Application of Virtual Reality in Neuro-Rehabilitation: an Overview

Lucia F Lucca[1], Antonio Candelieri[1,2] and Loris Pignolo[1]
[1]S. Anna Institute and RAN - Research in Advanced Neuro-rehabilitation, Crotone,
[2]Laboratory of Decision Engineering for Health Care Delivery, University of Cosenza,
Italy

1. Introduction

Virtual reality (VR) collectively refers to the realistic, albeit artificial environments that are simulated by computer and are experienced by end-users via human-machine interfaces involving multiple sensory channels. In this respect, comparable technical solutions are applicable across different domains such as *cyberspace, virtual environments, teleoperation, telerobotics, augmented reality,* and *synthetic environments.* This makes application possible in a variety of conditions such as (1) design, engineering, manufacturing, and marketing; (2) medicine and healthcare; (3) online monitoring of children and the elderly at home and accident prevention; (4) hazardous operations in extreme or hostile surroundings; and (5) training in military and industrial machine operation, medical teaching and surgery planning/training. An implement of VR with live direct or indirect view of a physical real-world environment whose elements are purportedly enhanced (*augmented*) by virtual computer-generated imagery to meet the viewer needs, Augmented Reality is extensively used in open surgery, virtual endoscopy, radiosurgery, neuropsychological assessment and medical rehabilitation. Application in psychotherapy ranked 3rd among 38 psychotherapy interventions predicted to increase in use in the next future (Gorini & Riva, 2008a; Gorini & Riva, 2008b).

Application in rehabilitation is increasing and expanding; innovative technical solutions in motor and sensory-cognitive rehabilitation result in substantial developments from the available procedures and in prototypes for clinical testing. The clinical results appear promising.

2. Rationale for VR-mediated neuro-rehabilitation

The rationale for application mainly rests on the available evidence that a functional re-arrangement of the injured motor cortex can be induced with the mediation of the mirror neurons system (Eng et al, 2007; Holden, 2005; Rose et al, 2005) or through the subject's motor imagery and learning (Gaggioli et al, 2006). Intensive training (*repetition*) facilitating re-arrangement of cortical function and *motivation* reinforced by *feedback information* about the ongoing improvement are necessary for motor learning to be possible after brain damage. These conditions are easily made available in VR-mediated neuro-rehabilitation paradigms. Motor impairment and recovery can be measured in real time (*e.g.* at the end of each trial or a series of trials) to give the user the knowledge-of-performance (about his/her movement patterns) and knowledge-of-results (about the outcome predictable at each time point during

rehabilitation) that reinforce motivation and the training procedure itself. VR allows online or offline feedback, that has been extensively investigated with a general agreement that it improves learning (Bilodeau & Bilodeau, 1962; Gentile, 1972; Khan & Franks, 2000; Newell & Carlton, 1987; Winstein, 1991; Young & Schmidt, 1992; Woldag & Hummelsheim, 2002). The expectation is, that VR-mediated rehabilitation should improve the approach efficacy and the outcome by making tasks easier, less demanding and less tedious/distractive, and more informative for the subject. Interactive VR environments are flexible and customizable for different therapeutic purposes; individual treatments can be personalized in order to facilitate movement retraining, to force the user to focus on the task key elements, and to facilitate transfer of motor patters learned in VR environments to the real world.

3. Studies

3.1 VR in the upper limb motor rehabilitation

VR was first applied in the rehabilitation of the paretic upper-limb after stroke in a setting designed to promote motor (re)learning for different movements (hand, elbow and shoulder) and functional tasks or goals (Holden et al, 1999). The approach implemented a learning-by-imitation paradigm through three components: a motion tracking device to record the trajectories to be performed in the VR environment, a desktop computer display and a VR editing software specifically developed to create suitable 3D-simulated tasks at varying level of complexity. Once the scenario had been defined, the programmed motor learning tasks to be performed within the virtual environment were stored into the motion tracking device. Patients were then requested to reproduce the trajectories set by the *virtual teacher* or to devise appropriate trajectories in the absence of it, while the upper limb movements were monitored by the *virtual teacher*, displayed in real time and recorded. The approach also assessed the degree of matching between the *virtual teacher* and the patient's trajectories and provided trainer and trainee with a measure of each trial efficency. In a pilot study (Holden et al, 1999), two chronic patients with massive stroke were trained on a reach-and-grasp task involving shoulder flexion, elbow extension and forearm supination at six increasing levels of complexity. Efficacy was assessed through a 3D kinematic reach test performed in the real world before and after VR-supported rehabilitation; the Fugl-Meyer Test of Motor Recovery for Stroke test (Fugl-Meyer et al, 1975) and the motor task section of the Structured Assessment of Independent Living Skills (SAILS) test of UE function (Mahurin et al, 1991) were used for clinical evaluation. The patients were able to export the abilities learned in VR to the real world and to similar but untrained activities, but hand orientation proved difficult to learn. In successive studies (Holden et al, 2001; Holden et al, 2002), information about the specific (as measured in real tasks designed to evaluate generalization in space, gravitoinertial force, combined spatial/gravitoinertial force, and in tasks requiring novel recombination of trained movement elements, and control tasks with untrained elements) and non-specific (as measured by variations in motor recovery tests after VR-supported training activity) motor generalization was used to measure in detail the ability to transfer to the real world what learned in VR. Patients improved in three standard clinical tests of function, even if practicing in two movements only during VR training. It was suggested that VR-mediated rehabilitation is an effective and efficient approach to (re)train a set of basic tasks with upgrading to a wide variety of skilled movements (Holden, 2005).

Piron et al. (2005) replicated these results in a study on 50 patients with impaired upper limb motion after stroke. The VR-supported rehabilitation system included a virtual environment (a

PC workstation with a wall screen), a motion tracking device and the dedicated software for editing 3D-scenarios in a learning-by-imitation rehabilitation process with a *virtual teacher*. Therapists set the virtual scenarios characteristics and the motor training complexity to match each patient's motor impairment and rehabilitation protocol, set the starting position, target location and orientation, designed simple/complex tasks, added or removed non-pertinent virtual objects (distractive elements) to increase/reduce the task level of difficulty, recorded trajectory of the desired movement to be (re)learned by the subject, with *the virtual teacher* visible or hidden as advisable. The degree of motor impairment or recovery and the attained levels of autonomy in daily living activities were measured by the Fugel-Meyer (FM) UE score and the Functional Independence Measure scale (FIM) before and after the therapy, and by means of kinematic measures such as the movement morphology and mean duration and speed. Improvement was observed in the FM UE and FIM mean scores (with 15% and 6% increases, respectively) and in the movement mean duration (18%) and speed (23%), with better regularity of trajectories. Improvements do not appear to have been influenced by age, time since stroke or site of brain damage, as already noted in previous studies (Jeffery & Good, 1995; Johnston et al, 1992; Bagg et al, 2002; Tangeman et al, 1990; Dam et al, 1993). Instead, the severity of impairment was crucial for the outcome and a severe initial impairment was more difficult to rehabilitate. Comparison between the degrees of recovery attained after standard or VR-reinforced learning in two randomly assigned post-stroke patient groups (Turolla et al, 2007) showed significantly increased FM UE scores in all 30 patients, but improvement was greater after VR-supported therapy. The different outcome was ascribed, at least in part, to the feedback information about knowledge-of-results and knowledge-of-performance provided by the system (Todorov et al, 1997; Schmidt & Young, 1991; Winstein et al, 1996) and to the reinforced learning provided by the VR-based rehabilitation approach (Barto, 1994; Doya, 2000; Fagg & Arbib, 1992; Rummelhart et al, 1986).

3.2 VR in the lower limb motor rehabilitation

Several VR applications were designed to recover efficient walking in patients with lower limb motor impairment after stroke (Deutsch et al, 2002 and Deutsch et al, 2004). Fung, et al. (Fung, et al 2004, 2006), performed studies on gait training by using a treadmill mounted on a 6-degree-of-freedom motion platform with a motion-coupled VR environment. The system provided the unique feature of simulated turning within the environment; also provided auditory and visual cues as positive/negative feedback. Subjects were required to wear 3D stereo glasses to visualize the virtual environment. Test results from this project demonstrated improved gait speed with training. More recently, Mirelman et al. studied the effects on impaired gait kinetics of robot-assisted rehabilitation with or without VR support (Mirelman et al, 2007). Subjects in the two subgroups were trained with the same exercises; requested movements were inversion and eversion, dorsiflexion and plantar flexion, or combinations of these. A motion capture system was used to measure movements in association with a force-feedback system permitting navigation within a virtual environment displayed on a computer screen. Gait was estimated at baseline, one week after the training session, and three months after end of the therapy. Feedback information was provided directly by the system to the patients treated in the VR setting and by the therapist to those undergoing rehabilitation withouth VR support. Both groups improved, but patients treated with VR support did better, with increased ankle strenght at the end of treatment and at follow-up. Patients undergoing robotic- assisted rehabilitation without VR support reported fatigue earlier.

Park and colleagues (Park et al, 2007) developed a VR system for motor rehabilitation with a PC camera and two markers of movement in a very simple virtual scenario with a crossing-stepping stone task. The success rate in 9 hemiplegic patients with stiff-knee gait after stroke was computed as the ratio of successful trials to the total gait cycles, with a ~30% improvement after treatment.

3.3 VR and telemedicine: the upper limb tele-rehabilitation

VR settings are usable in the transfer of available occupational treatments to a platform for rehabilitation at home, with remote control by therapist. Broeren and coworkers have emphasized the reduced labor, logistics and costs of the state-of art web-based video/audio systems for telemedicine and tested their protocol in a case study, with VR associated to the haptic force feedback necessary for VR object manipulation. The hand fine dexterity and grip improved after treatment (Broeren et al, 2002). More recently, Trotti and colleagues proposed VR-supported training as an integration of the conventional rehabilitation protocols (Trotti et al, 2009). They used kinematics indexes (such as movement execution time and precision) and validated clinical scales, such as Nine-Hole Peg Test (NHPT) (Mathiowetz, 1985), Frenchay Arm Test (FAT) (Heller, 1987), Medical Research Council (MRC) (Florence, 1992), Motricity Index (MI) (Bohannon, 1999), and the Motor Evaluation Scale for Upper extremity in Stroke Patients (MESUPES) (Van de Winckel, 2006) to measure the upper limb impairment in a patient with stroke before and after therapy with VR-supported upper limb rehabilitation. Kinematic analysis and most clinical scales (MRC of fingers, MESUPES and NHPT time, but not MI and FAT) showed a decrease in movement execution time and increase in precision, with improved muscle strenght and movement control (Trotti et al, 2009).

VR-mediated telerehabilitation was further investigated (Piron et al, 2009) by comparing two groups (18 subjects each) of patients with stroke treated for four weeks by a VR-assisted rehabilitation program operated through Internet or by conventional therapy. Motor impairment was assessed one month before, at the beginning and end of therapy, and one month later by means of the Fugl-Meyer Upper Extremity (FM EU), Abilhand (Penta et al, 2001) and Ashworth (Bohannon & Smith, 1987) scales. The setting included a *virtual teacher* showing the correct trajectories as set by the therapist in association with the patient's actual movement. The knowledge-of-performance was provided via videoconference. No differences were observed when comparing the assessments one month before and at beginning of therapy, but both groups improved after therapy and the improvement was evident also one month after the end of therapy. The FM UE showed better recovery for patients treated through VR-based telerehabilitation.

4. Systems and applications

4.1 Systems and applications for VR-supported upper limb rehabilitation

A VR system purported to measure the impairment in speed, strength, fractionation and range of fingers movements was designed to be distributed over three sites connected via Internet (for rehabilitation, data storage and data access, respectively) (Boian et al, 2002). At the rehabilitation site, the system featured a workstation and two sensing (cyber and haptic) gloves; the data storage site organized the information acquired during the VR-supported rehabilitation; open access to data was through Internet. An algorithm was implemented to increase or decrease according to the achieved performance the difficulty of the target task. The system was tested in a pilot study on 4 patients with stroke. A screen provided the patients with knowledge-of-results and performance (feedback) through a transparent hand

representing the target and numerical scores about the trial execution. Trained patients achieved various degrees of improvement, with a good retention in gains and a positive evaluation of the system both by patients and therapists. A virtual tabletop environment for the upper limb rehabilitation after traumatic brain injury was developed (Wilson et al, 2007) to measure the residual function and kinematic markers like speed, precision, distance, accuracy of targeting. The system was innovative because flexible, automated, and relatively inexpensive, with components specifically designed to be user-friendly: LCD panels easy to carry and reducing the set-up time were favored; the virtual environment was displayed on the LCD panel placed horizontally on a tabletop surface, and users could interact with the system by moving sensing-objects over it; knowledge of results was provided to the patient via another LCD panel. Distractive elements appeared on the LCD to increase or decrease the task difficulty. Low-cost implements, such as commercial game controllers and marker tracking were used. Wilson and coworkers suggested that psychometric measures should be preferred in the future and predicted broad application in assessing movement impairment after stroke and ischemic or traumatic brain damage or in movement disorders (e.g. Parkinson or Huntington's diseases).

Therapy WREX (T-WREX) was designed by Reinkensmeyer and Housman (2007) for the hand and arm rehabilitation after stroke to make rehabilitation possible also in the absence of the therapist, with exercises mimiking the daily living activities in VR environment and a feedback information procedure. The system featured a passive gravity-balancing orthosis based on the Wilmington Robotic Esoskeleton (WREX) (Rahman et al, 2007), a hand grip sensor and the software needed for VR and performance evaluation, but was not a robotics/VR integration because WREX assisted patients only against gravity and by elastic bands. It focused on the re-training of function on a plane, therefore displaying the movement on the plane of interest. The system bypassed the problems of 3D complexity, but limitated the movements to be re-learned. Most patients nevertheless found T-WREX less boring than conventional therapy and their progress during rehabilitation easier to track. Reiteration of motor training by T-WREX reduced motor impairment (as measured by the Fugl-Meyer scale) in a preliminary randomized controlled study (Reinkensmaeyer & Housman, 2007).

4.2 Low-cost and open source systems for VR-supported tele-rehabilitation

Interest on tele-rehabilitation as a possible alternative to the traditional treatment of inpatients in hospital increased in recent years with the increment of costs and commitment by the private and public healthcare. Sugarman and colleagues assumed it is impossible for the therapist to monitor patients performing rehabilitation at home, emphasized the therapist's role in motivating the patient and the need of efficient communication between the therapist and patients at any time and place, including home (Sugarman et al, 2006). Approaches combining VR and mechanical devices for rehabilitation (Fasoli et al, 2004; Coote & Sokes, 2005; Broeren et al, 2004; Reinkensmeyer et al, 2002; Jadhav & Krovi, 2004) appear encouraging, but the systems specifically developed for these purposes have high costs. In alternative, Sugarman and colleagues adopted a commercial feedback joystick in association with a specifically designed armrest and a PC with Internet connection. Their proposed VR solution could be operated in two different modes: stand-alone or cooperative. In the former, patients exercised at home without Internet connection; in the latter, the patient and therapist were online and the therapist could monitor and tutor the patient performing.

Open-source tools stand as inexpensive alternatives to promote the development of user-friendly, customized VR systems for rehabilitation and are being tested. Riva and colleagues proposed NeuroVR, a cost-free software platform based on open-source available solutions (Riva et al, 2009). The platform allows users with no technical background to easily interface with the virtual environment and modify the scenario according to the specific needs; 2D and 3D objects may be selected from a database and incorporated into the virtual environment by a user-friendly graphical interface; therapists can supplement the database with pictures of persons or objects belonging to the patient's real life and suitable as stimuli or stressors. A further improvement of NeuroVR (Algeri et al, 2009) was the integration with the open-source software CamSpace aimed at developing a cost-free system overcoming some operational limits related to the joypad, mouse or keyboard use. A further extention was CamSpace 7, through which patients can interact with the virtual environment simply by hand or body movements and allowing design both motor and balance rehabilitation exercises (Weiss Tamar et al, 2004). NeuroVR is also in use in the treatment of a variety of conditions, including obesity (Riva et al, 2006), alcohol abuse (Gatti et al, 2008), anxiety disorders (Gorini & Riva, 2008a,b), and in the rehabilitation of cognitive impairment (Morganti et al, 2007).

4.3 VR-based systems for sensory, cognitive and behavioural rehabilitation

The traditional protocols for cognitive-behavioural rehabilitation are mostly based on imaginary or *in-vivo* exposure; the Virtual Reality Exposure Therapy (VRET) is an altered form of behavioral therapy and may be a possible alternative to standard in vivo exposure, for example in the therapy of anxiety disorders (Krijn, 2004). VR allows immersive or semi-immersive interaction with virtual environments incorporating suitable stimuli, therefore reducing the limits of representing real tools to brain damaged subjects unable to chategorize (Rizzo et al, 2005). VR systems are today in use in the management of patient with stroke, to support cognitive rehabilitation by providing logopaedic help and reducing the somatic effects of paresis though a multi-sensorial brain stimulation approach (Probosz et al, 2009). Marusan and colleagues (Marusan et al, 2006) and other groups (Rose et al, 1998; Tomasino & Rumiati, 2004) suggested the use of mental rotation paradigms (Shepard & Metzler, 1971) in VR neuro-rehabilitation setting, with extention to the brain injured of the use of mental images that is critical in cognitive tasks involving memory, reasoning and problem solving in everyday life (Zacks et al, 1999; Podzebenko et al, 2005). Marusan and coworkers main goal was to develop a VR-based technical solution for neurorehabilitation of traumatic brain injury (TBI) patients; their secondary goal was ease of use for the patient at home via common technical supports such as PC, mouse and keyboard devices to be available anywhere and anytime without special equipment (3D glasses, gloves, suits, etc) requiring expert help.

Koenig and colleagues (Koenig et al, 2009) proposed a VR approach to assess the patient's performance in tasks of way-finding and in the training of spatial orientation skills in brain injured patients. Several standardized outcome measures were used: Money Road-Map Test (Money et al, 1965), Zoo Test (Wilson et al, 1996), Object Perspective Taking Test (Kozhevnikoy & Hegarty, 2001), Virtual Reality Navigation Task, Real-World Navigation Task, Santa Barbara Sense of Direction Scale (Hegarty et al, 2002), Mental Rotation Task, Card Rotation Task, and Surface Development Task (Ekstrom et al, 1976). Complexity was increased with the protocol and subject's progressing in order to promote generalization of regained abilities, with the addition of naturalistic features or constraints (*e.g.* locked doors or detours) and varying conditions of illumination. Performance was evaluated as navigation errors, timing and orientation behaviour.

Interactive multimodal rehabilitation may enhance the efficacy of cognitive rehabilitation after cerebrovascular brain injury. Salva and co-workers (Salva et al, 2009) have developed a novel Mixed Reality (MR) approach reportedly promoting neural plasticity. An evolution of classical VR merging and overlapping virtual and real environments, MR creates an augmented reality without losing contact with the real setting and preserving sensory feedback and interaction without any requirement for adaptation. The Mixed Reality Rehabilitation System (MRRS) was meant to avoid crucial problems in the traditional therapy such as the limitations in resources and decreasing levels of participation and interest. Pilot studies seem to indicate remarkable potentialities in neurorehabilitation though MR, mostly by allowing patients to interact with and experience both the virtual scenario and the real world (Standen and Brown, 2005). Also based on Augmented Reality tools is GenVirtual (Correa et al, 2007), a musical game helping patients in colors and sounds memorization tasks. The approach proved acceptable to the patient with cognitive deficits and useful in rehabilitation, inexpensive and applicable to integrate standard rehabilitation in hospital as well as at home.

5. Comment

VR stands as a potentially useful tool for diagnosis, therapy, education and training. Application in neuro-rehabilitation is still unsystematic and limited, yet there is evidence supporting its applicability in a variety of paradigms that can allow the patients avoid the real world challenges in a secure environment and to freely explore, experiment, feel, live and experience feelings and thoughts. Motor rehabilitation has been applied in patients with acquired brain injury with some success, but application in the rehabilitation of these subjects' cognitive deficits remains unsystematic and its potentialities appear high but still undocumented.

The differences among studies in the design, procedures for data acquisition and analyses, and criteria of admission do not allow a direct comparison of the efficacy of different VR setups. VR is a new tool for upper limb stroke rehabilitation, but evidence about its efficacy is still regarded as weak to moderate (Henderson, 2007). Application of VR procedures in the rehabilitation of the upper limb emphasizes the lack of agreed criteria to assess the kinetics and kinetic impairment in neurology and these limitations are only in part compensated for by the motor scales in use in neuro-rehabilitation (Lucca, 2009). The training conditions to be favored in the clinical practice and/or in research on large populations therefore remain unidentified. Systematic neuroimaging research is today mandatory for the cortical functional re-arrangement to be correlated in full detail with the neurorehabilitation clinical effects irrespective of the applied rehabilitative procedures. It would allow document the cortical functional damage as well as the efficacy of training. In this prospective, today's limits in the long-term efficacy of VR rehabilitation procedures may challenge physicians, physiatrists, psychologists and bio-engineers without questioning the potentialities of the approach.

Rehabilitation needs to be intensive over long periods of time and requires dedicated staff, resources and logistics. The duration of the rehabilitation effects after discontinuing VR training is crucial and should be determined in controlled follow-up studies, which remain unsystematic to date. This discrepancy contrasts with the increased availability of advanced and limited-cost technologies and the need for reliable criteria to help define cost/benefit ratios and priorities in private and public health facilities. VR would also mediate between the therapist's and the real world and is forseen as possibly promoting the patients' earlier

AUTHOR,YEAR	PATIENT	INTERVENTION
UPPER LIMB REHABILITATION		
Holden et al, 1999	Stroke	Learning-by-imitation paradigm.
Holden et al, 2002	Stroke	Motor generalization: ability to transfer to the real world what learned in VR.
Boian et al, 2002	Stroke	VR system and two sensing cyber and haptic gloves) measures the impairment in speed, strength, fractionation and range of fingers movements. Difficulty of the target task increases or decreases according to the achieved performance.
Piron et al, 2005	Stroke	Different level of difficulty: the motor training complexity to match each patient's motor impairment and rehabilitation protocol.
Wilson et al, 2007	Traumatic brain inj.	A virtual tabletop environment to measure the residual function and kinematic markers.
Reinkensmeyer and Housman, 2007	Stroke	Hand and arm rehabilitation in absence of the therapist, with exercises mimiking the daily living activities in VR environment. The system featured a passive gravity-balancing orthosis.
LOWER LIMB REHABILITATION		
Fung et al, 2004, 2006	Stroke	Gait training by using a treadmill mounted on a 6-degree-of-freedom motion platform with a motion-coupled VR environment. Auditory and visual cues as positive/negative feedback.
Mirelman et al, 2007	Stroke	Robot-assisted rehabilitation with or without VR support Force-feedback system permits navigation within a virtual environment displayed on a computer screen.
Park et al, 2007	Stroke	VR system for motor rehabilitation in a very simple virtual scenario with a crossing-stepping stone task.
COGNITIVE REHABILITATION		
Rizzo et al, 2005	Brain injury	VR immersive or semi-immersive with suitable stimuli, reduces the limits of representing real tools to subjects unable to chategorize.
Marusan et al, 2006	Traumaticbrain inj.	Use of mental rotation paradigms in VR neuro-rehabilitation setting.
Correa et al, 2007	Brain injury	Augmented Reality: a musical game helping patients in colors and sounds memorization tasks.
Probosz et al, 2009	Stroke	VR systems support cognitive rehabilitation by providing logopaedic help and reducing the somatic effects of paresis though a multi-sensorial brain stimulation approach.
Koenig et al.,2009	Brain injury	VR approach to assess the patient's performance in tasks of way-finding and in the training of spatial orientation skills.

Table 1. Summary of studies

discharge from hospital and transfer to programs for rehabilitation at home, with improved quality of life and clinical outcome.

In general, the scenario would motivate research to achieve widespread application, possibly by making home rehabilitation under remote control a realistic option and by extending VR use to the computer or technology illiterate.

6. References

Algeri, D., Carelli, L., Gaggioli, A. and Riva, G. (2009). A free tool for motor rehabilitation: NeuroVR 1.5 with CamSpace. In *Annual Review of Cybertherapy and Telemedicine*, 7. 1554-8716

Bagg, S., Paris Pombo, A. and Hopman, W. (2002). Effect of age on functional outcomes after stroke rehabilitation. *Stroke*, 33, 179-185. 0039-2499

Barto, A. G. (1994). Reinforcement learning control. *Curr Opin Neurobiol*, 4, 888-893. 0959-4388

Bilodeau, E. A. & Bilodeau, I. M. (1962). Motor skills learning. *Annual Reviews of Psychology*, 13, 243–280. 0066-4308

Boian, R., Sharma, A., Han, C., Merians, A., Burdea, G., Adamovich, S., Recce, M., Tremaine, M. and Poizner, H. (2002). Virtual-reality-based post-stroke hand rehabilitation. *In Proceedings of Medicine Meets Virtual Reality 2002 Conference*, IOS Press, Newport Beach CA, January 23-26 2020, 64-70.

Bohannon, R. W., Smith, M. B. (1987). Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther*, 67, 2, 206-7. 1538-6724

Bohannon, R. W. (1999). Motricity Index Scores are Valid Indicators of Paretic Upper Extremity Strength Following Stroke. *Journal of Physical Therapy Science*, 11, 59-61. 09155287

Broeren, J., Georgsson, M., Rydmark, M. and Stibrant Sunnerhagen, K. (2002). Virtual reality in stroke rehabilitation with the assistance of haptics and telemedicine. *In Proc. 4th Intl Conf. Disability, Virtual Reality & Assoc. Tech., Veszprém, Hungary. ICDVRAT/University of Reading,* UK; ISBN 07 049 11 43 4

Broeren, J., Rydmark, M. and Sunnerhagen, K. S. (2004). Virtual reality and haptics as a training device for movement rehabilitation after stroke: a single case-study. *Archives of Physical Medicine and Rehabilitation*, 85, 1247-1250. 0003-9993

Coote, S. and Stokes, E. K. (2005). Effect of robot-mediated therapy on upper extremity dysfunction post stroke – a single case study. *Physiotheraphy*, 91, 250-256. 0031-9406

Correa, A. G. D., De Assis, G. A., do Nascimento, M., Ficheman, I., and de Deus Lopes, R. (2007). GenVirtual: An augmented reality musical game for cognitive and motor rehabilitation. *In Proceedings of Virtual Rehabilitation Conference, IEEE*, 27-29 Sept. 2007; 1–6.

Dam, M., Tonin, P. Casson, S., Ermani, M., Pizzolato, G., Iaia, V. and Battistin, L. (1993). The effects of long-term rehabilitation therapy on poststroke hemiplegic patients. *Stroke*, 24, 1186-1191. 0039-2499

Deutsch, J. E., Merians, A. S., Adamovich, S., Poizner, H. and Burdea, G. C. (2002). Development and application of virtual reality technology to improve hand use and gait of individuals post-stroke. *Restorative Neurology and Neuroscience, 20,* 1-16. 0922-6028

Deutsch, J. E., Paserchia, C., Vecchione, C., Mirelman, A., Lewis, J. E., Boian, R. and Burdea, G. (2004). Improved Gait and Elevation Speed of Individuals Post-Stroke After Lower Extremity Training In Virtual Environments. *JNPT*, 28, 4, 185-186. 1557-0576

Doya, K. (2000). Complementary roles of basal ganglia and cerebellum in learning and motor control. *Curr Opinion Neurolbiol*, 10, 732-739. 0959-4388

Ekstrom, R. B., French, J. W., Harman, H. H. and Dermen, D. (1976). Kit of factor-referenced cognitive tests. Educational Testing Service, Princeton, NJ.

Eng K., Siekierka E., Pyk P., Chevrier E., Hauser Y., Cameirao M., Holper L., Hägni K., Zimmerli L., Duff A., Schuster C., Bassetti C., Verschure P. & Kiper D. Interactive visuo-moto therapy system for stroke rehabilitation. *Medical & Biological Engineering & Computing 2007*, September, 45, 9, 901-907

Fagg, A. H. and Arbib M. A. (1992). A model of primate visual-motor conditional learning. *Adaptive Behavior*, 1, 3-37. 1059-7123

Fasoli, S. E., Krebs, H. I. and Hogan, N. (2004). Robotic technology and stroke rehabilitation: translating research into practice. *Topics in stroke Rehabilitation*, 11, 11-19. 1074-9357

Florence, J. M. (1992). Intrarater reliability of manual muscle test (Medical Research Council scale) grades in Duchenne's muscular dystrophy. *Phys Ther,* 72, 115-122. 1538-6724

Fugl-Meyer, A.R., Jaasko, L., Leyman, I., Olsson S & Steglind S. (1975). The post-stroke hemiplegic patient: a method for evaluation of physical performance. *Scandanavian Journal of Rehabilitation*, 7, 13–31. 1650-1977

Fung, J., Malouin, F., McFadyen, B. J., Comeau, F., Lamontagne, A., Chapdelaine, S., Beaudoin, C., Laurendeau, D., Hughey, L. and Richards, C. L. (2004). Locomotor rehabilitation in a complex virtual environment. *EMBC 2004 Conference Proceedings 26th Annual International Conference*. 4859-4861

Fung, J., Richards, C. L., Malouin, F., McFadyen, B. J. and Lamontagne, A. (2006). A Treadmill and Motion Coupled Virtual Reality System for Gait Training Post Stroke. *CyberPsychology Behavior*. 9, 2, 157-162. 2152-2715

Gaggioli, A., Meneghini, A., Morganti, F., Alcaniz, M. & Riva, G. (2006). A strategy for computer-assisted mental practice in stroke rehabilitation. *Neurorehabilitation and Neural Repair*. 20, 4, 503-507. 1545-9683

Gatti, E., Massari, R., Saccelli, C., Lops, T., Gatti, R. and Riva, G. (2008). Why do you drink? Virtual reality a san experimental medium for the assessment of alcohol-dependent individuals. *Stud Health Technol Inform*, 132, 232-137. 0926-9630

Gentile, A. M. (1972). A working model of skill acquisition with application to teaching. *Quest*, 17, 3-23. 1011-226X

Gorini, A. and Riva, G. (2008a). Virtual reality in anxiety disorders: the past and the future. *Expert Review of Neurotherapeutics*, 8, 2, 215-233. 1473-7175

Gorini, A. and Riva, G. (2008b). The potential of Virtual Reality as anxiety management tool: a randomized controlled study in a sample of patients affected by Generalized Anxiety Disorder. *Trials*, 9, 25. 1745-6215

Hegarty, M., Richardson, A. E., Montello, D. R., Lovelace, K. and Subbiah, I. (2002). Development of a selfreport measure of environmental spatial ability. *Intelligence*, 30, 425-447. 0160-2896

Heller, A. (1987). Arm function after stroke: measurement and recovery over the first three months. *Journal of Neuroloy, Neurosurgery, and Psychiatry*, 50, 714-719. 0022-3050

Henderson, A., Korner-Bitensky, N., Levin M. (2007). Review Virtual reality in stroke rehabilitation: a systematic review of its effectiveness for upper limb motor recovery. *Top Stroke Rehabil*, 14, 2. 52-61. 17517575

Holden, M.K., Todorov, E., Callahan, J. & Bizzi E. (1999). Virtual environment training improves motor performance in two patients with stroke: case report. *Neurology Report*. 23, 57–67. ISSN 1085-049X

Holden, M.K., Dyar, T., Callahan, J., et al. (2001). Quantitative assessment of motor generalization in the real world following training in a virtual environment in patients with stroke. *Neurology Report,* 25,129–130.

Holden, M.K., Dyar, T. (2002). Virtual environment training: a new tool for rehabilitation. *Neurology Report*. 26, 62–71.

Holden, M., Dyar, T.A., Schwamm, L., et al. (2005). Virtual-environment based telerehabilitation in patients with stroke. *Presence: Teleoperat Virtual Environ.* 14(2), 214-233.

Holden, M. (2005). Virtual enviroments for motor rehabilitation: review. *Cyberpsychol Behav* 8, 3, 187-211, 10949313

Jadhav, C. G. and Krovi, V. (2004). A Low-cost framework for individualized interactive telerehabilitation. In *26th Annual International Conference in IEEE Engineering in Medicine and Biology Society (EMBS)*, San Francisco.

Jeffery, D. R. and Good, D. C. (1995). Rehabilitation of the stroke patient. *Curr. Opin. Neurol.*, 8, 62-68, 1473-6551

Johnston, M. V., Kirshblum, S. Zorowitz, R. and Shiflett, S. C. (1992). Prediction of outcomes following rehabilitation of stroke patients. *Neuro. Rehabil.*, 2, 4, 72-97. 1053-8135

Khan, M. A. & Franks, I. M. (2000). The effect of practice on component submovements is dependent on the availability of visual feedback. *J. Motor Behav.*, 32, 227-240. 0022-2895

Koenig, S.T., Crucian, G.P., Dalrymple-Alford, J.C., Dünser, A. (2009). Virtual reality rehabilitation of spatial abilities after brain damage. *Stud Health Technol Inform.*, 144, 105-107. 1959-2742

Kozhevnikoy, M. and Hegarty, M. (2001). A dissociation between object-manipulation spatial ability and spatial orientation ability. *Memory and Cognition*, 29, 745–756. 0090-502X

Krijn, M., Emmelkamp, P. M. G., Olafsson, R. P., and Biemond, R. (2004). Virtual reality exposure therapy of anxiety disorders: A review. *Clinical Psychology Review*, 24, (3), 259-281. 1524-5832

Lucca, L.F. (2009). Virtual Reality and motor rehabilitation of the upper limb stroke patients: a generation of progress? *J Rehabil Med*, 41, 1003-1006. 1650-1977

Mahurin, R. K., Debettignies, B. J. & Pirozzolo, F. J. (1991). Structured assessment of independent living skills: preliminary report of a performance measure of functional abilities in dementia. *Journal of Gerontology*. 46, 58–66, 0022-1422

Marusan, M., Kulistak, J. and Zara, J. (2006). Virtual Reality in neurorehabilitation: mental rotation. In *Proceedings of the Third Central European Multimedia and Virtual Reality Conference*. Veszprèm: Pannonian University Press. 77-83. 963 9495 89 1

Mathiowetz, V. (1985). Adult norms for nine hole peg test of manual dexterity. *Occup Ther J Res*. 5, 24-37. 0276-1599

Mirelman, A., Patritti, B. L., Bonato, P. and Deutsch J. E. (2007). Effects of Robot-Virtual Reality Compared with Robot Alone Training on Gait Kinetics of Individuals Post Stroke. *Virtual Rehabilitation*, 65-69, 978-1-4244-1204-4

Money, J., Alexander, D. and Walker, H. T. (1965). A standardized road-map test of direction sense. *Johns Hopkins Press*, Baltimore.

Morganti, F., Gaggioli, A., Strambi, L., Rusconi, M. L. and Riva, G. (2007). A virtual reality extended neuropsychological assessment for topographical disorientation: a feasibility study. *Journal of Neuroengineering and Rehabilitation*, 4, 26. 1743-0003

Newell, K. M. & Carlton, M. J. (1987). Augmented information and acquisitionof isometric tasks. *J. Motor Behav.*, 19, 4-12. 0022-2895

Park, J., Ku, J., Cho, S., Kim, D., Kim, J., Kim, I. Y. and Kim, S. I. Development and Clinical Test of Virtual Reality Rehabilitation Training System for stiff-knee gait of stroke patients. *Virtual Rehabilitation*, 81-81, 978-1-4244-1204-4

Penta, M., Tesio, L., Arnould, C., Zancan, A., Thonnard, J.L. (2001). The ABILHAND Questionnaire as a Measure of Manual Ability in Chronic Stroke Patients Rasch-Based Validation and Relationship to Upper Limb Impairment. *Stroke*. 32, 1627-1634, 0039-2499

Piron, L., Tonin, P., Piccione, F., Iaia, V. and Trivello, E. (2005). Virtual environment training therapy for arm motor rehabilitation. *Presence*, 14, 6, 732–740

Piron, L., Turolla, A., Agostini, M., Zucconi, Cortese, F., Zampolini, M., Zannini, M., Dam, M. and Tonin, P. (2009). Excercises for paretc upper limb after stroke: a combined virtual-reality and telemedicineapproach. *Journal of Rehabilitation Medicine*, 41, 12, 1016-1020, 1650-1977

Podzebenko, K., Egan, G. F. and Watson, J. D. G. (2005). Real and imaginary rotary motion processing: functional parcellation of the human parietal lobe revealed by fMRI. *Journal of Cognitive Neuroscience*, 17, 1, 24-36. 0898-929X

Probosz, K., Wcislo, R., Otfinoski, J. Slota, R., Kitowski, J., Pisula, M. and Sobczyk, A. (2009). A multimedia holistic rehabilitation method for patients after stroke. In *Annual Review of Cybertherapy and Telemedicine*, 7, 261-263. 1554-8716

Rahman, T., Sample, W., Seliktar, R., Scavina, M.T., Clark, A.L., Moran, K., Alexander, M.A. (2007). Design and testing of a functional arm orthosis in patients with neuromuscular diseases. *Neural Systems and Rehabilitation Engineering, IEEE*. 15, (2), 44 – 251. 1534-4320

Reinkensmeyer, D. J., Pang, C. T., Nessler, J. A. and Painter, C. C. (2002). Web based telerehabilitation for the upper extremity after stroke. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 10, 102-108. 1534-4320

Reinkensmeyer, D. J., Housman, S. J. (2007). "If I can't do it once, why do it a hundred times?": Connecting volition to movement success in a virtual environment motivates people to exercise the arm after stroke. *Virtual Rehabilitation*, 44-48. 978-1-4244-1204-4

Riva, G., Bacchetta, M., Cesa, G., Conti, S., Castelnuovo, G., Mantovani, F. and Molinari, M. (2006). Is severe obesity a form of addiction? Rationale, clinical approach, and controller clinical trial. *CyberPsychology and Behaviour*, 9, 4, 457-479. 10949313

Riva, G., Carelli, L., Gaggioli, A., Gorini, A., Vigna, C., Algeri, D., Repetto, C., Raspelli, S., Corsi, R., Faletti, G., Vezzadini; L. (2009). NeuroVR 1.5 in Practice: Actual Clinical

Applications of the Open Source VR System. *Annual Review of Cybertherapy and Telemedecine Volume 7, 57-60. ISSN: 1554-8716*

Rizzo, A., Pair, J., McNerney, P. J., Eastlund, E., Manson, B., Gratch, J., Hill, R. and Swartout, B. Development of a VR therapy application for Iraq war military personnel with PTSD. (2005). *Stud Health Technol Inform*, 111, 407-413. 0926-9630

Rose, F. F., Atree, E. A., Brooks, B. M., Johnson, D. A. (1998). Virtual environments in brain damage rehabilitation: a rationale from basic neuroscience. *Virtual environments in clinical Psychology and Neuroscience.* In Giuseppe Riva, Brenda K. Wiederhold, Enrico Molinari (Eds.), Ios Press: Amsterdam, Netherlands.

Rose F. D., Broocks B. M. & Rizzo A. A. (2005). Virtual reality in brain damage rehabilitation: review. *Cyberpsychol Behav*. 8, 3, 241-262, 10949313

Rummelhart, D. E., Hinton, G. E. and Williams, R. J. (1986). Learning internal representations by error propagation. In Parallel distributed processing: explorations in the microstructure of cognition. In Rummelhart D. E. and McClelland J. L. (Eds) Bradford Books/MIT Press, 1, 318-362. Cambridge, Massachusetts.

Salva, A. M., Wiederhold, B. K., Alban, A. J., Huges, C., Smith, E., Fidopiastis, C., and Wiederhold, M. D. (2009). In *Annual Review of Cybertherapy and Telemedicine*, 7, 1554-8716. 1554-8716

Schmidt, R. A. and Young, D. E. (1991). Methodology for motor learning: a paradigm for kinematic feedback. *J Motor Behav*, 23, 13-24. 0022-2895

Shepard, R. N. and Metzler, J. (1971). Mental rotation of three-dimensional objects. *Science*, 171, 701-703. 0036-8075

Standen, P. J. and Brown, D. J. (2005). Virtual Reality in the rehabilitation of people with intellectual disabilities: Review. *CyberPsychology & Behaviour Journal*, 8, 3, 155-159. 10949313

Sugarman, H., Tiran, J., Weisel-Eichler, A. and Dayan, E. (2006). Low-cost Telerehabilitation using force feedback joysticks. In Annual Review of Cybertherapy and Telemedicine, 4, 137-143. 1554-8716

Tangerman, P. T., Banaits, D. A. and Williams, A. K. (1990). Rehabilitation of chronic stroke patients: Changes in functional performance. *Arch. Phys. Med. Rehabil.*, 71, 876-880.

Todorov, E., Shadmehr, R. and Bizzi, E. (1997). Augmented feedback presented in a virtual environment accelerates learning of a difficult motor task. *J Motor Behav*, 29, 147-158. 0022-2895

Tomasino, B. and Rumiati, R. I. (2004). Effects of strategies on mental rotation and hemispheric lateralization: neurophysiological evidence. *Journal of Cognitive Neuroscience*, 16, 5, 878-887. 0898-929X

Trotti, C., Menegoni, F., Baudo, S., Bigoni, M., Galli, M. and Mauro, A. (2009). Virtual Reality for the Upper Limb Motor Training in Stroke: A Case Report. In *Annual Review of Cybertherapy and Telemedicine, 2009.* 7, 257-260. 1554-8716

Turolla, A., Tonin, P., Zucconi, C., Agostini, M., Piccione, F., Dam, M. and Piron, L. (2007). Reinforcement Feedback in Virtual Environment vs Conventional Physical Therapy for arm motor deficit after Stroke. Virtual Rehbilitation, 49-52. 978-1-4244-1204-4

Van de Winckel, A. (2006). Can quality of movement be measured? Rasch analysis and inter-rater reliability of the Motor Evaluation Scale for Upper Extremity in Stroke Patients (MESUPES). *Clin Rehabil*, 20, 871-884. 0269-2155

Weiss Tamar, P., Rand, D., Katz, N., Kizony, R. (2004). Video capture virtul reality as a fleaxible and effective rehabilitation tool. *Journal of Neuroengineering and Rehabilitation*, 1, 12. 1743-0003

Wilson, B. A., Alderman, N., Burgess, P. W., Emslie, H. and Evans, J. J. (1996). Behavioural Assessment of the Dysexecutive Syndrome (BADS). *Thames Valley Test Company*, Bury St. Edmunds.

Wilson, P.H., Thomas, P.R., Shum, D., Duckworth, J., Gugliemetti, M., Rudolph, H., Mumford, N., and Eldridge, R. (2007). A virtual tabletop workspace for the assessment of upper limb function in Traumatic Brain Injury (TBI). *Proceedings of the Annual Conference on Virtual Rehabilitation.* Venice, Italy, September 27-29, 2007

Winstein, C. J. (1991). Knowledge of results and motor learning implication for physical therapy. *Phys Ther.*, 71, 140-149. 0190-6011

Winstein, C. J., Pohl, P. S., Cardinale, C., Green, A., Scholtz, L. and Waters, C. S. (1996). Learning a partial-weight-bearing skill: effectiveness of two forms of feedback. *Phys Ther*, 76, 985-993. 1538-6724

Woldag, H. & Hummelsheim, H. (2002). Evidence-based physiotherapeutic concepts for improving arm and hand function in stroke patients. *J. Neurol.*, 249, 518-528, 0340-5354

Young, D. E. & Schmidt, R. A. (1992). Augmented kinematic feedback for motor learning. *J. Motor Behav.*, 24, 261-273, 0022-2895

Zacks, J., Rypma, B., Gabrieli, J. D. E., Tversky, B. and Glover, G. H. (1999). Imagined transformations of bodies: an fRMI investigation. *Neuropsychologia*, 37, 9, 1029-1040. 0028-3932