0.30) – 0.11 [-0.44 – 0.78]	0.02 (0.54) – -0.06 [-0.78 – 1.00]	.23
T2 – T0	0.47 (0.46) – 0.44 [-0.11 – 1.33]	0.08 (0.35) – 0.06 [-0.44 – 0.56]	.07
Memory			
T0	-0.65 (0.57) – -0.44 [-1.72 – 0.05]	-0.61 (0.62) – -0.54 [-1.78 – 0.78]	.92
T1 – T0	0.30 (0.53) – 0.37 [-0.54 – 1.22]	0.15 (0.30) – 0.06 [-0.30 – 0.76]	.46
T2 – T0	0.47 (0.69) – 0.58 [-0.73 – 1.71]	0.25 (0.41) – 0.34 [-0.47 – 0.90]	.31
EF			
T0	-0.26 (0.88) – -0.32 [-1.64 – 1.13]	-0.09 (0.67) – -0.11 [-1.13 – 1.13]	.78
T1 – T0	-0.08 (0.59) – -0.03 [-1.55 – 0.85]	-0.04 (0.47) – -0.02 [-0.96 – 0.59]	.92
T2 – T0	0.22 (0.51) – 0.22 [-0.85 – 1.18]	-0.01 (0.53) – 0.00 [-1.25 – 0.70]	.40
SA			
T0	-1.60 (3.34) – -0.39 [-9.24 – 0.50]	-0.21 (1.43) – 0.50 [-3.93 – 0.50]	.29
T1 – T0	0.56 (3.15) – 0.00 [-6.19 – 7.08]	0.00 (0.83) – 0.00 (-0.88 – 1.77)	.27
T2 – T0	1.77 (3.29) – 0.00 [-0.88 – 9.73]	0.27 (1.25) – 0.00 [-1.77 – 2.65]	.35
GCF			
T0	-0.41 (0.73) – -0.30 [-1.80 – 0.39]	-0.11 (0.61) – 0.06 [-1.63 – 0.53]	.31
T1 – T0	0.29 (0.30) – 0.30 [-0.02 – 0.90]	0.04 (0.37) – -0.08 [-0.31 – 0.76]	**.04**
T2 – T0	0.42 (0.38) – 0.42 [-0.26 – 1.17]	0.11 (0.30) – 0.04 [-0.22 – 0.68]	.07

The differences at baseline and in improvement from baseline at T1 and T2 between depression subgroup were evaluated using the Wilcoxon rank-sum test W_s. The table shows the p-values (p) of the comparisons with values below .05 highlighted in bold. Abbreviations: ASCS, average standardized composite score; CGD, control group in depression subgroup; EF, executive functioning; EGD, experimental group in depression subgroup; GCF, generalized cognitive functioning; HAM-D, Hamilton Depression Rating Scale; SA, spatial awareness.

Next, we wanted to see how the improvement in the cognitive domains influenced the improvement in depression level in our subgroup. We included the improvements in ASCS at T1 (T1 – T0) and T2 (T2 – T0) in a linear regression to estimate the respective depression improvement (Table 5.6). We found a marginally significant prediction power of improvement in attention ASCS ($t(17) = -1.99$, $p = .06$) and a significant effect of improvement in memory ASCS ($t(17) = -2.35$, $p < .05$) to predict the patient's change in

HAM-D from baseline to follow-up. These results indicate that improvement in the domains of attention and memory is positively correlated with improvement in depression.

Table 5.6. Results from a linear regression on improvement in depression. The table provides the estimates (standard error) and the p-value (degrees of freedom) with values below .05 highlighted in bold

	Estimate (standard error)	p-value (df)
Attention		
(Intercept)	-0.36 (1.07)	0.74 (17)
Coefficient	3.93 (1.98)	**0.06 (17)**
Memory		
(Intercept)	-0.31 (0.98)	0.75 (17)
Coefficient	3.33 (1.42)	**0.03 (17)**

5.4. Discussion

In this randomized controlled pilot trial, we tested a novel rehabilitation program in RGS that trains several cognitive domains in conjunction. Together with a few other clinical trials (Faria et al., 2016, 2018), we are among the first in addressing the multidimensionality of cognitive impairment after stroke, by providing a VR-based cognitive training that adapts its difficulty optimally to the ability of the patient while providing an embodied training with rewarding feedback (Perez-Marcos et al., 2018). Our data set reveals interesting insights when a heterogeneous sample without a specific cognitive deficit is selected. Similar to prospective studies (Leśniak et al., 2008; Sascha M.C. Rasquin et al., 2004), we see that patients show an impairment in more than one domain. The majority was impaired in all four domains. Also, the impairments in the attention, memory, and executive function domain, but not in the spatial awareness domain, are correlated and remain so over time. The rationale behind the training scenarios is that several cognitive skills can be trained together in a multidomain fashion. With the Star Constellations scenario, we intended to address visuospatial working memory and attentional skills. The correlations between the median task parameters achieved after the first week of training and the scores of the neuropsychological test battery at baseline appears to confirm this intention: TMT A, TMT B, and WAIS C are timed and require online visual tracking ability (Pena-Casanova et al., 2009; Vazzana et al., 2010), whereas Corsi F, Corsi B, and WAIS B require working memory skills (Kessels, van den Berg, Ruis, & Brands, 2008; R. S. C. Lee, Hermens, Porter, & Redoblado-Hodge, 2012), which in the case of Corsi are paired with a visual component (Pena-Casanova et al., 2009). Besides, we found a correlation of the median constellation complexity level with WAIS C, a test that requires fast decoding of number-symbol combinations (Pena-Casanova et al., 2009). With the Quality Controller scenario, we intended to provide a speeded and distributed dual-task training. The correlations of four task parameters with TMT A and TMT B confirms a strong speed-of-processing and attentional switching component (R. S. C. Lee et al., 2012), whereas the correlation with Star refers to the visual components trained due to the spatially distributed task. The correlations between the timed task components (baking and taking out time) and the tests of the executive function domain supports the training of inhibition and initiation of responses (Chung et al., 2013) whereas the correlations with Corsi F, RAVLT I and WAIS B point additionally to a memory component inherent to the training (Kessels, van Zandvoort, Postma, Kappelle, & de Haan, 2000; R. S. C. Lee et al., 2012; van Zandvoort et al., 2005). We further demonstrated that our system successfully takes the individual impairment level into account and enables the patients to achieve similar success rates despite varying levels of impairment. The difference in the performance achieved between the two scenarios, especially by the non-impaired patients, might be due to a difference in difficulty between subsequent levels; i.e., in the Quality Controller scenario, the next difficulty level was too hard to achieve, so the patients remained on a lower level thus achieving higher success rates. This illustrates the importance of individualizing training through fine-graded difficulty levels to promote learning and rehabilitation but as well highlights the challenges of doing so (Cameirao et al., 2010; M. F. Levin et al., 2015).

Regarding the four cognitive domains assessed, only the EG shows a significant change over time in attention and spatial awareness. We did not see any significant change in the ASCS over time in the CG, who did cognitive pencil and paper exercises at home. In addition, generalized cognitive functioning increased in EG from baseline to follow-up. We are aware that due to the small sample size in this pilot study and the multiple testing, these results could be spurious, and we can therefore not claim any rehabilitation effect. However, the effect found in generalized cognitive functioning seems to be robust because it includes all ASCS and cannot be driven by the improvement in attention alone. Further, a positive change of attention ASCS and generalized cognitive functioning is still present in the depression subgroup analysis. Interestingly the significant changes in EG were confirmed for the follow-up period, as demonstrated by the post hoc analysis at this time point. We could speculate that this delayed effect of training could mean that the patient incorporated what they learned during the training later in their daily activities, similar to what has been observed in cognitive strategy training (McEwen et al., 2015).

Whether the significant changes in attention and spatial awareness ASCS are clinically relevant is difficult to evaluate, as there is no consensus in literature with regards to the clinically important difference (CID) in neuropsychological test batteries. CIDs reported in studies range from 0.5 SD (Wolinsky et al., 2006) to 1 SD (Dujardin, Defebvre, Krystkowiak, Blond, & Destée, 2001) up to 2 SD (Desmond et al., 1996). Applying a cut-off of 0.5 SD and 1 SD to our sample [see Appendix A Table A.5 and Table A.6] shows that still more patients in EG improve even above 1 SD from baseline, especially after follow-up. However, future studies should direct their efforts to find ways to standardize neuropsychological testing and establishing CIDs in well-powered clinical studies.

Regarding the secondary outcomes, the CG showed a significant change in the MMSE over time, with post hoc analysis revealing a significant difference between baseline and follow-up [see Appendix A Table A.4]. On the other hand, no change over time was observed in the MoCA for either group. Interestingly, according to MMSE, only one patient would have been classified as having a cognitive impairment at baseline. This finding is in line with literature, where it was observed that the MoCA is more sensitive to cognitive dysfunction than the MMSE (Pendlebury, Mariz, Bull, Mehta, & Rothwell, 2012). Also, we used at each assessment point a different test variation of the MoCA, so that the patients never repeated the same exercises. The MMSE, however, is only available in one version, and some exercises resemble the cognitive pencil and paper exercises used in the CG, which might have helped them to succeed in this test.

We further found a significant but small group difference in the FM-UE improvement after treatment in favour of the EG. Although the experimental intervention includes a stronger motor component than the control intervention, motor training was not the focus of the study. Therefore, only patients with sufficient active movement and able to overcome gravity (MRC > 2) were included, although the tasks were accomplished by moving the arms only horizontally supported by a table's surface. Also, the mean change is below the CID (Page et al., 2012) and MDC (Hsueh et al., 2008), although four patients surpassed the CID threshold of 4.25 [see Appendix A Figure A.1] at follow-up. However, in a general stroke population, motor and cognitive deficits likely co-occur (Corbetta et al., 2015), and cognitive deficits have a negative effect on functional outcome and independence (Paolucci et al., 1996). It has been stressed out that rehabilitation should combine motor and cognitive training (Perez-Marcos et al., 2018). It would, therefore, be interesting to investigate the effect of the proposed training paradigm that already includes a motor component in patients with lower motor functionality. We believe that patients with more severe motor impairments could easily participate in the ACCT program since no movement against gravity is required, and the adaptive difficulty algorithm could ensure that the arrangement of the interactive elements in the training scenarios does not surpass the patient's active range of motion. Besides, the ACCT program could be complemented the goal-oriented movement amplification presented in Chapter 4.

Lastly, the subgroup analysis revealed that, compared to the EG, the CG expressed higher depression levels after the intervention. The groups remained significantly different at follow-up. We cannot exclude that the non-blinding of group allocation or that the control task that had to be done at home negatively influenced the depression level in the CG. However, we also see a trend for EG to reduce their depression level. This could be due to the alleviation of rumination, a known symptom of depression, which has been proposed by the attention restoration theory to occur when a patient successfully breaks away from routine physical and mental tasks and switches from effortful, directed attention to an interest-driven form of attention – both of which can be achieved by providing an adequate environment that is stimuli rich, coherently structured and allows for exploration (Gonzalez et al., 2009). The ACCT intervention in the hospital might provide such an environment, whereas the paper and pencil intervention at home does not. The subgroup analysis also replicated the sample's improvement over time in attention ASCS of the complete case analysis. Improvement in attention and memory ASCS predicted depression improvement at follow-up; the more patients improved in attention and memory ASCS, the more they improved in depression. Notice, however, that the directionality of this relationship remains unclear. However, the intercept indicates that there seems to be a negative improvement in depression if no improvement in attention or memory is present. It is known that depression correlates with cognitive deficits, specifically in nonverbal problem solving, verbal and visual memory and attention, and psychomotor speed (Kauhanen et al., 1999). We will explore this link further in Chapter 8. Potentially the improvement in attention or memory through training resulted also in a reduction of depression levels in our sample. Alternatively, the training induced a change in mood, which resulted in cognitive improvement. This subgroup analysis is particularly interesting because, according to our exclusion criteria, patients with mental illness should not have passed the screening process. This result underlines the notion that mental problems often remain undiagnosed or are neglected when assessing the health status of the patient, despite the known impact of depressive mood on cognitive ability, independence, impairment, and handicap (Kauhanen et al., 1999).

There are several limitations to this study. Firstly, this pilot comprises of a small sample size. More patients would be necessary to confirm the indicated results with adequate power. Also, a larger sample is necessary to check if specific cognitive aspects of the training scenarios influence groups of patients with similar deficit profiles differently. However, the number of neuropsychological tests performed was excessive for the sample size tested. Further, we are aware that the experimental intervention appears to be substantially different from the control intervention in terms of location (hospital versus home) and human interaction (therapist versus, possibly, caregiver). Although a control intervention in the hospital would appear appropriate on methodological grounds, our control condition represents the reality of community-dwelling stroke patients and is, therefore, closer to the “best available” treatment (Cicerone et al., 2000). Besides, the EG did not receive more attention from a therapist than the CG. The patients at the hospital were independently completing their daily tasks, only receiving technical support from the therapist when needed and no performance feedback. However, it cannot be excluded that the different locations might have exposed the patients in the EG to a richer environment and influenced our results. Hence future studies should test for the potential effect of location on cognition or depression and take it into account when designing their protocols. Further, we were not able to blind the patients and could only partly blind the outcome assessor. This is, unfortunately, a problem frequently encountered in studies evaluating VR-interventions. Nevertheless, we believe that our results support the growing evidence that recovery of cognitive functioning after stroke is possible. Since we were able to train stroke survivors with heterogeneity in cognitive impairment, it fuels the hope that rehabilitation approaches in VR that are grounded on neuroscientific principles of recovery could potentially address co-occurring symptoms even independent of disease or aetiology (Borsboom & Cramer, 2013). Future work should, therefore, test the proposed training paradigm in other patient groups with similar cognitive symptomatology.

In this chapter we have shown that the stroke rehabilitation approach, called ACCT, was able to adapt the training to the individual cognitive deficit of the patients, and initial results indicated that the training reduced the impairment in two out of four cognitive domains. In addition, a positive change in the mental wellbeing of the patients was observed. This work, therefore, highlights the importance of addressing cognitive domains in conjunction as well as considering the psychological sequelae after a stroke incident. We will take this though one step further and will explore in the next Chapter the psychosocial consequences after stroke.

Chapter 6

A SOCIAL INTEGRATION OF STROKE PATIENTS THROUGH THE MULTIPLAYER REHABILITATION GAMING SYSTEM

This chapter is based on:

Maier, M., Ballester, B. R., Duarte Oller, E., Duff, A., & Verschure, P. F. M. J. (2014). Social integration of stroke patients through the multiplayer rehabilitation gaming system. In *Games for Training, Education, Health and Sports, 4th International Conference on Serious Games, GameDays 2014, Darmstadt, Germany.*

How can we use principle-based technology to incorporate social interaction? As we have discovered in the previous chapters, physical and cognitive recovery can by influenced by psychological factors. The level of self-efficacy is an essential psychological construct in this regard – whereas high levels might support recovery, low levels are associated with depressive symptoms that impede improvement. Importantly self-efficacy is influenced as well by the appraisal of others. As caregivers can have limiting beliefs about the patient, it might help to include them directly into the augmented visuomotor feedback training of the patient. In this chapter we explore the hypothesis that the exploitation of the principle of social interaction within the training has a positive impact on the self-efficacy of the patient and the psychosocial dynamics between patient and their social environment. For this reason, we developed a multiplayer training scenario within the RGS framework and use the goal-oriented movement amplification presented in Chapter 4 to level out performance differences between the players that might arise because of physical disabilities. We first conduct a psychosocial study to understand the social environment of the patient better. We then evaluate the method in a laboratory setting. Lastly, we perform an at-home intervention with two patients and their main informal caregivers. The preliminary results suggest that the method can equalize performance differences and show promising effects on self- and social perception. These positive outcomes are encouraging, not only from a clinical perspective but as well from a practical one: the ability to include social interaction into the recovery process through the virtual world opens great opportunities for long-term care in community-dwelling stroke patients.

6.1. Background

Stroke leaves survivors mostly with serious long-term impairments that reduce the ability to act, communicate and perform activities of daily living. These physical disabilities also affect the relation and interaction patients have with their social environment (B. Han & Haley, 1999). On the other hand, the social environment of the patient plays an important amplifying role in the rehabilitation process (Pellerin et al., 2011). Modern rehabilitation attempts should therefore not only focus on physical recovery but also address psychological consequences like social isolation or lower contentment with life. Virtual reality (VR) environments are powerful tools to address challenges that could not be solved with previous technologies and methods (Jack et al., 2001; Sandlund, McDonough, & Häger-Ross, 2009; P. F. M. J. Verschure, 2011). Present virtual rehabilitation programs and serious games however seem to focus often on regaining the patient's motor function only and neglect other implications related to the social interaction with the environment. In this study we explore the potential of a RGS to incorporate the social dynamics into the rehabilitation process (Cameirao et al., 2010). We use the goal-oriented movement amplification that was presented in Chapter 4 to diminish the differences in motor performance between a disabled and a healthy player. Incorporated into a multiplayer training scenario we aim to positively influence the social interaction between stroke patients and their informal caregivers and change their mutual perception.

6.1.1. Importance and role of social environment in stroke rehabilitation

Since stroke patients are left with physical and cognitive impairments, they face radical changes in the performance of daily activities and their social roles. These so-called life habits or Activities of Daily Living (ADL) ensure the person's wellbeing in society and depend on the social environment the person is in (Di Loreto, Van Dokkum, Gouaich, & Laffont, 2011). After an acquired brain injury like a stroke the social environment needs to undergo a structural change and redistribute the social roles (Ryan, Wade, Nice, Shenefelt, & Shepard, 1996). As post-stroke rehabilitation techniques have improved over the past years and the pressure to reduce public health costs has increased, more patients return home earlier, forcing families to provide follow-up care at home (Ryan et al., 1996). Therefore, therapists prescribe home exercises as part of the outpatient therapy. Unfortunately, patients often do not accomplish these home exercises due to lack of motivation and supervision. It is therefore necessary to find new strategies for encouraging and motivating patients to keep on training at home (Alankus, Proffitt, Kelleher, & Engsberg, 2011). The importance of the patients' relatives in the recovery process needs therefore to be considered in rehabilitation (Pellerin et al., 2011; Ryan et al., 1996). A successful rehabilitation is the result of a close interaction between the patient gaining competence in ADL, their abilities, and the social and physical aspects of the environment. Hence, rehabilitation should assist patients in optimizing the use of their physical, mental, and social abilities, in relation to their daily environment (Lilja et al., 2003).

6.1.2. VR-Based multiplayer environments for rehabilitation

How can the advantages of VR-systems and the need for social interaction in rehabilitation be combined? Studies have shown that playing interactive games may not only lead to improvements in movement quality and mobility but also to a higher motivation, self-efficacy and feeling of social acceptance (Sandlund et al., 2009). Multiplayer games in particular offer a shared experience, collaboration possibilities and the reward of being socialized into a community of players (Ducheneaut, Yee, Nickell, & Moore, 2006). These games are especially beneficial for physically disabled individuals as limited mobility causes a lack of social interaction possibilities. They help to form new bonds and bridges by providing social interaction in the virtual space (Trepte, Reinecke, & Juechems, 2012). So far RGS covers only individual physical training of impaired motor functions. By implementing a multiplayer game, we explore if such a VR-system can assist patient in overcoming social barriers despite their physical limitations. Through augmenting the goal-directed movements of the paretic limb we can diminish the motor disabilities of the patients, enabling them to compete on equal levels with healthy individuals. Besides lifting their self-efficacy and changing the perception of their own abilities, we assume to influence the valuation that the social environment has of them. To validate and test our hypothesis we analysed the social environment of patients, evaluated the system with healthy subjects and ultimately conducted two at home experiments with patients and their informal caregivers.

6.2. Methods

6.2.1. Training scenario

The aim of this study was to explore the potential of the goal-oriented movement amplification in RGS to enable a patient and a healthy subject to interact in a multiplayer environment and thus to enhance social functioning and acceptance. For this purpose, we designed and developed a training scenario that resembles the popular two-player air puck or air hockey game. Optimal performance in this task requires speed and precision, two attributes that are also requested in many rehabilitation tasks. The goal of the task is to hit with the hand a puck over a playing field towards the other player. Whenever a player fails to hit the puck back, the opponent player wins a point, and a new puck is spawned. The puck only moves on the horizontal plane over the playing field (maximal range of x-offset: 1.15 m). In addition, players are awarded with extra points when hitting any of the bonus boxes appearing in random locations on the playing field (Figure 6.1).

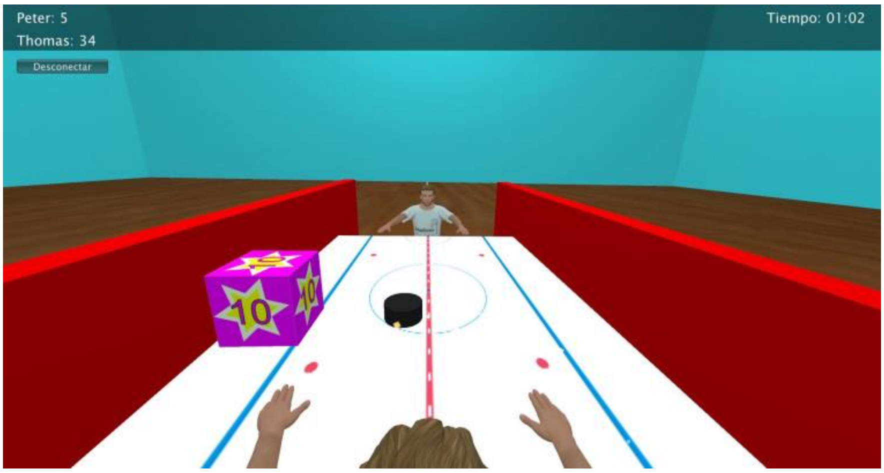


Figure 6.1. Picture of the two-player multiplayer training scenario in RGS called Air Hockey. Two players facing each other and tossing a puck with the movement of their limbs over the playing field. The pink bonus box, which appears at random moments and locations in the game, offers 10 extra points to the player.

The goal-oriented movement amplification applied to the players virtual limbs facilitates the accomplishment of the task. The system adapts to the individual capabilities of the patients and learns how much aid the users' movements need in order to achieve the task, thus allowing the patients to perform movements in the virtual environment they otherwise might not be able to achieve. By enhancing their performance, we aim to provide the patients with a better match between intended action and observed result. The amplification is relative to the current position of a given target, which in this case is the air puck. As described in Section 4.2.5 the value of the gain applied to the movement of the limbs is the inverse of the reach ratio. The reach ratio is calculated by dividing the vector of the user's real movement towards the target by the vector of the starting position of that movement to the target. The reach ratio sets the modification of the virtual arm for the next arriving target, resp. puck. The gain is then applied to the movement vector as well as to its projection on the vector from the start position to the target position. The interpolation between these two vectors results in the angle of the modulated virtual arm position. The higher the reach ratio, the closer the modulated virtual arm movement is to the real arm movement respectively the less gain and steering are applied. Before the angles are finally applied to the visible virtual arms, they are weighted by blending 80 % of the modified mapping with 20 % of the original mapping. This ensures that the mapping will never help the user too much, keeping a good balance between challenge and help. Although the virtual movements are constantly modulated, the perceived correlation of real and virtual arm movements and the sense of ownership are preserved (Nirme et al., 2011). The adaptive mapping algorithm is applied to the movement of both players.

This training scenario adds the principle of social interaction (Section 2.3.15) to the principles primarily addressed through the goal-oriented movement amplification (goal-oriented practice, action observation, implicit feedback and explicit feedback). In addition it incorporates the principles of multisensory stimulation (Section 2.3.8) by providing rich visual and auditory stimuli and variable practice (Section 2.3.6) by providing various movement requirements.

6.2.2. The set-up

For this study the clinical set-up of RGS was extended with an additional Desktop PC and a Microsoft Kinect (Figure 6.2). The two computers and their Kinects are placed back to back in the middle of large table (laboratory table, or dining table) so that both players had enough space to move their arms. The training scenario is synchronized over a local area network connection (server and client connection) between the two computers, presenting no lag between the two players. The same set-up was used at the patients' homes.

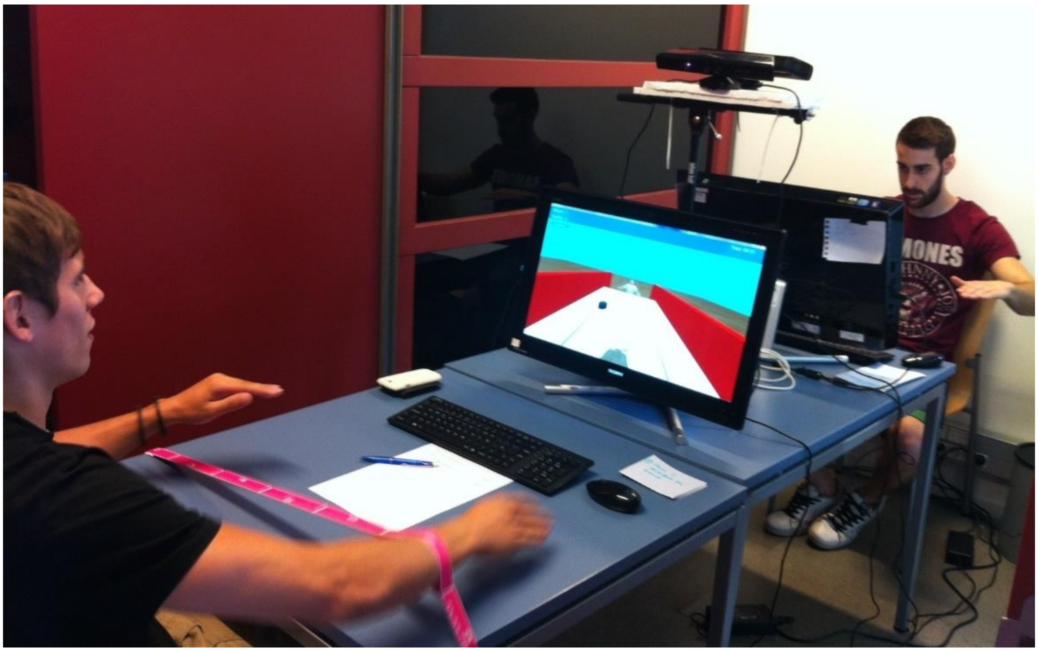


Figure 6.2. Experimental set-up in the laboratories of SPECS.
Two healthy subjects are competing against each other, whereas one subject's harm is restricted with an elastic band. Horizontal arm movements were not required by the game.

6.2.3. Subjects and experimental protocol

We first describe the psychosocial study that was performed in the clinic, then the validation experiment in the laboratory and lastly the case study experiments at two patient's home.

6.2.3.1. Psychosocial study in the clinic

We conducted a pre-study to gain a deeper insight into the relation between the patients and their social environment. Patient and informal caregiver described and evaluated their relation through two separate questionnaires. This allowed us to understand to which extent a multiplayer training scenario in RGS could be beneficial for the rehabilitation process from a psychosocial point of view. We interviewed 21 stroke patients (13 male, mean age = 56.6, SD = 14.86) recruited from the Rehabilitation Unit of Hospital de l'Esperança in Barcelona. They were selected through the occupational therapists in charge of the patient's rehabilitation. All subjects had suffered a stroke and displayed different deficits in motor function of varying levels of severity. The patients were interviewed in the hospital during their rehabilitation program. Subsequent to the interview, the patients were asked to pass the questionnaire to their closest informal caregiver. 17 informal caregivers (14 female, mean age = 52.8, years SD = 15.7) filled out the questionnaire. The first set of questions in the questionnaire was based on a previous study that analysed the psychosocial variables associated with the informal caregivers' burden of dependent older people in Spain (Garcés, Carretero, Ródenas, & Sanjosé, 2009). The second set of questions was taken from a study that elaborated the Chronic Pain Self-Efficacy Scale (CPSS) which measures chronic pain patients perceived and their self-efficacy to cope with the consequence of chronic pain (Anderson, Dowds, Pelletz, Thomas Edwards, & Peeters-Asdourian, 1995). The patients had to rate how certain they feel in performing various ADL's on a 6-point scale from very uncertain to very certain (see Table 6.1). The informal caregiver evaluated the capacities of the patient through the same questions but from their own point of view. This part was used again in the questionnaire of the at-home intervention. This enabled us to cross-validate the perception of patient and informal caregiver.

Table 6.1. Questionnaire to measure perceived capabilities in performing various ADLs. The questions were answered by patient and informal caregiver on a 6-point scale (very uncertain, moderately uncertain, slightly uncertain, slightly certain, moderately certain and very certain).

Number	Statement
S.1	How certain are you that you / the patient can continue most of your / his/her daily activities?
S.2	How certain are you that you / the patient can walk 1 km on flat ground?
S.3	How certain are you that you / the patient can lift a 4 kg box?
S.4	How certain are you that you / the patient can perform the daily at-home rehabilitation program?
S.5	How certain are you that you / the patient can perform household chores?
S.6	How certain are you that you / the patient can shop for groceries or clothes?
S.7	How certain are you that you / the patient can engage in social activities?
S.8	How certain are you that you / the patient can engage in hobbies or recreational activities?
S.9	How certain are you that you / the patient can engage in family activities?

6.2.3.2. System evaluation in the laboratory

In order to validate the goal-oriented movement amplification in the RGS Air Hockey training scenario, we tested the method on 18 healthy participants (8 females, mean age = 27.72 years, SD = 4.74). The subjects played in pairs in one session that consisted of five subsequent rounds of the game. The first round served as a training and provided baseline data. In the four following rounds the right hand of one player was constrained to the table (each player was constrained for two rounds) by using a rubber band to simulate a motor impairment, while the other player was able to move freely. The adaptive mapping was alternating switched on and off. All participants experienced four different conditions while playing (Table 6.2): constrained with adaptive mapping, non-constrained with adaptive mapping, constrained with no adaptive mapping and non-constrained with no adaptive mapping. Through this system evaluation we ensured that the goal-oriented movement amplification can level out the differences when constrained and non-constrained subjects are playing together.

Table 6.2. Condition scheme of the four applied conditions in one experimental session. All participants experienced all conditions; each player was constrained for two rounds, while the adaptive mapping was alternating switched on and off.

	Adaptive mapping	Non-adaptive mapping
Constrained	1. Condition	3. Condition
No constrain	2. Condition	4. Condition

6.2.3.3. At-home intervention with stroke patients

After the system evaluation we tested the method in a home-based intervention, as social interaction between patient and informal caregiver mainly takes place through the daily activities at home. Out of the subjects that took part in the psychosocial study, two patients (PL, PJ) and their respective informal caregivers (CP, CA) were randomly selected by an occupational therapist. The patients were two male subjects (age 61 and 66). The informal caregiver was in both cases their spouse (age 60 and 65). In the case of one patient and caregiver pair (PJ and CA), the daughter (CS) participated in one experimental session instead of the caregiver. In order to conduct the experiment, the RGS system was stationary set up at the subjects' home. Over three subsequent days, patient and informal caregiver participated in three gaming sessions. In each gaming session the subjects were asked to play two rounds of three minutes each, but they had the opportunity to play more if they liked to. The limited intervention period was due to time constraints from patient's side. After each session we passed both subjects a questionnaire to detect changes in the mutual perception between patient and informal caregiver. The questionnaire was the same set of questions used in the psychosocial study related to the Chronic Pain Self-Efficacy Scale (CPSS), and the Perceived Competence Scale (PCS). Besides the qualitative assessment we measured the physical activity and performance of the patient during the gaming sessions.

6.3. Results

6.3.1. Psychosocial study

The psychosocial provided us with new insights about the structure of the social environment of the patient. Most patients that took part in the study live together with their partner and other family members. Therefore, the informal caregiver was in almost 60% of the cases the spouse. Most patients reported to stay in a frequent contact with friends, followed by the family. Only 5 % stated that they do not have contact with people outside of the caregiving situation. In most of the cases the patients receive visits from other people, or they keep up with their social network over the telephone or through letters. Only a few patients are going out to meet people. The lack of out-of-home social contact could be related to the limited mobility that most stroke patients face due to motor impairments. Further we compared the rating that patient and informal caregiver gave on the patients' perceived capabilities in performing ADLs (Figure 6.3 and Table 6.1). Since not all informal caregivers completed the questionnaire, the statistical analysis included data from only 34 subjects (17 patients and the response of their informal caregivers). In general, patients rated their capabilities higher than the informal caregiver (Figure 6.3). Except for the rating pair regarding the rehabilitation at home (S.4), all ratings did not differ significantly between patient and informal caregiver (Mann-Whitney test). The patients' rating (median = 5) on the ability to perform the prescribed daily rehabilitation program at home was significantly higher than the rating of the informal caregiver (median = 4, $U = 60.00$, $z = -2.99$, $p < .05$, $r = -.51$).

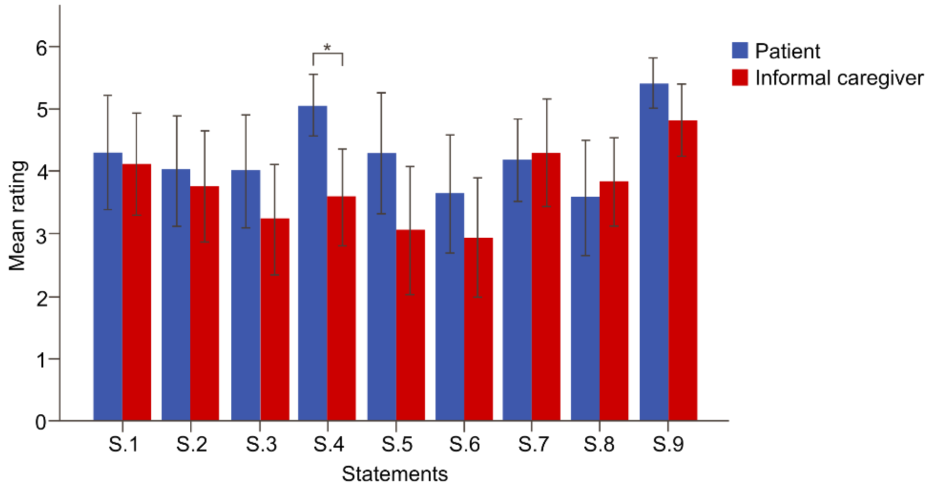


Figure 6.3. Results of the questionnaire regarding the capacities of the patient, as perceived by patient and caregiver.
Comparison between the patients self-rating and the rating of the informal caregiver on the perceived secureness of the patients' ability to perform various ADLs. Error bars indicate 95% confidence interval.

6.3.2. System evaluation

In order to test the efficacy of the system to level out differences between a handicapped (constrained right hand) and a healthy player (non-constrained) we analysed the 4 different conditions (Table 6.2). We compared the distance covered with the real non-modulated hand to the distance covered by the virtual modulated hand, augmented by the goal-oriented movement amplification (condition 1 and condition 2). As shown in Figure 6.4. Comparison of right-hand movement during movement amplification. the right constrained real hand in condition 1 covered significant less distance than the right non-constrained real hand in condition 2 (paired samples t-test, p < .05). The goal-oriented movement amplification is overcoming this handicap and converts the movement effectively in the virtually augmented right hand. There was no significant difference in the distance covered between the constrained augmented hand of condition 1 and the non-constrained augmented hand of condition 2 (ns). The distance covered by the left hand (augmented and real hand) shows no significant difference (ns) in both conditions, which suggests that the adaptive mapping is not affecting the non-impaired movement. Regarding the score there is no significant difference (repeated-measures ANOVA test, ns) between the points made in condition 1 (mean [SD] = 8.75 [5.604]) and in condition 2 (mean [SD] = 6.81 [4.415]). All distances were significantly normal (Kolmogorov-Smirnov test, D(18), ns).

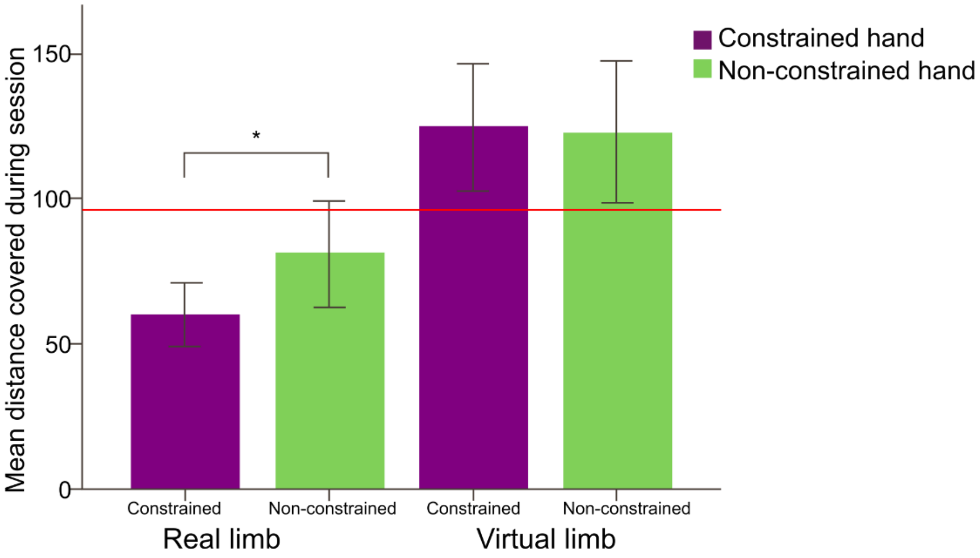


Figure 6.4. Comparison of right-hand movement during movement amplification. Comparison of mean distances covered with the right hand (real and augmented virtual arm), when the hand was constrained (purple) and when no constraint was applied (green) while the movement amplification was applied. The red line marks the grand mean of the movement of left and right hand gained in the test round (baseline). Error bars indicate 95% confidence interval.

6.3.3. At-home intervention

In order to test the system in a real social context, two at-home experiments with patients and their informal caregiver were conducted. Although the subjects were asked to play only two rounds each session, they all wanted to play more. In total both case study groups played 21 gaming rounds with a total of 63 minutes (3 minutes per game round). In the end both groups played 75 % more than they were requested.

In order to see how the game affects the patient's motor behaviour we analysed the interquartile range of movement (ROM) of both patients' hands in the horizontal axis (x-axis). This range strongly depends on the ability of the user to perform shoulder adduction/abduction movements. Results suggest that the interquartile ROM in the horizontal axis was higher for the patients' non-paretic limbs (mean [SD] = 0.184 [0.081], p = .063, Wilcoxon rank-sum test) compared to their paretic limbs (mean [SD] = 0.138 [0.096]). This difference disappeared when analysing the virtual limbs' amplified movement (p = .4812, Wilcoxon rank-sum test). In addition, we found significant differences between the interquartile horizontal ROM of the patients' paretic limbs (mean [SD] = 0.138 [0.096]) and the amplified paretic limbs (mean [SD] = 0.217 [0.1545], $p <$ .001, Wilcoxon rank- sum test). These differences demonstrate the effect of the goal-oriented movement amplification to overcome the patients reduced ROM with the paretic limb. Further, we compared the patients' performance with the caregiver's performance along all rounds by counting the number of pucks they failed to hit back. A Wilcoxon rank-sum test revealed no significant differences between groups in the number of missed pucks (p = .4215). This result was confirmed by comparing the number of scores achieved by each group (Figure 6.5 and Figure 6.7). We will now explain the detailed results for each patient and caregiver group.

6.3.3.1. Case Study Group PL and CP

This group played nine rounds in total, in which the patient was more successful in gaining points than the informal caregiver (Figure 6.5). The patient won five out of nine rounds. The patient's average score was 53.89 (SD = 16.16), while his informal caregivers' average score was 40.78 (SD = 17.39).

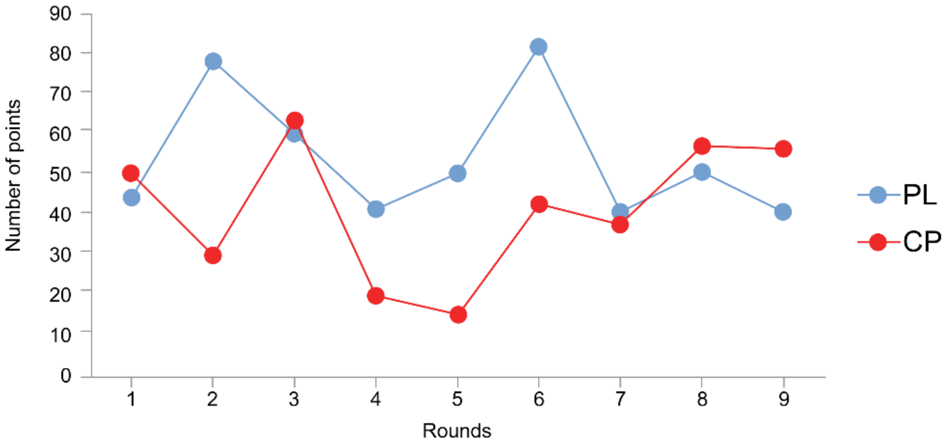


Figure 6.5. Number of points won by round (PL and CP).
PL: patient and CP: informal caregiver.

In order so see if these gaming sessions had any impact on mutual perception, we analysed results from the questionnaire and compared the ratings of patient and informal caregiver (Figure 6.6). Statement 2, 6 and 8 were rated higher by both, the patient and the informal caregiver.

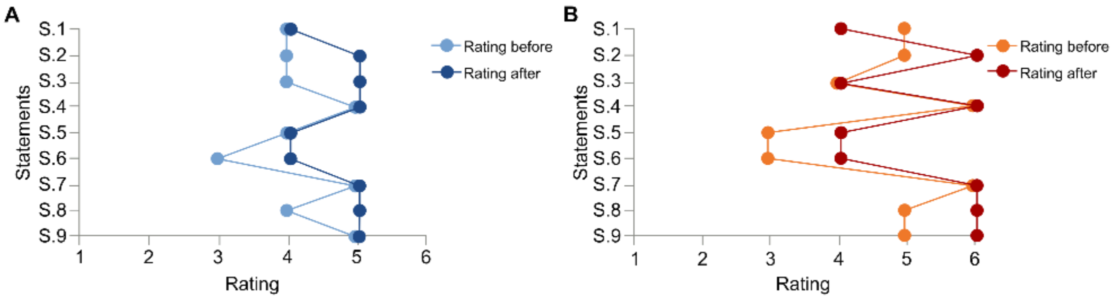


Figure 6.6. Comparison of ratings for ADL-statements (PL and CP).
A) ratings of patient PL, B) ratings of informal caregiver CP, before and after the at-home intervention.

6.3.3.2. Case Study Group PJ and CA

Patient PJ was less successful in gaining points and rounds than his informal caregiver (CA), respectively his daughter (CS), who played in the second session with him (Figure 6.7). Out of the 12 rounds two were won by the patient. The average number of points he made were 39.67 (SD = 12.61), CA average points were 50.14 (SD = 11.54) and the average points made by CS were 51.8 (SD = 11.01).

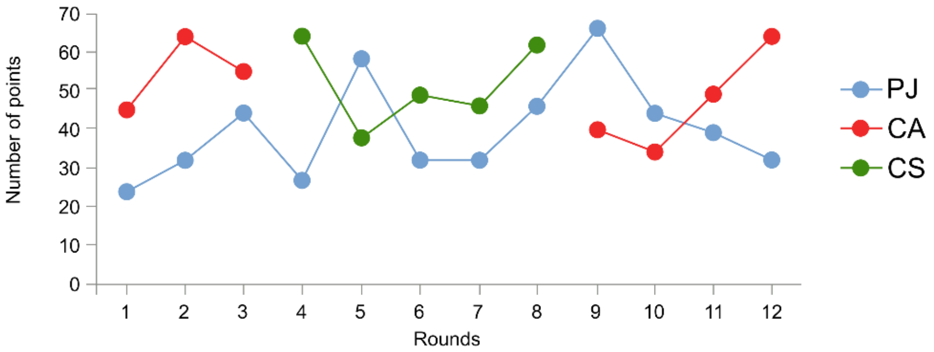


Figure 6.7. Number of points won by round (PJ, CA and CS).
PJ: patient, CA/CS: informal caregivers.

Also, in this group we compared the ratings of patient and informal caregiver before and after the at-home intervention (Figure 6.8). Statement 4, 7 and 8 were rated higher by both, the patient and the informal caregiver. Especially the 2-point increase in the rating of social interaction by the caregiver is of interest.

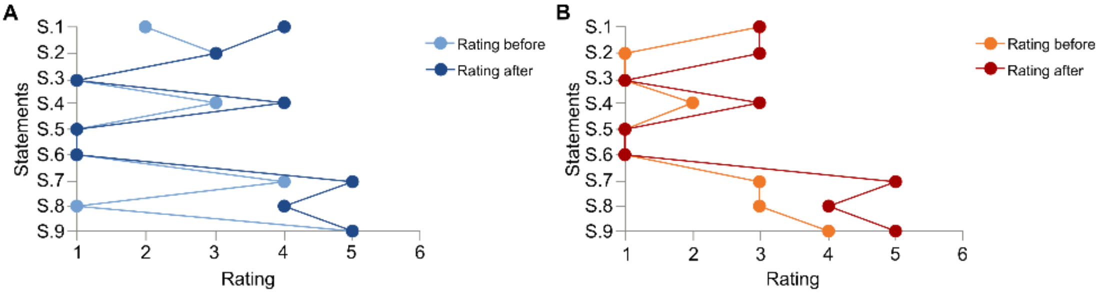


Figure 6.8. Comparison of ratings for ADL-statements (PJ and CA).
A) ratings of patient PJ, B) ratings of informal caregiver CA, before and after the at-home intervention.

6.4. Discussion

Combining virtual reality with social interaction through a multiplayer game can lead to new ways to mobilize the social environment during the rehabilitation process and to assist the patient to find their new role in their social network. The RGS Air Hockey training scenario allows patients and their social environment to interact in a playful way and to experience a new common ground for equal social interaction. We hypothesized that this will ultimately lead to a changed mutual perception of capabilities.

The results from both, the system evaluation and the at-home experiments, suggest that the goal-oriented movement amplification can level out performance differences between two players. The system successfully overcomes the difference in moving distance and range between an impaired / restricted and a healthy / non-restricted limb. This influences the outcome of the game insofar that the physical status of the player (healthy caregiver or impaired patient) does not determine who will win or lose the game. Moreover, the training scenario and the interaction appears to be entertaining since both at-home groups were willing to play more rounds than they were requested.

When looking at the ratings in the questionnaire in the at-home experiments, we see that overall the ratings appear to be lower before the sessions than after. However, the changes vary from group and participant (patient or caregiver). Nevertheless, two interesting overall observations can be made. First, the only statement that was consistently higher, was the one regarding the ability to engage in hobbies and recreational activities (S.8). Both patients rated their ability in this dimension higher after the session, and this was shared with both caregivers. In addition, both caregivers rated the statement regarding the ability of the patient to engage in family activities (S.9) higher after the sessions. Both statements are associated with specific pleasurable and social activities, in contrast to the other statements that are more related to physical abilities and of which at least one was always rated higher as well. This might be an indication that the perception of the social role of the patient in the interaction was changed. Also, that both patients rated various statements higher after the intervention (PL: 4, PJ: 5), might indicate that the interaction, which provided them with an augmented visuomotor feedback about their physical performance, gave them a small “boost” in self-efficacy.

The analysis of the patients’ social situation revealed many aspects in favour of a multiplayer training scenario. Most patients are embedded into a social network of family and friends. Only a few patients live alone and/or have no frequent contact to other people. Since their disabilities limits the mobility, our system would enable the patients to interact with their social network at home or even online. Extending the multiplayer training into the online world, could also allow socially isolated patients to interact, possibly with other patients in the same situation. In our psychosocial study we found a slight discrepancy in the ratings regarding the patient’s ability to perform ADL, although not at a statistically significant level. The patients show a tendency to rate most of their own abilities higher than the informal caregiver. The same trend can be observed in the results from the at-home experiments where both the patients’ and the caregivers’ reported higher ratings after the gaming sessions.

Our findings suggest that a multiplayer training scenario could be beneficial in addressing the requirements of modern stroke care with an emphasis on an integrated motor, psychological and social approach that could be provided in the long-term. As outpatient therapy will become more important and the involvement of the patient’s social environment increases, these kinds of technology-based rehabilitation systems like RGS support the reintegration process, ensuring a sustainable rehabilitation approach in the service of enhancing quality of life. Moreover, we believe that further investigation based on our results will shed light on the psychosocial changes stroke patients face and helping to better understand the impact of self-efficacy and social appraisal beyond the motor impairment.

This study evaluated the influence of including social interaction into RGS. We have shown that the system successfully equalizes the performance differences between a healthy and a disabled player influencing self- and social perception. First observations in this direction could be seen in the change of ratings before and after the at-home interventions. Moreover, the game-like scenario of RGS Air Hockey might provide an entertaining and motivating way to socially interact, as evidenced by the willingness to accomplish more rounds than requested. Given the small sample, especially in the case of the at-home experiments, these preliminary results serve as an initial case study, that shows a trend towards the outlined proposal. Nevertheless, we believe that the multiplayer training in RGS is a valuable tool for further investigation of our claims and for assessing its impact on future stroke recovery.

In the last part we will cover how the data obtained from the interventions presented in the current part can be used to gain a more complete picture about the underlying deficits.

Part IV

VR-based Approaches for Diagnostics

Chapter 7

VIRTUAL REALITY REHABILITATION FOR PATIENTS WITH SPATIAL NEGLECT: A CASE STUDY

This chapter is based on:
Maier, M., Ballester, B. R., San Segundo Mozo, R. M., Duff, A., & Verschure, P. F. M. J. (2015). Virtual reality rehabilitation for patients with spatial neglect. A case study. *Proceedings of the International Conference on Recent Advances in Neurorehabilitation 2015, Valencia, Spain*

What can we learn about spatial neglect from applying principle-based technology? In this chapter we take a closer look at the data that was obtained in Chapter 4, which investigated the use of the goal-oriented movement amplification for counteracting learned non-use. We analyse the case study of one patient that was diagnosed with spatial neglect while participating in the study. This highlights the difficulty of diagnosing spatial neglect; many patients are not aware of their impairment or are able to compensate well, so that the standard screening process yield often unreliable results. We analysed the patient’s performance in the real-world evaluation task and compare it to the performance of a non-neglect patient, before and after the intervention. As the stimuli in the real-world task are not static, the patients cannot compensate by using scanning strategies. The visualisation of the probability to reach for targets in this task shows to interesting features: On the one hand, we are able to identify the neglected area at the beginning of the intervention, and on the other hand, we can observe a change in that neglected area after the intervention. These preliminary results might give an indication that this task could serve as an unbiased diagnostic tool, and that the augmented visuomotor feedback was beneficial to counteract the neglect.

7.1. Background

After brain lesions some patients show a reduced response to stimuli contra lateral to the lesion due to spatial neglect, in some cases without sensory loss (Parton, Malhotra, & Husain, 2004). As the condition is not well understood and some patients are not aware of their impairment, diagnostics is difficult and successful therapies are sparse. Here we investigate the possibility to use RGS for spatial neglect diagnostics and rehabilitation. We hypothesize that by encouraging to explore the neglected side with the paretic arm during training, the perception of the neglected area would be restored in an action oriented bottom-up approach (Barrett et al., 2006). By analysing two case studies, we identify the potential and challenges of action-oriented VR based rehabilitation and diagnosis offered by RGS with emphasis in inter-patient variability and the need for the individualization of therapy.

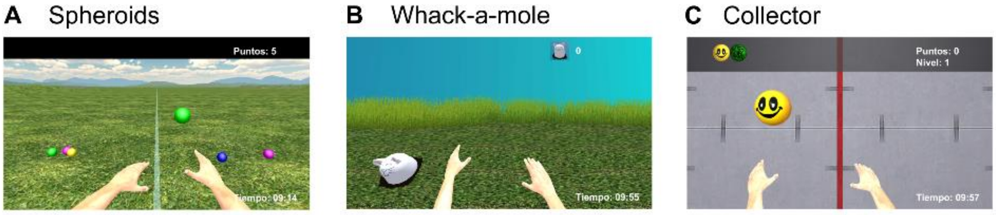


Figure 7.1. Rehabilitation training protocols in RGS.
The training scenarios aim animate the patient to use the arms in a goal-directed embodied fashion. In A the patient has to intercept approaching spheres, in B the patient has to hit moles that appear at random locations in the work space and in C the patient has to collect marbles that match the samples in the top part of the screen.

7.2. Methods

We analyse here the data of two chronic right hemisphere stroke patients (24 months post stroke), one with (Patient 1) and one without neglect (Patient 2), that took part the 6 weeks daily training sessions with RGS that we presented in Chapter 4. The neglect Patient 1 was excluded in the main analysis presented in Chapter 4. To summarize the protocol: One daily session consisted of three different rehabilitation training protocols that treat motor deficits (Cameirão et al., 2012) (Figure 7.1 A-C). Training was presented through the same RGS set-up used for the study in Chapter 4 (Figure 7.2 A). In the training scenarios the patients had to touch targets in the virtual world that would appear randomly in the paretic (left) or non-paretic (right) workspace in front of them by moving their arms accordingly. This forced them to constantly observe both sides of the workspace. The patient's abilities were tested weekly in a real-world evaluation scenario (Figure 7.2 B), where the patient had to physically touch randomly appearing dots that were projected on a table. In this evaluation scenario, that was inspired by the Bilateral Arm Reaching Test (BART) of a study by Han et al. (C. E. Han et al., 2013), the patients had to reach physically for randomly appearing dots that were projected from the overhead projector on the table. The movement of their limbs was also tracked with the Kinect that was mounted next to the overhead projector. The targets were arranged similarly as in the Whack-a-mole scenario (Figure 7.1 B, for detailed explanation see section 4.2.3) in four semicircle arrays with angles of ±5, ±15, ±25, ±35 ±45, ±55, ±65, ±75 and with radii of 21, 27, 33 and 39 spreading out from the body mid-line of the patients. The patients had to do blocks: in one they were free in selecting one limb or the other for a given target and in the other they had to use the paretic limb. As in the Whack-a-mole training scenario there were two start positions where the hands had to be placed in order to start a trial. No feedback on success or failure was given to the patient.

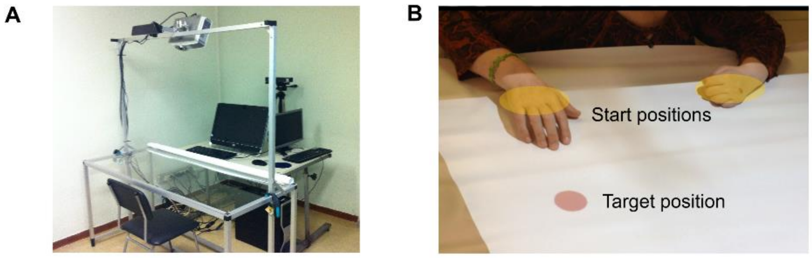


Figure 7.2. Set-up and experimental tasks.
The RGS set-up in the hospital consists of a table, a touch screen computer, a Microsoft Kinect and a projector (A). In order to convert the table to a real-world workspace, a white cloth can be rolled out on its surface. The projector is used to project the targets and start positions (B) onto the workspace and the Kinect is able to detect the movement of the patient's arm. The patient is asked to perform a reaching movement (reach out and come back) from the start position as fast as possible.

Table 7.1. Clinical scales. Before and after the training period, the progress of neglect patient 1 and non-neglect patient 2 was measured through clinical scales.

	CAHAI		**Fugl-Meyer**		**Barthel**	
	Baseline	End	Baseline	End	Baseline	End
Patient 1	7	7	16	29	48	48
Patient 2	45	45	43	51	95	95

7.3. Results

According to the outcome of the clinical scales (Table 7.1) both patients show motor recovery (as measured by the Fugl-Meyer) but no functional recovery of arm and hand, and no change in the activities of daily living. In order to understand these results, we looked at the change in probability of directing the hand to targets in the real-world evaluation scenario, when only the use of the paretic arm was allowed (Figure 7.3). We divided the workspace into 3x6 clusters and applied a Gaussian kernel filter with a standard deviation of 5 in order to obtain the heat maps. When we compare the baselines of the two patients, we see that the neglect patient had a worse initial reaching probability than the non-neglect patient, concentrated in the paretic resp. neglected side (left). Importantly, neither patient had difficulties in doing cross-reaching with the paretic arm towards targets appearing in the right workspace. Looking at the difference between the baseline (evaluation of the first week) and the last two sessions (evaluation of the last two weeks), we see that Patient 1 improved the reaching probabilities, mainly in the front region of the initially neglected side. This is almost the same area of improvement for the non-neglect patient. This could indicate an improvement in the ability to extend the arm. Interestingly, the largest change appears to be an area close to the paretic limb, where the patient showed low probabilities at baseline. This suggests that the training transferred to the real-world workspace of the neglected side, which might have contributed to the motor recovery, but not the functional outcome. This approach helped us, to gain insight into the patients' improvement and allocate it to specific areas in their workspace that could be potentially targeted in a specific treatment.

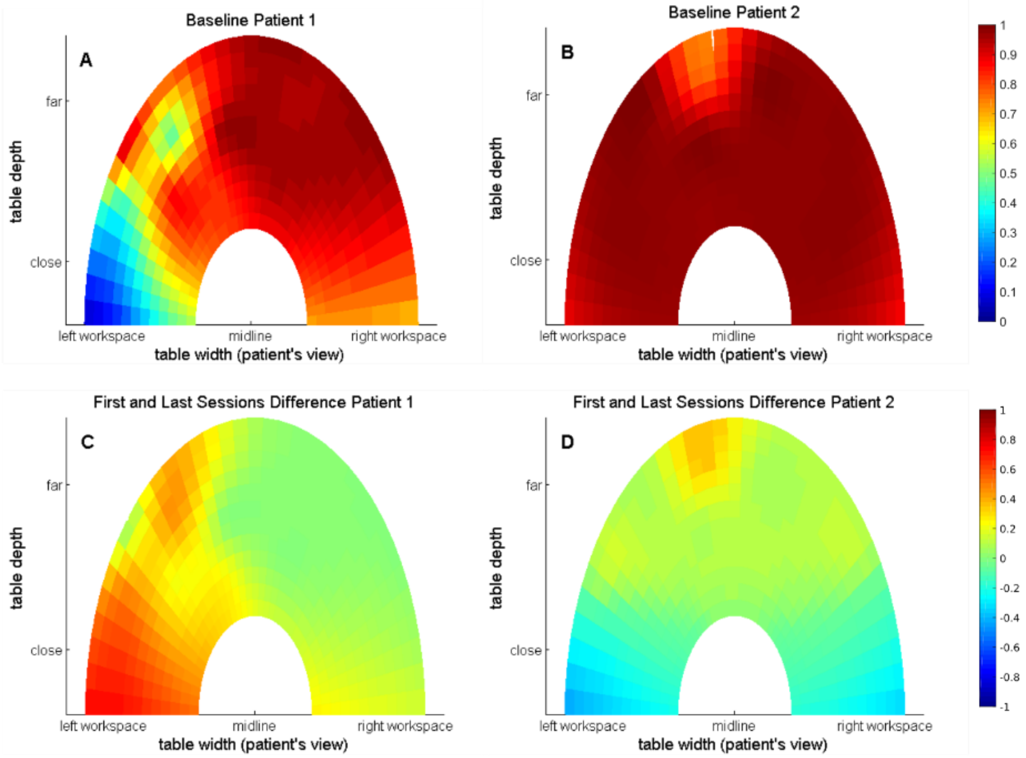


Figure 7.3. Reaching probabilities with the paretic limb (left arm) in the real-world workspace. Baseline probabilities (A and B) and the difference in probabilities between first two and last two sessions (mean, C and D) to reach for targets in a 2D horizontal workspace with the paretic left arm.

7.4. Discussion

We have addressed the question of whether RGS could be useful to diagnose and treat spatial neglect. Our data shows that we can identify the neglected areas and the patient shows and improvement to reach targets in the neglected workspace. Interestingly, the largest change appears in the area close to the paretic limb, and we, therefore, conclude that the observed changes are independent of the functional motor recovery observed. This suggests that the underlying mechanisms are independent and possibly sequentially coupled, i.e. functional recovery requires first a reorganization of the systems underlying neglect followed by motor recovery. Through the goal-oriented movement amplification, the patient could, therefore, be made aware of the whole work area, which in turn, could improve the perception of the otherwise neglected visual workspace. Through encouragement to execute and observe actions in the neglected workspace, he might re-establish the link between perception and action. RGS integrates both steps into the training and could target specifically the neglected spots identified in the patient.

Chapter 8

DEPRESSION MODULATES ATTENTIONAL PROCESSING AFTER STROKE

This chapter is based on the published work in:

Maier, M., Low, S. C., Ballester, B. R., Leiva Bañuelos, N., Duarte Oller, E., & Verschure, P. F. M. J. (2018). Depression modulates attentional processing after stroke. In *Proceedings of the 4th International Conference on NeuroRehabilitation (ICNR* 2018), Pisa, Italy.

With newer information integrated from the following work that is in preparation:

Maier, M., Low, S. C., Ballester, B. R.., & Verschure, P. F. M. J. (2019) Cognitive abilities modulate top-down function in attentional task. The validation gate as a novel diagnostic method. (*In preparation)*

What can we learn about depression from applying principle-based technology? In this last chapter, we explore further the data obtained from the clinical study presented in Chapter 5, which investigate the conjunctive training of several cognitive deficits by using an adaptive difficulty algorithm. We analyse the data of the depression subgroup while they were performing one of the evaluation tasks. Similar to spatial neglect, post-stroke depression often remains undiagnosed. Our exclusion criteria did exclude patients with major depression. However, the HAM-D that was obtained in a subgroup of 19 patients indicated a spread of depressive mood up to 15 points. We analysed the subgroups' performance in one evaluation task that measures psychophysical ability. This task induces increasing cognitive load during the execution. We expected to see that cognitive performance, as measured by the MoCA, might influence performance in this task. However, we found that the depression level was indicative of performance together with visuoperceptual speed and working memory capacity. In specific top-down conscious processing of stimuli is modulated by these measurements. Partial correlation analysis reveals that mainly visuoperceptual speed and working memory capacity explain the variance in performance, with depression acting indirectly on the cognitive impairment on these two domains. These results might indicate that depression is acting like cognitive load, burdening cognitive executive processing. It is hence important to consider the level of depression when evaluating cognitively impaired patients. The presented task here could serve as a diagnostic tool to detect the extension of the influence of depression on cognition.

8.1. Background

Stroke and depression co-occur frequently (Hackett & Pickles, 2014), with detrimental effects on quality of life. Post-stroke depression is linked to the severity of impairment and poorer recovery results (Gillen et al., 2001; Robinson & Jorge, 2016) and affects roughly 31% of stroke patients (Hackett & Pickles, 2014). As stroke becomes more prevalent (Feigin et al., 2016), the detection and treatment of depression become important factors in therapy, especially for cognitive rehabilitation. The reason is that as a psychological disorder its strongest impact would be felt in the cognitive functioning of the patient (R. S. C. Lee et al., 2012), not on the motor impairment. Considering the known links between post-stroke depression and cognitive deficits (Kauhanen et al., 1999), depression would likely hamper the rehabilitation of cognitively impaired stroke patients. The dynamic of that interaction, however, remains an open question. One way to investigate cognitive dynamics is through psychophysical tasks, such as the validation gate (VG) task used here (Mathews, I Badia, & Verschure, 2012). It is generally accepted that attention occurs through the interaction of two processes (Kastner & Ungerleider, 2000)— a bottom-up one, driven by the intrinsic characteristics of stimuli, and a top-down one, predicted by higher-order cognitive functions that include working memory (WM). Under certain conditions, they can be dissociated even in healthy subjects (Mathews et al., 2012), showing that subjects have less cognitive resources to attend to a primary task when a secondary task increasingly demands WM capacity and reduces performance in behaviours that involve WM-dependent processing. However, bottom-up processes, being WM-independent, remain unaltered. Studies have shown that depression significantly influences WM (R. S. C. Lee et al., 2012) and processing speed (McDermott & Ebmeier, 2009), both of which are crucial in cognitive and conscious processing. Therefore, we hypothesized that depression might affect WM similarly to a cognitive load (CL) in the VG task. Cognitively impaired patients with depression performed the task, allowing us to analyse how depression severity influences cognitive processing alongside cognitive deficits. These results were obtained from the evaluation task that was part of the study on the adaptive conjunctive cognitive training (ACCT) presented in Chapter 5.

8.2. Methods

8.2.1. Patients

The data presented in this chapter was obtained from patients that took part in the study presented in Chapter 5, and for whom all the outcome measures were available, including the Hamilton Depression Rating Scale (HAM-D, n = 19, see 5.3.3 Depression subgroup analysis). In short, the patients were recruited from Hospital de l’Esperança, Barcelona and the inclusion criteria were: a) Cognitive impairment (Montreal Cognitive Assessment, MoCA < 26) due to a first-ever stroke over six months ago, and b) aged between 45 and 75 years old. Patients specifically presenting hemianopia, spasticity, severe cognitive, physical or perceptual impairments that interfere with the execution of the experiment were excluded. This study was approved by the local Ethical Committee and registered at ClinicalTrials.gov (NCT02816008). Patients’ characteristics can be found in Table 8.1.

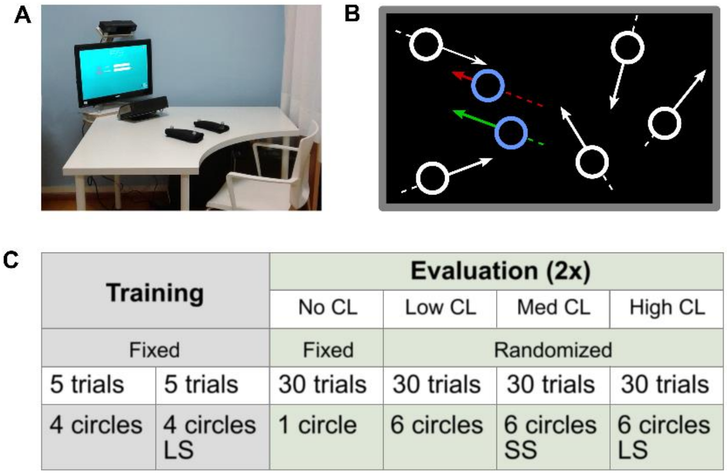
Table 8.1. Patients' characteristics.

Characteristics	**(n = 19)**
	n (%)
Gender, female	9 (44.44%)

Impaired limb, right	9 (44.44%)
Etiology	
Ischemic	10 (52.63%)
Hemorrhagic	8 (42.11 %)
Capsulo lenticular	1 (5.26%)
	Mean (SD) – Median [2.5th and 97.5th percentile]
Age, years	64.79 (7.11) – 63 [53.00 – 76.00]
Days after stroke	1015.74 (898.58) – 688 [190.00 – 3503.00]
MoCA	21.37 (3.71) – 22 [12.00 – 25.00]
MMSE	27.32 (2.03) – 28 [23.00 – 30.00]
MRC	3.74 (0.45) – 4 [3.00 – 4.00]
FM-UE	54.79 (14.90) – 62 [15.00 – 66.00]
BI	95.53 (7.97) – 100 [80.00 – 100.00]
HAM-D	5.58 (5.14) – 4 [0 – 15]

8.2.2. Set-up and experimental protocol

We report here the first evaluation session that the patients performed at the start of the intervention presented in Chapter 5, using the same clinical set-up. During the evaluation session, each patient completed the VG task (Mathews et al., 2012) while their eye movements were recorded (Tobii T120 eye tracker, Tobii Technology AB, Stockholm, Sweden). They were seated in front of a desktop computer (Sony Vaio All-in-One PC). The patients observed white circles moving linearly over a dark background (Figure 8.1). Every 2.5–4s, one of the circles was displaced to a random position within a radius of 40 pixels from the previous location. After the displacement, it continued in its original trajectory. The patients reported detected displacements by pressing the spacebar on a keyboard. Concurrently, they were required to perform the Auditory Span Task (AST) (Conway, Kane, & Al, 2005) in the last 2 of following 4 conditions with varying cognitive load (CL): 1) observing 1 circle only (no CL), 2) observing 6 circles on-screen (low CL) 3) observing 6 circles on-screen while listening to short sentences (medium CL), and 4) observing 6 circles on-screen while listening to long sentences (high CL). Each condition is presented twice during the experiment pseudo-randomly, totalling in 8 blocks (Figure 8.1 C). The patients performed 2 training blocks at the start, one with and one without the AST.



Training		Evaluation (2x)			
		No CL	Low CL	Med CL	High CL
Fixed		Fixed	Randomized		
5 trials	5 trials	30 trials	30 trials	30 trials	30 trials
4 circles	4 circles LS	1 circle	6 circles	6 circles SS	6 circles LS

Figure 8.1. Experimental set-up and task.
The RGS set-up in the hospital consists of a table, an All-in-One PC and an eye tracker (A). In the VG task (B) consist of white circles that move on a linear trajectory over a black background. When hitting the edge of the screen, the circles "bounce" off and continue moving. Occasionally one of the circles (indicated here in blue) displaces to a random location and continues moving (red arrow) in its original direction (green arrow). The experimental protocol (C) consists of a training block and 2 evaluation blocks with varying cognitive load on which the analysis is based. Abbreviations: CL, cognitive load; LS, long sentences; SS, short sentences; Med, medium.

8.2.3. Outcome measures and analysis

All patients were evaluated by a neuropsychologist using a neuropsychological test battery, as well as secondary clinical scales before the start of the task (see 5.2.4 Outcome measures in Chapter 5) that cover various cognitive abilities, motor functioning, and depressive mood. VG outcome variables are the proportions of correctly detected displacements by keypresses (i.e. conscious detections) and by saccades (i.e. subconscious detections), and the latencies of keypresses and saccades. Correct key presses had to occur between 200ms after the displacement to 3s before the next displacement. For the saccade-detected displacements, following typical procedures with such data, the raw eye-tracking data was first cleaned and further processed by interpolating missing values for both eyes. The interpolated data was passed through a low-pass filter (Butterworth) before angular displacement, and angular velocity were calculated. A data point was labelled as a saccade when the angular velocity exceeded 30°/s, had a duration greater than 75ms and an angular distance of more than 0.5°. We extracted the first valid saccade within 100ms to 800ms after a displacement. The proportion of keypresses and saccades that were valid were averaged over all patients per condition. The resulting mean values for conscious and subconscious detections were first compared across loads using Friedman's ANOVA test statistic (χ_F^2). In case of significance a post hoc analysis was performed using Wilcoxon's sign rank test (T) comparing the loads. The outcome values were then correlated with the neuropsychological test battery and the secondary outcomes using the Spearman's correlation coefficient (r_s). Lastly, we performed a partial-correlation analysis using the significant zero-order correlations. Non-parametric tests were used because most data were not normally distributed. All data processing and analysis were performed using MATLAB 2017b.

8.3. Results

The analysis of the conscious detections (button presses) and the subconscious detections (saccades) over all patients revealed that there is no significant difference between medium CL and high CL, neither in conscious detections nor in subconscious detections (Figure B.1 in Appendix B). We therefore combined the data of these two loads into one condition (high CL), since both required the patient to listen to the AST as a secondary task. Consequently, the cognitive loads modulated well conscious responses. That is with increasing load the patients did report significant fewer displacements (no vs. low CL: *T* = 0.5, *r* = -.60, *p* < .001, no vs. high CL: *T* = 0, *r* = -.62, *p* < .001, low vs. high CL: *T* = 0, *r* = -.62, *p* < .001, see Figure 8.2 A), and their reaction time increased significantly (no vs. low CL: *T* = 176, *r* = .53, *p* < .01, no vs. high CL: *T* = 190, *r* = .62, *p* < .001, low vs. high CL: *T* = 187, *r* = .60, *p* < .001, see Figure 8.2 B). The proportion of subconscious decisions was in general higher in both, low CL and high CL (no vs low CL: *T* = 147.5, *r* = .55, *p* < .001, no vs high CL: *T* = 153, *r* = .59, p < .001), but there was no significant difference between the two load conditions, as well as no significant difference in saccade latencies across all load conditions (Figure 8.2 C and D).

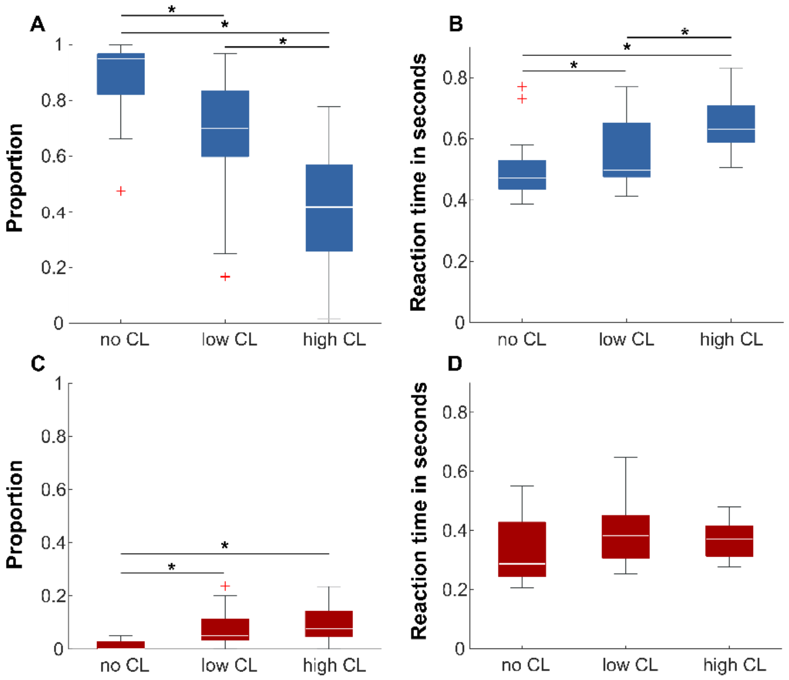
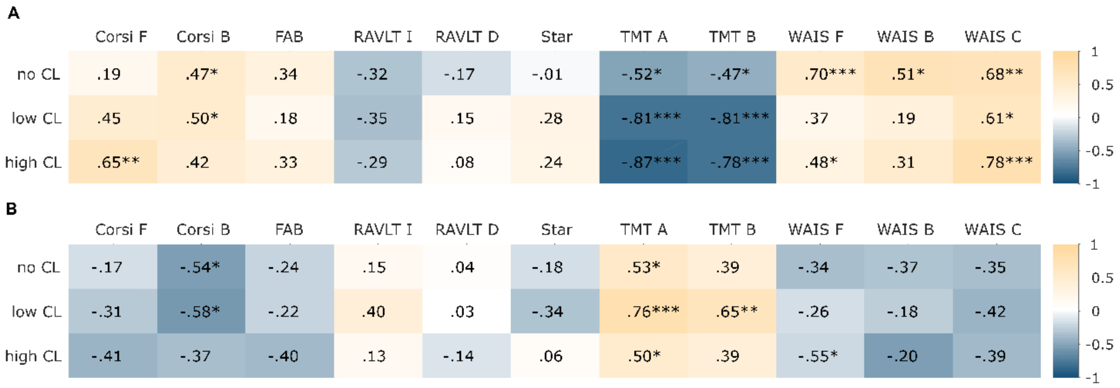


Figure 8.2. Conscious and subconscious detections across cognitive load conditions.
A) The proportion of all displacements that were consciously detected by button-presses. B) The latency of button presses. C) The proportion of all displacements that were subconsciously detected by saccades towards the displacement position. D) The latency of saccades. Significant differences between load conditions (post hoc analysis) are indicated with a star. Abbreviations: CL, cognitive load.

Correlation analysis revealed significant relationships between conscious detections (button presses) and the neuropsychological test battery, as well as the HAM-D. No consistent relationships with the subconscious detections (saccades) were found, and no other secondary outcome correlated with conscious detections. From the secondary outcomes only HAM-D correlated negatively with the ability to report stimuli for low and high CL (low CL: $r_s = -.47$, $p < .05$, high CL: $r_s = -.47$, $p < .05$). The tests within the neuropsychological test battery that correlated consistently well with conscious detection proportion across all load conditions were TMT A, TMT B and WAIS C (Figure 8.3 A). TMT A showed also a consistent positive correlation with the latency in detecting displacements (Figure 8.3 B). Moreover, besides Corsi F ($r_s = -.61$, p < .001) only TMT A and TMT B correlated positively with HAM-D (TMT A: $r_s = .46$, $p < .05$, TMT B: $r_s = .47$, $p < .05$). These results indicate a unique relationship between the conscious detection proportions in high and low CL, the TMT tests and HAM-D.



A

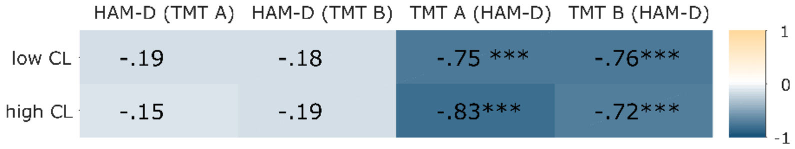
	Corsi F	Corsi B	FAB	RAVLT I	RAVLT D	Star	TMT A	TMT B	WAIS F	WAIS B	WAIS C
no CL	.19	.47*	.34	-.32	-.17	-.01	-.52*	-.47*	.70***	.51*	.68**
low CL	.45	.50*	.18	-.35	.15	.28	-.81***	-.81***	.37	.19	.61*
high CL	.65**	.42	.33	-.29	.08	.24	-.87***	-.78***	.48*	.31	.78***

B

	Corsi F	Corsi B	FAB	RAVLT I	RAVLT D	Star	TMT A	TMT B	WAIS F	WAIS B	WAIS C
no CL	-.17	-.54*	-.24	.15	.04	-.18	.53*	.39	-.34	-.37	-.35
low CL	-.31	-.58*	-.22	.40	.03	-.34	.76***	.65**	-.26	-.18	-.42
high CL	-.41	-.37	-.40	.13	-.14	.06	.50*	.39	-.55*	-.20	-.39

Figure 8.3. Correlations between conscious detection proportion and latency and neuropsychological test battery across all load conditions.
A) proportion of conscious detections (button-presses). B) The latency of conscious detections. Significant p-values are indicated * p < .05, ** p < .01, *** p < .001 and the number and colour represent the coefficient (Spearman's r). Abbreviations: Corsi B, Corsi Block Tapping Test Backward; Corsi F, Corsi Block Tapping Test Forward; FAB, Frontal Assessment Battery; RAVLT, Rey Auditory Verbal Learning Test; RAVLT I, RAVLT Immediate; RAVLT D, RAVLT Delayed Recall; Star, Star Cancellation Test; TMT A, Trail Making Test A; TMT B, Trail Making Test B; WAIS, Wechsler Adult Intelligence Scale IV; WAIS F, WAIS Digit Span Forward; WAIS B, WAIS Backward; WAIS C, WAIS Digit Symbol Coding.

In order to further evaluate the relationships between the TMT tests, HAM-D and conscious detection proportion in low and high CL we performed a partial correlation while controlling for the effect of either TMT A, TMT B or HAM-D as independent variables. We observe that the significant correlation between HAM-D and the ability to consciously detect displacements disappears when controlling for either the effect of TMT A or TMT B. On the contrary when controlling for the effect of HAM-D the correlation between the TMTs and the conscious detection proportion remains significant for the low and high cognitive load (Figure 8.4).



	HAM-D (TMT A)	HAM-D (TMT B)	TMT A (HAM-D)	TMT B (HAM-D)
low CL	-.19	-.18	-.75 ***	-.76***
high CL	-.15	-.19	-.83***	-.72***

Figure 8.4. Partial correlation across cognitive loads for conscious detection proportion. The controlled variable is given in brackets. Significant p-values are indicated * p < .05, ** p < .01, *** p < .001 and the number and colour represent the coefficient (Spearman's r). Abbreviations: CL, cognitive load; HAM-D, Hamilton Depression Rating Scale; TMT A, Trail Making Test A; TMT B, Trail Making Test B.

8.4. Discussion

We found that patients' bottom-up processing (saccadic eye movements) in a cognitive task was unaffected by cognitive ability or with increasing levels of depression. This means that while the stimuli are processed subconsciously equally well by all cognitively impaired patients, it is the conscious detection and reporting ability that appears to be affected. Top-down performance dropped with increasing levels of depression, and as well the performance in TMT A and TMT B. The TMT tests are timed and require online visual tracking ability. Whereas TMT A is considered to measure visuoperceptual speed, TMT B is considered to be a measure for attentional switching and working memory (Sánchez-Cubillo et al., 2009). On the other hand, it has been shown that depression correlates with poor psychomotor speed as well as nonverbal problem solving, verbal and visual memory and attention (Kauhanen et al., 1999). Our analysis revealed that there is a correlation between the low performance in the TMT tests and reduced mood, confirming that there are links between depression and cognitive performance.

The partial-correlation aids in understanding the relationship between conscious behaviour (proportion of key presses), the mental state of the patient (depressive mood as measured by HAM-D) and specific cognitive disability (poor performance in TMT A and TMT B). Although all three variables correlated significantly, it appears that the relationship between depression and the reduced ability to consciously detect displacements with higher cognitive loads can be explained mainly by a deficit in visuoperceptual speed and working memory ability. Although correlations do not explain directionality, it appears unlikely that a deficit in visuoperceptual speed and working memory is causing a trait like depression. It appears more likely that the deficits in performing TMT A and TMT B are a result of the depressive mood. Hence, visuoperceptual speed and working memory impairment might be a deficit that is caused by depression. These results support the idea that depression can affect attentional processes similar to a CL, burdening WM and thus the executive functioning of the patient. This implies several things. Firstly, depression should be considered for the evaluation and the treatment of cognitive function after stroke. Secondly, that cognitive diagnostics may be currently misinterpreted—if depression acts as a WM burden, compromising conscious processing, poor scores in neuropsychological tests might reflect a combination of cognitive deficits and post-stroke depression instead of cognitive deficits alone. Technological tools, such as eye-tracking and virtual reality tasks, can aid in understanding these relationships as they provide crucial data that completes existing clinical diagnostics. In the future, we will not only study how cognitive rehabilitation modulates depression and cognitive abilities but also if the results found here can be replicated in other patient groups with similar pathologies.

Part V

Discussion

Chapter 9

DISCUSSION

With this work, we addressed the multidimensionality of outcomes after stroke. We showed that by using technology, we could provide a multifaceted training to heterogeneous groups of patients through one set-up. This is possible because we are incorporating specific principles of neurorehabilitation that we have identified as effective to foster learning. By combining them into integrated training protocols that exploit the interdependencies between motor, cognitive, mental and social deficits, we were able to show positive effects on recovery. We do not say that technology is the only solution to enhance recovery, but technology can offer advantages that allow us to implement principles more effectively into rehabilitation than real-world means.

We start the first part of this dissertation by providing a synthesis of 15 principles of neurorehabilitation that have been shown to be effective for fostering learning (Chapter 2). In specific, we identified, through a computerized search across reviews, the following principles: Massed practice/repetitive practice, spaced practice, dosage, task-specific practice, variable practice, increasing difficulty, multisensory stimulation, rhythmic cueing, explicit feedback/knowledge of results, implicit feedback/knowledge of performance, modulate effector selection, action observation/embodied practice, mental practice/motor imagery and social interaction. We summarized for each principle the theoretical background, the evidence for motor learning and the clinical effectiveness. We intended to provide a clear definition of each principle as we discovered that many are currently poorly operationalized. We do not claim that this review is exhaust, but it could be the first step to promote more critical approach regarding the active ingredients in current and future rehabilitation methods (Proffitt & Lange, 2015). We advocate that one possible reason for the emergence of a proportional post-stroke recovery is because current rehabilitation methods do not matter *enough*. This could be due to the low intensity, repetition and duration, (N. S. Ward, 2017) but as well because current standard rehabilitation might not provide the right training elements that could foster learning (Janssen et al., 2014; Krakauer et al., 2012). We argue that, before we increase the intensity of a rehabilitation method, we must be certain that its active ingredients are based on scientific grounds and have a prospect to positively change behaviour, at least in healthy animals or humans (Proffitt & Lange, 2015). We hope that future studies will incorporate the operationalization provided in this review, also to make interventions more transparent and comparable (Renton et al., 2017; Veerbeek et al., 2014).

We then present the results of a meta-analysis where we explored whether VR-based systems that were specifically built for rehabilitation show a superior effect in the recovery of upper limb function and activity than off-the-shelf recreational systems, by comparing their outcomes to conventional therapy (Chapter 3). We hypothesized that custom-made VR systems might be more effective, because their technological design process was guided by principles, unlike systems created for recreational purposes, which are typically not accessible for modification. The analysis included 30 randomized controlled trials of high quality and the results confirmed a larger impact on recovery, both on body function and activity, for specifically built systems, but not for off-the-shelf recreational systems. Moreover, we identified six principles of neurorehabilitation that were present in more than 50% of the custom-made systems: variable practice, increasing difficulty, knowledge of results, knowledge of performance, task-specific practice and promote effector selection. We see this result as a first indication, that principle-based systems make, indeed, a difference on impairment and disability. Although this proposal does not need to be limited to VR-based systems, we argue that only technology allows to fully exploit the potential of the principles of learning, as it allows us to go beyond the realms of reality.

Following this proposal, we explored, in the second part of this dissertation, how RGS, a VR-based rehabilitation tool, can address physical, cognitive and social issues in chronic stroke patients, by capitalizing on principles of neurorehabilitation identified in Chapter 1. In its core, RGS builds on the neuroscientific paradigm in which action execution and observation of the same action fosters brain plasticity by restoring sensorimotor contingencies. This premise is grounded on the principles of goal-oriented practice and action observation / embodied practice.

In specific, we show in the first study how reinforcement learning can counteract learned non-use in chronic stroke patients (Chapter 4). We hypothesised that a visual manipulation that reduces error-feedback and increases exposure to success could promote the use of the paretic limb when paired with the embodied goal-oriented training. As such, this novel approach called Reinforcement-Induced Movement Therapy (RIMT) exploits the principles of implicit and explicit feedback, respectively, to address effector selection. We conducted a randomized, double-blind clinical trial with 18 chronic hemiparetic stroke patients that lasted for six weeks. The experimental group was exposed to the goal-oriented movement amplification during training, whereas the control group followed the same protocol without movement amplification. The results indicated that although both groups made a significant improvement in impairment after the intervention, only the experimental group continued to improve at 12-weeks follow-up. We argue that this positive effect was due to the increased paretic arm use during training that led to a clinically important functional gain (Shelton et al., 2001), which possibly fostered daily paretic arm use even in the absence of training. We propose that the prolonged exposure to positive explicit and implicit reinforcement during the RGS sessions might have positively influenced self-efficacy. Consequently, the increased perceived competence could have promoted the reincorporation of the paretic arm in ADL (Folkman & Lazarus, 1988; Timmermans et al., 2009). Future research should seek to investigate this link and compare whether mechanisms driving recovery found in this study are similar to those of CIMT. Although not explicitly tested, we are confident that RIMT is suitable for severely impaired patients more than CIMT (Kwakkel et al., 2015).

Using the same embodied goal-oriented training paradigm in RGS, we then demonstrated that physical therapy could be extended with cognitive training (Chapter 5). In specific, we acknowledged that stroke patients typically express deficits in various cognitive domains and that the domains likely depend on each other. The Adaptive Conjunctive Cognitive Training (ACCT) adapts task parameters automatically to the patient’s ability, addressing various cognitive deficits within the same training scenarios. Hence, patients train always at the optimal challenge level, exploiting the principle of increasing difficulty (Nirme, 2011). We conducted a randomized controlled pilot trial with 30 chronic cognitively impaired stroke patients, that lasted for six weeks. The experimental group followed ACCT, whereas the control group solved standard cognitive tasks at home. The results indicated that the system adapted well to the heterogeneous sample. Further, the experimental group improved in three out of five cognitive measures at follow-up, which was not observed in the control group. We argue that patients might have acquired cognitive strategies, that transferred to activities outside the intervention (McEwen et al., 2015). Although we only included patients with mild motor impairments, we showed a small effect in the FM-UE, too, similar to other studies (Faria et al., 2018). Further research is therefore encouraged to combine motor therapy with conjunctive training of various cognitive deficits and test it in a more severely impaired group. With a larger sample, also the evolution of subgroups with similar deficit profiles could be investigated to better understand the interdependencies of the recovery of different cognitive domains. In addition, we identified that depression might covary in this heterogeneous sample. This work stresses the need that the level of depression should be identified when the recovery of cognitively impaired patients is investigated. The observation of improvement in cognitive domains together with a positive trend for reducing depression might point to a similar psychological mechanism as in RIMT. Indeed, resilient self-efficacy is a result of preservant effort, which is given when success and failure are kept in balance (Albert Bandura, 2008). Thus, providing an optimal cognitive challenge throughout training might re-establish self-efficacy affected in depression (Robinson-Smith et al., 2000).

We further extended the embodied training in RGS to the social realm of the patients (Chapter 6). By capitalizing on the principle of social interaction, we designed a novel multiplayer training scenario. To level out any performance disadvantages that could arise due to physical disabilities, we incorporated the goal-oriented movement amplification explored in RIMT. Hence patients and caregivers could compete against each other on the same challenge level. We hypothesized that this would change the caregiver's perception of the abilities of the patient besides increasing the patient's self-efficacy. We evaluated the method in the lab, conducted a psychosocial study to learn more about the patients' social environment, and tested the method in two at-home case studies. We showed that both caregiver and patient overall increased their ratings on a questionnaire that measures the perception of the patient's capabilities to perform different ADLs. We propose that an enhancement of self-efficacy could underly the change in perceived ability ratings. Reclaiming self-efficacy is not only shaped by one's own successful attempts, but also by the affirmative evaluation of those attempts by others (Albert Bandura, 2008; Mukherjee et al., 2006). On the one hand, dyad interventions might not only be beneficial for the patient (Bakas et al., 2014). On the other hand, it has been shown that the caregiver's perception of family disharmony, the patient's physical functioning and the feelings of hope, predict the caregiver's level of depression (Thompson, Bundek, & Sobolew-Shubin, 1990). The experience that the patient can compete on the same challenge level help to reduce these limiting beliefs of the caregiver. However, the results of this proof of concept study rely on very few subjects. Future studies could further investigate this hypothesis and the link to self-efficacy in a larger sample and extend the training over several weeks.

Together, these studies show that by following a systematic principle-based approach and using a versatile technology-based system, a variety of training scenarios can be created that optimally address specific issues within and across post-stroke deficits. The manipulations presented here, e.g. the visual manipulation of movement feedback and the automatized personalized difficulty, would not be possible in a real-world setting. In two studies, we show an improvement in FM-UE in chronic stroke patients, which supports the possibility of an extended critical window (Ballester et al., 2019). Also, the intervention dose was rather low (30 minutes per day over 6 weeks), if compared to CIMT (Smania et al., 2012) and current recommendations for beneficial dose (Kwakkel, van Peppen, et al., 2004; Veerbeek et al., 2014). Hence, not only high intensity and dosage that can lead to significant gains but also the careful consideration of active ingredients (Proffitt & Lange, 2015) or the principles of neurorehabilitation, realized through technology-based training scenarios. Consequently, RGS incorporates significant elements currently missing in standard care (Johansson & Ohlsson, 1996; Krakauer et al., 2012). A common mechanism brought forward in all three studies discussed in this part of the dissertation is the concept of enhancing self-efficacy. Perceived competence might be a strong driver to enter into a virtuous loop of health-promoting behaviour – A hypothesis that we are keen to explore explicitly in our future studies.

In the third and last part, we considered how the data obtained from the training in virtual reality could be used for diagnostic purposes. In spatial neglect patients, it might aid in understanding the neglected area better (Chapter 7). In cognitively impaired patients, it could be used to further elucidate the relationship between cognitive abilities and depression (Chapter 8). Using technology for diagnostics has various advantages above the standard paper and pencil tasks, widely used in occupational therapy. First, data gathered through technology is unbiased by the person administrating the diagnostic tool. Second, we see it as unlikely that the patient can develop strategies to perform well in these tasks, as the patient must act timely in a goal-oriented manner which is more probable to capture true behaviour. Lastly, digital data has a higher resolution than clinical scales. It can, for instance, give detailed information about the kinematics of arm movements, or the psychomotor behaviour by tracking the eye in cognitively demanding tasks. If paired with established clinical scales and brain imaging data, digital data can help to obtain a better and more complete insight about the ongoing recovery process of the patient, independently of the complexity of their impairment.

We believe that integrated systems like RGS can address adequately the global burden associated with stroke on multiple levels – clinically, socially and economically. All the protocols presented here can be provided within one set-up, requiring only a computer and a Kinect. It is unrealistic to think, that the health care system will at any point be able to give patients long-term access to an occupational therapist, a language therapist, a physical therapist, a neuropsychologist and a social worker for the training amount required. This is not to say that VR-based rehabilitation systems should replace all these professions, but it can support them in their work, and increasing therapy time when access to a health care team is limited, for instance in remote areas or in countries with lower health care resources. A home-based therapy system can allow the patient to interact with the health care professional remotely, whereas it provides the individual therapists with valuable data of at-home training that allows them to constantly track the patients' progress and tailor the training scenarios to the individual needs. RGS has already been successfully tested in domiciliary settings (Ballester et al., 2017). It might foster an enriched environment that can animate patients to be more active, both in the hospital or at home (Janssen et al., 2014). Further, it can be combined with other advanced therapy methods, such as neurofeedback (Mottaz et al., 2018).

Overall, the work conducted in this thesis provides evidence that *stroke rehabilitation can matter enough*. We propose, however, that this does not entirely depend on intensity, dose or duration, but more importantly on the specifics of the training provided. Using principles as active ingredients, we might provide training that fosters learning to reduce impairment, also in the chronic phase. We advocate using technology to implement principle-based scenarios, not only because of its practical advantages in tackling the global burden of stroke but in specific for its ability to surpass reality and for its scientific value in providing alternative data to investigate post-stroke recovery.

Part VI

Appendices

Appendix A Additional files for Chapter 5

Table A.1. Cut-off scores considered for the minimization procedure.

	1st stratum	2nd stratum	3rd stratum	4th stratum
BI (Supervia et al., 2008)	< 51	> 50 and < 76	> 75	Na
Corsi F (Pena-Casanova et al., 2009)	< 4	> 3 and < 6	> 5	Na
Corsi B (Pena-Casanova et al., 2009)	< 4	> 3 and < 6	> 5	Na
FAB (Appollonio et al., 2005)	< 13.7	> 13.6 and < 14.26	> 14.25	Na
FM-UE (Woodbury, Velozo, Richards, & Duncan, 2013)	< 20	> 19 and < 47	> 46	Na
MoCA (L. Friedman, Speechley, & Teasell, 2012)	< 11	> 10 and < 21	> 20 and < 26	> 25
MMSE (L. Friedman et al., 2012)	< 11	> 10 and < 21	> 20 and < 27	> 26
RAVLT I (Van der Elst et al., 2005)	< 24	> 23 and < 28	> 27 and < 32	> 31
RAVLT D (Van der Elst et al., 2005)	< 4	> 3 and < 5	> 4 and < 6	> 5
Star (Raspelli et al., 2012)	< 44	> 43	Na	Na
TMT A (Pena-Casanova et al., 2009)	> 103	< 104 and > 62	< 63	Na
TMT B (Pena-Casanova et al., 2009)	> 266	< 267 and > 156	< 157	Na
WAIS F (Pena-Casanova et al., 2009)	< 4	4	> 4	Na
WAIS B (Pena-Casanova et al., 2009)	< 2	> 1 and < 5	> 4	Na
WAIS C (Pena-Casanova et al., 2009)	< 13	> 12 and < 25	> 24	Na

Table A.2. ASCS complete case analysis (CC) and last observation carried forward analysis (LOCF). Evaluation of within-group change over time and improvement T1-T0 and T2 -T0, as well as between-group differences at these time points.

ASCS		Baseline (T0)	After treatment (T1)	Follow-up (T2)	Friedman's ANOVA		T1-T0	T2-T0
		Mean (SD) – Median [2.5th and 97.5th percentile]						
Attention								
CC	EG	-0.35 (0.88) – -0.28 [-2.11 – 1.22]	-0.13 (0.94) – -0.17 [-1.67 – 1.33]	**0.06 (0.92) – 0.17 [-1.44 – 1.67] ***	$\chi_F^2(2)$	**.01**	0.22 (0.39) – 0.17 [-0.44 – 0.89]	0.41 (0.46) – 0.44 [-0.44 – 1.33]
	CG	-0.16 (0.83) – 0.11 [-1.78 – 0.89]	0.02 (0.80) – 0.28 [-1.78 – 1.00]	0.03 (0.92) – 0.22 [-1.67 – 1.67]	$\chi_F^2(2)$	.25	0.17 (0.50) – 0.17 [-0.78 – 1.00]	0.19 (0.32) – 0.17[-0.44 – 0.78]
between-group		*Ws* .39				*Ws*	.80	.21
LOCF	EG	-0.44 (0.84) – -0.33 [-2.11 – 1.22]	**-0.23 (0.91) – -0.33 [-1.67 – 1.33] ***	**-0.08 (0.91) – 0 [-1.44 – 1.67] ****	$\chi_F^2(2)$	**.00**	0.20 (0.36) – 0.11 [-0.44 – 0.89]	0.36 (0.44) – 0.44 [-0.44 – 1.33]
	CG	-0.35 (0.90) – -0.22 [-2.00 – 0.89]	-0.23 (0.90) – -0.11 [-2.00 – 1.00]	-0.22 (0.98) – -0.11 [-2.00 – 1.67]	$\chi_F^2(2)$	.42	0.11 (0.44) – 0.00[-0.78 – 1.00]	0.12 (0.30) – 0.11 [-0.44 – 0.78]
between-group		W_s .54				W_s	.36	.09
Memory								
CC	EG	-0.76 (0.69) – -0.57 [-2.27 – 0.05]	-0.54 (0.91) – -0.31 [-2.17 – 0.76]	-0.43 (0.91) – -0.30 [-2.19 – 0.89]	$\chi_F^2(2)$	.30	0.21 (0.50) – 0.23 [-0.70 – 1.22]	0.33 (0.65) – 0.47 [-0.73 – 1.71]
	CG	-0.72 (0.82) – -0.54 [-2.38 – 0.40]	**-0.52 (0.73) – -0.44 [-1.78 – 0.56] ***	-0.37 (0.83) – -0.52 [-1.37 – 1.52]	$\chi_F^2(2)$	.42	0.20 (0.31) – 0.10 [-0.30 – 0.76]	0.34 (0.51) – 0.34 [-0.47 – 1.29]
between-group		*Ws* .85				*Ws*	.82	.92

LOCF	EG	-0.93 (0.76) – -0.85 [-2.27 – 0.05]	-0.71 (0.95) – -0.57 [-2.22 – 0.76]	**-0.61 (0.96) –** **-0.45 [-2.22 – 0.89]** *	$\chi^2_F(2)$	.20	0.22 (0.49) – 0.14 [-0.70 – 1.22]	0.32 (0.61) – 0.43 [-0.73 – 1.71]
	CG	-0.83 (0.78) – -0.78 [-3.21 – 1.79]	**-0.66 (0.75) –** **-0.70 [-2.24 – 0.56]** *	**-0.55 (0.84) –** **-0.70 [-2.24 – 1.52]** *	$\chi^2_F(2)$	.18	0.17 (0.28) – 0.08 [-0.30 – 0.76]	0.28 (0.46) – 0.23 [-0.47 – 1.29]
between-group		*Ws* .70				*Ws*	.64	.91
EF								
CC	EG	-0.34 (1.01) – -0.335 [-1.64 – 1.32]	-0.29 (1.18) – -0.38 [-2.09 – 2.02]	-0.15 (1.19) – 0.15 [-1.97 – 1.68]	$\chi^2_F(2)$	.43	0.05 (0.61) – 0.04 [-1.55 – 0.96]	0.19 (0.62) – 0.22 [-0.85 – 1.55]
	CG	-0.45 (1.38) – -0.27 [-2.67 – 1.79]	-0.28 (1.33) – -0.02 [-2.60 – 2.02]	-0.28 (1.40) – -0.21 [-2.60 – 1.91]	$\chi^2_F(2)$	.47	0.17 (0.54) – 0.17 [-0.30 – 0.76]	0.17 (0.56) – 0.18 [-1.25 – 1.00]
between-group		*Ws* .92				*Ws*	.57	.79
LOCF	EG	-0.53 (1.08) – -0.50 [-2.70 – 1.32]	-0.49 (1.23) – -0.54 [-2.70 – 2.02]	-0.38 (1.25) – -0.09 [-2.70 – 1.68]	$\chi^2_F(2)$	.47	0.04 (0.56) – 0.00 [-1.55 – 0.96]	0.15 (0.57) – 0.00 [-0.85 – 1.55]
	CG	-0.69 (1.40) – -0.69 [-3.21 – 1.79]	-0.59 (1.39) – -0.38 [-3.21 – 2.02]	-0.59 (1.44) – -0.38 [-3.21 – 1.91]	$\chi^2_F(2)$	.85	0.10 (0.48) – 0.00 [-0.96 – 0.99]	0.10 (0.50) – 0.00 [-1.25 – 1.00]
between-group		*Ws* .92				*Ws*	.66	.88
SA								
CC	EG	-2.88 (6.57) – -0.39 [-25.17 – 0.50]	**-0.67 (3.95) –** **0.50 [-15.43 – 0.50]** *	**0.33 (0.36) –** **0.50 [-0.39 – 0.50]** *	$\chi^2_F(2)$	**.00**	2.21 (6.55) – 0.88 [-6.19 – 24.78]	3.21 (6.57) – 0.88 [-0.88 – 25.66]
	CG	-0.58 (1.44) – 0.05 [-3.93 – 0.50]	-0.20 (1.44) – 0.50 [-4.81 - 50]	-0.52 (1.90) – 0.50 [-6.68 – 0.50]	$\chi^2_F(2)$	.53	0.38 (1.08) – 0.00 [-0.88 – 2.65]	0.06 (1.95) – 0.00 [-5.31 – 2.65]

between-group		*Ws* .45					*Ws*	.24	.10
LOCF	EG	-2.53 (6.05) – -0.39 [-25.17 – 0.50]	**-0.58 (3.62) – 0.50 [-15.43 – 0.50] ***	**0.26 (0.40) – 0.50 [-0.39 – 0.50] ****	$\chi^2_F(2)$	**.00**		1.96 (6.02) – 0.88 [-6.18 – 24.78]	2.79 (6.09) – 0.88 [-0.88 – 25.66]
	CG	-0.81 (1.94) – 0.50 [-6.58 – 0.50]	-0.44 (1.95) – 0.50 [-6.58 – 0.50]	-0.67 (2.19) – 0.50 [-6.58 – 0.50]	$\chi^2_F(2)$	.37		0.37 (0.99) – 0.00 [-0.88 – 2.65]	0.10 (0.00) – 0.00 [-5.31 – 2.65]
between-group		*Ws* .35					*Ws*	.18	.07
GCF									
CC	EG	-0.56 (0.79) – -0.44 [-1.92 – 0.39]	**-0.20 (0.80) – -0.10 [-1.64 – 0.91] ****	**-0.12 (0.83) – 0.25 [-1.56 – 0.99] ****	$\chi^2_F(2)$	**.00**		0.36 (0.36) – 0.34 [-0.06 – 0.90]	0.44 (0.42) – 0.54 [-0.56 – 1.17]
	CG	-0.38 (0.90) – 0.00 [-2.00 – 0.69]	-0.17 (0.81) – 0.10 [-1.93 – 0.75]	-0.16 (0.94) – 0.06 [-1.98 – 1.59]	$\chi^2_F(2)$	.93		0.21 (0.45) – 0.13 [-0.31 – 1.27]	0.22 (0.37) – 0.14 [-0.22 – 0.90]
between-group		*Ws* .49					*Ws*	.12	.12
LOCF	EG	-0.66 (0.78) – -0.58 [-1.92 – 0.39]	**-0.33 (0.82) – -0.26 [-1.72 – 0.91] ****	**-0.27 (0.86) – -0.14 [-1.72 – 0.99] ****	$\chi^2_F(2)$	**.00**		0.33 (0.30) – 0.32 [-0.06 - 0.90]	0.39 (0.41) – 0.42 [-0.56 – 1.17]
	CG	-0.56 (0.95) – -0.21 [-2.17 – 0.69]	-0.41 (0.92) – -0.16 [-2.17 – 0.75]	-0.40 (1.01) – -0.25 [-2.17 – 1.59]	$\chi^2_F(2)$	.94		0.15 (0.40) – 0.00 [-0.31 – 1.27]	0.17 (0.33) – 0.00 [-0.22 – 0.90]
between-group		*Ws* .73					*Ws*	**.04**	**.04**

For within-group change over time, we used Friedman's ANOVA test statistic, for within-group post hoc analysis of the differences Wilcoxon's sign rank test, and between-group Wilcoxon's rank-sum test. Significant comparisons with respect to baseline are indicated with * for p-values < .05 and ** for p-values < .01. ASCS, average standardized composite score; CC, complete case analysis; CG, control group; GCF, generalized cognitive functioning; EF, executive functioning; EG, experimental group; LOCF, last observation carried forward; SA, spatial awareness; χ^2_F , Friedman's ANOVA test statistic; *T*, Wilcoxon's sign rank test; *Ws*, Wilcoxon's rank-sum test.

Table A.3. Neuropsychological test battery complete case analysis and last observation carried forward analysis.
Evaluation of within-group change over time and improvement T1 - T0 and T2 - T0, as well as between-group differences at baseline, T1 - T0, and T2 -T0.

Scale		Baseline (T0)	After treatment (T1)	Follow-up (T2)	Friedman's ANOVA	T1-T0	T2-T0
		Mean (SD) – Median [2.5th and 97.5th percentile]					
Corsi F							
CC	EG	5.56 (1.59) – 5.50 [3.00 – 9.00]	6.06 (2.08) – 6.00 [3.00 – 9.00]	**6.81 (2.17) –** **6.00 [4.00 – 11.00]***	χ^2_F (2) .13	0.50 (1.59) – 0.50 [-3.00 – 4.00]	1.25 (1.91) - 2.00 [-2.00 – 5.00]
	CG	5.57 (1.60) – 6.00 [3.00 – 9.00]	5.86 (1.46) – 5.00 [4.00 – 8.00]	6.14 (1.51) – 6.00 [4.00 – 9.00]	χ^2_F (2) .40	0.29 (2.05) – 0.50 [-4.00 – 3.00]	0.57 (2.03) - 1.00 [-5.00 – 3.00]
between-group		*Ws* .88			*Ws*	.87	.45
LOCF	EG	5.32 (1.60) – 5.00 [3 – 9]	5.84 (1.98) – 6.00 [3.00 – 9.00]	**6.47 (2.14) –** **6.00 [4.00 – 11.00]****	χ^2_F (2) .08	0.53 (1.50) – 0.00[-3.00 – 4.00]	1.16 (1.80) - 2.00 [-2.00 – 5.00]
	CG	5.37 (1.54) – 5.00 [3 – 9]	5.53 (1.43) – 5.00 [4.00 – 8.00]	5.74 (1.52) – 6.00 [4.00 – 9.00]	χ^2_F (2) .61	0.16 (1.77) – 0.00 [-4.00 – 3.00]	0.37 (1.77) - 0.00 [-5.00 – 3.00]
between-group		*Ws* .86			*Ws*	.36	.09
Corsi B							
CC	EG	4.31 (1.78) – 5.00 [1.00 – 6.00]	5.00 (2.03) – 5.00 [2.00 – 10.00]	4.88 (1.86) – 5.00 [2.00 – 4.86]	χ^2_F (2) .59	0.69 (1.58) – 0.00 [-2.00 – 4.00]	0.56 (1.67) - 0.50 [-2.00 – 4.00]
	CG	4.57 (2.10) – 5.00 [2.00 – 9.00]	4.93 (2.20) – 5.00 [2.00 – 9.00]	4.86 (1.46) – 5.00 [2.00 – 7.00]	χ^2_F (2) .85	0.36 (1.22) – 0.00 [-1.00 – 3.00]	0.29 (1.73) - 0.00 [-2.00 – 3.00]
between-group		*Ws* .95			*Ws*	.54	.69
LOCF	EG	4.21 (1.72) – 5.00 [1 – 6]	4.74 (2.02) – 5.00 [2.00 – 10.00]	4.63 (1.86) – 5.00 [2.00 – 8.00]	χ^2_F (2) .79	0.53 (1.50) – 0.00 [-2.00 – 4.00]	0.42 (1.57) – 0.00 [-2.00 – 4.00]

	CG	4.47 (1.87) – 4.00 [2 – 9]	4.74 (1.91) – 5.00 [2.00 – 9.00]	4.68 (1.29) – 4.00 [2.00 – 7.00]	χ_F^2 (2)	.67	0.26 (1.10) – 0.00 [-1.00 – 3.00]	0.21 (1.51) – 0.00 [-2.00 – 3.00]
between-group		*Ws* .91			*Ws*		.63	.74
FAB								
CC	EG	16.38 (1.45) – 16.50 [14.00 – 18.00]	16.44 (2) – 17.00 [11.00 – 18.00]	16.75 (1.88) – 17.50 [12.00 – 18.00]	χ_F^2 (2)	.25	0.06 (1.48) – 0.00 [-3.00 – 2.00]	0.38 (1.36) – 0.00 [-2.00 – 3.00]
	CG	16.00 (2.42) – 17.00 [11.00 – 18.00]	16.43 (1.65) – 17.00 [13.00 – 18.00]	16.43 (1.95) – 17.50 [13.00 – 18.00]	χ_F^2 (2)	.22	0.43 (1.45) – 0.00 [-2.00 – 3.00]	0.43 (1.55) – 0.50 [-4.00 – 3.00]
between-group		*Ws* 1			*Ws*		.76	.73
LOCF	EG	15.95 (1.99) – 16.00 [10 – 18]	15.95 (2.39) – 17.00 [10.00 – 18.00]	16.21 (2.37) – 17.00 [10.00 – 18.00]	χ_F^2 (2)	.40	0.00 (1.37) – 0.00 [-3.00 – 2.00]	0.26 (1.28) – 0.00 [-2.00 – 3.00]
	CG	15.68 (2.87) – 17.00 [8 -–18]	15.89 (2.45) – 17.00 [8.00 – 18.00]	15.89 (2.60) – 17.00 [8.00 – 18.00]	χ_F^2 (2)	.67	0.21 (1.32) – 0.00 [-2.00 – 3.00]	0.21 (1.40) – 0.00 [-4.00 – 3.00]
between-group		*Ws* 0.81			*Ws*		1	.94
RAVLT D								
CC	EG	4.69 (2.70) – 4.00 [0.00 – 10.00]	5.25 (3.15) – 4.50 [0.00 – 11.00]	5.63 (2.73) – 6.00 [1.00 – 11.00]	χ_F^2 (2)	.48	0.56 (1.90) – 0.00 [-2.00 – 5.00]	0.94 (2.46) – 0.50 [-3.00 – 6.00]
	CG	5.21 (2.99) – 5.50 [0.00 – 10.00]	6.21 (2.49) – 6.00 [2.00 – 10.00]	6.50 (2.47) – 6.00 [3.00 – 13.00]	χ_F^2 (2)	.54	1.00 (1.88) – 0.00 [-2.00 – 5.00]	1.29 (2.76) – 0.50 [-2.00 – 6.00]
between-group		*Ws* .50			*Ws*		.43	.85
LOCF	EG	4.16 (2.77) – 4.00 [0 – 10]	4.84 (3.11) – 4.00 [0.00 – 11.00]	5.16 (2.81) – 6.00 [1.00 – 11.00]	χ_F^2 (2)	.36	0.68 (1.92) – 0.00 [-2.00 – 5.00]	1.00 (2.38) – 0.00 [-3.00 – 6.00]
	CG	4.95 (2.74) – 5.00 [0 – 10]	**5.84 (2.43) – 6.00 [1.00 – 10.00]***	6.05 (2.46) – 6.00 [1.00 – 13.00]	χ_F^2 (2)	.23	0.89 (1.66) – 0.00 [-2.00 – 5.00]	1.11 (2.40) – 0.00 [-2.00 – 6.00]

between-group		*Ws* .31				*Ws*	.49	.99
RAVLT I								
CC	EG	32.38 (9.70) – 34.00 [10.00 – 44.00]	32.69 (10.71) – 34.50 [8.00 – 48.00]	35.06 (11.37) – 36.00 [7.00 – 49.00]	χ^2_F (2)	.53	0.31 (5.62) – -0.50 [-7.00 – 14.00]	2.69 (6.59) – 2.00 [-6.00 – 15.00]
	CG	32.57 (10.82) – 34.00 [14.00 – 47.00]	32.64 (9.34) – 32.50 [17.00 – 45.00]	35.57 (9.74) – 38.50 [20.00 – 54.00]	χ^2_F (2)	.17	0.07 (5.48) – 0.00 [-7.00 – 11.00]	3.00 (6.04) – 3.00 [-10.00 – 13.00]
between-group		*Ws* .82				*Ws*	.93	.71
LOCF	EG	30.53 (9.9) – 33.00 [10 – 44]	31.63 (10.68) – 31.00 [8.00 – 48.00]	33.63 (11.46) – 35.00 [7.00 – 49.00]	χ^2_F (2)	.45	1.11 (6.27) – 0.00 [-7.00 – 16.00]	3.11 (6.83) – 2.00 [-6.00 – 16.00]
	CG	30.21 (10.49) – 29.00 [13 – 47]	30.79 (9.34) – 30.00 [13.00 – 45.00]	**32.95 (10.14) – 30.00 [13.00 – 54.00]***	χ^2_F (2)	.09	0.58 (4.91) – 0.00 [-7.00 – 11.00]	2.74 (5.31) – 3.00 [-10.00 – 13.00]
between-group		*Ws* .98				*Ws*	.98	.80
Star								
CC	EG	50.19 (7.42) – 53.00 [25.00 – 54.00]	**52.69 (4.47) – 54.00 [36.00 – 54.00]***	**53.81 (0.40) – 54.00 [53.00 – 54.00]***	χ^2_F (2)	**.00**	2.50 (7.40) – 1.00 [-7.00 – 28.00]	3.63 (7.43) – 1.00 [-1.00 – 29.00]
	CG	32.57 (1.63) – 53.50 [49.00 – 54.00]	53.21 (1.63) – 54.00 [48.00 – 54.00]	52.86 (2.14) – 54.00 [46.00 – 54.00]	χ^2_F (2)	.53	0.43 (1.22) – 0.00 [-1.00 – 3.00]	0.07 (2.20) – 0.00 [-6.00 – 3.00]
between-group		*Ws* .45				*Ws*	.23	.10
LOCF	EG	50.58 (6.84) – 53.00 [25 – 54]	**52.79 (4.09) – 54.00 [36.00 – 54.00]***	**53.74 (0.45) – 54.00 [53.00 – 54.00]****	χ^2_F (2)	**.00**	2.21 (6.80) – 1.00 [-7.00 – 28.00]	3.16 (6.88) – 1.00 [-1.00 – 29.00]
	CG	52.53 (2.20) – 54.00 [46 – 54]	52.95 (2.20) – 54.00 [46.00 – 54.00]	52.68 (2.47) – 54.00 [46.00 – 54.00]	χ^2_F (2)	.37	0.42 (1.12) – 0.00 [-1.00 – 3.00]	0.16 (1.92) – 0.00 [-6.00 – 3.00]

between-group		*Ws* .35			*Ws*		.18	.08
TMT A								
CC	EG	74.06 (39.83) – 66.00 [31.00 – 154.00]	73.69 (40.13) – 73.50 [22.00 – 150.00]	**63.19 (32.65) – 52.00 [26.00 – 132.00]***	χ^2_F (2)	.26	0.38 (13.80) – 0.50 [-28.00 – 34.00]	10.88 (23.26) – 8.50 [-48.00 – 50.00]
	CG	75.86 (49.98) – 65.00 [29.00 – 176.00]	**58.36 (27.91) – 50.50 [29.00 - 126.00]***	72.43 (57.57) – 55.50 [20.00 – 240.00]	χ^2_F (2)	.14	17.50 (27.32) – 10.50 [-16.00 – 3.00]	3.43 (29.11) – 7.00 [-75.00 – 43.00]
between-group		*Ws* .72			*Ws*		**.03**	.52
LOCF	EG	76.79 (37.89) – 66.00 [31 – 154]	75.11 (37.60) – 78.00 [22.00 – 150.00]	**66.26 (31.66) – 62.00 [26.00 – 132.00]***	χ^2_F (2)	.18	1.68 (13.91) – 0.00 [-28.00 – 34.00]	10.53 (21.83) – 7.00 [-48.00 – 50.00]
	CG	79.68 (47.37) – 66.00 [29 – 176]	68.05 (34.99) – 56.00 [29.00 – 159.00]	78.42 (53.70) – 62.00 [20.00 – 240.00]	χ^2_F (2)	.45	11.63 (25.77) – 7.00 [-23.00 – 93.00]	1.26 (25.47) – 0.00 [-75.00 – 43.00]
between-group		*Ws* .93			*Ws*		.22	.22
TMT B								
CC	EG	228.75 (129.82) – 180.50 [70.00 – 402.00]	228.44 (136.98) – 185.00 [52.00 - 402.00]	211.25 (130.59) – 169.00 [48.00 – 402.00]	χ^2_F (2)	.26	0.31 (91.27) – 1.00 [-264.00 – 142.00]	17.50 (90.31) – 4.00 [-192.00 – 229.00]
	CG	212.36 (140.95) – 177.00 [44.00 – 402.00]	209.21 (138.36) – 178.50 [51.00 - 402.00]	225.29 (152.69) – 202.00 [38.00 – 402.00]	χ^2_F (2)	.90	3.14 (35.33) – 0.00 [-80.00 – 75.00]	-12.93 (44.37) – 0.00 [-126.00 – 55.00]
between-group		*Ws* .60			*Ws*		.59	.20
LOCF	EG	242.42 (132.66) – 198.00 [70 – 402]	242.16 (138.56) – 200.00 [52.00 – 402.00]	227.68 (135.04) – 173.00 [48.00 – 402.00]	χ^2_F (2)	.26	0.26 (83.32) – 0.00 [-264.00 – 142.00]	14.74 (82.70) – 0.00 [-192.00 – 229.00]

	CG	241.26 (137.47) – 242.00 [44 – 402]	237.84 (136.67) – 219.00 [51.00 – 402.00]	249.68 (145.01) – 267.00 [38.00 – 402.00]	χ^2_F (2)	.74	3.42 (30.35) – 0.00 [-80.00 – 75.00]	-8.42 (38.75) – 0.00 [-126.00 – 55.00]
	between-group	*Ws* .86				*Ws*	.66	.31
WAIS B								
CC	EG	3.44 (0.73) – 3.00 [2.00 – 5.00]	3.81 (1.38) – 4.00 [2.00 – 7.00]	3.81 (1.11) – 4.00 [2.00 – 6.00]	χ^2_F (2)	.36	0.38 (1.15) – 0.00 [-1.00 – 3.00]	0.38 (1.02) – 0.00 [-1.00 – 3.00]
	CG	3.36 (1.22) – 3.50 [2.00 – 5.00]	3.43 (1.02) – 3.00 [2.00 – 5.00]	3.64 (1.08) – 3.50 [2.00 – 5.00]	χ^2_F (2)	.22	0.07 (0.92) – 0.00 [-2.00 – 1.00]	0.29 (0.91) – 0.00 [-2.00 – 2.00]
	between-group	*Ws* .85				*Ws*	.63	.98
LOCF	EG	3.26 (0.81) – 3.00 [2 – 5]	3.58 (1.39) – 3.00 [2.00 – 7.00]	3.58 (1.17) – 4.00 [2.00 – 6.00]	χ^2_F (2)	.36	0.32 (1.06) – 0.00 [-1.00 – 3.00]	0.32 (0.95) – 0.00 [-1.00 – 3.00]
	CG	3.37 (1.16) – 3.00 [2 – 5]	3.42 (1.02) – 3.00 [2.00 – 5.00]	3.58 (1.07) – 3.00 [2.00 – 5.00]	χ^2_F (2)	.22	0.05 (0.78) – 0.00 [-2.00 – 1.00]	0.21 (0.79) – 0.00 [-2.00 – 2.00]
	between-group	*Ws* .83				*Ws*	.62	.88
WAIS F								
CC	EG	4.88 (1.26) – 5.00 [3.00 – 7.00]	5.19 (1.28) – 5.00 [3.00 – 7.00]	5.13 (1.31) – 5.00 [3.00 – 8.00]	χ^2_F (2)	.17	0.31 (0.60) – 0.00 [-1.00 – 1.00]	0.25 (0.86) – 0.00 [-1.00 – 3.00]
	CG	5.36 (1.08) – 5.00 [3.00 – 7.00]	5.36 (1.15) – 5.50 [3.00 – 7.00]	5.5 (1.29) – 5.00 [3.00 – 8.00]	χ^2_F (2)	.71	0.00 (0.88) – 0.00 [-1.00 – 2.00]	0.14 (0.77) – 0.00 [-1.00 – 2.00]
	between-group	*Ws* .26				*Ws*	.18	.82
LOCF	EG	4.84 (1.17) – 5.00 [3 – 7]	5.05 (1.22) – 5.00 [3.00 – 7.00]	5.00 (1.25) – 5.00 [3.00 – 8.00]	χ^2_F (2)	.37	0.21 (0.63) – 0.00 [-1.00 – 1.00]	0.16 (0.83) – 0.00 [-1.00 – 3.00]

	CG	5.11 (1.20) – 5.00 [3 – 7]	5.10 (1.24) – 5.00 [3.00 – 7.00]	5.75 (5.21) – 5.00 [3.00 – 8.00]	χ^2_F (2)	.71	0.00 (0.75) – 0.00 [-1.00 – 2.00]	0.11 (0.66) – 0.00 [-1.00 – 2.00]
	between-group	*Ws* .39				*Ws*	.24	1
WAIS C								
CC	EG	29.25 (13.32) – 27.00 [10.00 – 59.00]	30.06 (13.43) – 29.00 [8.00 – 59.00]	29.69 (14.30) – 29.50 [5.00 – 54.00]	χ^2_F (2)	.26	0.81 (5.09) – 2.50 [-13.00 – 6.00]	0.44 (6.90) – -0.50 [-8.00 – 17.00]
	CG	26.29 (15.13) – 26.00 [5.00 – 57.00]	27.29 (16.51) – 25.00 [7.00 – 61.00]	26.86 (14.34) – 27.50 [5.00 – 54.00]	χ^2_F (2)	.44	1.00 (4.76) – 1.50 [-7.00 – 10.00]	0.57 (4.99) – 2.00 [-9.00 – 8.00]
	between-group	*Ws* .53				*Ws*	.77	.43
LOCF	EG	28.21 (13.40) – 26.00 [9 – 59]	29.10 (13.75) – 26.00 [8.00 – 59.00]	28.79 (14.44) – 29.00 [5.00 – 54.00]	χ^2_F (2)	.22	0.89 (4.71) – 2.00 [-13.00 – 6.00]	0.58 (6.35) – 0.00 [-8.00 – 17.00]
	CG	24.32 (14.03) – 25.00 [5 – 57]	25.16 (15.26) – 24.00 [6.00 – 61.00]	24.84 (13.53) – 25.00 [5.00 – 54.00]	χ^2_F (2)	.48	0.84 (4.39) – 0.00 [-7.00 – 10.00]	0.53 (4.56) – 0.00 [-9.00 – 8.00]
	between-group	*Ws* .35				*Ws*	.62	.52

For change over time, we used Friedman's ANOVA test statistic, for within-group post hoc analysis of the differences Wilcoxon's sign rank test, and between-group Wilcoxon's rank-sum test. Significant comparisons with respect to baseline are indicated with * for p-values < .05 and ** for p-values < .01. CC, complete case analysis; CG, control group; Corsi B, Corsi Block Tapping Test Backward; Corsi F, Corsi Block Tapping Test Forward; EG, experimental group; FAB, Frontal Assessment Battery; LOCF, last observation carried forward; RAVLT, Rey Auditory Verbal Learning Test; RAVLT I, RAVLT Immediate; RAVLT D, RAVLT Delayed Recall; Star, Star Cancellation Test; TMT A, Trail Making Test A; TMT B, Trail Making Test B; WAIS, Wechsler Adult Intelligence Scale IV; WAIS F, WAIS Digit Span Forward; WAIS B, WAIS Backward; WAIS C, WAIS Digit Symbol Coding. χ^2_F , Friedman's ANOVA test statistic; *T*, Wilcoxon's sign rank test; *Ws*, Wilcoxon's rank-sum test.

Table A.4. Secondary outcomes of complete case analysis and last observation carried forward analysis. Clinical scales at baseline, after treatment and follow-up. Evaluation of within-group change over time and improvement T1 - T0 and T2 - T0, as well as between-group differences at these time points.

Scale	Baseline (T0)	After treatment (T1)	Follow-up (T2)	Friedman's ANOVA	T1-T0	T2-T0

		Mean (SD) – Median [97.5th and 2.5th percentile]						
MoCA								
CC	EG	21.05 (2.71) – 21.50 [16.00 – 25.00]	21.38 (4.11) – 21.00 [13.00 – 29.00]	22.25 (2.82) – 23.00 [17.00 – 25.00]	$\chi^2_F(2)$	.70	-0.13 (3.10) – -0.50 [-4.00 – 7.00]	0.75 (2.05) – 0.50 [-2.00 – 5.00]
	CG	20.21 (4.04) – 21.00 [12.00 – 25.00]	22.21 (3.68) – 23.50 [15.00 – 28.00]	22.29 (3.73) – 22.00 [16.00 – 30.00]	$\chi^2_F(2)$	.31	2.00 (3.53) – 2.00 [-4.00 – 7.00]	2.07 (3.97) – 1.50 [-4.00 – 9.00]
between-group		*Ws* .46				*Ws*	.09	.46
LOCF	EG	20.32 (3.92) – 21.00 [12.00 – 25.00]	20.74 (5.09) – 21.00 [12.00 – 29.00]	21.47 (4.41) – 23.00 [12.00 – 28.00]	$\chi^2_F(2)$	.65	0.42 (3.66) – 0.00 [-4.00 – 10.00]	1.16 (2.85) – 0.00 [-2.00 – 10.00]
	CG	20.05 (3.79) – 20.00 [12.00 – 25.00]	**21.79 (3.69) – 23.00 [15.00 – 28.00] ***	21.84 (3.73) – 22.00 [16.00 – 30.00]	$\chi^2_F(2)$	.35	1.74 (3.31) – 1.00 [-4.00 – 7.00]	1.79 (3.66) – 0.00 [-4.00 – 9.00]
between-group		*Ws* .76				*Ws*	.19	.77
BI								
CC	EG	95.31 (7.18) – 100.00 [80.00 – 100.00]	94.38 (9.29) – 100.00 [70.00 – 100.00	95.63 (8.92) – 100.00 [70.00 – 100.00]	$\chi^2_F(2)$	.07	-0.94 (3.75) – 0.00 [-15.00 – 0.00]	0.31 (4.64) – 0.00 [-15.00 – 5.00]
	CG	87.86 (21.64) – 100.00 [20.00 – 100.00]	88.57 (21.52) – 100.00 [20.00 – 100.00]	88.57 (21.52) – 100.00 [20.00 - 100.00]	$\chi^2_F(2)$	.50	0.71 (1.82) – 0.00 [0.00 – 5.00]	0.71 (3.31) – 0.00 [-5.00 – 10.00]
between-group		*Ws* .45				*Ws*	.09	.63
LOCF	EG	95.00 (7.64) – 100.00 [80.00 – 100.00]	94.21 (9.32) – 100.00 [70.00 – 100.00]	95.26 (9.05) – 100.00 [70.00 – 100.00]	$\chi^2_F(2)$	.07	-0.79 (3.44) – 0.00 [-15.00 – 0.00]	0.26 (4.24) – 0.00 [-15.00 – 5.00]
	CG	86.11 (20.04) – 95.00 [20.00 – 100.00]	87.22 (19.79) – 95.00 [20.00 – 100.00]	87.22 (19.79) – 95.00 [20.00 – 100.00]	$\chi^2_F(2)$	.23	1.11 (2.74) – 0.00 [0.00 – 10.00]	1.11 (3.66) – 0.00 [-5.00 – 10.00]
between-group		*Ws* .15				*Ws*	.05	.92
FM-UE								

CC	EG	52.38 (15.16) – 58.50 [15.00 – 66.00]	**53.94 (14.69) – 59.50 [15.00 – 66.00] ***	54.06 (13.46) – 59.00 [16.00 – 66.00]	$\chi^2_F(2)$	.11	1.56 (2.25) – 0.50 [-1.00 – 6.00]	1.69 (5.11) – 1.00 [-8.00 – 13.00]
	CG	53.08 (19.01) – 62.00 [5.00 – 66.00]	52.85 (19.10) – 63.00 [5.00 – 66.00]	53.25 (20.70) – 62.50 [6.00 – 66.00]	$\chi^2_F(2)$	.25	-0.23 (1.09) – 0.00 [-3.00 – 1.00]	0.15 (2.73) – 1.00 [-6.00 – 4.00]
between-group		*Ws* .71				*Ws*	**.03**	.43
LOCF	EG	53.79 (14.36) – 60.00 [15.00 – 66.00]	**55.11 (13.82) – 60.00 [15.00 – 66.00] ***	55.21 (12.73) – 60.00 [16.00 – 66.00]	$\chi^2_F(2)$	.11	1.32 (2.14) – 0.00 [-1.00 – 6.00]	1.42 (4.71) – 0.00 [-8.00 – 13.00]
	CG	50.44 (19.45) – 62.00 [5.00 – 66.00]	50.25 (19.50) – 60.50 [5.00 – 66.00]	50.56 (20.10) – 60.00 [6.00 – 66.00]	$\chi^2_F(2)$	.25	-0.19 (0.98) – 0.00 [-3.00 – 1.00]	0.13 (2.45) – 0.00 [-6.00 – 4.00]
between-group		*Ws* .74				*Ws*	**.03**	.48
MMSE								
CC	EG	27.19 (2.20) – 27.50 [23.00 – 30.00]	27.50 (1.46) – 27.50 [25.00 – 30.00]	27.44 (2.06) – 28.00 [22.00 – 30.00]	$\chi^2_F(2)$	.67	0.31 (1.49) – 1.00 [-2.00 – 2.00]	0.25 (1.29) – 0.00 [-2.00 – 3.00]
	CG	27.07 (1.82) – 27.50 [24.00 – 29.00]	27.62 (2.36) – 28.00 [24.00 – 30.00]	**28.14 (1.99) – 28.50 [24.00 – 30.00] ****	$\chi^2_F(2)$	**.03**	0.29 (2.09) – 0.50 [-4.00 – 4.00]	1.07 (1.07) – 1.00 [-1.00 – 3.00]
between-group		*Ws* .78				*Ws*	.98	.06
LOCF	EG	27.00 (2.08) – 27.00 [23.00 – 30.00]	26.74 (2.79) – 27.00 [17.00 – 30.00]	26.68 (3.07) – 28.00 [17.00 – 30.00]	$\chi^2_F(2)$	.85	-0.26 (2.73) – 0.00 [-10.00 – 2.00]	-0.32 (2.63) – 0.00 [-10.00 – 3.00]
	CG	26.68 (2.31) – 27.00 [22.00 – 29.00]	27.05 (2.84) – 28.00 [22.00 – 30.00]	**27.63 (2.65) – 28.00 [22.00 – 30.00] ****	$\chi^2_F(2)$	**.02**	0.37 (1.89) – 0.00 [-4.00 - 4.00]	0.95 (1.13) – 1.00 [-1.00 – 3.00]
between-group		*Ws* .79				*Ws*	.77	**.04**

For change over time, we used Friedman's ANOVA test statistic, for within-group post hoc analysis of the differences Wilcoxon's sign rank test, and between-group Wilcoxon's rank-sum test. Significant comparisons with respect to baseline are indicated with * for p-values < .05 and ** for p-values < .01. BI, Barthel Index; CC, complete case analysis; CG, control group; EF, executive functioning; EG, experimental group; FM-UE, Fugl-Meyer Assessment for the upper limb; LOCF, last observation carried forward; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; SA, spatial awareness; χ^2_F, Friedman's ANOVA test statistic; *T*, Wilcoxon's sign rank test; *Ws*, Wilcoxon's rank-sum test.

Table A.5. Improvement or deterioration in ASCS from baseline to after treatment split by different cut-offs as a percentage of total patients (n=30) per group.

Group	Attention		Memory		EF		SA		GCF	
Improvement	*>0.5 SD*	*>1 SD*	*>0.5 SD*	*>1 SD*	*>0.5 SD*	*>1 SD*	*>0.5 SD*	*>1 SD*	*>0.5 SD*	*>1 SD*
EG	13.33%	0	13.33%	3.33%	13.33%	0	30.00%	13.33%	23.33%	6.67%
CG	13.33%	0	10.00%	0	16.67%	0	16.67%	10.00%	13.33%	3.33%
Deterioration	*<-0.5 SD*	*<-1 SD*	*<-0.5 SD*	*<-1 SD*	*<-0.5 SD*	*<-1 SD*	*<-0.5 SD*	*<-1 SD*	*<-0.5 SD*	*<-1 SD*
EG	0	0	6.67%	0	3.33%	3.33%	3.33%	3.33%	3.33%	3.33%
CG	3.33%	0	0	0	6.67%	0	10.00%	0	3.33%	0

CG, control group; EG, experimental group, EF, executive functioning; GCF, generalized cognitive functioning; SA, spatial awareness

Table A.6. Improvement or deterioration in ASCS from baseline to follow-up split by different cut-offs as a percentage of total patients (n=30) per group.

Group	Attention		Memory		EF		SA		GCF	
Improvement	*>0.5 SD*	*>1 SD*	*>0.5 SD*	*>1 SD*	*>0.5 SD*	*>1 SD*	*>0.5 SD*	*>1 SD*	*>0.5 SD*	*>1 SD*
EG	20.00%	3.33%	26.67%	3.33%	13.33%	6.67%	33.33%	20.00%	33.33%	10.00%
CG	10.00%	0	16.67%	6.67%	10.00%	3.33%	16.67%	13.33%	20.00%	0
Deterioration	*<-0.5 SD*	*<-1 SD*	*<-0.5 SD*	*<-1 SD*	*<-0.5 SD*	*<-1 SD*	*<-0.5 SD*	*<-1 SD*	*<-0.5 SD*	*<-1 SD*
EG	0	0	3.33%	0	6.67%	0	3.33%	0	0	0
CG	0	0	0	0	3.33%	3.33%	10.00%	6.67%	3.33%	3.33%

CG, control group; EG, experimental group, EF, executive functioning; GCF, generalized cognitive functioning; SA, spatial awareness

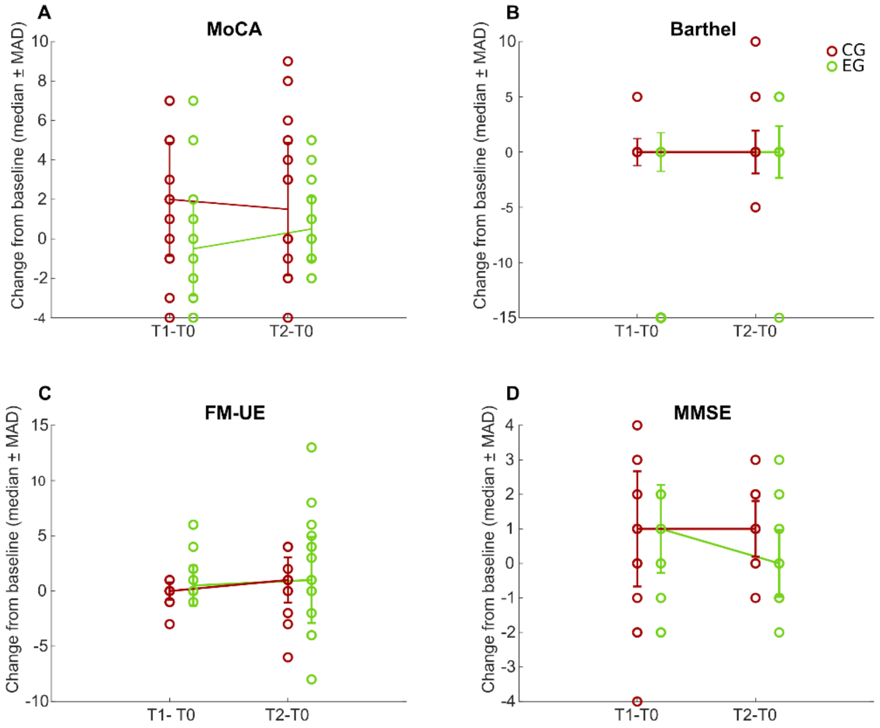


Figure A.1. Secondary outcome measurements.
Change in (A) MoCA, (B) BI and (C) FM-UE and (D) MMSE from baseline to after treatment (T1) and to follow-up (T2) for the experimental group (EG, green) and control group (CG, red). Error bars indicate median absolute deviation (MAD) for each group. The individual data for each subject is indicated with dots.

Appendix B Additional files for Chapter 8

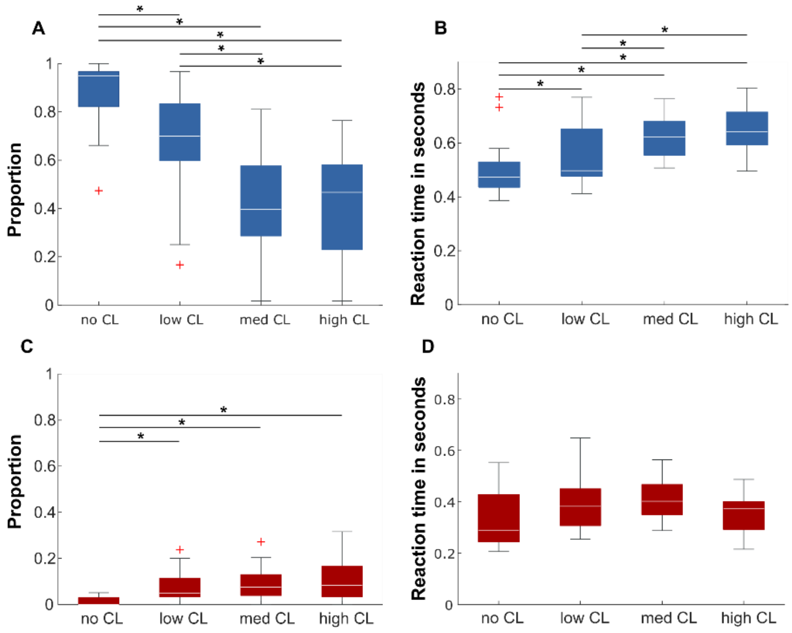


Figure B.1. Conscious and subconscious detections across all cognitive loads.
A) Proportion of all displacements that were consciously detected by button-presses. B) Latency of button presses. C) Proportion of all displacements that were subconsciously detected by saccades towards the displacement position. D) Latency of saccades. Significant differences between load conditions are indicated with a star. Abbreviations: CL, cognitive load; mid, medium.

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