TÉCNICO LISBOA

Virtual Reality for Stroke Rehabilitation with BCI and Hand Tracking Sensors

Simão Pedro Santiago Mateus Soares

Thesis to obtain the Master of Science Degree in

Electrical and Computer Engineering

Supervisor(s): Prof. Alexandre José Malheiro Bernardino
Prof. Athanasios Vourvopoulos

June 2021

Abstract

Post-stroke upper limb motor rehabilitation is an especially relevant topic in today's society since factors such as improvements in acute stroke treatments and ageing population have contributed to a substantial increase in the number of stroke survivors, the majority of them suffering from moderate to severe motor impairments. Traditional rehabilitation paradigms require significant human and monetary resources to keep up with the increased number of patients, and with the variability in therapeutic demands. Recent technological advancements have enabled the development of alternative treatment methodologies that complement traditional ones. Virtual Reality (VR) is one of the most promising methods of content presentation for the activation of neural processes involved in motor recovery after stroke. VR maximizes the sense of embodiment, reinforces engagement mechanisms, and allows for the implementation of personalized training activities tailored to each patient. However, VR often requires volitional movement as a means of interaction with the Virtual Environment (VE). To circumvent this issue, we will implement a combination of hand tracking with an EEG-based Brain-Computer Interface (BCI), to serve as a natural method of user interaction, resulting in the inclusion of a higher number of patients with distinct levels of motor impairments. Ultimately, we aim to develop a VE with integrated training tasks that will maximize upper limb motor rehabilitation results by employing Motor Learning Principles (MLPs) and that will contribute to the advancement of the field of technology-based approaches to post-stroke motor rehabilitation.

Keywords: Virtual Reality, hand tracking, Brain-Computer Interfaces, Motor Learning Principles

Contents

Chapter 1

Introduction

Stroke has been one of the leading causes of long-term adult disability for the past decades [1]. As an answer to this unignorable fact, there has been a substantial body of work developed by researchers worldwide, aiming to understand this deadly condition, all its repercussions on the human brain, and the best therapeutic methods for the optimisation of post-stroke recovery. The ever-accelerating pace of technological advancements has provided new tools and protocols to approach this problem. Some of the most promising ones take advantage of new developments in Virtual Reality (VR).

VR and its Virtual Environments (VEs) allow for the most natural interaction one can have with the virtual world, substituting real-world sensations with computer-generated sensory information. In the context of post-stroke recovery, this technology allows for a level of environment and feedback control that could not be achieved in traditional rehabilitation. However, the interaction with VEs often requires an increased level of motor control, which raises a problem since most stroke patients suffer from moderate to severe motor impairments [2]. As a solution, researchers have implemented new ways for patients to interact with these environments through the use of assistive natural-user-interfaces (NUIs) like hand tracking through optical sensors or by bypassing the central nervous system through the use of Brain-Computer Interfaces (BCIs). These allow the establishment of an alternative pathway between the patient's brain and the virtual environment so that even patients with the most acute motor impairments can engage in therapeutic activities [3].

Combining these two novel technologies allows for the establishment of a new paradigm for post-stroke upper limb motor rehabilitation. One that takes full advantage of these new interfaces and of the new possibilities of patient interactions that they provide. Some of which, already established as a better alternative to traditional rehabilitation methodologies (VR mediated therapy for upper limb motor rehabilitation [4]). This new paradigm could also support a significant degree of training personalization, and rather than substitute traditional supervised rehabilitation training (something that is still unfeasible in the near future), it could complement it as a means for patients to regain fine motor skills, to potentiate telerehabilitation by providing training at home [5], and also by allowing cognitive progress to be made even before the patient can perform the targeted motor capabilities [6][7].

1.1 Motivation

A stroke, also known as cerebrovascular accident (CVA), is defined as an interruption of the blood supply to part of the brain. This life-threatening medical condition prevents brain tissue from receiving oxygen and nutrients, causing directly affected cells to die by necrosis [8]. There are two main types of strokes. The most common (87%) are ischemic strokes characterized by a blockage (either by a blood clot or a piece of atherosclerotic plaque) in one of the main arteries that supply the brain. A hemorrhagic stroke is caused by a rupture or leakage of blood vessels, resulting in bleeding into the surrounding brain tissue, causing swelling (cerebral edema), that combined with the blood accumulation, increases intracranial pressure that causes further damage [9].

Over 13,7 million strokes occur a year globally. One in every four people over the age of 25 will statistically have a stroke in their lifetime. There are over 80 million people living today who have experienced a stroke [2]. According to the American National Stroke Association (NSA), approximately 12% of them have recovered or will recover almost fully, 29% with minor impairments, and the remaining 59% with moderate to severe cognitive and motor impairments, resulting in a loss of independence in their daily life (self-care tasks and participation in social activities).

Stroke incidence rates double with every decade after the age of 50 years [10]. This fact, combined with the growing and ageing population, and with the progress made in acute stroke treatments, will result in an inevitable rise in the number of stroke survivors in the near future, and consequently, in the risk of stroke recurrence, increasing the need for investments in post-stroke rehabilitation facilities and personnel [11].

In order to reduce the impact of stroke, upper limb motor recovery has been a recurrent focus on stroke rehabilitation research since it has crucial functional implications on patients' ability to perform Activities of Daily Living (ADLs) independently and ultimately in their overall quality of life. Many patients show significant upper limb motor impairments, even after completing subacute rehabilitation programs. This translates into a need for further development of alternative methods and strategies to tackle post-stroke upper limb motor recovery [12].

1.2 Challenges

Traditional rehabilitation therapies have evolved immensely over the past decades, and their impact on the lives of millions of stroke victims cannot be understated. However, they are not without drawbacks and limitations. One of the most prominent is the need for significant human and monetary resources. Specifically, the need for investment in rehabilitation facilities and personnel, in response to the imminent increase in the number of stroke survivors, would be an added burden on the world's health care organizations that already face one of the most demanding periods in recent history.

Focusing on the impact of this disease inside one medical facility: the increased number of patients combined with the variability in therapeutic demands – dictated by the patient's level of motor impairments – can limit rehabilitation results. Due to the simple fact that human resources grow scarce [13].

Patients' turnover rates would need to increase in response to this issue, which would limit the patients' access to supervised treatment, and could hinder their recovery progress.

Patient's motivation and engagement levels must also be taken into account when analyzing the traditional paradigm of post-stroke motor rehabilitation. Many of these therapies rely on intensive repetitive training tasks that could make the rehabilitation process a frustrating or even tedious one if not adequately adapted to the individual patient's needs. A certain degree of patients' emotional instability can also work as a catalyst for these difficulties. As he(she), especially at earlier stages of recovery, is still coming to terms with this new reality of physical impairment and cannot perform specific motor tasks that were once trivial [14].

Another aspect to consider is the difficulty, mainly in the early stages of recovery, to bypass severe motor impairments. Traditional therapies have this caveat – they rely primarily on physical feedback from the patients, resulting in a barrier that affects those with little to no upper limb motor capabilities. Combined with the fact that most motor recovery occurs in the first three months after stroke, it accentuates the significance of getting over that barrier as soon as possible to make the most out of this critical window of opportunity [15].

1.3 Goals

Our main goal is to optimize post-stroke upper limb rehabilitation outcomes, and increase the efficiency of motor recovery training by employing novel technology-based approaches. Consequently we will also contribute to the reduction of the workload of healthcare professionals (and, in turn, the healthcare system) when dealing with an increasing number of stroke patients with different levels of motor impairments. To achieve this, we will tackle the restoration of lost upper limb motor functions essential for the performance of ADLs, like grasping and handling objects in realistic real-life scenarios. Those are essential skills that a patient must recover in order to become once again independent and significantly improve his(hers) quality of life.

We will use a VE as the main method of content presentation, taking advantage of all the properties of VR that make it one of the most efficient ways to promote the sense of presence and embodiment – both multicomponent psychological constructs – critical when trying to optimise the recovery process. This VE will be interactive and for that we will need to make it compatible with a seamless combination of hand-tracking sensors and a BCI, as this is the method that grants accessibility to the greatest number of patients with different levels of upper limb motor impairments.

Using a VR-BCI paradigm will contribute to the advancement of technology-based approaches to post-stroke upper limb rehabilitation – an ever-growing field of research that aims to solve all of the challenges listed above. Previous work in this area will provide us with already developed and thoroughly tested tools: from Head-Mounted Displays (HDMs) and assessment tools (clinical scales) to electroencephalography (EEG) analysis software and hand tracking modules.

Access to these technologies and metrics will allow us to build and test an interactive rehabilitation application consisting of a VE with incorporated upper limb training tasks. A crucial aspect of this application will be the pursuance of the best implementation of Motor Learning Principles (MLPs) – defined as the set of processes associated with practise or experience that leads to relatively permanent changes in the ability to perform actions [16].

Every MLP will be considered during development and will be listed and characterized later in this report. However, a few will be prioritized since their implementation was not a primary focal point in earlier studies [12][17]. Consequently, they present an attractive opportunity for advancement in this field by improving patients' levels of engagement throughout training, as previous findings suggest [4].

Firstly, there is the principle of Adaptability – the application must be easily adaptable to each patient's initial needs and also to their progression throughout the rehabilitation process.

The second one is Motivation. The application, to increase patients' motivation and consequently their engagement during training, will employ Gaming Elements – intrinsic characteristics of games, thoroughly tested by a mature gaming industry, that continuously provides insights that can, and have been, applied successfully in therapeutic contexts [18].

Last but not least, we will evaluate the impact of Enriched Environments – environments populated with assets/stimuli (visual or auditory) peripheral to the main activity/task used to enrich the experience – and how to exploit them as drivers of novelty and engagement [19].

However, to keep the development feasible in the time we have, some boundaries/limitations will naturally need to be considered. An important one is the range of impairment levels that our application will be able to handle. As mentioned earlier, impairment levels vary significantly between patients. They are dictated not just by the time it has passed since the stroke and by the rehabilitation therapy they have been exposed to, but also by age, individual genetic differences, and common stroke comorbidities, such as diabetes.

Another boundary/limitation to consider is the number of training tasks that should be implemented. Novelty plays a vital role in patients' motivation and engagement. However, too much of it affects our ability to deliver a sufficiently polished overall experience.

1.4 Proposed Approach

We will use the *Unity* game engine for the development of the interactive VE for upper limb motor rehabilitation. This application will be composed of two main components that will have to seamlessly complement each other while being developed and iterated in parallel – the VE itself and the training tasks incorporated in it. During their development, some guidelines will be followed in order to uphold the objectives mentioned in the section above:

- First-person perspective during the performance of training tasks - the patient will have a first-person view of a virtual representation of their upper limbs in the VE, as this will contribute to the maximization of the sense of embodiment (described later in section 2.7.1);

- Training Task Modularity - this feature will be regarded as paramount during development. It contributes to two of the main MLPs described before – Adaptability and Motivation through Gaming

Elements. When a patient can comfortably perform a certain number of simple training tasks, these will be combined to increase the associated level of difficulty. Allowing patients to re-learn more complex and demanding motor skills [20][21];

- Challenge progression - Challenge is a highly significant and debated Gaming Element when applied to the context of rehabilitation therapies. We must avoid situations in which patients, due to motor limitations, lose the ability to directly control the task at hand. This can be done by implementing the last point correctly and also by properly modifying, not only the range and complexity of the movement(s) targeted in the specific task, but also the time available to complete such task.
- Narrative Structure - another Gamified Element that has been shown to increase levels of motivation. Narrative elements can deliver an interesting dramatic arc facilitating engagement, comprehension of the training objectives and even deliver a sense of progress in a more mentally complex and satisfying way;
- Enriched Environments were described earlier as a distinct MLP as they can and should be exploited as drivers of novelty and engagement. However, they can also indirectly contribute to higher levels of engagement by positively impacting motivation levels through gamified elements – for example, by complementing the Narrative Structure.

The development and testing of our post-stroke upper limb motor recovery application will be divided into three main stages: development, pilot testing with healthy subjects and lastly, implementation in a clinical environment with stroke patients at a rehabilitation unit.

1.5 Organization of the Document

This project proposal is divided into the following chapters:

- Chapter 1 integrates the introduction of the research area in which this project is inserted and the facts that motivated it. We also introduce the challenges faced currently by this project's primary stakeholders (stroke patients and medical professionals) and how they influence the advancement of this research area. Lastly, we briefly establish what we hope to accomplish with this project and how we will approach its development;
- Chapter 2 expands on all the significant concepts, practises, and methodologies that should be understood before tackling this project. We also describe and interpret some recent studies that compose the State of the Art;
- Chapter 3 is where we describe what we have already defined regarding our approach and how we aim to combine all the information presented in Chapter 2 in order to contribute to the advancement of VR based upper limb post-stroke rehabilitation;
- Chapter 4 is were we will enumerate the results we expect to obtain during the testing and clinical implementation phases of the thesis project;

- Finally, in Chapter 5, we describe and schedule the different phases of the thesis project.

Chapter 2

Background and State of the Art

2.1 Impact of Stroke

Before describing some of the most relevant concepts and methods that underlie the current practices in post-stroke upper limb rehabilitation, it is important to understand the human brain's basic structure and functional elements and how they are affected by a stroke. The brain is primarily composed of neurons – electrically excitable cells that communicate with other cells via specialized connections called synapses – and glial cells that give them structural and metabolic support. A neuron is made up of the soma – the cell's body containing the nucleus; dendrites – that act as signal receptors; and the axon – a cable-like structure that can extend up to thousands of times the diameter of the soma in length. Its primary function is to output nerve signals, and it can undergo extensive branching, enabling the transmission of information to many targeted cells. Groups of interconnected neurons that carry out a specific function when activated, form a neural circuit [22].

During a stroke, the blockage or rupture/leakage (respectively from an ischemic or hemorrhagic stroke) of one of the main arteries that supply the brain causes a gradient of reduced blood flow. This blood supply shortage initiates a cascade of metabolic failure and other chemical/biological reactions that, if not quickly attended to, provoke irrevocable tissue damage [23]. Hemorrhagic strokes have the added complication that the swelling caused by blood accumulation presses against the adjacent brain cells and further damages them. These events result in a localized injury, meaning that the severity of tissue damage decreases with the distance from the lesion's center, being less severe in the surrounding areas.

2.2 Neuroplasticity

Neuroplasticity is a complex, multifaceted, fundamental property of the brain defined as the ability of neurons and neural circuits/networks to, in response to new conditions or information, change their connections and behavior through growth and reorganization. There are a plethora of phenomena that can trigger neuroplasticity, from brain development to damage, sensory stimulation, and even psychological stress.

Throughout most of the twentieth century, this brain property was believed to only be manifested during childhood, based on the complex architecture and functions of the mammalian brain and on a lack of compelling evidence countering it [24]. Nowadays, this type of neuroplasticity is referred to as developmental plasticity as it's characterized by an intense and rapid branching of the neurons in the young brain, forming new synapses. These synapses are then modified by processed sensory information, strengthening some of them, weakening others, and even eliminating some completely (synaptic pruning). This process is carried out throughout childhood and results in the establishment of efficient networks of neural connections.

Technical advances potentiated new research over the past years, and discoveries were made showing that even though the developing brain exhibits a higher degree of plasticity, there are many aspects of the adult brain that are also prone to structural and functional change, although under different circumstances and to a more limited extent [25]. These circumstances include, but are not limited to: physical changes like the loss of a limb or a sensory organ, reinforcement of sensory information through experience (during the process of learning or memorization) and, most importantly for us in the development of this project, direct damage to the brain caused, for example, by a stroke.

Earlier literature has shown that, following a stroke-caused ischemic lesion, there's a cascade of molecular, genetic, physiological, and anatomical events that facilitate the reorganization of perilesional (located around the lesion) and contralesional (located in the half of the brain away from the lesion) brain networks [26]. These mechanisms allow for a certain degree of spontaneous recovery, facilitating the rearrangement of disrupted neural circuits. However, the intrinsic regenerative capabilities of the adult central nervous system are limited by: the proximity between affected (denervated) regions and healthy neurons capable of axonal reinnervation of those affected areas; the injured territories; the injury modality and severity (regenerative responses to ablation and traumatic brain injury are more limited compared with ischemic injury); age; individual genetic differences and common stroke comorbidities, such as diabetes [23]. Earlier literature has also shown that such rehabilitation mechanisms, drivers of neural reorganization patterns, can be catalyzed by behavioral experiences, since reinnervation was found to be facilitated by activity in the remaining afferents. These findings present an opportunity to influence brain reorganization in a manner that optimizes rehabilitation and functional outcomes [27].

2.3 Traditional Rehabilitation Paradigm

Traditional post-stroke rehabilitation methods and therapies all aim to maximize neuroplasticity since it is the main mechanism that allows stroke victims to regain lost motor and cognitive capabilities. There are several different ones being employed today in rehabilitation clinics and hospitals around the world, and it's important to understand how they exploit intrinsic brain recovery faculties. We'll now describe some of these methods and therapies, and their individual benefits:

- Intensive and repetitive motor training [28]: Research has shown that patients that engage in repetitive task training are more likely to improve upper limb function and their recovery is accelerated by as much as 6 months, when compared to patients receiving usual care.

- Mirror Therapy [29]: Mirror Therapy is a simple, inexpensive, patient-directed treatment that uses a mirror to reflect the non-affected limb and its movement giving the illusion of normal movement in the affected limb. This technique is established as an effective complementary rehabilitation method. Patients benefited more, in terms of motor recovery and hand-related functioning, when exposed to a combination of this method with conventional therapy compared to patients subjected only to conventional therapy.

- Action observation (AO) [30]: The mere observation of goal-oriented motor actions can have a positive effect on motor recovery after stroke [4]. This method is one of two forms of motor simulation, together with Motor Imagery. It is well documented that AO induces an internal motor representation of the observed movement, making it an effective method for neurorehabilitation.

- Motor Imagery (MI) [31]: Motor imagery is a type of mental imagery (visualisation), it can be further specified as kinaesthetic imagery (first person imagery) or visual movement imagery (third person movement imagery). The first one is the most relevant for this project, for reasons we'll discuss further on, and can be defined as seeing oneself move one's body or body part(s) and feeling it without actually physically moving it. It is known that, during motor imagery, the patterns of brain activation are similar to the ones observed during actual motor execution [32]. This method provides rehabilitation alternatives for stroke patients suffering from moderate to severe motor impairments.

These last two methods involve motor and motor-related brain regions that overlap, not only with regions involved in motor execution but also with each other. There is convincing evidence that combining the two elicits increased activity in motor regions of the brain [4]. When analysing brain activity during the application of MI and AO techniques, researchers found that the Mirror Neuron System (MNS) was actively involved. As such, they concluded that it might represent an important neurophysiological substrate for regaining impaired motor function after stroke [33] by providing an alternative source of motor training.

2.4 Content presentation through Virtual Reality (VR)

There has been a plethora of evidence, gathered by researchers over the years, supporting the use of VR to drive neural processes involved in motor recovery and rehabilitation after stroke, especially for upper limbs, where it has been established as a superior alternative to traditional therapy [4]. VR is an approach to user-computer interface that, for decades, was shrouded, concealed under expensive and under-performing hardware producing clunky visual experiences. As with most emerging technologies, the pursuit from an ever growing number of enthusiastic visionaries, turned into what it is today – an immersive real time simulation of an environment, scenario or activity that allows user interaction through multiple sensory channels (visual, auditory and even kinaesthetic).

VR technologies, in their current state of development and availability, allow for a new degree of freedom when it comes to the personalization of rehabilitation training tools. Nowadays, VEs can be used as safe simulated environments with strictly defined training tasks that, if the above practises are correctly implemented, provide a low-cost approach to rehabilitation that can even be effective from the patients home (telerehabilitation) [5].

A user's immersion in a VE is paramount when applying this technology for stroke rehabilitation purposes. Immersion can be evaluated by a patient's sense of presence, that in spite of being consensually characterized as a multicomponent construct and not having a standardized definition, can be understood as the psychological state in which an individual is unable to acknowledge that a certain experience is computer generated [34].

Embodiment is another multicomponent psychological construct that goes hand in hand with presence. Embodiment's cognition theories can be divided into two components: agency and body ownership. The first one refers to the sense of ability to control one's body movements, while the second can be defined as the perception that the body that one inhabits is one's own [35]. There are VR practises that accentuate these components and, as a consequence, facilitate embodiment in VEs:

- Effectively and correctly mapping the user's movement, in real time, to the virtual avatar they control will increase its sense of agency;
- Body ownership is potentiated by increasing the correlation between physical stimulation and the virtual body.

Another important characteristic of VR systems that, together with agency and body ownership, greatly contributes to the sense of embodiment in a VE, and consequently to the effectiveness of VR-mediated therapies, is self-location (or perspective). Its contribution is harnessed by providing the user with a first-person view of the VE and the virtual body he/she controls, as well as synchronous visuotactile correlations.

2.5 Gamification

Stroke patients have a tendency to become complacent with respect to the frequency and intensity of their rehabilitation exercises, which often impacts their recovery. The gamification of VR rehabilitation tools has been an approach explored by researchers to trigger patients' engagement and motivation throughout the rehabilitation process.

A mature gaming industry has provided thoroughly tested tools and patterns that should be taken into consideration when designing a gamified rehabilitation application [18]. A commonly used game development framework is the MDA (Mechanics, Dynamics, Aesthetics) [36]:

- The game's Mechanics are central to its identity and definition. They define the rules and purpose of the game. They also restrict the players' capabilities in a way that enhances their experience and structures their progression;

- Dynamics define the nature of player interactions and describe the run-time behaviour of the mechanics acting on player's inputs and outputs over time;

- Aesthetics greatly influence the player's experience by leveraging sensory feedback (graphics, audio and haptics) to mediate his(hers) emotional and intellectual responses.

This framework provides valuable insights on how to structure the gamification of an interactive VE for stroke rehabilitation. All three elements must strive to optimise player engagement and motivation, in order to promote neuroplasticity and consequently the recovery of patients' lost motor functions. To that end we will further characterize and divide these elements into more concrete and easily applicable principles – Motor learning principles – later on in the report.

2.6 Control Interfaces

The effectiveness of a VE for post-stroke rehabilitation is largely dependent on its interface. The VE itself can be optimised to ensure the greatest levels of presence and embodiment but, if the controls that allow the patient to interact with such an environment are not properly developed, tested and implemented then the application as a whole will fail to deliver on its goal of promoting neuroplasticity and consequently contributing to the recovery of patients' upper limb motor capabilities.

2.6.1 Hand Tracking

Most interactive VEs are highly dependable on the user's volitional upper limb movement. This interaction occurs mostly through controllers that are tracked either by external sensors or sensors implemented in the HMD. These movements are then mapped and translated into the VE. In the context of post-stroke rehabilitation the need for patients to be able to handle hand-held controllers is usually inadequate. However, there are some cases where specialized controllers are developed and implemented in order to provide accessibility to severely impaired users [37].

Nevertheless, most off-the-shelf VR controllers add a layer of complexity between the patient and the VE and this often complicates the rehabilitation process by restricting training to movements that have to involve them. There is also an inevitable exclusion of patients with severe impairments since they, in some cases, cannot fully grasp objects, meaning that they wouldn't be able to properly handle these controllers.

An alternative that has been explored extensively by researchers has been optical hand tracking [37][38], an unobtrusive method allowing for natural user interaction as well as full hand/finger tracking for quantification of movement. The implementation of this method is usually done by means of depth sensing cameras and allows for the elimination of control intermediaries between the VE and the patients, ultimately contributing to their sense of embodiment.

2.6.2 BCI

The combination of VR-mediated post-stroke rehabilitation therapies with Brain-Computer Interfaces has gained a significant level of popularity and acceptance over the past years. BCIs have the ability of translating brain signals into control commands, and introduce a complementary form of interaction with the VE. This is especially beneficial for stroke patients with moderate to severe upper limb motor impairments since it enables a narrowing of the gap between motor intention and motor execution. BCIs establish an alternative pathway between the patient's brain and the computer system introducing the possibility of training the central nervous system directly. This allows motor simulation treatment methods such as AO and MI to stimulate neural networks through the activation of the MNS [12]. BCI integration ultimately contributes to the generalization of this rehabilitation paradigm to a greater number of stroke patients, as it empowers them with the ability to interact with an environment that otherwise would require volitional motor capabilities that they have lost.

2.7 VR for rehabilitation – Best practises and considerations

2.7.1 Motor Learning Principles

Even though Motor Learning Principles (MLPs) have rarely been analysed specifically for VR interventions, their impact in more traditional rehabilitation methods is well established and they can be found embedded in some VEs for motor rehabilitation [39]. In the Introduction section we briefly mentioned Motor learning principles and specified three of them – Adaptability, Motivation and Enriched Environments. Now we will describe every principle and briefly summarize the literature supporting their individual contribution to post-stroke recovery, starting with the ones that weren't yet mentioned.

- Intrinsic and extrinsic feedback - intrinsic feedback is the naturally occurring sensory perception experienced during and after a movement. Extrinsic or augmented feedback is a layer of perception that can be built atop the latter, providing additional information to the patient. This can facilitate skill learning by employing the concepts of knowledge of performance (KP) and knowledge of results (KR) [40].
- Task specificity has long been a fundamental characteristic to consider during the design of rehabilitation applications and methodologies. However, in the case of VR-based rehabilitation, the extent to which practice conditions must align with the ones present in the execution of real-world tasks is still a controversial topic [4]. Although there are evidences supporting the application of the principle of specificity – motor learning is more effective when practice includes environmental and movement conditions similar to those required for the execution of the movement – in VR training, perfect congruence with a real-world (ADL) task may not be required.
- Dosing depends on three distinct but complementary parameters: training duration, frequency and number of repetitions performed. Research has reported that the proper combination of these parameters is crucial when trying to achieve motor learning [41] as it, under the right circumstances,

triggers neuroplasticity. The literature shows that trials providing at least 15h of VR-based therapeutic intervention outperformed those that provided less than 15h. Although the results used to reach this conclusion were deemed statistically insignificant [17], it still constitutes a valid and feasible benchmark of total training duration.

After careful consideration and literature review, the next three principles were chosen to have a more prominent role in the development of our application. We will now expand on their brief introduction (section 1.3), and specify how they constitute an attractive opportunity for the advancement of the VR-BCI post-stroke upper limb rehabilitation paradigm:

- Enriched environments - environments populated with assets/stimuli (visual or auditory) peripheral to the main activity/task used to enrich the experience. Exposing post-stroke patients to enriched environments that motivated exploration, physical training, and social interaction increased their activity and decreased their alone time [19];
- Adaptability - task repetition during training is essential, but not enough to trigger neuroplasticity. As some animal studies strongly suggest, a repetitive task that requires little to no learning doesn't produce changes in motor maps or neural morphology [42], meaning that the task must induce a tolerable but challenging level of difficulty in order to trigger neuroplasticity. This poses a challenge when developing a VR tool for upper limb rehabilitation, since the level of a patient's motor impairments dictates their ability to perform distinct motor training tasks with different ranges, and this varies not only between patients, but also for the same patient, in different stages of recovery;
- Motivation through gamified elements - Motivation is defined as the set of forces, intrinsic or extrinsic, that moves an individual to act. There is a consensus when it comes to the application of gaming elements to improve patients' motivation during post-stroke rehabilitation [43][18]. However, there is still no established paradigm dictating which, of these elements, have the greatest impact in a motor rehabilitation context. Nevertheless we will now present the strongest candidates according to the literature:
  - Goal setting - most VEs designed for motor rehabilitation only establish achievable goals in two time frames – immediate or long-term. A better alternative would be to integrate goals (in both cognitive and motor domains) at multiple time scales achieved through non-trivial decision making [44];
  - Rewards - the learning process, in the context of rehabilitation, can be enhanced through appropriate feedback [45], either positive or negative, through visual or auditory cues. This provides KP and KR to the patients and facilitates skill learning. However, rewards can also be detrimental to the patient's engagement and progress when their number, timing and quality are not properly managed;
  - Challenge - this gamified element is closely related to the previously described principle of Adaptability. A constant calibration of difficulty levels is required during the rehabilitation process in order to introduce a controlled challenge. The most intuitive ways of altering these

challenge levels would be to modify the necessary range of movement, and/or to modify the time available to perform a given training task. Some studies have applied different methods of challenge progression, one of the most interesting being task combination. In advanced stages of recovery, when trying to teach more complex and demanding motor skills, these should consist of combinations between simpler skills that were already mastered by the patients;

– Narrative Structure - flat and static tasks can easily become monotonous and eventually limit engagement. Curiosity, evoked either by novel environments and sensations or by a desire for knowledge was shown to be an essential driver of user engagement [46]. Narrative elements can and should be incorporated in a VR tool for upper limb motor rehabilitation, by delivering an interesting dramatic arc they can facilitate engagement, comprehension of the training objectives and even deliver a sense of progress in a mentally complex and satisfying way.

2.7.2 VR Design Factors and Development Principles

When developing a VE for post-stroke rehabilitation there are some potential issues that may arise related specifically to this method of content presentation [18]:

- The first is what the literature calls *uncanny valley* – the region of realism that reduces the observer's comfort level. This effect is observed as a response to 3D computer animations, like the ones implemented in VEs, and also in robotics, as a reaction to the verisimilitude of an humanoid robot as it approaches indistinguishability from reality. As a way to prevent this issue and the adverse responses it may trigger in patients, it is often better to strive for believability instead of realism. Meaning that a VE that does not try to mimic the real world but instead adopts a contextually consistent representation of it will be less likely to trigger this uneasy feeling that could hinder rehabilitation;

- Motion sickness in VR is caused by a delay between the user's input and the visual effects of such input. The human nervous system is responsible for the reafference process that requires a correspondence between real and virtual motion/interaction in order to prevent this issue. More specifically the lag between virtual and real motion/interaction should, at least, be less than 15ms and preferably closer to 7ms [47];

- "Learned helplessness" is especially prominent in older demographics, and consists of a self-acceptance of not being competent with technology. It can also be triggered if the VR experience is not accessible and successful from the beginning. To prevent this issue it's crucial to provide proper induction, orientation and training especially for patients having their first experience with VR;

- Depth perception is key when interacting with a VE, especially for upper limb training since it involves manipulation of objects in a 3D space. There are multiple cues in the real world, gathered and processed by our central nervous system, that help us to perceive depth. In a VE there are techniques that can be implemented to substitute some of these cues, these are: object occlusion, perspective projection, relative scaling of objects, surface texturing, lighting and shadow effects, motion parallax, and colour shading;

- Perceptual capacity and load is especially important to consider when dealing with stroke victims due to the impact it might have on levels of cognition, attention span, brightness aversion and other sensitivities;

- There are also some physical health effects of VR that can be detrimental to recovery and as such should not be overlooked: eye strain, physical fatigue, discomfort due to the HMD (weight, warmth, fit).

2.8 Systems and Devices for content presentation and interaction

2.8.1 Non-VR virtual therapeutic alternatives

Before focusing on VR systems it's sensible to mention some virtual post-stroke upper limb rehabilitation systems and approaches that explore alternative methods of content presentation. Consumer entertainment technology has played a disruptive yet vital role in the field of virtual rehabilitation [4]. Researchers have been able to explore new therapeutic methodologies that utilize systems such as: Sony's EyeToy – a camera based motion-based capture system compatible with the Playstation 2 console [48]; the Wii by Nintendo, featuring two accelerometer-based controllers and infrared motion capture capabilities [49]; and Microsoft's Kinect – a peripheral for the Xbox series that uses a depth-sensing camera to detect and map user's movements [50].

Most studies that utilized these systems predate the establishment of VR as an affordable and efficient method for the maximization of embodiment and consequently as a superior driver of motor recovery. Therapeutic methods using these systems relied mostly on monitor displays or projectors to present content. However, Microsoft's Kinect, as the most recent of the three, has also been successfully combined with VR systems producing promising results in the improvement of patient's motor functions [51].

2.8.2 VR, BCI and Hand tracking systems - Custom and Off-the-Shelf

VR systems

Therapeutically competent VR systems (HMDs) – with specifications that could be relevant for the advancement of post-stroke upper limb motor rehabilitation – have been commercially available for a relatively short period of time. Before 2010 most studies utilized custom developed systems – specifically designed hardware and software for rehabilitation [4]. The employment of these systems had it's advantages and disadvantages:

- Their computational power was significantly higher than that of the commercially available systems of the time, allowing for an increased degree of flexibility and freedom when designing VEs, consequently empowering researchers to answer a higher number of research questions;
- The main disadvantage was the overhead (time and resources) associated with the intricate process of developing a custom system.

Most recent studies on post-stroke upper limb rehabilitation employ off-the-shelf systems such as the Oculus Rift DK1 HMD (Oculus VR, Irvine, CA, United States) [12], the Oculus Quest (Facebook Technologies, LLC, Menlo Park, CA, USA) [37], the HTC Vive, among others. These systems have revolutionized the field of post-stroke VR-based rehabilitation as they allowed researchers to take advantage of powerful processing capabilities without the need to build their own custom VR system.

The vast majority of modern HMDs still need to be connected, wired and sometimes wirelessly, to an external computer that performs all or most of the processing required. However, there are a couple of devices that possess integrated processing units, such as the Oculus Quest and the Oculus Quest 2 (Facebook Technologies, LLC, Menlo Park, CA, USA). These devices took an important step towards portability and thus to the rise in accessibility of VR rehabilitation methods.

BCI systems

Regarding BCIs, non-invasive electroencephalography (EEG) has been established as the most commonly used signal acquisition technology. This technology employs the use of electrodes with specific spatial distribution configurations that capture signals from sensory-motor areas of the brain. These signals are then processed in order to distinguish wave patterns with distinct frequency domains – known as EEG bands or rhythms. EEG signals can only approximately measure the spatial resolution of neural activity and the translation between cognitive states and motor intentions is a complex and inexact process. Nonetheless, the literature has shown that EEG-BCI-based is a promising alternative to conventional forms of post-stroke treatment in promoting restorative neuroplasticity [52].

Other BCI options that have also been utilized in post-stroke rehabilitation studies are magnetoencephalograms (MEG) and near-infrared spectroscopy (NIRS). However, both these modalities require significantly more expensive equipment, especially MEG.

Hand tracking systems

Apart from Microsoft's Kinect, another commonly used system for upper limb tracking is the Leap Motion controller (LMC) – an optoelectronic hand tracking module that is able to accurately capture both hands simultaneously. Some of the key features of this device are:

- Compatibility with the majority of HMDs;
- Robust and reliable skeletal model;
- Motion-to-photon latency below the human perception threshold.

The LPC and Microsoft's Kinect are part of a category of motion sensing technologies known as non-wearable devices [37]. Another type of controllers that also belongs to this category is robot-based controllers or controllers with three degrees of freedom [53]. These are specially designed for motor impaired users and they overcome the previously described difficulties that arise when using off-the-shelf VR controllers (2.6.1). They also typically incorporate haptic capabilities that contribute to the patient's sense of immersion by simulating interaction forces with tools in a VE. However, the application of custom robot-based haptic controllers is an extremely complex and expensive alternative to patient-VE interaction and the overhead related to their development and proper implementation may not be compatible with many present-day research efforts.

Wearable devices for motion sensing are divided into data gloves and the use of exoskeletons [37]. There has been a plethora of studies applying these technologies as they allow for the collection of high frequency data including force or torque measurements.

2.9 Examples of gamified upper limb and VR rehabilitation tools

- Mou-Rehab Project (2016) [54]: This project aimed to develop, and evaluate the employment of, a mobile game-based upper limb VR application for post-stroke rehabilitation. 24 patients participated in a total of 10h of therapy divided into 1h sessions in a span of two weeks. During those sessions patients received visual and auditory feedback from a tablet and their movements were tracked by a smartphone, held in their hand or strapped to their upper or lower arm, depending on the exercise. The study concluded that this paradigm effectively promoted upper limb motor recovery, surpassing results achieved by conventional therapy. It was also shown to reduce depressive moods for up to one month after the last session.

- Project GesAircaft (2017) [55]: This project intended to determine if there was any correlation between therapy enjoyment and upper limb motor recovery, by exposing stroke survivors to a gamified therapeutic tool. The criteria for the selection of participants were: diagnosis of unilateral ischemic or hemorrhagic stroke 6 months prior to the experiment; residual motor impairments in the upper limbs; minimum of 10 degrees of active wrist extension and supination; ability to follow instructions. Upper limb's positions and movements were tracked using the LMC and used to control an aircraft through an obstacle course. The difficulty of this task was calibrated according to the range of motion of the individual's wrist and forearm. Each patient participated in a total of 9 hours of therapy divided into 30 minute sessions 3 times a week during 6 weeks. The results obtained demonstrated that the GesAircraft is a safe, feasible and gratifying system for upper limb motor therapy of patients with advanced ages (average of 69,5 years old). It also successfully confirmed its premise – increased therapy enjoyment facilitates motor recovery.

- Benoit et al. (2015) [56]: This project aimed to measure the acceptability of senior citizens (average age of 68.9) to a VR environment using an image-based rendering technique. 18 participants were exposed to a control environment and three others – each one with different levels of familiarity (patient's home city, national landmark and an unknown location). It was concluded that VR is appropriate for therapeutic use with senior citizens without any significant levels of fatigue or other detrimental physical health effects.

- NeuRow BCI-VR Protocol (2019) [12]: This protocol was employed in a pilot study to examine the effects of a MI paradigm as a treatment for upper limb motor dysfunction. One 60 year old participant, suffering from left hemiparesis following cerebral infarct 10 months before, was recruited. The patient underwent a total of 2.5 hours of VR-BCI training separated into 15 minute sessions in a span of 3 weeks. Clinical scales and electrophysiological data gathered throughout this study illustrated significant improvements in motor function and brain activation. MI training and VR feedback promoted neuroplastic changes in the targeted areas. These results suggested that a self-paced and ecologically valid scenario through VR feedback could substantially benefit chronic stroke patients suffering from reduced upper limb motor function.

Chapter 3

Approach

Our approach will consist of a gamified VE with integrated training tasks for post-stroke upper limb motor rehabilitation. During the development of this application, we will focus on achieving the best implementation of motor learning principles, and of VR design factors and development principles. We will also adopt some techniques used currently in traditional post-stroke motor rehabilitation (AO and MI). As the literature suggests, these guidelines will contribute to the maximization of the sense of embodiment felt by the patients throughout the rehabilitation process, consequently triggering neuroplastic changes and the recovery of lost motor capabilities. The application will be developed using the Unity game engine. It will consist of a “tabletop farming simulator” (TFS) where the patient will need to perform increasingly complex upper limb movements in order to plant, care for, and harvest their crops. The patient will see the VE through a first-person perspective, and his(hers) upper limb positions and movements will be tracked, and accurately translated, into an embodied avatar representation.

Our hope is that this concept proves to be appealing to the older demographic that composes the large majority of stroke survivors [2][10]. Other favorable attributes of this concept are:

- Versatility – it allows for the implementation of a plethora of different upper limb movements;

- Continuity between training sessions – the interactions a patient has with the VE, through the training tasks, in one session will influence the state of the VE in subsequent sessions.

3.1 Hardware Systems

During the development of this project we will use the Oculus Rift HMD for visualizing and testing the VE. This device has been previously used in the context of post-stroke rehabilitation as it possesses some important characteristics such as: high resolution (1080×1200 per eye), a lightweight and ergonomic structure, high refresh rate (90 Hz), 360° positional tracking and integrated audio. For user-VE interaction we will employ a combination of hand tracking using the LMC module and an EEG-based BCI.

3.2 Development Guidelines

3.2.1 Application of Motor Learning Principles

In a practical development setting almost all motor learning principles are interconnected. When implementing a new feature, aiming to introduce or advance the fulfilment of a certain principle, we should expect, and be ready to deal with, repercussions that could affect other principles. A large number of these relations will only be apparent during the development and testing processes. Nevertheless, at this stage, we should recall the theoretical background layed out in the last chapter, anticipate the features that should be implemented, and describe how these features could be applied in the context of a TFS.

The modularity of training tasks, and the calibration of challenge levels are two components that must seamlessly complement each other. Their successful combination will allow our application to adapt its difficulty levels accurately and effectively in order to meet the demands of the patient in his/hers specific stage of recovery. The versatility of a TFS concept, in regards to the different types and ranges of movements we can implement, facilitates the integration of these components.

All of the training tasks will be modular, meaning that they will target specific upper limb movements related to certain objectives to accomplish in the VE. For example, watering plants, pulling out weeds, swatting insects among others. This allows for an intuitive method of challenge progression – when a patient has mastered a number of simpler training tasks these will be combined to create a new task with an increased associated level of difficulty.

The calibration of the challenge level will need to be a dynamic and iterative process. There are many factors that may influence the performance of a patient throughout rehabilitation, even during a single training session, and we need to be able to adapt the difficulty levels of a given task in sync with even the most sudden decrease in motor capabilities. These calibrations can be made by altering the range of movement necessary, or the time available, to accomplish a task.

A TFS concept's main narrative element will be the fact that crops will grow even when the application is not being used, and the success rate of a given training session will determine the state of the crops in subsequent sessions. This feature will deliver a clear sense of progress and hopefully facilitate patients' engagement and investment in the recovery process. Other narrative elements could also be implemented, like the ability to sell the harvested goods in an in-game store, and the ability to use that profit to invest in different and more lucrative crops or in more advanced farming tools.

There are also many ways to exploit the contribution of enriched environments in the context of a TFS. Some examples of peripheral visual and/or auditory stimuli may be: dynamic landscape and weather conditions, integration of non-playable characters (NPCs) such as insects or birds that the patient can interact with.

Regarding intrinsic and extrinsic feedback modalities, we will take advantage of the plethora of sensory feedback that a VE allows us to implement. Nevertheless, always considering that most patients will be of advanced ages, some of them may have never played a video game before, and as such will be especially sensitive to any kind of virtual sensory stimuli. We will need to carefully consider the therapeutic advantages of extrinsic feedback, and also how it can become detrimental if the training experience overwhelmes the patient.

Regarding task specificity, apart from the types and ranges of movements to be performed by the patient when exposed to our application, the tasks' characteristics listed in this section deviate greatly from any type of ADL. However, knowing that congruence between the training tasks and ADLs, in the context of VR-based rehabilitation, has not been shown to affect the recovery process [4], we can assume that the similarity of movement types is enough so that patients can, without needing significant acclimatization, employ the motor skills that they recover during this process in their daily lives. This assumption allows us to then pursue higher levels of user embodiment by freely exploring VE and task customization options.

Lastly, regarding dosing, in the description of the state of the art we mention a benchmark of 15h hours for the total duration of a VR-based post-stroke rehabilitation intervention. We will strive to reach that mark provided we find a way to feasibly and appropriately distribute these 15h through a still undetermined number of training sessions. By feasibly we mean – by scheduling these training sessions in a way that is convenient for all the implicated stakeholders such as patients, medical staff, supervisors etc; By appropriately we mean – in a manner that maximizes patient's motivation and engagement.

3.2.2 Application of Motor Simulation practises

As was described in section 2.3 a combination of Action Observation and Motor Imagery techniques elicits increased activity in motor regions of the brain and activates the Mirror Neuron System – an alternative source of motor training. These techniques are also possible to implement in the context of a VR-based rehabilitation tool such as our TFS concept:

- By adding an NPC guide, positioned in front or by the side of our patient's avatar, that performs the movement(s) required for the completion of the training task (AO);
- Also, after the patient watches the NPC guide perform the that task we could ask him(her) to imagine themselves performing that(those) specific movement(s) (MI);
- Lastly, a representation of the patient controlled avatar's upper limbs would perform that task, without any need for the patient to intervene (AO).

Only then, after these three steps would we instruct the patient to perform the required movement(s) to complete the training task.

3.2.3 Application of VR design factors and development principles

Every virtual object presented in a VE is composed of polygons, a Low poly art style reduces the number of polygons that is needed to represent an object. If we adopt this art style, when developing the VE, we will minimize computational needs, consequently lowering the values of latency and increasing frame rates [57]. This strategy will solve the issue of motion sickness in VR since it allows for a reduction of the latency between virtual and real motion/interaction; and it will also counter the “uncanny valley” effect as we aim to build a consistent Low poly representation of the world instead of striving for realism.

The success of our rehabilitation tool will be highly dependable on sufficient and efficient communication between patients, medical professionals, and ourselves. Not only during,but also in between training sessions. We should be able to adapt every feature or characteristic, from the VE or from the training tasks, that we are able to identify as potential obstructions to recovery if not properly tailored to the patient.

Chapter 4

Expected Results

The core target of this project is the creation of a novel post-stroke upper limb motor rehabilitation tool, that takes advantage of technological methodologies to maximize recovery. As such, the main result that we expect to achieve is lasting upper limb motor improvements in the patients that will take part in the clinical implementation of our application.

4.1 Overall System and Therapeutic Experience

In this section, we will present a list of summarized functionalities that we aim to implement as part of our rehabilitation tool and of the overall therapeutic experience. Every one of them will play an important role in the process of reaching our core target defined above:

- Efficient communication with the patient and with the medical professionals involved before, during and after the training session;
- Effective and attentive familiarization of the patient with the equipment and with the application;
- Natural and precise translation of upper limb and head movement from reality to the VE;
- Physically accurate interactions with the virtual assets present in the VE;
- Simple and intuitive user interfaces;
- Detailed performance assessment during training with automated and dynamic calibration of challenge levels;
- Delivery of satisfying and informative extrinsic feedback to the patient;
- MNS activation by means of AO and MI;
- Compelling narrative elements that expand beyond the scope of a single training session;
- VE with abundant yet carefully selected and placed peripheral visual and auditory stimuli;
- Collection of useful EEG and upper limb movement data;

We will also devise two questionnaires as additional methods of complementary data collection — one intended for the patients and another for the medical staff. In the patients' questionnaire, we will pose quantitative questions about their sense of immersion, satisfaction, and standard VR-related issues (listed in section 2.7.2). In the medical staff's questionnaire, we will ask quantitative questions about the patient's mood and activity levels before, during, and after the training session. This feedback will be especially valuable if those medical professionals have accompanied the patients throughout their rehabilitation process prior to our intervention. Their professional knowledge and broader perspective will undoubtedly result in relevant complementary information to that gathered from the patients.

Chapter 5

Project Calendarisation

In this chapter, the thesis project will be divided into stages and scheduled. The main stages are: research and literature review; development of the VE; definition of the training tasks; implementation of the training tasks; pilot testing with healthy subjects; implementation in a clinical environment with stroke patients at a rehabilitation unit; writing the dissertation.

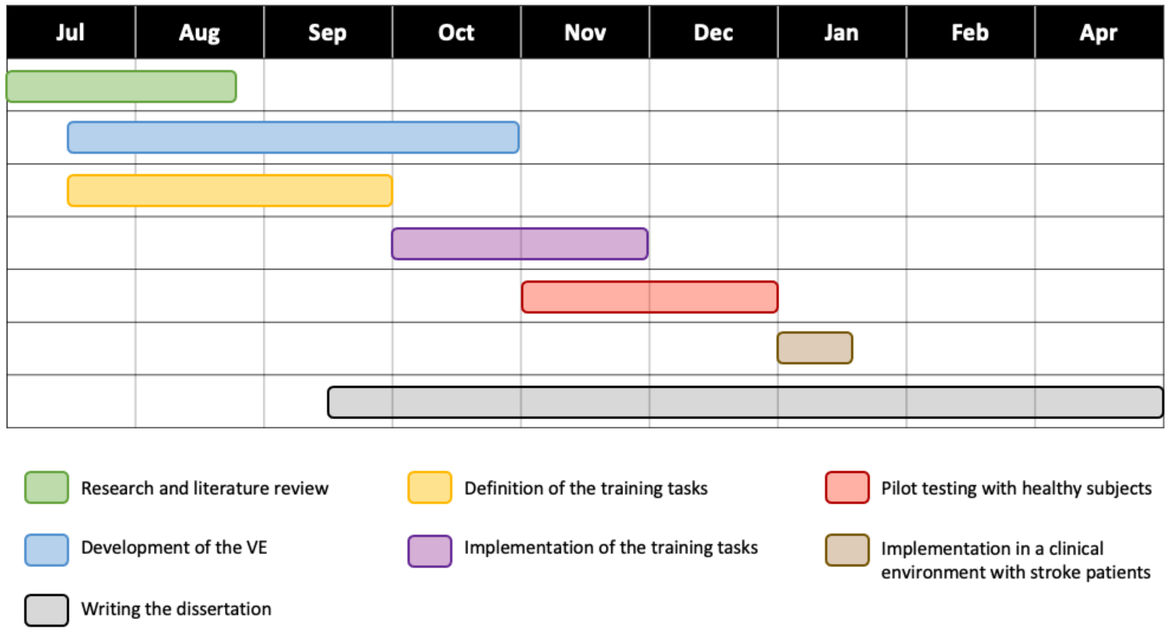

Figure 5.1: Thesis Schedule

Bibliography

[1] T. Truelsen and S. Begg. The global burden of cerebrovascular disease. *World Health Organization*, 01 2006.

[2] M. P. L. C. Author), B. Norrving, R. L. Sacco, M. Brainin, W. Hacke, S. Martins, J. Pandian, and V. Feigin. World stroke organization (wso): Global stroke fact sheet 2019, 2019.

[3] A. Vourvopoulos and S. Bermúdez I Badia. Motor priming in virtual reality can augment motor-imagery training efficacy in restorative brain-computer interaction: a within-subject analysis. *J Neuroeng Rehabil*, 13(1):69, 08 2016.

[4] S. Bermúdez i Badia, G. Fluet, R. Llorens, and J. Deutsch. *Virtual Reality for Sensorimotor Rehabilitation Post-Stroke: Design Principles and Evidence*, pages 573–603. 07 2016. ISBN 978-3-319-28603-7. doi: 10.1007/978-3-319-28603-7_28.

[5] A. Nuara, M. Fabbri-Destro, E. Scalona, S. E. Lenzi, G. Rizzolatti, and P. Avanzini. Telerehabilitation in response to constrained physical distance: an opportunity to rethink neurorehabilitative routines. *J Neurol*, Jan 2021.

[6] K. Ang and C. Guan. Brain-computer interface in stroke rehabilitation. *Journal of Computer Science and Engineering*, 7:139–146, 06 2013. doi: 10.5626/JCSE.2013.7.2.139.

[7] M. A. Cervera, S. R. Soekadar, J. Ushiba, J. D. R. Millán, M. Liu, N. Birbaumer, and G. Garipelli. Brain-computer interfaces for post-stroke motor rehabilitation: a meta-analysis. *Ann Clin Transl Neurol*, 5(5):651–663, May 2018.

[8] B. Puig, S. Brenna, and T. Magnus. Molecular communication of a dying neuron in stroke. *International Journal of Molecular Sciences*, 19:2834, 09 2018. doi: 10.3390/ijms19092834.

[9] E. L. Miller, L. Murray, L. Richards, R. D. Zorowitz, T. Bakas, P. Clark, and S. A. Billinger. Comprehensive overview of nursing and interdisciplinary rehabilitation care of the stroke patient: a scientific statement from the American Heart Association. *Stroke*, 41(10):2402–2448, Oct 2010.

[10] Y. Béjot, H. Bailly, J. Durier, and M. Giroud. Epidemiology of stroke in Europe and trends for the 21st century. *Presse Med*, 45(12 Pt 2):e391–e398, Dec 2016.

[11] Y. Béjot, H. Bailly, M. Graber, L. Garnier, A. Laville, L. Dubourget, N. Mielle, C. Chevalier, J. Durier, and M. Giroud. Impact of the ageing population on the burden of stroke: The dijon stroke registry. *Neuroepidemiology*, 52:78–85, 01 2019. doi: 10.1159/000492820.

[12] A. Vourvopoulos, C. Jorge, R. Abreu, P. Figueiredo, J.-C. Fernandes, and S. Bermúdez i Badia. Efficacy and brain imaging correlates of an immersive motor imagery bci-driven vr system for upper limb motor rehabilitation: A clinical case report. *Frontiers in Human Neuroscience*, 13:244, 2019. ISSN 1662-5161. doi: 10.3389/fnhum.2019.00244. URL `https://www.frontiersin.org/article/10.3389/fnhum.2019.00244`.

[13] A. M. Hughes, J. H. Burridge, S. H. Demain, C. Ellis-Hill, C. Meagher, L. Tedesco-Triccas, R. Turk, and I. Swain. Translation of evidence-based Assistive Technologies into stroke rehabilitation: users' perceptions of the barriers and opportunities. *BMC Health Serv Res*, 14:124, Mar 2014.

[14] T. M. Damush, L. Plue, T. Bakas, A. Schmid, and L. S. Williams. Barriers and facilitators to exercise among stroke survivors. *Rehabil Nurs*, 32(6):253–260, 2007.

[15] C. Stinear, C. Lang, S. Zeiler, and W. Byblow. Advances and challenges in stroke rehabilitation. *The Lancet Neurology*, 19, 01 2020. doi: 10.1016/S1474-4422(19)30415-6.

[16] C. Winstein, R. Lewthwaite, S. Blanton, L. Wolf, and L. Wishart. Infusing motor learning research into neurorehabilitation practice: A historical perspective with case exemplar from the accelerated skill acquisition program. *Journal of neurologic physical therapy : JNPT*, 38, 05 2014. doi: 10.1097/NPT.0000000000000046.

[17] K. Laver, B. Lange, S. George, J. Deutsch, G. Saposnik, and M. Crotty. Virtual reality for stroke rehabilitation. *Cochrane Database of Systematic Reviews*, 11, 11 2017. doi: 10.1002/14651858.CD008349.pub4.

[18] D. Charles, D. Holmes, T. Charles, and S. McDonough. Virtual Reality Design for Stroke Rehabilitation. *Adv Exp Med Biol*, 1235:53–87, 2020.

[19] H. Janssen, L. Ada, J. Bernhardt, P. McElduff, M. Pollack, M. Nilsson, and N. Spratt. An enriched environment increases activity in stroke patients undergoing rehabilitation in a mixed rehabilitation unit: A pilot non-randomized controlled trial. *Disability and rehabilitation*, 36, 04 2013. doi: 10.3109/09638288.2013.788218.

[20] M. Cameirão, S. Bermúdez i Badia, E. Duarte, and P. Verschure. Neurorehabilitation using the virtual reality based rehabilitation gaming system: Methodology, design, psychometrics, usability and validation. *Journal of neuroengineering and rehabilitation*, 7:48, 09 2010. doi: 10.1186/1743-0003-7-48.

[21] C. Linehan, B. Kirman, S. Lawson, and G. Chan. Practical, appropriate, empirically-validated guidelines for designing educational games. pages 1979–1988, 05 2011. doi: 10.1145/1978942.1979229.

[22] D. Purves, G. J. Augustine, D. Fitzpatrick, W. C. Hall, A.-S. LaMantia, and L. E. White. *Neuroscience, Fifth Edition*. Sinauer Associates, Inc., 2012.

[23] T. Jones and D. Adkins. Motor system reorganization after stroke: Stimulating and training toward perfection. *Physiology (Bethesda, Md.)*, 30:358–70, 09 2015. doi: 10.1152/physiol.00014.2015.

[24] B. Leuner and E. Gould. Structural plasticity and hippocampal function. *Annu Rev Psychol*, 61: 111–140, 2010.

[25] E. Fuchs and G. Flugge. Adult neuroplasticity: More than 40 years of research. *Neural plasticity*, 2014:541870, 05 2014. doi: 10.1155/2014/541870.

[26] N. Dancause and R. J. Nudo. Shaping plasticity to enhance recovery after injury. *Prog Brain Res*, 192:273–295, 2011.

[27] T. A. Jones and D. L. Adkins. *Behavioral influences on neuronal events after stroke*, page 23–34. Cambridge University Press, 2010. doi: 10.1017/CBO9780511777547.004.

[28] B. French, L. H. Thomas, J. Coupe, N. E. McMahon, L. Connell, J. Harrison, C. J. Sutton, S. Tishkovskaya, and C. L. Watkins. Repetitive task training for improving functional ability after stroke. *Cochrane Database Syst Rev*, 11:CD006073, 11 2016.

[29] M. Yavuzer, R. Selles, N. Sezer, S. Tomruk Sütbeyaz, J. Bussmann, F. Köseoğlu, M. Atay, and H. Stam. Mirror therapy improves hand function in subacute stroke: A randomized controlled trial. *Archives of physical medicine and rehabilitation*, 89:393–8, 03 2008. doi: 10.1016/j.apmr.2007.08.162.

[30] D. Eaves, M. Riach, P. Holmes, and D. Wright. Motor imagery during action observation: A brief review of evidence, theory and future research opportunities. *Frontiers in Neuroscience*, 10, 11 2016.

[31] A. Kho, K. P. Liu, and R. Chung. Meta-analysis on the effect of mental imagery on motor recovery of the hemiplegic upper extremity function. *Australian occupational therapy journal*, 61, 10 2013. doi: 10.1111/1440-1630.12084.

[32] H. Ehrsson, S. Geyer, and E. Naito. Imagery of voluntary movement of fingers, toes, and tongue activates corresponding body-part-specific motor representations. *Journal of neurophysiology*, 90: 3304–16, 12 2003. doi: 10.1152/jn.01113.2002.

[33] K. Garrison, C. Winstein, and L. Aziz-Zadeh. The mirror neuron system: A neural substrate for methods in stroke rehabilitation. *Neurorehabilitation and neural repair*, 24:404–12, 03 2010. doi: 10.1177/1545968309354536.

[34] G. Riva. Is presence a technology issue? some insights from cognitive sciences. *Virtual Reality*, 24, May 2009. doi: https://doi.org/10.1007/s10055-009-0121-6.

[35] M. Tsakiris. My body in the brain: A neurocognitive model of body-ownership. *Neuropsychologia*, 48:703–12, 10 2009. doi: 10.1016/j.neuropsychologia.2009.09.034.

[36] R. Hunicke, M. Leblanc, and R. Zubek. Mda: A formal approach to game design and game research. *AAAI Workshop - Technical Report*, 1, 01 2004.

[37] W.-S. Kim, S. Cho, J. Ku, Y. Kim, K. Lee, H.-J. Hwang, and N.-J. Paik. Clinical application of virtual reality for upper limb motor rehabilitation in stroke: Review of technologies and clinical evidence. *Journal of Clinical Medicine*, 9:3369, 10 2020. doi: 10.3390/jcm9103369.

[38] S. Cho, W.-S. Kim, N.-J. Paik, and H. Bang. Vbbt : Upper limb function assessment using virtual box and block test in patients with unilateral hemiplegic stroke. *IEEE computer graphics and applications*, 36, 01 2015. doi: 10.1109/MCG.2015.2.

[39] P. L. T. Weiss, E. A. Keshner, and M. F. Levin, editors. *Virtual Reality for Physical and Motor Rehabilitation*. Springer-Verlag New York, 2014.

[40] B. Lauber and M. Keller. Improving motor performance: Selected aspects of augmented feedback in exercise and health. *European Journal of Sport Science*, 14:36–43, 02 2014. doi: 10.1080/17461391.2012.725104.

[41] G. Kwakkel, R. Peppen, R. Wagenaar, S. Wood-Dauphinee, C. Richards, A. Ashburn, K. Miller, N. Lincoln, C. Partridge, I. Wellwood, and P. Langhorne. Effects of augmented exercise therapy time after stroke: A meta-analysis. *Stroke; a journal of cerebral circulation*, 35:2529–39, 12 2004. doi: 10.1161/01.STR.0000143153.76460.7d.

[42] M. Remple, R. Hines, P. VandenBerg, C. Goertzen, and J. Kleim. Sensitivity of cortical movement representations to motor experience: evidence that skill learning but not strength training induces cortical reorganization. *Behavioural brain research*, 123:133–41, 10 2001. doi: 10.1016/S0166-4328(01)00199-1.

[43] O. Mubin, F. Alnajjar, A. Mahmud, N. Jishtu, and B. Alsinglawi. Exploring serious games for stroke rehabilitation: a scoping review. *Disability and Rehabilitation: Assistive Technology*, pages 1–7, 06 2020. doi: 10.1080/17483107.2020.1768309.

[44] R. Kizony, M. F. Levin, L. Hughey, C. Perez, and J. Fung. Cognitive load and dual-task performance during locomotion poststroke: a feasibility study using a functional virtual environment. *Phys Ther*, 90(2):252–260, Feb 2010.

[45] B. Molier, E. van Asseldonk, H. Hermens, and M. Jannink. Nature, timing, frequency and type of augmented feedback; does it influence motor relearning of the hemiparetic arm after stroke? a systematic review. *Disability and rehabilitation*, 32:1799–809, 03 2010. doi: 10.3109/09638281003734359.

[46] T. Malone and M. Lepper. Making learning fun: A taxonomy of intrinsic motivations for learning. *Making Learning Fun: A Taxonomy of Intrinsic Motivations for Learning*, 3, 01 2005.

[47] K. Raaen and I. Kjellmo. Measuring latency in virtual reality systems. In *Entertainment Computing - ICEC 2015*, pages 457–462, 09 2015. ISBN 978-3-319-24588-1. doi: 10.1007/978-3-319-24589-8_40.

[48] G. Yavuzer, A. Senel, M. Atay, and H. Stam. "playstation eyetoy games" improve upper extremity-related motor functioning in subacute stroke: A randomized controlled clinical trial. *European journal of physical and rehabilitation medicine*, 44:237–44, 06 2008.

[49] N. Ribeiro, D. Ferraz, Pedreira, Mascarenha, A. Pinto, M. Neto, L. Aguiar, M. Pozzato, R. Pinho, and M. Masruha Rodrigues. Virtual rehabilitation via nintendo wii® and conventional physical therapy effectively treat post-stroke hemiparetic patients. *Topics in Stroke Rehabilitation*, 22: 1074935714Z.000, 02 2015. doi: 10.1179/1074935714Z.0000000017.

[50] I. Pastor, H. Hayes, and S. Bamberg. A feasibility study of an upper limb rehabilitation system using kinect and computer games. *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference*, 2012:1286–9, 08 2012. doi: 10.1109/EMBC.2012.6346173.

[51] D.-S. Park, D.-G. Lee, K. Lee, and G. Lee. Effects of virtual reality training using xbox kinect on motor function in stroke survivors: A preliminary study. *Journal of Stroke and Cerebrovascular Diseases*, 26, 06 2017. doi: 10.1016/j.jstrokecerebrovasdis.2017.05.019.

[52] R. Mane, T. Chouhan, and C. Guan. Bci for stroke rehabilitation: Motor and beyond. *Journal of Neural Engineering*, 17, 06 2020. doi: 10.1088/1741-2552/aba162.

[53] S. Adamovich, G. Fluet, A. Merians, A. Mathai, and Q. Qiu. Incorporating haptic effects into three-dimensional virtual environments to train the hemiparetic upper extremity. *IEEE transactions on neural systems and rehabilitation engineering : a publication of the IEEE Engineering in Medicine and Biology Society*, 17:512–20, 09 2009. doi: 10.1109/TNSRE.2009.2028830.

[54] Y.-H. Choi, J. Ku, H. Lim, Y. h. Kim, and N.-J. Paik. Mobile game-based virtual reality rehabilitation program for upper limb dysfunction after ischemic stroke. *Restorative neurology and neuroscience*, 34, 05 2016. doi: 10.3233/RNN-150626.

[55] D. Putrino, H. Zanders, T. Hamilton, A. Rykman, P. Lee, and D. Edwards. Patient engagement is related to impairment reduction during digital game-based therapy in stroke. *Games for health journal*, 6, 09 2017. doi: 10.1089/g4h.2016.0108.

[56] M. Benoit, R. Guerchouche, P.-D. Petit, E. Chapoulie, V. Manera, G. Chaurasia, G. Drettakis, and P. Robert. Is it possible to use highly realistic virtual reality in the elderly? a feasibility study with image-based rendering. *Neuropsychiatric disease and treatment*, 11:557–63, 03 2015. doi: 10.2147/NDT.S73179.

[57] J. E. R. Dias. A digital game in immersive environments to support the stroke victims. Master's thesis, Universidade de Aveiro, 2018.