Retraining of fine movement of paretic hand through VR gaming, presence and musical rhythmical stimuli, based on cognitive feedback

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Abstract

Physical Medicine Rehabilitation regards the enhancement of experience-dependent neuroplasticity, the influence of motor learning and the augmentation of the functional muscles' output. Nowadays, the extensive employment of Augmented/Virtual Reality (AR/VR) Technologies has greatly enhanced the rehabilitation process by providing less or non-invasive methods. The latter, consisting of greater motivation and a multi-sensory environment for training, enables a comprehensive, easy-to-follow and, consequently, more effective, rehabilitation process.

To the best of our knowledge, in the field of patient rehabilitation and especially at home there are no VR applications, which combine VR environments and the sense of presence with music and neurofeedback techniques. Furthermore, the majority of current platforms of rehabilitation at home lack a proper and efficient feedback, which would allow for better patient guidance in executing the exercises.

Our aim is to provide an alternative and efficient way to contribute to the stroke rehabilitation field by improving the fine movements of the paretic hand in stroke patients. Combining novel Presence Positive Technologies for Well-being, music and techniques of Neurologic Music Therapy, we have developed a VR game using an HMD Oculus Rift for securing the sense of presence and a Leap Motion device to track fingers' and hands' motion. The idea of the game is authentic and doesn't concern an existing design-for-fun game. Additionally, a team of doctors of KAT hospital in Athens has advised us in order to determine the adequate movements that will constitute the proper exercises.

Our expected outcome, contributing to the current game-based Rehabilitation Field, regards to a new integrated platform offering a more motivating and efficient way for patients being in a chronic phase of a stroke, to continue their exercises' program at home. Our intention is to provide an adequate feedback, a proper guidance, a better motivation and an additional aid for stabilizing the movement based on musical stimuli. Moreover, as we expect from the patient to perceive the musical rhythm and fit his/her movement into it, we also deal with the cognitive processes of him/her, that most of the times are not taken into account.

Attestation

I understand the nature of plagiarism, and I am aware of the University's policy on this.

I certify that this dissertation reports original work by me during my University project except for the following

Signature **Date**

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1 Introduction

Stroke is one of the major worldwide causes of human disability leading to sensory, cognitive and motor impairment as well as to a difficulty in social involvement or in communication activities, restricting social participation. These directly affect the quality of life, making the creation of alternative, faster and more effective ways of rehabilitation mandatory. The most widely recognized and thoroughly studied impairment caused by stroke is the motor one, which limits the motion and the function of the body, especially in activities of daily living, which are necessary for self-dependence. However, there are other common impairments such as those of speech, language and cognition and rarely of swallowing and sensation. The long-term effect of a stroke incident is determined firstly by the site and the size of the initial stroke lesion and secondly by the extent of subsequent recovery [1].

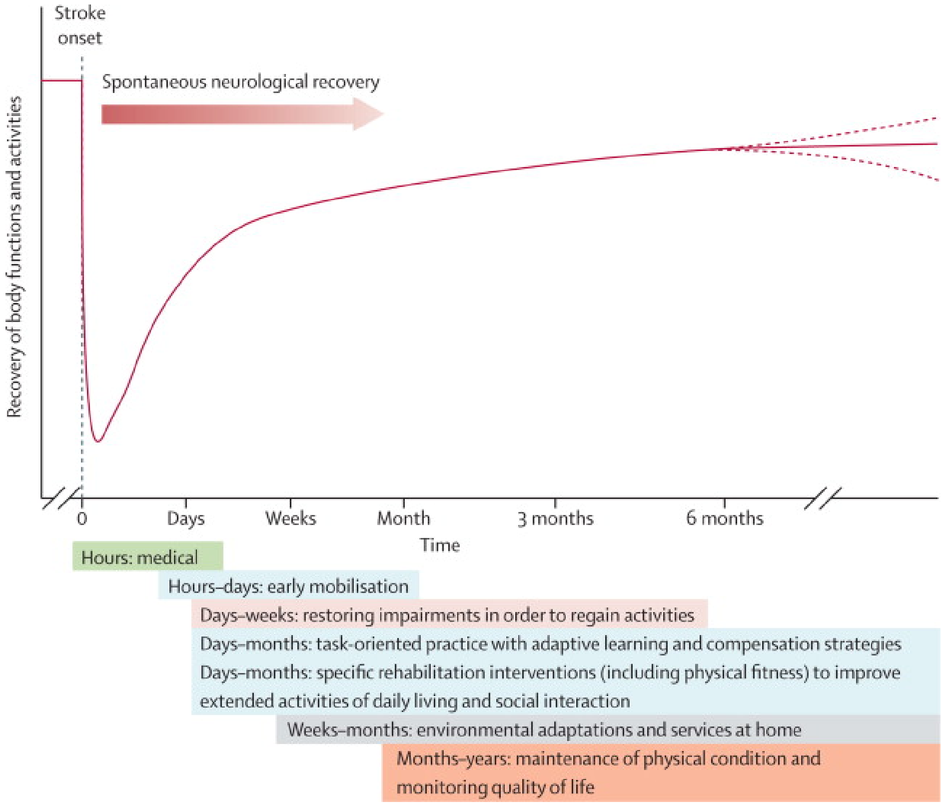

Figure 1-1. Hypothetical pattern of recovery after stroke with timing of intervention stretegies

Colour coding: green = pathology, blue = activities (limitations), pink = body function and structure (impairments), orange = participation (possible restrictions) [1]

Stroke recovery constitutes a complex, challenging problem of critical importance, demanding new approaches that will provide more efficient rehabilitation programs. The main purpose of rehabilitation is to enhance experience-dependent neuroplasticity, influence motor learning [3] and augment the functional muscles' output. This reveals that recovery concerns a combination of instinctive and learning-dependent processes, including

- *restitution* : restoration of damaged neural tissues,
- *substitution* : reorganization of partly-spared neural pathways to relearn lost functions, and
- *compensation* : improvement of the disparity between the impaired skills of a patient and the demands of their environment [2].

This cyclical process involves assessment for identification of patient's need, setting of realistic and feasible goals, intervention to serve the goals and reassessment to evaluate the efficiency of the selected program.

The major issue, though, can be summarized into defining the principles of stroke rehabilitation. Substantial evidence introduces multidisciplinary team care as the basis of delivery of stroke rehabilitation [4] consisting of a medical, nursing, therapy and social work staff. Such a team can provide a framework for a multidisciplinary assessment, identification and understanding of problems, establishment of short, as well as, long term rehabilitation goals and decision-making. Positive rehabilitation outcome, however, seems to be associated with patient's and family's motivation and engagement. Therefore, *setting goals* that can boost the specific rehabilitation needs of an individual, might improve this outcome. Goals should be evaluated according to specificity, aim and time so that they can be efficient and effective, given that recovery is a dynamic process that cannot be encapsulated at one time point.

Moreover, another principle is *task-specific training*, which constitutes a rehabilitation approach where specific functional tasks are practiced repeatedly and consistently and it is a well-accepted principle in motor learning. This approach suggests that training should target the goals that are relevant for the needs of patients [1].

The last principle concerns the *intensity of therapy* and, although there are no clear up-to-date guidelines for the optimal levels of practice, the proposition that increased intensive training is helpful, is widely accepted [5]. Moreover, although recovery can continue for months or years after stroke, there is a widespread agreement that rehabilitation should begin as soon as possible after stroke [6].

Although these principles have been identified to be able to ensure the fulfilment of patient's requirements to the greatest possible extent, the need of therapy-based rehabilitation at home remains a challenging and difficult problem to cope with. The development of a proper platform that can support such a need could result in an earlier discharge from the hospital as well as in a higher potential to regain independence in daily activities. As the incident of a stroke has an intense effect on both patients and relatives and is associated with a vast economic burden, the contribution of such a platform will expand also on satisfaction of other issues, like functional or financial. For example, the capacity of rehabilitation centres is not relevant to the number of stroke patients, which results in limited rehabilitation sessions and exercises by the therapists. Moreover, the mean rehabilitation cost is not always affordable by the patients. In order to achieve better performance and control, stroke patients are encouraged to perform most of the rehabilitation exercises at home. The repetitive nature of conventional exercises and the lack of supervision though imply a patients' deviation to the therapists' instruction. So, how we can ensure the finest quality and the efficiency of this kind of rehabilitation still remains a question.

Taking into account all the aforementioned, several novel therapies have been developed and tested, including Virtual Reality (VR), Motor Imagery (MI) and novel robotic techniques. VR technology, with the multi-sensory training that it can support, has the potential to meet the standards of the new rehabilitation methods' need and provide an enhanced environment in which people with stroke can improve their abilities in order to facilitate their lives long-term. Taking advantage of the opportunity that VR offers, to bring the complexity of the physical world into a controlled environment [7], there is a great amount of studies that have applied it in different types of rehabilitation. VR technology, as an interactive computer gaming technology, works on the principle of providing the patients with an interactive user interface and implementing different task-oriented scenarios [8]. Typical user interfaces consist of a tracking device, e.g. camera, and a graphical environment to reproduce the perceived movement. Recently, the employment of VR Head-Mounted Displays has enhanced the sense of "presence" and, thus, the familiarity to the game resulting into more efficient rehabilitation systems. Presence and immersion are the key concepts related to VR. Immersion refers to the extent to which the user perceives the difference between the virtual environment and the real world and is related to the design of the software and hardware [11]. Presence, on the other side, is the subjective experience of the user and is contingent on the features of the VR system, the virtual task as well as the characteristics of the user.

1.1 State-of-the-art

Taking advantage of the opportunity that VR offers, to bring the complexity of the physical world into a controlled environment [7], there is a great amount of studies that have applied VR in different types of rehabilitation. The majority of the research concerns motor impairment and especially of the upper extremity, which is experienced by more than half of stroke survivors [134]. Greanleaf and Tovar were the first who tested VR in the rehabilitation field concerning human motion and motor control [135]. Until now there are more than 40 studies involving more than 1000 patients referring to *upper extremity impairment* [136][137][3][15][138][139], *lower extremity impairment* [140][143][142] and *gait and balance impairment* [141][144] [145].

The main purpose of a rehabilitation program is to enhance experience-dependent neuroplasticity, influence motor learning [3] and augment the functional muscles' output. A virtual environment (VE) - based system can satisfy the former purpose combining intensity control, interactivity of practice, motivation and task-oriented training [15]. Moreover, the possibility of mirroring the non-affected limb, which allows the application of Mirror Therapy (MT), complements the above. MT is based on the illusion that one action is performed normally, no matter what the condition is [146]. This beneficial effect on motor function of triggering action observation and action execution networks has already been positively assessed by some studies [146] [147].

Taking into account that maximal plasticity can be acquired during the first few months after the stroke, the optimal efficacy of rehabilitation should be expected during this period. Paticipants in the studies were typically in the chronic phase post stroke (usually greater than 3 months)[13] or even in the sub-acute phase [14][15]. We are referring to the upper extremity training and one of the most typical recent example concerning the sub-acute phsase is the one of Brunner et al. with their platform VIRTUES and the YouGrabber system as hand tracking device with which they noticed an enhancement of movement for the VR group. Moreover, the study of Turolla et al [149], which constitutes the largest study in this field so far, with their VRRS platform and a 3D motion-tracking system, (Polhemus Liberty) examined 376 patients of all ages, mainly of sub-acute and chronic phase, concluding that the observed differences were significantly higher in the VR group. A more recent and advanced VR platform is the one of the company MindMaze, called MindMotion, with a more accurate 3D motion tracking system, which was just brought into the market and it looks like really promising [169].

However, there are a few exceptions, like Cameirão [148], with its Rehabilitation Gaming System (RGS), who studied patients in the early acute phase (less than 30 days) arguing that the amount of plastic changes that happen during this period can possibly maximize the recovery. Albeit controversial concerning the intensity of the exercise during this period [150], Cameirao showed that the implementation of a VR rehabilitation system in such patients can lead to a maintained progress which follows a defined logarithmic pattern compared with a control group of a controversial kind of therapy, which managed to be stabilized almost after five weeks. We need to mention that all the aforementioned studies, as well as the majority of the studies concerning the integration of VR platforms in rehabilitation, combine the VR training with the conventional therapy. The aim is to complement and, if possible, to accelerate the rehabilitation process and not to replace the conventional methods. Studies that have tried to use only VR training versus the conventional one, have concluded that they didn't receive the expected positive feedback from the patients and the improvement between the experimental groups were almost the same [151]. Undoubtedly, a VR environment contributes to a more efficient way to provide feedback [3], which, on its own, is really promising.

Used tracking devices may vary according to the needs of the examined scenarios and the abilities of each of the patients. Up-to-date technology permits the choice among several of such devices that will allow the satisfaction of patients' needs with the use of existing design-for-fun games or design-for-rehabilitation ones. These devices concern Nintendo, Sony and Microsoft products, such as Wii remotes [152], Sony Eye Toy [153], Xbox Kinect [155] and Microsoft Kinect [154]. There has been no substantiated proposal yet of which one is the most efficient. Moreover, usual is the use of other kind of tracking devices such as gloves or 3D motion-tracking systems. Greanleaf and Tovar [135], who were the first to integrate the VR technology into the rehabilitation field, used VPL data gloves and since then, the use of data gloves was the most usual one[15] [148], although they serve mostly the tracking of finger movements. For the arm movement a vision based tracking system [148] or a 3D motion tracking system as Polhemus Liberty [149] or Polhemus 3SpaceFasTrack [138] was used. Recently, the use of Leap Motion was noticed by Vourvopoulos et al, [156] who combined the technology of VR with this of Motor Imagery for patients with stroke.

As mentioned before, a stroke can also cause cognitive impairments, such as memory and attention deficits, spatial perception difficulty and several kinds of problems in executive function, problem – solving and awareness. Up-to-date literature has failed to provide sufficient information, concerning possible effect sizes on cognitive processes [12][157]. This is a result of inadequate trials including assessments of cognition as well as a possible weakened attention to this topic compared to motor impairments. Grealy et al [158] used first VR technology, combined with exercise, for improving cognitive function in patients with brain injury with efficient outcomes. Mirelman et al. [140], however, were the first who tried to use a VR system for retraining and improving both motor and cognitive functions in patients with Parkinson's disease who appeared, at the end, to be positively affected by this kind of intervention.

Another way, but not so usually used, to complement and even complete the rehabilitation process is the Music Therapy (MT). MT extends from music listening and musical instrument playing to Neurologic Music Therapy (NMT), which constitutes a new neuroscience-based model of music perception and production and examines the possible influence of music in brain structure and function as well as behavioral changes [170]. Listening to music activates an interconnected network of subcortical and cortical brain regions, including amygdala, hippocampus and hypothalamus, which help patient to train memory and attention functions and cope with stress. Music production is not so commonly used for rehabilitation purposes although music production activates regions like cerebellum and basal ganglia that are responsible for movement and accurate timing [173]. However, therapists have begun to trust some of the new techniques supported by the NMT, specialized mainly for arm rehabilitation: the Patterned Sensory Enhancement (PSE) and Therapeutic Instrumental Playing (TIMP).

These techniques, based on rhythmic entrainment, convert the patient's movement to a cyclical repetitive pattern guided by an auditory rhythm [172]. A research group published really recently a study protocol with which they want to examine if TIMP technique would be actually useful and efficient for stroke patients, being in the chronic phase of the stroke, who continue their rehabilitation program at home [171]. A positive result would be able to trigger the rehabilitation community and constitute music an integral part of the rehabilitation process. The heretofore bibliography hasn't revealed yet any study combining VR and the aforementioned use of music.

Research activity, based on the up-to-date bibliography, reveals the need for a complete rehabilitation program referring to behavior, cognitive and motor impairments of patients with Cerebral Vascular Accident (CVA), in order to improve the overall quality of life both for patients and their families. This intervention will rely on VR technology consisting of well-designed gaming and evaluation trials, Brain Computer Interfaces (BCIs) and neurofeedback, introducing a novel augmented human performance platform based on different kinds of feedback like musical, specific rhythmic-based sensory feedback. In order to take advantage of the benefits of neuroplasticity, this system will be able to be used as soon as the condition of the patient allows it.

To the best of our knowledge, no such VR platform for rehabilitation, featuring Presence ("feeling of being there"), Augmented human performance and interaction in the connected and shared Virtual Environment combined with the benefits of music, exist up to date in the field of stroke patient rehabilitation.

2 The Stroke

2.1 Neurological background

Stroke, also known as CVA as we mention before, is the sudden development of injury to the brain caused by the disruption of blood flow. The two main causes of this disruption are ischemia and haemorrhage. The unifying pathophysiology of thrombotic, embolic, and lacunar stroke is cerebral ischemia from compromise of cerebral blood flow. The location and temporal development of cerebral injury varies with the etiology. Thus, ischemic strokes are a result of a cerebral vessel blockage due to thrombosis, which is the formation of a blood clot, or embolism. The latter is the migration of a blood clot through vessel. Haemorrhage is the bleeding inside the brain or in a surrounding area [9]. Unlike ischemic strokes, however, haemorrhagic does not obey the anatomic distribution of a vessel but dissects through tissue planes. Such damage can be significant, resulting in increased intracranial pressure, disruption of multiple neural tracts, and other serious neurological problems. Both causes result in oxygen deprivation to the surrounding cells and in death or injury of brain tissue, leading to short-term and long-term effects. The site of the lesion, as well as the size and cause, determine the quality and quantity of symptoms the patient will experience. In general, ischemic strokes constitute approximately the 80% of all strokes, while haemorrhagic ones account for the remaining 20%, resulting though in a higher mortality rate. It is important, that haemorrhagic strokes have initially worst prognosis, with a 80% mortality, than ischemic strokes, but they have better functional outcome. Concerning the patient with haemorrhagic stroke, after the most severe period of acute phase, all parameters of limitation shows a rapid and most correct recovery than those of ischemic strokes. So, those who survive haemorrhagic stroke often experience rapid neurological recovery during the first 2 or 3 months [122]. Additionally, the haemorrhagic patients usually are younger than those with ischaemia, so the therapeutic background is different.

2.2 Stroke consequences

Stroke, is a severe medical condition with serious consequences, as a result of central nervous system injury by which physical, cognitive, psychological functioning and social and occupational participation becomes impaired. When a focal region with all neural systems that exist within this area are damaged by vascular accident, specific impairments appear. The primary motor area (M1 cortex) is located along the cortex of the precentral gyrus. Axons from these cortical cells descend via the internal capsule to the pyramidal tract in the brain stem, where they cross and descend in the corticospinal tract of the spinal cord, giving neural control in all movements of the limbs and trunk. All coordinated and tiny movements of the body are transferred from the brain cortex via pyramidic system to the whole body.

Occasionally, a stroke can cause different symptoms. The most usual one is hemiparesis or hemiplegia, which ranges from weakness to full paralysis of one side of the body, which is the opposite one from the damaged brain area. Depending on the brain's side of the lesion, several cognitive impairments can occur. Specifically, a stroke in the left hemisphere can result in right hemiparesis, aphasia or apraxia [10]. The term aphasia refers to a language and communication disorder, concerning comprehension, expression, perception and formulation of language's elements, while apraxia constitutes a motor planning or organization impairment. Stroke in the right hemisphere can cause left hemiparesis, visual field deficits, spatial neglect, a lack of insight and judgment abilities, or impulsive behavior [10].

Although patients can recover some physical or cognitive functionality within the first few weeks after stroke, some of them may make improvements on functional tasks many months after having a stroke [12]. However, as the permanent physical impairment is most commonly reported, attention is given on encouraging functional recovery, so that it would give the opportunity to the patients to be able to participate in many of the activities of daily living (ADL) independently. Encouragement and inspiration are the reasons why the new aforementioned techniques have been developed in order to complement the existed conventional therapies and the, greatly useful, family support so that patients can improve or maintain their quality of life and health.

Hemiparesis usually affects the upper extremities more severely than the lower ones [10], making ADL capabilities even more difficult and limited. Based probably on that, the majority of the newly developed platforms for rehabilitation concerns the recovery of upper extremity and the most of the times, without combining it even partially, with cognitive one. Although neural plasticity allows a spontaneous gain in the time period directly after stroke, a complete rehabilitation program is important in order to fully take advantage of the brain's ability to recover. However, the optimal period for a patient to receive such a program is still controversial, as a lot of studies [13][14][15] associate the rehabilitation's result with the plasticity phase, which is absolutely connected with the total period since the onset of the stroke, referred as stroke phase.

2.2.1 Motor control and strength

In hemiplegia, we initially meet weakness and poor control of voluntary movement, followed by reduced resting muscle tone. As voluntary movement returns, non-functional mass flexion and extension of the limbs are first noted (**Table 1-1**). Synergy patterns, or mass contraction of multiple muscle groups, are presented. Afterwards, movement patterns can be independent of synergy.

Table 1-1: Synergy Patterns in Motor Recovery

	Upper Limb	***Lower Limb***
Flexor synergy	Shoulder retraction	Hip flexion
	Shoulder abduction	Hip abduction
	Shoulder external rotation	Hip external rotation
	Elbow flexion	Knee flexion
	Forearm supination	Ankle eversion
	Wrist flexion	Dorsiflexion
	Finger flexion	Toe extension
Extensor synergy	Shoulder protraction	Hip extension
	Shoulder adduction	Hip adduction
	Elbow extension	Knee extension
	Forearm pronation	Ankle inversion
	Wrist extension	Plantar flexion
	Finger flexion	Toe flexion

2.2.2 Motor Coordination and Balance

Trunk control and stability, coordination of movement patterns, and balance involve complex extrapyramidal systems that are frequently disrupted by stroke. Extrapyramidal disorders can be a major impediment to functional recovery but are often amenable to therapeutic exercises. Anatomically, premotor area is important in motor planning. Multiple fibre tracts from this region descend via the anterior limb of the internal capsule to the basal ganglia and the cerebellum, with input from the vestibular, visual, and somatosensory systems. Lesion of these tracks, to either the efferent or the afferent systems (or both) can cause poor static and dynamic balance as well as movement disorders such as ataxia and others.

2.2.3 Spasticity

Spasticity is a velocity-dependent increase in resistance to muscle stretch that is developed as a consequence of an upper motor neuron injury within the central nervous system, as happened in stroke [123]. When severe, spasticity can cause reduced flexibility, posture, and functional mobility, as well as joint pain, contracture, and difficulty with positioning for comfort and hygiene, and other daily activities of self-independence. Spasticity evolves shortly after a completed stroke and is initially manifested as an increased response to tendon reflexes and a slight catch with passive ranging. Later, ranging can become difficult, and the patient might show inappropriate positioning in flexion or extension. As voluntary motor activity returns, a reduction in tone and reflex response is often noted, but if recovery is incomplete, spasticity usually remains [122]. Spasticity obviously is a barrier to motor training and education of new motor pattern, because is a limiting factor for movement coordination and timing.

2.2.4 Sensation

Loss of sensation after stroke can have a significant effect on joint, skin and overall protection, balance, coordination, and motor control. Although lesion to the sensory pathways typically causes hypoesthesia or reduced sensation, patients with lesions in the thalamus or spinothalamic tract occasionally experience severe pain that can interfere with functional recovery and rehabilitative care. Sensory impairment is rare in stroke patients, except of kinesthetic perception disturbances due either to loss of deep sensation or cognitive deficit.

2.2.5 Language and Communication

Aphasia is an impairment of language. Typical lesions that cause aphasia affect comprehension and the use of symbolic material for communication and meaning. So, aphasia is substantially an impairment of communication. Testing of language should include an examination of oral expression, verbal comprehension, naming, reading, writing, and repeating. Although the anatomical classification of aphasia (kinetic (Broca), sensory (Wernicke), global etc) is useful for functionally describing communication problems after stroke and for determining prognosis, it is not very useful for guiding therapy. A trend now is to describe aphasia as a psycholinguistic approach [124].

Although language is considered as a function of the left or dominant hemisphere, some elements of communication such as prosody have non-dominant hemisphere control. Prosody is concerned with those elements of speech that are not individual phonetic segments (vowels and consonants) but that are properties of syllables and larger units of speech. These contribute to linguistic functions such as intonation, tone, stress, and rhythm. Thus, prosody is the rhythmic pattern and vocal intonation of speech that add emphasis and emotional content to language. Some clinical and pathological evidence exists mentioning that prosody might have similar anatomical topography as the verbal language in the non-dominant hemisphere [125].

2.2.6 Apraxia

Apraxia is a motor disorder in which the patient faces a difficulty with the motor planning in order to perform tasks or movements when asked, provided that the request or command is understood and he/she is willing to perform the task. The nature of the brain damage determines the severity, and the absence of sensory loss or paralysis helps to explain the level of difficulty. Patients with apraxia often have difficulty performing simple functional activities such as using a spoon or a comb, or they perform them in a clumsy manner. Apraxia is often difficult to be tested and assessed in the presence of a language deficit because the examiner must be assured that the patient understands the command. Apraxia is most commonly seen in left hemisphere strokes and affects the left non-hemiplegic limb. Apraxia attributes in a disconnection of the right cortical motor association area from the left hemisphere as a result of an injury of the anterior callosal fibers. So, the right brain cannot know what the left brain wants to do [122].

2.2.7 Neglect syndrome

Hemispatial neglect is defined as a failure to report, respond, or orient to novel or meaningful stimuli presented to the side opposite a brain lesion [126]. It is important to exclude visual, somatosensory, or motor impairments that would explain the lack of response before attributing it to neglect. Hemispatial neglect significantly contributes to disability after stroke because it has a negative impact on sitting balance, visual perception, mobility and safety awareness, skin and joint protection, and fall risk. Patients with neglect have difficulty completing self-care activities on the affected side, failing, for example, to eat food items in the neglected visual space [127].

2.2.8 Dysphagia

Dysphagia is common after stroke, occurring in 30% to 65% of patients with unilateral or bilateral hemispheric and brain stem infarctions. Risk for aspiration pneumonia is strongly associated with a delayed initiation of pharyngeal swallow, which must be accordingly evaluated.

2.3 Stages of stroke

Understanding the role of brain plasticity after the stroke is the key for developing rehabilitation strategies. During the first weeks and sometimes months following a stroke, a patient's ability, like the oral one, mental clarity and physical movements may improve. It depends on the person, though, if these improvements can continue to increase several months, or even years, after the stroke. However, while recovering, support and encouragement from friends and family, as well as the patient's own attitude, are vital for making substantial progress.

Recovery following a stroke starts as the brain responds to what's happened. The brain's function will be adjusted to the new information, accounting for the death or reduction of the affected area. In general [17],

- 10% of stroke survivors recover almost completely

- 25% recover with minor impairments
- 40% experience moderate to severe impairments requiring special care
- 10% require care in a nursing home or other long-term care facility
- 15% die shortly after the stroke

Thus, stroke is divided in three phases according to the onset of the stroke, the possible impairments and the needs of the patients, based on which the appropriate recovery program is implemented.

2.3.1 Acute stage (1-10 days)

Acute phase refers to the first 10 days since the onset of the stroke. It is a pure clinical process where the patient usually is not in control of the situation. The goal of the acute management of stroke patients is to stabilize them and to complete initial evaluation and assessment. Initial medical care for a patient with acute stroke requires careful and frequent neurologic monitoring to prevent and manage medical complications that compromise cerebral tissue perfusion.

Although working with patients during the acute phase could be considered a risk, the intention is to take full advantage of neuroplasticity, which is maximized the very first days after stroke. Daprarti [18] also mentioned that attempts to apply different neurorehabilitation methods could be more effective during this period. Moreover, FMRI studies have revealed an over-activation of both motor and non-motor cortical areas in either hemisphere, with displacement of the maximum activation in the primary motor cortex [19]. This acute phase bilateral hyperactivation lessens with time, with repeated performance of specific tasks.

However, the intervention during the first week post stroke might be a pitfall as many patients might be excluded. During this period, they deal with body and spatial perception deficits, strong cognitive impairments and poor motor performance. Therefore, there is a need for attempting to bridge this period and consequently our proposal consists of a VR-based mental practice, consisting of Motor Imagery (MI) and Visual Imagery (VI), as well as neurofeedback, boosted by specific musical rhythms. For this kind of training to be feasible it is necessary that the brain permits any kind of intervention and that the patient is ready to accept it.

2.3.2 Subacute stage (10-30 days up to 3 months)

After the stabilization of the general medical condition and the elimination of the risk for patient's life, a rehabilitation program needs to be started in order to restore stroke consequences. The re-education programs for cognitive deficits will have to be implemented in the same way as those for motor control training. Rehabilitation program starts with simple action, guiding the patient, when there are no cognitive deficits, in the action planning as well as the imaginary of motor activities. This will prepare patients to accept the re-training programs more easily and efficiently, at the next stage. The aim is to establish a new frame of action, in order to take advantage of the potentials offered by neurorehabilitation procedures. The main purpose is for the patient to start having control of each limb separately as well as start obtaining cognitive awareness.

2.3.3 Chronic of Rehabilitation (re-education) stage (3-6 months up to 2 years)

Stroke is fundamentally a chronic condition, in the sense that enough time is needed to complete the rehabilitation process and that its consequences evolve over the years. So, the attempt is to span the entire course of rehabilitation, from the early actions taken in the acute care hospital through reintegration into the community. The end of formal and more intensive rehabilitation (commonly by 3–4 months after stroke) of course should not mean the end of the restorative process. In many respects, stroke has been managed medically as a temporary or transient condition instead of a chronic condition that warrants monitoring after the acute event. The chronic stage of stroke begins normally from the first month after the episode and extends up to 2 years. It is the period of re-education. In this stage, all specialized techniques and methods of functional learning, aiming at facilitating the patient's functionality, are applied, and the greatest potential for improvement is presented. The main goal at this stage is the social and occupational reintegration and participation. Beyond this time, improvement refers to daily adjustments and accommodations to the remaining motor deficits and dysfunction.

Currently, unmet needs persist in many domains, including social reintegration, health-related quality of life, maintenance of activity, and self-efficacy (ie, belief in one's capability to carry out a behaviour). For instance, apathy is manifested in >50% of survivors at 1 year after stroke [128], fatigue is a common and debilitating symptom in chronic stroke [129], daily physical activity of community-living stroke survivors is low [130] and depressive symptomology is high [131]. By 4 years after onset, >30% of stroke survivors report persistent participation restrictions (e.g., difficulty with autonomy, engagement, or fulfilling societal roles) [132].

This is the fundamental reason for purposeful rehabilitation programme planning, through the whole course, from initial time till finally the social reintegration. Rehabilitation procedures are the primary mechanism by which functional recovery and the achievement of independence are promoted. The array of rehabilitation services delivered to stroke patients generally vary in many ways, as: a) the type of care settings used, b) in the duration, intensity, and type of interventions delivered, and c) in the degree of involvement of specific medical, nursing, and other rehabilitation specialists (rehabilitation team). The nature and organization of rehabilitation stroke services have changed considerably over time in response to various forces, including the increasing integration of hospital and outpatient care delivery systems, the organization of medical and other specialty rehabilitation groups [133].

2.4 Rehabilitation in stroke syndrome

Rehabilitation care for stroke patients is a compelling and complicated procedure. Stroke is a common syndrome, and its rehabilitation effort consists a great challenge for all members of the typical rehabilitation team. The fact that even two strokes are not alike and no patients react similarly to their situations and to any therapeutic procedure applied means that caring and treating for patients with stroke is also a distinct experience requiring individual attention. Most patients who experience stroke can and do have improvement in functional ability as well as, partly, in their self-dependence. The amount, rate, timing, pattern, type, and ultimate functional outcome of the improvements differ across patients and across situations. Therefore, the approach required for appropriate assessment and treatment of stroke patients demands specialized knowledge, skills, and creativity.

The past 20 years a transformation in the therapeutic approach applied to the stroke rehabilitation has been observed, spurred by a growing literature on motor recovery after focal brain injury [20]. It is now evident, both clinically and scientifically, that improvement in motor control after stroke is *training dependent,* responding best to repetitive practice mixed with continuous modification of the program to keep training tasks challenging and motivative for the patient [21]. When the therapeutic approach is focused on sensorimotor retraining in the hemiplegic upper or lower limb, it is called *task-oriented therapy*. Newer research is now leading beyond just therapeutic exercise, adding novel interventions such as pharmacology, new modalities, virtual reality environment training and robotics, as a potential enhancement of the results of motor retraining, preparing patients for better final functional outcome.

The emergence of training-dependent recovery and task oriented therapy has pushed rehabilitation team, and every scientist, whose interest is in this field, to carefully assess the balance between the restoration of neurologic control and focus on functional independence with compensatory techniques, either in in-patient rehabilitation or in an out-patient, as an effort to gain more independence in daily living. This is particularly challenging in the acute inpatient rehabilitation setting, where the desire to facilitate neurologic recovery is most desirable and most obvious but the need to discharge the patient home safely, functionally and participatory, is most real and imminent. Fortunately, the interdisciplinary rehabilitation team tradition is well suited to addressing these modern challenges.

Although therapeutical interventions such as exercise and sensorimotor retraining comprise the most prominent components of the rehabilitation process, there are many other aspects of the program that are equally important. Many rehabilitation activities, exercises and functional programs, extend beyond the specific therapy treatment sessions. For example, integrating motor training of functional activities, learned in formal therapy, into regular self-care activities for independence, under the supervision of inpatient nursing staff or other people of patient close environment, or later in the home environment, can significantly reinforce newly gained skills. Recreational programs, like gaming and music or both together, often serve as major therapeutic interventions, taking advantage of the fine motor task that offered by the game playing and the recreation offered by the desirable music and game. These programs, dealing with psychological and social issues, can often be a more complicated clinical activity than the routine motor control enhancement strategies through the common motor training exercise programs. Interactions among programs and patients can provide both emotional support and practical suggestions regarding functional skill performance. Most critically, the amount and nature of the interactions between patients and professionals of rehabilitation team (programs) can be highly motivating and instructive for patients and their families. It is great for the patient that a “therapist” is occupied excessively for him, and is focused to his own problem in order to find for him the best solution. A positive and encouraging rehabilitation environment typically provides the opportunity for these “less formal” therapeutic interactions.

The major underlying purpose and fundamental target of all rehabilitation interventions is to maximize quality of life for patients with stroke and not simply to improve motor control, functional independence, or community placement. *The goal of enhancing quality of life* is paramount and affects both the choices of specific interventions and the manner in which clinical and theurapeutic activities are performed. The comprehensive rehabilitation management program is characterized by a holistic approach, in which patient and his overall situation are considered, rather than merely focusing on isolated aspects of existence. This goal usually includes helping the patient to achieve as much functional independence as possible. The main target of rehabilitation team therefore is to help the patient to help himself. Toward this goal, rehabilitation team must have the assistance of patient’ s environment, which contributes to the integration of the main aim of this team. So, the patient’s relatives must know the approaches applied in order to enhance patient effort, facilitating final functional outcome.

Understanding stroke and the rehabilitation of patients who sustain stroke is important and challenging, not only because stroke is a common diagnosis among patients in rehabilitation programs, especially those in functionally ages, but also because it provides an opportunity to learn more about the function of the central nervous system, as well as the application of rehabilitation principles in general. This is the reason why new approaches and modalities, concentrated on motor training and function improvement, is constantly emerging in the rehabilitation practice, and most of them are incorporated into clinical use and from there to common and everyday living.

2.5 The potential for recovery and repair following stroke

Almost all patients suffering from a stroke often undergo some degree of functional recovery. The extent of this recovery can be predicted to some degree on the basis of specific parameters such as lesion size and site, age and premorbid health, the clinical severity of the accident, some psychological, social and ethical items, etc. However, significant variations occur, implying that outcome is influenced by many variables. It is the responsibility of the clinician and the rehabilitation team to assess the influence of these variables, in order to facilitate the best possible outcome for each patient. It is important that every patient react in a different way that lead to the specific applied rehabilitative procedure. To date the cornerstone of restorative neurology in the field of stroke has comprised supportive medical care and more specific therapies (physiotherapy, occupational therapy, speech and language therapy). However, members of rehabilitation team are becoming aware of advances made in the basic sciences, which will add a new dimension to the treatment of functional deficits in patients suffering stroke and other single insult brain injuries.

2.5.1 The basis of stroke rehabilitation management

In the first few minutes and hours after stroke, physicians make an active approach to management, in order to preserve as much brain tissue as possible [22]. Many neuroprotective drugs have been tested successfully in animal models of stroke, but none has been proved effective in randomized trials in human. However, other nonpharmacological strategies are often employed to protect the brain from further ischaemia and extension of infarction. For example, systolic blood pressure can be maintained within a given range, antipyretic drugs given for fever and blood glucose maintained within the normal range. Nevertheless, despite these measures many patients with stroke continue to have significant disability after the acute period. Hence, enhancing recovery using modern rehabilitation techniques continues to play an essential part in stroke treatment.

The best way to enhance recovery is to admit the patient to a stroke unit [23]. These benefits are achieved not simply by gathering the patients together in a single location labeled ‘stroke unit’, but by the development of a specialized multidisciplinary team who have background in the complex problems experienced by patients in acute and post-acute stage of the lesion. These problems are focused on many vital signs (pulmonary and cardiac system) and many stroke effects, as perception, recognition and cognitive efficacy, as well as motor and sensory deficits. How much each component of stroke syndrome contributes to the success of the stroke unit management is not entirely clear, but the support of effectiveness of early rehabilitation program for stroke patients in the post-acute phase in this unit is evident. A meta-analysis combining results of seven randomized controlled trials on the effects of different intensities of therapy after stroke reported small but significant reductions in mortality and significant improvements in activities of daily living (ADL) scores as a result of higher intensity therapy [24]. Furthermore, nine trials of exercise programs in stroke patients was examined involving a large number of patients (n=1051), and it was concluded that there was a small but significant correlation between the intensity of therapy and the outcome [25]. In addition, targeted therapy may have a specific rather than non-specific effect, e.g. greater intensity of leg rehabilitation improves functional recovery and health related functional status, whereas greater intensity of arm rehabilitation results in small improvements in hand dexterity [26]. This suggests that failures to demonstrate a benefit with specific exercise' programs in the past might be related to the fact that assessments were often made using global ADL scales, rather than parameters relating directly to the form of training being given.

It might be argued that the only truly *relevant* measurements are the global functional assessments in the home or work environment. However, if someone wishes to investigate the mechanisms of recovery, it is important to document and assess the induced changes carefully. For example, although patients may perform well on ADL tasks, they may still exhibit reduced skillfulness of the affected hand, despite regaining the ability to solve simple spatial motor problems [27] as a result of focused training. Although it is essential to know whether a patient becomes independent, it is also of great importance to know, for example, what effect the motor and sensory experience of rehabilitation program cause on the motor system. These two different questions concern the relationship between possible changes in the nervous system and consequent functional recovery. To begin to understand mechanisms of recovery and potentially to be able to manipulate them, we have to look at scientific basis of all news procedures methods and techniques that aim to improve functional status of the patients, with faster and more successful social and occupational reintegration.

2.5.2 Neurorehabilitation

The aim of *Neurorehabilitation* is the restoration and maximization of functions that have been lost due to impairments caused by injury or disease of the nervous system [28]. The main group of interests is the patients with injury or lesion of the brain and spinal cord. According to the social model of disability adopted by the World Health Organization (WHO), "impairment" refers to an individual's biological condition whereas "disability" denotes the collective, social, cultural, and economic disadvantage encountered by people with impairments [29]. These definitions have replaced older distinctions of the WHOs, where "impairment" referred to a biological condition (stroke) and "disability" referred to the loss of a specific function: for example, loss of locomotor ability consequent to the impairment; and “handicap” referred to the loss of functioning in society. The recent classification has considered the social participation basic level for handicap definition. In recent years, this state of affairs has begun to change as rehabilitation teams have started to recognize the continuity existed from molecular pathophysiology to impairments to disabilities and handicaps. Neurorehabilitation has come to represent the application of this continuum to neurologically impaired individuals. Therefore, neurorehabilitation is concentrated on improving the patient’s functional status suffering from brain lesion, by taking advantage of their potential for recovery through *neuroplasticity* and *neural repair* by means of techniques and procedures that can facilitate specific neurophysiological processes.

2.5.3 Neuroplasticity and its principles

The term *neuroplasticity* is used to describe the ability of neurons and neurons’ aggregates to adjust their activity and even their morphology to alterations in their environment or patterns of use. Neuroplasticity refers to the ability of the central nervous system to be reorganized and remodeled, particularly after central nervous system injury or specific type of lesion. The term encompasses diverse processes, as from learning and memory in the execution of normal activities of life, to dendritic pruning and axonal sprouting in response to injury or lesion. Once considered overused and trite, the term “neuroplasticity” has regained currency in the neurorehabilitation community as a concise way to refer to hypothetical mechanisms that may underlie spontaneous or coaxed functional recovery after neural injury or lesion and can now be studied in humans through modern functional imaginary techniques.

For many years, it was thought that neuroplasticity only occurred, to a significant extent, before adulthood. During the last 2 decades, significant advances have been made in the neuroscience research field demonstrating that the adult human brain is capable of adaptive plasticity after injury or lesion. With the development of functional magnetic resonance imaging (fMRI) and noninvasive brain stimulation techniques (transcranial magnetic stimulation (TMS), we now have a better understanding of some of the processes that might underlie the recovery of function after stroke (especially after specialized task oriented training). This advancement has allowed the development and testing of new strategies focused on enhancing neurologic recovery and functional ability, even in the chronic phase.

Several principles of neural plasticity have been proposed based on animal research showing changes in synaptic processing in the cortex. Research in rats, for example, has shown that motor training will alter neural signaling pathways by up-regulating early immediate gene expression, such as c-Fos expression, which in turn can alter protein translation [30]. Additionally, changes in neuronal activity can produce changes in neurotransmission and synaptic strength. The altered synaptic strength, ie. synaptic plasticity, produces changes in intracortical microcircuitry altering the topography of cortical maps. These changes really can provide the basis for long-term changes in motor performance [31]. Changes in synaptic function can induce activity in previously silent latent connections (unmasking activity) or dendritic sprouting in animals [32]. Such changes occurring in the human cortex can only be strongly hypothesized, because indirect support comes only from observed alterations in cortical physiology [33] reflecting in clinical response to therapy.

2.5.4 Activity-dependent neuronal plasticity (synaptic plasticity)

In addition to modulation of neurogenesis, changes in the strength of synapses and reorganization of neuronal circuits play an important role in brain plasticity. Synaptic plasticity refers additionally to changes in the strength of neurotransmission induced by activity experienced earlier by the synapse. Changes in the frequency or strength of activation across synapses can result in long-term increases or decreases in their strength. The frequency and strength of synaptic activation play a decisive role in following increased or decreased synaptic action. These processes referred as either **long-term potentiation** (LTP) in increased synaptic activation, or **long-term depression** (LTD) in decreased synaptic activation [34]. These activity-dependent changes occur in all excitatory synapses that use glutamate as their neurotransmitter as well as in some inhibitory GABAergic synapses [35]. They can be mediated by changes in: a) the release of neurotransmitter from presynaptic terminals, and b) the number of excitatory receptors on postsynaptic neurons. LTP can be produced experimentally by rapid repetitive presynaptic stimulation of synapses on pyramidal neurons in the CA1 region of the hippocampus and this is the most studied form of synaptic plasticity. Rapid stimulation of synapses opens NMDA-type glutamate receptors in the postsynaptic membrane leading to an increase in intracellular calcium and insertion of AMPA type glutamate receptors in the postsynaptic membrane

In contrast to LTP, LTD is produced by slow repetitive stimulation of excitatory synapses and is related to a reduction in AMPA receptors in the postsynaptic membrane as they move into the cytoplasm into endosomes [34]. Another form of LTD is caused by the stimulation of type I metabotropic glutamate receptors that activate phosphoinositide turnover in dendritic spines. This form of plasticity is prominent in the cerebellum. LTP is associated with memory formation in the hippocampus, but LTP and LTD form the basis for activity-dependent reorganization and stabilization of developing neuronal networks in sensory-motor cortex [38]. Prolonged in vivo imaging of neurons in rodent cerebral cortex indicates that sensory experience drives the continuous sprouting and retraction of synapses located on dendritic spines in order to remodel neural circuits [36]. Similar mechanisms are probably responsible for enhanced excitability in cerebral cortex that has been documented following short periods of motor skill training using the hands or lower legs [37].

2.5.5 Neural repair

The term *neural repair* has been introduced in the last few years describing the range of interventions by which neuronal circuits, lost to injury or disease, can be restored. In this terms means are included in order to enhance axonal regeneration, the transplantation of a variety of tissues and cells to replace lost neurons, as well as the use of prosthetic neuronal circuits to bridge parts of the nervous system that have become functionally separated by injury or disease. Although there is an overlap with aspects of "neuroplasticity," the term "neural repair" generally refers to processes that do not occur spontaneously in humans to a degree sufficient to result in functional recovery. Thus, therapeutic intervention is necessary to promote repair. The term is useful as part of the basic science of neurorehabilitation because it encompasses more than "regeneration" or "transplantation" alone. In recent years, concepts of neural plasticity have been accepted as important elements in the scientific understanding of functional recovery. The rehabilitation community has been slower to embrace repair as a relevant therapeutic goal. "Neural repair" is used in the title in order to convey the breadth of subject matter that it covers and is now considered relevant to neurorehabilitation.

2.6 Mechanisms of functional recovery (Mechanisms of neuroplasticity)

Several recent studies following stroke suggest that the injured brain has the potential for extensive reorganization [39][40]. Possible mechanisms of neural plasticity, contributing to functional recovery might, include dendritic sprouting over time, new synapse formation, and the processes of long-term potentiation and depression. Reorganization after stroke might also involve undamaged areas of cortex taking on functions of infarcted regions. Different forms of reorganization and accommodation can simultaneously contribute to functional recovery.

2.6.1 Diaschisis

Many areas of the brain are connected through vast organized neuronal pathways and circuits that allow one area of the brain to influence others, more distal to it. Understanding the course and function of all these dense neural pathways helps to link a lesion causing brain damage in one area of the brain with the degeneration of a more distal brain area. A focal lesion causes damage that also disturbs the structural and functional connectivity to the brain areas distal to the lesion. This concept refers to functional deactivation of other, undamaged areas of the central nervous system that are remoted from the lesioned area [41]. *Diaschisis* is a sudden loss or change of function in an intact area of the brain connected to a distant area, which suffer from a lesion or damage. While the damage is concentrated in a cortex area, diaschisis happens in a different remote area, without any lesion. The site of the originally damaged area and the diaschisis are connected to each other functionally by neurons. Therefore, the loss of the damaged structure disrupts the function of the remaining intact systems and causes a physiological imbalance. The injury is produced by an acute focal disturbance in an area of the brain, from traumatic brain injury or stroke, for example. Some function may be restored with gradual readjustment of the intact but suppressed areas through intervention and the brain's natural neuroplasticity.

Modern imaging studies in stroke patients with lesions in motor areas have shown diaschisis in cerebellar structures [42]. Similar findings were also observed when stroke involved other domains such as regions related to language and vision processing [43]. In this manner, resolution of cerebellar diaschisis has been proposed as one of the mechanisms contributing to recovery of motor function after stroke. For example, it has been suggested that one of the mechanisms by which amphetamines might benefit recovery after stroke is by accelerating the resolution of diaschisis. Currently the term diaschisis is used to describe a depression of regional *neuronal metabolism* and *cerebral blood flow* caused by dysfunction in an anatomically separate, but functionally related, neuronal region. The concept of neurophysiological changes in distant brain tissue to the focal lesion led to a widespread clinical interest, without being able to explain how diaschisis could describe the signs and symptoms of brain lesions [44].

The primary mechanism of diaschisis is functional deafferentation [44], which is the loss of the input of information from the part of the brain that is now damaged. The decrease in information transmission and the neural firing to the distal brain area force those distal synaptic connections to weaken and initiate a change in the structural and functional connectivity around that area, which was intact at the beginning of the stroke, leading finally to diaschisis. This process is also influenced by many other factors, including stoke, brain swelling, and neuroanatomical disconnection. The severity of these factors is manifested in altered neuronal excitability, hypo-metabolism, and hypo perfusion [44].

2.6.2 Peri-infarct Reorganization

Another suggested mechanism of recovery is the alterations of cortical motor output maps after focal cortical lesions in the primary motor cortex [45]. This form of plasticity, known as *vicarious reorganization*, refers to the possibility of a healthy region of the brain to take over the function of another lesioned brain area. Evidence for this form of plasticity comes from human and nonhuman primate studies. For example, a study in a highly-selected group of stroke patients who had a small lesion located in the primary motor cortex (M1) found that recovery of finger movements was associated with a dorsal shift of the cortical activation areas within the M1 region [46]. It is important to keep in mind, however, that these focal cortical lesions restricted to M1 are not frequently seen in stroke patients. Other studies in humans have also failed to show a correlation between the peri-infarct activation (using fMRI) and magnitude of motor recovery, except of some case reports [47]. The latter raises the question of what degree the peri-infarct reorganization contributes directly to motor recovery.

2.6.3 Activity in the Ipsilesional Hemisphere

The increasing levels of activation in a distributed ipsilesional network that includes many cerebral areas as primary motor cortex, premotor cortex, supplementary motor area, and bilateral Brodmann area 40, have been reported as another mechanism of recovery in stroke patients. This process is closely correlated to the previous mechanism, peri-infarct reorganization, but extents in more than one area. Significant findings can be obtained from modern functional neuroimaging techniques. These findings correlates positively with one index of motor recovery (hand score of motricity index) [48]. Taken together, these neuroimaging studies suggest that *activation in ipsilesional motor areas plays an important role in the recovery process.* Neurophysiological studies have also demonstrated that transient disruption of activity in the ipsilesional M1 and dorsal premotor areas of patients with good motor recovery after stroke caused transient deficits in motor performance of the paretic hand. All these findings indicate that recovery of motor performance in the paretic hand of patients with stroke appears to rely predominantly on activity that arise from reorganized areas within the lesioned hemisphere [40].

2.6.4 Activity in the Contralesional Hemisphere

As mentioned above, identification of optimal treatment strategies to improve recovery is limited due to the incomplete understanding of the neurobiological principles of recovery. Motor cortex (M1) reorganization of the *lesioned hemisphere* (ipsilesional M1 area) plays a major role in post-stroke motor recovery and is a primary target for rehabilitation therapy. The unaffected hemisphere is another important locus of reorganization after stroke, since reorganization of M1 in the hemisphere contralateral to the stroke (contralesional M1) may, however, serve as an additional source of cortical reorganization and related recovery [49]. Increased levels of contralesional sensorimotor activation have been identified during simple movements of the paretic hand. The magnitude of contralesional activation appears to decrease, however, in M1 at 3 to 6 months relative to 1 week after the stroke [39]. The intensity of contralesional M1 activity also does not correlate to the degree of recovery. These findings might suggest that contralesional activation is not functionally relevant to recovery or that it is insufficient to compensate.

The extent and outcome of such reorganization depend on many factors, as the lesion size and the time since stroke. In the chronic phase post-stroke, the M1 area in the opposite side of the lesion (contralesional) seems to interfere with motor function of the paretic limb in some patients. This possibly attributes to the abnormally increased inhibition of lesioned M1 by the contralesional M1. In such patients, a decrease in contralesional M1 excitability, happening via cortical stimulation (transcranial magnetic stimulation-TMS), may results in improvement in the performance of the paretic limb [50]. However, some evidence suggests a potential supportive role of contralesional M1. After infarction of M1 or its corticospinal projections and neuronal circuits, there is an abnormally increased excitatory neural activity and parallel activation in contralesional M1, which correlates with favourable motor recovery. Decreasing contralesional M1 excitability in these patients may result in deterioration of paretic limb performance [51]. In animal stroke models, reorganizational changes in contralesional M1 depend on the initial lesion size and rehabilitation treatment. These changes of reorganization of non-lesioned area include long-term changes in neurotransmitter systems, dendritic growth, and synapse formation. Therefore, while there is some evidence that activity in contralesional M1 may impact on the extent of motor function of the paretic limb in the subacute and chronic phase post-stroke and may serve as a new target for rehabilitation treatment strategies, the precise factors that specifically influence its role in the recovery process will remain to be defined.

2.6.5 Plasticity in the Normal Brain

The term *plasticity* or *neuroplasticity* is often used for mechanisms of recovery after focal brain injury, as in stroke. Over 70 years ago, at 1947, Hebb postulated that increments in synaptic efficacy occured during learning, when firing of one neuron repeatedly produced firing in another neuron to which it was connected [52]. This expresses the notion that a change in behavior (i.e. learning) is associated with a neurophysiological change of function at the level of the synapse. In a more general framework, a definition of plasticity might, specifying a change in structure over time with a consequent change in function and the cortex, with its myriad synaptic connections, is the ideal site for this plasticity to take place [53].

Using this loose definition of plasticity, it is considered that changes at the cortical level can occur in several ways. Firstly, it has been repeatedly demonstrated that enriched environments and motor learning in adult animals are associated with morphological changes in the cortex, suggesting increases in the number of synaptic connections. These changes include mainly growth of dendrites, increases in dendritic spines and synaptogenesis [54]. Secondly, long-term potentiation (LTP) and long-term depression (LTD) have long been known as mechanisms of changing synaptic efficacy in the context of learning studies, particularly in the hippocampus [55]. More recently there has been evidence that these processes can occur in the neocortex if certain conditions, such as a concurrent ascending input (as in specialized training programs) are in place [56], and that motor skill learning is accompanied by changes in the strength of connections within primary motor cortex in animal models [57]. Lastly, the influence of one cortical neuron on another can be altered by factors other than external environment or practice, suggesting that cortical maps are maintained at least in part by GABA, and can be altered by pharmacological manipulation [58].

Studying the human brain creates clearly greater limitations, and very different techniques are needed to study alterations in cortical function and neural circuity. Studies using transcranial magnetic stimulation (TMS), have demonstrated changes in cortical function in response to sensory input [59], motor imagery [60], and motor practice [61]. Functional imaging has been also used to demonstrate changes in the organization of neural networks during motor learning [62]. Up to this point, we have been discussing the potential for plastic change in the normal brain, but it is important to consider whether plasticity also occurs in the damaged brain, and whether this process in any way contributes to functional recovery.

2.6.6 Plasticity in the Lesioned Brain

It is fundamental that the lesioned brain and the normal brain are different when it concerns the potential for plastic change. There is much evidence now to support the idea that the lesioned brain has an increased capacity for plastic change. Recent work for example demonstrates that following ischaemic damage in adult rats, new progenitor neurons migrate from the subventricular zone and dentate gyrus to the site of damage. In this case, these new cells express morphological characteristics of the recently damaged cells [63]. Structural changes have also been observed as mentioned in normal brain, with evidence of neurogenesis, increased dendritic branching and synaptogenesis. The correlation between some of these changes and behavioral recovery becomes clearer when considering that the magnitude and temporal course of cellular events often parallel this recovery [64]. It is also interesting to consider the spatial distribution of such changes, with synaptogenesis [65] and axonal outgrowth seen in perilesional tissue in rats, and evidence of dendritic branching in homotopic cortex in the non-lesioned hemisphere [66]. The changes in cortical structure and function that might mediate recovery, may therefore occur at sites distant from the lesion.

The idea that intact areas of the brain become functionally and metabolically inactive because they are disconnected from the site of focal lesions, a phenomenon known as diaschisis, as described above, and that this might have an impact on the clinical presentation as well as on recovery of this focal damage, was first discussed at the beginning of the last century by Von Monakow in 1914. There are two types of diaschisis. The first is *focal diaschisis*, which refers to the remote neurophysiological changes that are caused by a focal lesion based on classical definition. The second one is *non-focal diaschisis* and it focuses on the changes in the strength and direction of neural pathways and connectivity between brain areas. This type of diaschisis has become a topic in recent studies as a result of the advancement of brain imaging tools and technology, allowing better understanding of the organization of the brain connectivity and further investigation into new types of diaschisis. This new type of diaschisis relates much more closely to clinical findings [44].

In a human PET study, survival of the metabolically active cortex surrounding an infarct area, is correlated with neurological recovery in acute stroke patients [67]. The evidence that reversal of diaschisis (rather than recovery of inactive or damaged cells in the ischaemic penumbra) contributes to functional recovery is conflicting. Resolution of ipsilateral thalamocortical diaschisis seems to correlate with improvements in cognition and neglect [68], but does not seem clearly related to motor outcome. In a human SPECT scans study in 50 unselected patients with cerebral infarcts at the time of infarct and 3 months later [69], demonstrated that diaschisis independently added to the clinical deficit after stroke, and found no correlation between recovery and reduction in diaschisis.

In human studies, using different imaging techniques, there is also evidence of changes in the organization of cortical networks following focal brain lesions. Enlargement of cortical motor maps demonstrated with TMS correlates with functional improvement in stroke patients and also changes in activation maps of recovered patients post-stroke have been demonstrated in both motor [70] and language studies [71]. However, there has been no direct evidence yet to suggest that the lesioned human brain has an increased capacity for plastic change compared to the unlesioned brain. Furthermore, many of the animal models mentioned are models of cortical damage, and it is not clear that these data are relevant to subcortical stroke. However, the data available from animal models, encourage us to speculate that we may be able to take advantage of changes in the human lesioned brain to promote functional recovery.

2.6.7 Promoting Functional Recovery after Stroke

Given that the brain has the capacity for plastic change, and that this seems to increase in the lesioned brain as a consequence of expression of trophic factors and other changes, how can we take advantage of such changes to influence outcome? This constitutes a crucial question with a serious clinical aspect. Several studies have demonstrated that these changes depend not only on the lesion, but on experiential demand. For example, in rats subjected to damage of unilateral sensorimotor cortex, when the impaired forelimb was restrained, there was a reduction of dendritic arborization in surrounding cortical tissue. This effect is not observed if the impaired limb continues to be used.

Animal studies have been supportive of the idea of *task specific training* effects in cortically injured animals, and have begun to shed light on the underlying mechanisms. Nudo et al [45], trained squirrel monkeys in the execution of a complex motor task using a hand. Focal infarcts of a small portion of the hand representation in cortex were induced and 5 days after an intensive retraining identical to the previous one, this representation was undertaken. This was continued until pre-infarct levels of performance were attained. Using intracortical microstimulation techniques, they found that spared hand areas had either been preserved or had expanded into regions previously occupied by elbow and shoulder representations. The important was that animals, in whom retraining had not been attempted and in whom recovery had been less marked, had lost remaining hand representation in the cortex. Rehabilitative specific training would therefore seem to have influenced reorganization of intact cortex, as measured by changes in cortical maps, with a consequent beneficial effect on motor recovery.

Exposure of animals to an *enriched environment* enhances dendritic growth and synapse formation and has also been demonstrated to enhance recovery after brain injury [72]. This effect is likely to be related to experience (training and learning) and to consequent cognitive processing, as simply physical exercise on its own does not produce such significant results on post-injury motor recovery [73]. Human studies have demonstrated more or less the same. In particular, improvements in motor performance in the chronic setting have been demonstrated with *constraint induced therapy* (CIT), based on overcoming learned non-use of the affected, and have been accompanied by increases in cortical representation in the area of the affected limb [74]. Underpinning all these techniques is the concept of activity-driven change and the notion that by increasing the activity of neurons in strategically located cortical regions. Thus, structural change will ensue, resulting in improvement of function. An example is that of an increase in pinch grip strength induced by 2 hours of median nerve stimulation in hemiparetic patients [75]. This notion is useful but likely to be oversimplified. Many aspects of language and motor function in the normal brain are still under active investigation. Motor learning, for example, is the product of complex dynamic interactions between cortical and subcortical structures, which is likely to be optimized and yield the best functional results by certain conditions and learning techniques [76]. Until we have an empirical understanding of these optimal parameters in both health and disease, our attempts to promote functional recovery will not have the well-grounded theoretical basis that is required for progress.

A critical issue, also, concerns the *timing of interventions*. The evidence presented seems to suggest that many of the neurophysiological changes that take place after stroke and many changes that we may need to take advantage of to promote functional change, occur early after the lesion (between 0-3 days). Therefore, it would seem likely that, to take full advantage of these changes, intervention must occur relatively soon after stroke. However, there has been a skepticism to use many interventions (such as forced therapy) in the acute setting because of alternate evidence that such an approach may lead to exacerbation of cortical damage [66]. This overuse-dependent exaggeration of injury can be blocked by administering MK-801 (an NMDA antagonist), suggesting that glutaminergic mechanisms are involved.

The question of the proper time for an intervention may therefore be critical, because as mentioned, there are definite changes in the molecular and cellular environment at a certain time point after injury. For example, it has been hypothesized that during early development new synapses with high NMDA:AMPA receptor ratios are formed. This ratio rapidly becomes like the one seen in adults. In any period where new synapses are forming, such as early development, new learning, or after focal brain damage [65] *use-dependent plasticity* is likely to occur in the new synapses with high NMDA:AMPA receptor ratios. This effect may explain why NMDA antagonists, although thought to be protective in acute ischaemia, may slow down or prevent plastic changes occurring in perilesional tissue, with subsequent impairment of functional recovery [77]. Understanding of these processes is crucial if we are to use interventions correctly.

It is worth considering that *the capacity for plastic change* in the brain may be finite, particularly with ageing. Functional imaging studies have examined differences in recruitment of brain regions during both motor [78] and cognitive tasks [79], and many of these studies have shown greater activations in several regions in older subjects when compared with younger subjects. However, this may only be the case for those older subjects whose level of performance is comparable to that in the younger subjects [78]. It has been suggested that interruption of the normal neural networks, subserving cognitive performance by age-related neurodegenerative and neurochemical changes, underlies decline in function, but in some people these compensatory processes in cortical and subcortical function allow maintenance of performance level. We also know that after injury-induced re-organization of the brain, the capacity for subsequent adaptive change is reduced [80]. It is possible that the adaptive changes, observed in older brains and injured brains, may in turn limit the capacity for further reorganization after injury. This clearly has implications for what we can expect from therapeutic techniques designed to promote cerebral reorganization after stroke in older subjects. A greater understanding of age-related changes in the functional reorganization of the brain will be crucial in unraveling the relationship between normal ageing and pathological process [81].

2.7 Therapeutic Approaches to the Upper Limb

Rehabilitation of the hemiparetic upper limb is the focus of functional re-education of stroke patients. Walking is a massive kinetic activity on a single level of action, while fine upper limb movements are a multidimensional lever system with fine adjustments and controls at 6 degrees of freedom of movement, requiring highly sophisticated training. Thus, while walking is easier to carry out usually using an assistive device, the restoration of the movements and fine movements of the affected upper limb has an overwhelmed prognostic expectation and require persistence and motivation to pursue re-training programs.

Due to the majority of strokes occuring in the territory of the medial cerebral artery (MCA), motor impairment of the upper limb tends to be more severe than that of the lower one. This in fact confirms the importance of training the infected upper limb. Inherent differences also exist in rehabilitation of the upper limb compared with the lower limb after stroke. Many basic self-care activities can be performed with a single, neurologically intact upper limb. In contrast, standing and walking are basic functions of the lower limb, activities that generally require the use of both lower limbs. Although walking activity is a rough action, requires the use of both feet, but the completion of many daily living activities can be accomplished by using only one hand. The use of both hands significantly improves the functional result, although probably initially slows down the whole process. This basic difference in the functional demands of the upper limb compared to the lower limb becomes even more consequential given that learned nonuse prohibits volitional use of the neurologically impaired upper limb, and use of the impaired limb is a critical requisite for inducing the neuroplastic changes that lead to motor recovery[108].

The greatest impetus by far for the ongoing major change in stroke rehabilitation has been the widespread acceptance of the notion that the adult human brain is capable of significant adaptive plasticity after acquired injury. This adaptive capacity of the affected brain is greatly facilitated, quantitatively and qualitatively, by implementing appropriate re-education and learning programs. This fundamental change in thinking has lead to the development and evaluation of a number of new therapies, methods and modalities, focused on improving neurological recovery of the impaired upper limb.

Before discussing therapies more recently developed, techniques that have been traditionally used to promote recovery will be described briefly. Although a number of therapeutic rehabilitation techniques promoting neurological recovery have been developed in the past, the science background to support their efficacy has been weak at best. Taken together with the historical lack of compelling evidence that the adult human brain has the capacity for significant adaptive plasticity after acquired injury, the use of these rehabilitation interventions has been based largely on tradition. As a consequence, none of these procedures have become the standard of care within the broader rehabilitation community. Commonly referred to as sensorimotor techniques, these treatments encompass a range of therapies intended to promote motor recovery. The most basic of these approaches include strengthening, range of motion (ROM) exercises, balance training, and postural control. All these programs do not seem to outweigh either the other or the control groups, but they provide a basis on which to build the framework of education that will allow us to take advantage of the possibilities offered by the brain plasticity.

A therapeutic technique, specifically developed for patients with stroke, was proposed by Brunnstrom and encourages early movement based on well-recognized patterns of motor recovery. Bobath [109] developed the therapeutic approach now known as neurodevelopmental technique, which was originally designed for treatment of children with cerebral palsy. It inhibits abnormal postures and movement, and seeks to facilitate isolated muscle control. Proprioceptive neuromuscular facilitation intends to maximize proprioceptive input through quick stretches and spiral diagonal patterns of movement [110]. Rood proposed a technique that incorporates cutaneous stimuli to facilitate movement [111]. Finally, the task-oriented approach to therapeutic exercise described by Carr and Shepherd [112], encouraging movement during functional tasks. With the notable exception of task-oriented therapeutic movement, head-to-head comparisons of these techniques have not shown superiority of one over another. For many years, however, they formed the basis on which the basic therapeutic approaches of rehabilitation were built and supported, helping many people with stroke to reintegrate into everyday life and society. Also, these methods were the background for fundamental support for the development of newer and more efficient techniques and rehabilitation procedures.

Although the use of traditional sensorimotor techniques has been mainly based on traditional aspects than on science, they might still have value in stroke rehabilitation. The physiological mechanisms that promote adaptive plasticity have to be fully elucidated. Some of the mechanisms that have been postulated to underlie traditional sensorimotor techniques could theoretically facilitate adaptive plasticity. For example, proprioceptive feedback, such as the one that has been emphasized in proprioceptive neuromuscular facilitation techniques (PNF), is considered to be an important mechanism of motor recovery. A great deal of further study is needed. Many of these therapies can be adapted to current knowledge; namely, forced use of the paretic limb, massed practice, shaping, skill acquisition, and task specific movement. Some rehabilitation teams have adapted these traditional sensorimotor techniques to current concepts of neuroplasticity of the affected brain. Although the superiority of specific therapies must be demonstrated through rigorous science, at this stage in the evolution of stroke rehabilitation, the adaptation of traditional sensorimotor techniques to adhere to current concepts of neuroplasticity seems reasonable.

Constraint-induced movement therapy (CIMT) is one of the more recently developed therapies that have been based on the current concepts of neuroplasticity. CIMT may warrant the greatest attention because it is safe, does not require additional technology, and has been among the most extensively studied therapies [113][114]. CIMT is based on a theory proposed by Edward Taub according to which, patients with motor impairment in an upper limb after stroke learn to depend more on the unaffected limb for performing functional tasks because attempts to use the affected arm often result in failure and frustration. This is explained through the principles of operant conditioning, where failed attempts to use the upper limb produce a kind of negative feedback, which reduces future attempts even further. Taub demonstrated this in studies of primates who underwent dorsal root lesions that led to a deafferentation of an upper limb. Despite the preservation of motor control, these primates avoided to use the affected arm in functional tasks. More importantly, he demonstrated that the use of the affected limb could be augmented by forced use of the impaired limb through a process of restraining the intact upper limb with a body jacket. Taub also demonstrated that primates could be trained to perform tasks with the affected limb through successive approximations of the desired task, which is the behavioral technique known as shaping. These findings have been corroborated by studies showing that the normal and injured primate brain is capable of cortical reorganization in response to behavioral interventions [115].

This line of research has shown that repetitive movement alone is not sufficient. Instead, new skill acquisition or reacquisition of lost skills after stroke is required to induce cortical reorganization and promote recovery of motor function. These principles have been incorporated into CIMT and other therapies (including robotics and neuromuscular electrical stimulation (NMES)) to promote motor function after stroke in humans. CIMT in clinical trials has taken two general forms. The original CIMT program consists of 2 weeks of constraining the intact upper limb for 90% of walking hours combined with approximately 6 hr/day of institutionally based therapy designed to force use of the impaired upper limb during task-oriented activities. Participants must have at least partial wrist and finger extension, adequate proximal limb control, and sufficient balance during limb restraint. The EXCITE trial, a randomized clinical trial of 222 subjects in the subacute phase (3 to 9 months) after stroke, demonstrated the efficacy of CIMT using both laboratory and real world-based activities measures [116].

For others, however, the magnitude of the treatment effect was underwhelming, and a lack of control for treatment intensity in the comparison group continued to raise questions about the clinical significance of the results. The practicality of the original CIMT program has also been questioned extensively, both from a home implementation and a reimbursement standpoint. As a result, several investigators have developed and evaluated modified CIMT (mCIMT) programs that are provided for less-intensive treatment over a longer period. Many mCIMT programs constrain the intact limb for 5 hr/day for 5 days/wk combined with up to 3 hours of therapy three times per week, over 10 weeks. A small pre-test, post-test trial in chronic stroke suggests that a mCIMT program that requires formal therapy for 30 minutes, 3 days/wk over 10 weeks might have similar clinical benefits as the more intensive, original CIMT and might be more practical for conventional clinical rehabilitation [117]. In a recent Cochrane Review, the authors concluded that CIMT and mCIMT are associated with a moderate reduction in disability at the end of treatment, but the data to support a sustained effect on disability were insufficient [118]. CIMT, mCIMT, and other methods, such as patient education, that force the use of the impaired upper limb to repetitively perform functional activities are recommended for stroke survivors who are capable of participation in such programs.

When severe motor impairment precludes therapeutic or functional volitional use of the impaired upper limb, *Neuromuscular Electrical Stimulation* (NMES) can be a reasonable option. NMES refers to electrical stimulation of the lower motor neuron or its terminal branches, causing depolarization of the motor neuron and subsequent activation of the corresponding muscle. The term *neuroprosthesis* refers to a functional application of NMES where the paralyzed limb undergoes stimulation in a coordinated sequence resulting in functional movement. Because skill acquisition in performing functional activities is more effective than simple repetitive movement for inducing adaptive cortical reorganization, therapeutic and functional applications of NMES are likely to merge over time. The concepts underlying neuroplasticity suggest that extensive use of a neuroprosthesis in a community may convey the greatest therapeutic benefit in terms of motor recovery. Purely therapeutic applications of NMES for the affected (hemiparetic) upper limb have been studied extensively. Many stroke survivors plateau at a stage of recovery where proximal control is sufficient to position the hand within a small but adequate work volume, and flexor synergy patterns result in strong wrist and finger flexion but insufficient wrist and finger extension to permit hand opening.

NMES, applied to wrist and finger extensors, has been the most commonly studied application in stroke. Stimulated movement can be repetitively induced without user's input, triggered by the user, or proportionally linked to user's effort via electromyography (EMG) if the paralyzed muscle can generate an adequate signal. The concepts underlying neuroplasticity would suggest that EMG-triggered and EMG-controlled NMES are theoretically more likely to induce motor recovery, but these benefits have yet to be rigorously demonstrated. Several small clinical trials and a meta-analysis have demonstrated improved motor function resulting from therapeutic NMES [119]. A double-blind, randomized trial yielded similar positive results and additionally demonstrated cortical changes by fMRI in NMES treated subjects [120]. Overall, the data suggests a therapeutic effect of NMES. The effect size, however, has not been sufficient to consistently show improvement in clinically relevant outcomes such as activities. Because NMES is safe, alternative therapies for severely impaired stroke survivors might not be available, and community-based treatment is possible. NMES remains a reasonable therapeutic strategy for select patients, particularly those who are too impaired to participate in a forced use paradigm. Ongoing development of this technology will likely yield a wider variety of applications and improved clinical outcomes.

Robotic therapies for the upper limb have also been developed based on current concepts of neuroplasticity, namely forced use, massed practice, shaping, and skill acquisition. Among these, robotic therapy's greatest advantage could be its capacity to induce greater repetitions of upper limb movement (massed practice) within a given period compared with therapies based on volitional movement alone. Robotic-assisted motor retraining has been studied for upper limb rehabilitation after stroke. Robotic devices can induce passive or assisted limb movement that is typically directed toward a computer-generated visual target. More advanced iterations of the robot can provide tactile feedback that kinetically and kinematically corrects the user's movement, theoretically promoting movement during skill acquisition. Most robots are haptic, referring to the capacity of sensing the user's movement and provide feedback to the system that is used to plan subsequent motion output.

Robotic therapy also has the distinct advantage of inducing repetitions without the need for continuous involvement of a therapist, opening possibilities for a spectrum of treatment environments that include home-based treatment. Clinical trials suggest that robotic therapy can enhance upper limb motor recovery [121]. Early-generation robots target only shoulder's, elbow's, and in some cases wrist's movements, and do not directly address finger movements. The effect of robotic therapy on functional recovery remains unclear. Newer generations of robots seek to more fully address prehensile function. Further robotic therapies have been combined with virtual reality to address other significant limitations, such as the need for functional task specificity and the use of real world objects. These advances in robotic therapy are ongoing. With these advances though, robotic therapies are promising with respect to increased efficacy. With further development, however, engineering complexity and cost will likely increase, making access a continuing challenge for this type of therapy.

3 Virtual Reality (VR) in Neurorehabilitation

Recent developments in technology have succeeded in changing the practice of today's clinician. Indeed, technology has enhanced a variety of clinical, administrative, academic and personal tasks facing the clinician of the new millennium [82]. *Virtual reality (VR)* is one of the most innovative and promising developments and promises to have a considerable impact on neurorehabilitation over the next years [83]. VR technology, with the multi-sensory training that it can support, has the potential to meet the standards of the need to ameliorate the quality of a patient's life and provide an enhanced environment in which people with stroke can improve their abilities in order to facilitate their lives long-term. Taking advantage of the opportunity that VR offers, to bring the complexity of the physical world into a controlled environment [7], there is a great amount of studies that have applied VR in different types of rehabilitation.

VR typically refers to the use of interactive simulations created with computer hardware and software to present users with opportunities to engage in environments that appear and feel similar to real world objects and events [84]. Users interact with displayed images, move and manipulate virtual objects and perform other actions in a way that attempts to "immerse" them within the simulated environment thereby engendering a feeling of *presence* in the virtual world. One way to achieve a stronger feeling of presence is for the users to be provided with different feedback modalities including visual and audio feedback and, less often, with haptic and vestibular feedback of their performance. Depending on the characteristics of hardware, software and task complexity, VR aims to provide users with more than just an engaging experience, and is hence quite different in both scope and intensity than traditional computer simulation games. Over the past few years, the VR technology has been introduced in medical rehabilitation and is used to educate patients with motor or cognitive deficit. The purpose is to bring the patient into a virtual environment where overall activity could be facilitated.

3.1 Basic VR characteristics

Presence is widely considered to be the subjective feeling of being present in a simulated environment. Sheridan has defined it as being "… experienced by a person when sensory information generated only by and within a computer compels a feeling of being present in an environment other than the one the person is actually in". *Presence* is believed to be a major phenomenon characterizing a person's interaction within a virtual environment, but the term is used inconsistently by different researchers [85]. It is suggested that presence includes three aspects: a) the sense of “being there”, b) domination of the virtual environment over the real world and c) the user’s memory of visiting an actual location rather than a compilation of computer-generated images and sounds [86]. Another aspect correlates presence to the concept of *selective attention* [87]. Despite the numerous studies that have attempted to merge the various definitions of presence, it continues to be viewed as a complex concept that may be influenced by numerous interdependent factors [88].

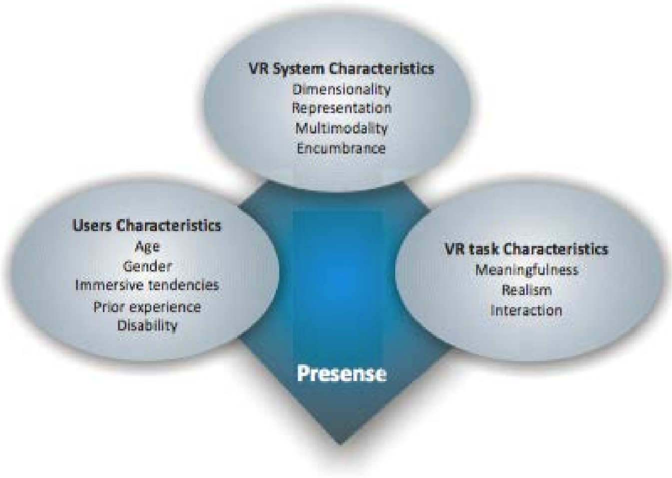

Figure 2-1. Factors contributing to the user’s sense of presence [82]

Figure 2-1 depicts the factors that contribute to the sense of presence which a user may experience. The first set concerns the characteristics of the system that presents the virtual environment. These include the extent to which the user is encumbered with sensors, the way in which the user is represented within the virtual environment [89], whether the platform supports two- (2-D) or three-dimensional (3-D) interactions, and the number and quality of feedback modalities. Another set of factors is related to a given user’s characteristics, where include age, gender, immersive tendencies, prior VR experience and disability [90]. Finally, a third set of factors is related to the characteristics of the virtual environment and the task that is being performed within it [89]. These include the meaningfulness of the task how realistic it is and the intuitiveness of the interaction [91].

A second key concept related to VR is *immersion*, which relates the extent to which the VR system succeeds in delivering an environment that refocuses a user’s sensations from the real world to a virtual world [85][86]. VR environments can range according to their degree of user’s immersion. Systems that include projection onto a concave surface, head-mounted display or video capture in which the user is represented within the virtual environment are generally described as immersive, whereas a single screen projection or desktop display are considered low immersive. Whereas immersion is an objective measure referring to the VR platform, it does not immediately correspond to the level of presence (which is a subjective measure), produced by the system. Immersion is thus dependent, in large part, on the quality of the technologies used with the VR system (e.g., their resolution and speed of response) [85]. Virtual environments may be delivered to the user via a variety of different technologies that differ in the extent to which they are able to “immerse” a user. In contrast to past references to immersive versus non-immersive VR systems, it is preferable to regard immersion as a continuum, ranging from lower to higher degrees of immersion. The relationship between the sense of presence, immersion and performance within the virtual environments is still not fully understood [89]. Nevertheless, there is considerable evidence indicating that a high sense of presence may lead to deeper emotional response, increased motivation and, in some cases, enhanced performance, which are helpful for rehabilitation patients. The use of a more immersive system does not necessarily generate a higher level of presence [91] nor guarantee clinical effectiveness. Taken together, there are many intertwined issues involved in building a successful VR rehabilitation tool.

A third issue is *cybersickness* which refers to the fact that some users experience side effects during and following exposure to virtual environments delivered by some of the more immersive VR systems; a factor that may limit its usability for all patients under all circumstances [92].

Side effects of VR applications noted while using some VR systems can include nausea, eyestrain and other ocular disturbances, postural instability, headaches and drowsiness. Effects noted up to 12 h after using VR include disorientation, flashbacks and disturbances in hand–eye coordination and balance [90]. Many of these effects appear to be caused by incongruities between information received from different sensory modalities. Other factors that may influence the occurrence and severity of side effects include characteristics of the user and the display, the user’s ability to control simulated motions and interactivity with the task via movement of the head, trunk or whole body [93]. VR systems, that include the use of a head mounted display (HMD), have a greater potential of causing short-term side effects, mainly oculomotor symptoms [94]. The potential hazard of side effects for patients with different neurological deficits has not been sufficiently explored although there is increasing evidence that their prevalence is minimal with video-capture VR systems that are growing in popularity for clinical applications [91].

3.2 VR attributes for rehabilitation

During the last few years, VR technologies have begun to be used as an assessment and training tool in rehabilitation field. The rationale for using VR in rehabilitation is based on several unique attributes of this technology [83]. These include the opportunity for experiential, active learning, which encourages and motivates the participant [88], especially if the scenario evolving in the virtual environment schedule enhances the interest and the motivation of the patient. Moreover, there is the ability for objectively measuring behavior in challenging but safe and ecologically valid environments, while maintaining strict experimental control over stimulus delivery, activities performance and measurement [95]. VR also offers the capacity and the greatest advantage to individualize treatment needs, mainly when activities of daily living are designed in VR environment, while providing in parallel increased standardization of assessment and retraining protocols. Virtual environments provide the opportunity for repeated learning trials and offer the capacity to gradually increase the complexity of tasks while decreasing the support and feedback provided by the therapist [83]. This enables the patient to be permanently and continuously independent of the device guidance and the feedback offered and to obtain an individual independent mode of execution. Moreover, the automated nature of stimulus delivery within virtual environments enables the therapist to focus on the provision of maximum physical support, when needed, without detracting from the complexity of the task. For example, several objects and parts of items can be displayed simultaneously from different directions while the therapist supports the patient's paretic shoulder or when training the fine movements of the digits. Finally, the ability to change the virtual environments relatively easily enables clinicians to assess more efficiently different environmental modifications, which endeavor to enhance clients' accessibility.

3.2.1 Executive functions deficits

VE have the potential to enhance cognitive neuropsychological tests of executive function, since they generate a better subjective perception of presence and immersion than artificial laboratory tests [94]. Moreover, virtual environments appear to offer a way to systematically assess and rehabilitate executive functions, since they have ecological validity and can be readily designed to simulate the demands found in everyday tasks as noted above [95]. For the rehabilitation purpose of executive functions concerning patients with TBI, V-STORE, an example of a desktop VR-based tool has been developed [94]. This environment requires from the patient to distinguish, choose and place different pieces of fruits in a basket in accordance with verbal commands. The complexity is various and evolves into 6 levels (six tasks are graded) with the aim of eliciting the need for executive functions, problem solving, behavioral control, categorical abstraction, memory and attention. A series of distracting elements are included to generate time pressure and elicit management strategies. An initial study of control subjects who used the V-STORE environment via an immersive HMD or a non-immersive flat screen display was carried out [96]. Outcome including physiological, neuropsychological and presence's measures showed no major differences between the VR systems.

In another study, there was a comparison between real world and virtual world "errand running" performance in five patients with TBI who had poor planning skills and in five normal control subjects [97]. The videotaped performance of subjects was coded and compared while performing a series of errands in the University of Aberdeen Psychology Department (real world) and within a flat screen VR scenario modeled after this environment. Performance in both real and virtual environments, defined as the number of errands completed in a 20-min period, was highly correlated. This finding suggests that performance in real and virtual worlds was functionally similar, emphasizing the ecological validity of the VR. Finally, measures of both real and virtual world performance showed concordance with staff observations of planning skills [98] .

A more recent study comparing the efficacy of a virtual environment over a physical one is that of Subramanian et al [3], who created two similar environments in terms of practice, training intensity and feedback. The virtual environment was distinguished from the real one as it has some additional visual effects that encouraged and motivated a bit more the patients. Both groups presented improvement in motor impairment measure but the interactivity and the motivation of the virtual environment offered a benefit to motor learning in stroke. VR consisted a more effective mean to provide feedback that helped patients to put a clearer cognitive effort, which finally helped them to have a better motor planning.

3.2.2 Motor deficits

The majority of VR-based interventions have been used to train motor deficits and motor control, especially in patients who have followed a stroke. In order to train reaching movements a virtual environment was used [99], for the assessment and training of motor coordination a haptic device was used [100], and for improvement of the hand strength have developed a force-feedback glove, ie a non-haptic glove to improve the range of motion and speed of hand movement [101]. Based on the results of the latter study, which included three stroke patients, it appears that training within a virtual environment may lead to improvements in upper extremity function in this population even when at a chronic stage [101].

Since many of the VR platforms for rehabilitation have used desktop VR systems where the user interacts with the virtual environment via a keyboard, mouse or joystick, the focus of intervention has often been cognitive, meta-cognitive or functional or even limited to wrist, digit or ankle movements. More recently the use of other interaction methods has enabled applications that can also be used for the improvement of motor deficits. For example, individuals with acquired brain injury have been trained to perform specific arm movements within a virtual environment and have then been able to generalize this ability and engage in daily functional use of the affected arm [102]. Kizony et al. [103] presented results of 13 patients who had a stroke and who used a number of virtual games via the GX-VR system. The findings showed that the system is suitable for use with elderly patients who had motor and cognitive deficits. In addition all participants expressed their enjoyment from the experience. The same VR system has been used to explore its potential to train balance for patients with spinal cord injury [104]. Such training for these patients is essential in order to help them achieve maximal independence in activities of daily living, namely remediation of motor deficits via compensatory strategies to maintain balance. Initial results from a usability study of nine patients showed that they enjoyed doing the tasks, were highly motivated to participate and they agreed to have repeated sessions with the VR system. More importantly, they were able to maintain balance under the very dynamic conditions available within the virtual environment [105] and appeared to make considerably more effort than during conventional therapy.

3.2.3 Instrumental activities of daily living

Education with VR systems show promise for training activities of daily living with different populations, especially in the delicate use of objects and devices such as those in the home, kitchen, bathroom or in the workplace environment. Three desktop applications for rehabilitation of daily tasks have been developed [106]: a virtual kitchen, a service and vending machine and a hospital and university way-finding environment. The functional tasks and the 3-D way finding within the virtual environment were carried out using an adapted keyboard or a touch screen. A virtual kitchen was also developed to enable practice that is safe, controlled and stimulating for patients with stroke and TBI, who have cognitive deficits, prior to practice within an actual kitchen [107]. These researchers developed a “telerehabilitation” system for home use under supervision by practitioners from a clinic, thus enabling training without having to relocate, which is difficult for many patients.

4 Music and affected brain

4.1 How music helps the injured brain to be retrained

The use of music in therapy for the lesioned brain has evolved rapidly as brain-imaging techniques have revealed the brain's plasticity, its ability to change and be reorganized, and have identified networks activated by music. Armed with this growing knowledge, doctors and researchers have employed music to retrain the injured brain. The target is to integrate music with its dynamic potentials into the healing process of Rehabilitation. Studies have revealed that, due to the same circuits that music and motor control share, music can improve movement in patients who have suffered a stroke or who have Parkinson's disease or in general who have a motor control deficit. Research has shown that neurologic music therapy can also help patients with language or cognitive difficulties or deficits after stroke, and the suggestion is that these techniques should become part of a complete rehabilitative care.

Biomedical researchers have found that music is a highly structured auditory language involving complex perception, cognition, and motor control in the brain, and thus it can effectively be used to retrain and re-educate the injured brain. In other words, music can be used as a sensory or cognitive stimulus to give a particular sensory or feedback stimulus to facilitate the lesioned motor control. Now, therapeutic team use music in rehabilitation as a powerful tool for brain education, in ways that are not only backed up by clinical research findings but are also supported by an understanding of some of the mechanisms of how music acts in brain function. So, evidence-based models of music in therapy have moved from soft science, or no science, to hard science. Neurologic music therapy does meet the standards of evidence-based medicine, and it should be included in standard rehabilitation care.

4.1.1 The neuroscience progress – the music as a stimulus

During the past two decades, new brain imaging and electrical recording techniques have been combined to reshape our view of music in therapy and motor or cognitive education. These techniques (functional magnetic resonance imaging (fMRI), positron-emission tomography (PET), electroencephalography (EEG), and magnetoencephalography (MEG)) allowed us for the first time to watch the living human brain while people were performing complex cognitive and motor tasks. Now it is possible to conduct brain studies of perception and cognition in the arts as music and dance [159].

From the beginning of imaging research, music was part of the investigation for those who could play a musical instrument or were professional musicians or even those who listened to music and used it as a sensory stimulus. Scientists used it as a model to study how the brain processes verbal versus nonverbal communication, how it processes complex time information, and how a musician‘s brain enables the advanced and complicated motor skills necessary to perform a musical work. After years of such a research, two findings stand out as particularly important for using music in rehabilitation. First, the brain areas activated by music are not unique to music and the networks that process music also process other functions. Second, music learning changes the brain (although this is mainly for musicians).

The brain areas involved in music are also active in processing language, auditory perception, attention, memory, executive control, and motor control [161]. Music efficiently accesses and activates these systems and can drive complex patterns of interaction between them. For example, the same area near the front of the brain (Broca‘s area) is activated whether a person is processing a problem in the syntax of a sentence or in a musical piece, such as the mistaken use of a verb in a sentence or a wrong note in a melody. This area, is also important in processing the sequencing of physical movement and in tracking musical rhythms, and it is critical for converting thought into spoken words. Scientists speculate, therefore, that Broca‘s area supports the appropriate timing, sequencing, and knowledge of rules that are common and essential to music, speech, and movement [162].

A key example of the finding that music learning changes the brain is that research clearly shows that, through such learning, auditory and motor areas in the brain become broader and interact more efficiently. This is why auditory area plays an important role in biofeedback technique in motor control training; because auditory signals incorporated into the whole processing. After novice pianists have just a few weeks of training, for example, the areas in their normal brain, serving hand control, become larger and more effective connected. It quickly became clearer that music could drive plasticity in the human normal brain, shaping it through training and learning .

In neurological rehabilitation field similar results have been described. It is supported that the brain changes in terms of structure and function as a result of learning, training, and environmental influences. Exposure and experience will create new and more efficient connections between neurons in the brain in a sort of rewiring process. This discovery fundamentally changed how therapists developed new interventions. Passive stimulation and facilitation were no longer considered effective; active learning and training promised to be the best strategy to help rewire the injured brain and recover as much ability as possible. Further clinical research has strongly confirmed this approach.

By combining these developments, brain imaging, insight into plasticity, and finding that musical and non-musical functions share similar systems, “therapists” in rehabilitation team finally could build a powerful, testable hypothesis for using adequately music in rehabilitation. Music can drive general reeducation of cognitive, motor, speech and language functions via shared brain systems, circuits and plasticity. Although once it was used only as a supplementary stimulation to facilitate treatment, music could now be investigated as a potential element of active learning and training.

4.1.2 The relation with the movement

In order to explore this neurophysiological hypothesis, shared mechanisms between musical and non-musical functions in motor control have to be studied. One of the most important shared mechanisms is *rhythm* and *timing*. Timing is the key to proficient motor learning and skilled motor activities. Without it, a person cannot execute movement appropriately and skillfully. Rhythm and timing are also important elements in music. Rhythm timing adds an anticipation component to movement timing. The necessary harness for all elements of musical sound architecture, the rhythm, is also important in learning the appropriate motor control in order to play music. It is hypothesized that by using musical rhythms as timing signals, may improve a person ‘s motor control during non-musical movement.

To test this idea, rhythmical auditory cues have been used in order to give people an external “sensory timer” with which they could try to synchronize their walking. When the effort is made with Parkinson‘s disease patients or with stroke, their improvements in certain areas were instantaneous and stunning [160]. By following the rhythmic cues, patients recovering from stroke were able to walk faster and with better control over the affected side of their bodies. Some of the more complex measures of movement control, such as neuromuscular activation, limb coordination, angle extensions, and trajectories of the joints and centers of body mass, also became significantly more consistent, smoother and flexible. For those with Parkinson‘s disease, it was interesting to see that music and rhythm could quicken their movements and also serve as an auditory trigger to keep the movements going and prevent freezing (the sudden halt of all movement), which occurs frequently in Parkinson‘s patients [160].

These improvements held up over long-term training and also proved to be superior in comparison with other standard physical therapy interventions. Then the same concept was applied to arm therapy, with similar success. The rhythmical auditory stimulation-based therapy is now considered as a part of the state-of-the-art repertoire in motor therapies. These results added weight to the idea that music could shape movements in therapy by accessing shared elements of musical and non-musical motor control (rhythm, timing) and thus powerfully enhance re-learning and re-training in a clinical environment. In another study [163] where brain imaging was utilized in patients with stroke, arm training with auditory rhythm triggered brain plasticity, as predicted. The training activated also additional areas in the sensorimotor cortex and the cerebellum. In comparison, standard physical therapy did not result in any evidence of new changes in brain activation.

4.2 Music-supported Therapy in Stroke-induced Motor Dysfunction

The effectiveness of standard physiotherapeutic approaches in stroke rehabilitation has been found to be quite limited, thus calling for innovative motor rehabilitation approaches [164]. Data indicates that repetitive massed practice of movements leads to improvement in motor function with changes being attributed to neural reorganization [165]. Other studies have shown rapid plastic adaptation due to music performance, which is not restricted to cortical motor areas but also involves auditory and integrative auditory–sensorimotor circuits [166][167]. This suggests that music-making, even in unskilled patients, might be an effective mean to induce plastic changes in the motor system.

While sharing the repetitive character of movements with other therapies, music could additionally shape movements through the immediate auditory feedback. Moreover, the high motivational value of music and, possibly, audio–sensorimotor coupling implies that music might be useful in the rehabilitation process. Preliminary data have shown positive effects of music-supported therapy [168].

5 Virtual Reality Rehabilitation based on Music (VRehaM)

5.1 Description of our VR platform

Our aim is to provide an alternative and efficient way to improve the fine movements of the paretic hand in stroke, or other neurological disease's, patients. Combining novel Presence Positive Technologies for Well-being and techniques of Neurologic Music Therapy, we have developed a VR game using an HMD Occulus Rift for securing the sense of presence and a Leap Motion to track fingers' and hands' motion. For the adequate movements that will constitute the proper exercises, a team of doctors of KAT hospital in Athens has advised us.

The idea of the game is authentic and doesn't concern an existing design-for-fun game.

Our expected outcome, contributing to the current game-based Rehabilitation Field, regards to a new integrated platform offering a more motivating and efficient way for patients being in a chronic phase of a stroke, to continue their exercises' program at home. Our intention is to provide an adequate feedback, a proper guidance, a better motivation and an additional aid for stabilizing the movement based on musical stimuli. Moreover, as we expect from the patient to perceive the musical rhythm and fit his/her movement into it, we also deal with the cognitive processes of him/her, which, the most of the times, are not taken into account.

5.1.1 The game

The environment and the set up of the game have been carried out in Unreal Engine 4.0 (UE4). The principal character of our game, which guides and helps patients to perform the exercises, has been designed, rigged and animated in Maya. Motion tracking has been done using Leap Motion and gestures have been carried out in Unreal Engine.

5.1.1.1 Unreal Engine 4 – The environment

For the development of the game, UE4 was used due to the possibilities it can offer and its easy of use.

Figure 5-1: Panoramic shot of the environment where the game takes place

The development of the environment was based on several possibilities and features offered by UE4. First of all, we used a skybox. In general, skybox is used to secure the existence of the sky. In our case, it was employed in order to help us to support the sense of a different planet. Thus, we created a cloudy atmosphere, giving the sense of outer space.

Figure 5-2: The skybox

For the lightning of the scene, a directional light was used combined with a sky light. The directional light represents the sun, while the sky light constitutes a type of area light that depicts the sky's appearance and its reflections and applies them to the scene. Moreover, the built-in global illumination of UE4 was added in order to have a more realistic lightning, bouncing from object to object. Finally, ambient occlusion was added in order to exaggerate indirect shadows and enhance the perception of proximity in the scene.

For the implementation of the platform that constitutes the overall environment where the game takes place we used the Landscape Editor.

In addition, in order to give the illusion of the existence of the wind, we created a shader using the Material Editor of UE4. For its implementation, several built-in functions of UE4 were used.

Finally, particles for the enhancement of the space attribute were created using cascade particle editor.

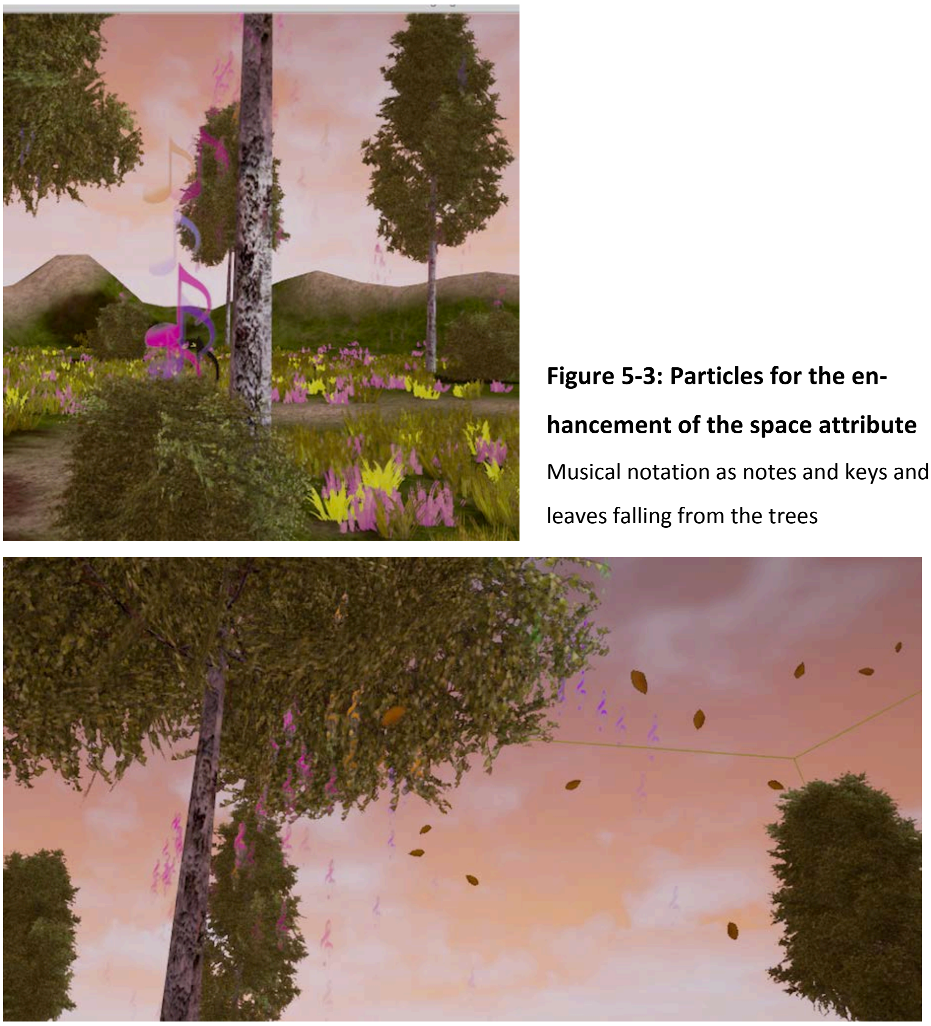

Figure 5-3: Particles for the enhancement of the space attribute

Musical notation as notes and keys and leaves falling from the trees

5.1.1.2 The character

Design, rigging and animation

Design, rigging and animation were implemented in Maya 2016.

Figure 5-4 : Orpheus

The model as presented in UE4.

Lip-syncing

Lip-syncing was performed via the creation of blendshapes in Maya 2016 and their combination in UE4. We created blendshapes for all the vowels and some of their possible combinations and then we converted them in animations for easily using them in UE4. Afterwards, we used an animation asset provided by UE4, the *Animation Sequence Editor*, where we took the animation sequences we had created and we synchronized them with the oral text.

5.1.1.3 Leap Motion

For the hand motion detection, leap motion v3 ORION was preferred. We used getnamo's plugin for the UE4 [179] in order to integrate leap motion SDK with UE4.

5.1.1.4 The exercises

The purpose of the game is the proper execution of four exercises. One intro exercise, which constitutes the salutation between Orpheus and the patients, and three more exercises concerning the fine movement of their hand were used, as we will describe below. Motion detection was performed with Leap Motion.

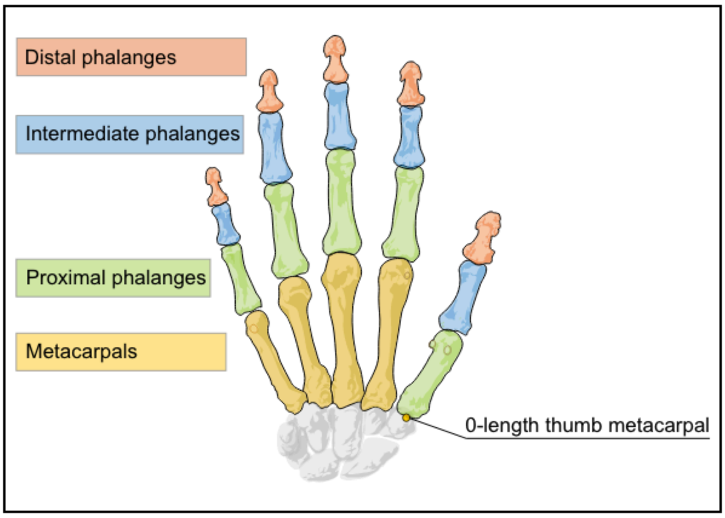

Figure 5-5: The hand bones as they are identified by the API overview of Leap Motion

For the *welcome exercise*, we used the vector *next* joint, provided by the API of Leap Motion, for the intermediate phalanges and we examined the change of position for each finger. We checked the angle between the created vectors. Mathematically, we used the cosine of the angle based on the formula:

$$\cos\theta = \frac{\alpha^{T} \cdot \beta}{\|\alpha\| \|\beta\|}$$

where α is the previous_next_joint and β is the current_next_joint. The successful execution was determined by a specific angle, which, at the end, we adapted at the patient's difficulties that we notices during our integration.

For the *exercise 1* (flexion and extension of the wrist), we used the vector *palm normal* of the SDK (vector vertical to the palm) and we examined the possible changes at the direction based on a baseline determined at the beginning.

For the exercise 2 (pronation and supination of the forearm), the built-in function of Leap motion SDK, Leap Right/Left Palm Roll, was used .

For the exercise 3 (opposition of the fingers with the thumb), we examined for each finger the distance of their fingertips (distal phalanges). Specifically, we took the distance between the thumb and the current finger we wanted to test and we assessed the changes in this distance.

5.1.2 Neurologic Music Therapy

The above movements were combined with specific neurologic music therapy techniques, such as Therapeutic Instrumental Playing (TIMP) and Patterned Sensory Enhancement (PSE). TIMP maps functional movements unto musical instruments (mostly percussion, keyboard, or digital sound surfaces) and engages the patient in practicing motions repetitively and cyclically via musical instruments. PSE regulates functional movement by translating the temporal, spatial, and force-dynamic components of movement kinematics into sound patterns, and then plays them back to provide feedback and feedforward regulation for enhanced motor control.

We chose to implement these techniques through a VE in order to provide patients with opportunities that they may not be able to physically have otherwise. This enabled them to play the instruments we selected not in the traditional way but in a more simple and easy way, assuring that it is still interesting for them. We chose musical pieces with intense and clear rhythm in order to support their movement. Moreover, these pieces were mainly well-known so that can make patients feel familiar with the process and enjoy it.

5.2 Integration of VRehaM

After the completion of the platform and the specific scenario that is believed to be able to guide the patient acting at the virtual environment, patients for assessing their efficiency were selected. Selected patients suffered generally from neurological damage, two (one female and one male) from a motor control lesion, such as stroke resulting in hemiplegia, and one female patient with a generalized neurological disease with predominant symptoms of muscular weakness and executive capacity, such as Guillain-Barré syndrome (GBS). These patients were thought to be able to meet the requirements of the scenario we created for the re-training the movements of the affected hand.

All patients had overtaken the acute stage of their condition and were in the stage of re-education and training. They did not have any other limiting factors that could affect their basic clinical picture or that could possibly have made it difficult for them to follow such programs of a mental nature. Restriction factors may be included: a) local upper limb lesions, such as previous lesions and injuries and factors that previously restricted the upper limbs movements, b) increased spasticity or other spastic condition that would interfere with the potentially active movements, c) stiffness of the upper limb joints with subsequent contractures and other muscle stiffness or atrophy, d) concomitant diseases that would affect learning, as neurological conditions that affect memory and movement (as Alzheimer's and Parkinson's disease) and other pathological conditions (respiratory and cardiological diseases) that can dynamically affect the patient's physical condition, strength and adequacy e) cognitive deficits that would make it difficult to process orders and general the patient’s perception, attention and concentration.

For the integration of our platform, 3 patients were selected, all of whom met the exclusion criteria.

5.2.1 Patients who received our VR procedure

Patient A – A 56 years old female patient suffering from stroke duo to medial cerebral artery occlusion (Figure 5-6). She was admitted to rehabilitation unit 20 days after the stroke. She presented a right hemiplegia, with serious deterioration in her upper limb movements, while her gait was satisfactory and with safe pattern. She immediately started her training program for her motor and cognitive deficit. The target of the program was to enhance the mobility of the hand and to increase its overall functionality, in order to be properly trained for the activities of daily life and self-care. She had no problem with her cognitive function, nor did she have any other limiting factor in her hand's function.

Figure 5-6 : Patient A

(Woman, 56 y, suffering from right hemiplegia due to stroke). Starting position. The patient prefers to follow the program in standing position. Normally he or she is sitting in front of the PC screen.

Patient B – A 32 years old male patient suffering from left hemiplegia hemorrhagic stroke due to cerebral benign tumor, which was removed, 2 months ago (Figure 5-7). After surgery, the young patient presented with left hemiplegia with a higher prevalence in the upper extremity while his walk was much less problematic. He was admitted to rehabilitation unit 15 days after the surgery and the establishment of the new clinical condition and followed a program for about 1,5 months. Upper limb movement deficit was very serious, manifesting weakness in almost all distal movements of the hand, while in the most central regions of the limb the movements were synergistic. The difficulty in training was significant from the very beginning and the main objective of the training was the attempt to include the affected upper limb into most of the daily life activities, even with a supportive role through a synergistic pattern.

Figure 5-7: Patient B

(Man, 32 y, suffering from left hemiplegia due to hemorrhagic accident-stroke). Starting position. The patient prefers to follow the program in sitting position.

Patients C – A 52 years old female suffering from GBS (Figure 5-8). This is a neurological clinical condition that was presented with rapid-onset muscular weakness caused by the immune system, damaging the peripheral nervous system. Unlike to the previous two cases, where we have had an attack on the central nervous system that substantially affects motor control alongside with another cognitive attack, this case refers to the peripheral nervous system, the executive part of the motor activity.

Figure 5-8 : Patient C

(*Woman 52 y, suffering from Guillain–Barré syndrome, a rapid-onset muscle weakness caused by the immune system damaging the peripheral nervous system. In this patient, there is a more severe attack on the right side while the left remains intact. 2 months after initial attach).* Starting position. The patient prefers to follow the program in sitting position.

There is a significant difference in these three cases. The first two cases refer to central nervous system damage, mainly to the brain, which presented with hemiplegia, where the patient is aware of what to do but cannot perform any action because the control carried by the central structures for motion action to the periphery, has been affected. The patient is well aware of what to do but cannot perform it because there is no coordination and collaboration between responsible muscle groups. In this case, the "periphery" is intact and is expected to provide the appropriate information (feedback) signals to use them in the process of motor education and re-training. The main objective of this training is to use the VE as a main tool, providing a proper sensory stimulus to the process of motor control retraining. On the other hand, the third case is a clear damage of the executive mechanism (the peripheral nervous system and the muscles) where, while the motor control mechanism is not affected, the patient is unable to perform motor attacks due to muscle weakness. In this case, the justification of education through the virtual environment is based on the possible ability to enhance muscle effort through the sensory feedback she receives after every effort. It works like the technique of “biofeedback”, with the difference that the internal signal for the hidden motor activity is taken from the virtual-mirror motor action and patient's transportation in a well-organized environment.

It should be mentioned that all patients were minutely informed of the procedure. The therapists, after having received the relevant update and instructions concerning the whole procedure, helped and guided the patient in order to be able to follow properly and efficiently the scenario. They tried to make patients feel familiar with the procedure by supporting that they will be in constant communication with an "extraterrestrial boy", Orpheus, whose main purpose is to help them overcome their difficulty of moving their hand, with his own different way in an also different environment. It was explained to the patients what exactly they will follow, how they participate, how they should react to what it is told to them and how they should participate using their environment and their own way of expression. This was followed by a series of motor activities selected for patients with motor control disorder following a serious neurological problem, like stroke.

The movements selected were focused on the extremity of the hand, wrist and fingers, referring to simple movements of mainly flexion-extension (Figure 5-9). However, in order to succesfuly complete the proposed motion, other characteristics of the motor pattern had to be effectively involved, such as coordination of the other muscular groups of the hand, agonists, antagonists and stabilizers muscles. In case of failure for self-supporting the hand, the therapist facilitated the process.

Figure 5-9: Preparation for the adaptations of the requirements of the VR environment.

The patient is guided for being able to manage the commands he or she will listen (by Orpheus) and learn how to react. The application is demonstrated in a healthy model-person.

In order to provide an additional motivation for a patient's pleasant and interesting involvement in the program, the movements were accompanied by several well-known and recognizable musical pieces. Each attempt was accompanied by a different style and consequently each movement by differently selected organs. Thus the patient's participation in the musical ensemble was highlighted. Specifically, the selected movements are:

Movement 1 (*Exercise 1*) - There is a responding greeting to the appearance of the Orpheus, referring to the extent of the wrist and the fingers, which is followed by bending only the phalanges of the fingers. Use of the affected hand that is projected forward by the patient by flexing the shoulder (Figure 5-10). This is the only movement that did not follow any music.

Figure 5-10: The first movements introduced to the patients

The first movement that is introduced to the patients, in the beginning of the game, is the greeting to "Orpheus" with the palm and fingers extended, a movement that followed by gentle flexion only of the fingers. The hand should be firmly held in place and positioned just in front of the patient. If the movement was correctly executed, it is confirmed with visual and audio signal.

Movement 2 (*Exercice 2* **)**– The second movement includes the flexion and extension of the wrist with the fingers in a neutral position, following the basic movement of the wrist. This movement requires the stabilization of the forearm and arm so that the movement of the wrist is accurately performed and excited in this particular context (Figure 5-11). The music that accompanied this movement was the 4/4 tango, written in 1935 by Carlos Gardel, "Por una cabeza". Each correctly executed patient's movement caused the production of percussion sound. Orpheus, as well as each patient, have in front of them one set of wooden bongos. The patient knew when it was the right moment for him/her to play, as his musical instrument was changing color (it was turned into green) in order to give a proper feedback and guidance.

At the end of each attempt, there was a "stick and carrot" type approach using a visual (green or red musical note) and audio (Orpheus giving reward or prompting the patient to try again) signal that verified the quality and efficiency of the execution of the movement.

Figure 5-11: The second movement introduced to the patients

The second movement introduced to the patient, is the extension and flexion of the wrist, while the elbow and shoulder is stabilized accordingly, by the patient or the therapist. This movement ends up fulfilling the goal that "Orpheus" has set in his own environment. The efficiency of movement's execution was confirmed with visual and audio signal offered by Orpheus and the overall virtual environment.

Movement 3 (*Exercise 3*) – The third movement includes the pronation and supination of the forearm with the movement concentrating on the area of the wrist and forearm, requiring also the stabilization of the shoulder and elbow. If this is not possible by the patient itself, it is supported by the therapist (Figure 5-12). The music that accompanies this movement is the 4/4 piece, written by Peter Green in 1968 and known by Santana, "Black Magic Woman". The patient with his movements plays the cymbals.

Figure 5.12: The third movement suggested to the patient

The third movement suggested to the patient, is the pronation and supination of the wrist, while the elbow and shoulder is stabilized accordingly, by the patient or the therapist. This movement ends up fulfilling the goal that “Orpheus” has set in his own environment. The efficiency of movement’s execution was verified with visual and audio signal offered by Orpheus and the overall virtual environment.

Movement 4 (*exercise 3***) –** The fourth movement concerns the opposition of the fingers with the thumb. It begins with the thumb-index, thumb-middle finger, thumb-ring finger and thumb-pinky finger oppositions. All these are considered to be the most difficult movement of the hand, which play an essential role in the functional performance, because it is related to its grasping ability, and of course it requires high hand stability (Figure 5-13). The music that accompanies this movement is the 5/4 jazz composition of Paul Desmond, which was recorded by David Brubeck Quartet in 1959, “Take Five”. The patients were encouraged to play the castanets.

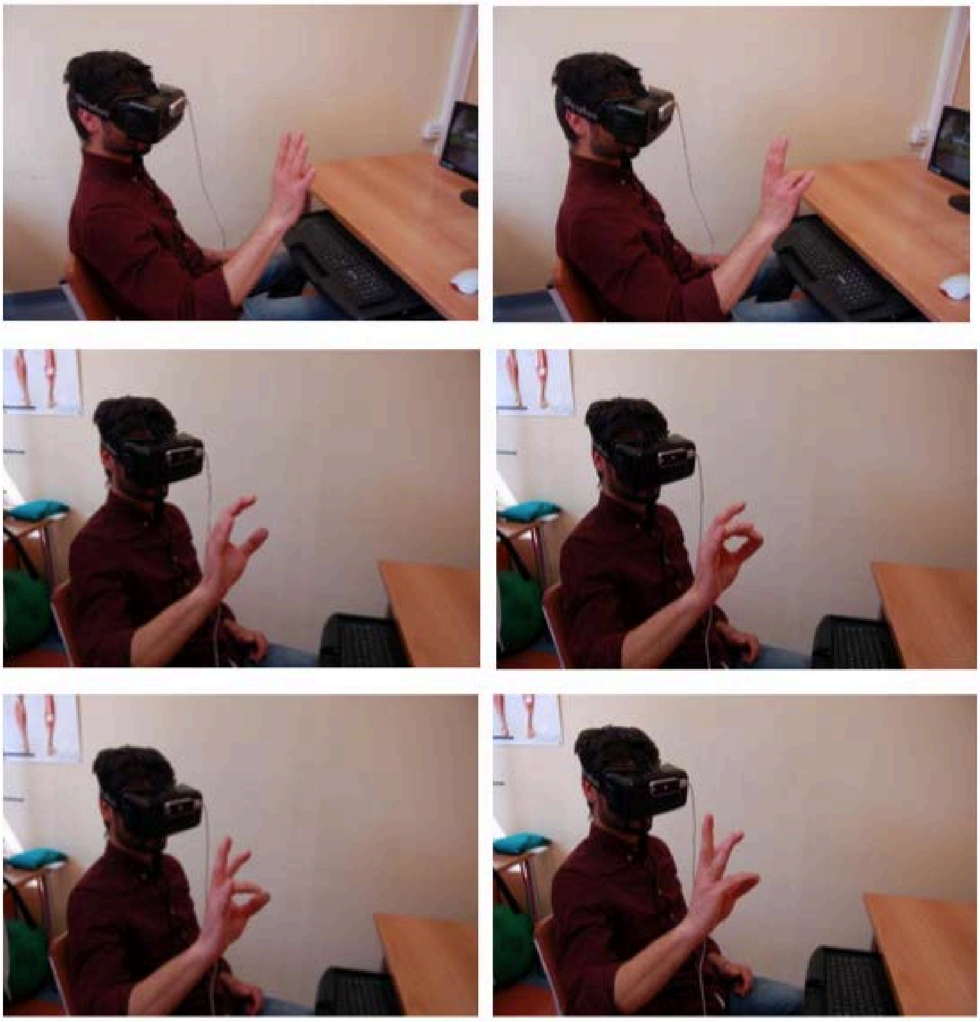

Figure 5-13: The forth movement introduced to the patients

The forth movement introduced to the patients, is the opposition of the fingers (against thumb), while the elbow and shoulder is stabilized accordingly, by the patient or the therapist. This movement ends up fulfilling the goal that "Orpheus" has set in his own environment. The efficiency of movement's execution was verified with visual and audio signal offered by Orpheus and the overall virtual environment.

During the game process, the motor actions followed a certain order, always the same for everyone, while offering opportunity to the patient for trying to imitate the Orpheus motor inducement. Subsequently, the patient can choose from the intro menu which exercise wants to repeat. The sound signals produced by the music and the patient's ability to be involved in music which is produced by himself (as a sensory information stimulus) offer a very important motivation and interest to complete the motor effort.

5.2.2 The integration

The integration of our platform was performed in the Occupational Therapy department of the Physical and Rehabilitation Medicine department of KAT hospital of Athens, and it was performed within the framework of the daily therapeutic program of the particular patients. All of them were previously notified in detail about the application and the scenario that would be followed. They were introduced exactly to what they would face and how they should be involved in the process. The order of application was randomized.

The room was totally quite, it was illuminated by daylight without intense brightness (which is also shown in the photographs taken) and there was no pictures or other evidence on the wall or in the environment that could draw the attention of the patient from the beginning. Inside the treatment room there was no other persons except the therapists and the program manager. It was selected morning time to be integrated into the daily schedule of patients therapy. Patients A and C were in patients, in the clinic of PRM department, and patient B was discharged and taken his therapy at out-patient basis.

At the end and at the beginning of the procedure, patients were persuaded to complete a questionnaire concerning stress, self-efficacy and optimism, in order to assess if our game has a different effect that can finally increase its efficiency.

5.2.2.1 Patient A

This 56 years old right hemiplegic woman, followed an occupational therapy program for about 2 months and had made a significant improvement in the movement of her hand, offering some help in carrying out daily activities. Of course, there was a major motor deficit regarding fine hand movements. The followed occupational therapy program was based on task-oriented therapy concept. So, she was familiar with the motor skills and motor patterns presented in the VRehaM.

In movement 1 (Figure 5-14) the main difficulty was the stabilization of the right hand to which the therapist helped. It was obvious that, despite the initial difficulty in carrying out the movement, after a few attempts and with the therapist guidance, she began to follow the extension pattern, indicating that it began to break and disrupt the flexion pattern of the hand that already prevailed.

Figure 5-14: Patient A – Exercise 1

(*Woman, 56 y, suffering from right hemiplegia due to stroke, 3 months after stroke*). She is going to make a greeting to "Orpheus". She is not able of executing the movement. At the beginning of the activity she is not able to stabilize her hand as it is supported by the therapist. However, after one or two attempts, the execution of the activity is better.

In movement 2 (figure 5-15), the clear predominance of the flexion pattern of the hand is evident. But it is indicative that, after a few efforts and the precise perception of Orpheus' instructions, this pattern was broken down and the patient began a successful extension of the wrist. This motor reaction seems to be facilitated with the help of Orpheus guidance.

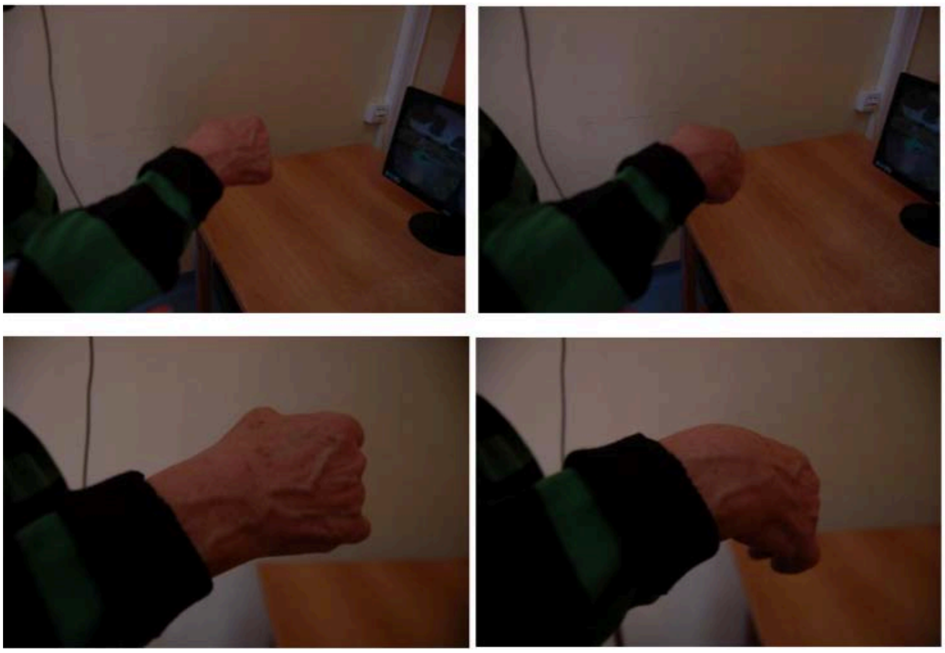

Figure 5-15: Patient A – Exercise 2

(*Woman, 56 y, suffering from right hemiplegia due to stroke, 3 months after stroke*). The flexion and extension of the wrist is signaled by the first attempt. But, after three repetitions and the guidance of Orpheus, the movement was completed in more successful way.

In movement 3 (Figure 5-16) great coordination is needed to complete the pronation and supination of the wrist. This movement requires cooperation of all muscle groups working on hand and that is why it stimulated synergistic movement pattern, as shown in picture. This synergistic motor pattern cannot be broken down by any therapeutic intervention.

Figure 5-16: Patient A – Exercise 3

(*Woman, 56 y, suffering from right hemiplegia due to stroke, 3 months after stroke*). Pronation and supination of the wrist is a very difficult movement that this patient is not able to perform despite the efforts she makes. It is also necessary for the hand to be supported, because of the lack of balance and the coordination of her movement.

For the last movement (figure 5-17) the degree of difficulty is great, because it is the finest movement of the hand. The finger opposition refers to the grasping capacity of the hand, which is its main function. However, after the perception of motor mechanism underlying this movement and after a few repetitions, we noticed that this activity can be completed, suggesting that the guidance imposed by the virtual environment can secure the required concentration and attention of the patient. The apparent effort of last two photos is just indicative that the ability to perceive motion is facilitated by the “program”.

In general, it appears that patient A has shown an improvement in her attitude to complete the movement in terms of the perception of motor action, which is shown by movement 4. This movement requires increased concentration and attention, which are indicative of the internal information given by the sensory information provided by virtual environment. It seems that these observations satisfy the basic concept of the whole process, since the sensory stimuli offered by the virtual environment shows that can improve patient ’s attention, as it is clearly shown through the improvement of the motor function.

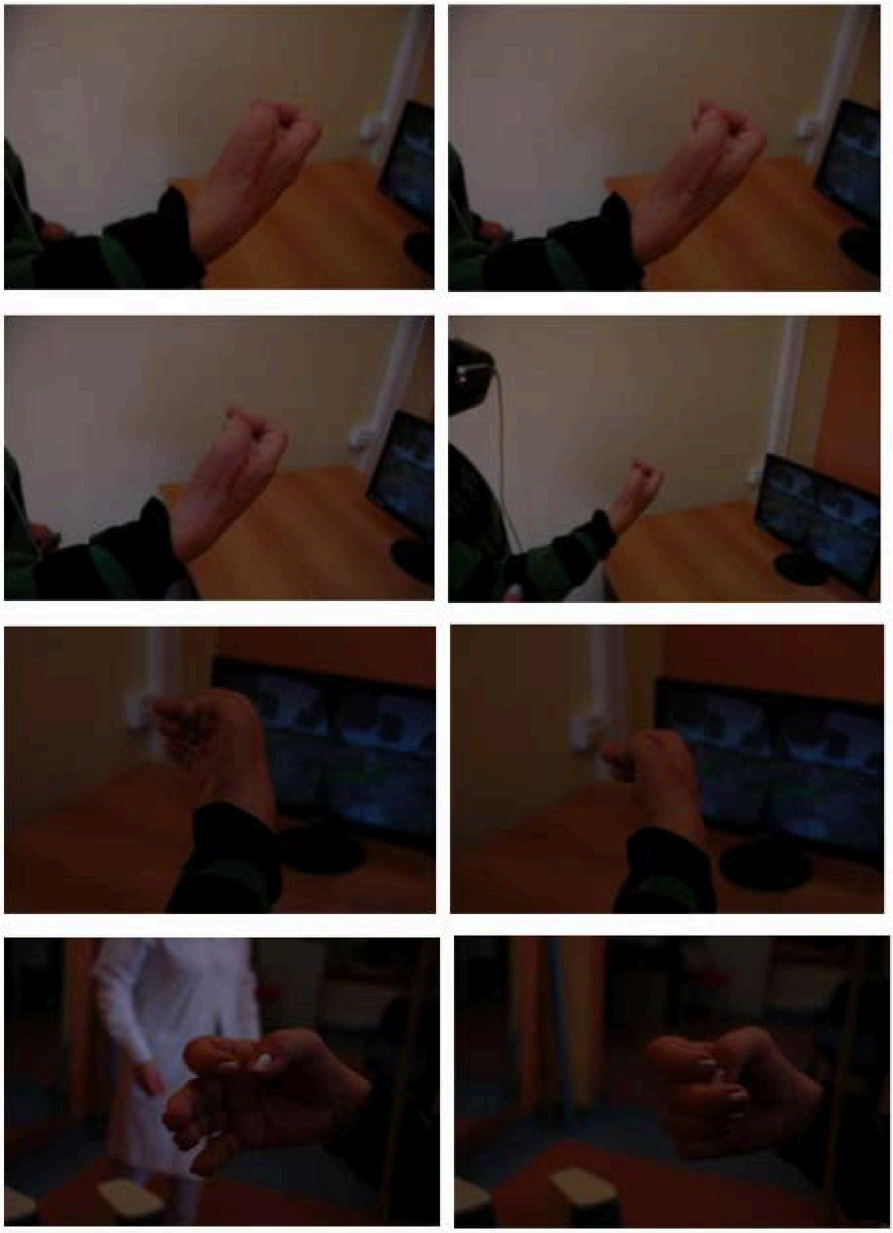

Figure 5-17: Patient A – Exercise 4

(*Woman, 56 y, suffering from right hemiplegia due to stroke, 3 months after stroke*). The oppositional movements of the fingers are very difficult and complicated movements with significant functional consequences, which are indicative of finger coordination and characteristics of fine grasping ability of the fingers. While at the beginning a clear difficulty in completing this movement is presented, after only a few attempts the movement becomes easier and extends to the other fingers, which were initially impossible.

5.2.2.2 Patient B

The 32 years old left hemiplegic young man presents a more significant difficulty because he shows increase spasticity at the affected upper limb. He followed an occupational therapy program for about 1,5 months after stroke, without any significant improvement in the motor pattern of his hand. Thus, there is a general motor deficit concerning the whole movement of the hand. The occupational therapy program that followed was based on task-oriented therapy concept. So, he was also familiar with the motor skills and motor patterns presented in the VRehaM.

Movement 1 (Figure 5-18) seems impossible because the flexion pattern of hemiplegia dominates. Any attempt to extent the wrist will therefore fire synergy. Although he concentrates and tries to execute the order, it is impossible due to spasticity.

Figure 5-18: Patient B - Movement 1

(*Man 32 y, suffering from left hemiplegia due to hemorrhagic stroke due to benign tumor, 1 and a half months after stroke*). He is going to make a greeting to “Orpheus”. The effort is being made but the flexion motor pattern of hemiplegia dominates. Nevertheless, in the third attempt, an effort is made to extend the wrist and especially the fingers towards the completion of the greeting activity.

Movement 2 (Figure 5-19) is also impossible due to flexion motor pattern. In the extension effort of the wrist, the flexion synergy of the hand manifesting with the extension of the fingers, especially the index, is triggered. At the same time, hand stability is disturbed due to the diffusion of motor synergy. But after some efforts and when the patient has received, interpreted and realized exactly what to do, the wrist has better stabilization and begins a motor action toward extension, independently of the synergistic pattern. The process is attributed to the patient’s high concentration and attention to the sensory stimuli of feedback information received from the virtual environment.

Figure 5-19: Patient B - Movement 2

(*Man 32 y, suffering from left hemiplegia due to hemorrhagic stroke, 1 and a half months after stroke due to benign tumor*). In this motion, the predominance of the flexion motor pattern of hemiplegia is extremely obvious. The extension of the wrist is impossible and only the extension of the fingers is indicated, which remains constant even when the patient is trying to flex the wrist. Finally, this effort breaks down the stability and balance of the hand. So, for this reason it might be supported by the therapist. There is no improvement course throughout the whole trial, because the flexion motor pattern is too strong and dominates.

Movement 3 (Figure 5-20) has the same outcome with the previous movement, because the same flexion motor pattern is triggered.

Figure 5-20: Patient B - Movement 3

(*Man 32 y, suffering from left hemiplegia due to hemorrhagic stroke, 1 and a half months after stroke due to benign tumor*). Pronation and supination of the wrist is a very difficult movement, as mentioned above, and the patient is not able to perform despite the efforts he makes. When the pronation begins, flexion is carried out due to the prevalence of the flexion pattern, while it raises the fact that after three attempts, during wrist supination, the flexion pattern was partly overcome and finally, this movement was followed by a visible extent of the wrist and the fingers. This asserts that the patient fully understands the movement, he knows what to do, he tries to execute it, but he is not able of doing it. Thus, with the help of Orpheus this becomes more understandable and starts the inversion effort.

Movement 4 (Figure 5-21) is a surprise. Even though it is considered a very difficult movement that requires high coordination, in this case the understanding of the movement offers the possibility of movement formation, as shown in the last two photographs. There is opposition despite the strong flexion motor pattern.

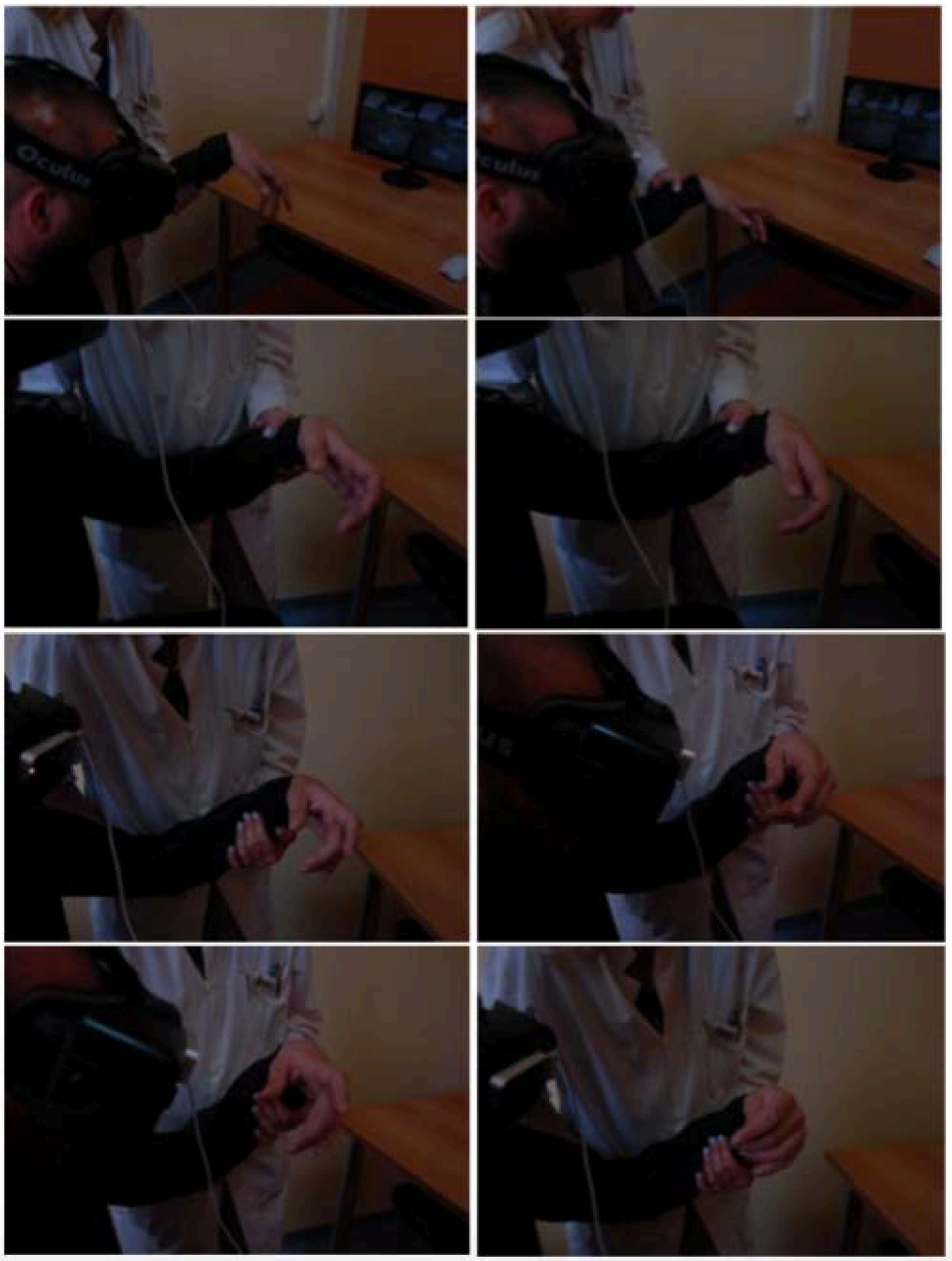

Figure 5-21: Patient B - Movement 4

(*Man 32 y, suffering from left hemiplegia due to hemorrhagic stroke, 1 and a half months after stroke due to benign tumor*). The oppositional movements of the fingers are the most difficult and complicated movements of all fine movements of the hand. The predominance of the flexion motor pattern makes the movement impossible. The impressive is that after few attempts, the patient perceives precisely its sequence of motion and he is now trying to complete its mechanism. This is evident in the last two photos, and it is considered surprising for the training of motor control in the hemiplegic patient.

5.2.2.3 Patient C

The 52 years old woman suffers from Guillain–Barré syndrome, a neurological condition that affects peripheral neurons system with muscle weakness and serious motor deficits due to this weakness. She followed an occupational therapy program for about 2 months after onset, with some improvement in the hand functioning. The occupational therapy program followed was based on task-oriented therapy concept. Although there was no problem in her cognitive function, there was an initial difficulty in understanding the whole process, but the patient eventually realized it completely and thus, she understood all the motor skills and motor patterns presented in the VRehaM.

In movement 1 (Figure 5-22), the difficulty focuses on muscle weakness due to peripheral nervous lesion. In this case, the muscle weakness is more evident in the distal parts of kinetic chain. This first movement of the program requires the stability of the wrist in order to complete to motor activity of flexion of the fingers, as a greeting. This movement is impossible to be achieved in this case; instead, an extension of the gingers is presented to replicate the effort, which is clearly perceived by the patient, but she is not able to execute it.

Figure 5-22: Patient C, Movement 1

(*Woman 52 y, suffering from Guillain–Barré syndrome, 2 months after initial attach).* The movement of greeting is impossible due to muscle weakness while the patients seems to have a complete understanding of the exercise.

Concerning movement 2 (Figure 5-23) on the contrary, despite the muscular weakness, the beginning of the movement is signaled, giving a small but certain range of motion between flexion and extension of the wrist. After a few attempts, this range of motion is increased, as a result of influence of the sensory feedback-information signal received by the patient from the VR system. This is an excellent response to the biofeedback process for enhancing muscle effort. The sensory information signal from her effort, received by Orpheus, acts as a mirror for the patient’s effort and it reinforces its effect, since she clearly understands that it moves it on her own. She attends her effort to deliver significant results. The VR system, thus, appears as a mirror of her active effort and offers to her the opportunity to strengthen and reinforce her motor effect. In other words, she observes via “Orpheus” the copy of her effort and the final outcome.

Figure 5-23: Patient C, Movement 2

(*Woman 52 y, suffering from Guillain–Barré syndrome, 2 months after initial attach).* The difficulty of performing the movement of flexion and extension of the wrist is clearly attributed to muscle weakness. However, after a few attempts the movement mechanism, that comes into play, begins to be perceived and thus begins to signal the flexion and extension of the wrist. The whole process functions as a biofeedback mechanism.

In Movement 3 (Figure 5-24) there is obviously a greater ability to perform, which is successfully completed since more central muscle groups are involved.

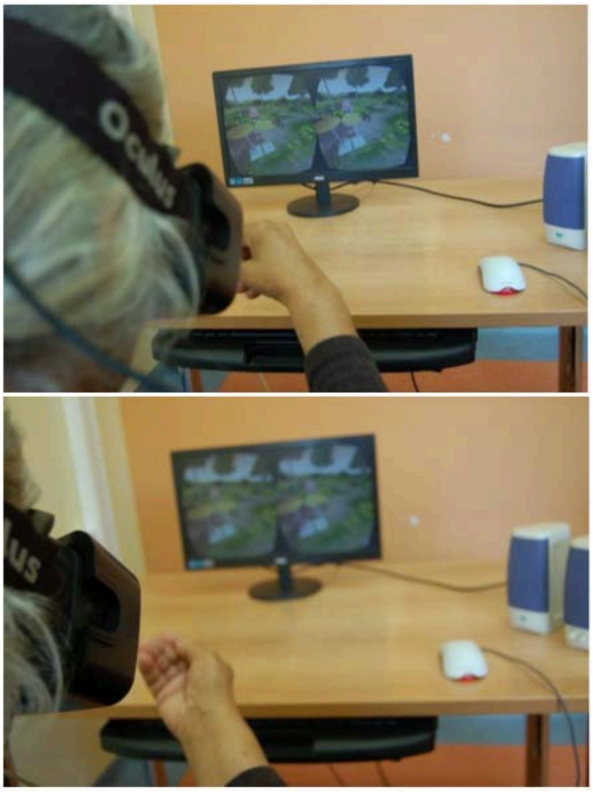

Figure 5-24: Patient C, Movement 3

(*Woman 52 y, suffering from Guillain–Barré syndrome, 2 months after initial attach).* Pronation and supination of the wrist are performed more easily because muscle weakness, which is more evident in the small muscle groups of the hand, maintaining a satisfactory level of functionality, which facilitates further training (with biofeedback concept).

Finally, (Figure 5-25) despite the greater peripheral weakness, movement 4 seems to work for the patient and apparently much more than it is expected. Moreover, the hand is not supported.

Figure 5-25: Patient C, Movement 4

(*Woman 52 y, suffering from Guillain–Barré syndrome, 2 months after initial attach).* Similar outcome as movement 3 is noticed, where the possibility for further education and training is obvious.

6 Discussion

Cerebral Vascular Accidents (CVA), to wit Stroke, and its consequences is a leading cause of death and disability around the world, and the majority of survivors experience mainly chronic motor deficits (and more rarely residual cognitive deficits) associated with reduced quality of life [1]. Stroke is a devastating disease for patients and their families and a leading cause of adult disability. The risk of stroke increases steeply with age; thus, with the aging of the population, an increase in the prevalence of stroke is expected. Between 55% and 75% of survivors continue to experience motor deficits, associated with reduced quality of life [174]. Consequently, concerning the aging population, more individuals are expected to face the challenge of managing diminished function after stroke. Current clinical practice guidelines for stroke rehabilitation are based on increasing evidence from basic science and clinical studies of the remarkable potential for brain remodeling due to neuroplasticity after neurological injury [174]. Specifically, recent studies have suggested that training has to be challenging, repetitive, task-specific, motivating, salient, and intensive for neuroplasticity to occur [175]. However, current resources are unable to fulfill the intensity requirement for optimizing post-injury neuroplasticity. Although standard rehabilitation (ie, physiotherapy and occupational therapy) helps to improve motor function after stroke, only modest benefits have been shown to date.

Neurophysiological data suggests that considerable amounts of practice are required to induce neuroplastic change and functional recovery and adaptive changes of these motor deficits [2]. These changes, of course, require a very high level of education and specialized retraining procedure, which should be intensive and lasting from the very first stages of the stroke, so that it is possible to take advantage of the potential of neuroplasticity. Because the programs to be implemented in these cases are longstanding, requiring the intimate collaboration of the patients himself, his close environment and of the rehabilitation team, this requisite high repetition becomes problematic. Moreover, observational data show that patients and their relatives generally perform only a part of the recommended program and a very limited number of movement repetitions in their traditional therapy sessions and rehabilitation programs also. Furthermore, many financial, environmental, insurance, social and individual barriers limit the efficacy of conventional therapy for post-stroke adults. These barriers affect the life of the patient and interfere with the whole family, relatives and working environment, disturbing the balance and the quality of their life in many levels.

Consequently, research is often focused on optimizing an individual's potential amount of recovery for a given amount of time in therapy. In practice, with the implementation of training programs focused on improvement of motor deficits in stroke, we are looking for the best result within the shortest possible time so that the patient can be disengaged, as soon as possible, from the therapeutic programs. Thus, the aim is the application of education programs that could offer optimal results, taking full advantage of the patient's potential, in order to achieve the best functional outcome for the everyday life. Such a perspective cannot be promised by traditional therapeutic methods. This is the main reason why new interventions, including robotics and VR technology, that target the inherent potential of the brain, such as neuroplasticity, are constantly been introduced.

6.1 Introducing VR into Rehabilitative strategies

One proposed method for optimizing the effects of therapy is the use of VR programs. VR and interactive video gaming have emerged as new treatment approaches in stroke rehabilitation. As mentioned above, VR can be defined as a type of user-computer interfaces that implements real-time simulation of an activity or environment allowing user interaction via multiple sensory modalities (8). VR therapies are an appealing avenue of research due to the benefits it can provide to patients and therapists, such as additional feedback during therapy, increase patient motivation, and dynamically adjustment of the difficulty of therapy. VR technology has the capability of creating an interactive, motivating environment in which practice intensity and feedback can be manipulated to create individualized treatments to retrain movement.

Virtual reality has been used previously in a variety of vocational training settings, such as flight simulation training for pilots and procedural training for surgeons. Within health care, the intervention has been used to treat phobias, post-traumatic stress disorder and body image disorders. Although its research in rehabilitation is becoming more prevalent as technology becomes more accessible and affordable, the use of VR is not yet commonplace in clinical rehabilitation settings. However, gaming consoles are ubiquitous and so researchers and clinicians are turning to low-cost commercial gaming systems as an alternative way of delivering VR [176]. Clinicians adapt these systems, which were initially designed for recreation, for therapeutic purposes. In addition, interactive video games are specifically being designed for rehabilitation [13].

In *virtual rehabilitation*, virtual environments and objects provide the user with visual feedback, which may be presented though a head-mounted device, projection system or flat screen. Feedback may also be provided through the senses, for example, hearing, touch, movement, balance and smell. The user interacts with the environment by a variety of mechanisms. These may be simple devices, such as a mouse or joystick, or more complex systems using cameras, sensors or haptic (touch) feedback devices. Thus, depending on the intervention, the user's level of physical activity may range from relatively inactive (for example, sitting at a computer using a joystick), to highly active (for example, challenging full-body movements). VR relies on computer hardware and software that mediates the interaction between the user and the virtual environment. As mentioned above, key concepts related to VR are *immersion* and *presence*.

VR and interactive video gaming may have some advantages over traditional therapy approaches as they can provide people with the opportunity for practicing everyday activities that are not or cannot be practiced within the hospital environment. Such type of therapy involves the use of computer-based programs designed to simulate real life objects and events.

Is interesting that VR therapies have been compared to "usual care" or "conventional therapy" (CT) as sophisticated technologies have become more readily available and affordable. VR therapy refers to a broad class of interventions, but can generally be defined as technological interventions that alter properties of the physical world. These properties might be perceptual, such as providing patient with additional sensory feedback about their movement in a virtual environment (VE). This could be considered as a great advantage since the modification of natural environment properties is the basis of adaptation. This change can therefore be directed toward two aspects: a) to the sensory stimuli that originate from the virtual environment in order to reach the patients towards it and to place itself as part of the particular environment, and b) from the side of the environment by defining the patient's requirements. It is an approach that does place a patient in a modified environment (conventional approach), but differentiates the environment according to the patient's needs, requirements and abilities and pushes him to work with these changes (modern approach).

Sometimes, VE training is integrated with exogenous forms of support such as robotic assistance or resistance, but we restricted our review to interventions that did not include such kind of support. Moreover, the advent of movement-controlled videogames such as the Wii (Nintendo), Move (Sony), and Kinect (Microsoft) has also allowed therapists to integrate commercial gaming (CG) systems into therapy [145][152][155][154] [153]. Although only a limited number of randomized controlled CG studies exist, CG research is appealing because these interventions offer some of the benefits of VE interventions, but have greater availability and a significantly reduced cost. Thus, a major objective is to quantitatively explore the effectiveness of VE and CG interventions compared to CT.

It is estimated that 50% to 75% of individuals who experience a stroke have persistent impairment of the affected upper limb (UL). Thus, there is a need to identify the best training strategies for retraining motor function of the upper limb. Two questions about the effectiveness of VR for UL rehabilitation in stroke were posed: a) Is the use of immersive VR more effective than conventional therapy or no therapy in the rehabilitation of the UL in patients with hemiplegia? b) Is the use of non-immersive VR more effective than conventional therapy or no therapy in the rehabilitation of the UL in patients with hemiplegia? There is level 1b evidence suggesting an advantage to training in immersive VR environments versus no therapy in UL rehabilitation, and level 5 evidence for training in immersive VR versus conventional therapy. There is level 4 evidence showing conflicting results for training in non-immersive VR versus no therapy, and level 2b evidence for training in non-immersive VR versus conventional therapy. The current evidence on the effectiveness of using VR in the rehabilitation of the UL in patients with stroke is limited but sufficiently encouraging to justify additional clinical trials in this population.

From another point of view, there is a meta-analysis and a systematic review that examines the effects of VR across levels of the ICF (International Classification of Functioning, Disability and Health) and compares the effect-sizes as a function of the type of VR therapy implemented. These findings build upon previous reviews that have explored VR therapy compared to "conventional therapy" (CT) in general. This review found positive effects of VR therapy across domains of the ICF and that the VR therapies were found to be effective when delivered as VE or CG. In this meta-analysis, time post-stroke and the type of VR intervention were not found to significantly affect outcomes. [177]

6.2 Comparison between commercial gaming and rehabilitation specific VR systems

The comparison between the effects of commercial gaming systems (CG) to rehabilitation-specific virtual environments (VE) in a therapy context for post-stroke adults is of a great value. However, there are only a really few studies that examine the differences between VE and CG, without being able to draw a substantial conclusion. The majority of the data are based on patients' testimonials, making the need of collection of more data mandatory in order to assess if the gain of CG intervention is reliable and if its effects can be translated into clinically meaningful results. Recent meta-analysis reviews provide strong evidence for the effectiveness of VE interventions and demonstrate promising initial data for the effectiveness of CG ones [8][178].

Movement-controlled games commercially available are increasingly investigated as therapeutic tools for individuals with neurological disorders such as cerebral palsy and stroke. An appealing aspect of movement-controlled games is combining aerobic exercise and motor skills practice, which may increase neuroplasticity during motor rehabilitation. As a result, commercial games have been investigated as tools for learning motor skills and for improving cardiovascular fitness. For example, Wii Sports (tennis, baseball and boxing), in adults with cerebral palsy, can increase energy expenditure to over 3 METs (Metabolic Equivalent of Task), suggesting that they can help these individuals meet recommended guidelines for physical activity. In addition to increasing energy expenditures, commercial movement games have been used therapeutically to improve balance, strength and coordination. Increased availability and lower cost are also potential advantages of using commercial games over VR systems especially designed for rehabilitation purposes.

One of the most important aspects in this comparison is patients' opinion concerning rehabilitation systems. Patients need to perform a rehabilitation program in a different, enjoyable and motivating way that will take into account their need for social interaction [8]. Moreover, all these should be summarized in a cost-effective system in order to be preferable. So far, we take for granted that patients prefer game-based rehabilitation, based on results taken from specific projects that have taken place in several hospitals or rehabilitation institutes all over the world, but for optimizing such a rehabilitation system we have to examine the criteria based on which patients select a system and the features they tend to prefer. Figure 6-1a depicts these criteria, showing clearly that patients are guided by therapists' recommendation.

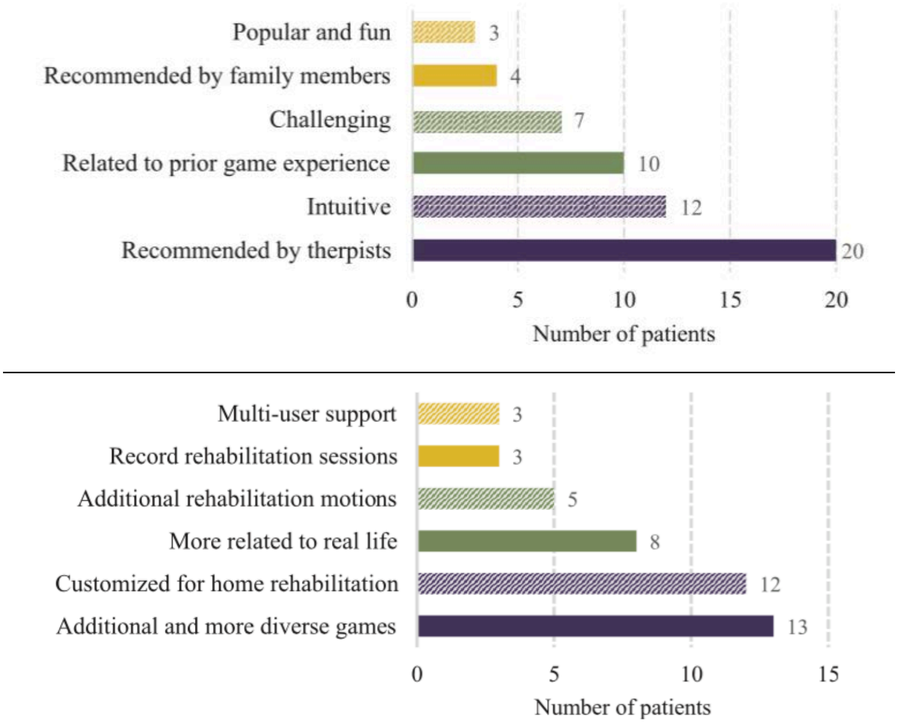

Figure 6-1:

a. (up) Game selection criteria of patients for rehabilitation systems, b. (down) Features for enhancing game-based rehabilitation systems. [8]

This indicates the huge responsibility that therapists have towards each patient, which means that they have to remain continuously updated for being able to correctly advice patients. All the other criteria are possibly correlated with the successfulness of a rehabilitation system and indicate other factors that have to be taken into account, as the role of the family, the game experience and the motivation. Figure 6-1b shows some features that have been pointed out by patients in order to enhance either existing game-based rehabilitation systems or potentially designed ones. We notice that the characteristic of which the majority of games lack is the diversity that will constitute games more motivated and consequently, efficient.

According to our opinion, commercial movement games, based on existing design-for-fun games like sports games, require increased abilities and capacities from the patients, which means that they can be usually used more effectively at the late chronic stage of the condition, integrating patients into everyday activities, as an exercise (general) program and as an attempt to fire motivation in order to maintain good physical condition. These games are considered inappropriate to be applied in the early stages of education, as they require well-coordinated, ready-to-answer and instant response, for participating actively in the game. Therefore, they cannot be compared to activities in the form of games depicted in VR “games” (transforming into a game, a virtual environment in which education takes place), the main purpose of which is to guide and, therefore, to educate the perception (the sensory feeling of the motion) of motor activity. By using similar VR games training, it is possible to combine the parts of the educated movement, to use simple actions as components of a larger functional activity and to have a staging for the difficulty provided in performing a more complicated motor activity.

Moreover, our intention is to increase the possibility of home rehabilitation in order for the patients to feel more familiar with the procedure. This highlights once again the role of therapists who should support this kind of intervention and train the patient in an adequate way in order to be able to handle a home-based rehabilitation system.

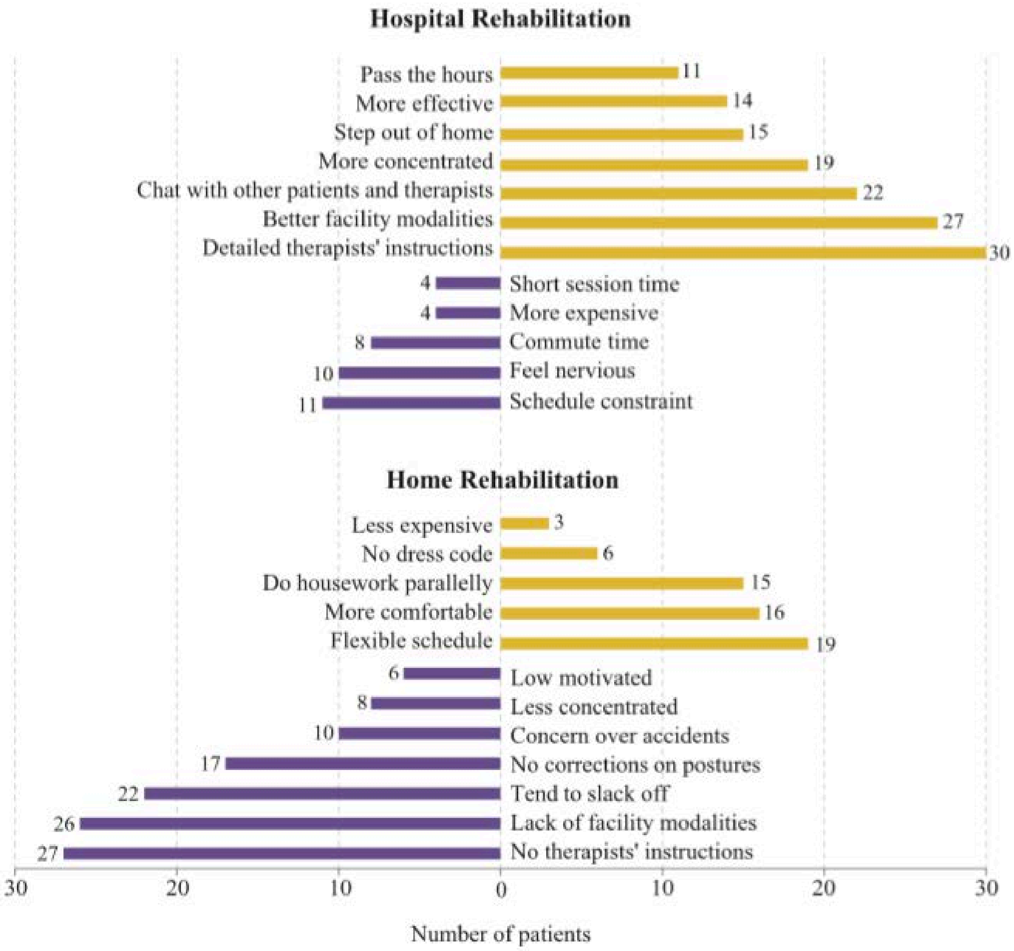

Figure 6-2 : Comparison of hospital and home rehabilitation [8]

As figure 6-2 indicates, home-based rehabilitation is not a well-known method so far as patients feel that they don't have the proper guidance and they are socially restricted.

6.3 Positive effects of VR therapy across ICF categories

The ICF provides a framework and a comprehensive perspective of functioning and disability in research and clinical practice [177]. It is a very good and reliable tool for identifying functionality and disability in the context of social participation and reintegration. The fundamental goal of rehabilitation for adults post-stroke is to restore the person's ability to participate in normal life roles providing as much independence as possible. This is the main goal of education that starts from the early stages of the stroke: to obtain, with the help of neuroplasticity, the greatest possible functionality that will adapt to everyday activities. This will largely ensure the participation and preservation of the personal, occupational and social role of the individual. Impairments at the body structure and function level may influence activity limitations, and activity limitations may influence participation restrictions. However, impairments and activity limitations do not necessarily affect the enjoyment of participation by individuals in various life situations. In a motor deficit, training plays the central role because it can be minimized, restricted and finally eliminated through the emergence of overall functionality and participation. It is, therefore, important for rehabilitation team to be clear about which ICF domains an intervention intends to, and actually does, impact.

Research in the literature has not identified any trials that examined outcomes related to body structures, personal factors, or environmental factors and only few (n=3) examined participation outcomes. There was a moderate but reliable advantage of VR therapy over CT in the categories of body function and activity, but outcome from other ICF categories should be included in future research. The advantage of applying VR to the training of motor control on patients with stroke seems to be of even greater value as long as it can be applied to any similar clinical case.

6.3.1 How does the VR intervention work?

VR can provide a great therapeutic benefit, as it offers several features, among which they are goal-oriented tasks and repetition. These characteristics have been proved to be important in neurological rehabilitation. Animal research has shown that training in enriched physical environments results in better problem solving and performance of functional tasks than training in basic environments. An enriched environment is what provides the animal with additional alternatives to its everyday life compared to a simple storage environment. With VR, a new creative and productive environment can be constructed, in which a more pleasurable activity is offered with greater motivation and interest. So, VR may have the potential to provide an enriched environment in which people with stroke can solve problems efficiently and master new skills. Virtual tasks have been described as more interesting and enjoyable by both children and adults, thereby encouraging higher numbers of repetitions [178].

A virtual environment, designed for a specific reason as education, can be tailored to the needs of the patients with stroke or other cognitive or sensory deficit in several ways: a) it can focus on desirable specific activities, b) it can provide a way out and solutions to specific problems that can be initially identified, c) it can offer controlled difficulties and obstacles to make their access easier and more convenient, d) it can offer degraded difficulties and successes, and finally e) it can support the ability to monitor the outcome in order to assess the evolution of education and training. Based on these characteristic, VR seems to constitute a powerful therapeutic tool, able to guide the affected brain, which has lost the peripheral control of coordinated movements, into specific neurophysiological pathways: a) how to perceive and process what seemingly is not possible to be done, b) how to achieve the prime motor target that is offered to him, c) how to act for the best possible functional outcome, d) to confirm the correct and proper performance of the proposed activity, e) to offer the possibility of accurate repetition.

Grading of tasks and immediate feedback have been shown to optimize motor learning. Changing the degree of difficulty of a motor action has, itself, great clinical significance in rehabilitation practice. A small initial degree of difficulty makes the perception of the movement and the understanding of its mechanism easier for the patient. The difficulty of the motor action should be increased only when the patient has fully accomplished the previous level and its execution is now comfortable, secure and fast. The gradual increase in the level of difficulty is interlaced with repetition and correct and proper execution. Therefore, the graded difficulty, by itself, is an educational tool.

VR does offer clinicians the ability to control and grade tasks in order to challenge the user, and programs often incorporate multimodal feedback provided in real time and in an environment that is totally guided. Furthermore, clinicians are able to trial tasks that the patient is totally unable to perform or it is unsafe for them to practice in the real world, such as crossing the street or the use of a knife in the kitchen. So, it is of great importance to guide and interpret the visual stimuli taken from the virtual environment so that the therapist's supervision gradually diminishes. Many programs are designed for being used without supervision, meaning also that increased dosage of therapy can be provided without increased staffing levels.

The rational interpretation of the VR implementation is based on the neurophysiological basis of biofeedback procedure. *Biofeedback* procedure is intended to highlight internal processes that are inherent but hidden (by a motor control disorder) by means of sensory signals coming from or focuses on specific movement processes. The purpose of this procedure-technique is to make the patient aware of obscured or disturbed motor activities so that, taking advantage of sensory signals, he can interpret and process them in order to be able to execute the proper motor behavior, which he can integrate at the end into his own overall daily motor activity. Since the elements added to the virtual environment are selected and defined to serve specific motor actions, it can be considered that this selected base acts as a mirror of activities, selected and urged by the manufacturer or the therapist to achieve the predetermined kinetic or motor effect, and receive “real-time” feedback on performance. Thus, both scenario and motor actions selected are intended to enhance the disturbed motor activity that appears to present a deficit or disorder in some of the motion characteristics such as coordination, timing, measure, purpose etc.

Keeping this in mind, the scenario and motor activities envisage as a “sensory stimulus” and they are guided in such a way to satisfy the conditions determined by the pathophysiology of the condition been treated, which in our case is the motor control disorder or muscle weakness. Thus, the appropriate movements to be learned through the VE are selected, the level of graded difficulty of the motor effort is determined and the successful motor outcome is rewarded.

6.4 VR and VE in parallel to conventional rehabilitation strategies – Is a new perspective?

It would be useful to pursue a comparison between traditional rehabilitation programs as they were shaped over time and the modern and enriched treatment environment as those offered by the VR and robotic systems. Since we refer to hand function in people with central or peripheral nerve lesion, emphasis is placed on the environment of occupational therapy, which is also responsible for improving the functionality of the hand in order to integrate it into the daily activities and the self-care context.

Undoubtedly, traditional physiotherapy programs such as neurodevelopmental and neurofacilitating techniques, neuromuscular facilitations and others, that focus on promoting motor control, are particularly important in the overall function and participation of the whole body in activities performed in the framework of occupational therapy. Without these interventions of physiotherapy in these specific fields, there can be no evolutionary educational and training process for individual functional interventions made by occupational therapy department, such as functional improvement of the hand and its integration into daily activities. Harmonious co-operation between these two fields of rehabilitation is therefore essential, without exaggeration and introspection.

As mentioned before, the major aim of all rehabilitation interventions is to maximize quality of life for patients with stroke. It is quality of life and not simply improved motor function, and functional independence that is the real goal of the rehabilitation program. The purpose of enhancing quality of life is paramount and affects both the choices of specific interventions and the way activities are performed. This goal is identical to the concept for helping the patient to achieve as much functional independence as possible.

Although a number of therapeutic rehabilitation techniques to promote neurologic recovery have been developed in the past, the science to support their efficacy has been weak at best. Due to the lack of evidence able to prove that the adult human brain has the capacity for adaptive plasticity after having acquired injury or lesion, the use of these rehabilitation interventions have been based on tradition. As a consequence none of these have become the standard of care within the broader rehabilitation community. All these methods, described before, are intended to promote motor recovery. With the exception of task-oriented approach, head-to-head comparisons of these techniques have not shown superiority of one over another.

Although use of traditional sensorimotor techniques has been based more on tradition than on science, some of the mechanisms that have been postulated to underlie these methods could theoretically facilitate adaptive plasticity. For example, proprioceptive feedback, as it has been emphasized in proprioceptive neuromuscular facilitations (PNF) technique, might be shown to be an important mechanism of motor recovery. So, many of these therapies can be adapted to current knowledge, that is, forced use of the paretic limb, massed practice, shaping, skill acquisition, and task specific movement, correlating these traditional sensorimotor techniques with current concepts of neuroplasticity.

All these traditional techniques with their expected results can be incorporated into new therapeutic approaches to rehabilitation, such as functioning in a virtual environment, together with many others benefits from the field of cognitive function. The creation of situations that closely resemble those of real world, with adjusting parameters and characteristics as needed, offers a unique opportunity to enhance therapeutic intervention. It is not proven though is such an intervention can stand efficiently alone; studies have shown that the combination of conventional and alternative therapies has the optimal results so far.

In our intervention, a great deal of attention was paid to the selection of motor activities be performed in the virtual environment. Key motor tasks were selected, such as flexion and extension of wrist and fingers, pronation and supination of the wrist as well as finger opposition. All these movements are essentially an indispensable part of all motor patterns of the hand and they participate in all the essential activities of daily living. No activities were focused on the elbow or the shoulder because it would have greatly broadened the field without any significant functional advantage. The aim was to select the simple stationary movements to enhance the effort of improving the function of the hand and to give a further stimulus to the patient's education and functional training.

From observations made during the use of our platform, as well as from interviews received by the selected patients at the end of the procedure, the application did not cause any difficulty to the patient, nor any problem at all, there was no interruption and they all completed the exercises successfully. Throughout the procedure, it was observed that when the patient understood the motor mechanism of the movement, then it gradually improved, as shown in many photographs, indicating that the virtual environment provides the appropriate sensory feedback stimulus concerning motor activity. It seems that further improvements could be made to the program in order to additionally facilitate, mainly the patients, to understand the mechanism of the movement faster and easier. Different kind of music, according to patients' preferences may be used also in order to examine if a further motivation can be produced.

The traditional occupational therapy approach is focused on the specific activities while the VR procedure takes advantage of more cognitive-sensory stimuli additionally to that given from the task-oriented approach. That is, the traditional approach is reinforced with an additional advantage, that of enriched information, that naturally gives greater motivation and interest to treatment. If there is a better clinical and functional effect, better designed prospective studies are needed for further proof.

7 Conclusions

Rehabilitation of patient with stroke or other neurological condition is a great challenge, both for the medical community and for the sciences that support this procedure. But the biggest challenge is the coupling of traditional intervention methods with modern technologies; The use of basic theoretical concepts and ideas that support traditional rehabilitation techniques, such as neurodevelopmental approach, proprioceptive neuromuscular facilitations and task-oriented therapies, based on the use of sensory biofeedback signal to improve motor control. The rationale of using an environment in which the patient can be "transported" for education, such as the virtual environment, is a modern approach that truly gives great promises. Based on this, we created a VR system with a very easy-to-read scenario of an extraterrestrial being, Orpheus, who approaches friendly the patient and transports him/her to his planet, Antiphon, in order to play music together. For the patient's participation, simple and basic movements were selected, which constitute the background of motor and functional pattern of the hand. Orpheus first performs these movements, in order to invite the patient to imitate them. This concept works like a stimulus-mirror of feedback signal that facilitate the retraining of affected motor control of patients with stroke or other neurological lesion. The platform was applied in three patients, two with stroke and one with Guillain Barré syndrome. No side effects were observed in all application, which were completely terminated. From our observations, it was found that this system truly helped patients to improve their kinetic performance, encouraging them to understand mainly the mechanism of motor action, with the help of the offered sensory feedback and the musical rhythm that helped them stabilized their movements.

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[179] https://github.com/getnamo/leap-ue4

Appendix 1

Publications arisen from this work

This work is a follow-up study, taken place at the Computation Vision and Robotics Laboratory of the Foundation for Research and Technology, concerning VR gaming and brainwave entrainment. This project led us to two publications:

Argento E., Papagiannakis G., **Baka E**., Maniadakis M., Trahanias P., (2017) "*Augmented Cognition via Brain Entrainment in Virtual Reality: an open integrated human augmentation system approach*", Augment Hum Res, 2:3. doi:10.1007/s41133-017-0005-3

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