VIRTUAL REALITY BASED STROKE NEUROREHABILITATION

Development and Assessment of the Rehabilitation Gaming System

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POMPEU FABRA

To

Juan, Agustín, Francisco, Mercedes, Carlos, Jordi, Francisco, Juan, Rafael, Juan, Manuel, Beatriz, Modesto, Boyan, Luís, Dora, Isabel, Luís, Merce, Vicente, José, Joaquín, Soledad, Natividad, Flor, Pilar, Concepción, Nicolás, Josep, Dolores, Juan, Antonio, José, Dolores, Florentina, Antonio, Adrián, Luisa, Josefa, Concepción, Gonzalo, Enrico, Valentín, Remedios, Maria Luisa, Teresa, Juan Carlos, Emilio, Manuel, Vicenç, Manuel, Josep, Ángeles, Elena, Enrique, Inma, Ayao, Jordi, Begoña, Maria, Montserrat, Asunción, Joana, Alfonso, Carme, Florencio, Ángel and Alfredo.

It would not have been possible without you. Thank you!

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Abstract

Given the high incidence and impact of stroke, the need has arisen to find more automated and self-managed rehabilitation approaches. A promising candidate is the use of Virtual Reality, and a number of systems have been proposed. Thus far, however, it is not clear what the benefits of these systems are when compared to conventional methods. Here we present the rationale, development and results on the clinical impact of one such system, the Rehabilitation Gaming System (RGS). RGS combines concepts of action execution and observation with a psychometric evaluation to provide a personalized and automated training. The RGS effectively adjusts to the individual features of the user, allowing for a minimally supervised deployment of individualized rehabilitation protocols. Our results show that rehabilitation with the RGS facilitates the functional recovery of the upper extremities in the acute and chronic stages of stroke, and that this system is therefore a valuable tool for rehabilitation.

Resumo

Dado o alto nível de incidência e impacto dos Acidentes Vasculares Cerebrais (AVC), surge a necessidade de encontrar estratégias de reabilitação mais automatizadas. Uma possível estratégia baseia-se no uso de sistemas de Realidade Virtual. Embora já existam alguns destes sistemas, não é óbvio quais são os seus benefícios em comparação com métodos de reabilitação tradicionais. Nesta tese, apresentamos o conceito, desenvolvimento e resultados do impacto clínico de um sistema deste tipo: o Rehabilitation Gaming System (RGS). O RGS combina a observação e execução de acções com uma avaliação psicométrica, para proporcionar um tratamento personalizado e automatizado. O RGS ajusta-se de forma efectiva às características do utilizador, permitindo desta forma a criação de protocolos de reabilitação individualizados. Os nossos resultados indicam que o RGS facilita a recuperação funcional das extremidades superiores nas fases aguda e crónica depois de um AVC, o que torna este sistema uma ferramenta valiosa para reabilitação.

Prologue

During the last century, technology has developed tremendously allowing mankind to progress in multiple areas. One of the main target areas has always been health. Partially due to the existence of new technologies, amazing advancements have been made during the last decades on the understanding, prevention, diagnostics, cure and rehabilitation of a number of pathologies. However, there is still much to be done, particularly in the understanding and rehabilitation of brain related diseases. This thesis aims at making a contribution in this field.

Here we investigated the use of new technologies for the rehabilitation of motor deficits following a brain lesion in particular due to stroke. Stroke has a high incidence level worldwide and leads to life-long motor and/or cognitive impairments with an enduring impact on the social and labor life of the patients. Moreover, taking into account that the recovery process following stroke is slow, it leads to high societal demands in terms of infrastructures and rehabilitation expenses. In addition, due to the high number of stroke cases and limited number of rehabilitation hospitals, these patients cannot always have the desired long-term rehabilitation. Thus, there is the need of developing novel strategies that optimize the rehabilitation process and maximize and/or accelerate recovery.

Given the life-long plasticity of the brain one could assume that recovery could be facilitated by the harnessing of mechanisms underlying neuronal reorganization. However, at the moment it is not clear how this reorganization can be effectively mobilized. Novel technology based neurorehabilitation techniques hold promise to address this issue. For instance, Virtual Reality (VR), that some years ago was only seen as an entertaining application, seems now to be a promising tool capable of stimulating and enhancing motor recovery. One of the main advantages of this technology is that it can be shaped to address the specific requirements for an effective rehabilitation treatment.

This thesis describes the development and assessment of a VR based system specifically designed to promote and maximize recovery following neurological damage: the Rehabilitation Gaming

System (RGS). The RGS was built on top of a number of premises concerning the mechanisms of brain recovery, and in the context of this thesis it has been shaped to address the rehabilitation of motor deficits of the upper extremities following stroke. The RGS tracks arm and finger movements in order to map them onto a virtual environment. In this manner, the user of the RGS controls the movements of two virtual limbs that are presented in a first-person perspective. The rehabilitation scenario presented in this thesis, Spheroids, consists of intercepting, capturing and placing spheres that move towards the user. The main hypothesis of the RGS is that bimanual task oriented action execution combined with the observation of virtual limbs that reproduce the executed movement creates the conditions that facilitate the functional reorganization of the motor and premotor systems affected by stroke. In this action execution and observation paradigm, recovery could be promoted through the engagement of undamaged motor areas or by recruiting alternative perilesional or contralesional circuits. This, however, requires that a communication channel exists that allows external modulation of the states of these alternative circuits. We hypothesize that such an interface could be provided by neurons such as those found in the Mirror Neuron System (MNS), which have the property of being active both during the execution of goal-oriented actions and during the observation of the same actions performed by others. It is exactly this connection between the perception of actions and their execution what RGS exploits even when the motor actions themselves cannot be performed due to a lesion. The work described in this thesis gives further support on the benefits of using VR derived methods applied to the field of neurorehabilitation. We believe that the results presented in this dissertation are encouraging and make a relevant contribution to the current state-of-the-art.

In the first two chapters of this dissertation we describe the background and main topics underlying the scientific hypothesis of the RGS. Specifically, in the first chapter we define stroke, describe its main symptoms and consequences and refer to the existing clinical assessment and rehabilitation procedures. In addition, we review the current state-of-the-art of VR systems that have been deployed for upper limb rehabilitation following stroke, and report their main results. In the second chapter, we review the neural substrates of the mechanisms mediating between perception and action, e.g. the MNS, and we discuss how they can be exploited in novel rehabilitation approaches. In the third chapter we introduce the RGS and how it combines concepts of action execution and observation with a psychometric evaluation to provide a personalized and automated training. In this chapter, the different components of the RGS such as the tracking system, the virtual scenario (Spheroids), and a model for individualized training (Personalized Training Module) are also described. Of particular interest is the development of the training module, which allows the individualization of training based on the psychometrics of the task, and the corresponding assessment trials with patients and healthy subjects. Finally, chapters four and five describe two clinical studies that were designed to assess the impact of RGS on stroke recovery. In a first study, patients in the acute phase of stroke used the RGS three times a week during approximately three months. The results of this pilot study evidence the benefits of using this technology in the early stages of stroke. In a second study, chronic stroke patients used the RGS five times a week for a month in three different interface configurations. This second study allowed us to identify which interface technologies are more beneficial and therefore should be included in the RGS in order to strengthen its effectiveness. In the last chapter, we present the conclusions of this thesis where we summarize the main achievements of our work and discuss the outlook.

Part of the work described in this thesis had the contribution of a number of people, mainly on what concerns the development of the hardware and software underlying RGS, and the recruitment and clinical evaluation of the patients. Sergi Bermúdez i Badia developed the tracking system (AnTS) and was involved in programming the virtual scenarios, and in the integration of RGS with the exoskeleton and the haptic interface; Armin Duff and Lukas Zimmerli were involved in programming the virtual scenarios, and together with Bernhard Spanlang developed the 3D avatar; Juan Camilo Moreno was involved in the integration of RGS with the exoskeleton; César Rennó Costa was involved in the integration of RGS with the haptic interface. The PERCRO group, Scuola Superiore Sant'Anna, provided us with the haptic interface (GRAB). On the clinical side, all clinical assessment was done in the Hospital de L'Esperança in Barcelona. Esther Duarte Oller provided all the conditions and support for the execution of the clinical trials, and was involved in the design of the study, and in the recruitment and clinical evaluation of the patients; Helena Renom was involved in the recruitment and clinical evaluation of the patients; Anna Morales provided support in the clinical evaluation of patients; and Nohora Rueda and Susana Redon provided support in the recruitment of patients.

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1. STROKE, REHABILITATION AND VIRTUAL REALITY

Parts of the content of this chapter have been published in (1):

(1) Cameirão MS, Bermúdez i Badia S, Verschure PFMJ: Virtual Reality Based Upper Extremity Rehabilitation following Stroke: a Review. Journal of CyberTherapy & Rehabilitation 2008, 1:63-74.

1.1 Introduction

The use of Virtual Reality (VR) in the field of neurorehabilitation has grown immensely in the last decade. VR is a set of computer technologies that provide an interactive interface to a computer generated environment. In this environment, the individual can see, hear and navigate in a dynamically changing scenario in which he or she participates as an active user by modifying the environment according to his or her actions. VR has been deployed in different rehabilitation contexts and a number of studies suggest that this technology could have a positive impact on functional recovery (see (Holden 2005; Adamovich, Fluet et al. 2009; Lucca 2009) for reviews).

The use of VR technologies in rehabilitation has a number of distinguishing features. First, it allows deploying specific scenarios based on previous knowledge of the mechanisms of recovery. Second, it allows a minimally supervised intensive training adjusted to the individual needs of the user. Third, training can be defined within scenarios that allow the patients to engage in task-oriented activities. Fourth, it is a real-time high-resolution monitoring tool, allowing for the quantitative assessment of relevant properties of deficits, performance and recovery. This latter aspect can be combined with more standard clinical evaluation methods, providing complementary data for measuring diagnostics. Fifth, the versatility of VR technologies can play an important role in engaging motivational factors, a key aspect in recovery (Maclean, Pound et al. 2000). And sixth, VR based rehabilitation systems easily transfer from clinic based training to at home applications for telerehabilitation, creating a continuum of diagnostics and training possibilities.

In this chapter we describe a number of VR paradigms with the objective to identify underlying principles and routes for future research and applications. We in particular analyze different systems and methods that have been developed for motor rehabilitation, focusing on the rehabilitation of the upper extremities following stroke. We start by briefly referring to the problematic of stroke, its assessment and its current rehabilitation strategies. Subsequently, we review studies of virtual reality systems for the rehabilitation of upper extremity deficits after stroke and describe their major results.

1.2 Stroke and its Rehabilitation

Stroke represents one of the main causes of adult disability and loss of quality of life worldwide, with about 16 million first event stroke incidences per year. In Spain, the estimated rate of incidence is of about 145 cases per 100,000 inhabitants (Vega, Zurriaga et al. 2009). It is one of the biggest sources of burden of disease in high- and middle-income countries (Mathers and Loncar 2006; Strong, Mathers et al. 2007; WHO 2008), with an estimated cost to society of over $102 billions in the United States and the European Union combined (Di Carlo 2009).

A stroke is a brain lesion of vascular nature that can be due to a blockage in a blood vessel that affects the blood supply (ischemic stroke), or due to a vessel burst (hemorrhagic stroke) (Figure 1.1). The ischemic strokes are the most common ones accounting for about 85% of the total number of cases (Squire, Albright et al. 2009). Depending on the mechanism causing the ischemic stroke, these can be classified as thrombosis (caused by a thrombus cutting the flow of blood), embolism (caused by a wandering clot that also cuts the flow of blood), or systemic hypoperfusion (caused by a decrease in the blood supply). In all those cases, the middle cerebral artery is usually the most affected one (Squire, Albright et al. 2009). Risk factors that lead to a stroke are among others hypertension, diabetes, heart disease, smoking, alcohol and drug abuse, obesity, and genetic factors.

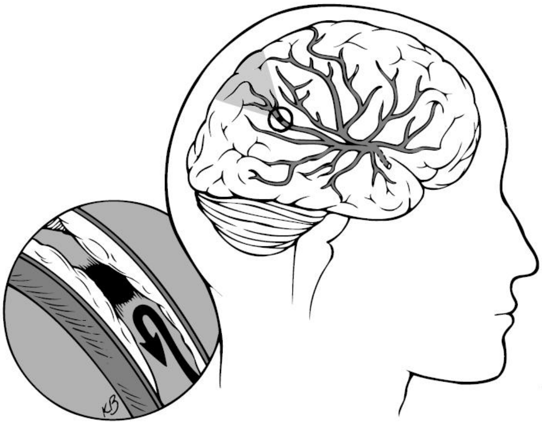

Figure 1.1. Ischemic stroke. A ischemic stroke occurs when a clot clocks a blood vessel, cutting off the blood flow to a part of the brain (ASA).

The initial diagnostics of stroke is done by imaging techniques (the most common are Computed Tomography Scans and Magnetic Resonance Imaging) and neurological examination. Here, the most widely used scale to gauge the severity of stroke is the National Institutes of Health Stroke Scale (NIHSS) (Brott, Adams et al. 1989). Moreover, there are classification systems for stroke that are based on the extent of the initial symptoms. This is the case of the Oxford Community Stroke Project Scale (Bamford, Sandercock et al. 1991) and the Trial of Org 10172 in Acute Stroke Treatment (TOAST) (Adams, Bendixen et al. 1993).

Following stroke, several cognitive and motor deficits may be present such as paralysis, abnormal posture, abnormal movement, loss of coordination, neglect, aphasia, and others depending on the lesion site (Kunesch 1995). Up to 85% of patients initially show a motor deficit of the arm contralateral to the lesion, and 55 to 75% display persistent functional limitations 3 to 6 months after stroke (Wade 1983; Lai, Studenski et al. 2002). Restoration of normal motor function in the hemiplegic upper limb is observed in less than 15% of patients with initial paralysis (Hendricks, van Limbeek et al. 2002). The deficits derived from stroke can be assessed by a number of scales designed specifically to evaluate the individual aspects (Table 1.1). Common symptoms of stroke are also mood disorders, depression (Thomas and Lincoln 2006) and pain (Chae, Mascarenhas et al. 2007). Hence, both the economical and the psycho-social impact of stroke emphasize the need to find effective diagnostics, treatment and rehabilitation approaches.

In the initial weeks after stroke, the brain undergoes some spontaneous recovery of the spared tissue through restitution of the penumbra and resolution of diaschisis (Kwakkel, Kollen et al. 2004). In principle, further recovery can be achieved through the rescue and/or cortical reorganization around the damaged brain areas, or by unmasking latent neural networks (Johansson 2000; Butefisch 2004; Krakauer 2005; Nudo 2006; Murphy and Corbett 2009). The question arises: how can these mechanisms be recruited to drive the rehabilitation process effectively? There is a considerable variety of treatment hypotheses and therapies, but their effectiveness is difficult to assess and compare due to the difficulty of performing studies with large enough homogenous groups of patients in terms of stroke type and functional deficit. Nevertheless, in the last years, effort has been made in developing neuroscience based methods that specifically take into account our understanding of the neural mechanisms underlying recovery and therefore aim to promote functional changes within surviving motor networks (Schaechter 2004; Kalra and Ratan 2007).

Irrespective of the method involved, stroke recovery has been shown to be strongly related to treatment frequency and intensity, and task-specificity (Kwakkel, Kollen et al. 2004; Schaechter 2004; Van Peppen, Kwakkel et al. 2004). Increasing the therapy time in the first months post-stroke has been shown to promote increased independence in Activities of Daily Living (ADL) and a reduction of the hospitalization period (Kwakkel, van Peppen et al. 2004; Sonoda, Saitoh et al. 2004). In addition, the repetitive training of movements has been shown to facilitate cortical reorganization (Seitz, Butefisch et al. 2004). Added benefits have been observed when the rehabilitative training is task-specific (Winstein, Rose et al. 2004; Bayona, Bitensky et al. 2005). Finally, there is evidence favoring the execution of simultaneous bilateral training over unilateral training during rehabilitation (Cauraugh and Summers 2005; Lin, Chen et al. 2010).

Table 1.1. Clinical assessment scales for stroke. Adapted from the Internet Stroke Center (www.strokecenter.org).

Property	Name of the Scale
Consciousness Level	Glasgow Coma Scale
Stroke deficit	NIH Stroke Scale Canadian Neurological Scale
Global disability	Rankin Scale
Disability in ADL	Barthel Index Functional Independence Measure (FIM)
Mental status	Folstein Mini-Mental State Examination Neurobehavioral Cognition Status Exam (NCSE)
Motor function	Fugl-Meyer Assessment Test Motor Assessment Scale Motricity Index
Balance	Berg Balance Assessment
Mobility	Rivermead Mobility Index
Spasticity	Ashworht Scale
Speech and language	Boston Diagnostic Aphasia Examination Porch Index of Communicative Ability (PICA) Western aphasia Battery
Depression	Beck Depression Inventory (BDI) Center for Epidemiologic Studies Depression (CES-D) Geriatric Depression Scale (GDS) Hamilton Depression Scale
Instrumental ADL	PGC Instrumental Activities of Daily Living Frenchay Activities Index
Manual Dexterity	Box and Block Test Nine Hole Peg Test
Family	Family Assessment Device (FAD)
Health status / quality of life	Medical Outcomes Study (MOS) Sickness Impact Profile (SIP)

A variety of other non-pharmacological treatments are being widely investigated (Kalra and Ratan 2007; O'Dell, Lin et al. 2009). The Constraint-Induced Movement Therapy (CIMT) aims at avoiding the non-use of the paretic upper extremity by restraining the movement of the non-affected arm (Blanton, Wilsey et al. 2008;

Sawaki, Butler et al. 2008). A number of neuromuscular electrical stimulation methods are used to initiate, facilitate and/or complete movement (Chae, Sheffler et al. 2008; Popovic, Sinkaer et al. 2009). Transcranial Brain Stimulation (TBS) aims at promoting plastic changes by directly inducing electrical currents in specific brain areas (Bolognini, Pascual-Leone et al. 2009). Other proposed therapies rely on the activation of brain areas bridging between perception and action by imagery or observation of actions (Ertelt, Small et al. 2007; Zimmermann-Schlatter, Schuster et al. 2008; Ezendam, Bongers et al. 2009; Garrison, Winstein et al. 2010).

Finally, in the recent years, there has been a growing interest in the use of more technology driven methods (O'Dell, Lin et al. 2009). This is the case of therapies that use robotics, haptic interfaces, VR, or combinations of these (Holden 2005; Lucca 2009; Reinkensmeyer 2009; Volpe, Huerta et al. 2009; Lo, Guarino et al. 2010). In the following section we present VR as rehabilitation paradigm and we review a number of VR based rehabilitation systems.

1.3 Virtual Rehabilitation

The term Virtual Reality (VR) was coined in the early 1980s by Jaron Lanier, who founded VPL research, the first company to sell VR products. Before that moment, VR has also been described as "artificial reality", "cyberspace" or "virtual worlds". VR is the result of the evolution of computers from a utilitarian instrument that was used to make numerical computations to a machine that could adapt to the user's cues to create an almost lifelike experience. Generally, VR is the term that is used to describe computer-simulated environments that can reconstruct real world environments as well as imaginary worlds. VR is often used to describe the wide variety of applications commonly associated with immersive, highly visual, 3D environments. Nevertheless, nowadays VR experiences are supported not only by realistic immersive graphics but also by means of sound and/or haptic/force-feedback systems. Although VR has been popularized as a new form of entertainment, it has applications in business, industry, and medicine.

Currently, several VR systems and methods have been developed for motor rehabilitation of the upper extremities following stroke based on different paradigms and hypotheses. Here we review a number of studies that explore the different aspects of VR based rehabilitation methods.

a) Virtual Teaching

VR systems that use the virtual teaching paradigm make use of a “virtual teacher”, whose movements are to be followed by the user (Figure 1.2a). This technique has the advantage of providing visual information on the correct movement trajectories to be performed, minimizing abnormal movement execution. It is being used since about one decade by Holden et al. as a “learning by imitation” paradigm that provides enhanced visual feedback (Holden, Todorov et al. 1999; Holden and Dyar 2002). The hypothesis is that the repeated observation of this virtual tutor leads to recovery through training of motor skills and/or by the activation of the primary motor area (M1) by means of perceptual systems. M1 is the main responsible of planning and execution of motor actions. In an initial pilot, two chronic stroke patients used the virtual teacher to train reaching movements in a task that consisted in placing an envelope in a virtual mailbox positioned at different locations and orientations (Holden, Todorov et al. 1999). Virtual and real movements were used to provide augmented feedback about the performance of the patients. Results showed that both patients improved in the virtual tasks and also in the real world reaching tasks, showing the ability to transfer VR task abilities to the real world. However, there were no significant changes in the standard clinical measures, with only one of the subjects presenting a slight increase of 17% in the total Fugl-Meyer Test for the upper extremities, a clinical scale that evaluates motor function (Table 1.1) (Fugl-Meyer, Jaasko et al. 1975).

In a later study, nine patients trained reaching tasks in a new version of this system that also included new virtual scenes besides the “virtual mailbox”, and a scoring system to provide additional feedback (Holden and Dyar 2002). This system captured the patient’s movement by means of electromagnetic motion tracking sensors and these movements were mapped onto the movements of a virtual representation of the upper extremities. Moreover, the subjects held a real object, e.g. a ball, which was also represented in the virtual scenes. The purpose of this was to increase the sense of immersion during the task and also to elicit the execution of natural movements. Patients showed improvements in the virtual task and also significant improvements in standard clinical tests. The authors emphasized that although the results were quite promising they could not warrant definite statements on what exact characteristics of their system triggered the improvements in function. Moreover, there is the added problem of not having a control group for comparison, necessary for an empirical validation. In a follow up study, further tasks were added to this virtual environment to train different movements (reaching, hand-to-body, and hand grasp/release) and it was used within a telerehabilitation system (Holden, Schwamm et al. 2005). Preliminary tests with two chronic stroke patients showed the advantages of this kind of systems in remote training. The patients showed improvements in the performance of the virtual task and also in the associated clinical measures, with sustained gains at follow-up. In a later study, an improved version of this system was used with eleven stroke patients, with significant clinical results at mid and end of treatment (3 and 6 weeks, respectively), and up to four months follow-up (Holden, Dyar et al. 2007). Unfortunately, again no controls were used in this study.

Piron et al. put particular emphasis on the importance of the delivery of appropriate feedback during motor recovery (Piron, Tonin et al. 2005). This feedback can be provided to inform about the quality of the performed movement (knowledge of performance) and the goal of the task (knowledge of results). The authors wanted to investigate whether continuous information provided on the quality of the movement of the patients combined with the observation of correct movements could lead to an enhancement in recovery. The used setup, the Virtual Environment Training (VET) system, had a set of exercises to train several reaching tasks by the imitation of a virtual therapist. Subjects were asked to grasp real objects that were tracked by a magnetic sensor (Figure 1.2b). The software was the same used by the group of Holden. The movement trajectories were displayed during the execution of the task and were also presented to the subjects at the end of the task. 45 chronic stroke patients used the system during 1 hour, five days a week, during 1 month. The results showed a significant improvement at the movement level, but with poor outcomes in the performance of activities of daily living. There were also observed improvements in the kinematics parameters of the reaching movements (mean velocity and mean duration). Moreover, the pattern of the grasping movements of the paretic arm approached the correct pattern of movements of the nonparetic one. In a later study, this same type of VR training was used with patients in the early stage of stroke (first three months) (Piron, Tombolini et al. 2007). 38 patients participated in this study, being separated in two groups: 25 subjects received Reinforced Feedback in Virtual Environment (RFVE) and 13 patients (control group) received a time matched amount of conventional therapy. After the treatment period, the RFVE group presented significant clinical improvements, as opposed to the control group. This evidenced the advantage of the use of VR in the early stages of stroke. Recently these authors investigated the effects of a similar system, but with the treatment being delivered remotely by internet to the home of the patients (Piron, Turolla et al. 2009). 18 stroke patients performed virtual tasks within this system five days per week during 4 weeks. 18 control patients underwent time duration matched conventional therapy. The treatment was supervised remotely by a therapist. At the end of treatment both groups showed significant improvement compared to baseline, the VR groups being significantly better than the control group at the Fugl-Meyer score for upper extremities. Gains were maintained at one month follow-up for both groups.

b) Haptic Feedback

Recently, VR training was also combined with haptic feedback. This multimodal input deployed to the user allows for an increase of the sense of immersion. For instance, Broeren et al. proposed a setup to train arm reaching. The setup consisted of a haptic force-feedback interface, PHANToM (SensAble Technologies, USA), connected to a virtual environment with stereoscopic vision, allowing for a sense of touch with virtual solid objects (Figure 1.2c) (Broeren, Rydmark et al. 2004; Broeren, Rydmark et al. 2007). Force-feedback was provided by a haptic stylus. In a single case study, a 3-month post-stroke patient improved finger dexterity, grip force and endurance after a 4-month VR treatment (Broeren, Rydmark et al. 2004). In addition, the patient reported an increase in the use of the paretic arm during activities of daily living. In a later pilot, five chronic stroke patients with hemiparesis used the system during five weeks (Broeren, Rydmark et al. 2007). All patients progressed to the highest difficulty in the game level and also some improvements in aspects of motor performance were observed. However, only one of the patients showed an improvement in the performance of ADLs.

c) Video Capture Virtual Reality

Video capture virtual reality is a technique that consists of tracking the movements of a user and mapping them to an image embedded in a virtual environment. This system is particularly useful in the case of severely impaired patients as it allows full-body interaction with the environment. The users can see themselves within a virtual scenario in a mirror image view, as opposed to the first-person point of view provided by head mounted displays (Figure 1.2d). This way, users can have feedback about their body posture and quality of movement. Weiss et al. are working with such systems and the pilots carried out to date suggest a positive impact on the recovery of functionality in stroke patients (Kizony, Katz et al. 2003; Kizony, Katz et al. 2004). Weiss et al. modified the VividGroup's Gesture Xtreme VR (www.vividgroup.com) (a platform formerly used for entertainment and education) in order to use it in neurological rehabilitation. In a preliminary usability case study, its impact on the recovery of a stroke patient six months post-stroke was assessed (Kizony, Katz et al. 2003). The tasks consisted of intercepting and/or avoiding virtual objects. The system had a good acceptance, and the patient was able to interact within the virtual scenarios without feeling side effects. Afterwards, a study was carried out with 13 stroke patients (Kizony, Katz et al. 2004). In addition to the clinical assessment, patients were inquired about their sense of presence, the perceived difficulty and their overall impressions during the tasks. The self-report questionnaires revealed that the patients enjoyed the virtual tasks, suggesting a positive contribution to the patient's motivation. Moreover, this study suggested that there is a relation between the personal characteristics of the patients and preferences, and the properties of the virtual environment that influence performance.

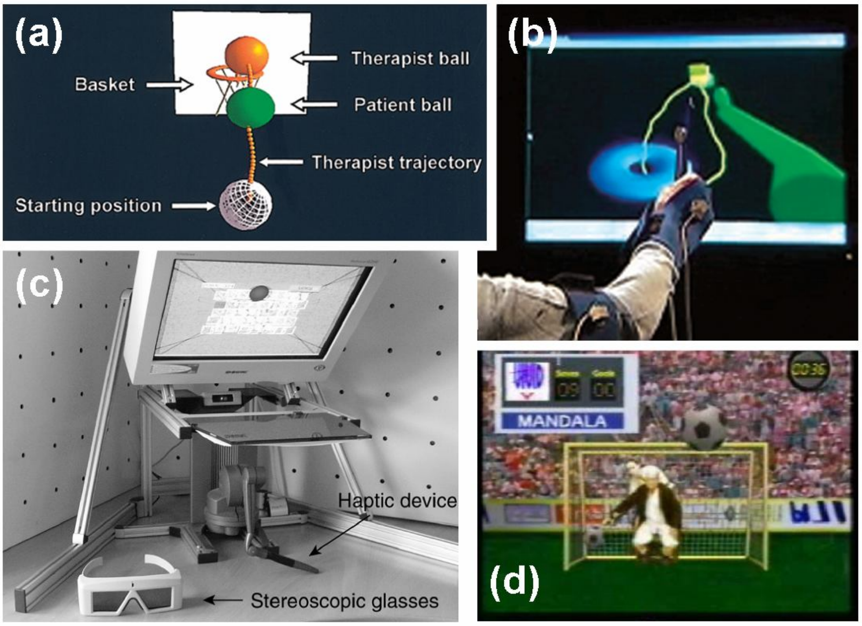

Figure 1.2. Virtual teaching, haptic feedback and video capture virtual reality. (a, b). Virtual teacher: the patient follows the movements of a virtual teacher who shows the correct movement trajectory in a given task. Adapted from (Piron, Tonin et al. 2005). (c) Workbench that combines haptic feedback with a virtual environment with stereoscopic vision. Adapted from (Broeren, Rydmark et al. 2007). (d) Video Capture Virtual Reality: with this setup the patients see a full-body mirror image of themselves within the virtual environment. Adapted from (Kizony, Katz et al. 2004).

d) Arm Weight Support

VR systems can also be augmented with advanced interface systems such as exoskeletons that allow arm gravity support, facilitating exercising. Arm support is commonly used in the early stages following stroke, being particularly relevant to patients with severe to mild impairment as they cannot sustain movement against gravity. One of VR system coupled with an exoskeleton is the T-WREX, which comprises an orthosis that facilitates the movement of the arm in a broad range, a grip sensor for grasp training, and software to train functionality (Figure 1.3a) (Sanchez, Liu et al. 2006). Patients can train with different games related to ADL with emphasis on the repetitive training of different ranges of movement and grips. The system was tested with 5 chronic stroke patients during 2 months in order to assess the effect of gravity balance on static positioning and the effect of gravity assisted movements in recovery. After training, the movements of the patients showed to be more effective when gravity balance was present, with an improvement in the properties of reaching. The subjects also displayed improvements in their ability to move their arms, with some of them showing increased grip strength and augmented distance of reaching with and without support. In a later randomized controlled study, chronic stroke patients were divided in two groups: 11 patients were assigned to 8 weeks of therapy with the T-WREX and 12 control patients received only conventional therapy for the upper extremities (Housman, Le et al. 2007). The group that used T-WREX showed significant improvements in the Fugl-Meyer scores when compared to the control group. Moreover, subjective questionnaires revealed a preference for the T-WREX when compared with standard therapy (Reinkensmeyer and Housman 2007). The T-WREX was also used in comparison with a control group that underwent conventional therapy performed on a table top to support against gravity (Housman, Scott et al. 2009). 28 chronic stroke patients (14 T-WREX + 14 Control) received 3 weekly sessions of one treatment condition during approximately 8 weeks, and were evaluated at the end of the treatment and at 6 months follow-up. Results showed that both groups improved significantly at the end of the treatment compared to baseline at most of the clinical evaluation scales. The T-WREX group was only better than the control group at the Fugl-Meyer test at the 6 month follow-up. The largest difference between groups was observed at the satisfaction level, with the large majority of T-WREX user preferring this treatment over traditional methods.

e) Robotics

More recently, VR scenarios were coupled with robotic systems to assist and/or aid movement (Masiero, Celia et al. 2007; Takahashi, Der-Yeghiaian et al. 2008). Robotic systems allow for controlled repetitive movement execution with minimal supervision. As an example we can find the HWARD, a hand-wrist pneumatically actuated robot (Figure 1.3c, d). It was used with stroke patients in a study where the main purpose was to compare the clinical improvement depending on the amount of assistance provided by the robot during a VR based task (Takahashi, Der-Yeghiaian et al. 2008). 13 patients participated in this study: in half of them the movements where assisted by the robot during all the treatment period, while in the other half patients received assisted movement during half of the treatment and non-assisted in the remaining period. Patients that received robot assisted movement during a larger period of time showed significantly larger improvements.

f) Motor Imagery

Imagination of action has been shown to activate a number of brain areas that are activated during action execution (Filimon, Nelson et al. 2007). This has direct applications in stroke rehabilitation, particularly in the case of more severely impaired patients. However, imagining the correct performance of the movement is not always straightforward. Mental practice techniques based on motor imagery can be assisted by VR systems to help generating motor images (Gaggioli, Meneghini et al. 2006; Gaggioli, Meneghini et al. 2007; Gaggioli, Morganti et al. 2009). As an example we find the VR Mirror, a system to guide mental practice in the rehabilitation of the upper limbs following hemiplegia (Figure 1.3b) (Gaggioli, Meneghini et al. 2006; Gaggioli, Meneghini et al. 2007; Gaggioli, Morganti et al. 2009). The system consists of a table with a back projected horizontal screen, a projector, a mirror and sensors for movement tracking. Basically, this system displays to the patient previously recorded and mirrored movements of their nonparetic arm. The observed movement is used to support mental rehearsals of the desired movement, and to promote the movement of the impaired limb by following the mirror image.

Figure 1.3. Arm weight support, motor imagery and robotics. (a) The weight of the arm can be supported by means of exoskeletons, which facilitate the execution of movements. Adapted from (Housman, Le et al. 2007). (b) The VR-Mirror: the patient observes mirrored movements of his nonparetic arm to later support mental rehearsal Adapted from (Gaggioli, Meneghini et al. 2007). (c, d) HWARD is a wrist/hand robot that assists movements during grasping tasks in a virtual environment. Adapted from (Takahashi, Der-Yeghiaian et al. 2008).

In a pilot, a chronic stroke patient used the VR Mirror during a period of 4 weeks, administered in 3 sessions per week. The treatment focused on training the flexion and extension of the wrist, rotation of the forearm, and flexion and extension of the elbow. Moreover, after the 4 weeks of training the subject was provided with a portable device to allow training at home during an additional period of 4 weeks. The patient showed an improvement on the Fugl-Meyer Assessment Test (Fugl-Meyer, Jaasko et al. 1975) and on the Action Research Arm Test (Lyle 1981), range of movement and grip strength after the 4 weeks of training, followed by a limited further improvement after the training at home. The same system and training protocol was later used with 9 chronic stroke patients during 8 weeks (Gaggioli, Meneghini et al. 2007; Gaggioli, Morganti et al. 2009). Unfortunately, no significant improvements were observed in the Fugl- Meyer and Action Research Arm scores. However, some patients subjectively reported an improvement in the performance of the ADL.

g) Combined Approaches

Other systems explore the combination of different features and paradigms within virtual environments. For instance, Merians and Adamovich combined the use of data gloves with force-feedback (Merians, Jack et al. 2002; Merians, Poizner et al. 2006). They proposed a system for upper limb rehabilitation that makes use of two complementary data glove systems (CyberGlove (Immersion, San Jose, USA) and Rutgers Master II force-feedback glove (Bouzit, Burdea et al. 2002)) to train range of movement, speed of movement, finger fractionation and strength (Jack, Boian et al. 2001). The CyberGlove comprises strain-gauge sensors that measure finger joint angles, abduction and wrist flexion, allowing for a complete capture of hand movement. On the other hand, the Rutgers Master II force-feedback glove is an exoskeleton that applies force to the fingertips by means of pneumatic actuators, allowing for strength training exercises. Four virtual tasks were implemented to train the different hand parameters (Figure 1.4a). In these tasks feedback was provided with respect to the movement goal (knowledge of results) and also related to the movement that was produced (knowledge of performance). A pilot with 3 chronic stroke patients showed improvement in some of the trained parameters and also functional gains after the training period, but with variable improvement patterns (Merians, Jack et al. 2002). In a later study, 8 chronic stroke patients used this system (with an updated speed of movement task) in an intensive 3-week program (Merians, Poizner et al. 2006). The patients showed improvements, with retained gains, in both the VR measures and in the clinical evaluation measures. Moreover the improvements were transferred to real world tasks. However, this study had the limitation that the patient group was not homogeneous, making it difficult to establish comparisons and make statements on the efficacy of the proposed method. The previous system has been recently updated and extended to allow also the training of arm movements (Adamovich, Fluet et al. 2008; Merians, Tunik et al. 2009). This new system combines the use of a CyberGlove for hand tracking, a CyberGrasp (Immersion, San Jose, USA) for haptic feedback to the hand, the Ascension Flock of Birds (Ascension Technologies, Burlington, USA) for arm tracking, and a Haptic Master (Moog FCS, Nieuw-Vennep, The Netherlands) to aid arm movement and provide haptic sensation to the arm. The VR scenarios use a virtual simulation of the user in tasks that train different aspects of arm and hand movements. In an initial pilot with 8 chronic stroke patients that used this system to train arm and hand movements together or separately, the results evidenced the benefit of using combined arm and hand training (Adamovich, Fluet et al. 2008; Merians, Tunik et al. 2009).

The L-EXOS is a force-feedback exoskeleton that has five degrees-of-freedom, allowing for several joint configurations, and also pronation and supination of the wrist (Figure 1.4b) (Montagner, Frisoli et al. 2007; Frisoli, Bergamasco et al. 2009). Force-feedback is applied by means of a controlled force to the palm of the user’s hand. The virtual reality scenarios are composed of tasks that promote different movements such as reaching and object manipulation. In a pilot, 3 chronic stroke patients used the L-Exos in 1-hour sessions, 3 times per week, during 6 weeks (Montagner, Frisoli et al. 2007). After the study, patients presented improvements in the therapy dependent measures, with a higher impact in reaching movements. In a later study, the L-EXOS was used by 9 patients following the previous protocol (Frisoli, Bergamasco et al. 2009). Results showed significant improvements at the end of the treatment at the Fugl-Meyer Assessment Test and also in Range of Movement.

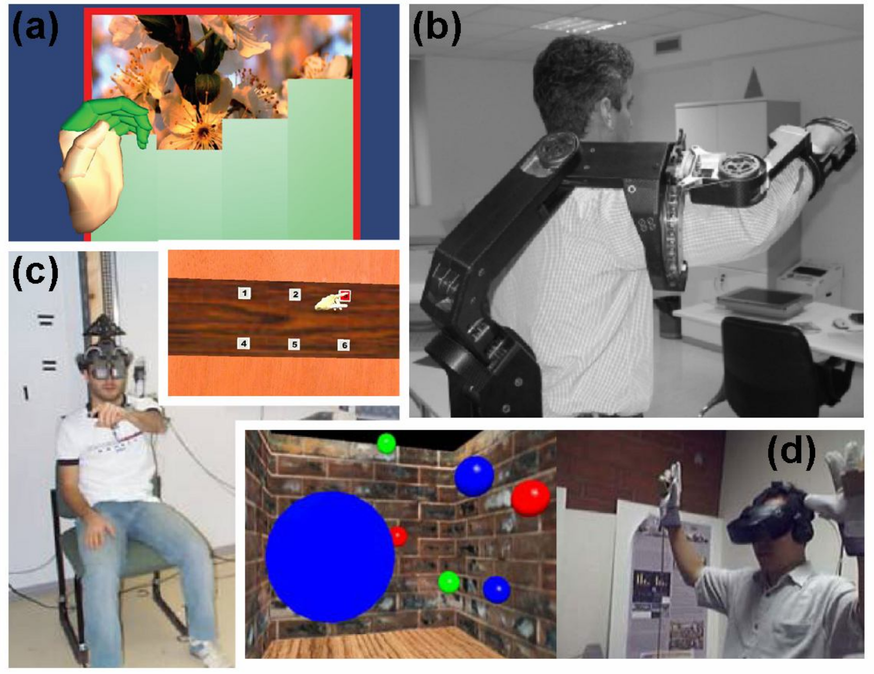

Figure 1.4. Other VR paradigms. (a) VR task to train the range of movement of the hand. Adapted from (Merians, Poizner et al. 2006). (b) The L-EXOS combines arm weight support with force-feedback. Adapted from (Montagner, Frisoli et al. 2007). (c) The virtual elevator allows training reaching movements. Adapted from (Subramanian, Knaut et al. 2007). (d) Some systems are fully immersive, allowing interaction within a 360-degree space. Adapted from (Rizzo, Cohen et al. 2004).

Subramanian et al. combined intensive practice and feedback elements to achieve rehabilitation of the upper extremities (Subramanian, Knaut et al. 2007; Subramanian, Knaut et al. 2007). A virtual elevator was created to train pointing movements (Figure 1.4c). Repetitive reaching in different directions is promoted and feedback about motor performance is provided supporting knowledge of performance and knowledge of results. The system comprises a head mounted display, a motion capture system and a data glove, and allows real time integration of hand, arm and body movements. 15 hemiplegic patients used this system in a real and virtual pointing task. The recorded kinematics data suggested that the training in the virtual environment could lead to more consistent improvements in movement execution.

Rizzo et al. developed different scenarios that aim at assessing and rehabilitating relevant perceptual-motor activities such as eye-hand coordination and range of motion (Rizzo, Cohen et al. 2004). The systems are based on stereoscopic graphic scenarios where the user interacts with virtual stimuli within a full 360-degree space using a head mounted display (Figure 1.4d). The environments promote reaching and targeting tasks, and allow analyzing body posture and body movement, as well as quantifying motor performance. The work of Stewart and collaborators takes a similar approach (Stewart, Yeh et al. 2007). Their system encloses different virtual tasks for motor skill learning, including reaching, interception, pronation and supination, and precision grasp. In this case, the subject experiences a three dimensional view that is provided by shutter glasses. The system makes use of magnetic trackers attached to the hand and objects for movement detection, and PHANToM devices to measure pinch. In addition, this system facilitates the control of practice intensity based on the capabilities of movement of each subject. As a feasibility test, 2 acute stroke patients with different impairment severity used the system during 12 sessions of 1-2 hours. Both patients showed improvements in the VR tasks. In addition, one of the patients showed improvements in hand grasp and release, and the other one showed improvements in the functional level.

1.4 Discussion

In the last decade, extraordinary improvements have been made regarding the development of virtual reality systems for motor neurorehabilitation. Several target populations have been considered, but within these, stroke has received special attention and especially in the rehabilitation of the upper extremities. In the context of VR applied to the rehabilitation of the arm, we reviewed some of the main systems that have been developed and we have described their major findings.

Table 1. 2. Taxonomy of the reviewed systems.

Approach	Tested on	Main Features	References
Virtual Teaching	Chronic Acute	Visual feedback on movement trajectories Knowledge of performance Knowledge of results	(Holden, Todorov et al. 1999; Holden and Dyar 2002; Piron, Tonin et al. 2005; Holden, Dyar et al. 2007; Piron, Tombolini et al. 2007; Piron, Turolla et al. 2009)
Haptics	Chronic Acute	Tactile feedback Increased immersion	(Merians, Jack et al. 2002; Broeren, Rydmark et al. 2004; Merians, Poizner et al. 2006; Broeren, Rydmark et al. 2007; Montagner, Frisoli et al. 2007; Stewart, Yeh et al. 2007; Adamovich, Fluet et al. 2008; Frisoli, Bergamasco et al. 2009; Merians, Tunik et al. 2009)
Video Capture VR	Chronic	Full-body interaction Flexibility of training	(Kizony, Katz et al. 2003; Kizony, Katz et al. 2004)
Arm Weight Support	Chronic	Support against gravity Movement facilitation	(Sanchez, Liu et al. 2006; Housman, Le et al. 2007; Montagner, Frisoli et al. 2007; Frisoli, Bergamasco et al. 2009; Housman, Scott et al. 2009)
Robotics	Chronic	Movement guidance Movement reproducibility Minimal supervision	(Merians, Jack et al. 2002; Merians, Poizner et al. 2006; Montagner, Frisoli et al. 2007; Adamovich, Fluet et al. 2008; Takahashi, Der-Yeghiaian et al. 2008; Frisoli, Bergamasco et al. 2009; Merians, Tunik et al. 2009)
Imagery	Chronic	Mental practice	(Gaggioli, Meneghini et al. 2006; Gaggioli, Morganti et al. 2009)

Different paradigms and therapy concepts have been used, which we grouped in different categories: virtual teaching, haptic feedback, video capture virtual reality, arm weight support, robotics, motor imagery, and combined approaches (Table 1. 2). All these systems have specific neuroscientific grounds. Indeed, VR based approaches allow us to shape the technology on the basis of well defined hypothesis on the mechanisms underlying recovery. We consider that this is a major step in motor rehabilitation that is also witnessed by a rapid development of this specific technology based approach towards neurorehabilitation in the last few years. Another improvement is the existence of an increasing number of studies that explore VR as a therapeutic tool. In general, the patients that have used VR environments presented significant improvements in various aspects of motor performance. Nevertheless, the results have showed a poor impact on the performance of ADL. Moreover, only a few studies included control groups and this is still an important methodological limitation if we want to assess the efficacy of VR, or any other therapy, in rehabilitation.

In summary, the advantages of the use of VR technologies are vast and we believe that important developments will take place in the next few years that will establish this technology as a major breakthrough in the treatment of pathologies of the nervous system.

2. ACTION OBSERVATION

It was acknowledged that the motor system can be activated by the simple observation of actions without overt movement execution (Rizzolatti and Craighero 2004). This effect is attributed to an action recognition system called the Mirror Neuron System (MNS), and has potential applications for the neurorehabilitation of motor deficits. Additionally, the recognition of actions through observation can be influenced by the goal of the observed task, the agent performing the task and/or the person perspective.

In this chapter we describe the MNS and its main properties. In addition, we discuss the responses of this system to the observation of actions performed by artificial agents and also the importance of the frame of reference during observation.

2.1 The Mirror Neuron System

The mirror neurons are a special population of neurons that have the property of being active both, during the execution of goal-oriented movements and during the observation of the same action performed by others. The mirror neurons in the monkey's brain were discovered by chance during single cell recordings in the area F5 of the premotor cortex while performing grasping tasks (di Pellegrino, Fadiga et al. 1992). It was observed that there were cells in this area that fired not only when the monkey was performing a grasp, but also when the monkey was sitting still and observing a human grasping for food (Figure 2.1). This represented a surprising and important discovery that since then has motivated several studies in order to understand the properties of the so-called Mirror MNS.

In monkeys, cells with mirror neuron properties were mainly identified in the posterior part of the inferior frontal cortex and in the anterior part of the inferior parietal lobe (Rizzolatti and Craighero 2004; Rizzolatti, Fabbri-Destro et al. 2009). The frontal mirror neurons were identified in area F5 (Figure 2.2) (Rizzolatti, Fadiga et al. 1996). This area is located in the rostral part of the ventral premotor cortex and is characterized by the presence of neurons that code goal-related motor actions such as hand and mouth grasping (Rizzolatti, Luppino et al. 1998). Single cell studies showed that F5 neurons code specific actions, being therefore subdivided in different classes (for example, holding or grasping).

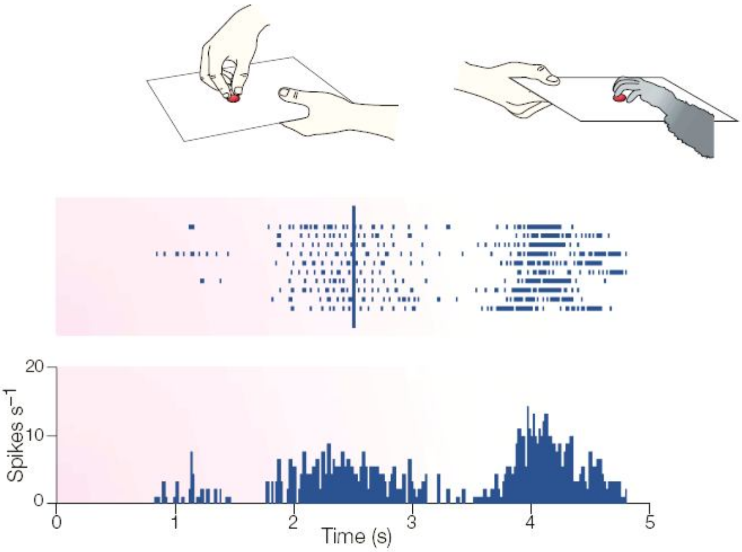

Figure 2.1. Typical response of a mirror neuron. There is strong activation in F5 when the monkey observes the experimenter grasping the food, and also when the monkey itself does the grasping. Adapted from (Rizzolatti, Fogassi et al. 2001).

In the inferior parietal lobe, mirror neurons were described in the area PF/PFG (Figure 2.2) (Rizzolatti, Luppino et al. 1998; Fogassi, Ferrari et al. 2005). The majority of neurons of this area respond to somatosensory stimuli, visual stimuli, or both. The PF mirror neurons code motor acts as belonging to an action sequence, predicting the target goal of complex movement (Fogassi, Ferrari et al. 2005).The posterior part of the inferior frontal cortex and the anterior part of the inferior parietal lobe are anatomically connected, forming a cortical mirror neuron circuit (Rizzolatti 2001; Rizzolatti, Fogassi et al. 2001; Rizzolatti and Craighero 2004; Fogassi, Ferrari et al. 2005).

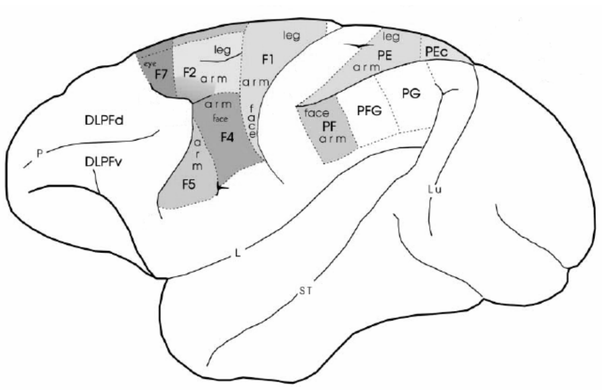

Figure 2.2. Lateral view of the monkey brain showing the parcellation of the motor cortex. DLPFd, dorsolateral prefrontal cortex, dorsal; DLPFv, dorsolateral prefrontal cortex, ventral; F1-F7 are frontal areas; L, lateral fissure; Lu, lunate sulcus; P, principal sulcus; PE, PEc, PEip, PF, PFG and PG are parietal areas; ST, superior temporal sulcus. Adapted from (Rizzolatti 2001).

Several studies led to the identification of the basic properties of the mirror neurons in primates. The most important property of these mirror neurons is that they fire while observing goal-directed hand and mouth actions, like grasping or object manipulation, performed by monkeys or humans (di Pellegrino, Fadiga et al. 1992; Gallese, Fadiga et al. 1996; Umilta, Kohler et al. 2001; Ferrari, Gallese et al. 2003; Rizzolatti and Craighero 2004; Fogassi, Ferrari et al. 2005). Mirror neurons seem not to respond to the sight of mere displacement of body parts in the absence of a target (Gallese, Fadiga et al. 1996). In a similar way, mirror neurons do not respond to the observation of an object alone, even if it is of interest to the monkey (Gallese, Fadiga et al. 1996; Rizzolatti, Fadiga et al. 1996). This means that mirror neurons require an interaction between a biological effector (mouth or hand) and an object. However, it was shown that mirror neurons also fire when actions are partially hidden, indicating that these cells can code abstract aspects of the actions of others (Umilta, Kohler et al. 2001). More evidence on the abstract coding of mirror neurons was raised when it was observed that these cells associate actions with familiar sounds even without watching the actions associated with those sounds (Kohler, Keysers et al. 2002; Keysers, Kohler et al. 2003).

An important functional aspect of the MNS is the relation between the visual and motor features. Different levels of congruence between the observed action and the executed action were defined (Gallese, Fadiga et al. 1996). Mirror neurons were divided into “strictly congruent” and “broadly congruent”. “Strictly congruent” mirror neurons stand for mirror neurons that fire when the observed and executed actions are substantially the same, i.e., the motor action and the observed action match both in terms of goal (for example, grasping) and in terms of how this goal is achieved (for example, precision grip). These kind of neurons represents about one third of the F5 mirror neurons. The majority of F5 neurons present a broader congruence, being restricted to the goal of the action. These “broadly congruent” mirror neurons do not require the observation of the exactly same action in order to fire (Rizzolatti and Craighero 2004).

It was also suggested that the mirror neurons of the parietal lobe code intention (Fogassi, Ferrari et al. 2005). Fogassi *et al*. recorded differential firings of the same cell during grasping movements associated with different intentions, as for example, grasping to eat or grasping to place. This seems to mean that the mirror neurons not only code the abstract representations of the movements of other individuals, but that they also code the intention associated with the observed actions (Iacoboni and Dapretto 2006).

Interestingly, the existence of mirror neurons in the lateral sector of area F5 that respond during actions performed with tools was recently reported (Ferrari, Rozzi et al. 2005). These so-called tool-responding mirror neurons are more responsive while the monkey observes the experimenter performing an action with a tool (for instance, a stick or pliers), compared with watching the same action performed with the hand or mouth. Concerning motor activity, these neurons also discharge when the monkey executes the action with his hand or mouth. It was argued that after some time, an association between the hand and the tool is internally created. That is, a skill acquired through visual experience. This would mean that after a period of time the monkey understands that the hand and the tool serve the same purpose of executing the same goal-oriented action.

There is strong evidence of the existence of mirror neurons in the human brain. A number of studies with electrophysiology or brain imaging identified areas with mirror neuron like properties in the ventral premotor cortex, inferior parietal lobe and in the inferior frontal gyrus (Iacoboni, Woods et al. 1999; Buccino, Binkofski et al. 2001; Rizzolatti, Fabbri-Destro et al. 2009; Rizzolatti and Fabbri-Destro 2010) (Figure 2.3). Specifically, humans seem to posses a MNS that is formed by the posterior portion of the inferior frontal gyrus (IFG), the adjacent ventral premotor cortex and by the rostral part of the inferior parietal lobe (IPL) (Rizzolatti and Craighero 2004; Iacoboni and Dapretto 2006). When actions are observed, these are mapped onto the corresponding motor representations of the frontal lobe, and in the case of effector-object interactions, onto the parietal lobe (Buccino, Binkofski et al. 2001). This means that when an individual observes an action, an internal replica of that action is automatically generated in the brain as if the individual was executing the action.

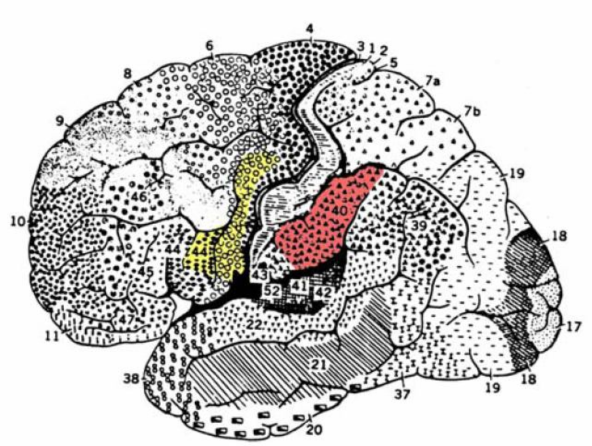

Figure 2.3. Human MNS. Lateral view of the human brain showing Brodmann cytoarchitectonic subdivision (Brodmann 1909). Yellow: frontal mirror areas. Red: parietal mirror areas. Adapted from (Rizzolatti and Fabbri-Destro 2010).

It was shown that the MNS is related to different body actions performed not only with the hands, but also with the feet and the mouth (Buccino, Binkofski et al. 2001). The recruitment of the motor system through observation depends however on the nature of the perceived action, with meaningful actions triggering the motor network to a larger extent (Decety, Grezes et al. 1997). This means that activation is stronger when there is a clear goal in the observed action. Moreover, in addition to goal coding, the human mirror neurons are also involved in understanding the intentions of others (Iacoboni, Molnar-Szakacs et al. 2005; Hamilton and Grafton 2008). This means that during action observation these neurons are able to discriminate the intention behind an action executed by other individual. For example, they respond differently to a grasp to drink or to a grasp to clean (Iacoboni, Molnar-Szakacs et al. 2005).

The effectiveness of the MNS in driving the motor system in humans was demonstrated by an increase in the excitability of the corticospinal pathway (Fadiga, Fogassi et al. 1995; Strafella and Paus 2000). In particular, an increase in motor evoked potentials during the observation of actions was observed, being the muscle activation pattern similar to the one related to the actual performance of those actions (Fadiga, Fogassi et al. 1995), even when those actions are physically impossible to perform (Romani, Cesari et al. 2005). However, the activation is more intense during the observation of actions that belong to the personal repertoire of the observer (Buccino, Lui et al. 2004; Calvo-Merino, Glaser et al. 2005; Aglioti, Cesari et al. 2008). For instance, a study with expert dancers showed that responses were stronger when subjects observed dance movements that they had been trained to perform (Calvo-Merino, Glaser et al. 2005). This means that the activation of the brain in response to action observation is influenced by the acquired motor skills of the observer.

In recent years, it was also suggested that the MNS is involved in mediating empathy and social interaction. Mirror neuron activation has been observed when individuals observed pain related emotions in other individuals (Avenanti, Bueti et al. 2005; Singer 2006). Additionally, there is strong evidence that autism is the consequence of an impairment of the MNS. Some studies showed that in autistic children the mirror neurons are silent during action observation and that the ability to understand the intentions of others is absent (Williams, Whiten et al. 2001; Dapretto, Davies et al. 2006; Rizzolatti, Fabbri-Destro et al. 2009).

Finally, due to its properties the MNS could be used to induce cortical reorganization and consequent motor recovery following a lesion in the brain (Pomeroy, Clark et al. 2005; Buccino, Solodkin et al. 2006; Rizzolatti, Fabbri-Destro et al. 2009; Garrison, Winstein et al. 2010). For instance, in the case of stroke patients, the motor system could be activated by the simple observation of goal-oriented actions. This could be of ultimate relevance in the case of patients that show no movement on their paretic side. In a preliminary study, 8 chronic stroke patients underwent 18 sessions of passive action observation treatment (Ertelt, Small et al. 2007). The therapy consisted in watching videos of arm and hand actions, followed by practicing the observed actions. At the end of the treatment the patients showed significant improvements, compared to baseline and to a control group, in a number of clinical scales. For example, significant gains were observed in motor function as assessed by the Wolf Motor Function Test (Wolf, Lecraw et al. 1989) and by the Frenchay Arm Test (De Souza, Hewer et al. 1980). This shows the potential benefits of the use of such a paradigm in the rehabilitation of motor deficits following stroke.

2.2 Observation of Artificial Agents

While discussing the activation of the mirror neurons through action observation, a pertinent question arises: Do mirror neurons in humans specifically fire to the observation of actions performed with a biological effector, or do they also fire to the observation of actions performed with an object or by an artificial agent? As mentioned in the previous section, a study with monkeys showed that the mirror neurons fired during the observation of grasping actions performed with tools, and also to the observation of grasping performed directly with the hand (Ferrari, Rozzi et al. 2005). This seems to indicate that the mirror neurons mostly code the goals of the motor actions. In an fMRI study, Gazzola et al. analyzed brain activation during the observation of grasping actions performed with a robot hand or with a human hand (Gazzola, Rizzolatti et al. 2007). The results showed that the mirror neuron network was activated in both conditions, indeed suggesting that for mirror neurons the goal of the action might be more important than the way in which the observed action is performed. Similarly, mirror neuron like activation was also observed during simultaneous manipulation and observation of an electromyographic prosthetic hand (Maruishi, Tanaka et al. 2004).

For what concerns the observation of actions performed by computer generated agents, there is evidence suggesting that the observation of virtual hands also leads to the activation of the MNS. In a fMRI study, thirteen healthy subjects observed finger movement sequences performed by a virtual hand (Adamovich, August et al. 2009). The results showed that observation and real time imitation of the virtual limbs was associated with the activation of frontal and parietal areas. These areas were similar to the ones involved in the mirror neuron network.

2.3 Frame of Reference

In the mirror neuron literature, the perceptual frame of reference is often not considered and the mirror neurons are mainly reported in a third-person perspective. However, it was shown that the observation of hand movements produces an increase in cortical excitability that is modulated by the orientation of the hand with respect to the observer, the response being stronger when the orientation of the hand is similar to the one of the observer (Maeda, Kleiner-Fisman et al. 2002). In addition, it was observed that a first-person perspective recruits the motor system to a greater extent than a third-person perspective (Jackson, Meltzoff et al. 2006). In an fMRI study, 16 subjects observed and imitated video clips of hand and foot movements from first- and third-person perspectives. Results showed an increased activity of the contralateral sensorimotor cortex (particularly in the precentral gyrus) when the subjects observed videos from the first-person perspective. In another study, the authors used transcranial magnetic stimulation to investigate the effect of posture and perspective during the observation of hand movements (Alaerts, Heremans et al. 2009). The results indicate that a first-person perspective is more effective in activating motor areas contralateral to the used hand. In a similar way, Lorey et al. used fMRI to analyze the effect of perspective during motor imagery (Lorey, Bischoff et al. 2009). 20 participants watched video clips of hand movements and were asked afterwards to imagine those movements from first- and third-person perspectives. As in the previous studies, the authors observed a stronger activation in motor areas (especially in the parietal lobe) when the movements were imagined in a first-person perspective.

2.4 Discussion

In this chapter we have discussed the neural correlate of action observation, and we have described the mechanisms by which motor areas can be activated by the simple observation of motor actions. In particular, we have described and discussed the main properties of the Mirror Neuron System, an action recognition system that mediates between perception and action. This system has a number of important features that makes it a potential key player in the rehabilitation processes after a brain lesion. First of all, the MNS is active both during the execution of actions and during the observation of the actions performed by others (di Pellegrino, Fadiga et al. 1992; Rizzolatti and Craighero 2004). Secondly, the MNS does not blindly respond to any motor action but to the observation of meaningful actions performed with an explicit goal (Gallese, Fadiga et al. 1996). Thirdly, the observation of actions can activate muscles similar to those involved in the actual execution of the movement being observed (Fadiga, Fogassi et al. 1995). Next, the observation of movements from a first-person perspective has been shown to recruit motor related areas to a larger extent (Maeda, Kleiner-Fisman et al. 2002). Finally, the degree of familiarity with the execution of the observed movements plays an important role, facilitating a larger extent of activation of the MNS (Calvo-Merino, Glaser et al. 2005). That is, actions belonging to the motor repertoire of the observer activate the MNS to a larger extent.

Hence, a system like the MNS capable of driving motor areas by the mere observation of motor actions has direct applications for stroke rehabilitation. Novel rehabilitation strategies exploiting these mechanisms may use the observation of movements to activate the motor system, even when the level of impairment is such that movements cannot be explicitly performed. Moreover, the combination of these premises with the fact that the activation of motor areas can also be triggered by the observation of artificially generated limbs (Gazzola, Rizzolatti et al. 2007; Adamovich, August et al. 2009) places VR technologies in a privileged position. In fact, it has been suggested that the goal of the observed action is more relevant for the MNS than the specifics of the actual movements with which the action is realized (Gazzola, Rizzolatti et al. 2007). Hence, we could use the movement execution and observation of a virtual agent to design rehabilitation scenarios to activate the motor network. One of the properties of VR that can render it more beneficial than other real world therapies is that it allows for the design of therapy tasks tailored to the specific needs of the patients. Furthermore, it also enables the manipulation of the visual feedback - movements that are being displayed – in real time.

3. THE REHABILITATION GAMING SYSTEM: METHODOLOGY, DESIGN, PSYCHOMETRICS, USABILITY AND VALIDATION

Parts of the content of this chapter have been published in (1) and (2) and have been submitted for publication in (3):

(1) Cameirão MS, Bermúdez i Badia S, Zimmerli L, Duarte Oller E, Verschure PFMJ: The Rehabilitation Gaming System: a Virtual Reality Based System for the Evaluation and Rehabilitation of Motor Deficits. Virtual Rehabilitation 2007.

(2) Cameirão MS, Bermúdez i Badia S, Verschure PFMJ: The rehabilitation gaming system: a review. Stud Health Technol Inform 145: 65-83. 2009.

(3) Cameirão MS, Bermúdez i Badia S, Duarte Oller E, Verschure PFMJ: Neurorehabilitation using the Virtual Reality based Rehabilitation Gaming System: Methodology, Design, Psychometrics, Usability and Validation. 2010.

3.1 Introduction

The brain, the organization of its neural networks and their function, and the individual neurons are susceptible to change throughout life via new experiences (Krakauer 2006; Nudo 2006; Murphy and Corbett 2009). The ability of learning by adding or removing connections, or even adding new cells, is commonly referred to as brain plasticity. Until recently, it was believed that neocortical areas were fixed in structure after childhood, and that learning was possible only via a change of strength in the existing connections. However, there is growing evidence that all brain areas remain “plastic” after childhood, suggesting that thinking, learning, and acting can change the brain's physical structure and its functional organization (Nudo, Wise et al. 1996; Cauraugh and Summers 2005; Krakauer 2006; Bolognini, Pascual-Leone et al. 2009).

Functional recovery after a stroke mainly relies on neuronal reorganization to allow other areas of the brain to take over functions of the lesioned areas (Seitz, Butefisch et al. 2004; Nudo 2006; Murphy and Corbett 2009). Therefore, the main target of rehabilitation after stroke is to support this neuronal reorganization. Several methods and therapy concepts were proposed aiming at promoting functional changes within surviving motor networks (see Stroke and its Rehabilitation, Chapter 1). However, it is not yet well understood how effective these different approaches are and how they exactly influence recovery.

Relatively novel tools in neurorehabilitation are based on Virtual Reality (VR) technologies. These technologies have the advantage of flexibly deploying scenarios that can be directed towards the specific needs of the patients. To date, a number of VR systems were proposed for the rehabilitation of motor deficits following stroke, with particular emphasis on the rehabilitation of the upper limbs and hands (see Virtual Rehabilitation, Chapter 1). Although a significant amount of work was done in this area with promising results, the relevant characteristics of VR systems and their impact on recovery are not yet clearly understood (Lucca 2009; O'Dell, Lin et al. 2009). As a result, we do not know how the different parameters of the proposed VR systems exactly affect recovery or whether they are effective at all. Furthermore, there is a need to take into account the individual variability in the deficits and the recovery behavior of the patients in order to optimize the impact of training (Prabhakaran, Zarahn et al. 2008). This actually means that some of the parameters of these VR systems would have to be automatically adjusted to each patient.

In this context we developed the Rehabilitation Gaming System (RGS), a VR based neurorehabilitation paradigm for the treatment of motor deficits resulting from brain lesions. RGS combines individualization with a brain based training rationale that explores the processes that mediate between perception and action (Cameirão, Bermúdez i Badia et al. 2007; Cameirão, Bermúdez i Badia et al. 2009). In the following paragraphs, we describe the main considerations related to the design and realization of this system.

The main hypothesis of the RGS is that bimanual task oriented action execution, combined with the observation of virtual limbs that reproduce the executed movement, creates conditions that facilitate the functional reorganization of the motor and premotor systems affected by stroke. This way, recovery could be promoted through the engagement of undamaged primary or secondary motor areas or by recruiting alternative perilesional or contralesional networks. This, however, requires that a communication channel exists that allows external modulation of the states of these alternative circuits. We hypothesize that such an interface could be provided by neurons such as those found in the Mirror Neuron System, which have the property of being active both during the execution of goal-oriented actions and during the observation of the same actions performed by other agents (see The Mirror Neuron System, Chapter 2). It is exactly this transduction channel between perception of actions and their execution what RGS exploits, even when motor actions themselves cannot be performed due to a lesion. Indeed, recent studies support the benefit of using passive action observation for rehabilitation following stroke (Ertelt, Small et al. 2007).

In the tasks proposed by the RGS, the user interaction with the virtual environment is done by means of two virtual arms that are viewed in a first-person perspective. RGS works with the hypothesis that a first-person view provides the most effective drive onto the multi-modal populations of mirror neurons simply because this is the perspective that the system is most frequently exposed to. Indeed, it was observed that a first-person perspective activates to a larger extent motor areas (see Frame of Reference, Chapter 2). Moreover, there is evidence that the observation of a virtual representation of a hand displayed in a first-person perspective activates a neural circuit similar to the frontotemporal mirror neuron network (Adamovich, August et al. 2009). Finally, it was shown that a high level of competence of the passive observer in the observed actions facilitates to a larger extent the activation of the MNS (Calvo-Merino, Glaser et al. 2005).

Since the Yerkes-Dodson law established the relationship between motivation and learning, it has been acknowledged that human performance is optimal at intermediate levels of arousal (Yerkes and Dodson 1908). This means that the optimum performance in any task is the one that is perfectly balanced so as to be neither too hard nor too easy (Csikszentmihalyi 2002). Given these considerations, individualization refers to the identification of a level of performance, i.e. failure rates that optimally challenge each user at their own level of competence. Hence, any automated therapy system should be able to assess the performance level of the subject and subsequently tune the therapeutic intervention in relation to this level. Therefore, here we sought to investigate the effect of each game parameter of a training scenario (Spheroids) on the task performance of stroke patients and healthy controls. The target was to develop a multi-dimensional psychometric model of the RGS training scenario that can be used to automatically adjust the difficulty of the task with respect to the measured performance and to capture specific properties of the individual arms of the user. That is, a Personalized Training Module (PTM). Here we show that the PTM implemented in RGS allows us to effectively adjust the difficulty and the parameters of the task to the user by capturing specific features of the movement of the arms. The PTM was integrated in RGS to deliver tasks of graded complexity for an incremental training, ranging from object interception to a grasp-and-release task. The task in the virtual scenario is accompanied by a scoring system that gives continuous feedback to the user on the performance level. Additionally, the correct execution of actions is reinforced with positive acoustic feedback.

Finally, with RGS we hypothesize that training in virtual environments leads to corresponding improvements of performance in the physical world. Therefore, to understand the transfer of performance between the virtual and the physical world, stroke patients and controls performed physical and virtual versions of a calibration reaching task. We show that individual movement properties and deficits are transferred between real and virtual worlds, supporting the equivalence of training in both environments.

3.2 Methods

a) Rehabilitation Gaming System (RGS)

The RGS was implemented using: a PC (Intel Core 2 Duo Processor, Palo Alto, USA) with a graphics accelerator (nVidia GeForce Go 7300, Santa Clara, USA); a 17 inch LCD display

(Samsung, Daegu, South Korea); a color CCD camera (KE-240CV, Camtronics, USA) positioned on top of the display; four color patches; and two 5DT data gloves (Fifth Dimension Technologies, Johannesburg, South Africa) that use optic fiber technology to measure finger flexure (Figure 3.1). The virtual tasks were implemented using the Torque Game Engine (TGE, GarageGames, Oregon, USA), a 3D graphics engine that provides robust networking, scripting, in-engine world editing and Graphical User Interface (GUI) creation. The movements of the upper extremities of the user were tracked using the custom developed vision based motion capture system, AnTS (Mathews, Bermúdez i Badia et al. 2007).

Figure 3.1. The Rehabilitation Gaming System. A subject sits on a chair with his/her arms on a table, facing a screen. Arm movements are tracked by the camera mounted on top of the display. The tracking system determines in real-time the position of color patches positioned at wrists and elbows and maps these onto a biomechanical model of the upper extremities. Two data gloves are used to detect finger movements. On the display two virtual arms mimic the movements of the subject's arms, hands and fingers.

i) Tracking System - AnTS

The movements of the upper extremities of the RGS users were tracked using the custom vision based tracking system AnTS. AnTS is a general purpose multiple object tracking tool based on Bayesian inference that contains a number of filters and color tracking methods as well as lens distortion and perspective correction techniques (Mathews, Bermúdez i Badia et al. 2007).

In RGS, AnTS tracks unique colored patches placed at the wrists and elbows of the user. In this way the visual segmentation task is easily resolved and potential ambiguities due to the crossing of the upper extremities are avoided. AnTS maps the RGB values received from a 640×480 pixel image captured by the video camera onto the Hue Saturation Value (HSV) color space. In this color space, the hue value alone encodes for the color identity of the markers, which makes their tracking more robust to changes in light conditions. AnTS uses Bayesian probabilistic methods to infer the most likely position of each of the patches given the image stream. This method is used to solve occlusions and crossing related problems given the known properties of the different color patches (size, color, movement history, etc). Once the color patches are located, a biomechanical model of the human torso is used to compute the joint angles for shoulder and elbows of both arms. In the design of the RGS tracking system we purposefully imposed the use of only one camera as a constraint. As a consequence, the system calibration requirements are reduced as well as its computational requirements. In order to map the tracked markers captured with a single camera to the 8 joint angles (pitch and yaw of the 4 tracked joints) of the avatar we use a perspective correction method to reduce distortions due to optics and view angle and an alignment model based on the human skeleton. The latter model prevents the motion capture system to deliver unrealistic joint angles. Hence, a number of approximations have been made to recreate 3D movements from a single 2D image. The motion capture system runs at an update rate of 30 Hz and the median error in the reconstruction of the angles is 11 degrees.

ii) Virtual Scenario: Spheroids

The RGS scenario evaluated here, Spheroids, consists of a green landscape populated with a number of trees against the background of a mountain range. Integrated in the virtual world is a model of a human torso with arms positioned in such a way that the user has a first-person view of the upper extremities (Figure 3.2).

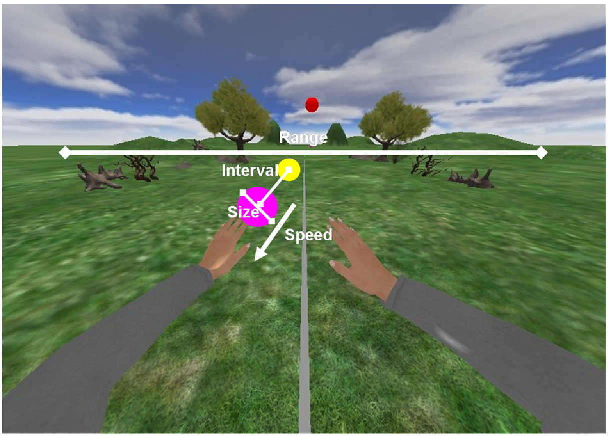

Figure 3.2. Spheroids and the virtual environment. The scenario represents a spring-like nature scenario. Within this scenario two virtual arms move accordingly to the movements of the user. The virtual arms are consistent with the orientation of the user, pointing towards the world, providing a first-person perspective. The difficulty of the sphere interception task is modulated by the speed of the delivered spheres, the interval of appearance between consecutive spheres and the range of dispersion in the field of view.

The movements of the user's physical arms that are captured by the motion tracking system and the data gloves are mapped onto the movements of the virtual arms. The latter thus mimic the movements of the user. Spheres move towards the user and these are to be intercepted through the movement of the virtual arms. The task is defined by different gaming parameters, i.e. the speed of the moving spheres, the interval between the appearance of consecutive spheres and the horizontal range of dispersion of the spheres in the field of view (Figure 3.2). RGS delivers tasks of graded complexity for an incremental training protocol during the rehabilitation process. At the first level, the ‘Hitting Game’, the moving spheres have to be intercepted. In this level the patients are required to practice proximal range of movement exercises. At levels of higher complexity we have the ‘Grasping Game’ and the ‘Placing Game’, where spheres have to be intercepted, grasped and released in baskets of matching colors at different positions (Figure 3.3). These levels therefore combine proximal and distal movements sequentially. Each time a sphere is handled correctly, the user obtains a number of points that accumulate towards a final score.

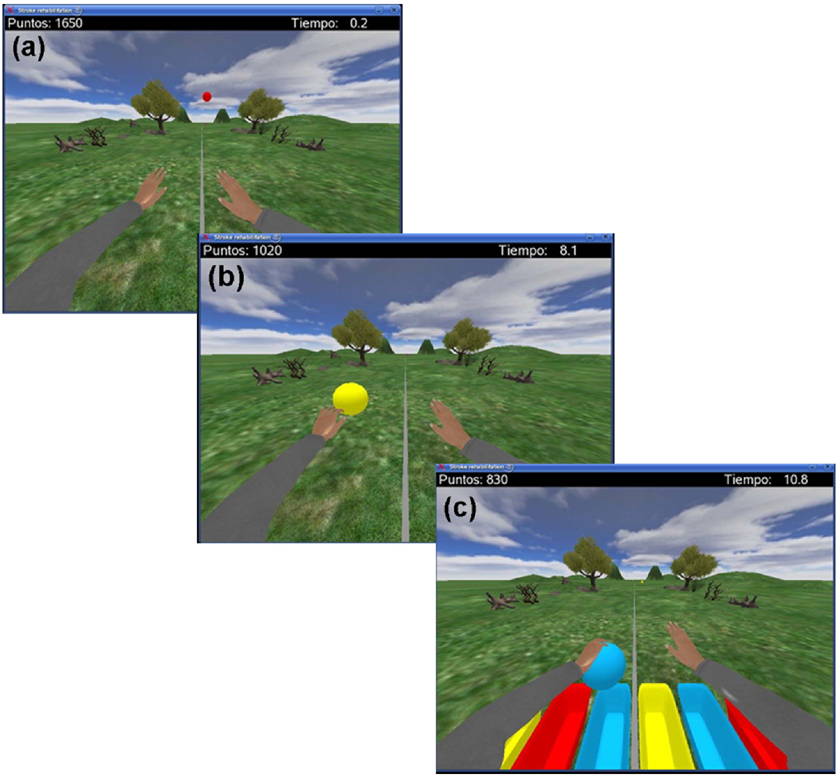

Figure 3.3. Tasks of graded complexity. (a) ‘Hitting Game’ to train range of movement, movement speed and precision. The approaching virtual spheres have to be intercepted with the movements of the virtual arms. (b) ‘Grasping Game’ to exercise finger flexure on top of movement range and speed. (c) ‘Placing Game’ to train grasp and release. The grasped spheres can now be released in a basket of correspondent color.

iii) Calibration and Diagnostics Task

In order to assess the ecological validity of the RGS task, we designed a directed pointing calibration and diagnostics task that evaluates specific properties of movements and analyzes their transfer between physical and virtual worlds. In this way RGS also obtains kinematics based diagnostic information. For the physical task, the user is asked to move their hands to numbered dots positioned in specific locations on the tabletop (Figure 3.4). There are four dots at each side of the table with increasing numbering corresponding to different reaching distances. The left dots are to be touched by the left hand only, whereas the right dots are to be touched by the right hand. The user is instructed by a text displayed on the RGS screen and an audio pre-recorded statement to move one of the hands from a resting position to a new position indicated by a number. In each trial each hand and position is randomly defined by the system.

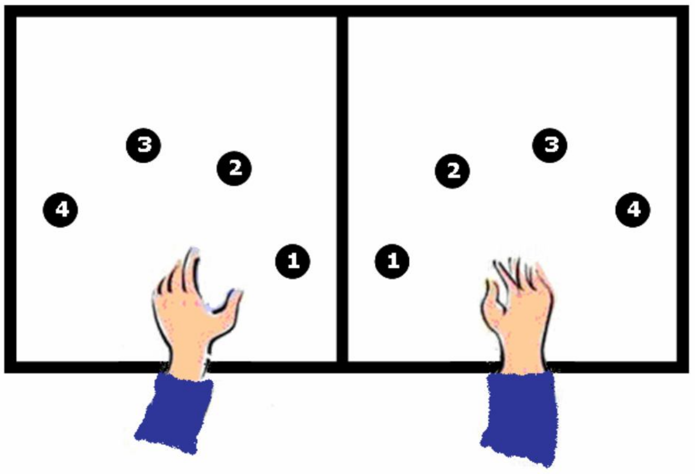

Figure 3.4. Calibration task. Numbered dots are positioned on both sides of the table. The user is asked to move one of their hands from the resting position to the location marked by the corresponding number. Target locations are randomly selected and instructions are provided in a standardized form on the display.

The virtual version of the task is identical to the physical one and the user observes on the computer screen a virtual replica of the table top with the numbered dots and the task is to be performed this time in the virtual scenario (Figure 3.5). In both, real and virtual, the calibration task extracts information on the speed of movement, range of movement (maximum arm extension) and latency (time to initiate a movement from a start cue). This information is used to compute the baseline parameters that will define the starting difficulty of the RGS training and to monitor its impact on arm kinematics over sessions. This task always precedes the Spheroids session.

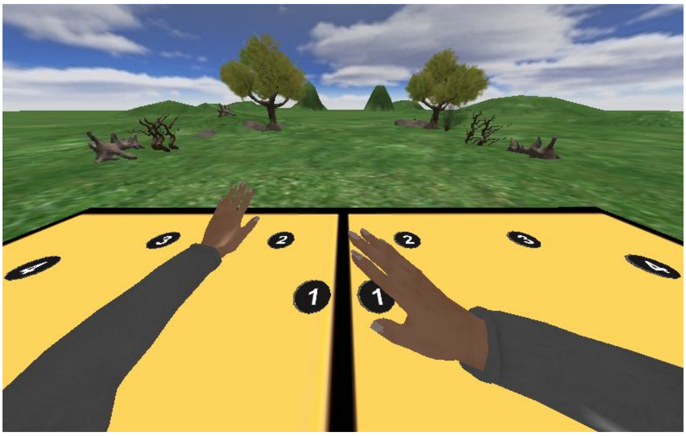

Figure 3.5. Virtual calibration task. This task corresponds to a virtual replica of a physical calibration task. The instructions are the same as in the real task, but now the task is to be performed with the virtual arms on top of the virtual table.

iv) Personalized Training Module (PTM)

The Personalized Training Module (PTM) can autonomously adjust the difficulty of the RGS sessions on a trial by trial basis. This automated procedure follows a number of steps (Figure 3.6). Before the training starts, a baseline level is defined by means of the calibration task described above. After every block of ten trials, i.e. delivery of ten spheres, the RGS adjusts the difficulty level given the performance of the user. For each new difficulty value the corresponding gaming parameters are computed taking into account the previous responses of the user to the individual parameters. In the instantiation of RGS presented here difficulty is increased with 10% when the user intercepts more than 70% of the spheres up to a maximum difficulty level of 100%. Conversely difficulty is lowered with 5% if the user intercepts less than 50% of the spheres. Hence, there is a continuous adaptation of the game parameters to the user's performance. Additionally, this individualization is done for each arm, computing different difficulty levels and thus game parameters, for individual arms.

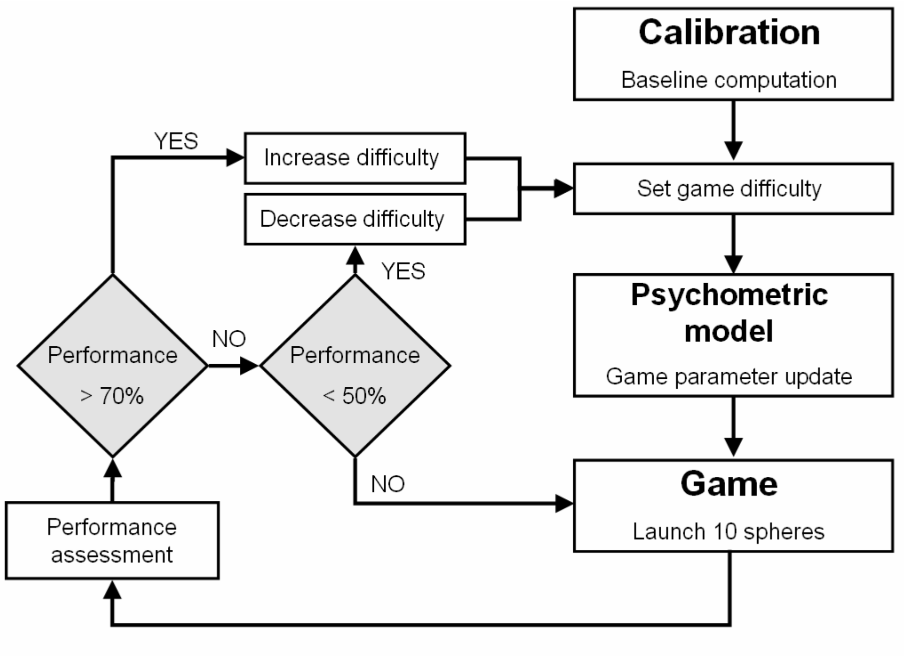

Figure 3.6. Flow diagram of the RGS Personalized Training Module. The game parameters are updated after each block of 10 trials based on the performance of the subject. This provides an automated adjustment of the difficulty of training over time based on a psychometrically validated user model.

In the context of the PTM, the performance of an RGS user in the Spheroids task is assessed as function of four individual parameters:

$$Performance = f(Speed, Interval, Range, Size) \tag{1}$$

The investigation of the effect of these individual parameters on performance allowed us to establish a quantitative relationship between multiple independent input variables (game parameters) and a single output variable (difficulty). Considering the broader case of a non-linear relation between the input variables (task properties) and the performance of the subject, we used a model that takes into account first-order terms, interactions (cross-product terms) and second-order terms (Cohen, Cohen et al. 2002). For three input variables (x_1, x_2, x_3) and one output variable (y) this renders:

$$\begin{aligned} y &= m_0 + m_1 \cdot x_1 + m_2 \cdot x_2 + m_3 \cdot x_3 + \ldots \\ &\ldots + m_{12} \cdot x_1 \cdot x_2 + m_{13} \cdot x_1 \cdot x_3 + m_{23} \cdot x_2 \cdot x_3 + \ldots \\ &\ldots + m_{11} \cdot x_1^2 + m_{22} \cdot x_2^2 + m_{33} \cdot x_3^2 \end{aligned} \tag{2}$$

where m_0 is a constant term, $m_1.x_1 \ldots m_3.x_3$ are the linear terms, $m_{12}.x_1.x_2 \ldots m_{23}.x_2.x_3$ are the interaction terms and $m_{11}.x_1^2 \ldots m_{33}.x_3^2$ are the quadratic terms. By fitting the model to the data of interest, we can extract the regression parameters (m coefficients), which best describe the contribution of their respective terms or independent variables to the dependent variable. In our case we evaluated the m coefficients that relate the game parameters to task difficulty.

b) Subjects

For the development of the Personalized Training Module (PTM), 10 control subjects (8 males and 2 females, mean age 29.0±6.1 years) and 12 hemiplegic patients (11 males and 1 female, mean age 57.4±12.1 years, 3.3±1.5 months after stroke) participated in the trials. For the assessment of the PTM and the study of transfer between physical and virtual tasks, 10 control subjects (8 males and

2 females, mean age 28.6±3.6 years) and 9 patients (4 males and 5 females, mean age 62.3±11.7 years, 11.0±5.1 days after stroke) participated in the study.

The control subjects were students with no history of neurological disorders, recruited from the SPECS Laboratory at the Universitat Pompeu Fabra in Barcelona. The hemiplegic subjects were receiving rehabilitation at the Hospital de L'Esperança in Barcelona (see Table 3.1 for details). Patients were required to pass the Mini-Mental State Examination (Folstein, Folstein et al. 1975). We excluded patients that displayed emotional and/or cognitive deficits that could interfere with the understanding and execution of the task, such as, for instance, global aphasia, apraxia, dementia and depression. The study followed accepted guidelines and was approved by the ethics committee of clinical research of the IMAS – Instituto Municipal de Asistencia Sanitaria (Barcelona, Spain) (see Appendix I).

c) Experimental Protocol

To be able to assess the relationship between game parameters and performance, stroke patients (n=12) and controls (n=10) performed the Spheroids Hitting task with random combinations of game parameters (i.e, speed, time interval, range and size). We varied the gaming parameters every 10 trials for a total of ~12500 trials (4^4=256 possible combinations). The parameter settings were chosen from a set of predefined values: Speed=[8, 14, 19, 25]m/s, Interval=[0.25, 0.5, 1.0, 1.5]s, Range=[0.42, 0.69, 0.83, 0.97], and Size=[0.07, 0.14, 0.21, 0.28]. We selected this set of parameters in order to cover the behaviorally relevant part of the parameter space while keeping the number of trials within practical limits. A random subset of combinations of parameters was assigned for each session. For each combination of parameters we assessed the average success rate (number of successful sphere interceptions). This allowed us to model the difficulty of the task and develop the PTM for the online adaptation of difficulty. To evaluate the performance of the resulting psychometric model, two new groups of patients (n=9) and controls (n=10) performed a 20 min session of the automated Spheroids task.

Table 3.1. Patient demographic information.

Group	ID	Age	G	Side of Lesion	Type of Stroke	Barthel Index	Brunn. Stage
Model Development	1	57	M	L	H	72	IV
	2	69	M	L	H	61	III
	3	57	M	L	I	100	VI
	4	43	F	R	I	96	V
	5	62	M	L	I	91	VI
	6	58	M	L	I	98	V
	7	73	M	L	I	84	IV
	8	45	M	L	H	56	V
	9	65	M	R	I	72	IV
	10	70	M	R	H	62	V
	11	58	M	L	H	78	V
	12	32	M	R	I	78	II
Model Assessment and Transfer Task	1	79	F	R	I	38	II
	2	60	F	R	H	42	III
	3	67	M	R	I	39	II
	4	55	M	R	I	41	II
	5	79	F	L	I	51	IV
	6	50	F	L	I	52	III
	7	52	M	R	H	31	II
	8	50	F	R	I	46	II
	9	69	M	R	I	43	III

Gender (G): M=male and F=female; Side of Lesion: L=left and R=right; Type of Stroke: I=hemorrhagic and I=ischemic. Barthel Index (Mahoney and Barthel 1965). Brunn. Stage: Brunnstrom Recovery Stages (Brunnstrom 1970).

To asses the transfer between the physical and virtual tasks in the RGS, the same group of patients (n=9) and controls (n=10) performed the physical and virtual versions of the calibration task.

d) Usability

In order to assess the usability aspects of the RGS, the acceptance of the training and overall satisfaction in the use of RGS, the group of patients (n=9) that performed the transfer task and the adaptive Spheroids session were given a self-report questionnaire. This questionnaire was presented in the format of a 5-point Likert scale and patients had to report their agreement/disagreement with respect to a number of statements (see Appendix II). With this questionnaire we assessed a number of aspects such as enjoyment of the task, understanding and ease of the task, and subjective performance. Here we focused on the more general aspects related to the usability and acceptance of the RGS. Therefore, we report on the answers given to two specific statements that aim at assessing enjoyment and ease of the task.

e) Data Analysis

To assess the main and interaction effects of the game parameters on the performance of the Spheroids task, we performed a four way analysis of variance (ANOVA) with the game score as the dependent variable and Speed, Interval, Range and Size as independent variables. Once we identified the main effects and interaction effects between the parameters of the training scenario and the user's performance, we quantified this relationship using a quadratic multiple regression model, and extracted the parameters of the regression for both patients and controls.

For the analysis of the performance data of the adaptive version of Spheroids, we extracted the difficulty level reached during the task (average of the 30 last trials) and the final score separated for individual arms. Subsequently, to analyze the mismatch between the performance of the two arms, we computed the ratio of the difficulty between the paretic and the nonparetic arm in patients, and between nondominant and dominant arms for controls. A ratio of 100% would represent a perfect performance matching of the arms. We also analyzed the relation between the adapted gaming parameters for both groups of subjects, by computing the average of the individual parameters over the entire session.

For the analysis of transfer between physical and virtual environments, we extracted the average speed during movement for the physical and virtual calibration tasks for individual arms. In addition, we computed the ratio between arms in patient and control groups, in both environments.

Within-subject data were compared using a paired Student’s t-tests or a Wilcoxon signed ranks tests. For between-subject comparisons we used an independent sample t-test or a Mann-Whitney test. The normality of the distribution was assessed using a single sample Lilliefors hypothesis test of composite normality. Average data is expressed as mean ± standard error of the mean in the text and the figures, unless otherwise stated. For all statistical comparisons the significance level was set to 5% ($p<.05$). All statistical analysis was done using MATLAB (MathWorks) and SPSS (SPSS-Inc).

3.3 Results

We first evaluate the basic properties of the RGS by means of a psychometric assessment of the performance of stroke patients (N=12) and control subjects (N=10), leading to the development of the RGS’ PTM. Additionally, we assess the performance of patients and controls while training within the PTM. Finally, we show how the performance of the users transfers between the physical and the virtual world.

a) Psychometric model

The Spheroids task is defined by a number of game parameters, i.e. Speed of the spheres, Interval of appearance between consecutive spheres, their Size, and Range of dispersal in the field (see Methods). Thus, the difficulty of the task is modulated by the effect of each of those parameters and their possible interactions. In a first experiment we assessed the performance of the control group to random combinations of parameters. The data of the controls’ performance indicates that the size of the spheres has little effect, while Interval, Range and Speed substantially modulate performance (Figure 3.7).

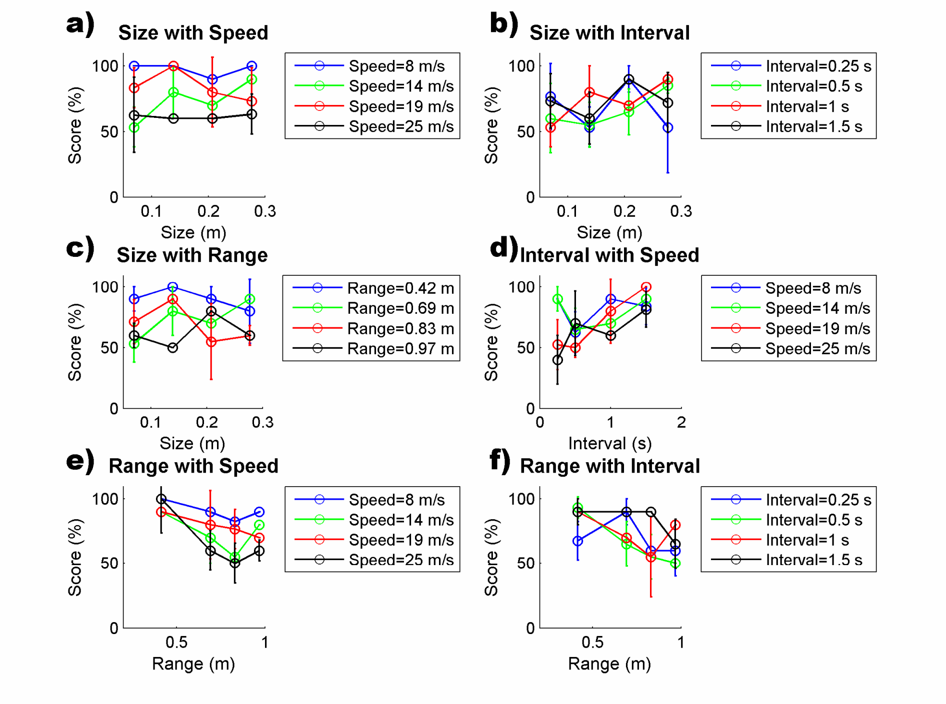

Figure 3.7. Performance versus game parameters. a) Performance as a function of Size and Speed; b) Performance as a function of Size and Interval; c) Performance as a function of Size and Range; d) Performance as a function of Interval and Speed; e) Performance as a function of Range and Speed; f) Performance as a function of Range and Interval. Performance is measured as the percentage of successful sphere interceptions.

In fact, a 4-factor ANOVA revealed main effects of Speed (F(2.62)=251.55, p<0.0001), Interval (F(2.62)=16.90, p<0.0001) and Range (F(2.62)=437.01, p<0.0001) while Size has no significant main effect (F(2.62)=4.26, p=0.2071). With respect to the interaction among the game parameters we observed that 3 out of the 6 possible interactions have a significant effect: Speed*Interval (F(1.90)=1.37, p<0.0001), Speed*Range (F(1.90)=1.89, p<0.05) and Interval*Range (F(1.90)=0.85, p<0.05). In our analysis we did not find any further higher order interactions. Hence, taking into account the significant main and interaction effects, it was reasonable to assume that the difficulty of the task is modulated mainly by the Speed, Interval and Range, and by the interactions Speed*Interval, Speed*Range and Interval*Range.

Then, the relationship between our task difficulty and the above mentioned parameters could be quantified by means of a regression on the data. In this case we used a quadratic model (see Methods):

$$
\begin{aligned}
&Difficulty = m_0 + m_1 \cdot Interval + m_2 \cdot Speed + m_3 \cdot Range + \ldots \\
&\ldots + m_4 \cdot Interval \cdot Speed + m_5 \cdot Interval \cdot Range + m_6 \cdot Speed \cdot Range + \ldots \\
&\ldots + m_7 \cdot Interval^2 + m_8 \cdot Speed^2 + m_9 \cdot Range^2
\end{aligned}
\tag{3}
$$

where we define *Difficulty* as being inversely proportional to the game's score.

In order to quantify how well our model could explain the performance, and thus *Difficulty* of the task, in both controls and patients, we fitted our model with the data sets from both groups. For the controls we obtained a model fit (R^2 = 0.3745, *F(2.37)* = 82.4866, p = 0) with:

$$
\begin{aligned}
m_0 &= -0.2412 \\
m_1 &= 0.1127 \\
m_2 &= -0.0023 \\
m_3 &= 0.1545 \\
m_4 &= -0.0001 \\
m_5 &= 0.0099 \\
m_6 &= 0.0007 \\
m_7 &= -0.0162 \\
m_8 &= -0.0000 \\
m_9 &= -0.0239
\end{aligned}
\tag{4}
$$

and a Mean Squared Error (MSE) of 0.0463.

Then, and in order to determine how well our model generalized, the stroke patient group also performed Spheroids following the same protocol. All patients were able to complete the task irrespective of their degree of impairment. Fitting our model to the data of the nonparetic hand we obtained a fit ($R^2 = 0.3853$, $F(2.37) = 140.1967$, $p = 0$) with:

$$\begin{aligned} m_0 &= -1.0948 \\ m_1 &= 0.1313 \\ m_2 &= 0.0212 \\ m_3 &= 0.4216 \\ m_4 &= -0.0003 \\ m_5 &= -0.0004 \\ m_6 &= 0.0001 \\ m_7 &= -0.0190 \\ m_8 &= -0.0001 \\ m_9 &= -0.0470 \end{aligned} \tag{5}$$

and a Mean Squared Error (MSE) of 0.0531.

The goal of the psychometric model is to provide a single and "blind" adaptive rule for the update of the game parameters that can apply to all patients. Thus, the objective would be that the paretic arm equals in performance the nonparetic one at the end of the treatment. For this reason we used the data of the nonparetic arm to fit the model because it represents an age matched approximation of the desired treatment outcome. We found that the correlation of the patients' model with the parameters of the fit of the healthy controls is 0.9557 ($p<0.0001$). This means that the relationship between *Difficulty* and Spheroids parameters was consistent in both groups. Nevertheless, despite this correlation, the weights found for the patients are higher than for the controls. This can be explained by the fact that the same game parameters in both groups represent a more difficult task for the patients.

b) Personalized Training Module

Given the fit of the data by this model we were able to explicitly define the relationship between task difficulty and the game parameters and exploit the PTM to adjust the properties of the game to the abilities of the user. This automated procedure follows a number of defined steps (Figure 3.6). As an illustration of the application of the PTM, consider the performance and difficulty of the task achieved by a patient during a single training session (Figure 3.8).

The data is separated for the paretic and nonparetic limbs. Analyzing the game events, i.e. hit and missed spheres during the task, we observe a higher degree of failures on the paretic side as a consequence of a smaller range of movement (Figure 3.8a). The detection of the successful and unsuccessful events for each arm adjusts the difficulty of the training specific to the considered arm based on the PTM. This means that we will have an individual pattern of difficulty for each arm (Figure 3.8b).

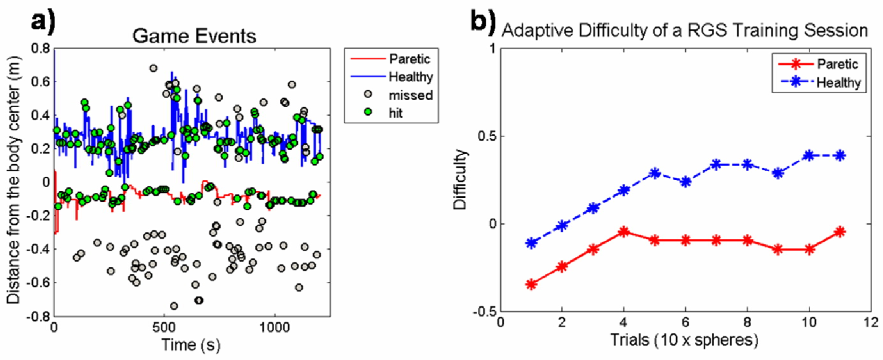

Figure 3.8. Game events and task difficulty. (a) Arm reaching distance for paretic (red) and healthy (blue) arms during a training session, with the corresponding game events (hit and missed spheres). (b) Difficulty over trials for paretic (red) and healthy (blue) arms. The difficulty level goes up to a maximum of 1.0.

On what concerns the performance within the PTM, the data from patients and controls showed that the model was able to capture individual properties of the arms by means of different game parameters for paretic and nonparetic arms, and the discrepancy in the difficulty level attained (Figure 3.9). As expected, the patients reached dissimilar difficulty levels for paretic and nonparetic arms, as opposed to the case of the controls. Consequently, the difficulty ratio between arms was around 100% in controls (99.49±4.11%) and lower in patients (52.27±17.54%), and these were significantly different [t-test, t(8.8)=2.62, p<.05] (Figure 3.9a). A correct adaptive procedure requires that the difficulty of the task is changed but the final score should be similar for both arms in controls and patients, and not different between groups. Indeed, the score ratio between arms in controls (95.17±1.93%) and patients (95.21±3.36%) was not significantly different [t-test, t(17)=-.009, p=.993] (Figure 3.9b).

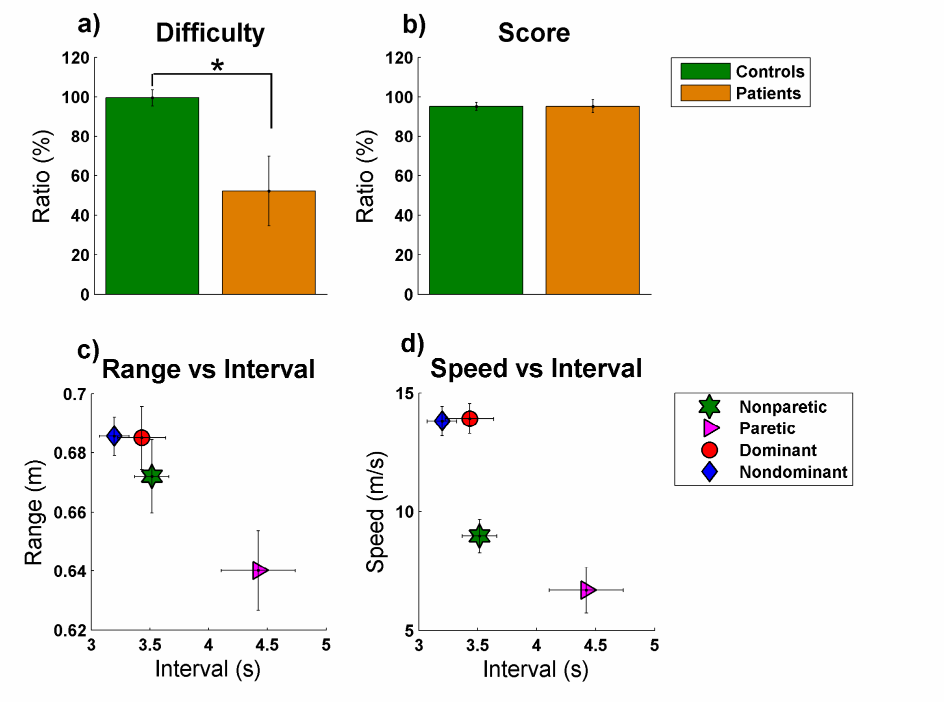

Figure 3.9. Adaptive game results. Difficulty (a) and score of arm ratios (b) for patients and controls. (c-d) Relation between game parameters for individual arms. * p<.05. Shown are means ± SEM.

The analysis of the individual gaming parameters (range, speed, and time interval between spheres) obtained for both arms in both groups allowed us to additionally identify specific properties of the individual arms (Figure 3.9c,d). For control subjects, we found no significant differences between dominant and nondominant arms in range [t-test, t(9)=-.055, p=.957], interval [t(9)=1.199, p=.261] and speed [t-test, t(9)=.233, p=.821]. This means that both arms showed similar properties during the task performance. On the other hand, we found significant differences between paretic and nonparetic arms in the patients' for interval [t-test, t(8)=-2.71, p<.05] and speed [z=-2.07, p<.05], the paretic arm requiring slower spheres and a longer time interval between consecutive spheres. The paretic arm also showed a smaller range, but the difference was not significant [Wilcoxon, z =-1.71, p=.086].

Comparing the performance of the individual arms between groups, patients' paretic arm showed significantly lower range and speed, and longer time interval, when compared with controls' dominant and nondominant arms (paretic-dominant: [t-test, t(17)=-2.64, p<.05] for range, [t-test, t(17)=2.69, p<.05] for interval and (z=-3.67, p<.001) for speed; paretic-nondominant: : [t-test, t(11.6)=-3.05, p<.05] for range, [t-test, t(10.5)=3.61, p<.01] for interval and (Mann-Whitney, z=-3.59, p<.001) for speed). In contrast, the patients' nonparetic arm showed a similar mean interval and range when compared to both arms of the controls (nonparetic-dominant: (Mann-Whitney, z=-1.06, p =.288) for range and [t-test, t(17)=.333, p=.743] for interval; nonparetic-nondominant: (Mann-Whitney, z=-.653, p=.514) for range and [t-test, t(17)=1.66, p=.116] for interval). However, it had a significant lower speed (nonparetic-dominant: [t-test, t(17)=-5.26, p<.001], nonparetic-nondominant:[t-test, t(17)=-5.18, p<.001]).

In summary, the nonparetic arm of patients showed similar properties as both of the arms of the control group, although being overall slower in the performance of the task. On the other hand, the parameters of the paretic arm were noticeably different from those of the control group and also from the contralateral arm. This means that our model is capable of capturing the specific features of both arms of the user and that it adapts the task parameters accordingly.

c) Transfer between Real and Virtual Environments

It has been shown that movement kinematics and improvements acquired in a virtual training context can be transferred to the real world (Holden, Todorov et al. 1999; Subramanian, Knaut et al. 2007; Subramanian, Knaut et al. 2007). However, the conditions that enable the equivalence of training in both virtual and real environments are not well understood. In the particular case of the RGS, it was essential to understand if our training environment allowed for the transfer of performance between the virtual and the physical world. The behavioral data from controls in the adaptive task showed that there is a non-specific reduction in the speed of movement in the virtual world when compared to the real world (Figure 3.10, upper panel). Nevertheless, the relationship between the performances of both arms remained preserved in real and virtual worlds. Thus, the movement speed of the dominant and nondominant arms was not significantly different in neither of the environments (real: [t-test, t(8)=1.91, p=.093]; virtual: [t-test, t(8)=.296, p=.775]). For the stroke patients (Figure 3.10, lower panel) we observed that there was a significant difference between nonparetic and paretic arms in both real [t-test, t(8)=4.565, p<.01] and virtual [t-test, t(8)=2.312, p<.05] environments. Specifically, the paretic-nonparetic speed ratio was 50.38±6.14% in the physical task and 65.67±17.75% in the virtual one, and these were not significantly different [Wilcoxon, z=-1.007, p=.314]. This means that although there was a non-specific decrease in speed, the relation between arms was preserved and the deficit was consistently transferred between environments.

Comparing the speed of the individual arms between the groups, we observed that the nonparetic arm was not significantly different from both arms of the control subjects in real and virtual worlds (nonparetic-dominant: [t-test, t(16)=-1.961, p=.068] for the real and [t-test, t(16)=-.925, p=.369] for the virtual tasks; nonparetic-nondominant: [t-test, t(16)=-.755, p=.461] for physical task and [t-test, t(16)=-1.040, p=.314] for virtual task). We observed that in all cases the speed of the paretic arm was significantly different from controls (paretic-dominant: [t-test, t(16)=-9.076, p<.001] for physical task and [t-test, t(16)=-2.508, p<.05] for virtual task; paretic-nondominant: [t-test, t(16)=-7.275, p<.001] for real task and [t-test, t(16)=-3.223, p<.01] for virtual task). In summary, despite a general decrease in speed in the virtual world, both physical and virtual tasks captured the movement speed of the upper extremities in patients and in healthy control subjects.

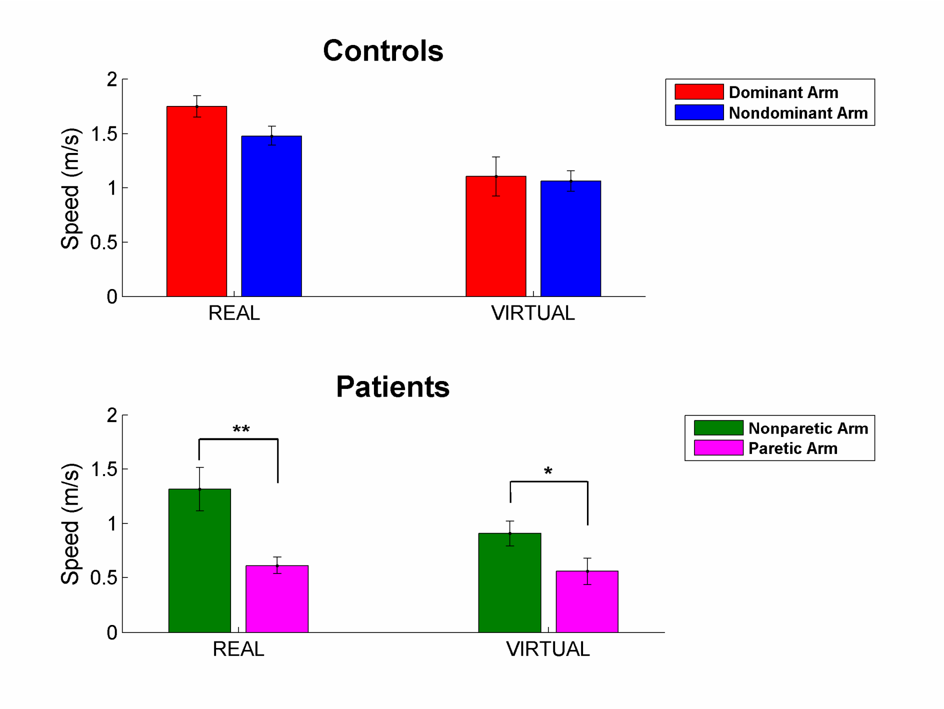

Figure 3.10. Movement speed in equivalent real and virtual calibration tasks. Speed (mean ± SEM) for both arms, in controls and patients, in real and virtual environments. * p<.05, ** p<.01.

d) Usability and Acceptance

In order to assess the acceptance and usability of the RGS in the clinical context, the patients participating in the previous trials were asked specific questions about their experience with the RGS (see Appendix II for further information on the questionnaire). Patients were asked to rate from 1 (strongly disagree) to 5 (strongly agree) a number of questions. Here we elaborated only on the two questions that address usability aspects of the training: *enjoyment* and *ease* of the task. To the statement “I had fun doing the task”, 44.4% of the patients strongly agreed, 44.4% agreed and 11.1% neither agreed nor disagreed. To the statement “The task was easy”, 22.2% strongly agreed, 55.6% agreed, 11.1% neither agreed nor disagreed and 11.1% disagreed. Based on these results and as an overall analysis we feel confident to conclude that the acceptance of the RGS and its tasks was very high.

3.4 Discussion

Stroke is a frequent cause of adult disability that can lead to enduring impairments. However, given the life-long plasticity of the brain one could assume that recovery could be facilitated by the harnessing of mechanisms underlying neuronal reorganization. Currently it is not clear how this reorganization can be effectively mobilized. Novel technology based neurorehabilitation techniques hold promise to address this issue.

Here we described a virtual reality based system, the Rehabilitation Gaming System that is based on a number of hypotheses on the neuronal mechanisms underlying recovery, the structure of training and the role of individualization. RGS exploits the observation of goal-oriented movements through a virtual representation of the body, allowing the training of specific components of movement through the systematic presentation of proprioceptive and visual feedback on one’s actions. Other groups deployed VR systems for upper limb rehabilitation with different paradigms (see Virtual Rehabilitation, Chapter 2). However, RGS provides a new contribution to the field by integrating a number of explicit hypotheses on the neuronal substrate of perception, learning and recovery, exploiting new insights in individualized task oriented training.

Of special relevance is the psychometric Personalized Training Module of the RGS for online adaptation of task difficulty. This model was developed by analyzing the relationship between performance and game parameters in stroke patients and controls. The individual game parameters are weighted to produce the appropriate task difficulty that is adapted online to the individual capabilities of the user. One of the main points of this model is to ensure that the task remains constantly interesting and challenging, but without reaching high levels of demand that could result in frustration or anxiety (Csikszentmihalyi 2002). If the PTM is capable of adapting to the capabilities of each of the arms in both patients and controls, it means that the task parameters reached during training should reflect it. Moreover, independent of the task parameters that the PTM applies during training, the scores and performance of both controls and patients should be kept constant at the end of the training session. In fact, here we showed that with the PTM implemented in Spheroids we were able to capture specific features of both arms in patients and controls, and to adapt the difficulty of the task accordingly. In patients, we were able to identify a dissimilar pattern of performance and task parameters in paretic and nonparetic arms. The paretic arm always required a lower level of difficulty in order to sustain performance. Consequently, the difficulty ratio between arms was significantly lower than for controls, which showed a balanced performance for both arms. By analyzing the individual game parameters (speed of the spheres, time interval between consecutive arms and range of dispersion), the performance of the paretic arm of the patients was significantly different from the contralateral arm and from the control group. On the other hand, the nonparetic arm of the patients shared the same aspects of the game dynamics with both arms of the controls, except for speed, the nonparetic arm requiring a significantly slower sphere speed during the game. We think that this difference in the speed could be related to a general slowing down in movements that has been reported in stroke patients (Yarosh, Hoffman et al. 2004; Horstman, Gerrits et al. 2010), or to the degree of unfamiliarity with VR interactive games.

In order to ensure the ecological validity of training with RGS we showed that movement kinematics was transferred between two equivalent tasks in real and virtual environments. We captured the same relationship between the upper extremities, for patients and healthy control subjects, in both environments. Performance was preserved, only showing a non-specific speed reduction in the virtual world. This is consistent with other studies that showed similar differences in performance in physical and virtual environments (Viau, Feldman et al. 2004; Subramanian, Knaut et al. 2007).

We believe that due to its relevant features the RGS is a valuable rehabilitation tool that has potential to lead to a beneficial impact on recovery. The RGS was tested in longitudinal pilot studies with both acute and chronic stroke patients. The results of these studies are discussed in the next chapters.

4. NEUROREHABILITATION WITH THE REHABILITATION GAMING SYSTEM IN THE ACUTE STAGE OF STROKE

Parts of the content of this chapter have been published in (1) and (2) and have been submitted for publication in (3):

(1) Cameirão MS, Bermúdez i Badia S, Duarte Oller E, Verschure PFMJ: Using a Multi-Task Adaptive VR System for Upper Limb Rehabilitation in the Acute Phase of Stroke. Virtual Rehabilitation 2008.

(2) Cameirão MS, Bermúdez i Badia S, Verschure PFMJ: The rehabilitation gaming system: a review. Stud Health Technol Inform 145: 65-83. 2009.

(3) Cameirão MS, Bermúdez i Badia S, Duarte Oller E, Verschure PFMJ: Virtual reality based rehabilitation speeds up functional recovery of the upper extremities after stroke: a randomized controlled pilot study in the acute phase of stroke using the Rehabilitation Gaming System. 2010.

4.1 Introduction

Virtual Reality is promising in the development of effective rehabilitative techniques as it provides rich controllable environments and the possibility for individualization. A number of studies showed evidence of the positive benefits of such systems in the rehabilitation of the paretic upper limb after stroke (Cameirão, Bermúdez i Badia et al. 2008; Lucca 2009). However, the impact of VR based approaches on recovery is not fully understood and its advantages with respect to traditional neurorehabilitation methods has not yet been convincingly proven (Lucca 2009; O'Dell, Lin et al. 2009).

Here we sought to investigate the impact of RGS supported rehabilitation on the recovery time course of stroke. Therefore the intervention was carried out in the acute/subacute stage during a 12 weeks period. Studies with VR in the acute stage after stroke are rare and little difference in motor function and disability between VR and conventional therapy has been found (Piron, Tonin et al. 2005). However, taking into account that most of the plastic changes and consequent outcomes happen in the first few months after stroke (Kreisel, Bazner et al. 2006; Murphy and Corbett 2009), one would expect that rehabilitation during this period should be more effective. Consequently, it becomes extremely important to investigate whether an early treatment with VR may speed up recovery.

The results presented in this chapter suggest that the Rehabilitation Gaming System speeds-up the recovery of the deficits of the upper extremities, with particular emphasis on functional aspects related to the performance of the activities of daily living. This evidences the potential benefits for neurorehabilitation of using VR based systems that directly target the neuronal substrate of recovery through the MNS.

4.2 Methods

a) Subjects and Experimental Protocol

Subjects were acute stroke patients admitted to the Physical Medicine and Rehabilitation unit of the Hospital de L'Esperança in Barcelona. Out of 142 patients admitted between November 2007 and January 2009, 25 (18%) satisfied the inclusion criteria to participate in the study. The inclusion criteria were: first episode stroke, acute stroke within three weeks post-stroke at baseline, severe to moderate deficit of the paretic upper extremity (2<=MRC<=3) (MRC 1976), no severe to moderate aphasia (Rosselli, Ardila et al. 1990), no other cognitive deficits as assessed by the Mini-Mental State Examination (Folstein, Folstein et al. 1975), cooperation, and age<=80 years.

After giving their informed consent, patients were randomly assigned to the Rehabilitation Gaming System (n=13) or to a Control group, consisting of either Intense Occupational Therapy (IOT, n=6) or Non-Specific interactive Games (NSG, n=6) using a standard game console. All patients received standard occupational and physical rehabilitation plus the added treatment condition during a 12-week period. The patients underwent extended clinical assessment at admittance (baseline), week 5, week 12 (end of treatment), and week 24 (follow-up). The study followed accepted guidelines and was approved by the ethics committee of clinical research of the IMAS – Instituto Municipal de Asistencia Sanitaria (see Appendix I).

Out of the original 25 patients selected for the study, one refused to participate and five patients left the study before the week 5 evaluation due to external reasons not related to the treatment (four moved to a different institution and one dropped all rehabilitation). The remaining 19 patients (RGS=10, Control=9 (IOT=5, NSG=4)) completed the study at least up to week 5 (see Table 4.1 detailed individual demographic information). We have missing evaluations for four patients at week 12 and 24: two dropped all the rehabilitation half-way the study, one moved to a different institution, and the other one had a second stroke.

b) Treatment

In addition to standard rehabilitation, patients had three weekly sessions of 20 minutes each of a given treatment condition (RGS or Control). Patients in the RGS performed Spheroids, which was online adjusted by the Personalized Training Module (see Chapter 3) according to individual performance. The sessions followed a structured training protocol with tasks of increasing complexity (Hitting, Grasping and Placing) (see Chapter 3) that train speed and range of movement, grasp and release respectively (Figure 4.1). The training sessions were preceded by the calibration task (see Chapter 3), which established the baseline of the task difficulty level at every session.

The Control group was split in two subgroups to control different aspects of the intervention. The IOT subgroup carried out pure extended occupational therapy with emphasis on motor tasks similar to the ones promoted by the RGS, namely object displacement, and object grasp and release (Figure 4.2a). To control for the role of body representation, computer use and game specific effects, patients allocated to the NSG subgroup performed games with the Wii system (Nintendo, Tokyo, Japan) that required movements with the paretic arm that did not show any virtual body in response to their actions (Figure 4.2b). This control had in common with the RGS group the gaming aspects. However, this control did not share the neuroscientific hypotheses on functional recovery based on an action observation paradigm.

All patients in the Control group performed the RGS calibration task once per week for between-group comparisons.

Table 4.1. Patient demographic information.

Group	ID	Age	G	E	NIHSS	Days after Stroke	Type of Stroke	Infarct Classif.	Side of Lesion
RGS	1	79	F	E	13	18	C	TACI	R
	2	60	F	E	4	4	H	-	R
	3	67	M	M	6	9	A	POCI	R
	4	55	M	E	6	13	A	POCI	R
	5	76	M	M	7	16	A	LACI	L
	6	79	F	E	4	7	U	POCI	L
	7	50	F	E	5	8	U	LACI	L
	8	52	M	E	7	19	H	TACI	R
	9	50	F	M	6	13	C	PACI	R
	10	69	M	E	4	8	A	PACI	R
Control IOT	1	66	F	M	7	15	C	LACI	L
	2	54	M	M	8	14	H	-	L
	3	47	M	M	6	22	C	TACI	R
	4	56	M	E	11	11	A	PACI	R
	5	74	F	E	5	22	A	TACI	R
Control NSG	1	65	F	E	2	7	A	LACI	L
	2	37	F	E	6	12	H	-	L
	3	65	M	M	6	18	A	TACI	R
	4	65	F	E	6	15	A	POCI	R

Control: IOT=Intense Occupational Therapy and NSG=Non-Specific Games. Gender (G): M=male and F=female. Education level (E): E=elementary and M=medium. NIHSS: Neurological deficit (Montaner and Alvarez-Sabin 2006). Days after stroke: at baseline. Type of stroke: H=hemorrhagic, C=cardioembolic, A=atherosclerotic, and U=undetermined (Adams, Bendixen et al. 1993). Infarct classification: TACI=total anterior circulation infarct, PACI=partial anterior circulation infarct, POCI=posterior circulation infarct and LACI=lacunar infarct (Bamford, Sandercock et al. 1991). Lesion side: L=left and R=right.

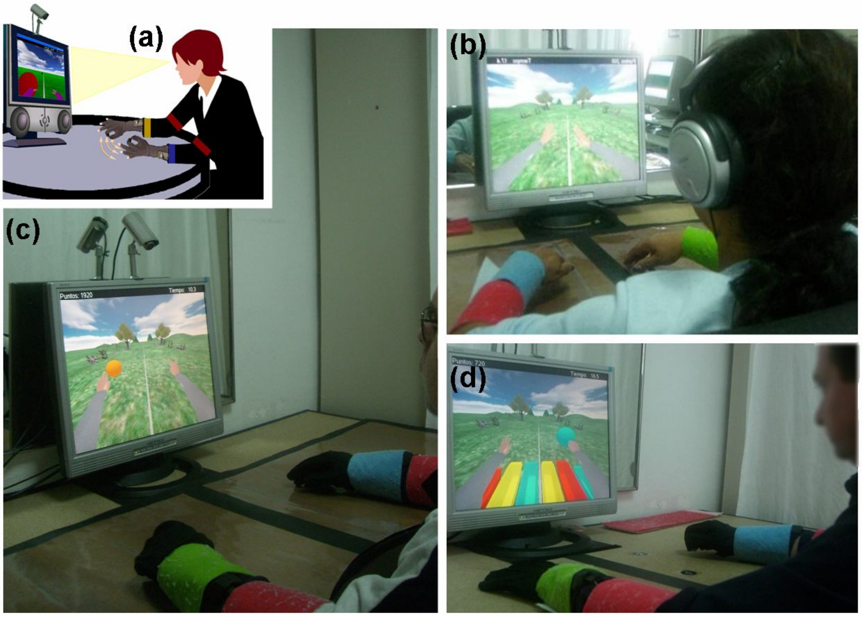

Figure 4.1. Rehabilitation Gaming System group. (a) The movements of the arms and hands are captured by a vision based tracking system and data gloves, and mapped onto the movements of the virtual arms. Spheroids provides tasks of increasing complexity: (b) Hitting for arm speed and range of movement; (c) Grasping to add finger flexure; and (d) Placing to add grasp, and release.

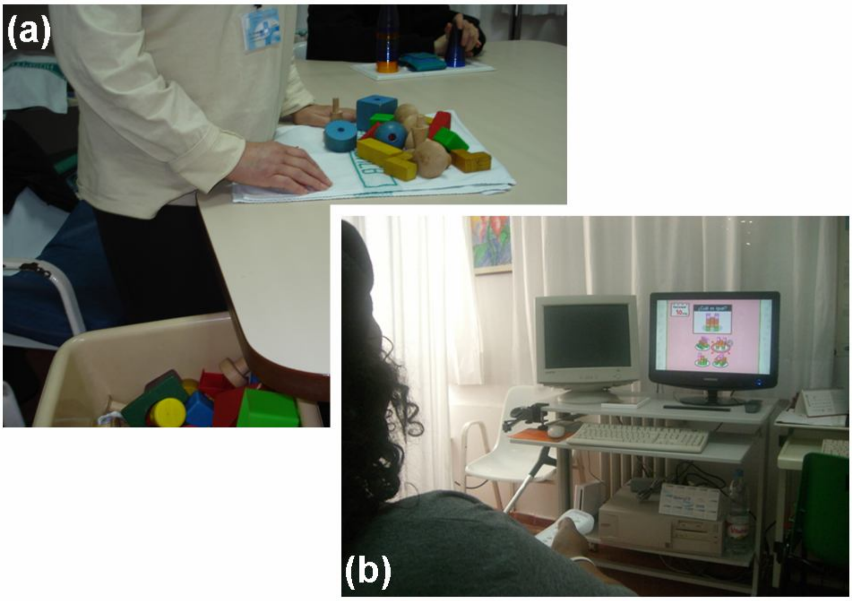

Figure 4.2. Control group. (a) IOT subgroup: extended occupational therapy; (b) NSG subgroup: non-specific interactive games with the Nintendo Wii.

c) Outcome Measures

The clinical assessment was performed at baseline, week 5, week 12, and week 24 (follow-up). The evaluators were blind to the assignment of each subject to either the RGS or the Control group. A number of standard clinical scales were used to assess different aspects of motor deficits and function: Barthel Index (Mahoney and Barthel 1965) for independence in activities of daily living, Medical Research Council Grade (MRC 1976) and Motricity Index (Demeurisse, Demol et al. 1980) (upper extremities) for muscle strength, Fugl-Meyer Assessment Test (Fugl-Meyer, Jaasko et al. 1975) (upper extremities) for motor and joint functioning, and Chedoke Arm and Hand Activity Inventory (CAHAI) (Barreca, Gowland et al. 2004) for the functional assessment of the paretic arm and hand. (The clinical scales are provided in Apendix III).

The Rehabilitation Gaming System calibration task allowed us to extract information in terms of speed for both RGS and Control group. In addition, specifically for the RGS group, from the training session we measured game related events. For example, successful/unsuccessful trials and achieved difficulty level for both the paretic and nonparetic arm.

To assess patients' subjective opinions with respect to a number of aspects of the treatment with RGS such as enjoyment, understanding and ease of the task, patients in the RGS group were given a short self-report questionnaire at the end of the treatment (Appendix II). This questionnaire was presented in the format of a 5-point Likert scale and patients had to report their agreement/disagreement with respect to a number of statements.

d) Data Analysis

It was reported that recovery following stroke shows a non-linear logarithmic pattern, with a faster improvement in the first weeks post-stroke followed by smaller improvements at later stages (Jorgensen, Nakayama et al. 1995; Kwakkel, Kollen et al. 2004; Kwakkel, Kollen et al. 2006). This makes it especially difficult to assess smaller improvements that are on top of this recovery curve.

In order to capture this behavior, we fitted a logarithmic curve to the individual clinical measures at the different measurement points (Figure 4.3) and assessed the strength of this relation by extracting the squared correlation coefficient, R^2. In addition, this logarithmic fit allowed us to estimate missing data.

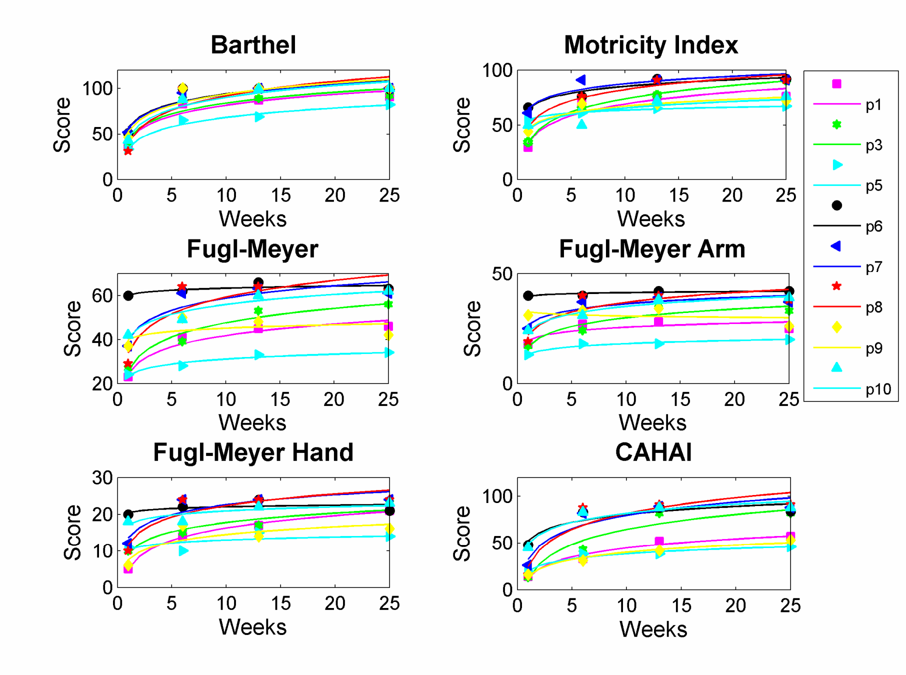

Figure 4.3. Pattern of recovery for the standard clinical scales. We performed a logarithmic fit to capture the trend over time. We show the data for patients in the RGS group with complete clinical evaluation at all time steps.

For each scale, for the entire group of patients, we computed the median R^2 and checked the presence of statistical outliers. We excluded from the analysis patients that were statistical extreme outliers (values that are more than 3 times the interquartile range above the 75th percentile or below the 25th percentile) in two or more clinical scales. This led to the removal of Patients 5 and 9 in the RGS group and of Patient 2 in Control NSG subgroup. The dissimilar pattern of recovery of these patients was in accordance with observed personal and clinical circumstances that interfered with the normal progress of these patients during the rehabilitation process.

In order to have an unbiased assessment of the similarities and differences between groups (RGS, IOT and NSG) in the clinical scores, we performed a Principal Components Analysis (PCA) that allowed us to investigate the structure of the data over the groups of patients over all the clinical scales at the end of treatment. We extracted the principal components and performed a between-group comparison using a two-tailed Mann-Whitney test. To correct for individual differences between participants we computed the Normalized Improvement (eq.6), which represents the improvement normalized to the total amount that each individual can gain with respect to their baseline.

$$\text{Normalized Improvement}_{i,j} = \left[1 - \frac{\left(\text{MaxScale}_j - X_i\right)}{\left(\text{MaxScale}_j - X_0\right)} \right] * 100 \qquad (6)$$

where X_i is a given measure of the scale j at time i. X_0 represents the baseline.

In order to check the balance between the groups, the absolute baseline measures were statistically compared using the chi-squared test for categorical data, and a 2-tailed independent samples t-test or a Mann-Whitney test for quantitative data. The normality of the distribution was assessed using a single sample Lilliefors hypothesis test of composite normality. To compare the intervention and the control group over time (baseline, end of treatment and follow-up) we performed a repeated measures ANOVA, with time as the within-subject variable and group as the between-subject variable. The between-group comparisons of the normalized improvements at different time points were performed using a 1-tail Mann-Whitney test. For within-group comparisons we used a 2-tail Wilcoxon signed ranks test.

In the analysis of the RGS data, we extracted the weekly average (relative to baseline) of the paretic arm speed in the calibration task for both groups of patients (see Methods). The speed time series was smoothed using a moving average with a span of two weeks and to show the trend over time we included a logarithmic fit (see Methods). To compare the intervention and the control group over time we performed a Time×Group repeated measures ANOVA, and used a 1-tail Mann-Whitney test for between-group comparisons at time points.

To analyze the evolution of the paretic arm in the Spheroids task, for the RGS group, we extracted the maximum difficulty reached during each session of the Hitting/Grasping task (eight weeks period) and averaged it over periods of two weeks, separately for paretic and nonparetic arms. We computed the difference in difficulty between both arms and removed the statistical outliers at every week (values that are more than 1.5 times the interquartile range above the 75th percentile or below the 25th percentile). We used a 2-tail Wilcoxon signed rank test to compare both arms at each point in time.

Data is expressed as mean ± standard deviation in the text and tables, unless otherwise stated. For all statistical comparisons the significance level was set to 5% ($p<.05$). All statistical analysis was done using MATLAB (MathWorks) and SPSS (SPSS-Inc).

4.3 Results

a) Outcome Measures

In order to have an unbiased assessment of the differences between the RGS group and, the Intense Occupational Therapy and Non-Specific interactive Game control subgroups, we performed a PCA of the clinical improvements at the end of treatment for all groups. The six principal components (PCs) explained 66.21%, 16.03%, 9.30%, 5.00%, 3.44% and 0.01% of the variability of the data, respectively. We observed the existence of a similar recovery pattern for both control interventions since they clustered together, being not separable from each other (Figure 4.4). Interestingly, we found a different improvement pattern for the RGS group, which was particularly salient in the third PC. The between-group comparisons of the PCs showed no significant differences between the control subgroups for any of the PCs (Mann-Whitney, p>.05). However, we found a significant difference between the RGS group and both control subgroups (Mann-Whitney, *RGS-CA*: Z=-2.635, p<.01, *RGS-CB*: Z=-2.245, p<.05) for the third PC. Therefore, taking into account that both control subgroups were statistically indistinguishable from each other while being different from the RGS group, we merged them. This consequently resulted in an increase of sample size enhancing the statistical power of our analysis.

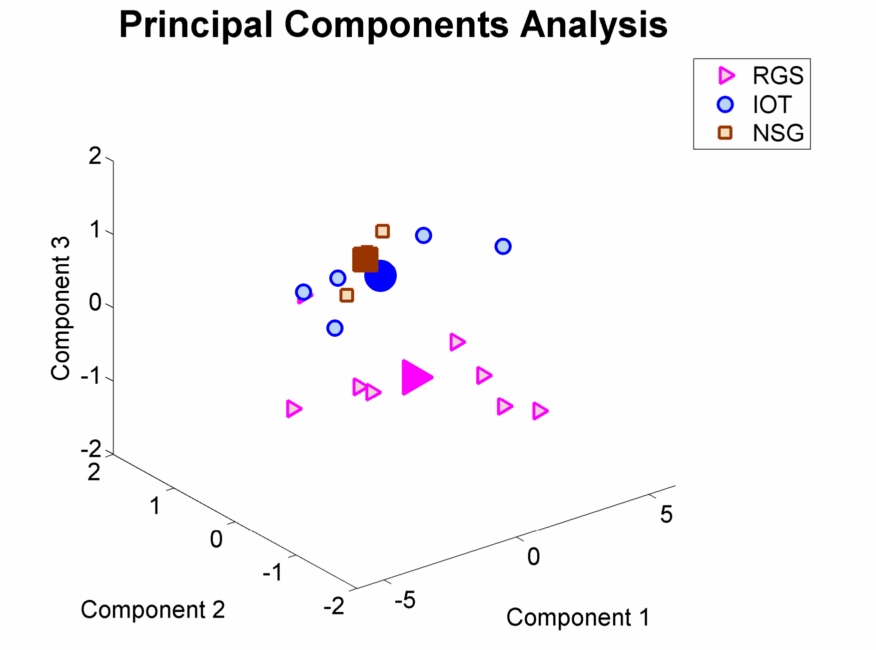

Figure 4.4. Structure of the clinical scores of the subjects using a Principal Component Analysis. Representation of the three first PCs (91.56% of variability explained) of the clinical scores at the end of treatment for the RGS group (pink), and the control IOT (blue) and NSG (brown) subgroups. The larger markers indicate the centroids (mean) of the distributions for each group.

Baseline balance between groups was confirmed for all demographic and clinical measures except for the Fugl-Meyer Assessment Test. The RGS group had a higher score in this measure due to differences in the wrist/hand subpart of the test (Table 4.2).

In the comparison of arm speed between groups in the RGS calibration task, the Time×Group repeated measures ANOVA revealed a significant main effect for Time (F(3.70, 44.36)=5.10, p<.01, partial eta squared=.298) and Group (F(1, 12)=6.08, p<.05, partial eta squared=.336). The Time×Group interaction was leaning towards significance (F(3.70, 44.36)=2.59, p=.053, partial eta squared=.178).

Table 4.2. Baseline demographic and clinical measures.

Variable	RGS (n=8)	Control (n=8)	p-value
Demographics			
Age	63.9±11.5	61.5±8.5	0.646 (T)
Gender (M/F)	4/4	4/4	1.000 (χ^2)
Education (E/M)	7/1	4/4	0.106 (χ^2)
Lesion Side (L/R)	2/6	3/5	0.590 (χ^2)
Days post stroke	10.8±5.4	15.5±5.2	0.093 (T)
NIHSS (max=42)	6.1±3.0	6.4±2.6	0.860 (T)
Clinical			
Barthel Index (max=100)	42.1±6.8	45.6±14.1	0.537 (T)
MRC (2/3)	4/4	4/4	1.000 (χ^2)
Motricity Index (max=99)	52.2±15.8	42.7±17.7	0.277 (T)
Fugl-Meyer (max=66)	37.9±12.1	24.4±11.4	0.038 (T)
Arm (max=42)	24.8±7.7	18.0±7.1	0.090 (T)
Wrist/Hand (max=24)	13.1±5.0	6.4±4.6	0.015 (M)
CAHAI (max=91)	29.5±15.1	24.5±12.9	0.528 (M)

Gender: M=male and F=female. Education level: E=elementary and M=medium. Lesion side: L=left and R=right. The categorical variables are expressed in terms of the ratio of cases and the quantitative variables are mean ± standard deviation. For the p-value, the text in brackets denotes the statistical test that was used for the comparison (T=2-tail independent samples t-test, M=2-tail Mann-Whitney Test, χ^2=chi squared test).

Concerning the evolution of speed over time, the RGS showed faster improvements in the paretic arm speed when compared to the control group, and these were systematically significant after the 9th week of treatment (Mann-Whitney, p<.05) (Figure 4.5). Although the control group showed a steep improvement during the first few weeks, it stabilized after week 5, approximately. This was not the case for the RGS group, which displayed a sustained improvement following a well defined logarithmic pattern (R^2 =.95).

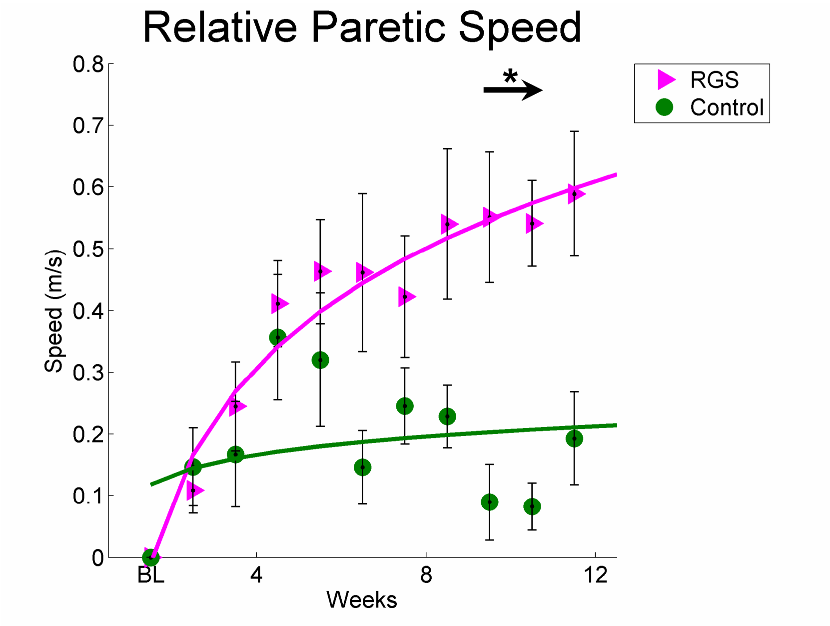

Figure 4.5. Speed of the paretic arm over time as measured in the calibration task. Relative average speed (mean ± standard error of the mean) over time (baseline, week 5 and week 12 are indicated) for RGS (pink) and control (green) groups. The time series are fitted with logarithmic curves. The arrow indicates the period when the difference between groups starts to be systematically significant, Mann-Whitney Test, * p<.05.

In the analysis of the specific clinical outcomes assessed by the different clinical scales, the 3(Time) × 2(Group) repeated measures ANOVA revealed a significant main effect for Time for all the clinical measures (*Barthel Index*: F(1.35, 18.89)=705.54, p<.001, partial eta squared=.981; *Motricity Index*: F(1.45, 20.33)=205.96, p<.001, partial eta squared=.936; *Fugl-Meyer*: F(2, 28)=177.51, p<.001, partial eta squared=.927; *Fugl-Meyer Arm subpart*: F(1.18, 16.52)=145.31, p<.001, partial eta squared=.912; *Fugl-Meyer Wrist/Hand subpart*: F(2, 28)=96.90, p<.001, partial eta squared=.874; *CAHAI*: F(1.32, 18.49)=388.86, p<.001, partial eta squared=.965). We found no significant main effect for Group at any measure. However, a significant Time × Group interaction was found for the CAHAI (F(1.32, 21.13)=4.09, p<.05, partial eta squared=.226). In addition, the between-subject comparisons of the normalized improvements at different points in time showed that at the end of the treatment (week 12) the RGS group was significantly better for the arm subpart of the Fugl-Meyer Assessment Test (Mann-Whitney, Z=-1.897, p<.05) and for the CAHAI (Mann-Whitney, Z=-1.957, p<.05), and that this difference was leaning towards significance for the Motricity Index (Mann-Whitney, Z=-1.629, p=.052) (Table 4.3, Figure 4.6).

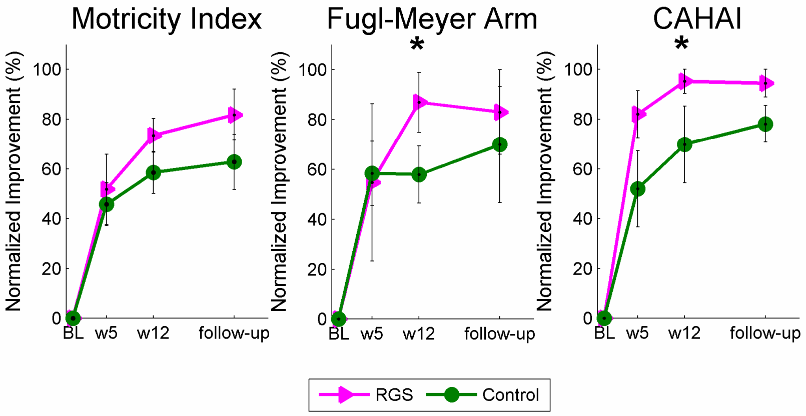

Figure 4.6. Normalized improvement over time for selected clinical scales. Improvement (median ± median absolute deviation) for RGS (pink) and control (green) groups for the Motricity Index, the arm subpart of the Fugl-Meyer Assessment Test, and the Chedoke Arm and Hand Activity Inventory. * p<.05, between-group comparison.

Table 4.3. Normalized improvement (%) at time points compared to baseline.

Variable	RGS	Control	p-value
Week 5			
Barthel	87.6±11.2	81.0±19.4	0.287
Motricity	52.4±30.0	51.4±22.5	0.253
Fugl-Meyer	62.0±30.9	55.6±22.1	0.439
Arm	57.1±36.2	52.9±25.7	0.439
Wrist/Hand	63.0±36.5	59.1±22.3	0.322
CAHAI	72.7±26.5	46.5±29.6	*0.065*
Week 12			
Barthel	94.9±8.9	88.0±17.8	0.221
Motricity	73.6±16.1	60.2±20.0	*0.052*
Fugl-Meyer	84.6±18.4	66.9±22.9	*0.065*
Arm	83.6±19.7	62.3±23.0	**0.032**
Wrist/Hand	85.0±21.3	70.6±32.2	0.191
CAHAI	90.2±17.0	70.6±18.2	**0.025**
Week 24			
Barthel	96.3±6.3	92.9±7.1	0.221
Motricity	81.3±15.9	66.3±20.9	*0.065*
Fugl-Meyer	79.1±19.0	72.0±18.8	0.252
Arm	78.7±24.3	64.6±25.3	0.139
Wrist/Hand	85.7±25.5	81.5±12.7	*0.080*
CAHAI	89.6±14.9	81.9±12.3	*0.080*

The normalized improvements are expressed as mean ± standard deviation. A 1-tail Mann-Whitney test was used for the statistical comparisons.

Although the RGS group always showed faster average improvements over time, we found no further significant differences between the groups. Both groups showed significant improvements between baseline and week 5 for all the clinical scales. Between week 5 and week 12, the RGS group improved significantly at all measures (Wilcoxon, *Barthel Index*: Z=-2.023, p<.05, *Motricity Index*: Z=-2.201, p<.05, *Fugl-Meyer*: Z=-2.201, p<.05, *Fugl-Meyer Arm subpart*: Z=-2.201, p<.05, *Fugl-Meyer Wrist/Hand subpart*: Z=-2.023, p<.05, *CAHAI*: Z=-2.521, p<.05), while the control group only improved significantly at the Barthel Index (Wilcoxon, Z=-2.201, p<.05) and the CAHAI (Wilcoxon, Z=-2.366, p<.05). This indicates that the RGS group showed a steeper improvement over time during the treatment period (Figure 4.6). No significant improvements were found between week 12 and follow-up for both groups. In summary, the RGS group displayed on average higher scores at the different points in time, and displayed a sustained faster improvement when compared to the control group.

Finally, we wanted to investigate how accurately the RGS task captured the functional level of the user over time and adjusted the difficulty. The analysis of the maximum difficulty reached over time for the RGS group showed as expected that the paretic arm always reached lower levels of difficulty when compared to the nonparetic arm (Figure 4.7). However, the paretic arm tended to converge towards the performance of the nonparetic arm during the treatment period. Indeed, the difficulty reached was significantly different between arms at week 2 (Wilcoxon, Z=-2.380, p=.05) and at week 4 (Wilcoxon, Z=-2.240, p<.05), and stoped to be significantly different after the 6th week of treatment (Wilcoxon, p>.05). These results show that the RGS captured the functional state, and therefore the recovery pattern, of the subject over time and that it autonomously generated the difficulty level accordingly during each session.

b) Acceptance and Satisfaction

In order to assess the acceptance level of the treatment and the overall satisfaction concerning the use of RGS, patients that performed the entire treatment period with RGS (n=8) were given a succinct self-report 5-point Likert questionnaire at the end of treatment. This allowed us to assess a number of aspects such as enjoyment, understanding and ease of the task. In addition, patients were also asked if they would like to continue the treatment with RGS. In terms of enjoyment, to the statement “The task was entertaining”, 50.0% of the patients strongly agreed and 50.0% agreed. To the statement “The task was too long”, 75.5% strongly disagreed and 25.0% disagreed. In terms of clarity and difficulty in using the system, to the statement “The task was easy to understand”, 87.5% of the patients strongly agreed and 12.5% agreed. To the statement “It was difficult to control the virtual arms”, 25.0% strongly disagreed, 50.0% disagreed, 12.5% neither agreed nor disagreed and 12.5% agreed. Finally, as a measure of overall satisfaction, to the statement “I would like to continue this treatment”, 50.0% of the patients strongly agreed, 37.5% agreed and 12.5% neither agreed nor disagreed. Based on the supportive answers of the patients and the overall analysis of the use of the Rehabilitation Gaming System, we feel confident to conclude that the acceptance of this system and its tasks was very high.

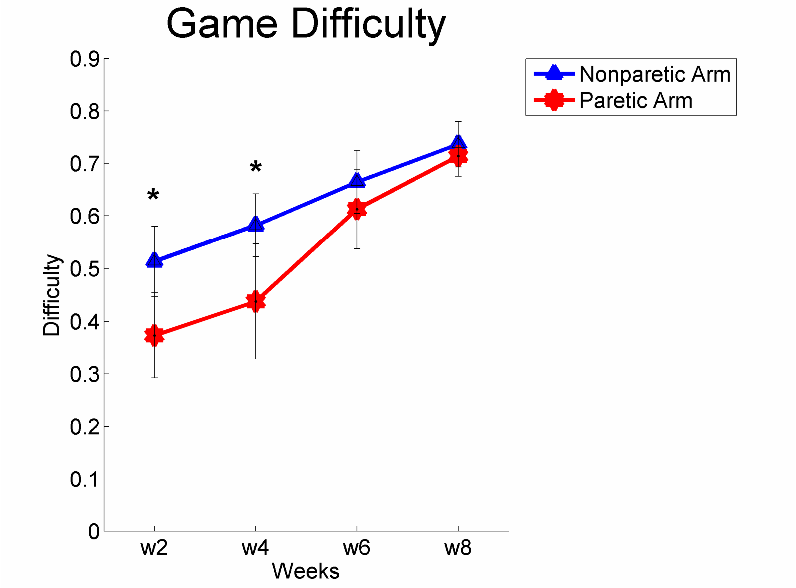

Figure 4.7. Game difficulty. Biweekly average of the difficulty level reached during the Hitting/Grasping task in the Spheroids game (mean ± standard error of the mean) for paretic (red) and nonparetic (blue) arms. The difficulty level goes up to a maximum of 1.0. * p<.05, pairwise comparison.

4.4 Discussion

Our VR based Rehabilitation Gaming System (RGS) comprises a number of neuroscience based explicit hypotheses on the positive effects on stroke rehabilitation of combined action execution and observation, and task oriented adapted training. Here we sought to investigate the impact of a 12 weeks treatment period with the RGS on the recovery of the deficits of the upper extremities in the acute stage of stroke, in comparison with a control group that followed an alternative treatment (extended occupational therapy or interactive gaming). Our results indicate that the RGS group followed a substantially different pattern of recovery when compared to the control group.

In the evolution over weeks of the average paretic arm speed in the RGS calibration task, the RGS group showed in general a higher movement speed when compared to the control group, and there was a statistically significant difference after the 9th week of treatment. This indicates that the treatment with RGS led to an increase of speed over time as compared to the control group. This could be related to the fact that higher arm speed is required in order to accomplish higher difficulty levels in the RGS tasks. Therefore RGS patients were developing higher movement speed skills.

In the analysis of detailed clinical outcomes assessed by standard clinical evaluation at the different time stages, we extracted the Normalized Improvement, meaning that the scores are normalized to the amount that each individual can gain with respect to their own baseline. This represents a measure of improvement within the “potential of recovery” of each individual. Patients allocated to the RGS group showed in general higher improvements and these were particularly salient at the end of the treatment, after week 12. Specifically, the between group difference was statistically significant for the arm subpart of the Fugl-Meyer Assessment Test and for the Chedoke Arm and Hand Activity Inventory, and leaning towards significance in the case of the Motricity Index. Hence, RGS supported rehabilitation seems to have a particular impact on the recovery of proximal movements and on the ability to perform functional activities of daily living. Since the RGS promotes proximal and distal movements, we would also expect to have a significant impact at the hand subpart of the Fugl-Meyer Test, but this was not the case. We have two possible explanations for this. First, it could be due to imbalance at baseline for this specific measure. Second, although RGS trains finger grasping and release, there are only virtual objects to be grasped and the patient has no physical contact with them. Therefore, there is no sensory information on the effectiveness of this movement. This may indicate the need to incorporate a graspable object preferably coupled with a haptic interface to provide sensorimotor feedback and increase the ecological validity of the task (Levin, Knaut et al. 2009). To address this issue, we developed an updated version of the RGS that integrates a haptic interface that provides sensorimotor feedback during the task.

Newer rehabilitation strategies such as robotics, constraint-induced motor therapy, functional electrical stimulation and transcranial magnetic stimulation have shown so far good outcomes at the movement level but with poor outcomes at the functional performance of activities of daily living (ADL) (Mehrholz, Platz et al. 2008; O'Dell, Lin et al. 2009). In contrast, in our study the RGS group showed a considerable improvement at the performance of ADLs, as measured by the Chedoke Arm and Hand Activity Inventory. We believe that RGS has this functional impact because it tackles the central nervous system, as opposed to other approaches that emphasize the manipulation of the peripheral skeleton-motor system.

The clinical scores over time showed that, although we observed significant group differences at the end of treatment, this significance was lost at follow-up (12 weeks after the end of the treatment). This could mean that rehabilitation with RGS predominantly accelerates recovery following stroke. Indeed, our results showed that only the RGS group improved significantly at all clinical scales, systematically from baseline to week 5 of treatment and from week 5 to end of treatment. I.e., the RGS group presented a steeper improvement over time during the treatment period. On the basis of this result it is important to investigate if the RGS just speeds-up recovery or if it could more markedly enhance recovery if we increase the intensity of the treatment and/or the longitudinal time duration of the intervention. We are currently running clinical trials that address the relationship between treatment intensity and duration. In addition, it is important to further assess the impact of VR on the early stages of stroke. Most plastic changes occur during this period and therefore recovery could be possibly maximized (Murphy and Corbett 2009).

Finally, we show that the RGS was able to capture the functional dissimilarities between paretic and nonparetic arms and adapt the difficulty of the task accordingly. In this way we provide an autonomous adaptable training regime that is directed towards the individual needs and capabilities of the patients. In addition, this results in higher levels of motivation and compliance with the treatment as shown by the results of our acceptance study. Indeed, the opinion of the patients that used the RGS showed that the majority would like to continue therapy with the RGS.

Our results indicate that rehabilitation with the Rehabilitation Gaming System facilitates the functional recovery of the upper extremities in the acute phase of stroke. Although further testing is needed with larger populations of patients, our results show promise in terms of the benefits provided by the RGS for the neurorehabilitation of motor deficits following stroke.

5. AUGMENTING THE REHABILITATION GAMING SYSTEM WITH AN EXOSKELETON AND A HAPTIC INTERFACE: A RANDOMIZED CONTROLLED STUDY IN THE CHRONIC STAGE OF STROKE

5.1 Introduction

In the previous chapter we showed that VR is a promising tool to induce functional recovery after lesions to the nervous system. This is due to the fact that VR systems can capture core parameters of effective neurorehabilitation, while combining them with a number of features that are specific for this technology (Cameirão, Bermúdez i Badia et al. 2008; Lucca 2009). An important research question, however, is the way in which this technology can be exploited maximally. There is still the need to further understand the relation between the characteristics of these systems and the impact on the recovery of their users.

This study aimed at assessing the impact of a virtual task for upper limb rehabilitation when it was performed with different interface technologies. We used the Rehabilitation Gaming System coupled with the standard vision based tracking system (AnTS), a haptic feedback system, and an exoskeleton. The rational behind the use of haptic interfaces is that we can increase the realism of the interaction and the scenarios by providing force-feedback to the user each time there is an interaction with a virtual object. This increases the ecological validity of the task while reinforcing it with additional feedback. Thus the task becomes more salient to the user (Levin, Knaut et al. 2009). Moreover, the additional feedback provided by the haptic interface can inform the user on the effectiveness of the performed movements. In fact, previous research with stroke patients that used VR augmented with haptics showed positive results on motor performance (see Virtual Rehabilitation, Chapter 1). Other interface devices that aim at facilitating the movement of the impaired limb are orthosis that support the weight of the limbs. Hence, it is possible that task-specific training with gravity support by means of orthosis – a passive exoskeleton in this case – may allow for a more effective movement performance. In addition, the benefits in terms of motivation provided by the use of such systems should not be disregarded (Housman, Scott et al. 2009).

The multi-modal task-specific individualized training provided by the RGS has already shown to have an impact on the recovery time course following stroke, with particular benefits on the performance of activities of daily living (Chapter 4). However, it is necessary to investigate how recovery can be further improved by means of interface systems. In the case of the current study, each new interface provided an additional feature to the existing system.

44 chronic stroke patients used one of the three versions of the RGS (standard, with haptics, or with arm support) five days a week during four weeks. We evaluated with standard clinical scales the functional improvements within all RGS configurations, and for how long the attained gains were preserved after the intervention period.

5.2 Methods

a) Setup

i) Rehabilitation Gaming System (RGS)

This setup was the standard RGS with the vision based tracking (AnTS) used in the previous studies. In the context of the current study and to preserve uniformity among the three systems, we did not use the data gloves to capture finger flexure since data gloves could not be combined with the other two interfaces. Only the movement of the arms was captured online and mapped onto the avatar’s movements. The subjects worked on a cut-out table top, facing a LCD screen (Samsung, Daegu, South Korea) (See Chapter 3 for more details on the standard RGS setup).

ii) Rehabilitation Gaming System with Haptics (RGS-H)

In the RGS-Haptics (RGS-H) setup, the RGS was coupled with a haptic interface made of two mechanical arms (GRAB, Percro - Scuola Superiore Sant'Anna, Pisa, Italy) (Figure 5.1). This device provided force-feedback on the end-effectors, specifically on two handles that the user had to grasp. This interface allowed the subject to have sensory feedback when touching the virtual objects. As in the case of the standard RGS setup, the arm position was tracked by means of the AnTS tracking system. Here, patients also worked on a cut-out table top, facing a computer screen.

iii) Rehabilitation Gaming System with Exoskeleton (RGS-E)

In the third setup, the RGS-Exoskeleton (RGS-E), the RGS was coupled with a bimanual passive exoskeleton with adjustable arm support (ARMEO, Hocoma, Volketswil, Switzerland) (Figure 5.2).

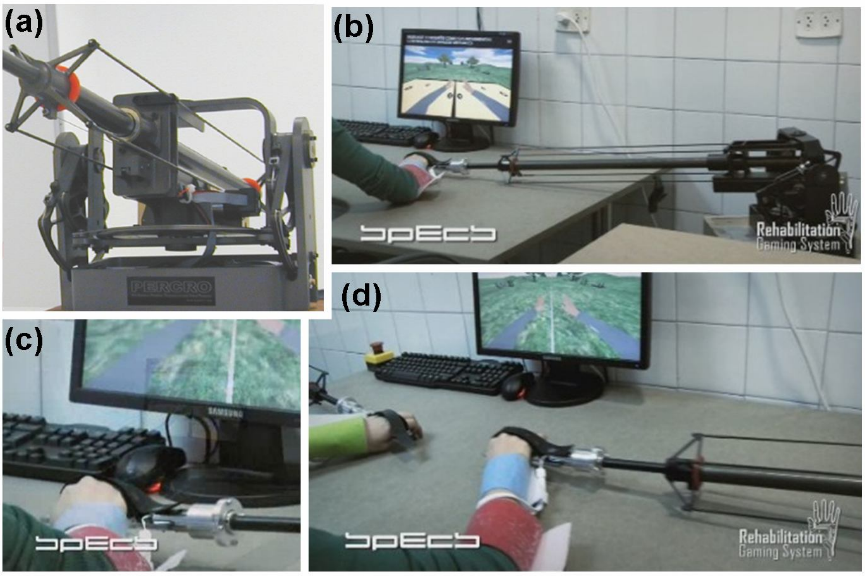

Figure 5.1. Haptic interface. The GRAB (a) is a robotic device that delivers force-feedback through two mechanical arms (b). The force-feedback is provided to the user by means of two handles that the user has to grab during the virtual reality experience (c, d).

The standard unimanual Armeo is based on the T-WREX (Housman, Le et al. 2007; Reinkensmeyer and Housman 2007; Housman, Scott et al. 2009), and facilitates movements by supporting the weight of the arms against gravity. For this study, we interfaced a unique bimanual version of this system allowing the use of the two arms during the performance of the task. Here, the position of the arms was captured by the exoskeleton itself and then mapped onto the corresponding angles on the avatar of the training scenario.

The exoskeleton has a number of adaptable components that allow adjusting the orthosis to the individual anatomical and functional features of the user (see Appendix IV for detailed schematics). The more relevant parts are the upper arm and forearm modules, which through simple mechanisms allow adjusting the length and the weight support of each arm segment. The individual measures of each patient were registered at baseline and used over all sessions (see Appendix IV for record sheet).

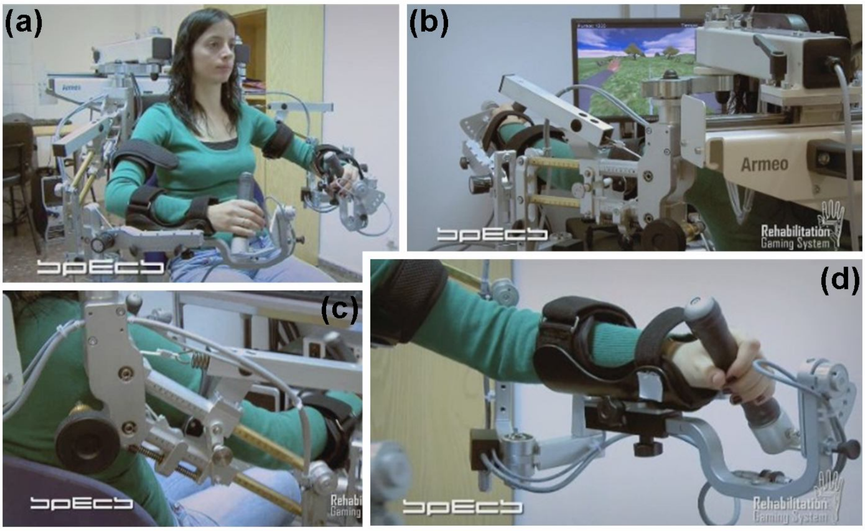

Figure 5.2. Exoskeleton. This system is a bimanual orthosis that supports the weight of the arms during training. (a) Front view. (b) Lateral view. (c) Upper arm (c) and forearm (d) modules provide adjustable length and weight support. A handle ensures a comfortable hand position (d).

iv) Task

The virtual task used in this study was the previously described Spheroids Grasping task, with online adjustable difficulty (see Chapter 3). In this study however, since finger flexure could not be captured by all the systems, the grasping action was a virtual grasping. I.e., each time a sphere was intercepted by virtual hand, it automatically grasped the sphere, independently if the patient could or not actually perform the grasp. Nevertheless, the patient was always instructed to try to grasp the spheres at the interception moment. This way, the patient could always observe the execution of the required movement. Before the daily Spheroids session, the patients also performed the virtual calibration task to define the baseline difficulty level at every session.

b) Subjects and Experimental Protocol

The subjects were chronic stroke patients that in the past had carried out inpatient post-stroke rehabilitation in the Physical Medicine and Rehabilitation unit of the Hospital de L’Esperança in Barcelona. A total of 48 patients with confirmed inclusion criteria were recruited for baseline evaluation. The inclusion criteria were: chronic stroke with a minimum one year post-stroke at baseline, discharge from rehabilitation since at least three months, severe to moderate deficit of the paretic upper extremity (2<=proximal MRC<=3) (MRC 1976), age<=80 years, cooperation, and stability in baseline measures. Exclusion criteria comprised severe to moderate aphasia (Rosselli, Ardila et al. 1990), other cognitive deficits as assessed by the Mini-Mental State Examination (Folstein, Folstein et al. 1975) and vision deficits that could influence the performance during the treatment. Six patients had mild aphasia (four Broca’s and two global) (Pedersen, Vinter et al. 2004) that did not interfere with the understanding and execution of the task.

After giving their informed consent, the patients were randomly assigned to one of the three treatment groups: RGS (n=17), RGS-H (n=16), or RGS-E (n=15) (Figure 5.3). The treatment consisted of 5 weekly sessions of 35 minutes of the assigned treatment condition. The patients underwent clinical assessment at baseline (evaluated twice with one week interval to ensure stability), week 4 (end of treatment), week 8 (first follow-up), and week 16 (second follow-up). The study followed accepted guidelines and was approved by the ethics committee of clinical research of the IMAS – Instituto Municipal de Asistencia Sanitaria (see Appendix I).

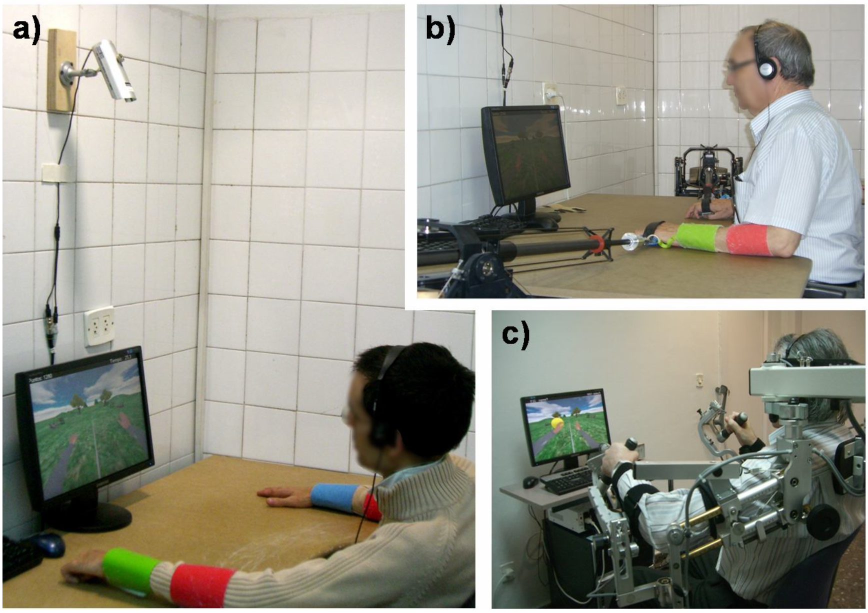

Figure 5.3. The three RGS configurations. a) **RGS:** patients work on a cut-out table top facing a computer screen. AnTS uses color detection to capture the movement of color patches located on the arms and map them onto the movements of the virtual arms. b) **RGS-H:** on top of RGS, two mechanical arms provide force-feedback to the patient during training. c) **RGS-E:** a bimanual exoskeleton provides support against gravity during the performance of Spheroids.

Out of the original 48 patients included in the study, four dropped the study before the end of the treatment (three due to reasons not related to the treatment, and one withdrawal). The remaining 44 patients (see Table 5.1 for demographic information) completed the entire treatment period. We have missing evaluations for three patients at the first follow-up (week 8), and for four patients at the second follow-up (week 16) because they were not available at the period of evaluation.

Table 5.1. Patient demographic information.

Group	ID	Age	G	Days after Stroke	Type of Stroke	Infarct Classif.	Side of Lesion
RGS	1	75	F	1976	H	-	L
	2	64	M	758	U	TACI	R
	3	34	M	963	A	PACI	R
	4	68	M	494	SVO	TACI	R
	5	80	F	456	C	TACI	R
	6	65	M	4261	A	PACI	R
	7	80	M	526	A	PACI	R
	8	69	M	2182	A	LACI	R
	9	64	F	1863	U	PACI	R
	10	74	F	370	U	LACI	L
	11	64	M	1877	A	LACI	R
	12	65	M	1211	A	LACI	L
	13	79	F	513	A	TACI	L
	14	74	F	3422	U	LACI	R
	15	74	F	2358	U	LACI	L
	16	70	M	3150	A	TACI	L
RGS Haptics	17	69	M	376	A	TACI	R
	18	67	F	479	C	LACI	L
	19	43	M	389	A	TACI	R
	20	53	M	1684	A	TACI	R
	21	50	F	1971	A	TACI	L
	22	70	F	431	C	LACI	R
	23	59	F	3626	H	-	R
	24	32	F	3596	H	-	R
	25	69	F	1355	A	POCI	R
	26	55	M	515	H	-	L
	27	77	F	1727	A	LACI	R
	28	76	M	1086	U	LACI	L
	29	67	M	425	U	LACI	L
	30	52	M	1018	A	LACI	L
RGS Exoskeleton	31	42	M	540	H	-	R
	32	52	M	1617	H	-	L
	33	67	F	2480	H	-	L
	34	65	F	495	R	TACI	R
	35	65	F	2555	H	-	R
	36	52	M	1985	A	TACI	R
	37	60	M	3054	A	TACI	R
	38	72	M	2343	A	LACI	L
	39	74	M	1787	A	LACI	L
	40	66	M	691	A	POCI	R
	41	57	M	482	U	PACI	R
	42	60	M	1803	C	LACI	R
	43	56	F	1731	A	TACI	R
	44	43	F	807	H	-	R

Gender (G): M=male and F=female; Infarct classification (Bamford, Sandercock et al. 1991): TACI=total anterior circulation infarct, PACI=partial anterior circulation infarct, POCI=posterior circulation infarct and LACI=lacunar infarct; Lesion side: L=left and R=right; Type of stroke (Adams, Bendixen et al. 1993): H=hemorrhagic, A=Atherosclerotic, C=Cardioembolic, SVO=small-vessel occlusion and U=undetermined.

c) Outcome Measures

An extended clinical assessment was carried out at the different evaluation stages. The evaluator was blind to the group allocation of each individual. A number of standard clinical evaluation scales were used to assess different aspects of motor deficit and function: Barthel Index (Mahoney and Barthel 1965; Granger, Albrecht et al. 1979) for independence in activities of daily living, Motricity Index (Demeurisse, Demol et al. 1980) (upper extremities) for muscle strength, Modified Ashworth Scale (Bohannon and Smith 1987) for spasticity, Fugl-Meyer Assessment Test (Fugl-Meyer, Jaasko et al. 1975) (upper extremities) for motor and joint functioning, Chedoke Arm and Hand Activity Inventory (CAHAI) (Barreca, Gowland et al. 2004) for the functional assessment of the recovering arm and hand, Nine Hole Peg Test (Oxford Grice, Vogel et al. 2003) for finger dexterity (showed just as baseline assessment as the number of patients that were able to complete the task is insufficient for further analysis), and Box and Block Test (Mathiowetz, Volland et al. 1985) for manual dexterity. More details on the clinical scales are shown in Appendix III.

To assess patients' subjective opinions with respect to a number of aspects of the treatment with RGS, RGS-E, or RGS-H, questionnaires were used. Patients were asked to report on aspects such as enjoyment, perceived improvement, and ease of the task, by means of a short self-report questionnaire at the end of the treatment (see Appendix II). Questions were presented in the format of a 5-point Likert scale and patients had to report their agreement/disagreement with respect to a number of statements.

d) Data Analysis

The absolute baseline measures of the clinical scales were statistically compared using the chi-squared test for categorical data, and a one-way ANOVA or a Kruskal-Wallis test for quantitative data. The normality of the distribution was assessed using a single sample Lilliefors hypothesis test of composite normality. To assess the overall impact of treatment over time we performed a Friedman test for the clinical scores from baseline to the different evaluation stages (end, follow-up one, and follow-up two). In addition, we computed the improvement in each clinical scale normalized to the maximum of the scale from baseline, except for the Box and Block test, which was normalized to baseline. For individual groups we performed pairwise comparisons with respect to baseline using a 2-tail Wilcoxon signed ranks test. The overall effect of group was assessed using a 3 samples Kruskall-Wallis test and for between-group comparisons of two samples we used a 2-tail Mann-Whitney test.

To assess the subjective opinion of the patients with respect to the treatment, we computed the average ratings for selected statements. In this case, for between-group comparison we used a Kruskall-Wallis test and 2-tail Mann-Whitney test.

Average data is expressed as mean ± standard deviation in the text and tables, unless otherwise stated. For all statistical comparisons the significance level was set to 5% ($p<.05$). All statistical analysis was done using MATLAB (MathWorks) and SPSS (SPSS-Inc).

5.3 Results

a) Outcome Measures

Baseline balance between groups was confirmed for all demographic and clinical measures, except for age, patients in the RGS group being the eldest (Table 5.2).

The analysis of the overall impact of the treatment over time showed that there was a longitudinal significant effect of the treatment from baseline to all time points for the Barthel Index, Motricity Index, Fugl-Meyer Test, arm and wrist/hand subparts of the Fugl-Meyer Test, and for the Chedoke Arm and Hand Activity Inventory (Table 5.3). We found no effect of treatment for the Modified Ashworth Scale and for the Box and Block Test.

Table 5.2. Baseline demographic and clinical measures.

Variable	RGS (n=16)	RGS-E (n=14)	RGS-H (n=14)	p-value
Demographics				
Age	68.7±10.9	59.4±9.7	59.9±13.0	0.028(KW)
Gender (M/F)	9/7	9/5	7/7	0.746 (χ^2)
Days post stroke	1649±300	1598±230	1334±297	0.358(KW)
Lesion Side (L/R)	6/10	4/10	6/8	0.729 (χ^2)
Clinical				
Barthel Index (normal=100)	89.4±11.5	90.4±10.4	89.4±6.6	0.743(KW)
MRC (2/3)	4/12	2/12	4/10	0.642 (χ^2)
Motricity Index (normal=99)	55.8±5.3	53.3±5.9	56.4±6.8	0.339(KW)
Ashworth (normal=0)	1.4±0.2	1.6±0.1	1.4±0.1	0.548 KW)
Fugl-Meyer (max=66)	34.9±11.0	32.7±12.1	35.9±12.4	0.767 (A)
Arm (normal=42)	18.8±6.9	17.4±7.1	18.8±8.2	0.836(KW)
Wrist/Hand (normal=24)	12.3±5.1	11.2±5.7	13.3±5.3	0.612 (A)
CAHAI (normal=91)	36.8±20.9	34.5±19.1	35.7±18.2	0.886(KW)
Nine Hole Peg Test (A/NA)	2/14	2/12	3/11	0.785 (χ^2)
Box & Block Test (A/NA)	7/9	6/8	6/8	0.998 (χ^2)

Gender: M=male and F=female; lesion side: L=left and R=right; Nine Hole Peg Test and the Box and Block Test: A=able to perform and NA=not able to perform. The categorical variables are expressed in terms of the ratio of cases and the quantitative variables are mean ± standard deviation. In the p-value, letters between brackets denote the statistical test that was used for the comparison (KW=Kruskal-Wallis Test, A=ANOVA, χ^2=chi squared test).

Table 5.3. Within-subject statistical comparison (Friedman Test) from baseline up to the different time points.

Measure	p-value		
	To End	To Follow-up 1	To Follow-up 2
Barthel Index	**0.021**	**0.006**	**0.001**
Motricity Index	**0.000**	**0.000**	**0.000**
Ashworth	0.206	0.274	0.480
Fugl-Meyer Test	**0.000**	**0.000**	**0.000**
Fugl-Meyer Arm	**0.002**	**0.002**	**0.004**
Fugl-Meyer Hand	**0.000**	**0.000**	**0.000**
CAHAI	**0.000**	**0.000**	**0.000**
Box & Block	0.808	0.662	0.798

Further pairwise analysis of the improvement in the clinical scores from baseline to separate time points for each group revealed dissimilar patterns of gains in the three groups (Table 5.4). The RGS group showed significant improvements at the end of treatment for all clinical scales, except for the Ashworth Scale and the Box and Block Test. These gains were maintained up to follow-up two (12 weeks after the end of treatment) except for the case of the arm and wrist/hand subparts of the Fugl-Meyer Test. The exoskeleton group (RGS-E) showed significant gains at the end of treatment for the Motricity Index, for the total Fugl-Meyer Test and its wrist/hand subpart, and for the CAHAI. However, only the gains for the Motricity Index and for the CAHAI were preserved at follow-up stages. The haptics group (RGS-H) showed significant improvements at the end of treatment for all clinical scales except for the Barthel Index, the Ashworth Scale and the wrist/hand subpart of the Fugl-Meyer Test. With the exception of the Box and Block Test, these gains were maintained up to follow-up two and the Barthel Index and the wrist/hand subpart of the Fugl-Meyer Test reached significance.

Concerning the effect of group allocation on the improvement at the different evaluation stages, we found that group was only significant for the Box and Block Test at the end of treatment [Kruskal-Wallis, $\chi^2(2, N=19)=9.015$, $p<.05$], and leaning towards significance at follow-up two for the Fugl-Meyer Test [$\chi^2(2, N=40)=5.097$, $p=.078$] and its arm subpart [$\chi^2(2, N=40)=5.412$, $p=.067$]. Indeed, pairwise group comparisons at individual time points showed that the RGS-H achieved significantly higher improvements than the RGS and the RGS-E for the Box and Blocks Test at the end of treatment [Mann-Whitney, $Z=-2.714$, $p<.01$ compared to RGS, and $Z=-2.166$, $p<.05$ compared to RGS-E] (Table 5.4, Figure 5.4). In addition, at follow-up two the RGS-H was significantly better than the RGS-E for the Fugl-Meyer Test [$Z=-2.149$, $p<.05$] and for the arm subpart of this scale [$Z=-2.230$, $p<.05$].

In summary, we can observe that the overall treatment with RGS led to significant improvements over time at several levels of motor function, as assessed by the different clinical scales. However, analysing the groups separately, there was some heterogeneity on the pattern of improvement. The standard RGS group and the haptics group (RGS-H) showed significant improvements at the end of treatment for a larger number of clinical scales, and the RGS-E displayed more modest results. All groups showed a similar trend over time on the performance of ADL, as assessed by the CAHAI, but with a higher gain in the case of RGS-H (Figure 5.1).

Table 5.4. Normalized improvement (%) at time points compared to baseline.

Variable	RGS	RGS-E	RGS-H
End			
Barthel	17.2±30.0*	8.9±19.3	2.7±10.9
Motricity	6.7±8.5*	7.0±9.6*	4.9±8.3*
Ashworth	-1.7±6.5	0.6±3.6	-3.3±8.9
Fugl-Meyer	13.5±17.4**	10.8±15.6*	13.0±11.6**
Arm	12.1±21.6*	7.0±18.7	14.0±12.0**
Wrist/Hand	16.4±17.4**	16.6±17.5**	10.6±22.6
CAHAI	8.3±17.6*	7.5±12.5*	12.4±13.4**
Box and Block	-17.9±23.0	-6.1±20.1	65.7±93.5*
Follow-up 1			
Barthel	18.7±30.9*	7.2±10.7	3.5±12.9
Motricity	9.8±10.1**	7.5±11.1*	5.8±10.9
Ashworth	-1.7±6.5	-3.4±9.4	-2.2±9.3
Fugl-Meyer	12.2±14.4**	9.0±17.2	12.8±11.8**
Arm	7.8±18.8	6.1±20.1	16.4±13.8**
Wrist/Hand	19.3±14.3**	9.0±39.3	6.3±18.6
CAHAI	13.1±23.9	7.2±10.8**	10.5±10.2**
Box and Block	0.8±47.9	5.8±10.4	72.7±101.8
Follow-up 2			
Barthel	9.6±15.5	12.9±15.1*	15.6±29.2*
Motricity	9.5±14.8*	8.2±8.1*	6.4±10.8*
Ashworth	2.6±13.5	-3.5±12.8	0.8±12.9
Fugl-Meyer	9.2±17.2*	3.9±10.7	15.0±10.0**
Arm	8.4±19.4	2.2±12.2	14.4±12.8**
Wrist/Hand	11.6±21.1	5.6±23.0	13.5±18.6*
CAHAI	10.9±19.4*	6.3±11.4*	10.7±11.7**
Box and Block	0.1±25.7	3.8±46.1	106.9±177.6

The improvements are expressed as mean ± standard deviation. Pairwise comparisons with respect to baseline: Wilcoxon, *p<.05, **p<.01.

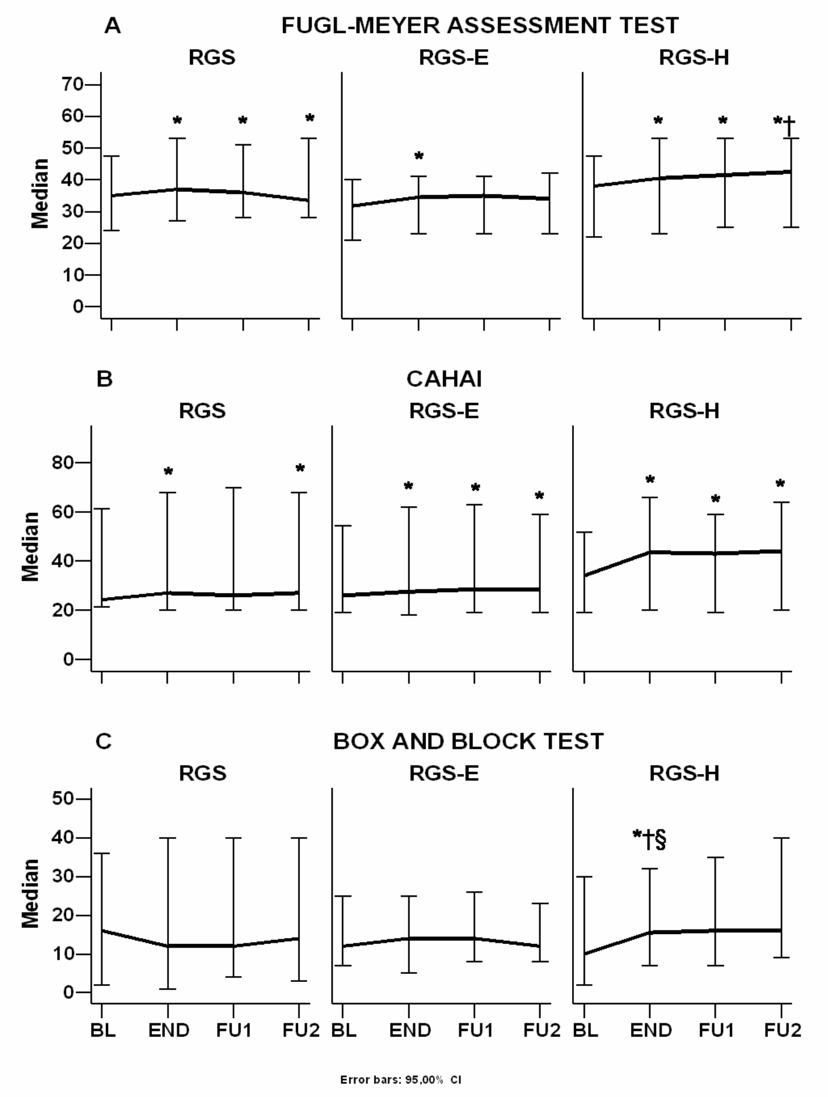

Figure 5.4. Clinical scores at the different evaluation stages for selected scales, separated by groups. Median of the absolute clinical scores at the different evaluation stages for the Fugl-Meyer Assessment Test, Chedoke Arm and Hand Activity Inventory (CAHAI), and Box and Block Test. Error bars indicate the 95% confidence interval. Across all groups, significant gains can be seen between baseline and end of treatment, the RGS-H group being the only group that improved significantly at the Box and Blocks Test. In addition, this group retained most of its gains up to follow-up two. Within-group comparisons: Wilcoxon, *p<.05. Between-groups comparisons: Mann-Whitney, § comparison RGS-H/RGS, p<.05; † comparison RGS-H/RGS-E, p<.05.

RGS and RGS-H groups showed more sustained benefits at the level of arm functioning (Fugl-Meyer, arm subpart), and the RGS-E group did not reach significance at the end of treatment. Moreover, the RGS-H group retained most of its improvements during a longer period of time (at least up to 12 weeks after the end of treatment). None of the groups showed a significant reduction of their level of spasticity.

b) Acceptance and Satisfaction

The analysis of the self-report questionnaire showed that the level of satisfaction in relation to the treatment was very high (Figure 5.5).

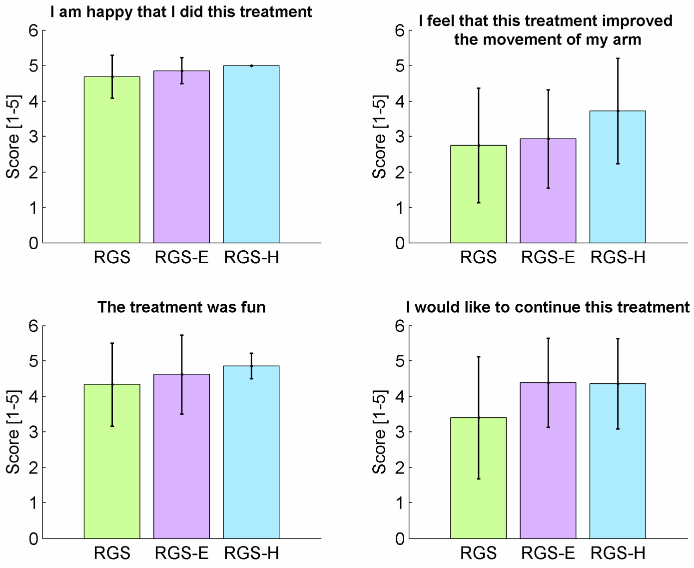

Figure 5.5. Subjective assessment in the self-report questionnaires. Average ratings (mean±standard deviation) for selected statements.

Patients in all groups reported positively their participation in the treatment. To the statement “I am happy that I did this treatment”, the average rating was 4.7 for RGS, 4.9 for RGS-E and 5 for RGS-H. Notice that 5 = “I totally agree”. In addition, the treatment was also rated as being very fun (4.3 for RGS, 4.6 for RGS-E and 4.9 for RGS-H). On what concerns the perceived impact of the treatment on the recovery of the paretic limb, here we found some differences in the ratings depending on group allocation. To the statement, “I feel that this treatment improved the movement of my arm” the average rating was 2.8 for RGS, 2.9 for RGS-E, and 3.7 in RGS-H. This means that in average, the haptics group considered that the mobility of their arms improved, as opposed to the RGS and RGS-E that on average were not aware of such improvements (although they did improve in the clinical scores). There was however no statistically significant difference between the ratings [Kruskall-Wallis, $\chi^2(2)=3.563$, $p<.168$]. Interestingly enough, the RGS-H was the group that showed higher levels of improvement in the clinical assessment. The satisfaction in relation to the treatment can also be assessed by the wish of continuing the treatment. Also here, the groups rated differently. To the statement “I would like to continue this treatment”, the average rating was 3.4 for RGS, 4.4 for RGS-E and 4.4 for RGS-H. Hence, although on average patients on all the groups wished to continue with the treatment, the patients in RGS-E and RGS-H were the ones that were more motivated to do so. However, again this difference did not reach significance [Kruskall-Wallis, $\chi^2(2)=4.736$, $p<.094$].

5.4 Discussion

There are a number of studies with VR systems that suggest that the use of this technology in rehabilitation can have a positive impact on the recovery of motor deficits brought by stroke (Holden 2005; Cameirão, Bermúdez i Badia et al. 2008). However, a number of aspects are not clearly understood. On the one hand, it is not yet obvious that VR approaches are more effective than other standard approaches (Lucca 2009). On the other hand, we do not know which characteristics of these systems are the most important ones and how they exactly affect recovery.

To address this issue we set-up three different configurations of the Rehabilitation Gaming System. The idea was to have the same training scenario but with different interfaces. I.e., we wanted to maintain the RGS's action execution and observation paradigm, and investigate how the outcomes in recovery could be modulated by the type of interaction. Therefore, we coupled the RGS with a bimanual exoskeleton (RGS-E) to provide arm support against gravity, and with a haptic interface (RGS-H) to provide tactile feedback. In this exploratory study, 44 chronic stroke patients were randomly allocated to one of the systems. Patients underwent 20 sessions of the Spheroids' grasping task during one month.

As a general outcome, all groups improved significantly from baseline to the end of treatment at most of the standard clinical scales. In addition, these gains were conserved to a large extent up to 12 weeks after the end of the treatment (follow-up 2). There was barely a statistically significant difference between the improvements of the different groups. Nevertheless, we observed different patterns of improvement among the three groups.

The clinical measures at which the three groups showed more uniformity were the Motricity Index, and the Chedoke Arm and Hand Activity Inventory (CAHAI). For both measures, all the groups improved significantly at the end of the treatment and retained the gains up to follow-up 2. This positive effect on the performance of ADL, as measured by the CAHAI, is particularly interesting as it contrasts with other studies that report that VR has a poor impact on functional aspects of recovery (Mehrholz, Platz et al. 2008; O'Dell, Lin et al. 2009). Since our previous study with acute patients (Chapter 4) also showed particular benefits on ADL, we assume that the improvements are mainly due to the characteristics of the RGS paradigm itself.

On the movement and joint functioning level as assessed by the Fugl-Meyer Test, there were particular dissimilar patterns of improvement in the three groups. Although all the groups improved significantly at the end of the treatment, the exoskeleton group had lost those gains one month after finishing the treatment. In addition, at follow-up 2, the RGS-H group was significantly better than the RGS-E and also the RGS groups, meaning that the haptics group was able to retain the achieved improvements during a longer period of time. If we divide the Fugl-Meyer Assessment Test in its arm and wrist/hand parts, we observe that the previously mentioned dissimilarities are mainly due to differences in the arm part. The exoskeleton group did not reach significance at the end of the treatment, showing a poorer improvement compared to the other two groups (7% against 12% of the RGS and 14% of the RGS-H). One possible explanation for this result could be that to some extent, patients allocated to the RGS-E group had less freedom of movements due to the fact of being 'tied' to the exoskeleton. As consequence, they could have been less dynamic during the performance of the task when compared to the other two groups. At the wrist/hand subpart of the Fugl-Meyer Test, again the RGS-H retained gains up to follow-up two, and this was not the case for RGS and RGS-E.

A notorious significant difference between groups was found at the end of the treatment for the Box and Block Test. Here the RGS-H was significantly better than the other two groups. This test consists in counting the number of blocks grasped and displaced from one box to another during one minute. It is interesting to recall that in the Spheroids' Grasping task, patients received tactile sensation during the virtual grasp. It is possible that this added sensorimotor feedback might have been determinant to achieve this strong improvement in object grasping.

The subjective self-reports of the patients led to a number of interesting observations. Patients in general were happy with the treatment with RGS in all configurations. Indeed, other studies reported that VR systems were preferred over standard rehabilitation methods (Housman, Scott et al. 2009). In addition, the treatment was considered to be very fun. Interestingly enough, the level of satisfaction was influenced by the interface to the virtual scenario. Here there seems to be a preference towards more sophisticated systems, such as the exoskeleton and the haptic interface in our case. Finally, in terms of perceived improvement, the group of patients that had a higher feeling of improvement was the one that indeed scored higher in the clinical assessment. I.e., the patients allocated to the RGS-H group.

Generally speaking, as the three RGS configurations led to significant improvements at the end of the treatment, we can say that all three set-ups are valid for stroke rehabilitation. Taking into account that the common feature shared by the systems is the action execution/observation based Spheroids task, we believe that this is the main attribute leading to these results. However, there is an obvious added benefit of using haptic feedback during the interaction. This feedback not only led to higher levels of satisfaction, but also to higher levels of improvement. Moreover, haptic feedback allowed retaining improvements during a longer period of time.

6. CONCLUSIONS AND OUTLOOK

In this dissertation we presented the Rehabilitation Gaming System, a novel paradigm for the rehabilitation of motor deficits after lesions in the central nervous system. The particular implementation presented in this project was focused on the rehabilitation of the upper extremities following stroke. We have reviewed the causes, consequences and mechanisms that are related to stroke and its rehabilitation. In this context we have designed RGS, a novel VR based rehabilitation system that is consistent with our current understanding of stroke and its aftermath, and the functional requirements of rehabilitative training. The main hypothesis underlying the RGS is that by means of an action recognition system – the mirror neuron system, a connecting pathway between perception and action – a functional motor recovery is possible (Rizzolatti, Fabbri-Destro et al. 2009; Garrison, Winstein et al. 2010). Particularly, the RGS exploits the mechanisms of action observation as an alternate circuit to activate motor areas and to drive recovery. RGS combines these hypotheses with additional considerations based on a number of therapies aiming at enhancing recovery following stroke (Kwakkel, van Peppen et al. 2004; Seitz, Butefisch et al. 2004; Winstein, Rose et al. 2004). Namely, it allows for a task-specific training that promotes the recurring practice of goal-oriented movements.

Some of the central features of our system are only possible by the use of Virtual Reality. Due to its versatility, VR allows the flexible creation of personalized rehabilitation scenarios directed towards the specific needs of the patients. In the case of the RGS, we use VR to exploit a controlled action observation paradigm within a virtual environment, where the observed movements are being driven by the actual movements of the user. The RGS captures the movements of the user by means of a vision based tracking system and maps them online to the movements of two virtual arms. This results in simultaneous observation of actions and goal-oriented task execution. Consistent with the literature, the actions are displayed on a screen in a first-person perspective to maximize the activation of the action recognition system (Maeda, Kleiner-Fisman et al. 2002; Lorey, Bischoff et al. 2009).

A unique contribution of RGS is the Personalized Training Module, which makes possible the non-supervised individualized training that adjusts the task in real time to the capabilities of the user. The PTM is a key component of RGS that was built from performance data from stroke patients and healthy subjects. In the particular implementation of this thesis, the PTM was based on the psychometrics of one rehabilitation scenario called Spheroids. In the Spheroids scenario the user had to interact with upcoming spheres, performing specific movements that go from basic arm extension, to grasping, object displacement, and release. We evaluated the PTM with 21 acute/subacute stroke patients and 20 healthy controls, and we showed that the PTM implemented in RGS allowed us to effectively adjust the difficulty and the parameters of the task to the user by capturing specific features of the movements of the arms. Thus, RGS provided an individualized and controlled training protocol that is neither too easy nor too hard in order to sustain motivation and avoid frustration (Yerkes and Dodson 1908; Csikszentmihalyi 2002).

A concern in VR rehabilitation systems has always been the generalization and ecological validity of the training when compared to the training in the physical world. In order to evaluate the generalization and ecological validity of RGS we have designed equivalent versions of a physical and virtual task and studied the transfer between the physical and virtual environments in healthy subjects and stroke patients. Consistent with previous findings, the results showed a consistent transfer of movement kinematics between physical and virtual tasks, supporting the equivalence of training with RGS (Viau, Feldman et al. 2004; Subramanian, Knaut et al. 2007).

One of the most important aspects of any therapy is the timing and the intensity of it. In the particular case of stroke, it is commonly assumed that the earlier the intervention the more effective it will be (Kreisel, Bazner et al. 2006; Murphy and Corbett 2009). This is because after a stroke, the brain undergoes a natural spontaneous recovery process that can be augmented by rehabilitation. Therefore, it is in this period when recovery can be maximized when we should intervene. Surprisingly, there is only a reduced amount of studies on the impact of rehabilitation based technologies in the early stages of stroke. This can be explained in part due to the methodological complexity of an inpatient study design in the acute stage of stroke. It requires training protocols of several months of duration and a large patient population in order to statistically overcome the variability caused by the initial period of spontaneous recovery and the lesion variability. Moreover, patient withdrawal is very high after the hospital discharge. In spite of this, we carried a 2-years study on the impact of RGS in the acute stage of stroke. Patients (n=8) used the RGS during 12 weeks in addition to conventional therapy. A control group (n=8) performed a time matched alternative treatment, which consisted of intense occupational therapy or non-specific interactive games. Our results showed that at the end of the treatment the RGS group displayed significantly improved performance in paretic arm speed that was matched by an improved performance in motor function and in the performance of ADL. The effect was particularly salient in the Chedoke Arm and Hand Activity Inventory (CAHAI) scale, which evaluates the performance of the paretic arm in ADL. In addition, the RGS group presented a significantly faster improvement over time for most of the clinical scales during the treatment period. The results contrast with results of other studies that report that VR has a poor impact in the ability to perform ADL (O'Dell, Lin et al. 2009; Kalra 2010). Most likely, this difference is due to the differences in the training paradigms since none of those studies shared the hypotheses of RGS on functional recovery.

Although the results at the end of the intervention favoured the RGS group, the improvements were not distinct from the control group 3 months after the end of the treatment. At this point a relevant question arises: did the RGS only have an impact by accelerating recovery? Or could it further maximize recovery with an extended training period? RGS training could be augmented in terms of working hours, or in terms of the longitudinal duration of the treatment. To answer these questions, further clinical trials should be performed in order to evaluate the effects of an intensive compact RGS training with a large-duration training protocol.

The above study also allowed us to investigate the usability aspects of RGS by collecting the subjective self-report of the patients in terms of acceptance and satisfaction. The questionnaire data showed that RGS was highly accepted by the patients as a rehabilitation tool. Specifically, patients reported that training with RGS was fun, easy, and that they would like to continue the treatment. The fact that the answers of the self-report were positive is very relevant as it is widely accepted that motivational aspects play a key role in the recovery following stroke (Maclean, Pound et al. 2000).

Although there is strong evidence on the beneficial effects of VR based rehabilitation, it is not well understood how the different aspects of these systems affect recovery. Consequently, we do not exactly know what features should be included to maximize the impact on stroke rehabilitation. To specifically address this issue we developed two extra configurations of the RGS, both of them sharing the core elements presented above. We used as basis the same scenario and task (Spheroids), but provided different interfaces to the virtual environment. Namely, we coupled the RGS with an exoskeleton and with a haptic interface. The exoskeleton facilitated movement through the support of the weight of the arms against gravity. On the other hand, the haptic interface added tactile sensation during the interaction with virtual objects, allowing for an increased feedback on the performance of the movements. 44 chronic stroke patients were randomly allocated to one RGS configuration (standard, with exoskeleton, or with haptics), and used the system 5 days a week during 4 weeks. Our results revealed significant improvements at most of the standard evaluation measures at the end of the treatment, for all groups. However, the improvements were particularly salient in the haptics group as patients in this group were able to retain the improvements during a longer period of time. In addition, the patients in this group were the ones reporting a higher level of perceived improvement. These results suggest the possibility of reinforcing the action recognition system by including haptic-feedback, and this should be considered in future versions of the RGS. Moreover, the RGS coupled with the haptic interface and exoskeleton was rated very positively in terms of satisfaction and enjoyment, what suggests an added motivational benefit.

Overall, our pilot studies and assessment of the RGS led to very exciting results in both the acute and chronic stroke patients. We believe that these results make an important contribution to the current state-of-the-art on what concerns the impact of novel technology derived methods in stroke neurorehabilitation.

Nevertheless, additional clinical trials should be carried out in order to further validate our assumptions. In particular, it becomes necessary to further validate the system using Brain imaging methods. Functional Magnetic Resonance Imaging (fMRI) is one such technique that can allow us to verify what the different systems engaged during the RGS training are, and whether our hypothesis about the activation of motor areas via the action observation paradigm is corroborated.

It is also very important the potential of RGS as a tool for continuous long-term at home rehabilitation and monitoring after hospital discharge. We believe that the development of low-cost and effective systems capable of delivering an automated and personalized training are necessary to cope with the increase of chronic patients with life-long lasting motor deficits, and to alleviate the unfeasibility of health systems to provide long-term and personalized rehabilitation.

Finally, here we proposed RGS as a paradigm for the rehabilitation of the motor deficits of the upper extremities following stroke. However, due to the power of its functional hypothesis, the RGS paradigm is versatile and can be further exploited in other target groups with deficits of the skeletal-motor system resulting from CNS lesions, as for instance patients with traumatic brain injury. Moreover, we believe that the RGS concept can smoothly generalize to address other more central perceptual and cognitive deficits such as neglect.

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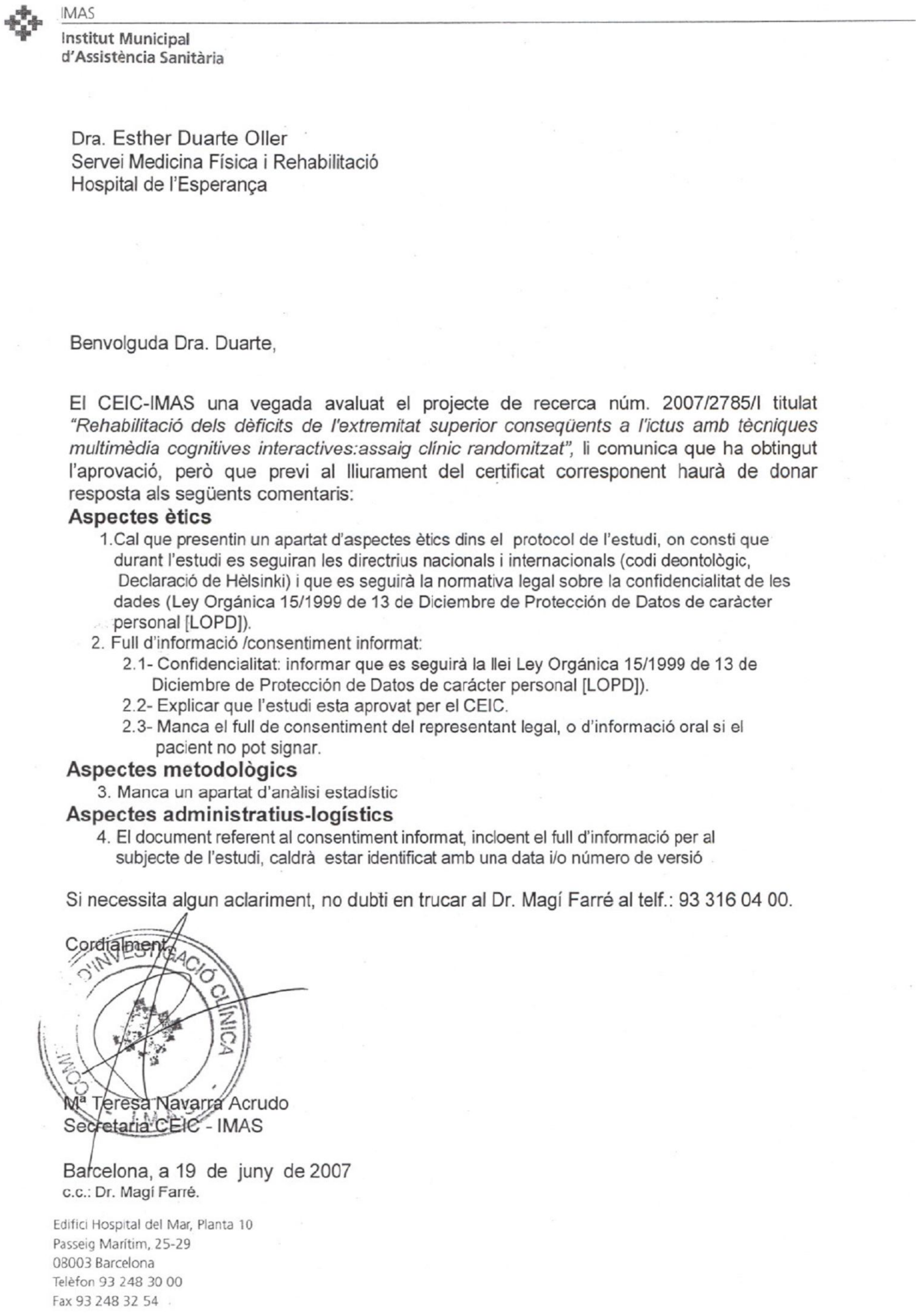
Appendixes

Appendix I – Ethics Committee Approval



IMAS
Institut Municipal
d'Assistència Sanitària

Dra. Esther Duarte Oller
Servei Medicina Física i Rehabilitació
Hospital de l'Esperança

Benvolguda Dra. Duarte,

El CEIC-IMAS una vegada avaluat el projecte de recerca núm. 2007/2785/I titulat *"Rehabilitació dels dèficits de l'extremitat superior conseqüents a l'ictus amb tècniques multimèdia cognitives interactives:assaig clínic randomitzat"*, li comunica que ha obtingut l'aprovació, però que previ al lliurament del certificat corresponent haurà de donar resposta als següents comentaris:

Aspectes ètics

1. Cal que presentin un apartat d'aspectes ètics dins el protocol de l'estudi, on consti que durant l'estudi es seguiran les directrius nacionals i internacionals (codi deontològic, Declaració de Hèlsinki) i que es seguirà la normativa legal sobre la confidencialitat de les dades (Ley Orgánica 15/1999 de 13 de Diciembre de Protección de Datos de caràcter personal [LOPD]).
2. Full d'informació /consentiment informat:
    - 2.1- Confidencialitat: informar que es seguirà la llei Ley Orgánica 15/1999 de 13 de Diciembre de Protección de Datos de carácter personal [LOPD]).
    - 2.2- Explicar que l'estudi esta aprovat per el CEIC.
    - 2.3- Manca el full de consentiment del representant legal, o d'informació oral si el pacient no pot signar.

Aspectes metodològics

3. Manca un apartat d'anàlisi estadístic

Aspectes administratius-logístics

4. El document referent al consentiment informat, incloent el full d'informació per al subjecte de l'estudi, caldrà estar identificat amb una data i/o número de versió

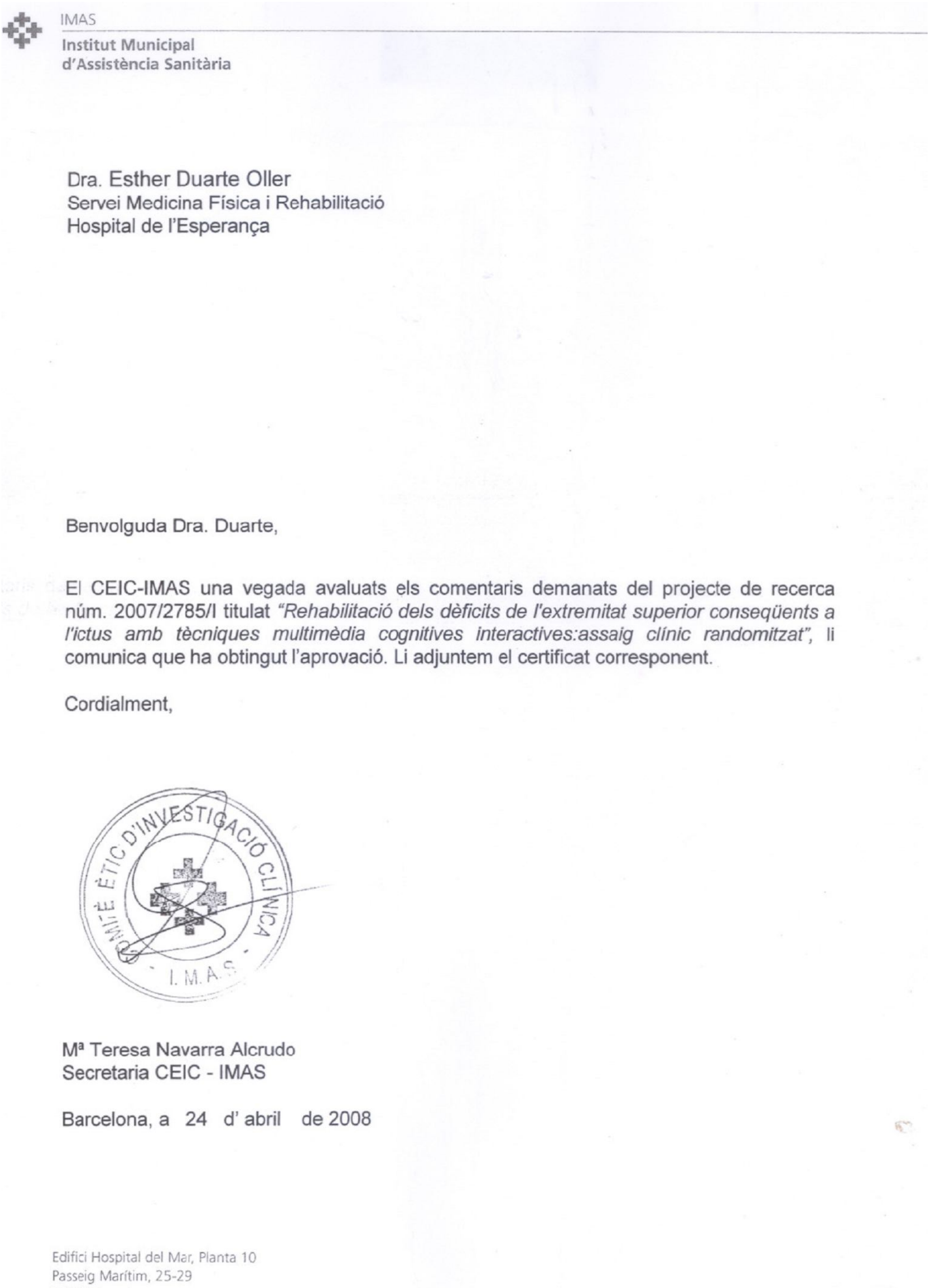
Si necessita algun aclariment, no dubti en trucar al Dr. Magí Farré al telf.: 93 316 04 00.

Cordialment,

Mª Teresa Navarra Acrudo
Secretaria CEIC - IMAS

Barcelona, a 19 de juny de 2007
c.c.: Dr. Magí Farré.

Edifici Hospital del Mar, Planta 10
Passeig Marítim, 25-29
08003 Barcelona
Telèfon 93 248 30 00
Fax 93 248 32 54



IMAS
**Institut Municipal
d'Assistència Sanitària**

Dra. Esther Duarte Oller
Servei Medicina Física i Rehabilitació
Hospital de l'Esperança

Benvolguda Dra. Duarte,

El CEIC-IMAS una vegada avaluats els comentaris demanats del projecte de recerca núm. 2007/2785/I titulat *"Rehabilitació dels dèficits de l'extremitat superior conseqüents a l'ictus amb tècniques multimèdia cognitives interactives:assaig clínic randomitzat"*, li comunica que ha obtingut l'aprovació. Li adjuntem el certificat corresponent.

Cordialment,

Mª Teresa Navarra Alcrudo
Secretaria CEIC - IMAS

Barcelona, a 24 d' abril de 2008

Edifici Hospital del Mar, Planta 10
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Telèfon 93 248 30 00
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IMAS
Institut Municipal
d'Assistència Sanitària

Informe del Comité Ético de Investigación Clínica

Doña Mª Teresa Navarra Alcrudo Secretaria del Comité Ético de Investigación Clínica del Instituto Municipal de Asistencia Sanitaria

CERTIFICA

Que éste Comité ha evaluado el proyecto de investigación clínica nº 2008/3303/I titulado *"Rehabilitation Gaming System"* propuesto por la Dra. Esther Duarte Oller del Servicio de Rehabilitación del Hospital de la Esperanza.

Que adjunta documento de consentimiento informado

Y que considera que:

Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.

La capacidad del investigador y los medios disponibles son apropiados para llevar a cabo el estudio.

El alcance de las compensaciones económicas que se solicitan está plenamente justificado.

Y que éste Comité acepta que dicho proyecto de investigación sea realizado en el Hospital de la Esperanza por la Dra. Esther Duarte Oller como investigadora principal tal como recoge el ACTA de la reunión del día 23 de Diciembre de 2008.

Lo que firmo en Barcelona, a 27 de Enero de 2009

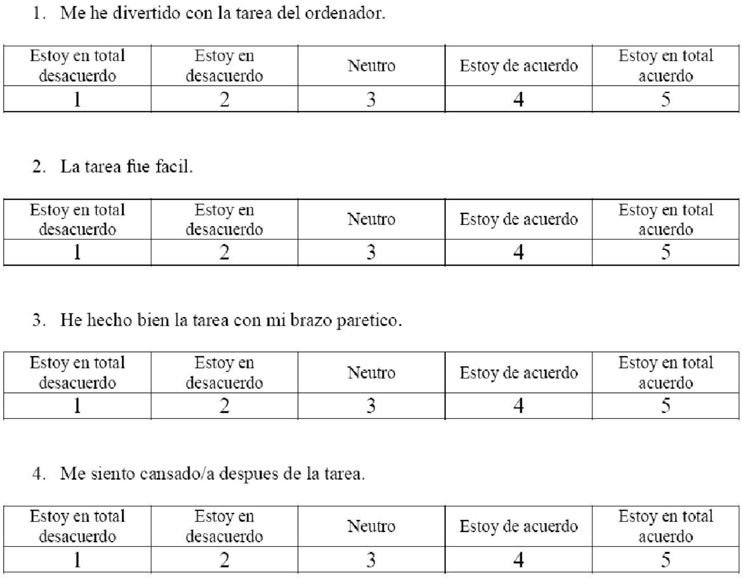
Firmado: ....
Doña Mª Teresa Navarra Alcrudo

Edifici Hospital del Mar, Planta 10
Passeig Marítim, 25-29
08003 Barcelona
Telèfon 93 248 30 00
Fax 93 248 32 54

CAA 350

Appendix II – Self-report questionnaires

Used in Chapter 3.



1. Me he divertido con la tarea del ordenador.

Estoy en total desacuerdo	Estoy en desacuerdo	Neutro	Estoy de acuerdo	Estoy en total acuerdo
1	2	3	4	5

2. La tarea fue facil.

Estoy en total desacuerdo	Estoy en desacuerdo	Neutro	Estoy de acuerdo	Estoy en total acuerdo
1	2	3	4	5

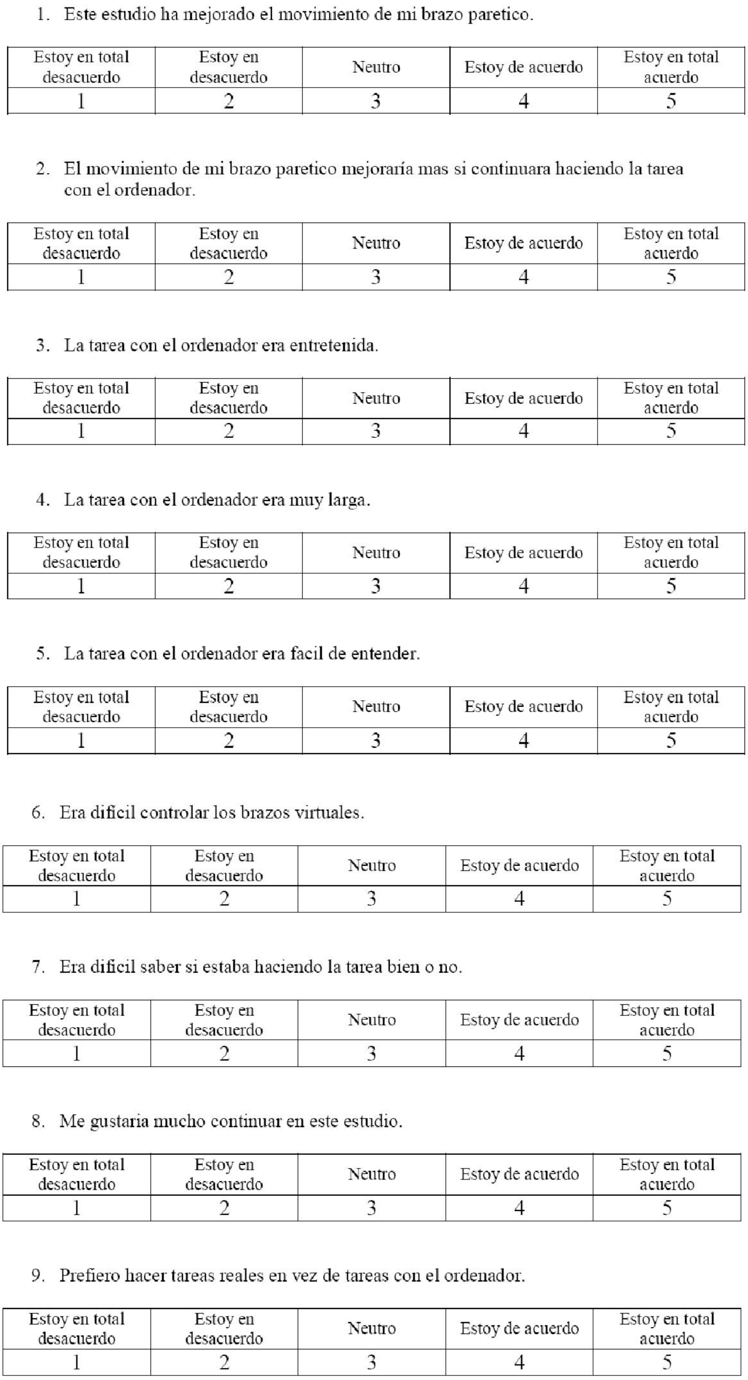
3. He hecho bien la tarea con mi brazo paretico.

Estoy en total desacuerdo	Estoy en desacuerdo	Neutro	Estoy de acuerdo	Estoy en total acuerdo
1	2	3	4	5

4. Me siento cansado/a despues de la tarea.

Estoy en total desacuerdo	Estoy en desacuerdo	Neutro	Estoy de acuerdo	Estoy en total acuerdo
1	2	3	4	5

Used in Chapter 4.



1. Este estudio ha mejorado el movimiento de mi brazo paretico.

Estoy en total desacuerdo	Estoy en desacuerdo	Neutro	Estoy de acuerdo	Estoy en total acuerdo
1	2	3	4	5

2. El movimiento de mi brazo paretico mejoraría mas si continuara haciendo la tarea con el ordenador.

Estoy en total desacuerdo	Estoy en desacuerdo	Neutro	Estoy de acuerdo	Estoy en total acuerdo
1	2	3	4	5

3. La tarea con el ordenador era entretenida.

Estoy en total desacuerdo	Estoy en desacuerdo	Neutro	Estoy de acuerdo	Estoy en total acuerdo
1	2	3	4	5

4. La tarea con el ordenador era muy larga.

Estoy en total desacuerdo	Estoy en desacuerdo	Neutro	Estoy de acuerdo	Estoy en total acuerdo
1	2	3	4	5

5. La tarea con el ordenador era facil de entender.

Estoy en total desacuerdo	Estoy en desacuerdo	Neutro	Estoy de acuerdo	Estoy en total acuerdo
1	2	3	4	5

6. Era dificil controlar los brazos virtuales.

Estoy en total desacuerdo	Estoy en desacuerdo	Neutro	Estoy de acuerdo	Estoy en total acuerdo
1	2	3	4	5

7. Era dificil saber si estaba haciendo la tarea bien o no.

Estoy en total desacuerdo	Estoy en desacuerdo	Neutro	Estoy de acuerdo	Estoy en total acuerdo
1	2	3	4	5

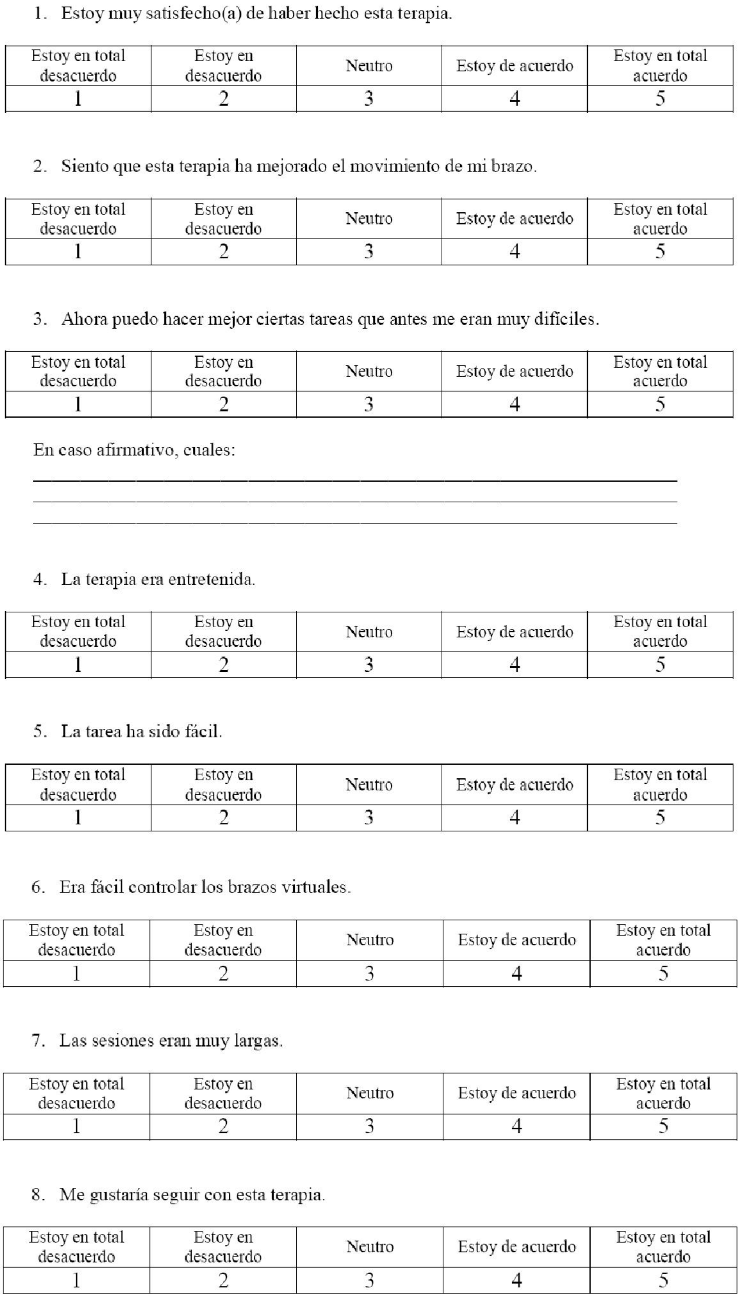
8. Me gustaria mucho continuar en este estudio.

Estoy en total desacuerdo	Estoy en desacuerdo	Neutro	Estoy de acuerdo	Estoy en total acuerdo
1	2	3	4	5

9. Prefiero hacer tareas reales en vez de tareas con el ordenador.

Estoy en total desacuerdo	Estoy en desacuerdo	Neutro	Estoy de acuerdo	Estoy en total acuerdo
1	2	3	4	5

Used in Chapter 5.



1. Estoy muy satisfecho(a) de haber hecho esta terapia.

Estoy en total desacuerdo	Estoy en desacuerdo	Neutro	Estoy de acuerdo	Estoy en total acuerdo
1	2	3	4	5

2. Siento que esta terapia ha mejorado el movimiento de mi brazo.

Estoy en total desacuerdo	Estoy en desacuerdo	Neutro	Estoy de acuerdo	Estoy en total acuerdo
1	2	3	4	5

3. Ahora puedo hacer mejor ciertas tareas que antes me eran muy difíciles.

Estoy en total desacuerdo	Estoy en desacuerdo	Neutro	Estoy de acuerdo	Estoy en total acuerdo
1	2	3	4	5

En caso afirmativo, cuales:
____
____
____

4. La terapia era entretenida.

Estoy en total desacuerdo	Estoy en desacuerdo	Neutro	Estoy de acuerdo	Estoy en total acuerdo
1	2	3	4	5

5. La tarea ha sido fácil.

Estoy en total desacuerdo	Estoy en desacuerdo	Neutro	Estoy de acuerdo	Estoy en total acuerdo
1	2	3	4	5

6. Era fácil controlar los brazos virtuales.

Estoy en total desacuerdo	Estoy en desacuerdo	Neutro	Estoy de acuerdo	Estoy en total acuerdo
1	2	3	4	5

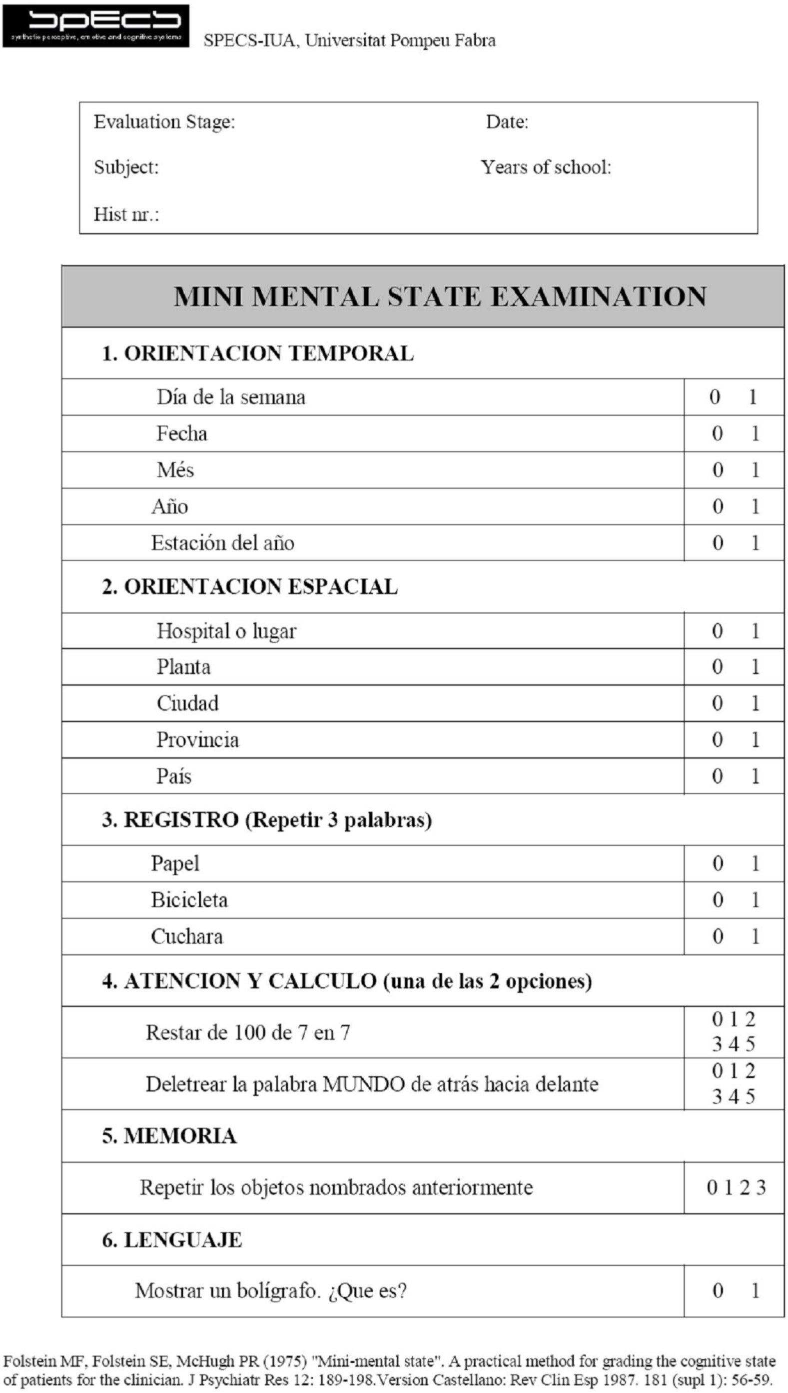
7. Las sesiones eran muy largas.

Estoy en total desacuerdo	Estoy en desacuerdo	Neutro	Estoy de acuerdo	Estoy en total acuerdo
1	2	3	4	5

8. Me gustaría seguir con esta terapia.

Estoy en total desacuerdo	Estoy en desacuerdo	Neutro	Estoy de acuerdo	Estoy en total acuerdo
1	2	3	4	5

Appendix III – Clinical evaluation scales



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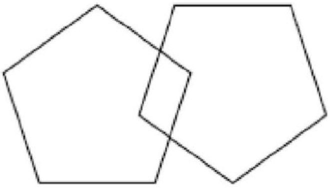
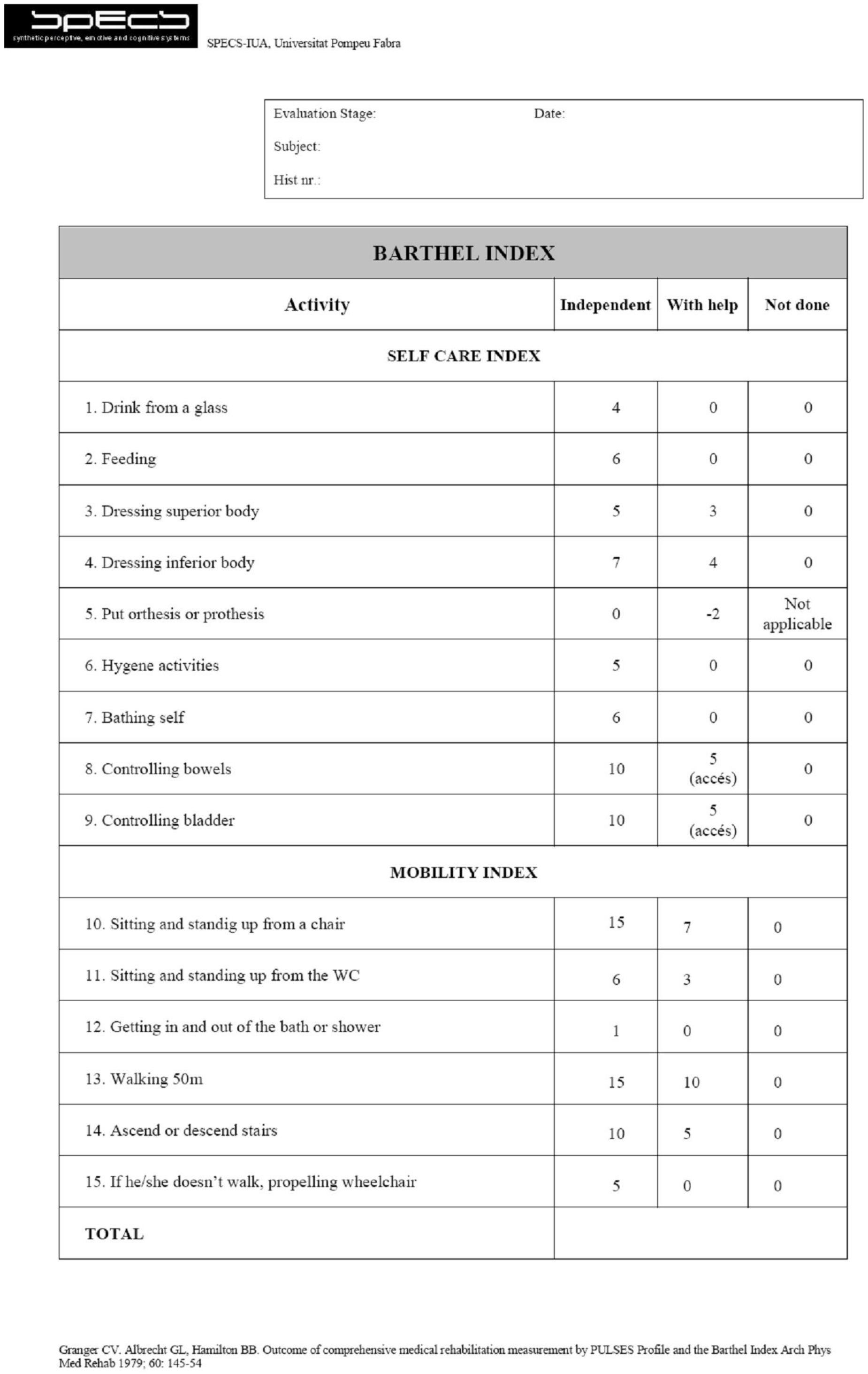
Evaluation Stage:	Date:
Subject:	Years of school:
Hist nr.:	

MINI MENTAL STATE EXAMINATION	
1. ORIENTACION TEMPORAL	
Día de la semana	0 1
Fecha	0 1
Més	0 1
Año	0 1
Estación del año	0 1
2. ORIENTACION ESPACIAL	
Hospital o lugar	0 1
Planta	0 1
Ciudad	0 1
Provincia	0 1
País	0 1
3. REGISTRO (Repetir 3 palabras)	
Papel	0 1
Bicicleta	0 1
Cuchara	0 1
4. ATENCION Y CALCULO (una de las 2 opciones)	
Restar de 100 de 7 en 7	0 1 2 3 4 5
Deletrear la palabra MUNDO de atrás hacia delante	0 1 2 3 4 5
5. MEMORIA	
Repetir los objetos nombrados anteriormente	0 1 2 3
6. LENGUAJE	
Mostrar un bolígrafo. ¿Que es?	0 1

Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12: 189-198.Version Castellano: Rev Clin Esp 1987. 181 (supl 1): 56-59.

Mostrar un reloj. ¿Que es?	0 1
Repetir la frase: "Ni si, ni no, ni peros"	0 1
Orden en 3 etapas: Coja el papel con la mano derecha, dóblelo por la mitad, y póngalo en el suelo.	0 1 2 3
Leer y hacer lo que esta escrito: **CIERRE LOS OJOS**	0 1
Escribir una frase:	0 1
Copiar el dibujo: 	0 1
TOTAL	

Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12: 189-198.Version Castellano: Rev Clin Esp 1987. 181 (supl 1): 56-59.



specs
synthetic perceptive, emotive and cognitive systems

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Evaluation Stage: Date:

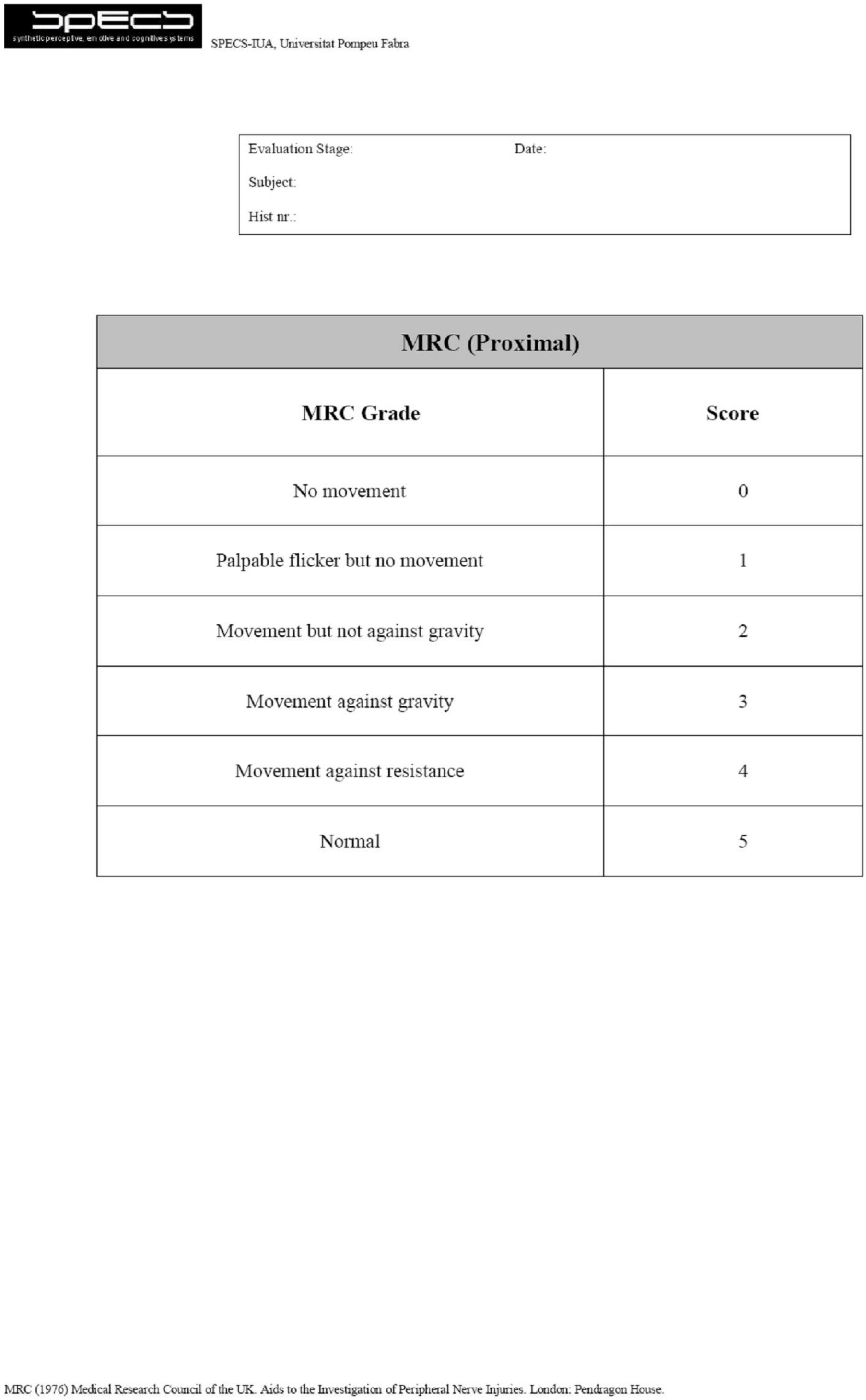
Subject:

Hist nr.:

BARTHEL INDEX

Activity	Independent	With help	Not done
SELF CARE INDEX			
1. Drink from a glass	4	0	0
2. Feeding	6	0	0
3. Dressing superior body	5	3	0
4. Dressing inferior body	7	4	0
5. Put orthesis or prothesis	0	-2	Not applicable
6. Hygene activities	5	0	0
7. Bathing self	6	0	0
8. Controlling bowels	10	5 (accés)	0
9. Controlling bladder	10	5 (accés)	0
MOBILITY INDEX			
10. Sitting and standig up from a chair	15	7	0
11. Sitting and standing up from the WC	6	3	0
12. Getting in and out of the bath or shower	1	0	0
13. Walking 50m	15	10	0
14. Ascend or descend stairs	10	5	0
15. If he/she doesn't walk, propelling wheelchair	5	0	0
TOTAL			

Granger CV. Albrecht GL, Hamilton BB. Outcome of comprehensive medical rehabilitation measurement by PULSES Profile and the Barthel Index Arch Phys Med Rehab 1979; 60: 145-54



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Evaluation Stage: Date:

Subject:

Hist nr.:

MRC (Proximal)	
MRC Grade	**Score**
No movement	0
Palpable flicker but no movement	1
Movement but not against gravity	2
Movement against gravity	3
Movement against resistance	4
Normal	5

MRC (1976) Medical Research Council of the UK. Aids to the Investigation of Peripheral Nerve Injuries. London: Pendragon House.

Evaluation Stage: Date:

Subject:

Hist nr.:

MOTRICITY INDEX (ARM PART)

TEST	**SCORE**
PINCH GRIP: using a 2.5 cm cube between the thumb and forefinger	
ELBOW FLEXION: from 90º so that the arm touches the shoulder	
SHOULDER ABDUCTION: moving the flexed elbow from off the chest	
TOTAL	

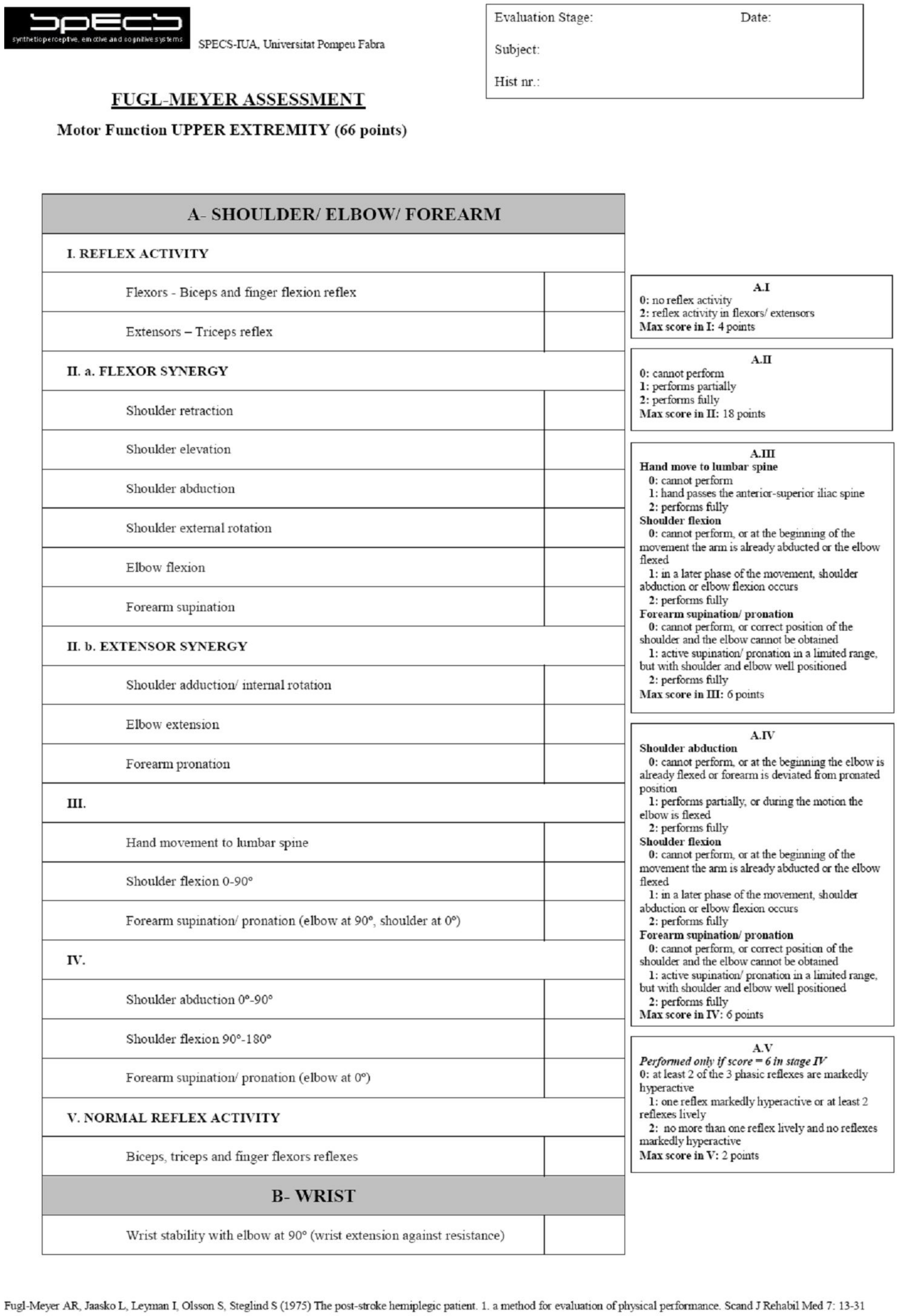
PINCH GRIP

0 = No movement
11 = Beginnings of prehension
19 = Grips cube but unable to hold against gravity
22 = Grips cube, held against gravity, but not against weak pull
26 = Grips cube against pull, but weaker than other/normal side
33 = Normal pinch grip

ELBOW FLEXION & SHOULDER ABDUCTION

0 = No movement
9 = Palpable contraction in muscle, but no movement
14 = Movement seen, but not full range/not against gravity
19 = Full range against gravity, not against resistance
25 = Movement against resistance, but weaker than other side
33 = Normal power

Collin C, Wade D (1990) Assessing motor impairment after stroke: a pilot reliability study. J Neurol Neurosurg Psychiatry 53: 576-579.



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Evaluation Stage: Date:

Subject:

Hist nr.:

FUGL-MEYER ASSESSMENT

Motor Function UPPER EXTREMITY (66 points)

A- SHOULDER/ ELBOW/ FOREARM	
I. REFLEX ACTIVITY	
Flexors - Biceps and finger flexion reflex	
Extensors – Triceps reflex	
II. a. FLEXOR SYNERGY	
Shoulder retraction	
Shoulder elevation	
Shoulder abduction	
Shoulder external rotation	
Elbow flexion	
Forearm supination	
II. b. EXTENSOR SYNERGY	
Shoulder adduction/ internal rotation	
Elbow extension	
Forearm pronation	
III.	
Hand movement to lumbar spine	
Shoulder flexion 0-90°	
Forearm supination/ pronation (elbow at 90°, shoulder at 0°)	
IV.	
Shoulder abduction 0°-90°	
Shoulder flexion 90°-180°	
Forearm supination/ pronation (elbow at 0°)	
V. NORMAL REFLEX ACTIVITY	
Biceps, triceps and finger flexors reflexes	
B- WRIST	
Wrist stability with elbow at 90° (wrist extension against resistance)	

A.I
0: no reflex activity
2: reflex activity in flexors/ extensors
Max score in I: 4 points

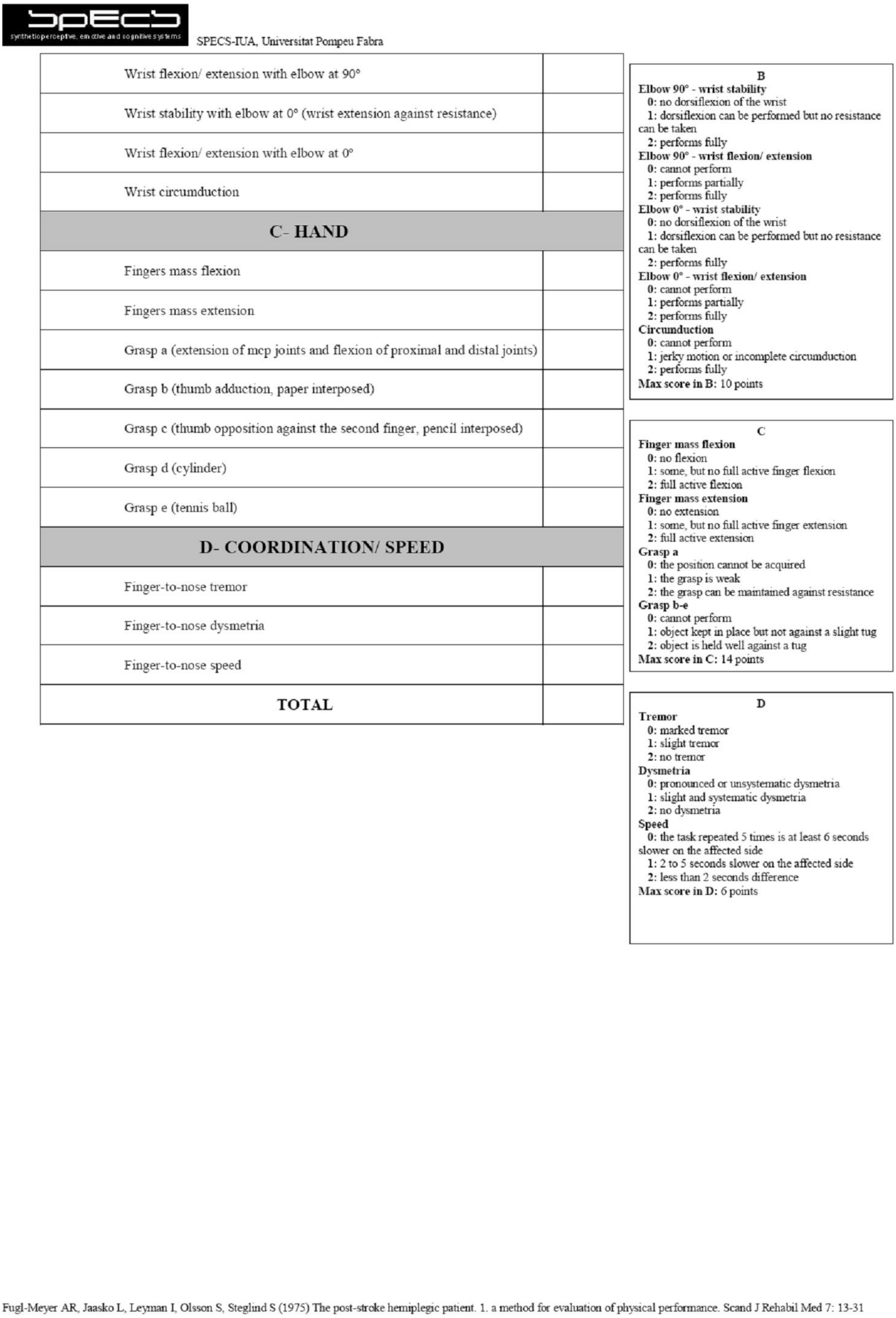
A.II
0: cannot perform
1: performs partially
2: performs fully
Max score in II: 18 points

A.III
Hand move to lumbar spine
0: cannot perform
1: hand passes the anterior-superior iliac spine
2: performs fully
Shoulder flexion
0: cannot perform, or at the beginning of the movement the arm is already abducted or the elbow flexed
1: in a later phase of the movement, shoulder abduction or elbow flexion occurs
2: performs fully
Forearm supination/ pronation
0: cannot perform, or correct position of the shoulder and the elbow cannot be obtained
1: active supination/ pronation in a limited range, but with shoulder and elbow well positioned
2: performs fully
Max score in III: 6 points

A.IV
Shoulder abduction
0: cannot perform, or at the beginning the elbow is already flexed or forearm is deviated from pronated position
1: performs partially, or during the motion the elbow is flexed
2: performs fully
Shoulder flexion
0: cannot perform, or at the beginning of the movement the arm is already abducted or the elbow flexed
1: in a later phase of the movement, shoulder abduction or elbow flexion occurs
2: performs fully
Forearm supination/ pronation
0: cannot perform, or correct position of the shoulder and the elbow cannot be obtained
1: active supination/ pronation in a limited range, but with shoulder and elbow well positioned
2: performs fully
Max score in IV: 6 points

A.V
Performed only if score = 6 in stage IV
0: at least 2 of the 3 phasic reflexes are markedly hyperactive
1: one reflex markedly hyperactive or at least 2 reflexes lively
2: no more than one reflex lively and no reflexes markedly hyperactive
Max score in V: 2 points

Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S (1975) The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. Scand J Rehabil Med 7: 13-31



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Wrist flexion/ extension with elbow at 90°	
Wrist stability with elbow at 0° (wrist extension against resistance)	
Wrist flexion/ extension with elbow at 0°	
Wrist circumduction	
C- HAND	
Fingers mass flexion	
Fingers mass extension	
Grasp a (extension of mcp joints and flexion of proximal and distal joints)	
Grasp b (thumb adduction, paper interposed)	
Grasp c (thumb opposition against the second finger, pencil interposed)	
Grasp d (cylinder)	
Grasp e (tennis ball)	
D- COORDINATION/ SPEED	
Finger-to-nose tremor	
Finger-to-nose dysmetria	
Finger-to-nose speed	
TOTAL	

B

Elbow 90° - wrist stability
0: no dorsiflexion of the wrist
1: dorsiflexion can be performed but no resistance can be taken
2: performs fully
Elbow 90° - wrist flexion/ extension
0: cannot perform
1: performs partially
2: performs fully
Elbow 0° - wrist stability
0: no dorsiflexion of the wrist
1: dorsiflexion can be performed but no resistance can be taken
2: performs fully
Elbow 0° - wrist flexion/ extension
0: cannot perform
1: performs partially
2: performs fully
Circumduction
0: cannot perform
1: jerky motion or incomplete circumduction
2: performs fully
Max score in B: 10 points

C

Finger mass flexion
0: no flexion
1: some, but no full active finger flexion
2: full active flexion
Finger mass extension
0: no extension
1: some, but no full active finger extension
2: full active extension
Grasp a
0: the position cannot be acquired
1: the grasp is weak
2: the grasp can be maintained against resistance
Grasp b-e
0: cannot perform
1: object kept in place but not against a slight tug
2: object is held well against a tug
Max score in C: 14 points

D

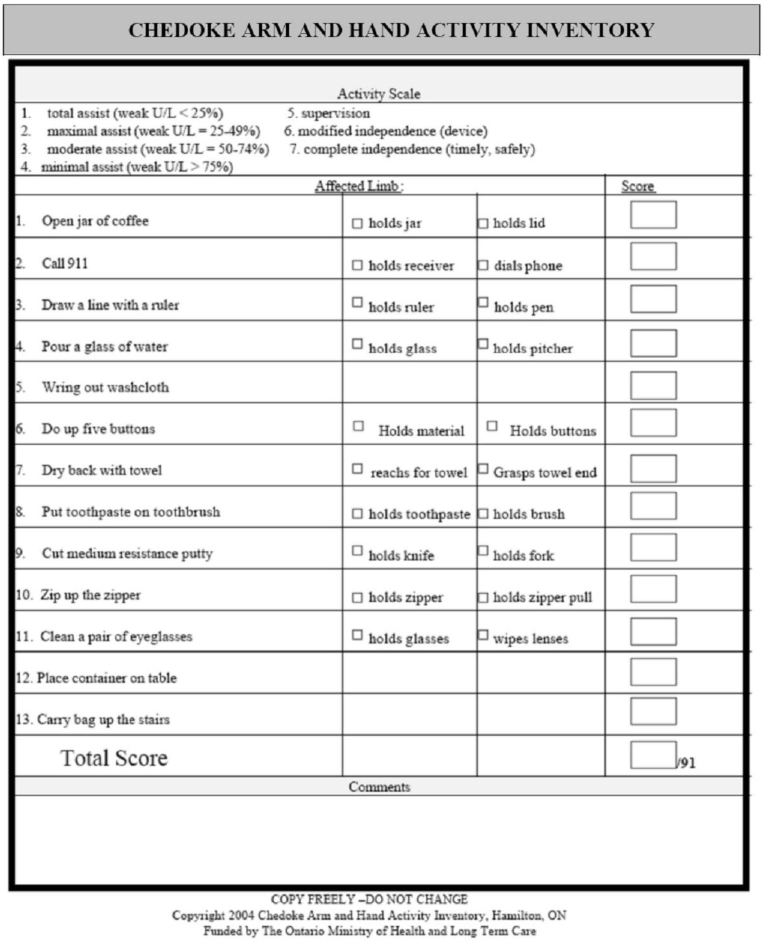
Tremor
0: marked tremor
1: slight tremor
2: no tremor
Dysmetria
0: pronounced or unsystematic dysmetria
1: slight and systematic dysmetria
2: no dysmetria
Speed
0: the task repeated 5 times is at least 6 seconds slower on the affected side
1: 2 to 5 seconds slower on the affected side
2: less than 2 seconds difference
Max score in D: 6 points

Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S (1975) The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. Scand J Rehabil Med 7: 13-31

Evaluation Stage: Date:

Subject:

Hist nr.:



CHEDOKE ARM AND HAND ACTIVITY INVENTORY

Activity Scale

1. total assist (weak U/L < 25%)
2. maximal assist (weak U/L = 25-49%)
3. moderate assist (weak U/L = 50-74%)
4. minimal assist (weak U/L > 75%)
5. supervision
6. modified independence (device)
7. complete independence (timely, safely)

	Affected Limb:		Score
1. Open jar of coffee	☐ holds jar	☐ holds lid	☐
2. Call 911	☐ holds receiver	☐ dials phone	☐
3. Draw a line with a ruler	☐ holds ruler	☐ holds pen	☐
4. Pour a glass of water	☐ holds glass	☐ holds pitcher	☐
5. Wring out washcloth			☐
6. Do up five buttons	☐ Holds material	☐ Holds buttons	☐
7. Dry back with towel	☐ reachs for towel	☐ Grasps towel end	☐
8. Put toothpaste on toothbrush	☐ holds toothpaste	☐ holds brush	☐
9. Cut medium resistance putty	☐ holds knife	☐ holds fork	☐
10. Zip up the zipper	☐ holds zipper	☐ holds zipper pull	☐
11. Clean a pair of eyeglasses	☐ holds glasses	☐ wipes lenses	☐
12. Place container on table			☐
13. Carry bag up the stairs			☐
Total Score			☐/91

Comments

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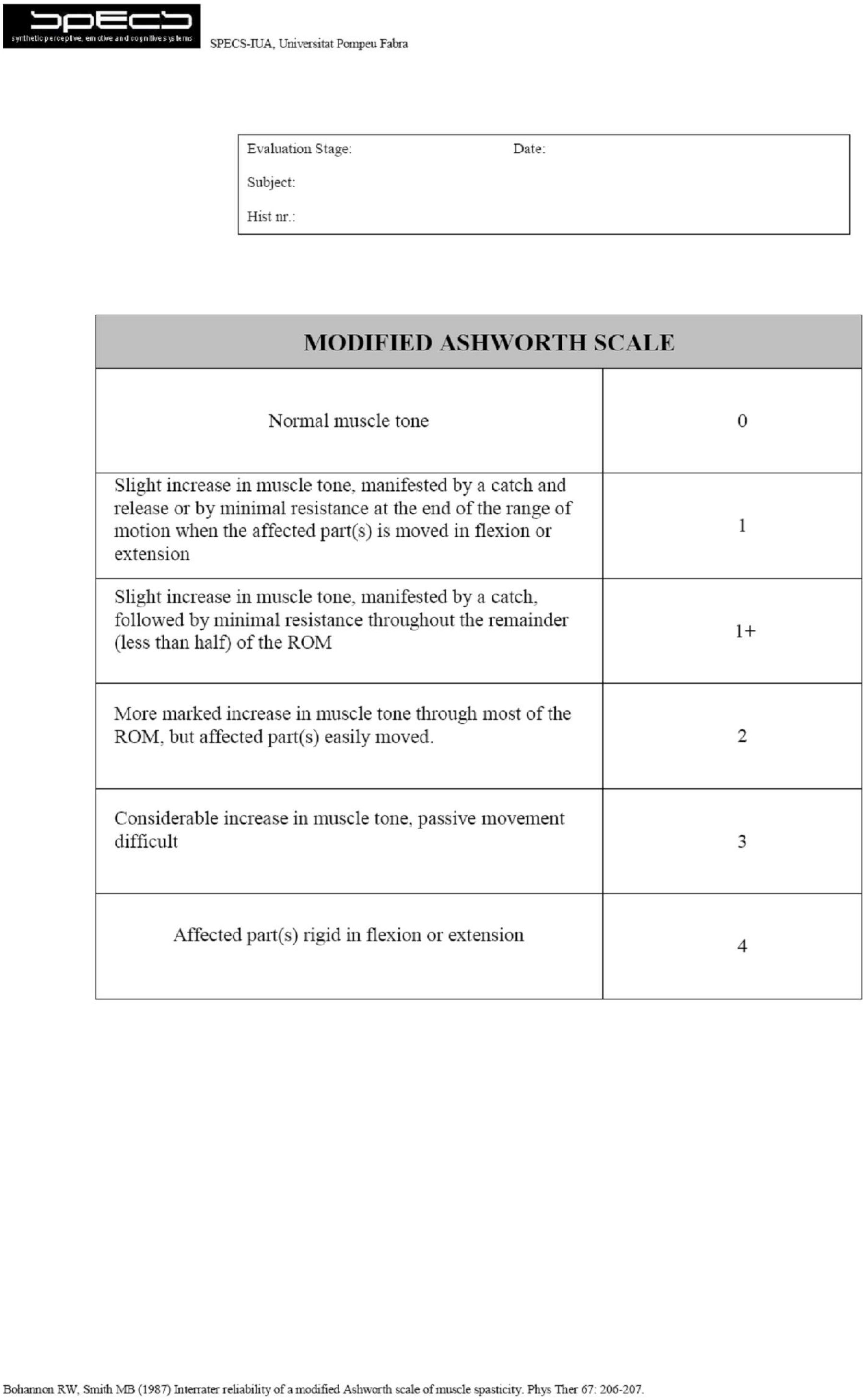
Funded by The Ontario Ministry of Health and Long Term Care

Barreca S, Gowland CK, Stratford P, Huijbregts M, Griffiths J, et al. (2004) Development of the Chedoke Arm and Hand Activity Inventory: theoretical constructs, item generation, a
selection. Top Stroke Rehabil 11: 31-42.



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Evaluation Stage: Date:

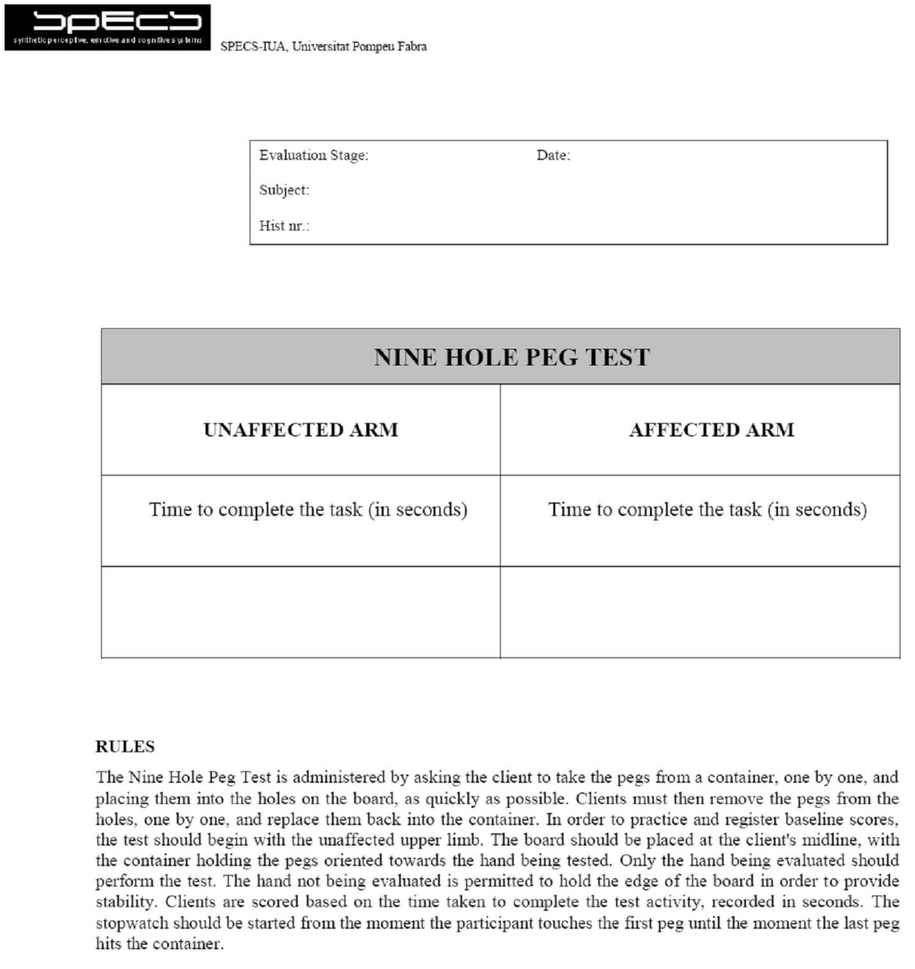
Subject:

Hist nr.:

MODIFIED ASHWORTH SCALE

Normal muscle tone	0
Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension	1
Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM	1+
More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved.	2
Considerable increase in muscle tone, passive movement difficult	3
Affected part(s) rigid in flexion or extension	4

Bohannon RW, Smith MB (1987) Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther 67: 206-207.



SPECS-IUA, Universitat Pompeu Fabra

Evaluation Stage: Date:

Subject:

Hist nr.:

NINE HOLE PEG TEST

UNAFFECTED ARM	AFFECTED ARM
Time to complete the task (in seconds)	Time to complete the task (in seconds)

RULES

The Nine Hole Peg Test is administered by asking the client to take the pegs from a container, one by one, and placing them into the holes on the board, as quickly as possible. Clients must then remove the pegs from the holes, one by one, and replace them back into the container. In order to practice and register baseline scores, the test should begin with the unaffected upper limb. The board should be placed at the client's midline, with the container holding the pegs oriented towards the hand being tested. Only the hand being evaluated should perform the test. The hand not being evaluated is permitted to hold the edge of the board in order to provide stability. Clients are scored based on the time taken to complete the test activity, recorded in seconds. The stopwatch should be started from the moment the participant touches the first peg until the moment the last peg hits the container.

Oxford Grice K, Vogel KA, Le V, Mitchell A, Muniz S, et al. (2003) Adult norms for a commercially available Nine Hole Peg Test for finger dexterity. Am J Occup Ther 57: 570-573 synthetic perceptive, emotive and cognitive systems SPECS-IUA, Universitat Pompeu Fabra

Evaluation Stage: Date:
Subject:
Hist nr.:

BOX & BLOCK TEST	
UNAFFECTED ARM	**AFFECTED ARM**
Number of blocks transferred in 60 seconds	Number of blocks transferred in 60 seconds

RULES

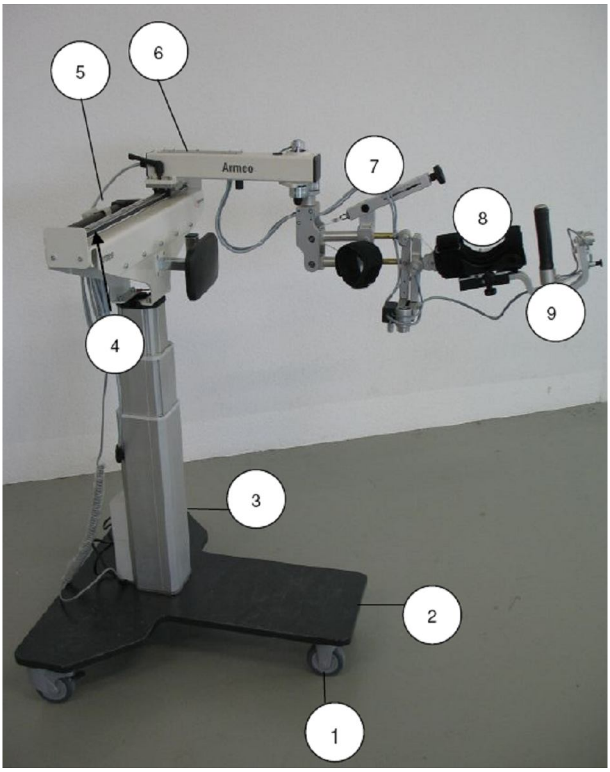
The Box & Block Test administration consists of asking the client to move, one by one, the maximum number of blocks from one compartment of a box to another of equal size, within 60 seconds. The box should be oriented lengthwise and placed at the client's midline, with the compartment holding the blocks oriented towards the hand being tested. In order to practice and register baseline scores, the test should begin with the unaffected upper limb. Before the trial, after the standardized instructions are given to clients, they should be advised that their fingertips must cross the partition when transferring the blocks, and that they do not need to pick up the blocks that might fall outside of the box.

Clients are scored based on the number of blocks transferred from one compartment to the other compartment in 60 seconds. During the performance of the test, the evaluator should be aware of whether the client's fingertips are crossing the partition. Blocks should be counted only when this condition is respected. Furthermore, if two blocks are transferred at once, only one block will be counted. Blocks that fall outside the box, after trespassing the partition, even if they don't make it to the other compartment, should be counted.

Mathiowetz V, Volland G, Kashman N, Weber K (1985) Adult norms for the Box and Block Test of manual dexterity. Am J Occup Ther 39: 386-391.

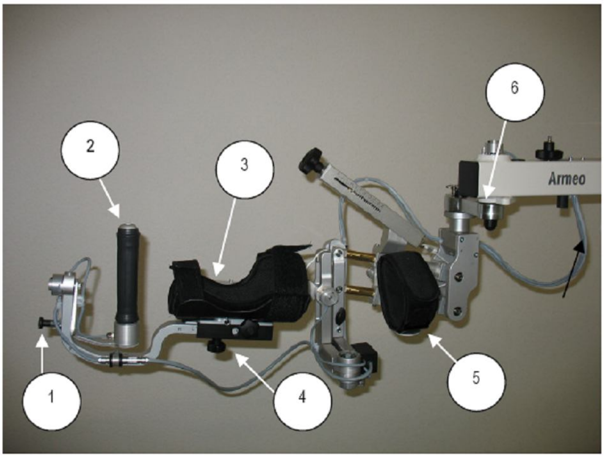
Appendix IV – Main Components of Armeo

The Armeo device is an arm orthosis equipped with various components, including a spring mechanism to provide adjustable arm weight support, thus facilitating functional arm movements.

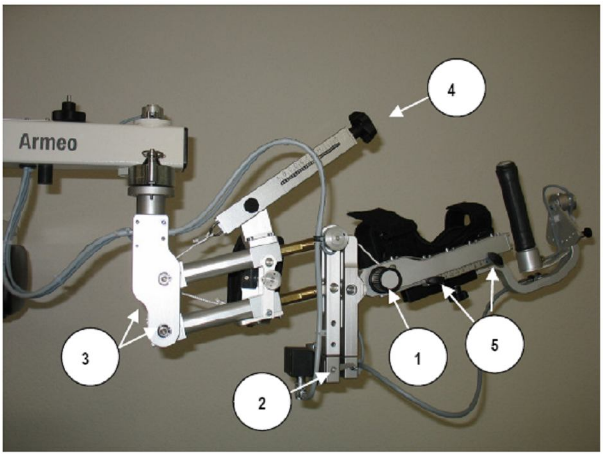


General overview of Armeo device

1. Caster
2. Base plate
3. Lifting column
4. Linear guide
5. Transport handle
6. Arm with integrated electronics
7. Upper arm module with weight compensation mechanism and cuff
8. Forearm module with weight compensation mechanism and cuff
9. Pressure sensitive handle with degree of freedom for pronation / supination



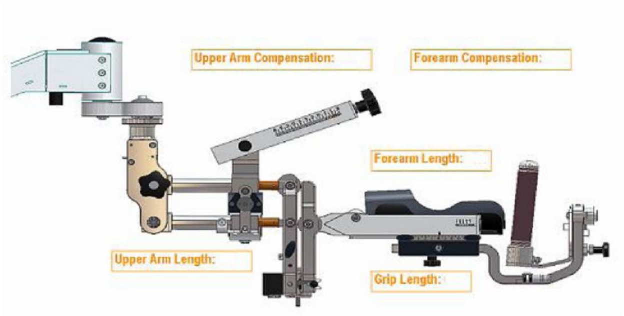
1. Lock mechanism pro/supination
2. Pressure-sensitive handgrip
3. Forearm cuff
4. Adjustment handgrip position
5. Upper arm cuff
6. Lock mechanism shoulder joint



1. Weight support adjustment forearm
2. Lock mechanism for elbow joint
3. Length adjustment for upper arm
4. Weight compensation adjustment for upper arm
5. Winged nuts for adjusting forearm length

Subject:

Hist nr.: Affected Side:

ARMEO SETTINGS	
Left	
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