The use of immersive virtual reality in neurorehabilitation and its impact in neuroplasticity

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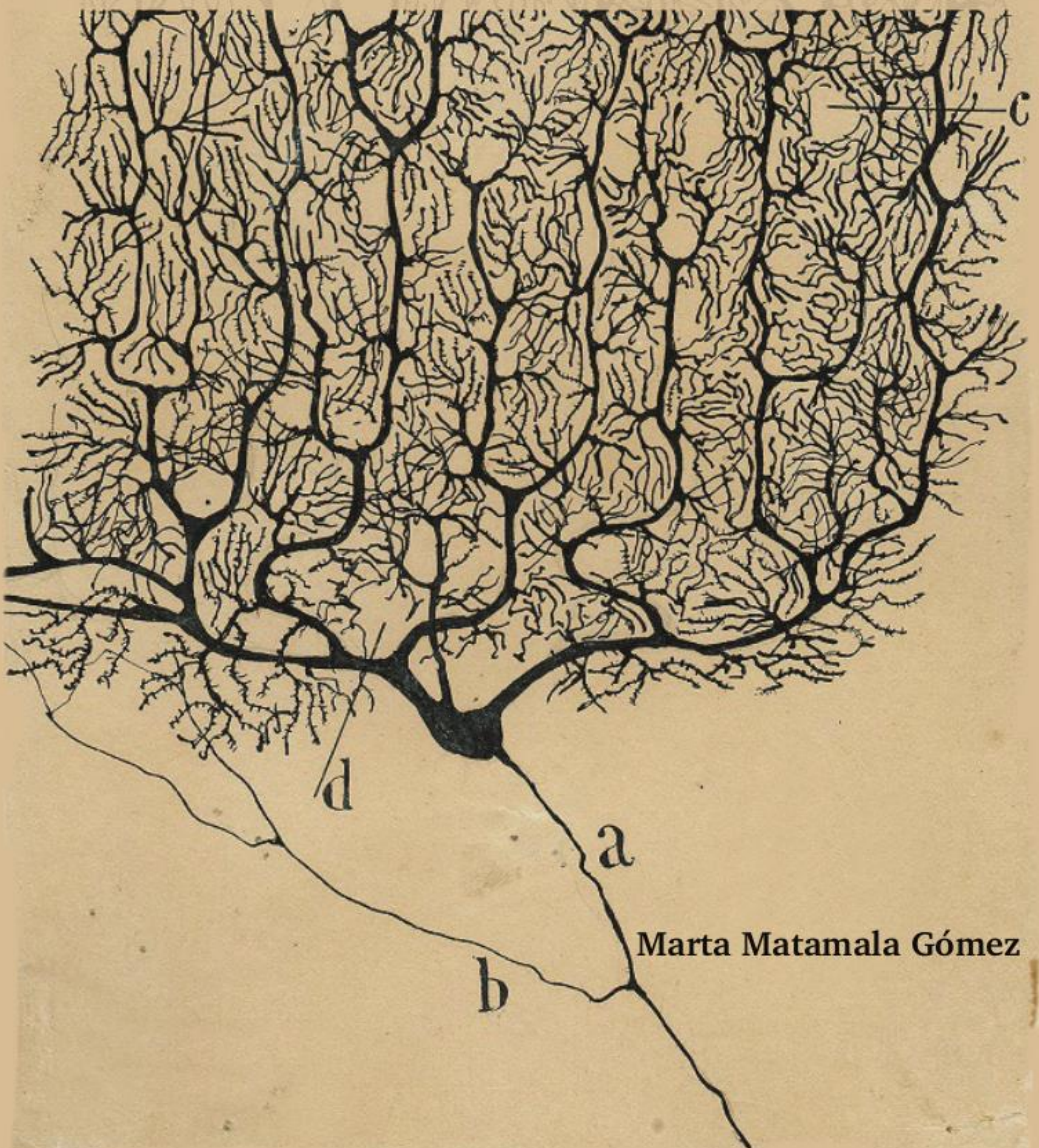

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The use of immersive virtual reality in neurorehabilitation and its impact in neuroplasticity

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2. Morone G, Matamala-Gomez M, Sanchez-Vives MV, Paolucci S, Iosa M. Watch your step! Who might return to be independent in stair climbing after stroke? European Journal of Physical and Rehabilitation Medicine. (Under review).

3. Matamala-Gomez M, Slater M, Sanchez-Vives MV. Motor-cognitive training through Immersive Virtual Reality during the immobilization period in distal radius fracture patients: a randomized control trial study (In preparation).

4. Matamala-Gomez M, Saenger VM, Duarte E, Sanchez-Vives MV. Using immersive virtual reality to rehabilitate the paretic upper limb in chronic stroke patient's pilot study (In preparation).

5. Matamala-Gomez M, Diaz Anna, Slater M, Sanchez-Vives MV. Relevance of the origin of chronic pain when using virtual reality in rehabilitation (In preparation).

List of abbreviations

AO	Action Observation
CAHAI	Chedocke Arm and hand Activity Inventory
Caud	caudatenucleus
Cb	cerebellarareas
CDM	Conventional Digit Mobilization
CRPS	Complex regional pain syndrome
DASH	Disability of the Arm, Shoulder and Hand questionnaire
DLPFC	DorsoLateralPreFrontal Cortex
DTI	Diffusion Tensor Imaging
FM	Fugl-Meyer test
fMRI	Functional Magnetic Resonance Imaging
HMD	Head Mounted Display
IOF	inferior orbito frontal
IPS	IntraParietal Sulcus
IT	inferior temporal
IVR	Immersive Virtual Reality
M1	Primary Motor cortex
medSF	medial superior frontal
MF	middle frontal
MI	Motor Imagery
MI	Motor Imagery
Mido	middle occipital
midT	middle temporal
MRI	Magnetic Resonance Imaging
Non-IVR	Non-Immersive Virtual Reality
NPRS	Numeric Pain rating Scale
PMC	PreMotor Cortex
PNI	Peripheral Nerve Injury
Postc	postcentralgyrus
PPS	Peri-Personal Space
Prec	precentralgyrus
Pre-SMA	Pre-Supplementary Motor Area
Put	putamen

QOL	Quality of Life
RHI	Rubber Hand Illusion
Rol	rolandicoperculum
ROM	Range of Motion
S1	primary somatosensory area
S2	secondary somatosensory area
SAM	Self-Assessment Manikin scale
SCR	Skin Conductance Responses
SS-QOL	Stroke Specific Quality of Life
STG	Superior Temporal Gyrus
Supo	superior occipital
Thal	thalamus
TMS	Transcranial Magnetic Stimulation
Ver	Vermis
VHI	Virtual Hand Illusion
vPMC	ventral PreMotor Cortex
VR	Virtual Reality
WMFT	Wolf Motor Functional Test

Chapter 1

Don't think about why you question, simply don't stop questioning. Don't worry about what you can't answer, and don't try to explain what you can't know. Curiosity is its own reason. Aren't you in awe when you contemplate the mysteries of eternity, of life, of the marvellous structure behind reality? And this is the miracle of the human mind-to use its constructions, concepts, and formulas as tools to explain what man sees, feels and touches. Try to comprehend a little more each day. Have holy curiosity.

Albert Einstein

Introduction

It is known that through the perception of different sensory inputs such as vision, sound, touch, force, taste and smell, which are active processes that combine bottom-up and top-down processing of the sensory inputs based on our previous experiences, we can be conscious of our immediate surroundings. In this regard, virtual reality (VR) systems are mainly focused on the sensory input of vision, and in addition they may have sound, and some tactile feedback as well. However, in VR even the visual feedback input alone is enough to create the illusion that the virtual environment or virtual body are real (Slater & Sanchez-Vives 2016). This means that VR could provide an alternative simulated reality, while not being a physical reality, but that VR best applies to the space that is just below what is commonly called the "reality horizon" (Slater & Sanchez-Vives 2016). To support this concept, when participants entered an "immersive virtual reality" (IVR) system and observed a knife attack on their virtual body, there was a motor cortex activation indicating that those participants experienced that "virtual" knife attack as a real attack, even though they knew that they were not going to be physically injured (see González-Franco et al. 2014).

Hence, we can argue that vision is one of the most important perceptive modalities to interact with the environment in our daily life. Consequently, many studies have been investigating the influence of visual feedback techniques in motor and pain rehabilitation (Adams et al. 1975; Adamovich et al. 2001; Eliassen et al. 2003; McCabe et al. 2008; Ramachandran & Altschuler 2009). In this line, mirror visual feedback was investigated by Ramachandran (2009), which is a non-invasive technique for the treatment of different injuries such as chronic pain of central origin (neuropathic pain), and motor disorders such as hemiparesis in stroke patients. Mirror visual feedback training is normally conducted by a mirror box where the patient has to place his affected limb on one side of the mirror and the healthy limb on the opposite side of the mirror. He then has to look where the healthy limb is reflected on the mirror so the reflection of the healthy limb seems visually superimposed on the location of the affected limb, creating the illusion that the affected limb has recovered. Hence, if the patient starts to do movements with the healthy limb, he gets the visual sensation that the affected limb is performing those movements. Inspired by this approach, a large amount of studies have been using visual feedback conveyed through mirrors (Avanzino et al. 2014; Deconinck et al. 2015; Ramachandran & Altschuler 2009), videos (Stefan et al. 2008; Pelosin et al. 2010), virtual reality (Llobera et al. 2013a; Laver et al. 2012; Mindy F Levin et al. 2015) and even through mental representation of the movements (Malouin, Philip L. Jackson, et al. 2013; G. Moseley 2006; Jeannerod 1995), which partially stimulate the same neural circuits as the ones activated by mirror visual feedback technique. Remarkably, some studies have demonstrated that the combination of these different visual feedback techniques, such as motor imagery by planning the movement and action observation, by the observation of the action through a mirror, a video or though virtual reality, could be a powerful approach to treat motor and chronic pain disorders (Wright et al. 2014; Nojima et al. 2015; Mirelman et al. 2013; Friesen et al. 2017; Diers et al. 2013; Nierula et al. 2017).

In addition, through IVR we can achieve situations that cannot be done in the physical world. Even more, through IVR we can have the conscious perception of being present in the virtual environment embodied in a virtual body (Slater et al. 2009; Sanchez-Vives & Slater 2005; Mel Slater, Spanlang, M. V. Sanchez-Vives, et al. 2010). This provides a powerful tool to improve traditional rehabilitation programs by making it more stimulating for the patient and by changing their motor mechanic and repetitive activity to something more stimulating, while also demanding cognitive effort. In the conventional rehabilitation programs the intensive repetition of mechanical movements leads the patient to repeat those movements in an automatic way, without paying attention to the aim of the exercise. In this regard, IVR allows to the patients to be ‘mentally active’ during the rehabilitation training as it also implies both motor and cognitive effort. In fact, IVR in rehabilitation has been described as a flexible technology that supports intensive and repetitive training that is often found to be motivating, engaging, and enjoyable (LeBlanc et al. 2013).

The use of IVR in the field of rehabilitation was previously limited because of the cost and a steep learning curve. However, with development of such IVR platforms using more user-friendly software has started a wave of powerful applications for clinical applications (Sveistrup

2004; Weiss et al. 2004). Virtual environments can be created and displayed on simple two-dimensional display platforms (Non-immersive virtual reality) as well as on more “immersive” three dimensional displays. In a lot of IVR and video gaming applications, visual feedback is supported by an auditory cue that provides information about task effectuation (Weiss et al. 2004; Rizzo & Schultheis 2004). Furthermore, for upper limb sensorimotor rehabilitation, patients can interact with virtual objects and perform actions that engender a feeling of “presence” in the virtual environment (more detailed information in section 1.1.2) (Slater 2009a). In addition, to provide appropriate sensory information during object interaction, tactile feedback can be incorporated into IVR applications via haptic gloves or robots (Merians et al. 2002).

On the other hand, IVR systems can be designed according to the individual needs of the patients to include meaningful, challenging, and progressive exercises that can be carried out in simple and different settings. According to this, IVR rehabilitation programs can be made task specific to achieve specific goals (Fluet et al. 2012). The fact that IVR systems allow matching task difficulty to the skill level of the patient is an important factor to prevent frustration and fatigue when engaging a patient in an exercise program (LeBlanc et al. 2013).

Nowadays, there are some contradictory findings about how virtual reality can be a helpful tool in the rehabilitation field. While some recent studies did not find important changes in motor recovery of the upper limb after a period of training with a non-immersive virtual reality compared to a conventional recreational activity in acute stroke patients (Gustavo Saposnik et al. 2016), others found important improvements in risk of falls with varied motor and cognitive deficits after a treadmill plus non-immersive virtual reality training compared to treadmill training alone (Mirelman et al. 2016). In this concern, several questions remain open to the researchers who develop and evaluate IVR applications in the field of rehabilitation. A primary question is regarding which type of patients are most likely to benefit from IVR trainings. Until now, most of the research on this field has been conducted with patients in the chronic stage after brain injury, so the potential for IVR to drive early neuroplasticity in acute or brain healthy subjects is still unknown. Second, there is not enough knowledge about how often a task needs to be practiced in a virtual environment to be learned (see Mindy F Levin et al. (2015) for a review).

Most of the research in the rehabilitation field for motor and pain disorders has been conducted with non-immersive virtual reality (Non-IVR) systems (Adamovich, August, et al. 2009; Cameirão et al. 2012; Piron et al. 2006; Hoffman et al. 2000; Laver et al. 2015; Daniel Senkowski & Heinz 2016; Mirelman et al. 2016). Moreover there are very few studies using immersive virtual reality (IVR) systems in clinical population or these include small sample sizes (Llobera et al. 2013a; Perez-Marcos, Solazzi, et al. 2012; Donati, Shokur, Morya, Campos, Shokur, et al. 2016; Gromala et al. 2016).

In this thesis, I aimed to test the effectiveness of a full-immersive virtual reality set-up as a rehabilitation tool in the neurorehabilitation field. More specifically, first in the study entitled ***Motor-cognitive training through Immersive Virtual Reality during the immobilization period in distal radius fracture patients: a randomized control trial study****,* we investigated whether a self-developed IVR training program based on mental training techniques, by which we induced ownership of a virtual body and allowed controlling the initiation of movements of the virtual arm, could improve the motor functional ability of a fractured arm in distal radius fracture (DRF)patients during the immobilization period and thus accelerate the rehabilitation process.

Second, a case study entitled ***Using immersive virtual reality to rehabilitate the paretic upper limb in chronic stroke patients: a pilot study,*** we investigated whether our self-developed IVR program improves the recovery of three chronic stroke patients without arm mobility. Due to our program being based on a motor-cognitive training approach, we expected to find improvements in motor dexterity of the paretic arm as well as in the cognitive capability and quality of life of the three chronic stroke patients after the IVR training period. In this study, we also explored whether the motor-cognitive improvements remain over time and whether we could further enhance those improvements by adding a second training period after a period of pause. A pre-post brain imaging analysis allowed us to identify the underpinning neuroplastic changes following the first IVR training.

Finally, the third study called ***Immersive virtual reality reliefs pain in patients with complex regional pain syndrome type I but not with peripheral nerve injury,*** aimed to study the effects of IVR visual feedback of the morphological characteristics of the virtual arm on pain perception in chronic pain patients. Since it is known that complex regional pain syndrome (CRPS) and peripheral nerve injury (PNI) have different underlying pain mechanisms (Baron 2006), we wanted to investigate whether different levels of transparency and size distortions of the virtual body affect pain relief by comparing the effects on CRPS type I patients as the experimental group to PNI patients, as a control group.

In the following section, details on the mechanisms underlying visual feedback and body illusions techniques applied in the neurorehabilitation field will be explained. Furthermore, the neural networks involved in these techniques will also be discussed. Finally, a detailed overview of what is known about the effectiveness of visual feedback techniques such as the rubber hand illusion (RHI), mirror visual feedback and IVR will be given.

1.1 Virtual Reality and embodiment

Virtual reality is often described as ‘reality’ that is ‘virtual’. This refers to the fact that, theoretically, things that can occur in reality can be programmed to occur in a virtual environment (Slater & Sanchez-Vives, 2016). Furthermore, through virtual reality we can fulfil things that cannot be done in the physical world.

The concept of IVR was first defined by Ivan Sutherland in 1965 (Sutherland, 1965) and then implemented with the “Sword of Damocles” head mounted display (HMD) described three years later (Sutherland 1968). This was the first study that implemented the concepts that make up an IVR system. An HMD is used to provide a stereoscopic computer-generated image, with one image for each eye. The 2D images are computed and rendered with appropriate perspective with respect to the position of each eye in the three-dimensional scene. Together, the images therefore form a stereo pair. The two small displays are placed in front of the corresponding eye. The displays are mounted in a frame, which usually has a mechanism to capture the position and orientation of the user’s head, and therefore gaze direction (assuming that the eyes are looking straight ahead). Consequently, when the user moves their head this information is directly transmitted to the computer that recomposes the images displayed on the screens. From the point of view of the user, they are surrounded by a life-size 3D environment. In fact, IVR differs from other types of human-computer interfaces in the sense that in IVR the term ‘user’ can be changed to the ‘participant’ as they are immersed in a virtual world with the possibility to really participate in the generated environment rather than use it. In addition, through an HMD with head tracking you can also see a virtual body substituting your own body, where the virtual body can be designed to look like the real body. Hence, an HMD is considered as an *immersive* device.

1.1.1 Immersion and Presence

Today, a common IVR system provides stereo vision that is updated as a function of the head-tracking, sometimes directional audio and some type of limited haptic interface. In IVR systems it has been shown that the concept of immersion is a description of the system’s characteristics where one system would be more ‘immersive’ than another if it was superior in at least one of the following characteristics: graphics frame rate (how long it takes to graphically represent the virtual environment), the overall extent of tracking (how much of the body movement is tracked, apart from the head), tracking latency (how long it takes between head movement and changes in the display image), the quality of the images (brightness, spatial, colour and contrast resolutions), the field of view (how large is the visual field of view, and much do the displays surround the participant), the visual quality of the virtual scene (how realistic are the objects and illumination depicted in the scene), the dynamics (how well does behaviour of objects conform to expectations) and the range of sensory modalities accommodated (Slater & Wilbur 1997a). Additionally, the sensorimotor contingences (SC) can also determine the immersion capacity of the system. SCs refer to the actions that we perform in order to perceive changes within environment, for example, moving your head and eyes to change your gaze direction (O'Regan & Noë 2001b; O'Regan & Noë 2001a; Noë 2004).

There is an elementary difference between an immersive and a non-immersive virtual system: in an ideal immersive system, it is possible to fully simulate, in a realistic manner, experiences that in a non-immersive system only appear to happen. By using a head-tracked HMD and by providing to the participants haptics and auditory feedback, we can construct a virtual environment in which participants can virtually realise all of the actions, and experience the virtual scenario as a real environment. However, this property of immersive systems it is not possible with a non-immersive display to really simulate the environment and actions as in the immersive system. The physical capabilities of these systems do not allow this level of immersion. Consequently, immersion has been described as a "*property of the valid actions that are possible within the system*" (Slater 2009a).

It should be noted that immersion describes the technical capabilities of a system. A subjective form of immersion is called *presence*(Sanchez-Vives & Slater 2005). Presence is the sense of being in a virtual environment rather than in the place in which the participant's body is actually located (Draper et al. 1998; Held & Durlach 1992; Sheridan 1992; Ellis 1996; Sheridan 1996; Slater & Wilbur 1997b). Presence refers to the sense of 'being there' in the virtual environment where the participant can really interact with the generated environment. This concept has been explained in other body-centred approaches, in which it is discussed that a close match between kinaesthetic proprioception and the flow of sensory information (e.g. by vision) is essential (Slater et al. 1998; Schubert et al. 2001). The minimal cues, that means the minimal elements, which a virtual environment must include to induce the sense of presence to the participant are, head tracking, frame rate, sound and interactions models (Slater 2002).

On the other hand, the phenomenon of presence is based on the transportation of consciousness to an alternative environment, such as a virtual environment, in which presence is consciousness within a virtual reality. In agreement with Damasio, "consciousness occurs when one can generate, automatically, the sense that a given stimulus is being perceived in a personal perspective; the sense that the stimulus is ‘owned’ by the organism in the perceiving; and, last but not least, the sense that the organism can act on the stimulus (or fail to do so)” (Damasio 1998). When someone is immersed within a virtual environment, all of these criteria can be accomplished and most of the aspects can be manipulated experimentally (Sanchez-Vives & Slater 2005). Therefore, presence occurs when computer-generated data successfully substitutes real sensory data, and when participants can participate with normal motor actions to perform some tasks, having the sensation of control over the virtual environment. This gives rise to the subjective illusion of “being there”.

In order to distinguish it from the multiple alternative meanings that have been attributed to the term *‘presence’*, the subjective illusion of “being there” has also been referred to as “place illusion” (Slater 2009b). This concept was introduced by Marvin Minsky (1980) describing a similar feeling when embodying a remote robotic device in a teleoperator system. Place illusion refers to the *strong illusion of being in a place in spite of the sure knowledge that you are not there* (Slater 2009b). Place illusion can happen even in a static environment where nothing happens, just looking around a virtual reality scenario and perceiving the virtual world making use of motor actions; such as head movements, to perceive in the same way as perceiving the real world, but with the knowledge that they are in virtual reality.

On the other hand, when events occur in the generated virtual environment, events that concern you, that respond to your actions and refer to you personally, can give rise to the illusion that what is apparently happening is really happening, even knowing that it is not happening in truth. This illusion is referred to as “Plausibility Illusion” (Slater 2009b). Consider a virtual scenario where there is a woman standing in front of you. From a perceptual point of view there is someone there, in the same space as you. For example, if you move your head from side to side, the image of the woman moves as it would in the real world, this is place illusion. Now the woman approaches and smiles at you, and suddenly you find yourself smiling back, even though there is no one there, this fact refers to plausibility. A similar scenario as the one described above has been created to study the responses of shy males when interacting with a virtual woman (Pan & Slater 2007). Hence one of the main factors that facilitate plausibility is the correlational principle. Another example that justifies this is the visual cliff scenario (Walk & Gibson 1960), which was implemented in a virtual scenario that is referred to as the ‘pit room’ (Slater et al. 1995). In this experiment, the participant is in a strange room where the floor is just a narrow ledge around an open hole to another room six meters below. One group of the participants had to get to the other side of the room. They observed that most of the participant border their way carefully around the ledge rather than simply drifting across the non-existent (virtual) pit. They expected to observe signs of anxiety in this group of participants.

Finally, we can say that plausibility is a consequent illusion related to the place illusion, one that occurs as an immediate feeling, produced by some fundamental evaluation by the brain of one's current circumstances, where the participant feels that the situation is real while of course, at a higher cognitive level, participants are aware that nothing is 'really' happening, and they can modify their responses according to that.

1.1.2 Virtual embodiment

Related to the concepts mentioned above, the body is a focal point where place illusion and plausibility are fused. In virtual reality, a virtual body can be represented collocated with the real physical body through an HMD. Through an HMD, when you look down to see your real body, instead of this you would see your virtual body. In fact, the action of looking at your own body provides very powerful evidence for place illusion, which means that your body is in the place where you perceive yourself to be. However, the virtual body displayed in the virtual scenario is not your body, but instead is a representation of you.

In addition, some studies in cognitive neuroscience concerned with body ownership are based on the rubber hand illusion (RHI) paradigm (explained in detail in section 1.2.1) (Botvinick & Cohen 1998a; K. Carrie Armel & Ramachandran 2003; Tsakiris & Haggard 2005; Pavani et al. 2000). The RHI has been repeated in a virtual reality environment, through synchronous visuotactile stimulation to the real and virtual hands, which signifies that the illusory virtual hand was seen to be tapped or stroked in the same place as the real hand was felt to be simulated, proving an ownership of a virtual arm (Slater et al. 2008).

Normally, when something strikes our body we feel it at the same place where we see it. However, when normal correlation between two sensory stimuli is changed, for example, as in Slater et al, (2008), where seeing a plausibly located virtual hand touched while simultaneously feeling the touch on the out-of-sight real hand, the brain starts a cognitive conflict and assigns ownership to the visible virtual hand. These methods have been also used to produce illusions of body morphing, adding supernumerary limbs to the body (Schaefer et al. 2009; Ehrsson 2009; H. Ehrsson et al. 2005), or by triplicating the length of the virtual arm, inducing a very long arm illusion (Konstantina Kilteni, Normand, et al. 2012). This type of technique, through visuotactile stimulation, has also been applied to give illusions of whole body displacement where the person in part feels themselves to be located outside of their body (Ehrsson 2007; Petkova & Ehrsson 2008; Lenggenhager et al. 2007), commonly known as out-of-the-body experiences. Then, through IVR we can not only transform our sense of place, and of reality, but also the morphological properties of your own body. In this regard, Slater et al. (2010), demonstrated that by being embodied in a virtual body, people experienced physiological and subjective responses as if it were their own body.

Another technique to induce body ownership is through visuomotor correlations. Now suppose that you move your limbs and automatically you see the limbs of the virtual body move in synchrony. This is considered a very powerful situation in the external world that is clearly related to you. In that moment, there is a correlation between proprioception and visual exteroception. Concerning this matter, Sanchez-Vives et al. (2010), demonstrated that synchrony between visual and proprioceptive information along with motor activity is sufficient to induce an illusion of ownership over a virtual arm, in the absence of tactile stimulation. This ownership illusion of the virtual body only occurs when both visuomotor and visuotactile stimulation are synchronous (Slater et al. 2009; Sanchez-Vives et al. 2010). Asynchronous stimulation of the real and rubber hand has been shown to inhibit the illusion of ownership and the mislocalization with the rubber hand (K Carrie Armel & Ramachandran 2003; Botvinick & Cohen 1998b; Tsakiris et al. 2010).

In addition, for cognitive neuroscience and psychology, the term embodiment is concerned with the inquiry of how the brain represents the body (Berlucchi & Aglioti 1997; Graziano & Botvinick 2002) and how under certain neurological conditions this representation could be altered (Lenggenhager et al. 2006; Metzinger 2009). The Sense of Embodiment has been referred to the group of sensations that emerge in conjunction with being inside, having, and controlling a body especially in relation to virtual reality applications

In agreement with de Vignemont (2011), a specific object "E" could be embodied if and only if some properties of E are processed in the same way as the properties of one's body. This definition is in line with Blanke & Metzinger (2009), who declare that embodiment includes the "subjective experience of using and 'having' a body". In fact, the term *embodiment* has frequently been attributed to the concepts of self-location (Arzy et al. 2006), the sense of ownership (Lopez et al. 2008) and the sense of agency (Newport et al. 2010). Accordingly, the properties of one's biological body could be described under the conceptual umbrella of these three terms.

1.1.3 Rubber Hand Illusion

How the brain represents our body is a fundamental question in cognitive neuroscience that tackles questions such as how to differentiate that our 'hand' is part of our body and a physical object like a 'book' is not. Commonly, we believe that our own internal body representation is stable, however some investigations have elicited the illusion of body ownership over objects that are not part of the body at all. Hence, our body representation is in truth highly malleable. In addition, out-of-body illusions research was reignited again by Botvinick & Cohen 1998 with the RHI study. In the RHI study, the participant sits by a table on which a rubber hand is placed in the same anatomical position and parallel to the participant real hand. The real hand is hidden behind an occluder. The experimenter, sitting in front of the participant taps and strokes the rubber hand and the hidden real hand synchronously by using two paintbrushes for ten minutes. During this stimulation time, participants are seeing the visuo-tactile stimulation applied on the rubber hand and at the same time feeling stimulation on the real hand (see ***Figure 1.1.1***). After a few seconds of the visuo-tactile stimulation, participants reported a strong illusion that the rubber hand was their own hand through a questionnaire. Most of the participants start to agree with statements such as 'It seemed as if I were feeling the touch in the location where I saw the rubber hand touched' and 'I felt as if the rubber hand were my hand'. This happens because the brain's perceptual system resolves this sensory conflict by integrating the two separate but synchronous inputs into one, as a result of which participants have the perceptual and proprioceptive illusion that the rubber hand is their real hand. However, if the visual and tactile stimulation are asynchronous the illusion does not occur.

On the other hand, Armel & Ramachandran (2003) demonstrated than even when the rubber hand is threatened, participants respond physiologically displaying strong skin conductance response (SCR). In this study they argue that our body representation is updated moment to moment based on the stimulus received. By synchronous multisensory perception we can feel that a rubber hand is our real hand due to the fact that the brain quickly generates the corresponding illusion as a way to resolve the contradiction between the seen and felt synchronous stimulation.

Figure 1.1.1 The rubber hand illusion set-up (image retrieved from the Event-lab). *In the picture, the real arm (right side) is hidden from the field of view of the participant and the rubber arm (left side) is in the field of view of the participant. The experimenter is in front of the participants, stroking synchronously both the real and the rubber hand, which will cause the illusion of ownership of the rubber hand.*

1.1.4 Neural mechanisms of the RHI and VHI

Neuroimaging studies have started to reveal the neural mechanisms of the RHI. First, Ehrsson et al. (2004) showed that prolonged synchronous visuo-tactile stroking of the real and a fake hand (placed in a plausible position), inducing illusory hand ownership activates ventral premotor cortex (vPMC), intraparietal sulcus (IPS) and the cerebellum (Ehrsson et al. 2004, 2005). Some years later, the same cortical areas showed de-activation when incongruent visuo-tactile stimulation was applied to the fake hand also presenting decreased hand ownership (Gentile et al. 2013). This activations pattern, especially in IPS, depends on visual information as occurring near the hand and on proprioceptive and visual bodily information. Moreover, Gentile & Petkova. (2011) demonstrated that these cortical areas not only process signals that are on or close to the arm but especially integrate multisensory information, when occurring in the surroundings of the centred-arm space, this space is called *peri-personal space* (PPS) of the arm. They compared neural activity associated to one stimuli (unimodal stimulation) 'touch' was applied to the hand, one stimuli applied near the hand 'vision' and two different stimuli (bimodal stimulation) applied at the same time within the PPS of the arm. Furthermore, posterior and inferior parietal cortex areas and premotor cortex (PMC) also showed higher activation patterns to bimodal, as compared to unimodal stimulation. Others, observed that when the fake hand is threatened, the supplementary motor area (Ehrsson et al. 2007) and parietal regions, including the inferior and superior parietal lobule are activated (Lloyd & Roberts 2006). Furthermore, the strength of hand ownership, measured by questionnaire ratings, was found to correlate with activity in the anterior insular and cingulate cortices (Ehrsson et al. 2007), PMC and cerebellum (Ehrsson et al. 2004). These findings were expanded by Tsakiris et al. (2007), who also reported a correlation between the strength of hand ownership with the activity in the right posterior insula and sensorimotor cortices (precentral and postcentral gyri).

Taken together, all these neuroimaging studies demonstrate that inducing illusory ownership of a fake hand through repeated and prolonged synchronous visuotactile stimulation recodes the space around the rubber hand as peri-hand space (Blanke et al. 2015). In this regard, some studies suggest that both PMC and intraparietal cortical areas represent the space surrounding the illusory fake hand, extending earlier single cell responses in area 5 and PMC to subjective hand ownership (Graziano 1999; Graziano et al. 2000).

1.1.5 Agency

The sense of agency refers to the sense of having “global motor control, including the subjective experience of action, control of the action intention, motor selection and the conscious experience of will” (Blanke & Metzinger 2009b). Congruent with this definition, others describe agency as the sense of intending and executing functions, including the feeling of controlling one’s own body movements, and as a consequence, the event associated with the movement in the external environment (Tsakiris et al. 2006). It is well known that to generate a movement we have to first centrally generate motor commands, and for that reason, the sense of agency involves a strong efferent component. In contrast, the sense of ownership involves strong afferent component through the various peripheral signals that indicate the state of the body. However, there is a correlation between agency and body-ownership; this means, that a body which obeys one’s intention will probably be one’s body and vice versa. Additionally, Tsakiris et al. (2007) stated that ownership does not imply a sense of agency, referring to self-generated movements not being necessary for ownership, in contrast, the sense of agency normally implies ownership. Further, investigations that provide agency toward a fake hand with the intention to induce body ownership illusion support such a relationship (Tsakiris et al. 2006; Sanchez-Vives et al. 2010; Dummer et al. 2009; Yuan & Steed 2010).

On the other hand, the study of Longo et al. (2008) observed that even though the participants did not actually move their hands, they reported a sense of agency towards the fake hand. In addition, some evidence suggests that just seeing a virtual arm seemingly coming out of the body in a feasible position is enough to induce the sense of agency (Perez-Marcos et al. 2009). In this last study, they showed how some aspects of the virtual hand illusion could also occur through motor imagery used to control the movements of the virtual hand. Although the participants do not move their real arm they could control the initiation of the virtual arm movements through motor imagery by using a Brain Computer Interface (BCI). Moreover, they also observed a strong feeling of 'inverse agency', that is, the feeling that if the virtual hand moves, your real hand would move too. In that statement motor imagery, instead of motor action, induced the signal to proportionate visuomotor correlations. Even only by applying visuotactile stimulations to the participants and displaying the movement within a virtual environment it is possible to generate the sense of agency over an action. Concerning this, in the study by Kokkinara et al. (2016), they demonstrated that although the participants in their experiment experienced the sensation of walking across a field, actually they were seated on a chair during the whole experiment.

Taken together, the use of virtual reality techniques allows to induce, to a certain extent, the sense of self-location, body ownership and agency, toward a virtual body. In this sense, by using virtual reality sensory evidence such as visual perspective can be given from body 'A' such that the participant feels self-located inside 'A'. At the same time, synchronous visuotactile correlations of the same spatiotemporal pattern between the participant's body and another body B of the same appearance, but in a different position, can be used to induce body ownership, although the induced sense of body ownership could be weak (see Petkova et al. 2011). In virtual reality, the physical movements of the participants can also be recorded with the seen movements of a third body C inducing the sense of motor control over C. Hence, by using IVR the sensations correlated with embodiment could be theoretically dissociated as coming from three separate bodies; self-location from A, body ownership from B, and agency from C (K. Kilteni, et al. 2012)

1.1.6 Virtual reality in clinical applications

Virtual reality can provide the appropriate experience to support rehabilitation processes (Levin 2011; Saposnik & Levin 2011; Mindy F. Levin et al. 2015; Burdea 2002). The capacity of IVR-based systems as a therapeutic tool for motor-functional recovery by activating brain circuits, such as motor areas, has been demonstrated (Adamovich, Fluet, et al. 2009). Furthermore, some review studies have shown that IVR systems can be effective and motivating for rehabilitation therapies involving repetition and feedback of the movements (Holden 2005). In rehabilitation applications based on augmented feedback using IVR, it has been shown that motivation plays a key role for the rehabilitation of motor skills of patients with neurological disorders (Robertson & Roby-Brami 2010). Particularly, some evidence demonstrates the effectiveness of such approaches for the rehabilitation of upper limbs in patients with stroke (Saposnik & Levin 2011; Gustavo Saposnik et al. 2016; Lucca 2009; Mindy F Levin et al. 2015). The clinical utility of using enriched training environments such as IVR environments allow for creation of a variety of flexible interventions and manipulation of the salient feedback that can be used to maximize neuroplastic processes (M. Levin et al. 2015). By using IVR treatment interventions, exercises can be manipulated to explicitly engage motivation, cognitive processes, motor control, and sensory feedback-based on learning mechanisms (Weiss et al. 2014).

One of the most important advantages of using IVR in clinical applications is that IVR environments allow clinical researchers or therapists to manipulate multimodal stimuli inputs, hence the patients' sensorimotor illusion of being 'present' in the displayed environment is maximized (Biocca & Frank 1997; Lombard & Ditton 1997; Slater 1999). Furthermore, through IVR we can provide realistic stimulation to multiple sensory channels at once, engaging the sensorimotor system with a higher magnitude than the simple stimuli used in therapies applied in the real world (Bohil et al. 2011). Following this approach, we can say that virtual environments are designed for multimodal sensory stimulation, making them an excellent tool for multisensory integration applications. It has been shown that multimodal stimulus control is also important to induce a sense of 'presence' in virtual environments, which is a basic requirement for the effectiveness of IVR training in medical, military and other educational and therapeutic applications (Bohil et al. 2011).

1.1.6.1 Virtual reality for pain relief

It has been shown that Immersive Virtual Reality (IVR) technology represents an effective tool for pain relief interventions using multisensory feedback with healthy subjects (Llobera 2013; Matteo Martini et al. 2013; Martini et al. 2014; Martini et al. 2015; Nierula et al. 2017) and also with chronic pain patients (Llobera et al. 2013; Gilpin et al. 2015; Mouraux et al. 2016; Preston & Newport 2011). In fact, pain experience is closely related to multisensory integration. Nowadays, there is a lot of evidence showing how pain perception can be modulated by manipulating multisensory signals (Longo et al. 2009; Wand et al. 2012). In addition, IVR technology allows the creation of multisensory environments that can be under the full control of the experimenter (Sanchez-Vives & Slater 2005). Furthermore, IVR allows one to feel immersed and present in a computer-generated environment, but it also makes possible the induction of the illusion of owning a virtual body (Sanchez-Vives & Slater 2005; K Kilteni et al. 2012), a body that can be modulated with the morphological characteristics that the experimenter determines (Banakou et al. 2013).

One important factor regarding pain relief is the perspective (first person or not) and collocation of the virtual body with the real one. Recently, Romano reported that physiological responses to pain (skin conductance reaction, more sweat) are reduced when participants had a first person perspective of the virtual body compared to the vision of the avatar's body turned 90 degrees from the real body. Furthermore, they also showed how skin conductance reaction responses are negatively correlated with the size of the virtual body, in a manner that the bigger the size of the virtual body, the lower the SCR responses in healthy subjects.

However, there are some conflicting results about how body illusions through visual feedback can reduce pain in clinical population. Subjects with chronic pain, which signifies pain that persists more than three months, often show a distorted body image and altered body perception of the painful part of the body (Boesch et al. 2016). To this extent, some evidence has shown that patients with chronic pain can respond in a different manner to the visual feedback of body illusions depending on the complexity of their pain origin. In this regard, complex regional pain syndrome (CRPS) is a complicated syndrome that has been investigated from a long time. CRPS can arise whether secondarily to trauma or spontaneously without the presence of any injury or inflammation. Several factors are considered to contribute to the pathophysiology of CRPS, including neurogenic inflammation (Parkitny et al. 2013), sympathetic nervous system activity (Drummond 2010), and maladaptive plasticity (Pietro et al. 2013). There are two types of CRPS: Type one, which does not present nerve injury, and CRPS type two, where patients present nerve injury. Due to this pathophysiological difference, it is not rare to think that we need different therapeutic intervention lines to treat chronic pain which comes from no nerve origin and chronic pain from nerve injury. In fact, some differences between CRPS type I and II have been investigated, showing a distorted mental representation of the affected limb in patients with CRPS type I (Lewis et al. 2010; Frettlöh et al. 2006; J. S. Lewis et al. 2007; H Ramakonar et al. 2011).

In line with these pathophysiological differences in chronic pain patients with or without nerve injury, one study recently showed that phantom limb in five amputee patients was reduced after 4 weeks of mirror therapy training; nevertheless, eight patients from the same study who reported telescopic distortion of the phantom limb displayed a gradual increase in the pain sensations (Foell et al.,2014). Likewise, viewing one's painful limb becoming smaller decreases pain in chronic pain patients (Moseley et al., 2008). The same effect was studied in healthy subjects and they found the opposite effect, probably due to the different pathophysiological characteristics between acute and chronic pain (Romano et al. 2015; Mancini et al. 2011).

On the other hand, the effects of visual perception of the body are classically related to bilateral body versus no-body paradigms (through seeing or not seeing the body part). In this line, Martini et al. (2015), investigated whether and how much the illusion of body ownership over a virtual body and pain thresholds change as the body becomes increasingly more transparent in healthy subjects. Here, they found a clear negative correlation between the transparency levels and the ownership of the virtual arm, meaning that the higher the level of transparency the lower the level of ownership of the virtual arm. Moreover, the more the participants felt that the transparent virtual arm was their own limb, the lower the pain thresholds.

1.1.6.2 Virtual reality for motor improvement

Over the past few years, various strategies and treatment approaches to improve motor function and quality of life of patients with motor disorders due to neurological or traumatic causes have been developed (Ifejika-Jones & Barrett 2011; Dobkin 2016; Cramer et al. 2017). Today, there is an increasing interest in mental training techniques in the field of neurorehabilitation, whereby patients mentally rehearse motor tasks when they are not able to perform them because of a physical or neurological impairment (Malouin, Philip L Jackson, et al. 2013). This recent approach has led to the design of new treatment techniques such as those using virtual reality (Mirelman et al. 2016; Bohil et al. 2011; Perez-Marcos, Solazzi, et al. 2012; G Saposnik et al. 2016; Donati et al. 2016; Tsoupikova et al. 2015; Subramanian et al. 2013; Cameirão et al.

2012). Using virtual reality is a relatively recent approach that allows simulated practice of functional tasks to a greater extent than traditional therapies (see review in Laver et al. 2015). Furthermore, virtual reality enables performing tasks that cannot be done in physical reality (Slater & Sanchez-Vives 2016), as in patients without arm mobility due to a bone fracture, for example in distal radius fracture patients, or due to a neural injury such as stroke.

In fact, normal movement patterns require the integration of different sensory signals occurring at different levels of processing (Driver & Spence 2000). Additionally, Kleim and co-workers reported better rehabilitation outcomes by integrating principles of motor control and motor learning involving relevant multimodal sensory feedback and cognitive processes (Kleim & Jones 2008). Particularly, motor tasks performance within virtual environments intend to enhance motor skill learning through the integration of multiple sensory processes such as proprioceptive, visual, auditory, and vestibular information with the engagement of cognitive processes. These multisensory interventions allow maximizing motor learning in patients with motor disorders (Kim 2005). In this regard, an IVR approach to provide a surrogate virtual body to exercise walking ability was proposed by Kokkinara et al. (2016). In this study participants were seated wearing an HMD, and without moving any body part except for their head, saw from a first-person perspective their virtual body standing and walking across a field. When participants looked down directly towards their legs, they observed their legs carrying out walking movements. They compared this experience with a third-person perspective condition and observed that participants have higher levels of body ownership and agency over the walking during the first-person perspective condition. Remarkably, in that study participants had to walk up a hill and participants in the first-person perspective had stronger skin conductance responses (more sweat) and greater mean heart rate as compared to before the hill climbing.

In this sense, IVR can be used to create virtual environments within which virtual limbs move and can be seen from a first-person perspective. This offers huge potential to carry out motor-cognitive trainings for patients with reduced or lack of mobility of the extremities. However, there are some contradictory findings about how virtual reality can be a helpful tool in the rehabilitation field. While some studies did not find important changes after a period of training with virtual reality (Gustavo Saposnik et al. 2016), others found important motor improvements after the virtual reality training (Mirelman et al. 2016; Cameirão et al. 2012; Donati et al. 2016). One reason for these differences could be the immersion in the virtual environments. To that effect, there are very few studies, typically with small sample sizes that evaluate the potential of IVR training for patients with motor disorders (see Donati et al. 2016).

Nowadays, the integration of mental practice techniques in rehabilitation programs involving mentally rehearsing motor tasks (e.g. moving the arm) when physical practice is not possible is becoming increasingly popular (Mirelman et al. 2013), as could be the case for patients without arm mobility due to a stroke or a bone fracture. The inability to move a limb could due to the neural mechanisms underlying action execution, motor imagery and action observation, which seem to rely on a common network (including premotor, supplementary motor, cingulate and parietal areas, basal ganglia, and cerebellum) (Macuga & Frey 2012); and hence mental rehearsal of movements promotes motor learning through mental practice (Malouin et al. 2013), although some controversy regarding the shared neural network still exists (Jeannerod 2001a). Not surprisingly, however, motor imagery and action observation have been recently proposed as adjunct treatments to conventional motor physiotherapy (Garrison et al. 2010a).

One way of integrating motor imagery, action planning and action observation is by using IVR, through which one can induce the illusion of owning a virtual body—or a virtual arm—when it is co-located with the real body—or real arm (Nierula et al. 2017; Romano et al. 2015), and by applying visuo-tactile correlations (Slater et al. 2009) (see section 1.2.3.2).As a result, IVR offers a promising tool to simultaneously imagine and observe motor actions of a virtual limb that is perceived as one’s own, and even allows incorporation of devices that enable control of the movement of the virtual limb. This may strengthen the neural network involved in motor execution and may consequently accelerate the rehabilitation process.

1.2 Neurorehabilitation

1.2.1 Fundamentals

Neurological rehabilitation can be described as the process of optimization of a person’s participation in society and the self-sense of well-being. This definition refers to several important features related to social functioning, as well as health or well-being and this applies to all patients left with long-term problems because of an injury that is disturbing the central neural system (Donaghy 2011). Theoretical and conceptual bases of neurological rehabilitation have been derived from the World Health Organisation’s International Classification of Functioning, the WHO ICF (Wade & Halligan 2004) and from a general problem-solving approach (Wade 2005).

Neurorehabilitation is a complex treatment process aimed at restoring and minimizing the functional deficits that have arisen in the patient as a consequence of an injury to the central nervous system. At a neurological level, it has been demonstrated that the function of each brain region cannot be understood in isolation but as a conjunction with other brain regions with which it interacts at rest as well as in active behaviour, in such a way forming neural networks. The organization of the brain into distributed neural networks has important implications for our understanding of central nervous system disorders and the consequent disrupted behaviours after brain injury (He et al. 2007). According to this, many years ago some of these implications have been shown by other early neurologist such as Jackson, Andral, Prince, von Monakoff, and Head (see Finger (1994) for a review), who suggested that after a neural damage, neurological deficits do not only affect the local area but also the secondary effects of the injury in secondary structures (Andral 1843). Concerning the effects of lesion on the brain's functional distribution, first, it has been shown that a focal injury can disrupt the synchronization between the site of the injury and other connected regions, leading to changes in the excitability all through the network. Second, these disrupted patterns of activity in large-scale networks normally correlate with the observed neurological deficits, observed at rest or during active behaviour. Such behavioural deficits do not only reflect structural damage to a specific part of a network but also after a neural injury there are functional imbalances all through the network as well as in other connected networks. Finally, the recovery of a specific function implies the reorganization of an entire brain network. Hence, the main goal of neurological rehabilitation is to restore the neural networks to a normal state or in some cases, enable a new state in which the affected function could be performed through compensatory strategies (He et al. 2007).

Today, medical advances have increased the number of survivors from central nervous system injury, increasing the number of people receiving neurological rehabilitation (Warraich & Kleim 2010). According to the aforementioned literature, neurological rehabilitation is a complex and intensive process that needs a multidisciplinary rehabilitation team, which entails high costs that further increase as the number of neurological surviving patients rise (Evers et al. 2004; Struijs et al. 2005). Furthermore, after a central nervous system injury symptoms such as movement paresis or neuropathic pain have been described (Jankovic 1994; Baron et al. 2010). Currently, mental practice techniques such as action observation through visual feedback and motor imagery are receiving a lot of attention within neurorehabilitation research to relieve motor and pain disorders (Ramachandran et al. 2009; Grosprêtre et al. 2016).

1.2.2 Visual feedback in neurorehabilitation

In our everyday life, we are surrounded by an extremely large amount of different sensory signals hitting our senses. Although vision is one of the most important perceptive modality (Wade & Swanston 2013), different sensory signals are simultaneously processed and integrated to interact with the environment. In this way, the brain has specific neural and cortical mechanisms to combine different sensory modalities in order to generate a coherent and unitary representation of an event or an object that guarantees adaptive behavioural responses (Driver & Noesselt 2008; Stein & Meredith 1993). This synergy between different sensory modalities merged with the coherent and unitary representation of the context is described as 'multisensory integration'.

Multisensory integration arises through the processing of stimuli from more than two different modalities, known as cross-modal stimuli. However, our brain always tends to organize this sensory information by imposing coherence to the different sensory stimuli. This process may lead to cross-modal illusions such as the ventriloquist effect, where perceived location of a sound by a visual stimulus presented simultaneously in a separate location (Welch & Warren 1980; Radeau 1994), and the McGurk effect, in which when a syllable like /ba/ is called onto the visual presentation of someone articulating a different syllable, subjects often report hearing the same syllable (McGurk & Macdonald 1976). Hence, when what we sense with one modality affects what we experience in another modality we need perceptual strategies in order to deal with such inter-sensory conflicts and with the intention to give coherence to the on-going perceptual experience, this requires of a minimum of cross-modal synchronization (Munhall et al. 1996; Bertelson et al. 1997). This cross-modal illusion function is based on automatic multisensory interactions in the brain that happens outside of conscious perception. With the intention to justify these automatic multisensory interactions, Bertelson and Ascherslelene developed a method to demonstrate automaticity of the visual bias of sound location (Bertelson & Aschersleben 1998), in which small interactions between intermodal discrepancies occur but the participants had no awareness of those discrepancies.

Following this approach, today there is a large amount of interest in how cross-modal illusions can be used in the neurorehabilitation field (Bolognini et al. 2015) to demonstrate how multisensory interactions can modify human perception and cognition through body illusions (Moseley et al. 2012). Recently, body illusions created by techniques such as the Rubber Hand Illusion (RHI) (Hari Ramakonar et al. 2011), the mirror visual feedback therapy (Ramachandran & Altschuler 2009) and Immersive Virtual Reality (IVR) (Mindy F. Levin et al. 2015), have been applied with clinical purposes in motor rehabilitation and pain relief. These new therapeutic approaches come from different areas of research such as sport psychology, cognitive psychology and cognitive neuroscience and differ from traditional physical movement repetition rehabilitation techniques, working as a mental training which demand a cognitive effort by the patient.

In addition to mental training techniques, there is increasing interest from researchers in the past ten years to investigate how they can accelerate or improve the rehabilitation process especially in patients who are not able to move a limb because of a motor impairment or because of pain. In this line, the two mental training techniques with the strongest claim to efficacy are motor planning through motor imagery (MI) (Jeannerod 1995; G. . Moseley 2004; Malouin, Philip L. Jackson, et al. 2013) and action observation (AO) (Garrison et al. 2013; Deconinck et al. 2015; Chan et al. 2007). Recently, researchers have been investigating the use of combined MI/AO approach in the neurorehabilitation field (Vogt et al. 2013), especially in motor rehabilitation where some investigations prove that the combination of MI and AO is more effective than AO or MI alone (Wright et al. 2014; Friesen et al. 2017; Nedelko et al. 2012).

One way of integrating motor imagery, action planning and action observation is by using body illusions through RHI, mirror visual feedback or more recently through IVR.

1.2.3 Body illusions in neurorehabilitation

1.2.3.1 RHI in clinical applications

In the field of neurorehabilitation, recent studies have been investigating how the RHI can be applied in clinical populations under the hypothesis that cross-modal illusions can be a powerful tool for changing and normalizing body representations (Ramachandran & Rogers-Ramachandran 1995).

1.2.3.1.1 RHI and pain relief

There are mixed results about how the RHI can increase pain thresholds in healthy subjects. Some investigations studying the analgesic effect of the RHI reported conflicting results as to whether the classical RHI decreases or increases thermal pain ratings (Valenzuela-Moguillansky 2011). Further, another previous study by Mohan et al. (2012), did not observe any effect of the RHI on thermal pain thresholds. However, recently it has been shown that the

RHI has an influence on reducing pain sensation in healthy subjects (Hegedüs et al. 2014). In that study, they also showed that the classical RHI is an appropriate experimental tool to investigate how the manipulation of cortical body representations can be used for acute pain management.

1.2.3.1.2 RHI in neurological disorders

In this regard, it has been shown that upper limb amputees can be made to experience a rubber hand as part of their own body (Ehrsson et al. 2008). This effect was achieved by applying synchronous touches to the stump, which was out of view of the patient, and to the index finger of the rubber hand, which was placed in a full view. Possible mechanisms include that tactile stimulation applied to the stump converged with the tactile stimulation applied to the index rubber hand, and then this information would be integrated and interpreted in multisensory areas leading to a spatial reorganization of the sense of touch to the rubber hand (Botvinick & Cohen 1998b; Ehrsson et al. 2004; Ehrsson & Holmes 2005; Makin et al. 2008). Besides, the RHI can temporarily alter some aspects of neglect, without altering basic visual encoding, in patients suffering from unilateral visual neglect after a short-term intervention (Kitadono & Humphreys 2007). Later, Reinersmann et al. (2013) investigated body ownership and the underlying multisensory integration of the RHI in complex regional pain syndrome (CRPS) patients for which (bilateral) cortical reorganization, sensory disturbances, and altered body representations are reported (Maihöfner et al. 2007; Maihöfner et al. 2003; Pleger et al. 2014; Pleger et al. 2004; Schwenkreis et al. 2003).

Another recent study conducted by Lenggenhager et al. (2013) investigated how the RHI influences the immediate sensory signals and body awareness in patients with spinal cord injuries with severe somatosensory impairments in 2 of 5 fingers. The study reveals that the patients experienced a strong illusion of ownership of the rubber hand during synchronous stroking reporting basic tactile sensations in their numb fingers. Furthermore, as the tactile stimulation increased the body awareness from seeing the rubber hand also increased. This study presents the opportunity to use multisensory illusions to modulate the re-emergence of sensory memories when sensory inputs are lost by updating a coherent body image in the brain in neurological patients.

1.2.3.2 Mirror Visual Feedback

After the RHI, one of the most famous cross-modal illusions is the mirror visual feedback technique (Ramachandran & Rogers-Ramachandran 1996). Mirror Visual feedback is a simple non-invasive technique initially introduced for the treatment of two neurological disorders; chronic pain of central origin, and motor disorders, such as hemiparesis after stroke injury.

The equipment needed for the mirror visual feedback therapy consists of a ‘mirror box’ of a 2 x 2-foot mirror vertically placed in the sagittal plane in the middle of a rectangular box (***Figure 1.2.1***). The top and front sides of the box are removed. The patient is in front of the mirror and places their affected limb in one side of the mirror and the healthy limb in the opposite site of the mirror. Then he looks to the healthy limb through the mirror and this reflection seems visually superimposed on the felt location of the affected limb; whereby creating the illusion that the affected limb has been recovered. Hence, while looking at the mirror if the patient sends motor commands to both hands to perform symmetrical movements, the patient acquires the visual impression that his affected hand is responding his motor command.

Figure 1.2.1The mirror box (Figure retrieved from Ramachandran et al. 2009)

Principally, the mirror visual feedback technique was inspired by early findings on action-perception integration for the relief of phantom pain in amputees. This sensory integration is commonly called the reafference principle (Holst & Mittelstaedt 1971; Ramachandran & Hirstein 1998a). The reafference principle refers to the interaction of the central nervous system and the periphery, for example, when we want to flex the arm, the efferent signals from the central nervous system send a motor command to periphery nerves of the flexor muscles which produce an afferent signal, 'the flexion movement'. These afferent signals are called 'reafference'. On the other side, the generation of a motor command is also accompanied by a parallel efferent signal, called efferent copy, which contains the sensory feedback generated for the movement. This means that the visualization of one's own movement also generates an efferent visual movement perception. With efferent movement perception, the look movement signals are added as efferent copies to the stationary retinal signals. Normally, during the observation process afferent and efferent movement perception occurs simultaneously (Grüsser & Grüsser-Cornehls 1969). This sensorimotor integration informs to the sensory systems that the stimulation produced by the movement is self-generated rather than generated for the environment. This information is crucial to distinguish between self and no-self (Feinberg & Irwin 1978a). After a motor-sensory injury due to central causes; such as stroke injury, or to peripheral causes as in amputees, motor commands are not simultaneously followed by the expected reafferent feedback and as a consequence are modified in order to evoke the expected sensory afference (Feinberg & Irwin 1978b). It is a conflictive situation that interrupts the efference-afference loop leading to a 'learned paralysis' according to some investigations (Ramachandran & Hirstein 1998b) or to a 'maladaptive plasticity' (Rossini et al. 2003). The main goal of the mirror visual feedback is to restore the efference-afference loop that has been interrupted by superimposing the visual image of the unaffected limb on the affected one using mirror visual feedback (***Figure 1.2.2***).

1.2.3.2.1 Neural mechanisms of mirror visual feedback

1.2.3.2.1.1 Neuromodulatory effects of mirror visual feedback

During the mirror visual feedback training there is a *cognitive conflict* between the expected afferent feedback and the real feedback and a *perceptual conflict* between visual and kinaesthetic feedback. This conflict becomes more obvious when performing unimanual or

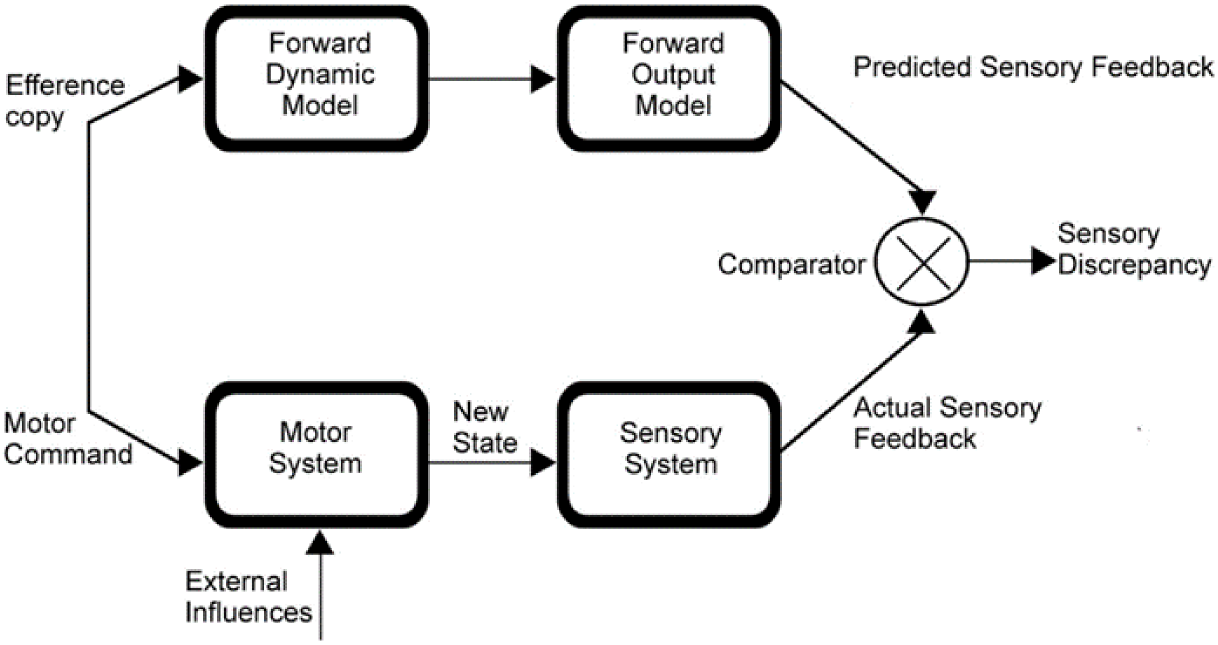


Figure 1.2.2 Efference–afference loop (Figure retrieved from Salomon et al. 2011)*. When we want to perform a movement, the motor command from the central nervous system produces an efferent copy while at the same time a forward model predicts the sensory consequences of the motion. When the movement is executed, the afferent sensory systems provide real-time information regarding the actual state of the system and this afferent information is compared with the predicted states of the forward model.*

asymmetric bimanual movements, and even during symmetric bimanual movements, the perfect interlimb symmetry is perceived as surreal. In the latter case, Michielsen et al. (2011) showed an increase of activity bilaterally within the bilateral superior parietal lobe (precuneus) and in the contralateral superior posterior cingulate cortex in stroke patients with paresis of the arm, during bimanual movements. Furthermore, other investigations have found increase in activity in the posterior cingulate cortex (G. R. Fink et al. 1999), and in the ipsilateral lateral sulcus (Wasaka & Kakigi 2012c; Wasaka & Kakigi 2012a) compared to a condition with full vision of the two real hands without superimposing the visual image of the unaffected limb on the affected one. However during unimanual movements, where there is a more extreme cognitive and perceptual conflict, an increase of activity within primary visual and somatosensory areas, as well as in the occipital and parietal cortex of the ipsilateral moving limb (Dohle et al. 2004; Fritzsch et al. 2014a; Wang, Fritzsch & Bernarding 2013; Wang, Fritzsch, Bernarding, et al. 2013; Matthys et al. 2009a). Other studies show increased activation in the right dorso-lateral prefrontal cortex (DLPFC) (G. Fink et al. 1999a), the contralateral secondary sensory cortex (SII) (Wasaka & Kakigi 2012d), the ipsilateral superior temporal gyrus (STG) (Matthys et al. 2009b), and the contralateral insular cortex (Wasaka & Kakigi 2012b).

Some studies also reported activity modulation of the primary motor cortex (M1), both ipsilateral and contralateral to the unaffected hand reflected into the mirror. Although most of the studies refer to an increase in ipsilateral M1 excitability (Touzalin-Chretien et al. 2010a; Praamstra et al. 2011a; Touzalin-Chretien & Dufour 2008a; Carson & Ruddy 2012a; Garry et al. 2005a; Kang et al. 2011a; Y. J. Kang et al. 2012; Fukumura et al. 2007a). However, it should be taken into account that some studies did not find changes in activity within the ipsilateral M1 provoked by mirror visual feedback (Mehnert & Brunetti 2013; Funase et al. 2007; Fritzsch et al. 2014b).

1.2.3.2.1.2 Neuroplastic effects after mirror visual feedback training

It has been shown that after a mirror visual feedback training period there is a gain in motor function of the affected hand (Hamzei et al. 2012a; Michielsen & Selles 2011a; Bae et al. 2012a; Laeppchen et al. 2012a; Nojima et al. 2012; Bhasin et al. 2012a). This motor gain seems to be related to an enhanced activation of the corticospinal pathway and the subsequent plastic change in the ipsilateral M1 that projects to the affected/untrained hand/arm. Furthermore, there is also evidence of the contralateral M1 to the 'affected' hand/arm. This fact means that after the mirror visual feedback training there is increased activation of the affected side and/or decreases activation of the unaffected side (Michielsen & Selles 2011a; Bae et al. 2012b; Bhasin et al. 2012b). This would imply a reestablishment of the inter-hemispheric balance that was disrupted by the injury. However, another study suggests that the improvement of the affected hand is related to the ipsilateral motor cortex, the contralateral M1 of the unaffected hand (Hamzei et al. 2012b).

In summary, three functional networks are involved in the perceptuo-motor process during the mirror visual feedback. First, higher activity in primary and secondary visual and somatosensory areas indicate an increment of the attentional resources necessary to deal with the perceptual incongruence (Wasaka & Kakigi 2012d; Wasaka & Kakigi 2012b). This increased activity is associated with the sensory feedback of control of the movements reflected in the mirror, commonly known as sense of agency over the reflected arm, as observed in the involvement of the insular cortex (Farrer & Frith 2002) and the DLPFC (Mima et al. 1998; G. Fink et al. 1999b). Furthermore, larger activation of the posterior aspect of the parietal and cingulate cortex supports greater attentional demands (Hagmann et al. 2008; Leech et al. 2012), and in the superior parietal cortex, especially in the precuneus associated with visuospatial information processing (Andersen 1995; Wenderoth et al. 2005).

Secondly, mirror visual feedback seems to increase activation of the STG (Matthys et al. 2009b), often linked to the visual identification of biological movement (Schultz et al. 2004a) and induces high engagement of the PMC (Hamzei et al. 2012b). The activation of the STG combined with the PMC, forms a network that promotes the imitation of biological movements and the acquisition of motor skills (Iacoboni et al. 2001; Buccino et al. 2006; Schultz et al. 2004b).

The third functional network involved in mirror visual feedback is the motor network. The activation of the M1ipsilateral to the unaffected hand (reflected hand) is projecting to the affected hand (hand behind the mirror). Finally, in accordance with various studies this is considered the final common pathway for the beneficial effects of the mirror visual feedback (Imai et al. 2008; Touzalin-Chretien et al. 2010b; Touzalin-Chretien & Dufour 2008b). Albeit, some investigations demonstrated that mirror visual feedback decreases the motor threshold and enhances corticospinal output of the ipsilesional M1 in stroke patients (Y. Kang et al. 2012; Praamstra et al. 2011b; Carson & Ruddy 2012b; Garry et al. 2005b; Kang et al. 2011b; Fukumura et al. 2007b). Probably, due to a reduction in interhemispheric inhibition to the contralateral to the ipsilateral hemisphere (Carson & Ruddy 2012b) and/or a reduction of intracortical inhibition (Laeppchen et al. 2012b). Finally, another promising therapeutic effect is the recruitment of the ipsilateral pathways that are correlated with the functional recovery of the affected limb.

1.2.3.2.2 Mirror visual feedback in clinical applications

1.2.3.1.2.1 Mirror visual feedback for pain relief

Mirror visual feedback was originally used to treat phantom limb pain in amputees (Ramachandran & Rogers-Ramachandran 1996). In this sense, Melzack (1992) proposed a central role of multisensory integration of body signals in the representation of the body image and the sensation of pain. Hence, through the visual input of movements of the missing limbs we can correct the incongruent sensory signals, reactivating the ‘latent’ cortical map of the missing limb and as a consequence, relief pain sensations (L. Moseley et al. 2008; Ramachandran & Altschuler 2009; Moseley & Flor 2012). Nevertheless, recently some studies reported contradictory results about pain relief through the mirror visual feedback techniques in amputees where participants experienced a telescopic distortion of the phantom limb (Foell et al. 2014; Hagenberg et al. 2014). In fact, the visualization movement of the phantom limb can even increase pain sensations in some amputees (Schmalzl et al. 2013). Later this technique was also used to treat chronic pain in complex regional pain syndrome (CRPS) patients (McCabe et al. 2003; G. Moseley 2004) and even in sensory re-education of severe hyperesthesia after hand injuries (Moseley & Flor 2012). The analgesic effects of the mirror visual feedback in different pain disorders is linked to the disruption of multisensory processing which influences body-related cortical representations, which can be normalized by the sensory-motor conflict balanced by the mirror visual feedback.

1.2.3.1.2.2 Mirror visual feedback for motor recovery

Mirror visual feedback is also widely used for the rehabilitation of hemiparesis in stroke patients (Michielsen & Selles 2011; Sathian et al. 2000; Yavuzer et al. 2008; Altschuler et al. 1999; Dohle et al. 2009; Thieme et al. 2013; Brunetti et al. 2015). In this line, neuro-imaging data highlights that the mirror visual feedback of the healthy limb movements superimposed on the paretic limb led to a notable motor recovery of the paretic limb (Michielsen et al. 2011b). Furthermore, the visualization of the self-generated movements in the mirror increased attentional demands for the integration of vision and proprioception, induced by the mirror, leading to a higher awareness of the affected limb (Michielsen & Selles 2011a; Michielsen et al. 2011b). The increased awareness of the affected limb by mirror visual feedback also showed beneficial effects in stroke patients with visual-neglect (Dohle et al. 2009b). In addition, some studies investigated the effects of self-observation in a mirror in patients with somatoparaphrenia, which is typically manifested as a defective sense of ownership of the left part of the body, reporting a decrease of somatoparaphrenia after the mirror visual feedback training. Finally, mirror visual feedback has been also used in distal radius fracture patients who cannot move their arm because of the cast immobilization. While some observed positive changes after the mirror visual feedback training, improving the passive range of motion of some movements (Altschuler & Hu 2008), others did not find differences with the conventional rehabilitation training (Bayon-Calatayud 2016).

1.2.4 Mental practice in neurorehabilitation

For many patients with neurological disorders or traumatic injures such as a bone fracture, execution of motor tasks is very difficult and even impossible in patients with a fracture during the immobilization period. Luckily, humans have the ability to generate mental correlates of perceptual motor tasks without any triggering external stimulus, this function is commonly known as imagery (Jackson et al. 2001). Motor imagery is considered as a cognitive process that can be used in mental practice techniques. To avoid the confusion between motor imagery and mental practice Leeuwen & Inglis (1998) describe motor imagery as the ability to imagine a movement and mental training as the act of repeating the imagined movements several times with the intention of learning a new ability or perfecting a known skill . Hence, motor imagery refers to a specific cognitive operation whereas mental practice will designate a training method that can use various cognitive processes, including motor imagery, action planning or action observation. Actually, the aforementioned body illusions techniques through visual feedback have been used as mental practice techniques, where the combination of different cognitive processes such as motor imagery and action observation have been investigated as a potentially effective neuro-rehabilitation technique (Magdalena Ietswaart et al. 2011; Braun et al. 2013; Malouin et al. 2013; Th Mulder 2007). In fact, there is a wealth of experimental evidence that supports that the combination of motor imagery (MI) with action observation (AO) through mirrors, videos or through virtual reality could be even more effective to treat motor, (Wright et al. 2014; Vogt et al. 2013; Nedelko et al. 2012; Mirelman et al. 2013; Kang et al. 2011b) and pain disorders (G. Moseley 2006; Boesch et al. 2016; MacIver et al. 2008).

Today, the possibility to access mental practice during absence of physical performance represents a new avenue for neuroscience and neural rehabilitation. Recently, in the field of motor cognition it was realized that motor actions involve a covert stage. This covert stage implies the future action planning, which includes the aim of the action, the means to reach the action and the following consequences with the body and the external world (Jeannerod 2001b). Hence, covert and overt stages represent a continuum, such that every physical action implies a covert stage, while a covert stage may not necessarily lead to into an overt action (Jeannerod 2001b). Mental practice uncovers different training methods such as observation and motor imagery. The neural mechanisms underlying action observation have been widely investigated (Hodges et al. 2007), as well as the neural mechanisms underlying motor imagery and their similarity to action execution (Grèzes & Decety 2001). Some investigations of MI highlight the importance of task instruction, which means the explanation of the task to be imagined, during the mental training (S H Johnson et al. 2002; Munzert & Zentgraf 2009). There are at least two different types of motor imagery, the kinaesthetic motor imagery from the first-person perspective and visual motor imagery from the third person perspective (Solodkin et al. 2004). In this regard, evidence demonstrates that kinaesthetic motor imagery has a higher activation in the M1, inferior parietal cortex and motor association cortex than visual motor imagery

(Stinear et al. 2006). On the other side, AO is suggested to advance motor memory formation (Stefan et al. 2005; Stefan et al. 2008). Nevertheless, it is not clear if AO alone is able to promote cortical changes correlated to motor learning (Celnik et al. 2006; Nedelko et al. 2010). The main feature of AO is that it stimulates and simulates the internal representation of motor patterns, by way of facilitating the retrieval of motor engrams, that can be used in MI to improve specific motor patterns (Celnik et al. 2008; Lotze & Halsband 2006). Actually, some studies suggest that there are stronger activations of the motor system during AO in combination with imagery than during AO alone, (Nedelko & Hassa 2012; Vogt et al. 2013; Filimon et al. 2007; Villiger et al. 2013; Berends et al. 2013; Wright et al. 2016; Eaves et al. 2016; Taube et al. 2015a). Furthermore, some investigations also proposed that there exists a common neural network underlying AO and MI processes (Caspers et al. 2010). However, others argue that the neural representations involved in observed and imagined actions are dissociable and hierarchically organized in which each technique relies on partially independent mechanisms (Macuga & Frey 2012). This means that those brain regions involved in AO trainings are mostly a subset of those involved in AO+MI trainings, which consecutively are a subset of those involved in AO with synchronized execution.

1.2.4.1 Neural networks involved in action observation and motor imagery

As commented above (see *Virtual reality in motor impairment, section 1.1.6.2*), common neural mechanisms have been described in AO, MI and action execution (Jeannerod 1994; Prinz 1997). Nevertheless, recent brain analyses showed only partial support for the hypothesis that AO and MI recruit the same neural representations involved in execution of the same action. A broad spectrum of cortical regions involved in sensorimotor control such as; premotor, pre-SMA, posterior parietal, superior temporal and primary sensorimotor areas, as well as subcortical regions such as thalamus and putamen, showed increased activation during all three techniques (AO, MI and action execution). However, evidence suggests that these common neural activations may be due to common visual stimulation, performance of the orienting task, and other common cognitive demands (e.g., attentional, higher-level action processing) shared in all three techniques.

In this regard, Macuga & Frey (2012) revealed important differences between AO, MI and action execution. On one side, synchronous action execution after action observation showed greater activation than MI and AO in bilateral sensorimotor cortex, cerebellum, supplementary motor area (SMA), parietal operculum (putative secondary somatosensory cortex), and in several motor-related subcortical areas. These first differences indicate a descending processing of the efferent signals and afferent feedback. Regarding MI, they observed higher activation in pre-SMA, cingulate, anterior insula, and left inferior frontal cortex, compared to AO. Hence MI provides more effective signals to engage neural activity in these areas of the sensorimotor network. In contrast, recently Taube et al. (2015) reported that AO, MI and AO+MI each have a unique neural designation, showing greater neural activity for AO+MI in the caudal supplementary motor area (SMA), basal ganglia, and cerebellum compared to AO; and bilateral cerebellum, and precuneous compared to MI. They also observed increased activity in areas such as the SMA and left precentral gyrus during MI compared to AO, whereas combined AO+MI further increased activity in those regions involved in both MI and AO independently. Others reported increased neural activity in parts of the cerebellum, inferior frontal gyrus, inferior parietal cortex, SMA (Nedelko & Hassa 2012), ventral premotor cortex and left insula (Villiger et al. 2013).

Finally, some investigations using single-pulse transcranial magnetic stimulation (TMS) over the motor cortex to study the effects of AO and MI have produced two relevant findings. First, during both AO and MI of hand gestures the corticospinal excitability measured through the amplitudes of motor evoked potentials is higher than control conditions (Williams et al. 2012; Grosprêtre et al. 2016; Naish et al. 2014). Secondly, AO+MI originate greater corticospinal excitability than AO alone (Wright et al. 2014; Wright et al. 2016), and MI as well (Mouthon et al. 2015).

To summarize, there is clear evidence for enriched and more extensive activity in the motor execution network during AO+MI, as compared to AO or MI independently. Hence, we can suggest AO+MI as the most effective mental training technique for motor learning, compared to either MI or AO alone.

One way of integrating motor imagery, action planning and action observation is by using IVR, through which one can induce the illusion of owning a virtual body—or a virtual arm—when it is co-located with the real body—or real arm (Nierula et al. 2017).

1.3 Virtual Reality for Rehabilitation

1.3.1 Fundamentals

A large number of clinical studies have investigated the effects of mental practice to improve functional recovery of patients with different disabilities (Malouin et al. 2013). More specifically, mental practice has been used as a rehabilitation training in motor impairments of the upper limbs such as, in distal radius fracture patients (Schott & Korbus 2014; Bayon-Calatayud 2016) or stroke patients with paresis of the upper limb (M. Ietswaart et al. 2011; Wright et al. 2016; Ballester et al. 2015), and in chronic pain disorders such as complex regional pain syndrome (CRPS) (G. L. Moseley 2006; Reinersmann et al. 2013; Ramachandran et al. 2009).

Based on the previous investigations mentioned above, we used these three pathologies in our thesis work to investigate the therapeutic potential of IVR as a neurorehabilitation tool in motor and chronic pain disorders of the upper limbs. In the following section we will introduce specific literature about the usual rehabilitation trainings implemented in these pathologies.

1.3.2 Distal Radius Fracture

Distal radius fractures are one of the most common fractures of the upper limbs (Nellans et al. 2012; McKay et al. 2001; Fernandez 2002),with a ratio of about 3:1 in females compared to males (Bentohami et al. 2014).After a distal radius fracture, patients are treated surgically or by casting. Regardless of the treatment, patients are immobilized for at least two to six weeks or even more in some cases (Freeland & Luber 2005).At the neural level, studies have found that plastic changes usually occur after a short period of immobilization, especially in the contralateral hemisphere (Huber et al. 2006), turning on motor changes as a consequence of sensorimotor reorganization (Facchini et al. 2002).

The rehabilitation process after a distal radius fracture is quite complicated and most of the patients continue with deficits for six months post-fracture. Moreover, during the period of immobilization, patients often keep their fractured hand in rigid postures, which leads to joint stiffness, nerve injury, tendon and ligament injuries, a massive reduction in range of motion (ROM), muscular atrophy, and loss of movement representation (Diaz-Garcia et al. 2011),resulting in the inefficiency of the central control of movements (de Jong et al. 2003).

The optimal time for initiation of the rehabilitation process after a distal radius fracture is during the immobilization period (Weinstock 1999). Additionally, previous investigations have found that 20% of patients with distal radius fracture had persistent symptoms, and 10% of those patients continued to have functional impairments after the conventional treatment period during the immobilization period. The conventional treatment during the immobilization period used to be the early digit mobilization of the affected hand (Kuo et al. 2013).

Rehabilitation is viewed as a learning process where old skills have to be re-acquired and new ones have to be learned on the basis of practice. Nowadays, it is known that motor recovery and motor learning have many aspects in common, such as both are largely based on response-produced sensory information (Th. Mulder 2007). Therefore, today there is an increasing interest in the integration of mental practice techniques, which involve forcing the patient to mentally rehearse motor tasks (for example, walking, writing) when physical practice is not possible, to promote motor learning in rehabilitation programs (Malouin et al. 2013).In addition, in the field of motor rehabilitation, both motor imagery and action observation have been proposed as adjunct treatments to conventional physiotherapy with the aim of maximizing the benefits of non-physical forms of practice (Garrison et al. 2010b; Th Mulder 2007).This approach could be very helpful for people that cannot move some part of their body, such as an arm in people who suffered a stroke or people with a cast due to a fracture.

The integration of technology at this frontier is of interest from a medical perspective (M. Levin et al. 2015)with evidence justifying the use of IVR in clinical applications (Adamovich et al. 2009; Llobera & González-Franco 2013; M Martini et al. 2013; Perez-Marcos et al. 2012)to speed up the rehabilitation process after cast removal.

1.3.3 Chronic Stroke

Stroke has grown into one of the principal causes of mortality among adult populations in developed countries (Bonneux et al. 2010; Banegas et al. 2003). Luckily, the one-year mortality rate after stroke has been declining due to better care after acute stroke thereby increasing the number of stroke survivors (Mimino 2011). As the number of stroke survivors increases, it is important to rigorously assess and design interventions to improve functional outcome and quality of life after stroke (Towfighi & Saver 2011). In fact, one of the most frequent sequelae after stroke is hemiplegia or hemiparesis. Patients with hemiplegia or hemiparesis present constrained mobility on one side of the body involving the paresis of upper and lower extremities (Carod-Artal & Egido 2009). Normally, upper extremity deficits persist at 55-75% in chronic stroke patients while they tend to recover faster lower extremity deficits and walking ability (Levin & Knaut 2009). Furthermore, deficits in the upper extremities can negatively affect the stroke survivor's quality of life (Martin & Rabin 2011).

After one year of the injury, stroke patients are in a chronic phase and their recovery is often considered to be in a *'plateau state'*. In chronic stroke patients, a *'plateau state'* is considered where recovery reflects diminished capacity for additional motor improvement within a focused time frame. After this time frame, chronic stroke patients are usually discharged from motor therapy because of the diminished capacity for additional motor improvement, depending on outpatient care, such as community-level rehabilitation (Taub et al. 2002; Page et al. 2004; Holden 2005). However, some studies demonstrate that cortical reorganization and functional changes that appear to precede motor improvement can occur in chronic stroke patients who have apparently reached this plateau state, suggesting that chronic stroke patients can further improve their motor dexterity through motor therapy (Smith et al. 1999; Luft et al. 2004; Page 2000; Dozza et al. 2005; Page et al. 2008; Harris-Love et al. 2011; Classen et al. 1998).

Over the past few years, various strategies and treatment approaches to improve motor function and quality of life of stroke patients have been developed (Langhorne et al. 2011; Ifejika-Jones & Barrett 2011). Today, there is an increasing interest in mental training techniques in the field of neurorehabilitation, whereby patients mentally rehearse motor tasks when they are not able to perform them because of a physical or neurological impairment (Malouin et al. 2013). This recent approach has led to the design of new treatment techniques such as action observation, motor imagery (Wright et al. 2014; Vogt et al. 2013), mirror visual feedback (Deconinck et al. 2015; Ramachandran & Altschuler 2009) and virtual reality (Mirelman et al. 2016; Bohil et al. 2011; Perez-Marcos et al. 2012). Using virtual reality is a relatively recent approach in stroke rehabilitation, that endows simulated practice of functional tasks to a greater extent than traditional therapies (see review in Laver et al. 2015).

1.3.4 Complex regional pain syndrome type I

Complex regional pain syndrome (CRPS) is a complicated syndrome that has been investigated for a long time. CRPS can arise secondarily to trauma or spontaneously without any injury or inflammation. Several factors are considered to contribute to the pathophysiology of CRPS, including neurogenic inflammation (Parkitny et al. 2013), sympathetic nervous system activity (Drummond 2010), and maladaptive plasticity (Pietro et al. 2013). There are two types of CRPS: type one, which do not present nerve injury and CRPS type two, where patients present nerve injury. Due to this pathophysiological difference, it is not rare to think that we need different therapeutic intervention lines to treat chronic pain which comes from no nerve origin than chronic pain from nerve injury. In fact, some differences between CRPS type I and II have been investigated, showing a distorted mental representation of the affected limb in patients with CRPS type I (Lewis et al. 2010; Frettlöh et al. 2006; J. S. Lewis et al. 2007; H Ramakonar et al. 2011).

In line with the pathophysiological differences in neuropathic pain patients, it has been shown that, although all neuropathic pain disorders have a common triggering event, that is, the injury of the somatosensory nervous system, the patterns of sensory signs and symptoms after the neuropathic injury are different between the different aetiologies and sometimes between patients with neuropathies of the same aetiology. Hence, the individual somatosensory profile allows to group patients depending of their pathophysiological dysfunctions of afferent processing (Baron et al. 2010; Maier et al. 2010). In this regard, one study recently showed that phantom limb in five amputee patients was reduced after 4 weeks of mirror therapy training, nevertheless eight patients reported telescopic distortion of the phantom limb displayed a gradual increase in the pain sensations (Foell et al.,2014). Likewise, it has been shown that viewing one’s painful limb as becoming smaller decreases pain in chronic pain patients (Moseley et al., 2008). In healthy subjects the opposite effect was found, probably due to the different pathophysiological characteristics between acute and chronic pain (Romano et al. 2015; Mancini et al. 2011).

For pain relief intervention, IVR technology represents an effective tool using multisensory feedback with healthy subjects (Llobera, 2013; M Martini et al., 2014; Matteo Martini et al., 2013) and with chronic pain patients (Llobera & González-Franco, 2013; Senkowski & Heinz, 2016). As a matter of fact, pain experience is closely related to multisensory integration. Nowadays, there is a lot of evidence showing how pain perception can be modulated through manipulating multisensory signals (Longo et al. 2009; Wand et al. 2012). However, there are some conflicting results about how body illusion through visual feedback can reduce pain in clinical population. Subjects with chronic pain, pain which persists more than three months, often show a distorted body image and altered body perception of the painful part of the body (Boesch et al. 2016). It has been shown that patients with chronic pain can respond in a different manner to the visual feedback of body illusions depending on the complexity of their pain origin.

Overall, in this thesis we hypothesize that IVR has great potential to carry out motor-cognitive trainings and to modulate pain perception for patients with reduced or lack of mobility in the extremities or in patients with chronic pain. Referring to the background provided in this section, we will next describe the objectives of this thesis.

1.4 Objectives

The objectives of this thesis work are:

1.4.1 General Objectives

1. To carry out a quantitative exploration of the effectiveness of immersive virtual reality in orthopaedic and neurological rehabilitation.

2. To explore the usefulness of immersive virtual reality for the treatment of neuropathic chronic pain.

1.4.2 Specific Objectives

1. To design, implement and test a whole set of exercises in an immersive virtual reality setup devoted to the rehabilitation of the arm, based on the principles of body ownership over virtual bodies, addressed towards motor rehabilitation and chronic pain therapy.

2. To measure the experience of agency of the virtual arm induced by the co-location of the virtual bodies with the real ones, and by allowing the participants to control the initiation of the movements of the virtual arm.

3. To quantify the neural activity in selected brain networks that may support motor re-learning via motor imagery/action planning and action observation through immersive virtual reality before and after immersive rehabilitation.

4. To investigate whether the level of pain in neuropathic chronic pain patients can be ameliorated by means of manipulating the body image representation and varying the

visual representation corresponding to the affected arm through immersive virtual reality.

5. To test clinically the impact of training in the generated virtual environment in patients with motor deficits and with neuropathic chronic pain of the arm.

Chapter 2

The scene is not just wider than the sky, it can contain many disparate elements – sensations, perceptions, images, memories, thoughts, emotions, aches, pains, vague feelings, and so on. Looked at from the inside, consciousness seems continually to change, yet at each moment it is all of a piece. The remembered present.

Gerald M. Edelman.

Materials and methods

In this thesis work we conducted three different studies; first, in the ***'IVR in orthopaedic rehabilitation study'*** we investigated the benefits of a self-developed IVR training program based on mental training for upper limb rehabilitation. This study aimed to improve the motor functional ability of the arm during the immobilization period, and accelerate the rehabilitation process in patients with distal radius fracture. Second, in the '***IVR in chronic stroke rehabilitation study'***, we investigated the effects of the same motor-cognitive program in three chronic stroke patients with the aim to improve their motor and cognitive capabilities. Finally, in the third study, ***'IVR in chronic pain study'***, we investigated the effects of visual feedback through IVR—by manipulating the morphological characteristics of the virtual arm—on pain perception in chronic pain patients with CRPS type I. In this chapter we present the materials and methods used in each study. All three studies share a common methodological part—embodiment in IVR—that will be explained in section 2.1 *Overall methodology*. More details for each study will be explained within this section. All three studies were approved by the Ethics Committee of the Hospital Clinic of Barcelona, Spain.

2.1 Overall methodology

2.1.1 Embodiment in IVR

In order to induce body ownership, embodiment in all studies was achieved through a recently described framework (see Spanlang et al. 2014 for a methods review) in which the elements to achieve multisensory and sensoriomotor integration that can provide the illusory ownership over the virtual body to enable the immersion in VR are basic modules, such as the virtual reality scene, visual displays, a real-time motion capture system, and a simple haptic system. In this section we present the modules and technologies that were specifically used in our studies.

2.1.1.1 The virtual scene

A virtual scene consists of various 3D objects with specific properties (geometry, material, light reflection, etc.) that make the scene functional and realistic (e.g. they follow the rules of physics). This set of objects includes a virtual human body. In our studies, we used a gender-matched realistic-looking virtual body approximately similar in size to our patients' real bodies. The same size virtual body was used for all participants. The virtual scene in all experimental studies also included a virtual table with a virtual chair that were placed inside a virtual room. Participants saw their virtual body from a first-person perspective (1PP) through a Head-Mounted display (HMD) seated in front of the table with the virtual arms resting on the table in the same position as their real arms (see ***Figure 2.1.1***). For the *IVR in orthopaedic rehabilitation study* and *IVR in chronic stroke study* two additional scenes were created, that depicting a virtual countryside or a virtual beach. Each week of the rehabilitation patients could choose if they preferred to be immersed in the virtual room, the virtual countryside or the virtual beach scene (***Figure 2.1.2*** A,B,C). In the case of *IVR in chronic pain study*, patients were only presented with the virtual room scene, which also included an interactive virtual blackboard, where a Numeric Pain Rating scale appeared after each experimental condition (see section 2.5). The virtual male and female bodies were taken from the Rocketbox library (Rocketbox Studios GmbH, Hannover). Lights and sound were also provided in all three virtual scenes in order to be more realistic.

Figure 2.1.1 Virtual body position. *In all three studies the virtual body of the patients sat in front of the table with the virtual arms resting on the same position as the real body and arms.*

The virtual scenes were created, managed, and rendered using the Unity3Dplatform(http://unity3d.com/). All interactions and dynamic changes in the environment were also handled in this platform.

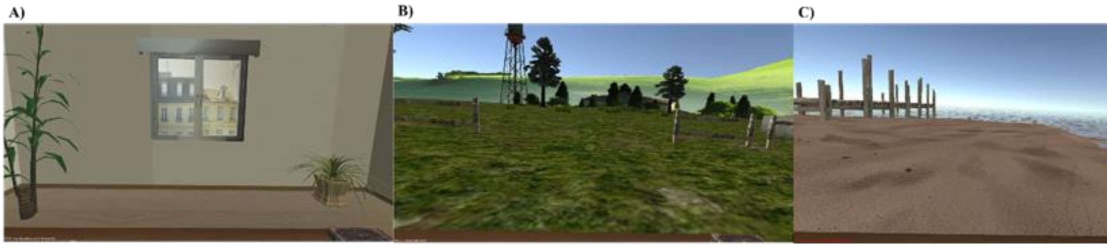


Figure 2.1.2 Virtual reality scenes. *In the IVR in orthopaedic rehabilitation and IVR in chronic stroke rehabilitation studies patients could choose one of these three virtual scenarios to carry out the training.* ***A)*** *Virtual room scene.* ***B)*** *Virtual country side scene.* ***C)*** *Virtual beach scene.*

2.1.1.2 Head-mounted display

In all three studies we used an Oculus Rift Development Kit 2 (Menlo Park, CA, USA) HMD with a resolution of 960 × 1080 pixels per eye and a nominal field of view of 100° (degrees), displayed at 75 Hz (***Figure 2.1.3*** A). For the *IVR in orthopaedic rehabilitation study* there was a control group, the Non-IVR training group, which visualized the same rehabilitation program used in the IVR training through a laptop screen without using the HMD, i.e. in a non-immersive way (further details about this control group are given in section 2.2.1) (Figure ***Figure* 2.1.3**B).

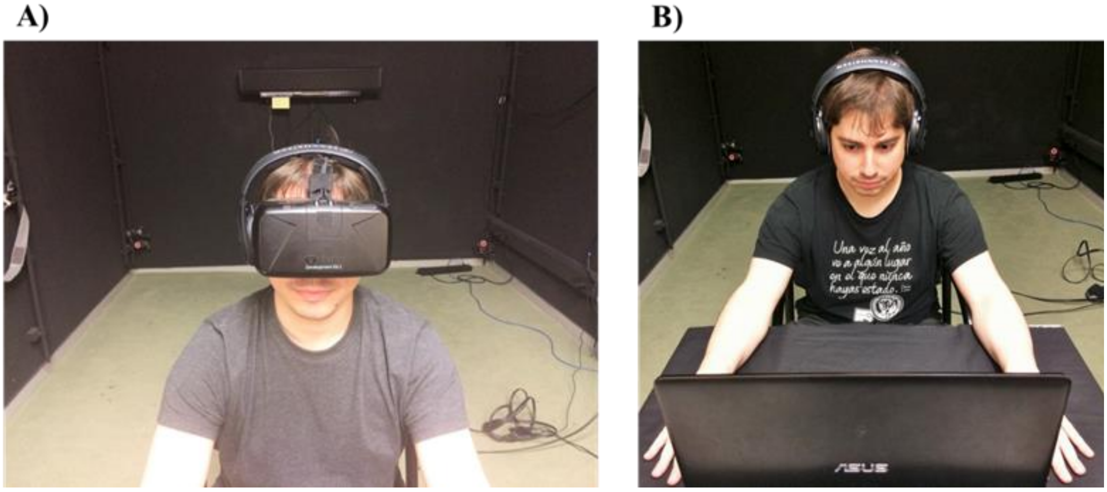


Figure 2.1.3Head-mounted display (HMD) and laptop screen set-ups. A) The HMD. *The HMD provides an immersive virtual reality experience.* ***B) Laptop screen.*** *The rehabilitation program was shown on a laptop screen that provided a non-immersive experience.*

2.1.1.3 First person perspective experience of the virtual body

It has been shown that first person perspective (1PP) view of the virtual body is essential for inducing body ownership in IVR (Slater et al. 2010). A 1PP point of view is provided though the HMD. Furthermore, head-tracking is essential in order to provide visual sensorimotor correlations. When patients move their head around they need to have an updated image of the virtual scene, and when they look down they need to see their virtual body (see ***Figure 2.1.4***).

Figure 2.1.4 First person perspective. *The person wearing the HMD looks down and sees a virtual body that substitutes their own real body. (Picture retrieved from Mel Slater et al. (2010))*

2.1.1.1 Visuo-tactile stimuli

Body ownership was induced through visuotactile stimulation between participants' bodies and their virtual counterparts following examples from earlier experimental setups (Tsakiris & Haggard 2005; Banakou et al. 2013; Slater et al. 2009; Nierula et al. 2017). Specifically, physical touch in all three studies was delivered via two vibrators that were attached to the dorsal distal phalanges of the affected index and middle fingers. The location of the vibrators was adjusted in order to match the contact points of the virtual object's (e.g. the ball) trajectory with the virtual body counterparts. Additionally, in the IVR training group of the *IVR in orthopaedic rehabilitation study* and in the *IVR in chronic stroke study* a third vibrator was attached to the palm of the hand of the patients, so patients felt a vibration on their palm, similar to the tactile feedback felt when they interacted with the objects during the arm movements. The vibrators were controlled by the same Unity program that controlled the visual input through an Arduino controller. Vibrations had a duration of 1 sec. In contrast, in the Non-IVR training group for the IVR in orthopaedic rehabilitation study there was no visuo-tactile stimulation.

2.1.1.2 Audio

In all three studies headphones were used in order to allow the patients to listen to the explanation of the task during the VR sessions. For the Non-IVR training group in the *IVR in orthopaedic rehabilitation study*, noise-cancelling headphones were used to isolate the patients from the environmental sounds, by playing pink noise (***Figure 2.1.5***).

As patients in the conventional digit mobilization (CDM) training group followed the doctor's directions, which consisted in opening and closing their hand 20 to 30 times per day and mobilizing their fingers at home, they did not use headphones.

Figure 2.1.5 The headphones. *In all three studies patients were guided throughout the session by the voice instructions heard through the headphones.*

2.1.1.3 Virtual arm movement activation

In the *IVR in orthopaedic rehabilitation* and *IVR in chronic stroke rehabilitation studies* the movement of the virtual arm was triggered by the patient; this allowed patients to choose when they were ready to perform the exercise, inducing a sense of agency—the feeling of being causally involved in an action—over the virtual arm movements.

2.2 Experimental protocols

2.2.1 IVR for orthopaedic rehabilitation

2.2.1.1 Participants

We recruited patients with distal radius fracture aged 18-80 years. Diagnosis of the distal radius fracture was confirmed by X-rays and patients were derived from the traumatology department of the hospital. Patients were excluded: if they had cognitive impairment detected by the Mini-Mental State Examination test (MMSE < 24/30) or Frontal Assessment Battery test (FAB <12/18) to ensure that they could understand the task instructions during the training period; if they had a history of seizures or epilepsy (except for febrile seizures of childhood); or if they had another condition to put the patient at risk (e.g., visual impairments or infection). Written informed consent was obtained from all patients.

2.2.1.2 Study design

We designed a motor-cognitive training program combining motor imagery/action planning with action observation in a first-person perspective through immersive virtual reality (see section 2.3 for further information about contents of the rehabilitation program). The intensity and duration of the interventions were the same in the three groups, consisting in a 4- to 6-week training period (depending on the evolution of the fracture of each patient, although there were no group differences), three days per week for 20 min. In the IVR and Non-IVR training groups, a physiotherapist administered the interventions for each patient in a one-to-one session. Patients were assessed at baseline (T0) for screening reasons, after the intervention period (T1), which was immediately after cast removal, and 6 weeks after cast removal (T2) as a follow-up (see section 2.5, outcome measures). Between T1 and T2 the patients followed the usual protocol after plaster removal, doing conventional rehabilitation therapy (***Figure 2.2.1***). After each session, the IVR training group and the Non-IVR training group filled out a six-item virtual reality (VR) experience questionnaire in Spanish (**see Appendix A).**

Patients were randomly assigned (1:1) by the researcher (physiotherapist) within the first week of the distal radius fracture onset to one of three different groups that did different training programs during the immobilization period: the experimental group (n=20), where patients did an Immersive Virtual Reality (IVR) training consisting in motor planning and action observation in an immersive virtual environment; a control group (n=20), where patients did the conventional digit mobilization (CDM) training at home; and another control group (n=14) that did a Non-Immersive Virtual Reality (Non-IVR) training consisting in action observation on a computer screen. Patients in the IVR and Non-IVR groups visualized the same exercise program but in an immersive or in a non-immersive way, respectively. The researcher (physiotherapist) and patients participating in this study were not masked to the intervention group, although patients were not aware of the existence of the other groups. All assessments were done by the physiotherapist.

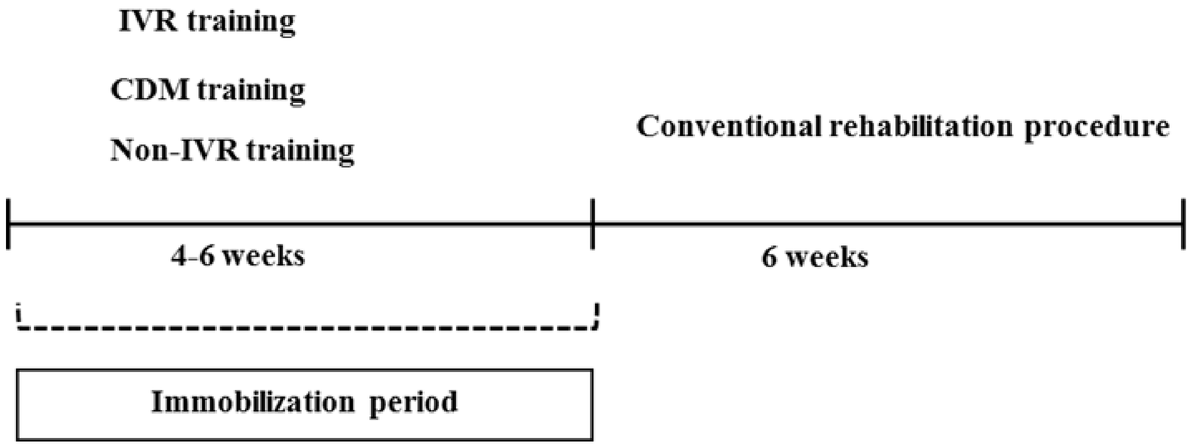


Figure 2.2.1 Study design of IVR in orthopaedic rehabilitation study. *In this study there were three diferent groups. One experimental group, in whichpatients did the training immersed in a virtual reality environment and embodied in a virtual body through an HMD during the immobilization period. Control group one, conventionaldigit mobilization CDM training group, in whichpatients followed the doctor’s directions, which consisted in opening and closing their hand 20 to 30 times per day and mobilizing their fingers at home during the immobilization period.And control group two, in whichpatients did the training from a non-immersive virtual reality environment during the immobilization period. In this study there were two assessment times, one after cast removal (T1) and the second one six weeks later (T2).*

2.2.2 IVR for chronic stroke rehabilitation

2.2.2.1 Participants

Three patients over 40 years old with chronic stroke injury and with poor mobility of the affected arm were recruited for this study. We considered as exclusion criteria the presence of moderate cognitive decline defined by a score of < 24 (out of 30) in the Mini Mental State

Examination (Folstein, 1983); epilepsy and visual impairments.All participants signed a consent form.

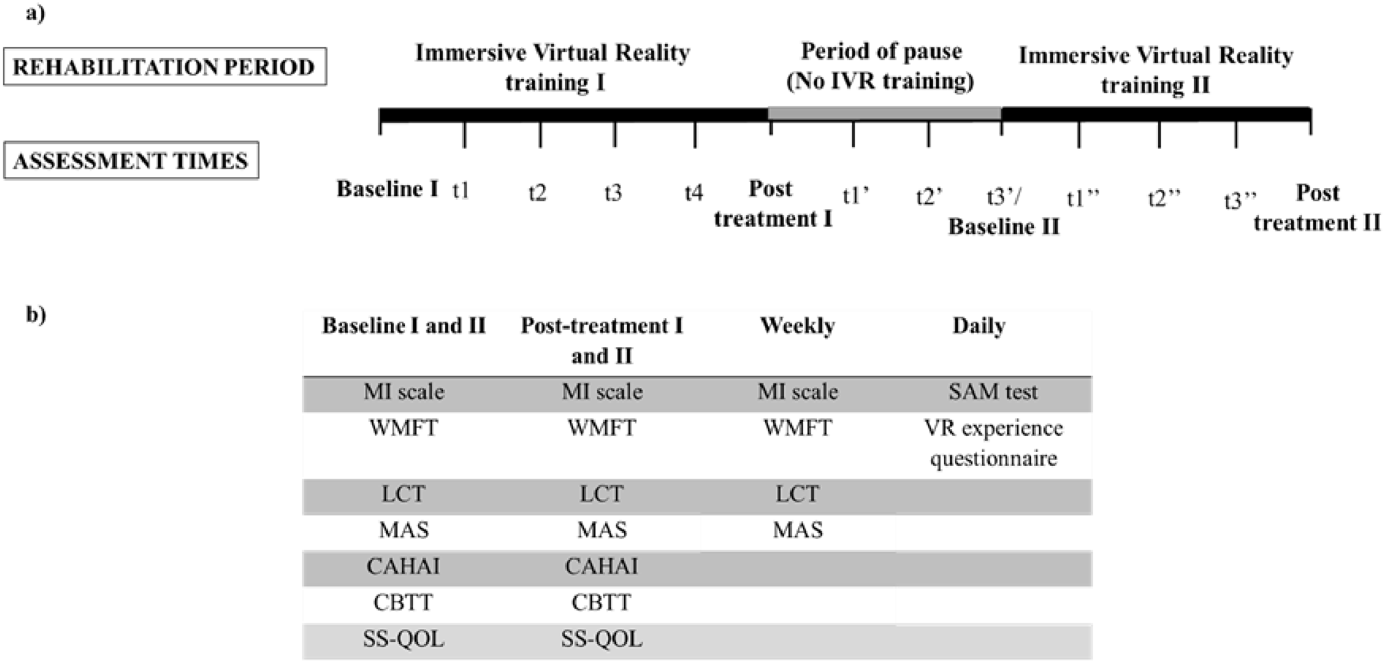
2.2.2.2 Study design

In order to see whether our IVR training improves the motor dexterity of the paretic arm, the cognitve capability and the quality of life of three chronic stroke patients, patients completed a motor-cognitive rehabilitation program based on kinesthetic motor imagery/action planning + action observation by providing the patients with visual feedback of virtual arm movements seen from a first-person perspective in an immersive virtual environment. We used the same IVR training that we used in the IVR in orthopaedic rehabilitation study *(see section 2.3 for further details of the rehabilitation program).*

The experiment was carried out over a period of three months comprising two IVR training periods and three weeks of rest in between, which was the follow-up (or period of pause) period after the first IVR training session (***Figure 2.2.2***). The first training period lasted five weeks while the second training period lasted four weeks. The training sessions were conducted from Monday to Friday at the Hospital de la Esperanza (Barcelona, Spain). Each IVR training session lasted 15-20 min.

Before and after both IVR training periods, we evaluated motor ability (motor dexterity, spasticity, functional ability, and muscular strength of the paretic arm), cognitive capability (working memory capacity measure, attention/concentration and visual-spatial dysfunctions) and quality of life of patients (performance of daily live activites and quality of life questionnaire) (***Figure 2.2.2***b; see section 2.5, to further details about the outcome measures). During the training periods, we did motor dexterity and cognitive assessments every week in order to assess possible improvements throughout the intervention periods. During the period of pause, there were three follow-up assessment times examining motor dexterity and cognitive capability to see if the changes observed after the first training remained over time. After each session during the training periods, the patients filled out a six-item Virtual Reality (VR) questionnaire in Spanish, and the Self-Assessment Manikin (SAM) test (Bradley & Lang, 1994) (see section 2.5).

In order to observe if our IVR training could induce neuroplastic changes in selected brain networks that may support motor re-learning via motor imagery/action planning and action observation examination, patients were subjected to two MRI scanning sessions. The first was at baseline I and the second at posttreatment I. Posttreatment I neuroimage data examinations were carried out within a range of 2 or 3 days after the last training I session. During the MRI scan sessions we used both diffusion tensor imaging (DTI) technique to observe structural brain changes and resting state technique to observe changes in functional conectivity (see section 2.5 to specific information in DTI and resting state techniques).



Baseline I and II	Post-treatment I and II	Weekly	Daily
MI scale	MI scale	MI scale	SAM test
WMFT	WMFT	WMFT	VR experience questionnaire
LCT	LCT	LCT	
MAS	MAS	MAS	
CAHAI	CAHAI		
CBTT	CBTT		
SS-QOL	SS-QOL		

Figure 2.2.2 Study design of IVR in chronic stroke rehabilitation study and summary of the assessment measures used at each time. a) *Study design. Each vertical line represents different assessment times during the IVR training and during the period of pause.* ***b)*** *Summary of the assessment measures.* ***Baseline time*** *was the time before to start IVR training period I and II.* ***Post-treatment time*** *was the time after the end of the training period.* ***Weekly*** *was his weekly assessment during training and during the period of pause.* ***Daily*** *was the time after the end of each session. MI: Motricity Index scale. WMFT: Wolf Motor Functional test. LCT: Letter Cancellation test. MAS: Modified Asworth scale. CAHAI: Chedocke Arm and Hand Inventory. CBTT: Corsi blocks-tapping test. SS-QOL: Stroke specific quality of life.*

2.2.3 IVR for chronic pain

2.2.3.1 Participants

Nineteen patients with neuropathic chronic pain on the upper limb between 40 and 55 years old were enrolled in this study. Patients were recruited and grouped in those with peripheral nerve injury (10 patients with PNI) and those without nerve injury (9 patients with CRPS type I). In order to ensure that all the patients had neuropathic chronic pain we used the painDETECT scale (Freynhagen et al., 2006). PainDETECT questionnaire is a screening questionnaire which allows the experimenter to distinguish pain severity and pain characteristics in patients with chronic pain. Score higher than eighteen indicates neuropathic pain. The following conditions were considered as exclusion criteria: the presence of a moderate cognitive decline defined as a Mini Mental State Examination (Folstein, 1983) score of less than 24 point (out of 30) and as a Frontal Assessment Batery (FAB) (Dubois et al., 2000) score of less than 12 (out of 18). The assessment of the cognitive state is important to receive feedback from the patient and for the correct understanding of the different tasks carried out during the session. Furthermore, patients with epilepsy and visual impairments were also excluded. All participants signed a consent form and received a monetary compensation for their participation (5 €).

2.2.3.2 Study design

In this study we investigated the effects of different visual feedback conditions on pain perception, which we assessed with two different virtual pain tests in which we manipulated the morphological characteristics of the virtual arm while participants were embodied in a virtual body.

Each patient received one session of 45 minutes. Each session counted with four parts, part one: baseline, part two: first virtual pain test, part three: period of pause and part four: second virtual pain test. In part one, before to start the visual test exposure patients underwent baseline assessment by PainDETECT, Mini Mental State Examination, Frontal Assessment Battery measures and the level of pain at baseline, in order to see if they could be included in our study. Patients also reported their mental representation of the affected limb before starting the experiment (**see Appendix C**). After the baseline assessment we started with the second part of the experiment and patients were submitted to the first virtual pain test. Once the first virtual pain test was done, there was ten minutes of rest when patients had to fill in a questionnaire related to the virtual reality experience and the body ownership levels, this was in the third part of the session. After the ten minutes of rest, the fourth part of the session started and patients were submitted to the second virtual pain test. The two virtual pain tests were presented in a counterbalance manner among the patients in order to avoid treatment effects.

During the experiment we studied two different virtual tests. The first test was the virtual arm transparency test, in which patients were exposed to four different conditions with the virtual arm transparency set at 0% (max opacity level), 25% (high opacity level), 50% (mid opacity level) or 75% (low opacity level). The virtual arm transparency test lasted 15 minutes. The second test was the virtual arm size distortion test where patients were exposed to three different conditions with the virtual arm size was presented in a big size (X2), normal size and small size (/2). The virtual arm size test distortion lasted 10 minutes.

With the intention to see if the different visual conditions of the virtual arm modulated pain perception, we used the pain intensity numerical rating scale (PI-NRS). Hence, in both virtual pain tests, after each visual condition exposure patients had to verbally report a number on a scale from 1 to 10 (“1”= no pain, “10” worst pain possible).

2.3 Contents of the rehabilitation program

The rehabilitation program that we designed consisted of five different exercise modules for the upper limb, which we describe below. It is a motor-cognitive training aimed to train movements of the joints in the upper limbs, but also fine skilled movements of the hand. Throughout the program, we increased the difficulty of the exercises in order to motivate and engage patients in the IVR training. This is comparable to traditional rehabilitation programs where the therapist increases progressively the difficulty of the training. Considering this, in both the ***IVR in orthopaedic rehabilitation and chronic stroke studies***, the IVR training started with the first module and changed to a new module every week in order to progressively increase the difficulty of the training.

The **first exercise module** consisted of five specific forearm and wrist joint movements. To ensure that participants learnt the movements, each movement was repeated ten times. The following movements were in the first exercise module:

- Wrist flexion – extension
- Wrist rotation
- Hand opening and closing
- Elbow flexion – extension
- Forearm pronation – supination

The **second module** required more cognitive effort as patients had to pay attention and touch different coloured virtual balls placed on the virtual table with their virtual hand. In this module the coloured virtual balls guided the direction of the virtual arm movements. In this second module, each exercise was repeated three times. The movements trained were the following:

- Cross arm movements, this means from up to down and from right to left

- Circles in clockwise and counter-clockwise arm movements

- Diagonals arm movements

In **module three**, the patient also had to touch the coloured virtual balls, but in that case, they appeared floating in front the virtual body. Each exercise was repeated three times. In this module the patient trained arm movements at 90º to 120º shoulder flexion in two different directions, with the coloured virtual balls guiding the direction of the arm movement. To clarify the direction of the arm movements, the following figures depicts the exercises of this module:

- From up to down arm movements

- From up to down in diagonals arm movements

Module four aimed to train fine motor skills of the hand. This module consisted of finger joint movements, and very precise catching movements, which demanded fine motor skills of the hand that also require more cognitive effort. Finger joint movements were repeated ten times, and the fine motor skills exercises were repeated three times.

The fingers joint movement exercises consisted of the following:

- Fingers flexion – extension.
- Fingers abduction – adduction.
- Opposition thumb movement with all the fingers of the hand.

The fine motor skills movements' exercises of this module consisted of the following:

- **The tridigital pinch exercise:** In this exercise patients had to train the tridigital pinch by catching different small geometric figures and placing it in the correspondent recipient. At the same time they were training their cognitive capability because they had to recognise the geometric form and colour of the different figures.

- **The digital tapping task exercise:** In this exercise patients had to tap the light blocks with the index virtual finger. When the patient reaches the block this emit a musical sound that is part of a song and at the end of the exercise the entire song sounds. Hence, represent that patients were composing a song with their fingers.

Finally, the rehabilitation program also included **'Random modules'**, module five, which contained another five blocks with different combinations of the exercises trained in modules 1 to 4 explained above. These random modules aimed at reviewing the trained movements and reinforcing the learned motor skills throughout the training periods.

2.4 Recruitment and procedures

In the ***IVR in orthopaedic rehabilitation*** and ***IVR in chronic pain*** studies we recruited patients from the Hospital Clinic de Barcelona with the collaboration of the doctors of the rehabilitation and traumatology departments, whereas in ***IVR in chronic stroke rehabilitation study*** we recruited the stroke patients from the Hospital de la Esperanza with the collaboration of the person in charge of the rehabilitation department.

2.4.1 Informed consent and data protection

In all experiments the following documentation was given to the patients:

- An information sheet describing the procedures of the study. This is different for each study (for an example see APPENDIX A, APPENDIX B and APPENDIX C).
- A consent form (for an example see APPENDIX A)

Patients were informed both verbally and in writing that they were free to withdraw at any time without being required to provide any explanation. All patients' data were anonymized by way of an identifier corresponding to each participant, relating to all information digitally stored. This identification number was assigned at the time that the participant arrived for the experiment. There were no computer records that tied up the name of the patients with the computer record of the results of the experiment. It was essential to keep a paper record that tied together the identification number of the patient and their contact details. The paper record connecting the identifier of the participant with their contact details was maintained throughout the analysis period of the experimental data only. No personal information regarding the patients was or will ever be published except in statistical and anonymous form. For example, quotes by patients could be incorporated in publications but no identifying information would be given. Patients of the *IVR in chronic pain* study received compensation for their participation at a rate of 5 euros.

2.4.2 Procedures

In all three studies, the IVR scenario was accomplished using a HMD and vibrators on the fingers and hand of the patients to augment the feeling of ownership of the virtual body that in turn was seen from a first-person perspective. Patients sat comfortably on a chair with both arms resting on a table in front of them. In all three studies patients were instructed not to move their arms during the experimental sessions (see ***Figure 2.4.1***A).

According to the *embodiment* section (section 2.1.1), patients in the IVR scenario saw a virtual male or female body (corresponding to the gender of the patient) collocated with their own body, seen from a first-person perspective through the HMD and with their virtual arms resting on a table in front of them in the same position as the real arms. Participants were then asked to concentrate on their injured virtual hand. They saw a ball tapping in random order the virtual index and middle fingers of the injured hand and felt synchronous tactile feedback (vibration) on their real index and middle fingers of the injured (***Figure 2.4.1***B).

Additionally, in the *IVR in orthopaedic rehabilitation* and in *IVR in chronic stroke* studies patients could activate the virtual arm movement; this allowed the patients to choose when they were ready to perform the exercise, inducing a sense of agency over the virtual arm movements.

In all three studies, patients were following the experimental sessions guided by a voice instructions displayed through the headphones. In the *IVR in orthopaedic rehabilitation* and in *IVR in chronic stroke* studies, the IVR task involved listening to task instructions describing the movement to be done through the headphones so that the patient would mentally plan each exercise. After this, they had to activate the virtual arm. Finally, patients could see the virtual arm doing the exercises from a first-person perspective (***Figure 2.4.1***C). In some exercises, patients had to interact with virtual balls or different virtual objects as targets of the task; when they reached the object they felt a vibration on the palm of their injured hand to enhance the sense of agency.

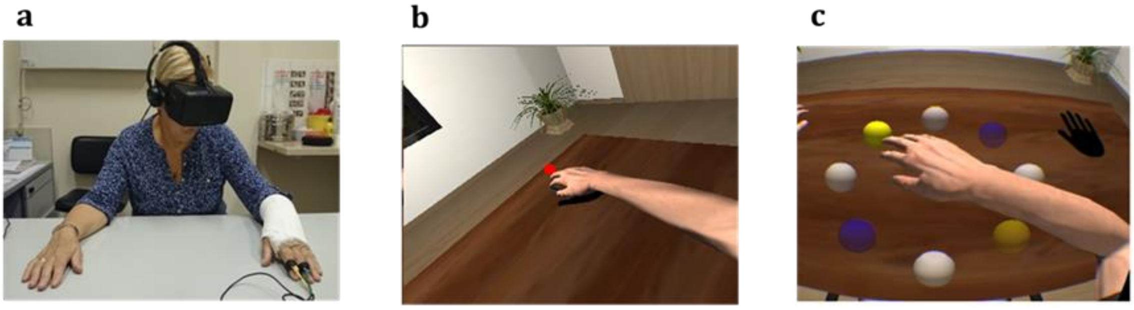
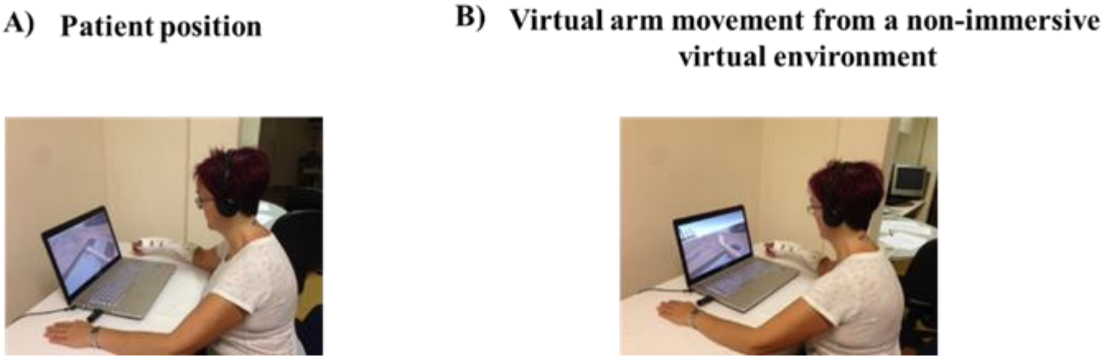


***Figure 2.4.1 Procedures and experimental set-up of the immersive virtual reality training**. A) Patients used a head-mounted display (HMD) that immersed them in a virtual environment, which allowed participants to feel embodied in a virtual body viewed from a first-person perspective. Patients also wore headphones through which they heard the task instructions describing the arm movements they had to perform. B) The virtual arms were collocated with the real arms. Virtual balls and objects tapped the fingers during the visuo-tactile stimulation phase at the beginning of each session to induce ownership and agency. Participants were asked to look at the virtual arm corresponding to the paretic real arm throughout the session. Then patients listened to the description of the arm movements after which they had to mentally plan the described movements. Next, patients activate the virtual arm movements. C) Patients could then see the virtual arm movement (visual feedback of the planned movement from an immersed virtual environment (i.e. motor imagery/action planning + action observation)).*

In the *IVR in orthopaedic rehabilitation study*, patients allocated in the CDM training group followed the doctor's directions, which consisted in opening and closing their hand 20 to 30 times per day and mobilizing their fingers at home. In contrast, patients in the Non-IVR group saw a virtual male or female arm (corresponding to the gender of the patient) located in the same position as their own arms. Patients were isolated from the environmental noise by pink noise through the headphones. In the Non-IVR training group patients only did action observation training. Finally, patients could observe the virtual arm doing the exercises on the computer screen, in a non-immersive virtual reality scenario (***Figure 2.4.2***).



A) Patient position

B) Virtual arm movement from a non-immersive virtual environment

Figure 2.4.2 Procedures and experimental set-up of the Non-IVR group. A) *The patient sat in front of the computer with their arms placed above the table co-located with the virtual arms. The patient wore headphones in order to be isolated from the external noise.* ***B)*** *The patient looked at the virtual arm movements from a third person perspective (Action observation paradigm).*

In the virtual scenario of the *IVR in chronic pain* study, there was a book above the table beside the painful arm. At the beginning of each virtual pain test, patients listened the following verbal instruction through the headphones *"pay attention to the arm that is collocated beside the book, please".* In order to ensure that patients were looking to the painful arm during the whole experiment, this verbal instruction was repeated before each visual condition presentation in each virtual test. Each condition started with 45 seconds of visuotactile stimulation (see ***Figure 2.4.3***A).

During the transparency of the virtual arm test, participants were exposed to four different conditions with the virtual arm transparency set at 0% (max opacity level) (a), 25% (high opacity level) (b), 50% (mid opacity level) (c) or 75% (low opacity level) (d) (***Figure 2.4.3***B,C,D,E).The four conditions were presented in a random order, each of them was presented three times, at the same time as the visuotactile stimulation to induce the ownership of the virtual arm in each transparency level condition. Hence, patients were exposed to a total of twelve visual conditions exposures. Each visual transparency of the virtual arm exposure lasted 45 seconds.

During the virtual arm size distortions test, participants were exposed to three different conditions, in the first condition, the size of the virtual arm was doubled (X2), in the second condition the virtual arm was normal sized and in the third condition it was small (/2) (see ***Figure 2.4.3***F,G,H). The three conditions were presented in a random order; each of them was presented three times, at the same time as the visuotactile stimulation to induce the ownership over the virtual arm in each different size condition. Patients were exposed to a total of nine visual conditions exposures. Each visual distortion of the virtual arm exposure lasted 45 seconds.

In both tests, two seconds after the visual condition had stopped, the screen of the HMD became black and a ‘Numeric Pain Rating Scale’ (NPRS) appeared with a voice instruction asking the participants to judge the intensity of pain over their painful arm. They were instructed to verbally report a number on a scale from 1 to 10 (“1”= no pain, “10” worst pain possible) to reply to the question: “Which is your pain intensity at this moment?” Participant’s ratings were promptly annotated by the experimenter after each condition.

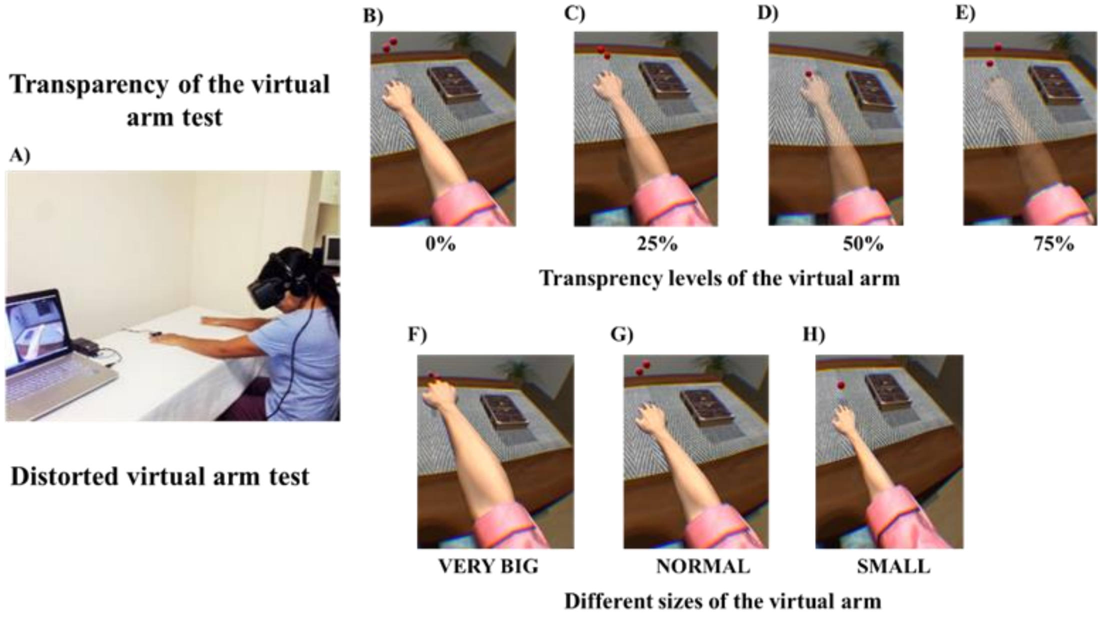


Figure 2.4.3 Procedures and experimental set-up of transparency and distorted virtual arm tests. A) *Patients used a HMD that immersed them in a virtual environment, which allowed participants to feel embodied in a virtual body viewed from a first-person perspective. Patients also wore headphones through which they heard the task instructions describing the arm movements they had to perform. The virtual arms were co-located with the real arms. Virtual balls and objects tapped the fingers during the visuo-tactile stimulation phase at the beginning of each session to induce ownership.* ***The transparency of the virtual arm test contains four different conditions. B)*** *virtual arm transparency set at 0%* ***C)*** *virtual arm transparency set at 25%* ***D)*** *virtual arm transparency set at 50%* ***E)*** *virtual arm transparency set at 75%.* ***The distorted virtual arm test contains three different conditions. F)*** *Virtual arm was presented in its doubled size.* ***G)*** *Virtual arm was presented in its normal size.* ***H)*** *Virtual arm was presented in a small size.*

After the first virtual pain test exposure, the HMD and the headphones were removed and patients had a period of rest during which they had to fill in a questionnaire related to the virtual reality experience and to how the different visual conditions affected the ownership illusion. After the second virtual pain test exposure, they filled in another virtual reality questionnaire related to the virtual pain test they completed in the second time.

2.5 Outcome measures

2.5.1 IVR for orthopaedic rehabilitation

2.5.1.1 Virtual reality questionnaire

After each session, the IVR training group and the Non-IVR training group filled out a six-item virtual reality (VR) experience questionnaire in Spanish (**see Appendix A).** Each question was scored according to a five-point Likert Scale, 1 meaning ‘totally disagree’ and 5 ‘totally agree’. Most of the questions of the virtual reality questionnaire were adapted and translated from Slater et al. (2010), and new questions related to the understanding of the task instructions and to the duration of the sessions were added.

2.5.1.2 Functional measures

The primary outcome measure was the recovery of the functional arm’s ability after cast removal as measured by the Fugl-Meyer (FM) test (Fugl-Meyer et al. 1975). We only assessed the upper limbs section. The FM test enables a volitional movement assessment: this includes flexor synergy, extensor synergy, movement combining synergies, movement out of synergy, wrist mobility, hand grip strength, and, arm coordination/speed. The FM test assesses the prognostic of the functional ability recovery, where a score ≤ 33 indicates a poor prognostic, a moderate prognostic, and ≥ 57 a good prognostic recovery of the functional ability.

Secondary outcomes after cast removal were: percentage of disability of the fractured arm assessed using the Disability of the Arm, Shoulder and Hand (DASH) questionnaire (Germann et al. 1999),which is a 30-item, self-reported questionnaire designed to measure physical function and symptoms in patients with musculoskeletal disorders of the upper limbs when performing activities and daily-life tasks; Range of Motion (ROM) improvement in six different movements: wrist flexion-extension, wrist cubital and radial deviation, and pronation-supination of the arm, carried out with a goniometer (Gajdosik & Bohannon 1987); grip and lateral pinch strength measured using a ‘JAMAR’ dynamometer (Schmidt & Toews 1970) (see ***Figure 2.5.1***); and the level of pain after cast removal, assessed by the Numeric Pain Rating Scale (NPRS) (Farrar et al. 2001), whereby patients reflected the intensity of their pain by selecting a number from 0 (no pain) to 10 (highest intensity of pain)*(**Figure 2.5.4**)*.

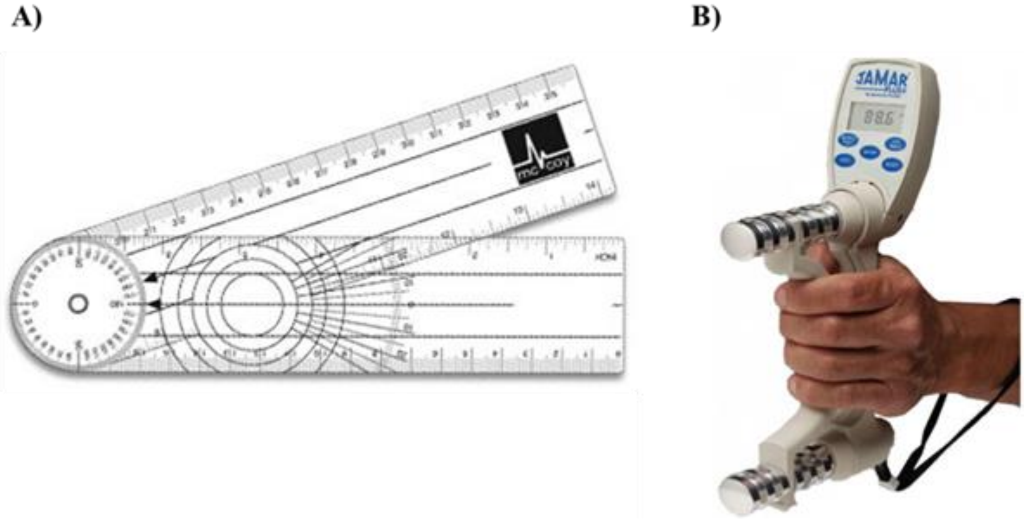


Figure 2.5.1 Range of motion and muscular strength assessment tools. A) Goniometer. *A goniometer was used to measure the range of motion of six different wrist joint movements after cast removal in all three groups.* ***B) JAMAR dynamometer****. A JAMAR dynamometer was used to measure the muscular strength of two different pinches (grip and lateral pinch), after cast removal in all three groups.*

2.5.2 IVR for chronic stroke rehabilitation

2.5.2.1 Virtual reality questionnaire and Self-Assessment Manikin measure

After each session during the training periods, the patients filled out a six-item (VR questionnaire in Spanish, and the Self-Assessment Manikin (SAM) test (Bradley & Lang, 1994). The VR questionnaire was used to evaluate the patients’ IVR experience. Most of the questions were adapted and translated from Kilteni et al. (2012) and Slater et al. (2010), and new questions related to the understanding of the task instructions and to the duration of the sessions were added (**see Appendix A**). Each question was scored according to a five-point Likert Scale, 1 meaning ‘totally disagree’ and 5 meaning ‘totally agree’ (Albaum 1997).

On the other hand, the SAM test is a non-verbal pictorial test that measures the level of pleasure, arousal, and dominance related to the emotional reaction of patients to a stimulus using a nine-point pictorial Likert scale (***Figure 2.5.2***).The patients had to cross the circle below the picture with which they felt most identified according to their emotional state. In our study, we were only interested in the pleasure state of the patients after each IVR session; therefore we only used the corresponding part of the test.

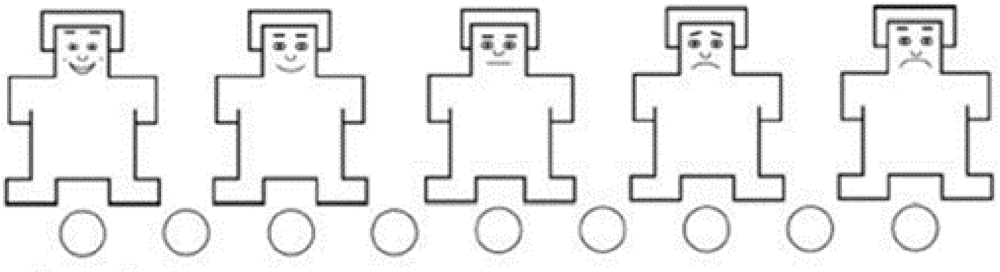


Figure 2.5.2 The Self-Assessment Manikin test. *SAM test was used in order to know the emotional state of the patients after each training session. In this scale, patients had to cross the circle below the picture with which they felt most identified. We only evaluated the pleasure state domain of the test.*

2.5.2.2 Functional measures

In order to assess motor dexterity improvements on the paretic arm, we used the Motricity Index (MI) scale (Heald et al., 1993) at the assessment times during the training and period of pause. The Motricity Index scale specially measures hand-grasp, elbow flexion, and shoulder abduction movements. Functional ability recovery of the affected arm was assessed with the Wolf Motor Functional Test (WMFT), which quantifies upper extremity motor ability through timed and functional tasks. This test also assesses the velocity to perform each task and the muscular strength of the paretic upper extremity. This test assesses the velocity to perform each task and the muscular strength of the paretic upper extremity. The test contains fifteen timed measures, and we also used this measure in the weekly assessments during the training and period of pause (Wolf et al., 2001). The Chedoke Arm and Hand Activity Inventory (CAHAI) (Barreca & Gowland, 2004) was used to assess the level of independence of the patients to perform thirteen daily life activities, such as opening a jar of coffee or pouring water into a glass. We used this measure to assess changes from baseline I and II to post-treatment I and II. The level of spasticity of the upper limb was assessed by the Modified Asworth Scale (Bohannon & Smith, 1987), which tests the resistance of the arm to passive movements of the patients done by the therapist. This was also assessed every week during the training and period of pause.

2.5.2.3 Cognitive measures

Considering that our IVR training also implied a cognitive effort for the patients, we examined whether there were changes at a cognitive level. For this, the Corsi block-tapping test was used at baseline I and II and post-treatment I and II to assess memory loss, spatial memory, and nonverbal working memory (see ***Figure 2.5.3***A). In this test, the examiner taps the blocks in sequences, starting with sequences of two cubes, and increasing the difficulty by progressively tapping longer sequences. The subject then tries to reproduce the given sequence by tapping the blocks in the same sequence they saw ("forward" task), or in a backward order ("backward" task) (Brunetti, Del Gatto, & Delogu, 2014). The Letter Cancelation Test (Uttl & Pilkenton-Taylor, 2010) was performed by the patient weekly during the IVR training I and II periods and during the period of pause to measure attention/concentration and visuo-spatial dysfunctions, such as spatial neglect (see ***Figure 2.5.3***B). The test consists of one 8.5″x11″ sheet of paper containing 6 lines with 52 letters per line. The stimulus letter H is presented 104 times. The page is placed at the patient's midline. The patient is told to put a line through each H that is found on the page. The time taken to complete the test is recorded. Finally, we evaluated changes in quality of life after the training periods by using the Stroke Specific-Quality of Life scale (SS-QOL) (Williams et al., 1999). ***Figure 2.2.2***b lists the various tests that were.

2.5.2.4 Neuroplastic changes measures

It is not yet known whether IVR exerts its positive effects in motor behaviour by influencing motor plasticity, in our pilot study *'IVR in chronic stroke rehabilitation'* a pre-post brain imaging study has allowed us to identify the underpinning neuroplastic changes following the first IVR training. We used diffusion tensor imaging (DTI) technique in order to observe the structural brain changes and functional magnetic resonance imaging (fMRI)-resting state technique to observe functional connectivity changes after the first IVR training with our

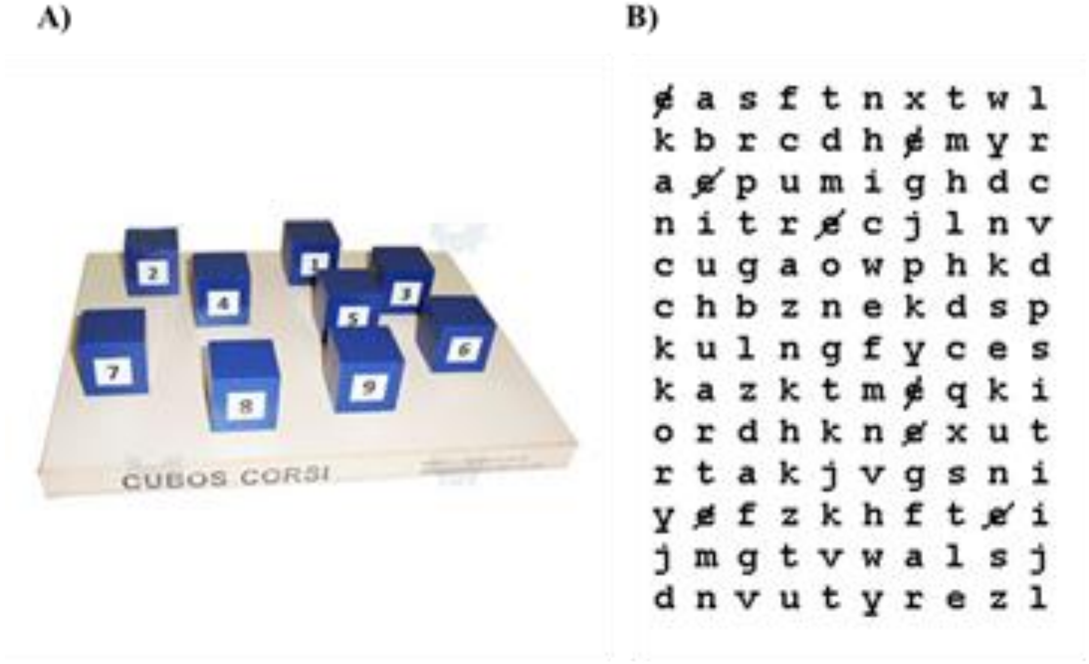


Figure 2.5.3 Cognitive assessment tools. A) Corsi-block tapping test. *The Corsi-block tapping test was used to assess memory loss, spatial memory, and nonverbal working memory at baseline I and II assessment times.* ***B) Letter cancellation test.*** *The letter cancellation test was used to measure attention/concentration and visuo-spatial dysfunctions, such as spatial neglect. This was administered to the patients weekly during the first and the second IVR trainings.*

motor-cognitive program. DTI is a non-invasive MRI technique which can identify both microscopic and macroscopic spatial organization of the white matter (WM), through the observation of translational molecular movement of water (Le Bihan 2003). DTI provide unique evidence to the complex architecture of neural tissues and to the associated changes due to physiological or pathological states. On the other hand, fMRI is another non-invasive technique for examining brain function by observing changes in blood oxygen level-dependent (BOLD) signal to identify increased or decreased neuronal activity in different brain areas (Logothetis 2003; Raichle & Mintun 2006). Recently, it has been shown that one great applicability of fMRI involves focusing in spontaneous modulations on BOLD signal during resting conditions (Fox & Raichle 2007). Hence, while patients are resting into the MRI scanner with the eyes closed or fixating in a crosshair, spontaneous modulations in the BOLD signal in the absence of any explicit input or output are recorded. Hence, the analysis of these spontaneous modulations in the BOLD usually are related to the identification of correlations between other brain areas, commonly referred to as functional connectivity (Dijkhuizen et al. 2012). In our pilot study we used fMRI-resting state technique in order to identify whether any change in functional connectivity had taken place after the first IVR training.

2.5.2.4.1 Neuroimage acquisition

MRI data set were acquired using a 3-T Siemens Magnetom Trio Tim syngo MR B19. During all the images acquisition period, patients were instructed to close their eyes and not move their body. Functional resting state images parameters were: (TR= 2500 ms, TE= 28 ms, flip angle= 80º, FOV= 240 mm, voxel size= 3x3x3, number of slices= 40, slice thickness= 3mm). Each resting state scan consisted in 8:07 minutes. Diffusion weighted images parameters were: (TR= 7700 ms, TE=89 ms, FOV= 244 mm, voxel size= 2x2x2, number of slices= 60, slice thickness= 2 mm). A high-resolution T1-weighted structural image using an MPRAGE sequence was also acquired for each subject (TR= 2300 ms, TE= 2,98ms, voxel size= 1x1x1, number of slices= 240, slice thickness= 1 mm). Imaging data were pre-processed using Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, http://www.fil.ion.ucl.ac.uk/spm) Matlab (Matlab R2012a) toolbox. Resting state pre-processing included alignment of the functional volumes to the first volume, co-registering with the structural image, correcting for slice timing, segmenting and normalizing. Data were smoothed using an 8-mm full width at half maximum Gaussian kernel. Anatomical parcellation of the spatially normalized single-subject high-resolution T1 volume was performed through the automatic anatomical labelling of activations technique. The whole cerebral cortex was parcelled into 90 anatomical regions of interest (ROIs) using the automated anatomical labelling (AAL) template (Tzourio-Mazoyer et al. 2002). This parcellation scheme will be referred as AAL-90 for the structural analyses. To the functional analyses we used the AAL116 (this means 90 labelled regions plus cerebellum regions) for the functional analyses.

2.5.3 IVR for chronic pain

2.5.3.1 Virtual reality questionnaires

After each test, participants had to fill in a 7-point Likert-type questionnaire, ranging from -3 to 3 (“-3”= totally disagree, to “3”= totally agree”). The Virtual Reality (VR) questionnaire was a nine-item questionnaire to judge the level of ownership during the different conditions presented during virtual reality test (**see Appendix C**).

2.5.3.2 Pain ratings measure

Pain intensity after the visualization of each condition was measured on an 11-point pain intensity numerical rating scale (PI-NRS), where 0 means no pain and 10 means worst possible pain (Farrar et al., 2001)(see ***Figure 2.5.4***).

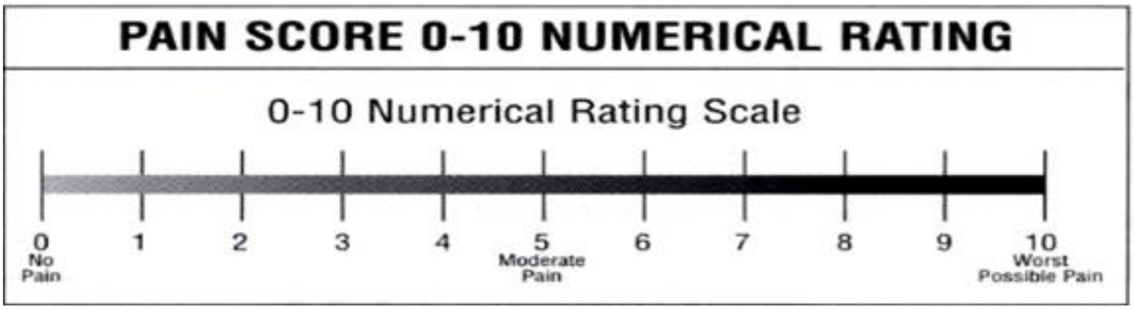


Figure 2.5.4 Pain intensity-numeric pain rating scale. *In the IVR in chronic pain study patients had to indicate the level of pain after the exposure to each visual experimental condition.*

2.6 Analyses

Statistical comparisons between groups in the *IVR in orthopaedic rehabilitation study* were conducted with SPSS 21 software (IBM SPSS Statistics, IBM Corporation, Chicago, IL). In the *IVR in chronic stroke study*, due to the small sample size (n=3) we did a descriptive analysis of the data (see Results section), but to be able to justify the relationship between different measures we conducted correlation analyses with SPSS 21 software (IBM SPSS Statistics, IBM Corporation, Chicago, IL, USA). In the *IVR in chronic pain study* all statistical tests were conducted in Stata 13 (StataCorp LP, College Station, TX, USA).

2.6.1 Specific analyses in IVR in the orthopaedic rehabilitation study

We first explored whether the data were normally distributed with the Kolmogorov-Smirnov test (p >0.05). We used the Kruskal-Wallis test if the data were not normally distributed and one-way ANOVA (one factor: “group” with three groups) if the data were normally distributed. In order to identify possible changes associated with the implementation of the IVR training, the analysis of data was carried out using one-way ANOVA (one factor “group”). The analysis was done separately at times T1 and T2 to study the outcome differences between IVR, CDM and Non-IVR training groups. As patients in the three groups did conventional rehabilitation training between T1 and T2, we expected to see a natural motor functional improvement in the fractured arm; for this reason we thought it was not necessary to do repeated measures analysis. In other words, the main interest in our study was to see the differences between groups at each specific assessment time (T1 and T2). *Post hoc* analyses were conducted with the Tukey HSD test. The significance level was set at $p < 0.05$. We compared the scores reported for the ‘virtual reality experience’ questionnaire between groups with the Mann-Whitney-U test. We explored the relationship between the recovery of the functional ability of the fractured arm (FM test) and the scores obtained in the virtual reality experience questionnaire with Spearman’s correlation test.

2.6.2 Specific analyses in IVR the chronic stroke rehabilitation study

Due to the small sample size (n=3) we did a descriptive analysis of the data (see Results section), but to be able to justify some correlations between different measures we performed Spearman’s correlation for not normally distributed data. As we could not justify our results through statistical analyses due to the small sample size, we tested the effectiveness of our IVR training on all measures from baseline to post-treatment. More specifically, we calculated the effect sizes of the changes after the first IVR training (Cohen 1988) on the motor-cognitive and quality of life recovery of the stroke patients.

We also specified the percentage of treatment effectiveness for each of the three stroke patients over all the measures except for the Letter cancellation test by applying the following calculation:

$$\left[\text{Percentage of treatment effectiveness} = \frac{\text{(Post treatment value – Baseline value)}}{\text{(Maximum measure score – Baseline score)}} \right]$$

2.6.2.1 Neuroimage analysis

To investigate if treatment had any impact on large-scale functional and structural connectivity, we calculated a magnitude change matrix *Mc* by computing the absolute difference between two given pre- and post-treatment connectivity networks for each of the three subjects. This is given by:

$$Mc = |M\text{pre} - M\text{post}|$$

Were *M*pre and *M*post can be either functional or structural connectivity matrices. Notice than in *Mc* terms, each link *ij* represents the connectivity magnitude change. To simplify the analysis, *Mc* was thresholded to collect the top 2% strongest links. This method allowed to identify those nodes and links presenting the largest change after treatment.

2.6.3 Specific analyses in IVR for the chronic pain study

We first explored whether the data were normally distributed with the Shapiro-Wilk test (p >0.05). Each patient carried out four different experimental conditions in the transparency of the virtual arm test and three different experimental conditions in the distorted virtual arm test. This is therefore a mixed-effects design, with fixed-effects "Conditions", and random effects over the "individual subjects", "Pain ratings" as dependent variable and sorting the data by "Test" was appropriately analysed by a Multilevel Mixed-Effects Linear Regression (the 'mixed' function in Stata). We analysed the data obtained in CRPS and PNI groups separately. To see if there was an interaction between "tests'' and '"Injury type" in pain ratings, we also used a Multilevel Mixed-Effects Linear Regression with fixed-effects "tests" and "Injury type", random effects over the "individual subjects" and "Pain ratings" as dependent variable. Differences between "Types of injury" in questionnaire responses and at baseline measures were analysed by Mann-Whitney-U-test for non-parametrical data (the Wilcoxon rank-sum test in Stata).

Chapter 3

> *In examining disease, we gain wisdom about anatomy and physiology and biology. In examining the person with disease, we gain wisdom about life.*
>
> *Oliver Sacks.*

Results

3.1 On IVR in orthopaedic rehabilitation

In the *IVR in orthopaedic rehabilitation study*, we screened 104 patients with distal radius fracture between March 1, 2014, and September 30, 2016. The most common reason for exclusion from the study was the presence of cognitive impairment (27 [25.96%] of 104 patients). Of the screened individuals, 77 patients were randomly assigned to different groups: 29 patients were assigned to the IVR training group, 27 patients to the CDM training group (control one) and 21 to the Non-IVR training group (control two). 25 (86.20%) of 29 patients in the IVR group, 23 (85.18%) of 27 patients in the CDM group and 14 patients (66.66%) of 21 patients in the Non-IVR group started the training sessions; 20 (80%) of 25 patients in the IVR group, 20 (86.95%) of 23 patients in the CDM group and 14 (100%) of 14 patients in the Non-IVR group completed the training period, which lasted between four to six weeks depending on the evolution of the patient, and were included in the analysis (***Figure 2.2.1***). Baseline balance between groups was confirmed for all demographics except for gender as there were more females than males in the study (Table 1), in line with distal radius fracture being more common in females (Kuo et al. 2013).We did not exclude males in our study and, since we did a randomized control trial (RCT), the number of males and females throughout the groups was not balanced

Table 1. Baseline characteristics of the intention to treat population of IVR in orthopaedic rehabilitation study (summarizes mean, SD and, percentages (%)).

	IVR	CDM	Non-IVR
Sex			
Male	0 (0%)	3 (15%)	5 (35.71%)
Female	20 (100%)	17 (85%)	9 (64.29%)
Age (years)	60.05 ± 12.84	61.60 ± 16.23	64.57 ± 13.46
MEC	34.70 ± 1.03	34.02 ± 1.50	34.35 ± 0.84
FAB	17.20 ± 0.90	16.50 ± 1.20	17.14 ± 1.23
Training weeks	3.20 ± 2.32	Training at home	2.64 ± 2.50

3.1.1 Prognostic recovery and percentage of disability

We observed that a higher percentage of patients in the IVR training group presented significantly better prognostic recovery of the functional ability of the fractured arm after cast removal and six weeks later compared with patients in the CDM and in the Non-IVR groups (***Figure 3.1.1***A) (one-way ANOVA, factor "group": F= 20.83, p< 0.0001). More specifically, 85% of patients in the IVR group presented good (score ≥ 57) prognostic recovery and only 15% presented moderate (score < 57) prognostic recovery of the functional ability after cast removal (T1; 95% CI 56.84-59.96). On the other hand, only 25% of patients in the CDM training group presented a good prognostic recovery of the functional ability after cast removal and 75% presented a moderate prognostic recovery (95% CI 46.52-52.48). Finally, 100% of the patients allocated in the Non-IVR training showed a moderate prognostic recovery of the functional ability of the fractured arm at T1 (95% CI 48.95-52.47). Overall, that the IVR training group obtained higher scores in FM test compared to the ones obtained in the CDM (Tukey post-hoc test: p< 0.0001) and in Non-IVR (p< 0.0001).

Six weeks later (T2), patients in the IVR also had better prognostic recovery (one-way ANOVA, factor "group": F=5,873, p=0.005). In particular, 90% of patients in the IVR training group again showed good prognostic recovery of the functional ability and only 10% still presented moderate prognostic recovery (95% CI 60.42-63.28). In contrast, 60% of the patients in the CDM training group presented good prognostic recovery and 35% continued to show moderate prognostic recovery of the functional ability of the fractured arm (95% CI 55.69-60.94). In the Non-IVR training group, only 50% of the patients presented good prognostic recovery and the other 50% presented moderate prognostic recovery of the functional ability of the fractured arm (95% CI 54.38-59.47). Again, patients in the IVR training group had better functional recovery compared with CDM (Tukey: p=0.038) and Non-IVR (p=0.007) groups. Regarding disability, patients in the IVR training group presented a significantly lower percentage of arm disability in performing daily life activities at home after cast removal (T1; one-way ANOVA factor "group": F=6.224, p=0.004) and a substantial decrease in the percentage of disability compared to CDM training at T2 (***Figure 3.1.1*** B) (one-way ANOVA at T2 factor "group": F=5.835, p=0.005). More specifically, the IVR group presented a lower percentage of disability of the fractured arm after cast removal compared to the CDM group at T1 (Tukey: p=0.003) and at T2 (p=0.025), and also did the Non-IVR show better results than did the CDM training group at T2 (p=0.009), revealing less disability in patients in the IVR and Non-IVR training groups (***Figure 3.1.1***).

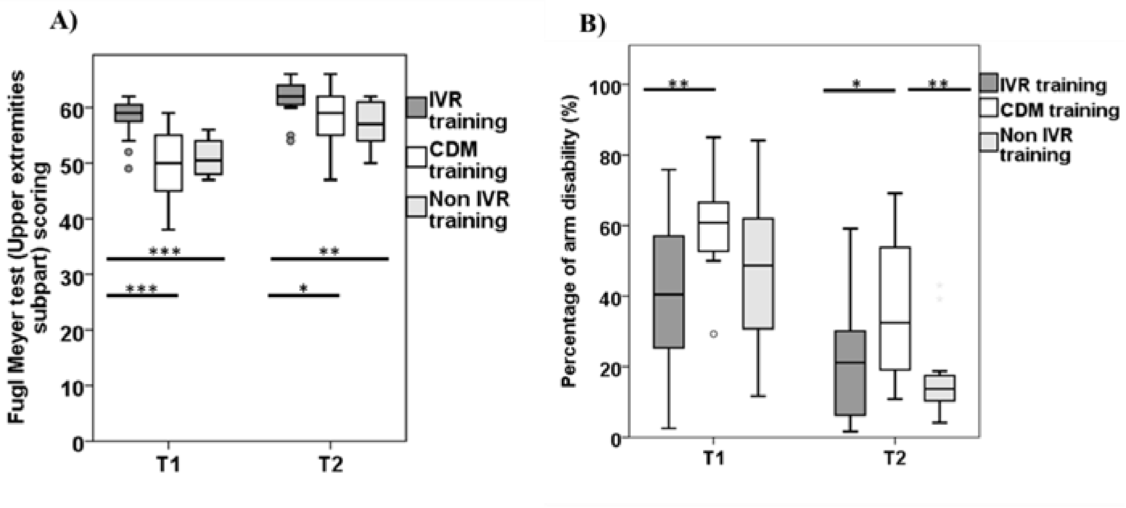


Figure 3.1.1 Functional ability recovery and decrease in percentage of disability. A) Functional ability recovery. *IVR training group presented higher functional motor ability recovery after the cast removal (T1) and six weeks later (T2) than CDM and Non-IVR training groups, assessed by Fugl-Meyer test.* ***B) Percentage of disability decrease.*** *IVR group presented lower percentage of arm disability after the cast removal (T1) than CDM and Non-IVR groups. At T2 IVR and Non-IVR groups presented lower percentage of arm disability compare to the CDM training group. The percentage of disability was assessed by DASH questionnaire. In the boxplots, the medians are shown as horizontal lines and the boxes are the interquartile ranges (IQR). The whiskers represent 1.5 x IQR. If there are values outside the whiskers these are conventionally called "outliers", and are shown by (◦)*

3.1.2 Range of motion

In terms of range of motion, we observed better improvements in patients in the IVR training group in wrist flexion (one-way ANOVA factor "group": F=4.121, p=0.023) and wrist extension (F=3.926, p=0.027) joint movement and some trend in pronation (F=2.933, p=0.063) after cast removal (T1) compared with those in the CDM and Non-IVR training groups (**figure 3.1.2**A). *Post hoc* analyses revealed differences only between IVR and CDM training groups at T1 in wrist flexion (p= 0.028) and in wrist extension movements (p= 0.021), and a trend between IVR and Non-IVR groups in pronation movement (p= 0.056). Likewise, at T2 we found significant differences between groups in wrist flexion (F=7.63, p=0.001) and radial deviation (F=4.40, p=0.025) movements. Post hoc analysis confirm that IVR training presented greater improvement in wrist flexion movement than CDM training (Tukey: p=0.001). However Non-IVR training presented significant higher degrees of movement in radial deviation movement than CDM training but no than IVR training (Tukey: p=0.023) (See ***Figure 3.1.2***A).

Patients that had visual movement feedback showed significant better recovery of the range of motion in IVR training and more significant than those that did the CDM training. Interestingly, they also showed greater improvement in some specific movements, what made us interested in the potential relationship between the amount of movement visualization during the IVR training and the improvement in the range of motion. We recounted the number of times that each of the six joint movements appeared throughout the training program in each exercise. As we only found significant differences in range of motion improvement after cast removal (T1) between the IVR and the CDM training groups, we calculated the difference in range of movement improvement between the IVR and CDM training groups and normalized it by the degrees of movement obtained in the CDM training group at T1. The normalization equation is:

[(degrees of movement in IVR (T1) – degrees of movement in CDM (T1)) / degrees of movement in CDM (T1)].

We then did a linear regression analysis ('normalized degrees of movement' as dependent and 'movement visualization' as independent variable), and we found a significant positive relationship between both variables during the IVR training program (***Figure 3.1.2*** B; Beta=0.246, p=0.001). It is not surprising that we found the main differences in those movements that patients had observed more times throughout the training: wrist flexion-extension.

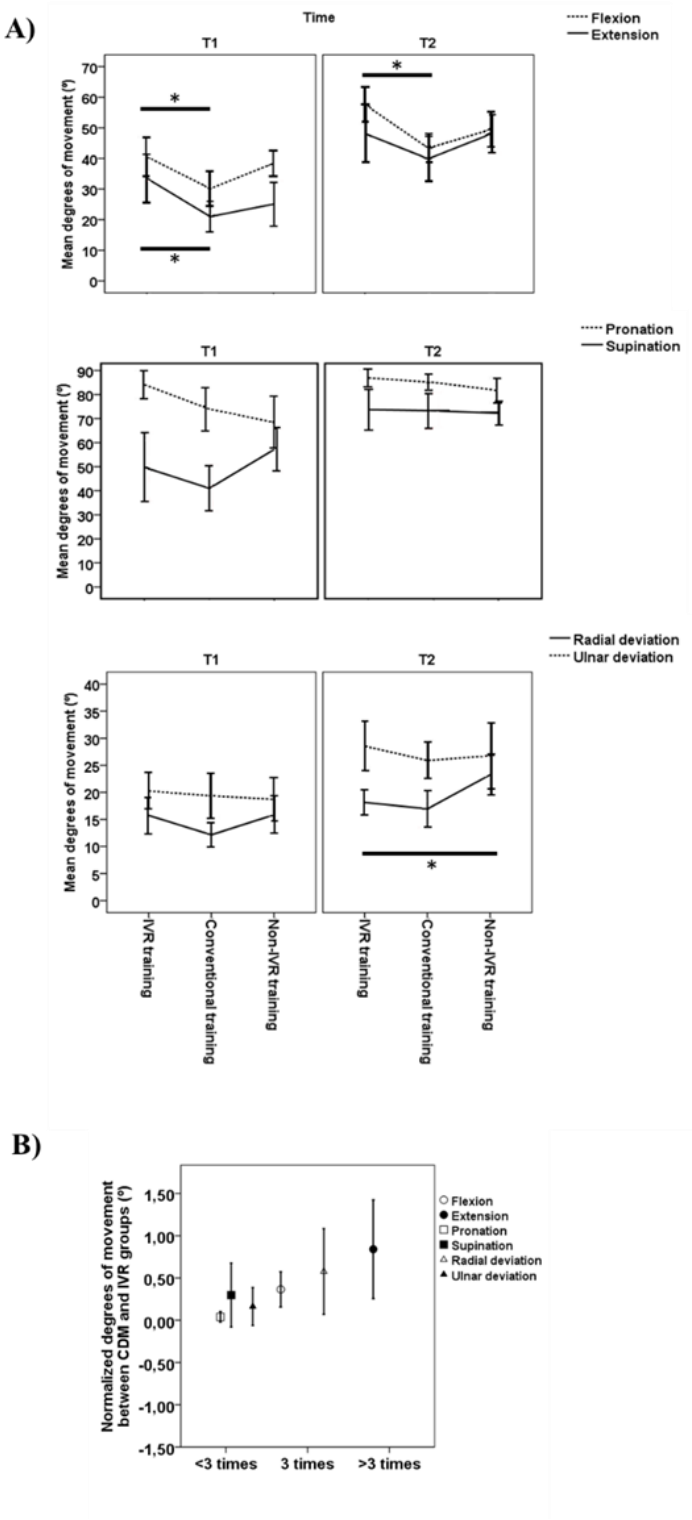


Figure 3.1.2 Range of motion improvement and the relationship with the amount of movement visualization. A) Range of motion improvement. *In the Range of motion assessment IVR training group presented more degrees of movement in wrist flexion-extension movements after the cast removal (T1) compared to CDM group. Again six weeks later (T2) IVR group presented higher degrees of motion than CDM group in wrist flexion movement. The lines show the difference of degrees of motion for each different movement between groups in T1 and T2 assessment. Error bars means 95%IC. *p <0.05 , **p < 0.01.* ***B) The amount of movement visualization is linked with range of motion improvement.*** *Differences between IVR and CDM groups are due to patients in IVR group were visualizing joint movements during the training period, furthermore patient in IVR group presented higher recovery in those movements that they visualizes more times during the training period. Error bars means 95%IC of the mean.*

3.1.3 Muscular strength

It is known that muscular strength and muscle fibre characteristics differ between males and females (Miller et al. 1993). Considering these sex differences, we split our sample into males and females to analyse grip strength and lateral pinch. Within the females (n= 46) we found differences between groups in lateral pinch force at T1 (***Figure 3.1.3***A.ii, one-way ANOVA: F=3.434, p=0.041) but no differences in grip force. Tukey *post hoc* analysis revealed higher muscular strength in the IVR compared to the CDM training group at T1 (p= 0.032). Since there were no males in the IVR training group and due to the small sample size in the males group (n=8), we decided not to analyse the differences in muscular strength in the males group. However ***Figure 3.1.3***A.iii and iv, displays greater muscular strength in CDM training compared to the Non-IVR training.

3.1.4 Pain ratings

Concerning pain ratings, we did not find differences in the Numeric Pain Rating Scale (NPRS) scores between groups. However, patients that did both IVR and Non-IVR trainings presented (non-significant) lower ratings of pain (***Figure 3.1.3***B).

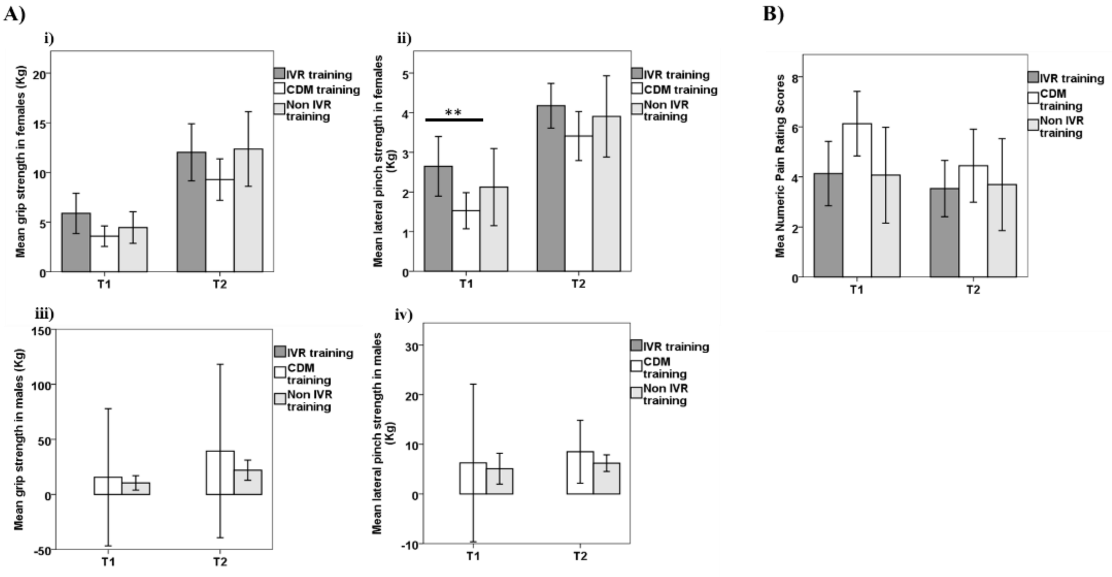


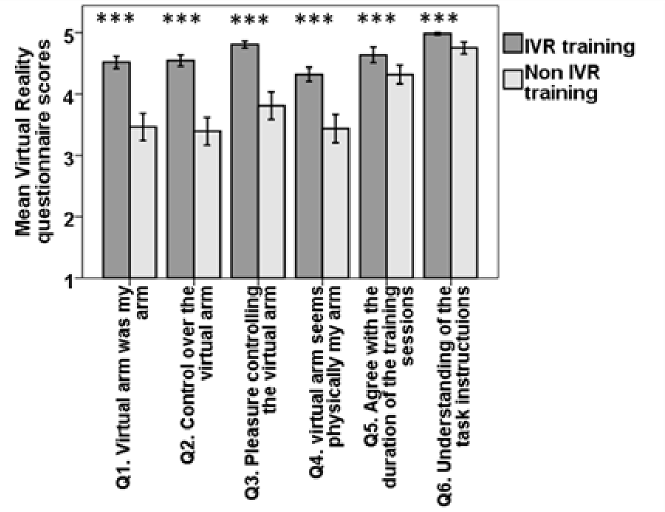
Figure 3.1.3 Muscular strength recovery and pain ratings. A) Muscular strength recovery.*Muscular strength recovery by females and males. After the cast removal (T1) females presented better recovery of the lateral pinch strength than females in CDM training group. Bar graph of the mean differences in muscular strength between groups split up by males and females. Error bars means 95%IC of the mean *p <0.05 , **p < 0.01.* ***B) Pain ratings.*** *There were no differences between groups in the Numeric Pain Rating Scale ratings. However patients in IVR and Non-IVR training groups presented lower pain ratings than those patients in the CDM training group. Bar graph of the mean differences in pain ratings between groups. Error bars means 95%IC of the mean.*

3.1.5 Virtual reality questionnaire scores

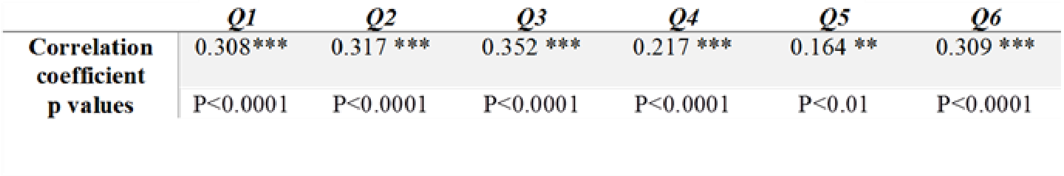
Finally, patients in the IVR training group reported much higher scores in all the questions of the VR questionnaire after the training sessions (T1) compared to those in the Non-IVR training group (***Figure 3.1.4*** A). The most important differences were in embodiment (owning the virtual body) (one-way ANOVA, factor “group”: Q1: $p<0.0001$; and Q4: $p<0.0001$) and in agency (the sense of controlling the virtual arm) (Q2: $p<0.0001$; and Q3: $p<0.0001$). Additionally, the IVR group reported higher level of pleasure of the sessions’ duration and the understanding of the task instructions (Q5: $p= 0.002$; Q6: $p< 0.0001$).

Interestingly, we found a positive relationship with the results obtained in the VR questionnaire and functional motor ability recovery (Fugl-Meyer test) in the IVR training group at T1 (***Figure 3.1.4***B), suggesting that being immersed in a virtual environment, feeling embodied in a virtual body and having the sense of agency of the virtual body had a positive influence on the functional ability recovery of the fractured arm after cast removal.

A)



B)



	Q1	*Q2*	*Q3*	*Q4*	*Q5*	*Q6*
Correlation coefficient	0.308***	0.317 ***	0.352 ***	0.217 ***	0.164 **	0.309 ***
p values	P<0.0001	P<0.0001	P<0.0001	P<0.0001	P<0.01	P<0.0001

Figure 3.1.4 Virtual reality questionnaire differences between IVR and Non-IVR groups and the relationship with functional ability recovery. A) Virtual reality questionnaire scores differences between IVR and Non-IVR groups. *There were significant differences between groups for all questions of the virtual reality questionnaire, showing higher scores in questions related to the sense of ownership of the virtual body and the sense of agency by controlling the virtual arm movement. The graph also present higher scores in addition to the understanding of the task instructions and pleasure during the training sessions.* ***B) Relationship between the functional ability recovery of the arm after the cast removal (T1) with virtual reality questionnaire scores in IVR training group.*** *There were a strong positive correlation with the fact to being embodied in a virtual body and the sense of controlling the virtual arm movements with the functional recovery of the fractured arm after the cast removal in IVR training patients.*

3.2 On IVR in chronic stroke rehabilitation

We included three chronic stroke patients (18-36 months after the stroke) in this case study. For details on the sample see **Table 2.** The three chronic stroke patients enrolled in this pilot study participated in 26 sessions during a first training period and 18±1 sessions during the second training period with a period of pause (three weeks) in between the two training periods (see Table 2 for patients' demographics and summary of training days).

Table 2. Summary of screening tests, demographic variables, clinical characteristics, and mean training days of IVR in chronic stroke rehabilitation study.

	Subject 1	**Subject 2**	**Subject 3**
Sex (male/female)	F	M	F
Age (years)	52	57	43
Type of stroke	Ischemic	Ischemic	Ischemic
Affected hemisphere	Right	Left	Left
Affect upper extremity	Left	Right	Right
Time since stroke (months)	18	36	36
MMSE	34	33	31
Mean training days (training I)	26	26	26
Mean training days (training II)	19	18	17

3.2.1 Motor dexterity

In relation to the motor improvements after our IVR training, we observed improvements in motor dexterity, functional ability, muscular strength and the spasticity of the paretic arm. After the first training period, the motor dexterity of the paretic arm improved progressively throughout the training from the baseline I to the post-treatment I periods for all the patients *(**Figure 3.2.1*** **a** (Right)). We consistently observed at during the period of pause that the improvements in motor dexterity remained over time (see ***Figure 3.2.1*** a (Left)).

3.2.2 Functional ability

Regarding to the functional ability of the paretic arm, we observed better results after the first IVR training in the functional ability of the paretic arm, in the velocity to perform each task and slight improvements in muscular strength, assessed by Wolf Motor Functional test

(***Figure 3.2.1*** b, c and d (Left)). We observed how these changes were progressive throughout the training session and remained over time (***Figure 3.2.1*** b, c, d (Right)).

3.2.3 Spasticity of the paretic arm

In terms of spasticity, there was an important decrease in the paretic arm for all three patients (***Figure 3.2.1*** e). Again, we observed a decrease of the spasticity in the weekly assessments during the first IVR training and that this decrease of the spasticity levels remained over time during the period of pause. In addition, we also found a relationship between the improvements in functional ability (r_s=-0.56, p=0,003) and motor dexterity (r_s=-0.63, p<0,0001) of the paretic upper extremity during the first IVR training with the reduction of the spasticity level for all three patients *(see **Figure 3.2.2**)*, which suggests that the lower the level of spasticity, the higher the motor dexterity and functional ability of the paretic arm. Overall, the results obtained in the weekly measures during the first IVR training and during the resting period demonstrate a progressive motor recovery of the paretic arm over time.

3.2.4 Cognitive capability

Regarding to the improvement of the cognitive capability after the IVR training, we observed better results in the Letter Cancellation test only in subject 3. During the periodic assessments we also observed better results in the Letter Cancellation Test only in subject 3, from baseline I to post-treatment I as she was the only one who presented deficits from baseline (***Figure 3.2.3*** A). Furthermore, we also found improvements in working memory capacity from baseline I to the post-treatment I period assessed by the Corsi block-tapping test cubs test (***Figure 3.2.3*** B). These results suggest that through our IVR training, patients could also improve their cognitive capabilities.

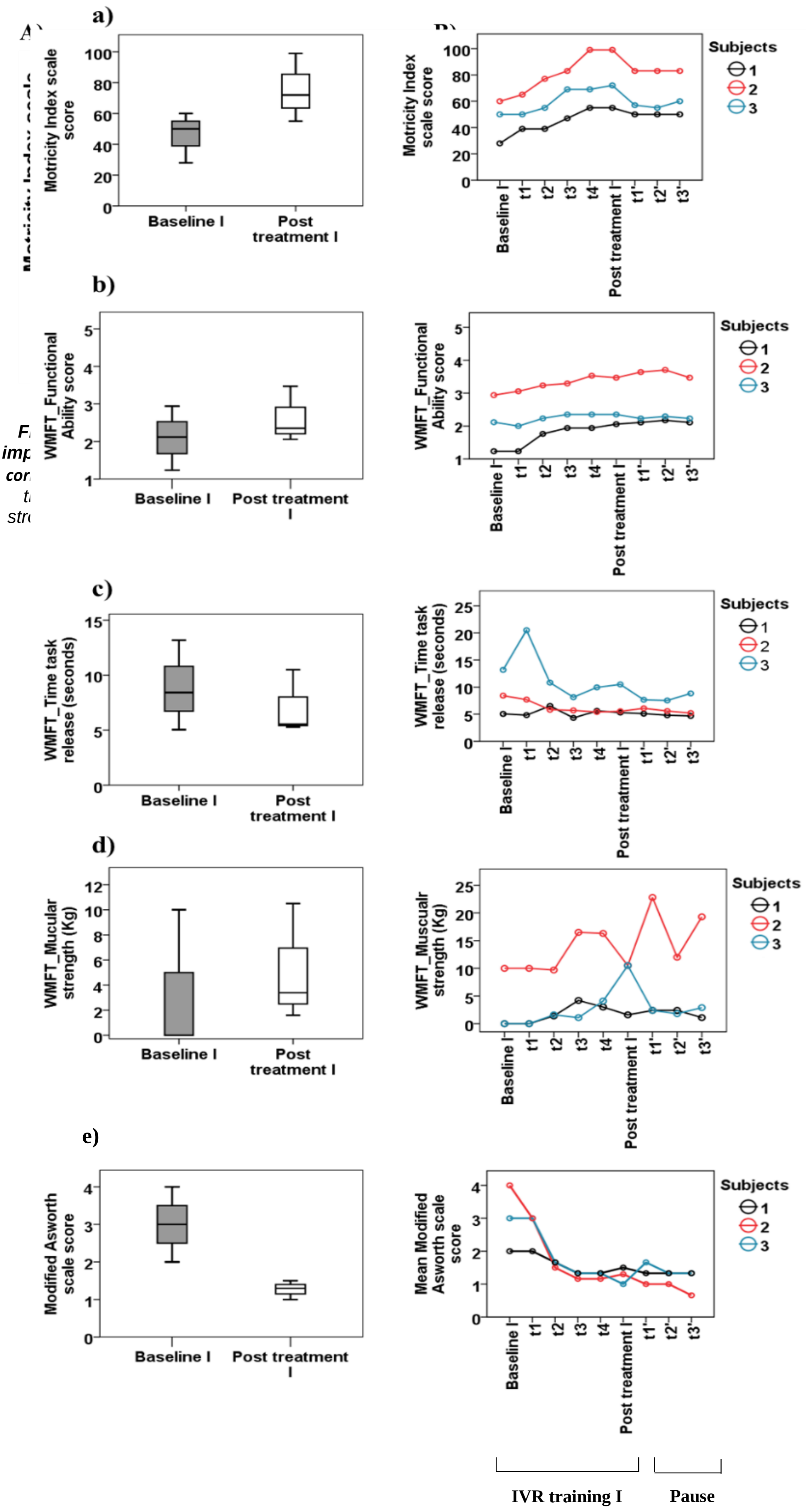


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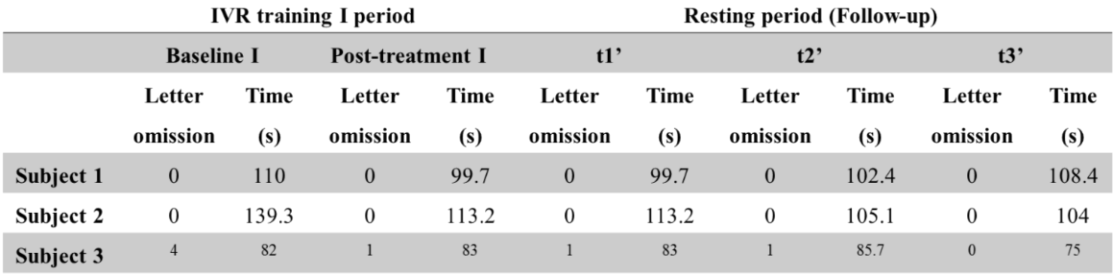
Figure 3.2.1 Motor dexterity, functional ability, time task release of the WMFT, muscular strength and the spasticity level of the paretic arm improves after four weeks of training using immersive virtual reality*.*a (left) *After the first IVR training period, all three chronic stroke patients presented greater motor dexterity of the paretic arm. Boxplots show the medians (horizontal lines), the interquartile ranges (IQR; boxes) and extreme data outside 1.5vIQR (whiskers).* ***a (right)*** *The motor dexterity improvements of the paretic arm remained over time during the resting period (follow-up) in all three chronic stroke patients.* ***b, c, and d (left side)*** *All three chronic stroke patients presented better results for functional ability of the paretic arm, time task release and muscular strength, after the first IVR training assessed by the Wolf Motor Functional test.* ***b, c, and d (right side)*** *Changes obtained after the first training period were maintained over time during the resting period**.** ***e)*** *The level of spasticity of the paretic arm decreases after the first IVR training for all three chronic stroke cases.*

A)



	IVR training I period				Resting period (Follow-up)					
	Baseline I		**Post-treatment I**		**t1'**		**t2'**		**t3'**	
	Letter omission	**Time (s)**	**Letter omission**	**Time (s)**	**Letter omission**	**Time (s)**	**Letter omission**	**Time (s)**	**Letter omission**	**Time (s)**
Subject 1	0	110	0	99.7	0	99.7	0	102.4	0	108.4
Subject 2	0	139.3	0	113.2	0	113.2	0	105.1	0	104
Subject 3	4	82	1	83	1	83	1	85.7	0	75

B)

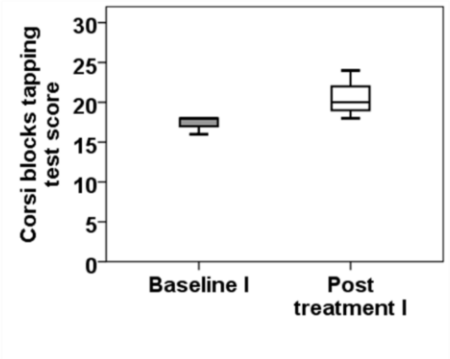


Figure 3.2.3 Cognitive capability enhancement after the first IVR training. A) Letter cancelation test improvements.*Subject 3 presented better results inLetter cancellation task test after the first IVR training and during the resting period.* ***B) Corsi-block tapping test improvements.*** *Working memory capacity improves after the first IVR training assessed by the Corsi block-tapping test for all three chronic stroke patients. Boxplots show the medians (horizontal lines), the interquartile ranges (IQR; boxes) and whiskers represent 1.5 x IQR. t1', t2' and t3' refers to the weekly assessments during the period of pause.*

3.2.5 Activities of daily live and quality of life

Along with the abovementioned motor improvements, we also observed a substantial recovery from baseline I to the post-treatment I time in the performance of daily life activities assessed by Chedocke Arm and Hand Activity Inventory, as well as in quality of life scores in all three stroke patients *(**Figure 3.2.4**)*.

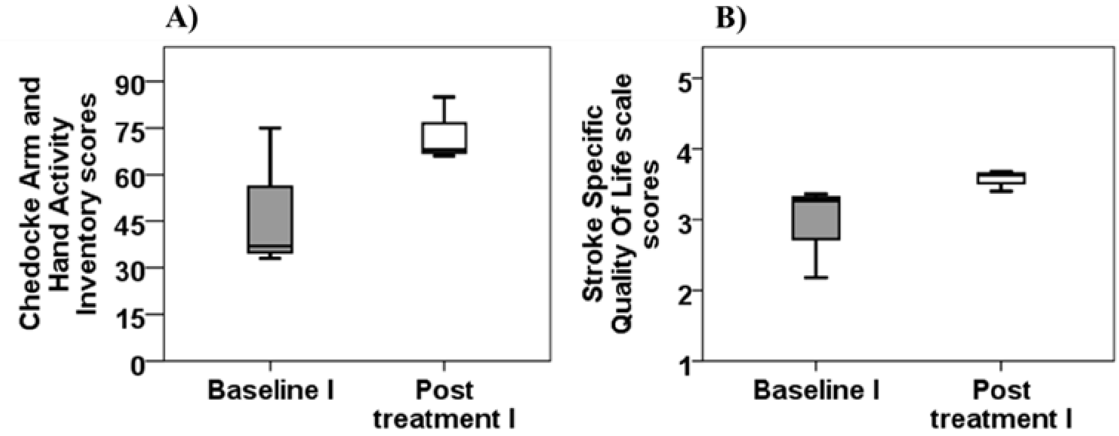


Figure 3.2.4 Performance improvements in daily life activities and quality of life. A) Activities daily live improvements after the first IVR training. *There was a large improvement in the ability to perform daily life activities task from baseline to the post treatment period after the first training period by assessed with Chedocke Arm and Hand Inventory questionnaire.* ***B) Quality of life improvements after the first IVR training.*** *In addition to the improvement in daily life activities task performance, data after the first training period shows higher quality of live scores assessed by the Stroke-Specific Quality of Life questionnaire. Boxplots show the medians (horizontal lines), the interquartile ranges (IQR; boxes) and extreme data outside 1.5vIQR (whiskers).*

We found that motor, cognitive and the quality of live changes obtained after the first IVR training were of a large size over the baseline I to the post-treatment I period for all the measures (Table 3).

Table 3. Percentage of IVR training effectiveness for motor, cognitive and quality of live measures from baseline I to the post-treatment I time and effect sizes after the first IVR training for each measure.

	MI	**WMFT_FA**	**MAS**	**CAHAI**	**SS_QOL**	**CBTT**
Subject 1	38.03%	21.86%	25.00%	60.34%	7.51%	0.00%
Subject 2	100.00%	25.69%	67.50%	62.50%	16.46%	14.29%
Subject 3	44.90%	8.15%	66.67%	53.70%	53.19%	50.00%
Effect sizes	1.79	0.62	-1.73	1.06	0.95	2.90

MI (Motricity Index scale). WMFT_FA (Wolf Motor Functional test, Functional ability subpart). MAS (Modified Asworth Scale). CAHAI (Chedocke Arm and Hand Activity Inventory). SS_QOL (Stroke Specific Quality of Life). CBTT (Corsi Block Tapping test). ***Effect size interpretation:*** *≥ 0.2 small, ≥ 0.5 moderate and ≥ 0.8 large clinical change.*

3.2.6 Brain functional changes

We analysed changes in functional and structural connectivity profiles in three subjects by exploring the connectivity magnitude change (see section 2.6). Functionally speaking, cerebellar areas presented a large rewiring shift in subjects 2 and 3, while the thalamus and the rolandic operculum showed a significant functional change in subject 1 (***Figure 3.2.5***). From a structural point of view, links from the precentral gyrus (primary motor cortex) seemed to have a large connectivity shift after the first IVR training period in all chronic stroke subjects *(**Figure 3.2.5***), pinpointing to a structural rebalance of the motor system.

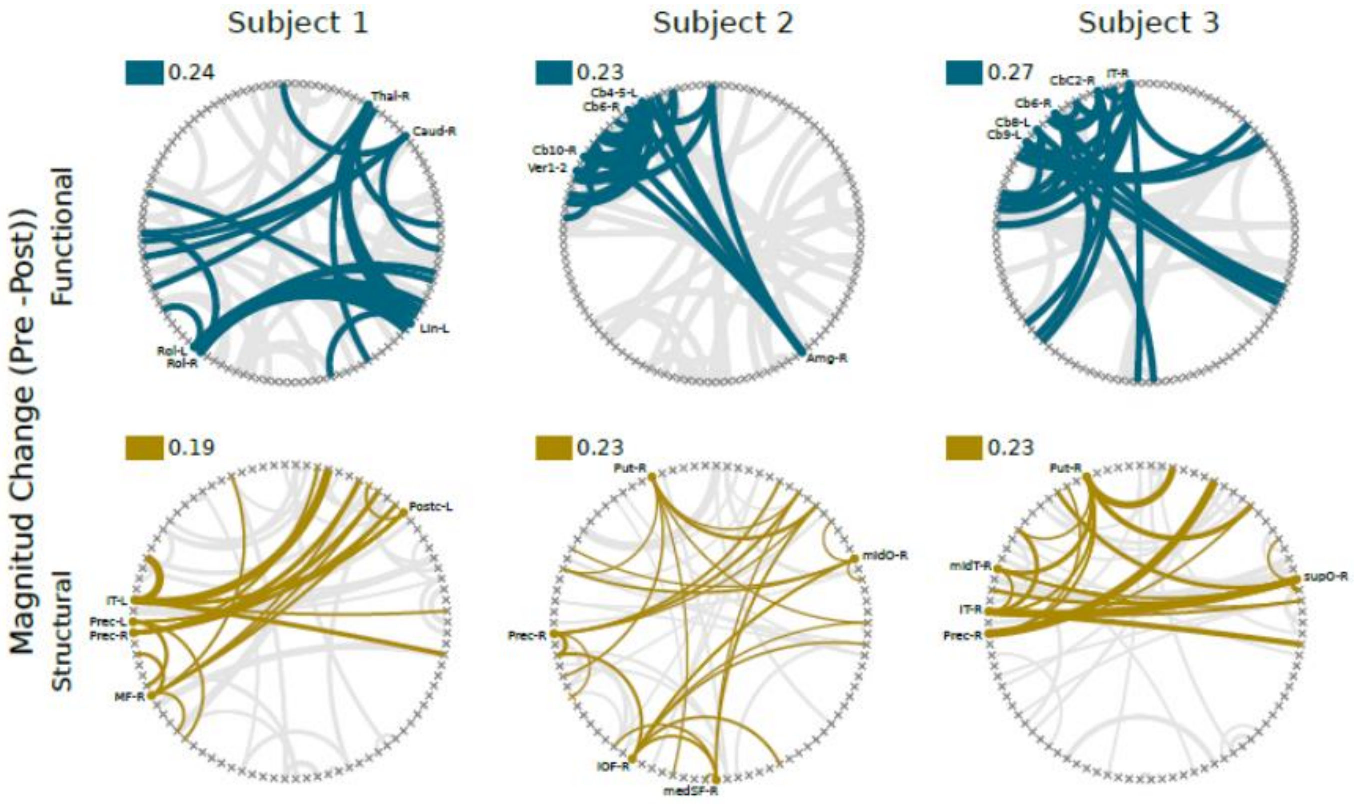


Figure 3.2.5 Large-scale connectivity changes after treatment. *Top row represents functional changes (blue) while structural changes are depicted in the bottom row (yellow). Only links surviving the connectivity threshold (see section 2.6.2.1) are shown, while coloured links represent only those from the top 5 nodes with the largest amount of connections. The number represents the proportion of links found within these top nodes out of the total. Abbreviations used in figure:* ***Rol:*** *rolandic operculum.* ***Thal:*** *thalamus.* ***Caud:*** *caudate nucleus.* ***Cb:*** *cerebellar areas.* ***Ver:*** *Vermis.* ***IT:*** *inferior temporal.* ***MF:*** *middle frontal.* ***Prec:*** *precentral gyrus.* ***Postc:*** *postcentral gyrus.* ***Put:*** *putamen.* ***IOF:*** *inferior orbito frontal.* ***medSF:*** *medial superior frontal.* ***midO:*** *middle occipital.* ***midT:*** *middle temporal.* ***supO:*** *superior occipital (check the attached atlas in appendix B for further reference).*

3.2.7 Second training period

Interestingly, we did not observe changes from the baseline II to the post-treatment II period in the second training period, implying that the additional second training period was not effective in further improving the motor-cognitive capabilities and the quality of life of the chronic stroke patients (Table 4). Subject 1 presented worst scores in LCT in the post treatment II assessment (Tables 5).

Table 4. Summary means and Standard Errors for all measures at baseline II and post treatment II times in the second training period.

	Baseline II	**Post treatment II**
MI	64.33 ± 9.77	64.33 ± 9.77
WMFT_FA	2.60 ± 0.43	2.82 ± 0.57
WMFT_TTR	6.24 ± 1.30	4.56 ± 0.66
WMFT_MS	7.77 ± 5.79	7.20 ± 4.90
MAS	1.11 ± 0.22	1.05 ± 0.39
CAHAI	64.67 ± 8.97	64.67 ± 11.21
SS-QOL	3.81 ± 0.08	3.78 ± 0.10
CBTT	16.00 ± 1.16	21.33 ± 2.40

MI (Motricity Index scale). WMFT_FA (Wolf Motor Functional_Functional Ability). WMFT_TTR (Wolf Motor Functional Test_Time task release). WMFT_MS (Wolf Motor Functional Test_Muscular strength). MAS (Modified Asworth scale). CAHAI (Chedocke Arm and Hand Inventory). SS-QOL (Stroke Specific Quality of Life scale). CBTT (Corsi block tapping test).

Table 5. Summary of Letter Cancellation test at baseline II and post treatment II in the second training period.

	Baseline II		Post treatment II	
	Letter omission	**Time (s)**	**Letter omission**	**Time(s)**
Subject 1	0	108.4	3	143
Subject 2	0	104	0	103.7
Subject 3	0	75	0	67.9

3.2.8 Virtual reality questionnaire and Self-Assessment Manikin scale scores

In the SAM scale patients reported high levels of pleasure (lower scores) in both training periods (***Figure 3.2.6*** A). SAM test is a non-verbal pictorial test that measures the level of pleasure, arousal, and dominance related to the emotional reaction of patients to a stimulus (see **section 2.5.2** and ***Figure 2.5.2***). In our study, we were only interested in the pleasure state of the patients after each IVR session; the lower the score the higher the level of pleasure. In fact, patients scored low during the two training periods (training I and II), showing that patients enjoyed the IVR training sessions. There were no important differences in the pleasure state of the patients between the two training periods.

In the VR experience questionnaire, patients reported high levels (scores of ‘4’ or ‘5’ out of 5) of embodiment and agency (control) over the virtual arm throughout both training periods. Patients also reported high scores on the understanding of the task instructions and the duration of the sessions. We did not find score differences in the VR experience questionnaire between the two training periods (***Figure 3.2.6*** B).

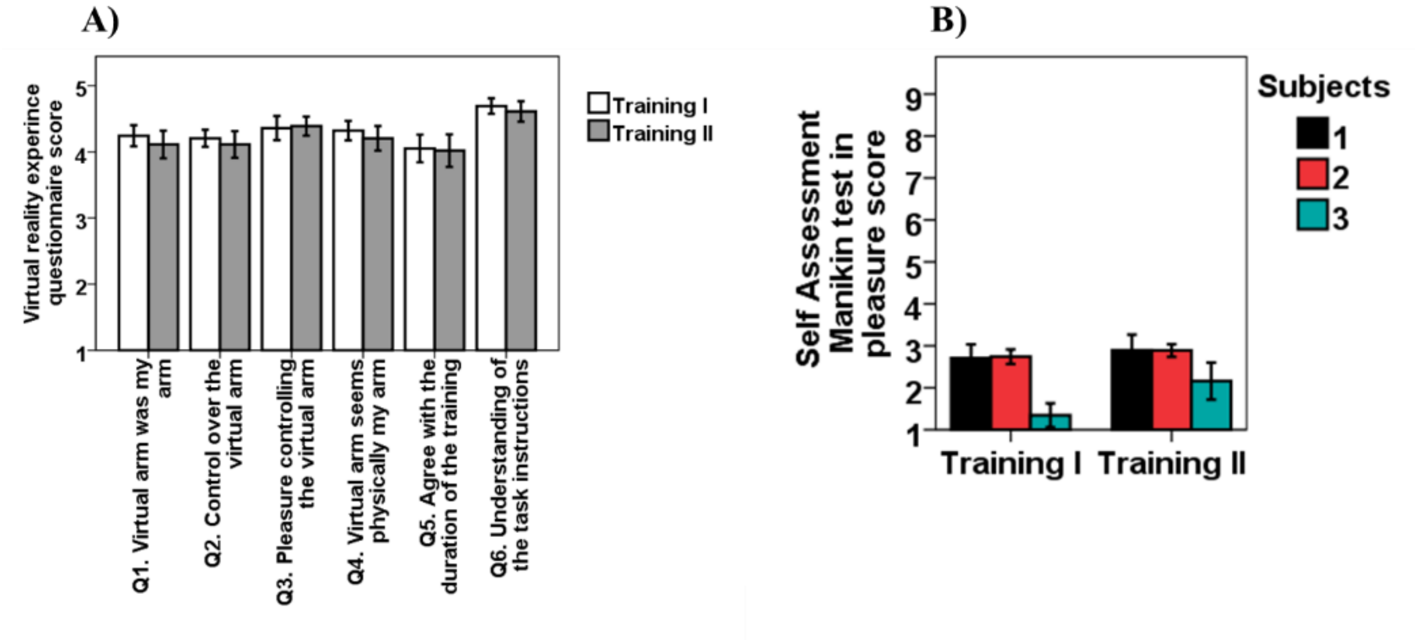


Figure 3.2.6 Virtual reality experience questionnaires and Self-Assessment manikin test scores.A) *After each training session all three chronic stroke patients reported high levels of pleasure state in both training I and II periods, assessed by the Self-Assessment Manikin Scale where the lower scores indicate higher levels of pleasure, in both first and second IVR training periods. No differences in pleasure state levels were observed between both periods.* ***B)*** *All three stroke patients reported high scores for embodiment of the virtual body, sense of agency by controlling the virtual arm movements and understanding of task instructions in both, first and the second training periods. No important differences were found between the training periods. Columns and vertical error bars respectively stand for group means and standard errors.*

3.3 On IVR for chronic pain

Twenty one chronic pain patients with complex regional pain syndrome and peripheral nerve injury were screened to participate in this study. Nineteen patients were finally recruited and grouped in those with peripheral nerve injury (10 patients with PNI) and those without nerve injury (9 patients with CRPS type I) (**see *section 2.2.3***).All of them presented a distorted body representation because of the injury and those in the PNI group presented neuropathic pain because a compression or injury of a nerve. Two amputees' patients were excluded of the sample. Although, amputee patients also present distorted body representations of the phantom limb (Makin et al. 2013), it is known that sensory signs and symptoms after the neuropathic injury are different between pathologies with different aetiologies (Baron et al. 2010; Maier et al. 2010).

We found significant differences (Mann Withney, $p < 0.05$) between groups at baseline in Frontal Assessment Batery test (FAB), which assist in discriminating between dementias with a frontal dysexecutive phenotype and Dementia of Alzheimer's Type (DAT), however the scores obtained from the FAB in both groups indicate a good enough cognitive level to participate in the experiment (score > 12/18). Furthermore no differences were found between groups in the MMSE test, indicating a good enough cognitive level to participate in the study.

There were also differences in age between groups; however this age difference did not affect the perception as all of them are in a relatively narrow range of age between 40 to 55 age years old. All patients had neuropathic chronic pain assessed by the painDETECT scale, as is reasonable patients into the PNI group presented higher neuropathic pain components because of the nerve injury than patients in the CRPS group without nerve injury. No differences between groups in pain ratings at baseline were found (see table 6).

Table 6. Summary of all demographics and means and standard deviations of the screening test and of pain ratings at baseline of IVR in chronic pain study

	CRPS	PNI	p-values
Sex			
Male	2	3	
Female	7	7	
Age (years)	43.77 ± 12.76	51.4 ± 12.52	< 0.0001
MMSE	34.44 ± 1.07	34.6 ± 0.66	0.619
FAB	17.33 ± 0.82	17.5 ± 0.93	0.004
Pain Detect scale	29.85 ± 3.19	37.4 ± 8.30	< 0.0001
Pain ratings at baseline	4.78 ± 2.40	5.30 ± 2.20	0.080

Mini Mental State Examination (MMSE). Frontal Assessment Battery (FAB).

3.3.1 Pain Ratings differences in transparency of the virtual arm test

After the transparency of the virtual arm test in which patients were exposed to four different conditions with the virtual arm transparency set at 0% (max opacity level), 25% (high opacity level), 50% (mid opacity level) or 75% (low opacity level). In CRPS patients increasing the transparency of the virtual arm tended to reduce pain ratings. Although the reported pain ratings did not show significant differences between conditions, in the transparency of the virtual arm condition we found a trend (z= -1.67, p= 0.096) in the CRPS group, which presented lower pain scores when the virtual arm became transparent (75% of transparency). Interestingly, patients in the PNI also reported lower pain ratings when the transparency of the virtual arm was set at 25% (z= -1, 20, p=0, 23) (***Figure 3.3.1*** A).

3.3.2 Pain Ratings differences in distorted virtual arm test

Regarding the distorted virtual arm test, in which patients were exposed to three different conditions with the virtual arm size presented in a big size (X2), normal size and small size (/2), the normal size visualization of the virtual arm, reduces pain ratings in CRPS patients. Pain ratings reported in the distorted virtual arm test showed differences between conditions in the CRPS group. The mixed effects ANOVA showed that CRPS patients reported lower pain rating scores this when “normal” size condition was presented (z=2.26, p= 0.024) compared to the “doubled” or “small” size conditions. Interestingly, no differences in pain ratings between conditions were found in the PNI group (see ***Figure 3.3.1*** B).

As the above mentioned results present, we found an interaction between the independent variable ‘Test’ that contains two different tests: the transparency of the virtual arm test and distorted virtual arm test, with the independent variable ‘Injury Type’, (CRPS and PNI) (Multilevel Mixed-Effects Linear Regression: z= -1.89, p= 0.058). These results justifies the different reactions to the different visual conditions in both tests between CRPS and PNI patients.

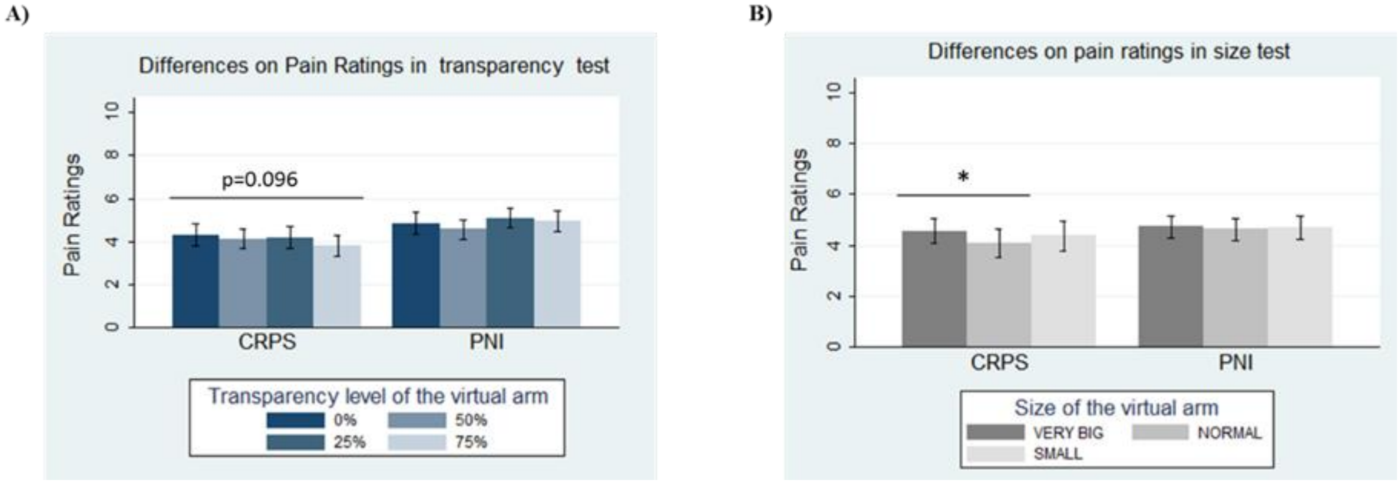


Figure 3.3.1 Pain rating differences between conditions within Complex Regional Pain syndrome (CRPS) and peripheral nerve injury (PNI) patients. *The experiment counts with two different test to see the effects of manipulate the morphological characteristics of the virtual arm on pain perception. One test was the transparency of the virtual arm test and the other was the distorted virtual arm test. The tests were presented in a counterbalanced manner among the patients. Between each test presentation there was 10 minutes of rest.* ***A) Pain rating differences in the transparency of the virtual arm test.*** *Patients in CRPS group reported lower pain ratings when the virtual arm became transparent.* ***B) Pain ratings differences in the distorted virtual arm test.*** *Patients in CRPS group reported lower pain ratings with the normal size of the virtual arm. Columns and vertical error bars respectively stand for group means and standard errors. *p< 0, 05.*

3.3.3 Virtual reality questionnaire responses

To analyse properly the data obtained from the questionnaires we had to remove some outliers as they were indicating false significant differences between CRPS and PNI groups in Q4 and Q7 in the transparency of the virtual arm test and in Q1 and Q8 in the distorted virtual arm test (**see *Figure 3.3.2* A and C to see the graphs with outliers**).

3.3.3.1 Transparency of the virtual arm questionnaire responses

In ownership related questions (Q2: *'virtual body was my own body'* and Q3: *'virtual arm was my arm'*) we observed significant differences between groups showing higher levels of ownership of the virtual body in CRPS group compared to the PNI group (Q2, z=4.25, p< 0.0001 Q3, z= 8.959, p< 0.0001). Even in the sense of agency over the virtual arm, this means the sense of being controlling the virtual arm movements (Q6, z= 4.803, p< 0.0001) CRPS group reported higher scores than patients in the PNI group. There were no differences in the illusion of the virtual body induction question (Q1), regarding to the sense of being touched by the virtual balls (z= 1.169, n.s). To the illusion-perception of the virtual body related questions (Q4 and Q5), drift of the virtual arm question (Q4), did not present differences between groups, presenting high scores for the drift of the virtual arm question in both groups. Nevertheless, in multiple arms question (Q5), CRPS reported a significant higher sensation of having multiple arms compared to the PNI group (z= 5.596, p< 0.0001). Related to the ownership on opacity/transparency of the virtual arm (Q7), patients reported no differences in the ownership of the transparent virtual arm, reporting high levels of ownership in both groups. Interestingly, patients in the CRPS group identified more the transparent virtual arm as their own arm compared with patients in the PNI group (see Q9), showing a significant difference between groups (z= -3.836, p< 0.0001). There was no significant differences between groups in Q8, related to the attention to the virtual arm (z = 0.928, n.s), presenting low scores in both groups (***Figure 3.3.2*** B).

3.3.3.2 Distorted virtual arm questionnaire responses

Regarding to the distorted virtual arm questionnaire responses, CRPS and PNI patients reported high scores in ownership related questions (Q1 and Q3). We did not observe differences between groups related to ownership of the virtual arm (Q1), presenting maximum score in both groups. However in Q3 related to the ownership of the virtual body patients in the CRPS group reported higher scores than those in the PNI group, showing a significant difference between them (z = 5.656, p < 0.0001). Furthermore in Q6, related to the sense of agency over the virtual arm, there was a significant difference between groups (z= 6.201, p< 0.0001), displaying larger scores in CRPS, reporting a higher sense of agency over the virtual arm. Differences between groups were also found in Q4 (‘*virtual balls touching my fingers’*) between groups, where patients in CRPS reported higher scores in the induction of the virtual body illusion (z = 2.858, p= 0.004). To the illusion-perception related questions (Q2:‘*drift of the virtual arm’* and Q5: ‘*having multiple arms*’), we found significant differences between groups. In this sense, curiously CRPS patients also presented higher scores reporting worst illusion-perception of the virtual body (Q2; z = 8.882, p< 0.0001 and Q5; z = 3.540, p= 0.0004). Related to the ownership on doubled/small size of the virtual arm patients from both groups, presented the mean maximum score, which indicates that both identified more the small virtual arm as their own arm compared to the very big virtual arm (Q8). Although there were no differences between groups in Q8, we found significant differences in Q9, where patients in the PNI group reported higher scores for the ownership of the small virtual arm (z = 5.525, p< 0.0001). Finally, regarding the attention to the virtual arm (Q7), patients in the PNI group were able to pay more attention to the virtual arm than those in the CRPS group, presenting significant differences between them (z = -4.609, p< 0.0001) (***Figure 3.3.2*** D).

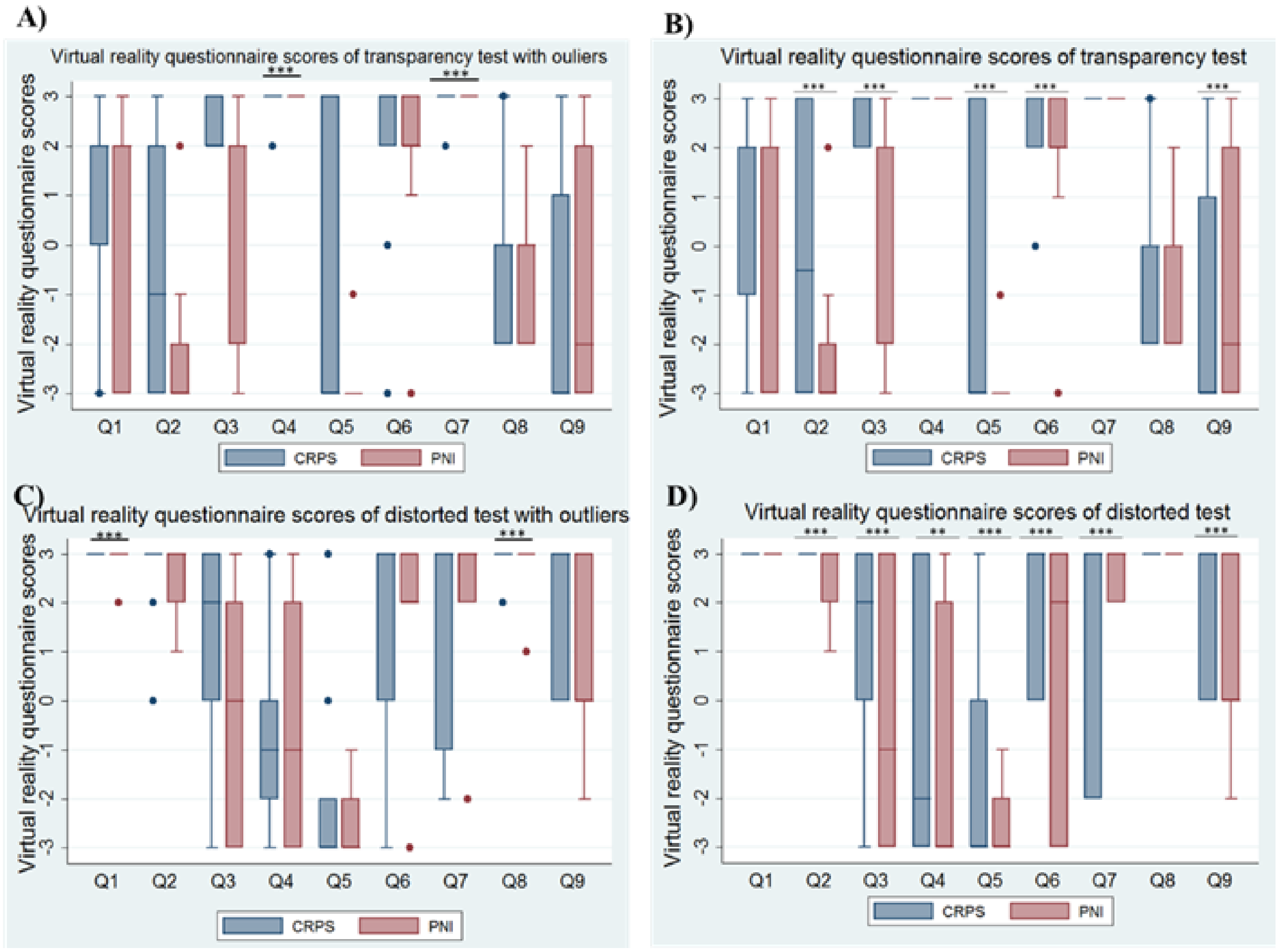


Figure 3.3.2 Virtual reality questionnaire score differences between groups. *In that experiment we tested the effects of the transparency of the virtual arm and the distortion of the virtual arm on pain perception in CRPS and PNI patients. After each test patients had to fill in a questionnaire related to the virtual reality experience.* ***A) Virtual reality questionnaire results of the transparency of the virtual arm test with outliers which were giving false significant differences between groups. B) Virtual reality questionnaire results of the transparency of the virtual arm test without outliers.*** *Patients in the CRPS group reported higher embodiment and agency scores and identified more the virtual arm as their own when it became transparent. Curiously, CRP patients reported worst illusion perception of their virtual body. Q1: virtual balls touching my fingers, Q2: virtual body was my own body, Q3: virtual arm was my arm, Q4: drift of the virtual arm, Q5: having multiple arms, Q6: agency over the virtual arm, Q7: ownership of the opaque/transparent virtual arm, Q8: attention to the virtual arm, Q9: ownership of the transparent virtual arm.* ***C) Virtual reality questionnaire results of the distorted virtual arm test with outliers which were giving false significant differences between groups. D) Virtual reality questionnaire results of the distorted virtual arm test without outliers.*** *Again, patients in the CRPS group reported higher embodiment and agency scores and identified more the virtual arm as their own when it became transparent, reporting worst illusion perception of their virtual body. Q1: ownership of the virtual arm, Q2: drift of the virtual arm, Q3: ownership of the virtual body, Q4: virtual balls touching my fingers, Q5: having multiple arms, Q6: agency over the virtual arm, Q7: attention to the virtual arm, Q8: ownership of the big/small virtual arm, Q9: ownership of the small virtual arm. Boxplots show the medians (horizontal lines), the interquartile ranges (IQR; boxes) and whiskers represent 1.5 x IQR. If there are values outside the whiskers these are conventionally called "outliers", and are shown by (◦).*

Chapter 4

The aim of argument, or of discussion, should not be victory, but progress.

Joseph Joubert.

Discussion

The common theme of this Thesis has been to thoroughly explore the potential of immersive virtual reality and embodiment of a virtual body as a tool for motor rehabilitation and pain relieve as well as the underlying brain mechanisms to these processes. A separate discussion for each one of these topics follows.

4.1 On IVR in orthopaedic rehabilitation

To our knowledge, this study is the first to investigate the effects of immersive virtual reality training on upper limb rehabilitation during the immobilization period in patients with distal radius fracture. Our main finding is that IVR training combining motor imagery through action planning and action observation significantly improves the functional ability of the fractured arm during the immobilization period and accelerates the rehabilitation process in patients with distal radius fracture compared with Non-IVR (active control) and CDM training. Remarkably, functional recovery was highly correlated with the feeling of owning and agency (sense of controlling) the virtual arm, hence emphasizing the potential of immersion in virtual reality techniques. Consistent with these findings, IVR training decreased the percentage of disability of the fractured arm after cast removal (T1) and six weeks later (T2) compared with CDM training; improved range of motion, especially in wrist flexion-extension movements, after cast removal compared with CDM training; and women in the IVR group obtained better results in lateral pinch strength than those in the CDM training group. Finally, we observed a non-significant trend towards lower pain ratings in patients that underwent IVR and Non-IVR training compared with those that did the CDM training. Even though this study was carried out in patients with distal radius fracture, the results obtained here highlight the potential of IVR training based on action planning and action observation for improving the motor functional ability and for accelerating the rehabilitation process of patients not only with fractures but also with other motor disabilities.

4.1.1 Mental training by IVR attenuates functional impairments

The finding that mental training by means of IVR from a first-person perspective attenuates physical and functional impairments in the upper limb after the immobilization period to a greater extent than did Non-IVR or the usual CDM training may be explained by at least two factors: first, by the repeated activation of the neural networks involved in motor action through action planning and action observation after the structural plastic changes occurring in the brain during immobilization periods; and second, by the visualization of the virtual arm movements being embodied in a virtual body leading to local changes of the affected arm by inducing micro-contractions of the muscles of the arm through which there is an increasing vasodilatation of the affected arm skeletal muscles (Brown et al. 2013; Ishii et al. 2013). The first factor involves that after a short period of immobilization, which leads to a reduction of motor output and sensory input, structural plastic changes in the brain result in a decrease in cortical thickness in contralateral sensory and motor areas in humans (Langer et al. 2012) and in motor representation in the contralateral motor cortex in animals (Lotze et al. 1999). Similar to the *use it or lose it* usually applied to muscles, an active brain will take longer to decay. Indeed, studies employing mental training techniques to avoid the suppression of sensorimotor functioning during the immobilization period have shown that mental practice and the preparation of movements share common neural mechanisms and are functionally equivalent (Jeannerod 1994). It is therefore not surprising that activating the brain regions by imagining or by observing movement strengthens in turn the motor (action) representation in the cortex, hence preventing the structural plastic changes that weaken this network, although some controversy exists (see next paragraph). In other words, mental training techniques can attenuate brain plastic changes during immobilization periods. In our case, we presumably activated this neural network not only by action planning or by action observation (e.g. through a mirror) but by combining both, such that when patients that did the IVR training mentally planned the movement with their fractured arm they also saw the virtual one doing so consequently potentiating the activation of the “action observation” neural network.

As mentioned above, there is still some controversy and ongoing debate about the common neural substrate underlying action observation and motor imagery (Jeannerod 2001a), and how these mental training techniques can prevent corticomotor depression during limb immobilization. For instance, Bassolino and colleagues (Bassolino et al. 2014) investigated the excitability of the left motor cortex in normal subjects immediately before and after ten hours of right arm immobilization by doing motor imagery or action observation during the immobilization. The authors found cortical plasticity changes in the left motor cortex due to visuomotor mechanisms link with action observation and action execution, but not with motor imagery. This could be explained since they did not use explicit motor imagery allowing the patients to mentally plan the action. In our study, explicit motor planning was integrated in the IVR training by describing the action through the headphones before starting each exercise and consequently linking mental practice to the planning processes that form the interface between higher level 'cognitive-executive functions', and lower level motor processes. It has been notice the importance of clear verbal instructions to planning the movements in mental trainings by motor imagery in order to create the appropriate representation of the action (Scott H Johnson et al. 2002).

4.1.2 Being embodied in a virtual body is correlated with functional recovery

In addition to delaying corticomotor depression through motor imagery and action observation, the second factor that can further explain the benefits of IVR and that can additionally justify the difference between IVR and Non-IVR training involves ownership and agency illusions induced by immersing participants in a virtual reality environment. In fact, we found that functional recovery of patients that did the IVR training was highly correlated with the scores about the virtual reality experience, demonstrating that patients in the IVR group had a stronger feeling of being embodied in a virtual body with a higher sense of control over the virtual arm movements presenting better functional motor recovery of the arm. We can speculate that this could be due to the fact that our rehabilitation system based on IVR includes the internalization (and ownership) of whole bodies. Nowadays, most current virtual rehabilitation systems do not integrate virtual environments (Mirelman et al. 2016; G Saposnik et al. 2016) or they present isolated virtual representations only of the tracked hands while interacting with the virtual environment (Cameirão et al. 2012). On the other hand, motor sense of agency in the voluntary control of body movement can influence body awareness by integrating distinct body parts into a coherent awareness of the body (Tsakiris & Haggard 2005). We want to point out that patients in the IVR group had to activate the virtual arm, and being able to control the start of the virtual arm movement in each exercise could have led to an increased sense of agency over the virtual arm, therefore allowing the patients to be not mere spectators but to become active actors (mentally and physically present) within the virtual environment.

4.1.3 Decreased percentage of disability and improved range of motion after IVR training

Consistent with the findings commented before, patients in the IVR training significantly decreased the percentage of disability, as measured by the DASH questionnaire, of the fractured arm after the cast removal (T1) compared with the CDM training group and again at T2. These findings suggest that patients in the IVR training were able to perform more activities of daily life at home after the cast removal and this result stayed consistent over time (T2). Moreover, improvements in Range of Motion (ROM), especially in wrist flexion-extension movements at T1 in patients of the IVR training group compared to the CDM training group were found. Interestingly our results suggest that the more the patients visualized a movement the higher the difference in range of motion degrees between CDM and IVR training group were. Moreover, patients in IVR and Non-IVR training group showed better results in muscular strength force than patients of the CDM training group, but we only observe significant differences between IVR and CDM training group in females for the lateral pinch measure.

However, although not to the same extent as IVR training, patients that did action observation training alone in the Non-IVR group also presented better results than those in the CDM training group, indicating that during an immobilization period mental training techniques positively influence the recovery of the fractured arm. More specifically, Non-IVR training improved disability, some range of motion movements and muscle strength with respect to CDM training. This is congruent with other studies showing similar results albeit using other techniques without (immersive or non-immersive) virtual reality such as motor imagery or mirrors (Clark et al. 2014; Roll et al. 2012), once again highlighting the plausible implication of a common neural network for motor imagery, action observation and action execution.

4.1.4 Movement visual feedback decreases pain ratings in IVR and Non-IVR groups

Moreover, pain ratings were lower (albeit not significantly) in the IVR and Non-IVR groups than in the CDM group, this result is coherent with others that demonstrated the influence of movement visualization or even the mere visualization of the virtual arm at the same position of the affected arm have an influence reducing pain ratings (Nierula et al. 2017; Llobera et al. 2013a; Ramachandran et al. 2009).

The present study has some limitations. First, there was no balance between male and females among the training groups and, furthermore, there were no males in the IVR group; however, there is evidence that justifies a large number of females with distal radius fracture compared to males with a ratio of about 3:1 (Bentohami et al. 2014) and, as we did a randomized study, we could not control how many males and females were participating in each group. Another limitation is that we did not control the amount of digit mobilization in the CDM group; nevertheless, this is the normal procedure after distal radius fracture where patients follow the physician's directions. As one of our interests in this study was to compare our IVR training with the conventional procedure, we did not count the number of times that patients in either group mobilized their hand and fingers at home. Finally, the therapist who carried out the IVR and Non-IVR trainings and who conducted all the assessments was not blind to the groups, which we should consider in future studies in order to have a double-blind design; however, patients did not know about the existence of other training groups to avoid subjectively influencing the recovery of the fractured arm.

In conclusion, being immersed in a virtual body and being able to control the movements of a virtual arm that is co-located with the real arm improves the functional ability recovery of the fractured arm. Based on our results, we can hypothesize that the motor and functional improvements observed in the fractured arm such as; improvements in functional ability, wrist flexion-extension range of motion, lateral pinch muscular strength, may be due to a reorganization of the cerebral cortex related to the affected limb, which probably occurred by combining action planning, action observation, as well as ownership and agency illusions induced by immersion in a virtual reality environment. Overall, the results of this study suggest that IVR can be used as a rehabilitation tool to speed up and improve the motor functional recovery of the fractured arm after the immobilization period, and to relearn motor skills in patients without movement in their upper or lower limbs due to fractures or to other motor disabilities.

4.2 On IVR in chronic stroke rehabilitation

In this pilot study, we conducted a systematic evaluation of the across session changes in the motor dexterity of the paretic arm, cognitive capabilities and quality of life in chronic stroke patients. We hypothesized that motor, cognitive and quality of life measures would improve due to motor learning processes occurring through a mental training based on motor imagery/action planning and action observation from a first-person perspective through IVR. Although we observed that the motor-cognitive improvements obtained after the first training period remained over time, our results indicate that a second training period with the same IVR training program after a period of pause was not effective in further improving the motor-cognitive state of chronic stroke patients. Furthermore, subject one presented worst results in Letter Cancellation Test at the post-treatment assessment II.

4.2.1 Functional recovery of the paretic arm after the first IVR training

In particular, our results show that after the first training period, all three chronic stroke patients presented a large motor recovery of the paretic arm, showing better motor dexterity, functional ability and muscular strength of the paretic arm performing the tasks of the wolf motor functional test faster and lower spasticity levels of the paretic arm. This is in line with the fact that rehabilitation approaches using high technology, such as IVR, allow the integration of the principles of motor control and motor learning involving relevant multimodal sensory feedback and cognitive processes (Mindy F. Levin et al. 2015). IVR allows manipulating the trajectory, smoothness, speed and precision of the virtual arm movements, therefore providing feedback to the patients of well-studied movement patterns. This is relevant since some evidence supports that movements are correctly executed when the hand trajectory is characterized by spatiotemporal smoothness and an adequate speed and precision (Fitts, 1954; Latash, 2012). In addition, evidence demonstrate that when we visualize a normal movement that is correctly executed, this multisensory processing of relevant proprioceptive, sensory and visual information is processed in the parietal lobe (Botvinick & Cohen, 1998a), contributing to perception of the movement and then linked to action execution. In addition to these findings, our results suggest that through visual feedback of the virtual arm movement seen from a first-person perspective while being embodied in a virtual body we can normalize movement pattern of the paretic arm leading to an improvement of motor dexterity and functional ability of the paretic arm, reducing the time in the wolf motor functional test task performance and improving the muscular strength of the paretic arm.

Another important result of our research the clear decrease of the spasticity of the paretic arm in all three patients. Spasticity is a sensory-motor control disorder resulting from the upper motor neuron system and is one of the most common post-stroke conditions that survivors face during their recovery, having a significant impact on their life (Zorowitz et al. 2013). After a stroke, the equilibrium of cortical excitability between the two hemispheres changes, leading to an inter-hemispheric competition (Cicinelli et al. 2003; Murase et al. 2004). While there is a decrease of cortical excitability and decreased representation of the affected muscles in the affected hemisphere, there is hyperexcitability in the unaffected hemisphere (Traversa et al. 1998; Manganotti et al. 2002). This hyperexcitability in the unaffected hemisphere leads to an abnormally high inter-hemispheric inhibition from the unaffected to the affected hemisphere, resulting in motor and muscle impairment. In fact, secondary to the cortical disinhibition after stroke, there is an imbalance between descending inhibitory and facilitatory regulation of spinal stretch reflexes (Li & Francisco 2015). Based on this evidence, we can speculate that by inducing the normalization of the movement pattern of the paretic arm with visual feedback through our IVR program we can also induce a normalization of the inter-hemispheric connection balance. Interestingly, our results (***Figure 3.2.1*** e) are in line with other studies where, by rebalancing the cortical excitability between the two hemispheres, the authors also found a decrease in spasticity (Sakamoto et al. 2014; Braun et al. 2016) and motor dexterity recovery of the paretic arm (Nowak et al. 2009), thus improving the quality of life of the stroke patients (Lin et al. 2009). Therefore, the reduction in spasticity of the paretic arm that we found here is possibly due to a rebalancing in cortical excitability achieved by motor-cognitive training through IVR.

4.2.2 Cognitive improvement after the first IVR training

In addition to motor recovery, our IVR training also successfully improved cognitive capabilities in all three chronic stroke patients, except for subject one after the second training period who presented a worst ability to letter cancelation task. However, all three patients improved their working memory capacity, especially after the first IVR training period. For a long time, motor cognitive techniques such as motor imagery, action observation and action planning have been investigated as a mental practice, which facilitate motor performance by allowing patients to rehearse the cognitive components of a task, such as action planning (Sackett 1934). According to these techniques, we speculate that the action planning task during our IVR training, preceded to the verbal task instructions describing the movement to be done through the headphones, plays a key role in the improvement of the working memory capacity. In fact, action planning is considered an executive function, and it has recently been investigated the link between working memory and executive functions suggesting that action planning and working memory share a common underlying attentional ability called 'executive attention' (McCabe et al. 2010). Furthermore, some functional magnetic resonance imaging (fMRI) studies suggest that working memory and executive functions recruit the same prefrontal cortical areas (Osaka et al. 2003), although others believe that they are disparate functions (Blair et al. 2005; Fletcher 1996; Pennington et al. 1996). Our results nonetheless support a link between working memory and executive function (Blair 2006; Duncan et al. 1996; Shallice & Burgess 1993; Engle & Kane 2003), suggesting that through our IVR training we can enhance cognitive capabilities, especially working memory capacity, by stimulating executive functions such as action planning.

4.2.3 Improvements in performance of daily live activities and quality of life after the first IVR training

Related to motor and cognitive improvements obtained after the first training period, all three chronic stroke patients presented better ability in performing activities of daily live (e.g. open a jar of coffee) and higher quality of life after the first training period compared to the baseline I. This results are in line with Kim et al. (2014) who found that the activities of daily living of chronic stroke patients are highly correlated with quality of life. Others also found a relationship in improvements of QOL with a decrease of the spasticity levels in stroke patients (Bergfeldt et al. 2015), with motor improvements after a period of robotic-assisted therapy (Kutner et al. 2010). Furthermore, Mitchell et al. (2010) observed that quality of life in people with neurological disorders, is highly influenced by specific cognitive deficits such an inattention, dysexecutive function and processing speed. Hence, according with these findings our results show that as patients improved their motor and cognitive capacities throughout the first training period, they also improved their ability to perform activities of daily live and quality of life.

4.2.4 Brain activity changes associated with IVR training

In line with the above mentioned motor, cognitive and quality of live improvements after the first IVR training, neuroplastic changes were also found after the first IVR in all three chronic stroke patients. Specifically, we observed functional connectivity changes in cerebellar areas in subjects 2 and 3, and in thalamus and the rolandic operculum in subject 1 ***(Figure 3.2.5)***. This is interesting given the fact that these areas have been linked with the cognitive control of movement via the cerebellar-thalamus pathways (Prevosto & Sommer 2013). Concerning to our findings, the thalamus is an important component of the motor system (Shirer et al. 2012) that some studies in both primates (Canavan et al. 1989) and humans (Lee & Marsden 1994) have shown to be important for motor learning and motor execution. Even more, in the field of motor recovery, it has been shown that increases in ipsilesional thalamic activation are correlated with better motor performance in chronic stroke patients after treadmill training (Enzinger et al. 2009). In addition, other studies have been found abnormalities in resting state functional connectivity in the thalamus and this abnormalities correlated with poor motor outcomes in stroke patients (Park et al. 2011; Wang et al. 2010). Remarkably, our findings regarding to subject 1 are in line with Enzinger et al, (2009), as we also found higher resting state functional connectivity activations in the ipislesional thalamus after the IVR training. Moreover the functional connectivity activations in the rolandic operculum has been also involved in sensorimotor control during phonological processing (Vigneau et al. 2006) and sensoryomotor processing (Ciccarelli et al. 2005). In accordance with these findings, we can argue that motor improvements after the post-treatment I in subjects 1 could be due to the functional connectivity changes observed in the thalamus and rolandic operculum.

On the other hand, from an neuroanatomical point of view, it is well known, that only a subset of neurons in the motor thalamus are concerned to motor actions, while others are related to the cognitive-related inputs to elaborate movement planning and execution (Prevosto & Sommer 2013). This functional distinction is also found in the cerebellum and basal ganglia, which are also implicated in more higher level aspects of the movements, and both are connected with the thalamus (Middleton & Strick 1994; Aglioti 1997; Haber & Calzavara 2009). In addition to the fact that the thalamus is not only associated with specific motor aspects of the movements Schlag-Rey & Schlag. (1984) , introduced the central controller hypothesis, which referred to the effect of visuo-motor feedback in central thalamus activation in monkeys. Furthermore, more recently Werf et al. (2002), demonstrated that activity modulations in central thalamic regions are highly related with cognitive processing functions such as working memory. In this regard, it has been shown the influence of working memory properties in motor preparation and motor execution in both humans and primates (Boyd & Winstein 2004; Constantinidis & Procyk 2004). Interestingly, in our pilot study all three subjects presented higher scores in the corsi-block tapping test, which assess working memory capability, at post-treatment I assessment compared to the baseline I assessment (see ***Figure 3.2.3).***

Similar findings concerning to the cognitive aspects of the movement control such as motor planning, motor learning, and the correction of inaccurate movements have been observed in the cerebellum (Mier & Petersen 2002). In fact, the cerebellum is one important component in motor control, and is known to influence cortical activity via the cerebello-thalamo-cortical circuits (Affifi & Bergman 1998; Horne & Butler 1995; M. M. Lewis et al. 2007; Palesi et al. 2015). Moreover, some studies shown the relationship between the thalamus and the cerebellum where the thalamus mediate the influence of the cerebellum in cognitive aspects of motor control (Prevosto & Sommer 2013). Interestingly, some investigations argued that increasing activations in the cerebellum, thalamus and putamen are related to an automatization of the motor tasks that characterize the controlled processing stage in motor learning (Lacourse & Turner 2004). In this sense, the large rewiring shift observed in the cerebellar areas in subject 1 and 2 after the first IVR training could lead to better motor control after the first IVR training. Even more, according to Lacourse and Turner. (2014), these functional connectivity changes in the thalamus and cerebellar areas could indicate the integration of the trained motor skills during the IVR training. This could be an explanation of the no motor-cognitive improvements after the second IVR training due to the patients have already previously integrated the trained motor skills during the first IVR training. Hence, during the second training were not learning nothing new (**see section 4.2.4 to further details**).

From a structural point of view, our results suggest that after the first IVR training the hemispheric activation balance shifts towards the affected hemisphere, presenting a large connectivity shift to the affected hemisphere, specifically in the precentral gyrus (primary motor cortex) for all three patients. This finding, is in line with previous studies showing a similar shift during the recovery phase in acute ischemic stroke patients (Askim et al. 2009) and after arm tracking training in chronic stroke patients (Lojovich 2004). Hence, in agreement with other studies aimed to investigate the effects of the mirror therapy in chronic stroke patients (Michielsen & Selles 2011a; Michielsen & Selles 2011b; Bhasin et al. 2012a; Saleh et al. 2017; Saleh & Adamovich 2014), in our pilot study we observed that a four weeks period of IVR training, caused a shift in activation balance M1 towards the affected hemisphere, suggesting neural reorganization. However, as we did not measure cortical activation at the resting period, we do not know whether these cortical changes persisted.

Overall, our results suggest that all three chronic stroke patients presented functional and structural changes in cortical areas related to motor planning and motor execution, within a cerebellum-thalamus-cortical loop, leading to the observed motor improvements in all three chronic stroke patients after the first IVR training.

4.2.4 No motor-cognitive improvements after the second IVR training

Interestingly, we did not observe significant changes during the second training period. One explanation of this could be that patients repeated the same exercises without variability after the resting period. In fact, introducing task variability in the motor acquisition sessions improves performance in the retention phase, this is when patients are learning or re-learning movement patterns (Shea & Kohl 1991; Kantak et al. 2010). Another explanation to we did not found changes during the second training period could be that in our pilot study patients were having IVR training every day from Monday to Friday. In addition to this speculation, one study with chronic stroke patients compared the effects of massed practice of a task with random practice in motor retention learning, and the authors found that those patients who learned with random practice showed superior retention of the trained movements (Hanlon 1996). During our IVR training, patients practiced new exercises every week, so one reason for having changes during the first training period but not during the second one could be that during the first training patients were considering each exercise as a problem to be solved, whereas in the second training they already knew the solution. This is in agreement with cortical changes likely occurring only with learning of new skills and not just with task repetition (Plautz et al. 2000). In contrast to these findings, Schmidt et al. (1988) proposed that one of the fundamental principles in motor learning and in the degree of performance improvement is the amount of practice. Nevertheless, more recent reports propose that motor learning can be accomplished in a number of ways that are more effective than massive practice of a specific task (Winstein et al. 2003). Similarly, introducing frequent and longer rest periods between repetitions improve performance and motor learning as well (Shea & Kohl 1991). This could justify that all three chronic patients maintained the improvements obtained after the first training period during the period of pause. Based on this, we should consider adding a day of rest between sessions to enhance the retention of the motor training instead of doing training sessions every day, and possibly also avoiding a second training session altogether, at least shortly after the first training session. This finding could be helpful to design better training paradigms for improving the efficiency of motor training in the context of neurorehabilitation in chronic stroke patients.

4.2.5 Enhancing motivation of chronic stroke patients by being embodied in a virtual body

Finally, patients reported high levels of ownership and agency over the virtual body as well as in the understanding of the task instructions meaning that through our IVR training patients can really fell that they are embodied in a new virtual body which is able to perform perfect movements. Even more, all three chronic stroke patients reported high levels of pleasure after the training sessions suggesting that IVR trainings are engaging and motivating for this population.

There are several limitations to this pilot study. Mostly, due to the small sample size, these results may not be generalizable to the greater population of stroke survivors; however, our findings are consistent and our IVR training shows great potential. Furthermore, there was no control group to compare the improvements with conventional rehabilitation. Further randomized controlled trials are needed to assess the efficacy of our IVR rehabilitation program in improving the upper limb motor dexterity, cognitive capabilities and quality of life in chronic stroke patients.

In overall, this pilot study suggests that neurorehabilitation training based on action planning with action observation feedback seen from a first-person perspective while being embodied in a virtual body can be a powerful motor-cognitive approach to rehabilitate chronic stroke patients while they are in a “plateau phase”. Most importantly, our IVR program improved the patients’ quality of life by increasing their motor dexterity, reducing the spasticity of the paretic arm, and enhancing their cognitive capabilities. We also suggest that a key point of the program may be the action planning that precedes the observation of the virtual arm movement from a first-person perspective experienced through immersive virtual reality. Such an approach could be a promising tool to improve the functionality of the paretic arm when the patients are in a chronic phase and the conventional rehabilitation sessions are over. Further clinical studies with our rehabilitation program based on IVR system as a clinical tool are warranted to verify our findings

4.3 On IVR in chronic pain

This study aimed to determine whether new visual mechanisms are able to modulate pain perception in healthy subjects by testing the effect of changing the virtual body visibility by making the avatar's body progressively more transparent and by distorting the virtual arm size, in chronic pain patients. Although, our group had previously tested the transparency of the virtual body was tested before in a healthy population (Martini et al. 2015), to our knowledge this is the first study addressed to investigate this effect in neuropathic chronic pain patients. Furthermore, even though the distorted visual feedback of the arm was studied in clinical population, this is the first time it is tested with patients in immersed in virtual reality. Since, CRPS is a complex syndrome, as it encompasses psychological, physiological and plastic changes in the central nervous system; we wanted to compare how the level of transparency and different sizes of the virtual body visibility changes pain ratings in CRPS type I patients comparing the results with PNI patients.

The results obtained from our study suggest that increasing the transparency of the virtual body (75% of transparency) we can reduce pain ratings in CRPS type I patients. Curiously, this effect does not occur in PNI patients. On the other hand, the presentation of a normal size of the virtual body significantly reduces pain ratings, while very large and small sizes of the virtual body increase pain ratings in CRPS type I patients. Once again, this is not happening in PNI patients where the different sizes of the virtual arm presentation do not influence pain ratings. Furthermore, the results in our study also present differences between CRPS type I and PNI patients regarding the sense of ownership and agency over the virtual body showing higher levels of ownership and agency in CRPS patients. Accordingly with other studies (Gierthmühlen et al. 2012; Baron 2006), our results suggest that the processing of pain is different for CRPS type I and PNI patients.

4.3.1 Transparency of the virtual arm reduces pain ratings in CRPS type I patients

The transparency of the virtual arm reduces pain ratings in CRPS type I. One interpretation is that the reduction of pain ratings with the transparency of the virtual body could be due to the disturbances of body representation in the central nervous system in CRPS patients (Birklein & Schlereth 2015). In fact, Galer and Jensen (1999) had previously suggested that for CRPS patients these disturbances of body representations are similar to those seen in neurological neglect, where patients described feeling the limb as if it were not part of their body. Furthermore, some studies support parietal dysfunction in CRPS patients (Kolb et al. 2012; Cohen et al. 2013), affecting visuospatial perception by altering the ability of hand laterality recognition (G. L. Moseley 2004). One reason of this 'neglect as symptom' in CRPS is that unilateral CRPS induces a somatosensory imbalance in the contralateral hemisphere to the affected limb, by providing 'exaggerated' pain input from the affected side, hence distorting visuospatial perception (Sumitani et al. 2007). This 'exaggerated' pain input also leads CRPS patients to experience a 'protective disuse' of the affected limb to avoid pain leading to a neglect of the affected limb (Galer et al. 2001). Moreover, some investigations suggest that the pain input could be activated by a distorted representation of the affected body part in the brain and that the chronic pain experience, such as triggered by bottom-up or top-down nociceptive inputs, maintains the local cortical representation of the affected limb, disrupting inter-regional connectivity in amputees (Makin et al. 2013). Magnetoencephalography research has revealed that in CRPS patients the representation of the affected limb in the primary somatosensory cortex is rearranged comparably with a phantom limb pain (Maihöfner et al., 2004). In addition to these investigations, our results suggest that as in the real world CRPS type I patients use to neglect their affected body part in the virtual world to avoid pain sensation, because of the distorted mental representation of the affected limb which activates pain, reporting lower ratings of pain when we increase the level of transparency of the virtual arm (75% of transparency), in the transparency of the virtual arm test (see ***Figure 3.3.1*** A). Our findings are in line with the results obtained in a study with amputees where they observed that those amputee patients with a telescopic distortion of the affected limb did not experience pain relief with the mirror training performance compared to the amputees without telescopic distortion of the affected limb (whom experienced pain relief after the mirror training) (Foell et al. 2014). Telescopic distortion is described as the feeling that the phantom limb is inside the stump in a bad position (Giummarra et al. 2007). Interestingly in a previous study in our group using a similar setting it was found that in healthy individuals, arm transparency increased pain threshold, an effect that was associated to the degree of ownership over the transparent arm (Martini et al 2015). However, the fact that the same arm transparency can be analgesic for certain chronic pain syndromes suggests that findings on pain threshold modulations found in healthy subjects should not be directly extrapolated to chronic pain levels.

4.3.2 Normal size of the virtual arm reduces pain ratings in CRPS type I patients

In addition to the disturbances of body representation in the central nervous system in patients with CRPS type I, some studies have shown substantial cortical reorganization within the primary somatosensory (S1), and secondary (S2) somatosensory areas (Juottonen et al., 2002; Maihöfner, Handwerker, & Neundörfer, 2003) as well as in motor and supplementary motor cortices and in the posterior parietal cortex (Cohen et al., 2013; Maihöfner, Baron, DeCol, Binder, & Birklein, 2007). Moreover, some CRPS patients with a disrupted body schema, reported a perceived distortion of the affected limb (J. Lewis et al. 2007). This could be due to a distortion of their subjective mental image of the affected extremity (Lewis et al. 2010), where the affected extremity is often perceived as larger than it really is (Peltz et al. 2011; Moseley 2005). Regarding this, most of our CRPS patients also reported a distorted body image, most of them perceiving the affected hand larger than it really is at the baseline assessment (see **Appendix C** to CRPS patients' verbal description of the mental representation of their affected arm). Interestingly, in this study, association of a substantial lower pain ratings with the normal representation of the virtual arm in the distorted virtual arm test was found compared with the representation of the very big virtual arm. This is contradictory to other findings in which they observed that a reduced representation of the affected arm was associated with lower pain ratings in CRPS patients (G. Moseley et al. 2008). Apparently, our findings suggest that pain relief depends on normalizing the perceptual body image dysfunction by changing how the painful body part looks (Boesch et al. 2016). Following this statement, the results obtained in the distorted virtual arm test indicate that by normalizing the body image of the affected arm through the presentation of the normal size virtual arm we can reduce pain rating in CRPS compared to very big size presentation of the virtual arm. Hence we are changing the affected arm image in the central nervous system, internally represented in a bad position, by normalizing the size of the virtual arm reducing pain sensations.

4.3.3 Differences in the sense of ownership of the virtual body between CRPS and PNI patients

The results obtained in the virtual reality questionnaires are in line with studies justifying that functionality of the brain regions associated with multisensory integration may be preserved in CRPS (Moseley & Wiech 2009; Reiswich et al. 2012; van Rijn et al. 2011), presenting higher scores in the induction of ownership illusion and agency in CRPS patients compared to PNI patients. Interestingly, our results also display worst scores for the questions related to the illusion-perception of the virtual body in CRPS patients. Although this result may seem contradictory with the high scores obtained in the sense of ownership of the virtual body in CRPS patients, again this could be because of the disturbances of body representation in the central nervous system in CRPS patients (Birklein & Schlereth 2015). As CRPS patients use to have a bad representation of their real body, it is not surprising to think that when they are embodied in a virtual body, they could have a strange internal representation of their actual virtual body, having the feeling that they had more than two arms or having the sensation that their virtual arm is drifted to the real one. These differences in the reported pain ratings to the virtual reality tests and in the virtual reality questionnaire scores between groups could be explained because patients in the PNI group experienced a higher sensory loss because of the nerve injury compared to patients with CRPS type I without nerve injury (Gierthmühlen et al. 2012).

In conclusion, our findings add to an increasing body of evidence that multisensory interventions by manipulating body image representations through immersive virtual reality can modulate pain perception in CRPS type I patients. These findings suggest that mechanisms like blurring the mental image of the affected arm representation increasing the transparency of the virtual arm and by introducing a new normal representation of the affected extremity through immersive virtual reality we can reduce pain rating in CRPS type I patients. In the present study we found higher scores in ownership and agency levels in the CRPS type I, which indicates that IVR could be a powerful tool to treat chronic pain patients with a distorted body image as in the case of amputees with chronic phantom pain (D Senkowski & Heinz 2016).

Chapter 5

Conclusions

1. Our IVR training combining motor imagery through action planning and action observation devoted to the rehabilitation of the arm significantly improves the functional ability and motor dexterity of the paretic or immobilized arm.
2. Embodiment of a virtual body and being able to control the movements of a virtual arm that is co-located with the real arm improves the functional ability recovery of the paretic or immobilized arm.
3. Action observation through Non-IVR training also presents better results than conventional rehabilitation training during immobilization, highlighting the positive effect of mental training techniques in motor-cognitive rehabilitation.
4. The IVR training described here when evaluated in chronic stroke patients decreased spasticity and improved motor dexterity in our sample, suggesting that it can be a powerful motor-cognitive approach for stroke rehabilitation.
5. Our IVR training combining motor imagery through action planning and action observation induces brain activity changes in cortical areas related to motor learning and motor execution.
6. Experimentally altering the visual representation of the virtual arm corresponding to the painful arm by increasing the transparency and by giving a normal-size visualization of the virtual arm through IVR, we can reduce pain ratings in neuropathic pain patients with CRPS type I but not with PNI.
7. IVR can be used as a neurorehabilitation tool to speed up and improve the motor functional recovery and to relearn motor skills in patients without movement in their upper or lower limbs due to orthopaedic lesions or to neurological disorders such as stroke.
8. IVR can be used as a neurorehabilitation tool to reduce pain rating in neuropathic pain patients with a distorted body image such as amputees or CRPS patients.

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Appendices

Appendix A

Materials of the **"Motor-cognitive training through Immersive Virtual Reality during the immobilization period in distal radius fracture patients: a randomized control trial study".**

INFORMACIÓN PARA LOS PARTICIPANTES

Este experimento forma parte de una larga serie de estudios para comprender las respuestas de la gente dentro de un entorno virtual. Este estudio ha sido aprobado por el Comité Ético de Investigación Clínica de la Corporación Sanitaria Hospital Clínic de Barcelona.

Por favor lea esta información y siéntase libre de preguntar cualquier duda a los experimentadores. Sin embargo los aspectos específicos que buscamos con este estudio no podrán ser comentados con usted antes de terminar la sesión. Intentaremos que el conjunto del estudio nos lleve el menor tiempo posible.

Por razones de seguridad, mujeres embarazadas, pacientes con epilepsia y personas que vayan a conducir coches/motos/bicicletas o a trabajar con maquinaria compleja o peligrosa inmediatamente después del experimento, no pueden participar en este estudio.

Usted va a usar un sistema de Realidad Virtual (RV) compuesto por unas gafas de RV. El equipo de visión puede ser usado sobre sus propias gafas. También utilizará unos auriculares por dónde podrá escuchar las instrucciones de los ejercicios que va a trabajar. Se le colocaran unos vibradores en los dedos con la intención de que sienta los ejercicios de la manera más real posible.

Usted permanecerá sentado toda la sesión, con los brazos encima de la mesa, colocados a la anchura de los hombros. No debe mover su brazo en ningún momento.

Al terminar la sesión, se le pedirá que conteste a algunas preguntas sobre su experiencia en el entorno virtual y sus sensaciones con relación a su cuerpo virtual (el avatar).

Usted va a realizar un programa de entrenamiento mental, para trabajar su brazo lesionado durante el periodo de inmovilización, 3 días a la semana.

Al final del programa se le hará una valoración del estado del brazo, el mismo día de la retirada del yeso o bien un día después. Una semana después se le pasará un cuestionario telefónico o por e-mail, para valorar las actividades que puede hacer con su brazo.

6 semanas después, se le volverá a hacer una evaluación de control, para comprobar que las mejoras se mantienen en el tiempo.

El estudio respeta la ley de protección de datos de acuerdo con la Ley Española 15/1999. La identidad de los sujetos es protegido mediante la asignación de un código a cada persona en nuestra base de datos electrónica. Esta base está protegida por medio de una contraseña a la cual solo los investigadores tienen acceso. Por otra parte, los datos nunca serán publicados de forma individual y no harán referencia a ninguna información identificativa de los sujetos.

IMPORTANTE

Cuando la gente usa un sistema de RV, algunas personas podrían experimentar cierta sensación de mareo o estrés. Algunos tipos de video podrían llegar a generar un episodio epiléptico, como se ha informado que ocurre en algunos videojuegos.

La información que hemos reunido nunca será mostrada de forma que pueda usted ser identificado individualmente. La información será transmitida de forma agrupada y estadística. Si se escribe un artículo de investigación, podría emplearse algún comentario verbal que usted haya hecho, aunque siempre de forma anónima.

Por favor tenga en cuenta que si en algún momento usted no desea continuar participando en el experimento, recuerde que es libre de salir sin tener que dar explicaciones.

Procedimientos que cada participante deberá comprender y aceptar:

- Se le pide que lea, comprenda y firme su consentimiento informado. Si usted lo firma, el estudio contará con su participación. Recuerde que usted puede abandonar dicho estudio en cualquier momento sin tener que dar razón alguna para ello.
- Apague el móvil antes de usar el equipo.
- Al final de la prueba se le puede pedir que responda a un número de preguntas de manera verbal o sobre papel.
- Usted se moverá en un entorno virtual usando un casco de realidad virtual o unas gafas estereoscópicas para ver en 3D en una pantalla. La pruebapuederealizarsetanto de pie comosentado.
- En la pantalla verá un cuerpo virtual. Es posible que se le pida concentrar su atención en alguna parte del cuerpo durante unos minutos.

- Por favor, no comente el estudio con otros durante los próximos 3 meses.

Si tiene alguna cuestión relacionada con el estudio, por favor contacte con nosotros:

- Dra.MariaV.Sánchez-Vives(msanche3@clinic.ub.es)
- Marta Matamala Gómez (matamala@clinic.ub.es)
- Dra. Isabel Sañudo (isanudo@clinic.ub.es

CONSENTIMIENTO INFORMADO DEL PARTICIPANTE

El voluntario deberá leer y contestar cuidadosamente las siguientes preguntas:

¿Ha leído toda la información sobre este estudio? SI/NO

¿Ha tenido la oportunidad de preguntar y comentar cuestiones sobre el estudio? SI/NO

¿Ha recibido respuestas satisfactorias a todas las cuestiones? SI/NO

¿Ha recibido la suficiente información sobre este estudio? SI/NO

¿Ha comprendido que usted es libre de abandonar este estudio? SI/NO

- En cualquiermomento SI/NO
- Sin dar ninguna razón SI/NO

¿Ha comprendido y aceptado los riesgos asociados con el uso de la Realidad Virtual? SI/NO

¿Está de acuerdo en tomar parte en el estudio? SI/NO

En el caso que necesitáramos grabar un vídeo ¿Está de acuerdo en ser grabado en vídeo? SI/NO

En caso que complete todo el estudio hasta el final ¿Se compromete a pasar la segunda evaluación 6 semanas después? SI/NO

Yo certifico que no padezco epilepsia.

Yo certifico que no conduciré ni coches, ni motos, ni bicicletas ni usaré ningún tipo de máquinas complejas que puedan ser peligrosas para mí o para otros, durante las tres próximas horas después de acabada la experiencia.

Firmado……………………………………………………………
Fecha……………………………

Nombre completo ………………………………………………….
Correo……………………………

¿Qué investigador le ha hablado sobre el estudio?……………………………………… (nombre y apellidos)

En caso que usted desee hacer alguna pregunta o comentario de este estudio en el futuro por favor contacte con:

Maria Victoria SanchezVives.SANCHEZ-VIVES LAB

Cortical Networks and Virtual Environments in Neuroscience (IDIBAPS).

C/. Rosselló, 149 – 153. 08036 – Barcelona. Spain

Maria-Victoria Sanchez-Vives (Investigador Principal)msanche3@clinic.ub.es

La información obtenida de su experimento nunca será public La información obtenida de su experimento nunca será publicada individualmente. Los datos serán analizados en grupos y aquellos comentarios verbales, en el caso que se publiquen, serán presentados de forma anónima.

CUESTIONARIO SOBRE LA EXPERIENCIA DE REHABILITACIÓN CON REALIDAD VIRTUAL

Indica hasta qué punto estás de acuerdo con las siguientes afirmaciones sobre tu experiencia de realizar un programa de rehabilitación con un sistema de realidad virtual.

1. Sentía como si el brazo que veía en el mundo virtual fuera el mío.

1. Totalmente en desacuerdo
2. Bastante en desacuerdo
3. Ni de acuerdo ni en desacuerdo
4. Bastante de acuerdo
5. Totalmente de acuerdo

2. Sentí que controlaba el brazo como si fuera mi propio brazo.

1. Totalmente en desacuerdo
2. Bastante en desacuerdo
3. Ni de acuerdo ni en desacuerdo
4. Bastante de acuerdo
5. Totalmente de acuerdo

3. ¿Qué piensa de la experiencia? ¿Cómo se sintió durante el experimento?

- **Me gusto poder controlar los movimientos del brazo virtual.**

    1. Totalmente en desacuerdo
    2. Bastante en desacuerdo
    3. Ni de acuerdo ni en desacuerdo
    4. Bastante de acuerdo
    5. Totalmente de acuerdo

- **Durante el experimento hubo momentos en los que el brazo virtual comenzaba a parecerse a mi propio brazo físicamente.**

  1. Totalmente en desacuerdo

  2. Bastante en desacuerdo

  3. Ni de acuerdo ni en desacuerdo

  4. Bastante de acuerdo

  5. Totalmente de acuerdo

- **El tiempo de tratamiento me ha parecido el adecuado.**
  1. Totalmente en desacuerdo

  2. Bastante en desacuerdo

  3. Ni de acuerdo ni en desacuerdo

  4. Bastante de acuerdo

  5. Totalmente de acuerdo

- **Las indicaciones para realizar los ejercicios eran claras y concretas**
  1. Totalmente en desacuerdo

  2. Bastante en desacuerdo

  3. Ni de acuerdo ni en desacuerdo

  4. Bastante de acuerdo

  5. Totalmente de acuerdo

- **Otros:**

Appendix B

Materials of the "Using immersive virtual reality to rehabilitate the paretic upper limb in chronic stroke patients: a pilot study".

INFORMACIÓN PARA LOS PARTICIPANTES

Este experimento forma parte de una larga serie de estudios para comprender las respuestas de la gente dentro de un entorno virtual. Este estudio ha sido aprobado por el Comité Ético de Investigación Clínica de la Corporación Sanitaria Hospital Clínic de Barcelona.

Por favor lea esta información y siéntase libre de preguntar cualquier duda a los experimentadores. Sin embargo los objetivos específicos que buscamos con este estudio no podrán ser comentados con usted antes de terminar el estudio con la intención de influenciar en su respuesta.

Por razones de seguridad, mujeres embarazadas, pacientes con epilepsia y personas que vayan a conducir coches/motos/bicicletas o a trabajar con maquinaria compleja o peligrosa inmediatamente después del experimento, no pueden participar en este estudio.

Usted va a realizar un programa de rehabilitación del brazo, para ello utilizará un sistema de Realidad Virtual (RV) compuesto por unas gafas o casco de RV. El equipo de visión puede ser usado sobre sus propias gafas. También llevará unos auriculares por los que podrá escuchar las instrucciones de los ejercicios que va a trabajar en cada sesión. Durante la sesión de rehabilitación usted colocará los brazos encima de la mesa sin moverlo en ningún momento.
Se le colocaran unos vibradores en los dedos con la intención de inducir un feedback sensorial cuando interactúe con objetos del entorno virtual.

El programa de entrenamiento para su extremidad superior se realizará cinco días a la semana (de lunes a viernes) durante cinco semanas en el primer periodo. Luego tendrá un mes de pausa y después de este mes realizaremos cinco semanas más de entrenamiento de lunes a viernes. La duración total del estudio piloto será de tres meses.

Con la intención de observar posibles cambios producidos por el entrenamiento, se le realizarán evaluaciones periódicas (semanalmente), así como al empezar y finalizar cada periodo. Finalmente durante el mes de pausa se le realizarán dos evaluaciones para observar si los hipotéticos cambios se mantienen en el tiempo.

Al finalizar cada sesión se le pedirá que conteste a algunas preguntas sobre su experiencia en el entorno virtual y sus sensaciones respecto el cuerpo virtual.

IMPORTANTE

Cuando la gente usa un sistema de RV, algunas personas podrían experimentar cierta sensación de mareo o estrés. Algunos tipos de video podrían llegar a generar un episodio epiléptico, como se ha informado que ocurre en algunos videojuegos.

La información que hemos reunido nunca será mostrada de forma que pueda usted ser identificado individualmente. La información será transmitida de forma agrupada y estadística. Si se escribe un artículo de investigación, podría emplearse algún comentario verbal que usted haya hecho, aunque siempre de forma anónima. El estudio respeta la ley de protección de datos de acuerdo con la Ley Española 15/1999. La identidad de los sujetos es protegido mediante la asignación de un código a cada persona en nuestra base de datos electrónica. Esta base está protegida por medio de una contraseña a la cual solo los investigadores tienen acceso. Por otra parte, los datos nunca serán publicados de forma individual y no harán referencia a ninguna información identificativa de los sujetos.

Por favor tenga en cuenta que si en algún momento usted no desea continuar participando en el experimento, recuerde que es libre de salir sin tener que dar explicaciones.

Procedimientos que cada participante deberá comprender y aceptar:

- Se le pide que lea, comprenda y firme su consentimiento informado. Si usted lo firma, el estudio contará con su participación. Recuerde que usted puede abandonar dicho estudio en cualquier momento sin tener que dar razón alguna para ello.
- Apague el móvil antes de usar el equipo.
- Al final de la prueba se le puede pedir que responda a un número de preguntas de manera verbal o sobre papel.
- Usted se moverá en un entorno virtual usando un casco de realidad virtual o unas gafas estereoscópicas para ver en 3D en una pantalla. La prueba puede realizarse tanto de pie como sentado.
- En la pantalla verá un cuerpo virtual. Es posible que se le pida concentrar su atención en alguna parte del cuerpo durante unos minutos.
- Por favor, no comente el estudio con otros durante los próximos 3 meses.

Si tiene alguna cuestión relacionada con el estudio, por favor contacte con nosotros:

- Dra. Maria V. Sánchez-Vives (msanche3@clinic.ub.es)
- Marta Matamala Gómez (matamala@clinic.ub.es)
- Dra. Esther Duarte (Hospital Esperanza) (eduarte@parcdesalutmar.cat)

Regions of interest included in the MNI Atlas

sROI_MNI_V4:

1	Precentral_L
2	Precentral_R
3	Frontal_Sup_L
4	Frontal_Sup_R
5	Frontal_Sup_Orb_L
6	Frontal_Sup_Orb_R
7	Frontal_Mid_L
8	Frontal_Mid_R
9	Frontal_Mid_Orb_L
10	Frontal_Mid_Orb_R
11	Frontal_Inf_Oper_L
12	Frontal_Inf_Oper_R
13	Frontal_Inf_Tri_L
14	Frontal_Inf_Tri_R
15	Frontal_Inf_Orb_L
16	Frontal_Inf_Orb_R
17	Rolandic_Oper_L
18	Rolandic_Oper_R
19	Supp_Motor_Area_L
20	Supp_Motor_Area_R
21	Olfactory_L
22	Olfactory_R
23	Frontal_Sup_Medial_L
24	Frontal_Sup_Medial_R
25	Frontal_Med_Orb_L
26	Frontal_Med_Orb_R
27	Rectus_L
28	Rectus_R
29	Insula_L
30	Insula_R
31	Cingulum_Ant_L
32	Cingulum_Ant_R
33	Cingulum_Mid_L
34	Cingulum_Mid_R
35	Cingulum_Post_L
36	Cingulum_Post_R
37	Hippocampus_L
38	Hippocampus_R
39	ParaHippocampal_L
40	ParaHippocampal_R
41	Amygdala_L
42	Amygdala_R
43	Calcarine_L
44	Calcarine_R
45	Cuneus_L
46	Cuneus_R
47	Lingual_L
48	Lingual_R
49	Occipital_Sup_L
50	Occipital_Sup_R
51	Occipital_Mid_L
52	Occipital_Mid_R

53	Occipital_Inf_L
54	Occipital_Inf_R
55	Fusiform_L
56	Fusiform_R
57	Postcentral_L
58	Postcentral_R
59	Parietal_Sup_L
60	Parietal_Sup_R
61	Parietal_Inf_L
62	Parietal_Inf_R
63	SupraMarginal_L
64	SupraMarginal_R
65	Angular_L
66	Angular_R
67	Precuneus_L
68	Precuneus_R
69	Paracentral_Lobule_L
70	Paracentral_Lobule_R
71	Caudate_L
72	Caudate_R
73	Putamen_L
74	Putamen_R
75	Pallidum_L
76	Pallidum_R
77	Thalamus_L
78	Thalamus_R
79	Heschl_L
80	Heschl_R
81	Temporal_Sup_L
82	Temporal_Sup_R
83	Temporal_Pole_Sup_L
84	Temporal_Pole_Sup_R
85	Temporal_Mid_L
86	Temporal_Mid_R
87	Temporal_Pole_Mid_L
88	Temporal_Pole_Mid_R
89	Temporal_Inf_L
90	Temporal_Inf_R
91	Cerebelum_Crus1_L
92	Cerebelum_Crus1_R
93	Cerebelum_Crus2_L
94	Cerebelum_Crus2_R
95	Cerebelum_3_L
96	Cerebelum_3_R
97	Cerebelum_4_5_L
98	Cerebelum_4_5_R
99	Cerebelum_6_L
100	Cerebelum_6_R
101	Cerebelum_7b_L
102	Cerebelum_7b_R
103	Cerebelum_8_L
104	Cerebelum_8_R
105	Cerebelum_9_L

106	Cerebelum_9_R
107	Cerebelum_10_L
108	Cerebelum_10_R
109	Vermis_1_2
110	Vermis_3
111	Vermis_4_5
112	Vermis_6
113	Vermis_7
114	Vermis_8
115	Vermis_9
116	Vermis_10

Appendix C

Materials of the **“Immersive virtual reality relieves pain in complex regional pain syndrome type I but not in peripheral nerve injury study”.**

INFORMACIÓN PARA LOS PARTICIPANTES

Este experimento forma parte de una larga serie de estudios para comprender las respuestas de la gente dentro de un entorno virtual. Este estudio ha sido aprobado por el Comité Ético de Investigación Clínica de la Corporación Sanitaria Hospital Clínic de Barcelona.

Por favor lea esta información y siéntase libre de preguntar cualquier duda a los experimentadores. Sin embargo los aspectos específicos que buscamos con este estudio no podrán ser comentados con usted antes de terminar la sesión. Intentaremos que el conjunto del estudio nos lleve el menor tiempo posible.

Por razones de seguridad, mujeres embarazadas, pacientes con epilepsia y personas que vayan a conducir coches/motos/bicicletas o a trabajar con maquinaria compleja o peligrosa inmediatamente después del experimento, no pueden participar en este estudio.

Usted va a usar un sistema de Realidad Virtual (RV) compuesto por unas gafas o casco de RV. El equipo de visión puede ser usado sobre sus propias gafas. También utilizará unos auriculares por dónde podrá escuchar las instrucciones que deberá seguir durante la evaluación. Se le colocaran unos vibradores en los dedos con la intención de darle a usted un feedback sensorial durante la sesión.

Usted permanecerá sentado toda la sesión, con los brazos encima de la mesa, colocados en la misma posición que el cuerpo virtual. **No debe mover los brazos en ningún momento.**

Al terminar la sesión, se le pedirá que conteste a algunas preguntas sobre su experiencia en el entorno virtual y sus sensaciones con relación al cuerpo virtual.

Usted va a realizar un estudio en el que deberá de decir la cantidad de dolor que está sintiendo del 0 al 10 en el brazo cada vez que así se lo indique las instrucciones. La siguiente evaluación consta de dos partes, la primera durará unos 15 minutos y la segunda 10 minutos. Entre estas dos partes habrá una pausa de 10 minutos, para descansar.

Al finalizar cada sesión se le pasará un cuestionario para que valore como ha sido su experiencia en el entorno virtual.

Al terminar la sesión usted recibirá 5 euros por participar en este experimento.

IMPORTANTE

Cuando la gente usa un sistema de RV, algunas personas podrían experimentar cierta sensación de mareo o estrés. Algunos tipos de video podrían llegar a generar un episodio epiléptico, como se ha informado que ocurre en algunos videojuegos.

La información que hemos reunido nunca será mostrada de forma que pueda usted ser identificado individualmente. La información será transmitida de forma agrupada y estadística. Si se escribe un artículo de investigación, podría emplearse algún comentario verbal que usted haya hecho, aunque siempre de forma anónima. El estudio respeta la ley de protección de datos de acuerdo con la Ley Española 15/1999. La identidad de los sujetos es protegido mediante la asignación de un código a cada persona en nuestra base de datos electrónica. Esta base está protegida por medio de una contraseña a la cual solo los investigadores tienen acceso. Por otra parte, los datos nunca serán publicados de forma individual y no harán referencia a ninguna información identificativa de los sujetos.

Por favor tenga en cuenta que si en algún momento usted no desea continuar participando en el experimento, recuerde que es libre de salir sin tener que dar explicaciones.

El estudio respeta la ley de protección de datos de acuerdo con la Ley Española 15/1999. La identidad de los sujetos es protegido mediante la asignación de un código a cada persona en nuestra base de datos electrónica. Esta base está protegida por medio de una contraseña a la cual solo los investigadores tienen acceso. Por otra parte, los datos nunca serán publicados de forma individual y no harán referencia a ninguna información identificativa de los sujetos.

Procedimientos que cada participante deberá comprender y aceptar:

- Se le pide que lea, comprenda y firme su consentimiento informado. Si usted lo firma, el estudio contará con su participación. Recuerde que usted puede abandonar dicho estudio en cualquier momento sin tener que dar razón alguna para ello.
- Apague el móvil antes de usar el equipo.
- Al final de la prueba se le puede pedir que responda a un número de preguntas de manera verbal o sobre papel.

- Usted se moverá en un entorno virtual usando un casco de realidad virtual o unas gafas estereoscópicas para ver en 3D en una pantalla. La prueba se realizarásentado.
- En la pantalla verá un cuerpo virtual. Es posible que se le pida concentrar su atención en alguna parte del cuerpo durante unos minutos.
- Por favor, no comente el estudio con otros durante los próximos 3 meses.

Si tiene alguna cuestión relacionada con el estudio, por favor contacte con nosotros:

- Dra.CarmeBusquets (BUSQUETS@clinic.ub.es)
- Dra.MariaV.Sánchez-Vives(msanche3@clinic.ub.es)
- Marta Matamala Gómez (matamala@clinic.ub.es)

VR questionnaire of the transparency of the virtual arm test

Indica hasta qué punto estás de acuerdo con las siguientes afirmaciones sobre tu experiencia.

1. Durante el experimento hubo momentos en los sentí que las bolas que tocaban los dedos virtuales tocaban mis propios dedos.

-3	**-2**	**-1**	**0**	**1**	**2**	**3**

Totalmentedesacuerdo **Totalmente de acuerdo**

2. Aunque el cuerpo virtual no se parecía físicamente a mi cuerpo, sentí que podía ser mi propio cuerpo.

-3	**-2**	**-1**	**0**	**1**	**2**	**3**

Totalmentedesacuerdo **Totalmente de acuerdo**

3. Durante el experimento hubo momentos en los que el brazo virtual empezaba a parecerse a mi propio brazo.

-3	**-2**	**-1**	**0**	**1**	**2**	**3**

Totalmentedesacuerdo **Totalmente de acuerdo**

4. Durante el experimento me pareció como si mi brazo real estuviera desviado respecto al brazo virtual

-3	**-2**	**-1**	**0**	**1**	**2**	**3**

Totalmentedesacuerdo **Totalmente de acuerdo**

5. Durante el estudio hubo momentos en los que me daba la sensación de tener más de un brazo.

-3	**-2**	**-1**	**0**	**1**	**2**	**3**

Totalmentedesacuerdo **Totalmente de acuerdo**

6. Durante el experimento hubo momentos en los que sentí que si movía mi brazo se movería el brazo virtual

-3	**-2**	**-1**	**0**	**1**	**2**	**3**

Totalmentedesacuerdo **Totalmente de acuerdo**

7. Cuándo el brazo virtual se volvía transparente seguía teniendo la sensación de que era mi propio brazo

-3	**-2**	**-1**	**0**	**1**	**2**	**3**

Totalmentedesacuerdo **Totalmente de acuerdo**

8. Durante toda la sesión he sido capaz de mantener la atención en el brazo situado junto al libro.

-3	**-2**	**-1**	**0**	**1**	**2**	**3**

Totalmentedesacuerdo **Totalmente de acuerdo**

9. Sentí que el brazo virtual era mi brazo cuando era

-3	**-2**	**-1**	**0**	**1**	**2**	**3**

Totalmentetransparente **Totalmenteopáco**

Describe brevemente lo que has observado durante esta sesión.

VR questionnaire of the distorted virtual arm test

Indica hasta qué punto estás de acuerdo con las siguientes afirmaciones sobre tu experiencia.

1. Durante el experimento hubo momentos en los que el brazo virtual empezaba a parecerse a mi propio brazo.

-3	**-2**	**-1**	**0**	**1**	**2**	**3**

Totalmentedesacuerdo

Totalmente de acuerdo

2. Durante el experimento me pareció como si mi brazo real estuviera desviado respecto al brazo virtual

-3	**-2**	**-1**	**0**	**1**	**2**	**3**

Totalmentedesacuerdo

Totalmente de acuerdo

3. Aunque el cuerpo virtual no se parecía físicamente a mi cuerpo, sentí que podía ser mi propio cuerpo.

-3	**-2**	**-1**	**0**	**1**	**2**	**3**

Totalmentedesacuerdo

Totalmente de acuerdo

4. Durante el experimento hubo momentos en los sentí que las bolas que tocaban los dedos virtuales tocaban mis propios dedos.

-3	**-2**	**-1**	**0**	**1**	**2**	**3**

Totalmentedesacuerdo

Totalmente de acuerdo

5. Durante el estudio hubo momentos en los que me daba la sensación de tener más de un brazo.

-3	**-2**	**-1**	**0**	**1**	**2**	**3**

Totalmentedesacuerdo **Totalmente de acuerdo**

6. Durante el experimento hubo momentos en los que sentí que si movía mi brazo se movería el brazo virtual

-3	**-2**	**-1**	**0**	**1**	**2**	**3**

Totalmentedesacuerdo **Totalmente de acuerdo**

7. Durante toda la sesión he sido capaz de mantener la atención en el brazo situado junto al libro.

-3	**-2**	**-1**	**0**	**1**	**2**	**3**

Totalmentedesacuerdo **Totalmente de acuerdo**

8. Sentí que el brazo virtual era mi propio brazo cuando era

-3	**-2**	**-1**	**0**	**1**	**2**	**3**

Muygrande **Muypequeño**

9. Cuándo el brazo virtual se volvía pequeño seguía teniendo la sensación de que era mi propio brazo

-3	**-2**	**-1**	**0**	**1**	**2**	**3**

Totalmentedesacuerdo **Totalmente de acuerdo**

Describe brevemente lo que has observado durante esta sesión.

Mental representation of the affected arm in CRPS type I patients

S_01: I feel that my arm is swollen in comparison to my healthy arm. However, I do not feel any type of distortion in my affected arm.

S_02: I feel that my affected hand is heavier compared to my healthy arm. I also feel a pain that starts in the hand and goes to the ear.

S_03: I feel that my affected arm is bigger and has an exaggerated size compared to the healthy arm. I also feel it numb.

S_04: I feel that my affected arm is shorter compared to the healthy arm. I also feel as if this arm was not part of my own body.

S_05: I feel that my affected arm is bigger than my healthy arm. I also feel as if it has a disproportionate size.

S_06: I feel that my affected arm is heavier than my healthy arm. I also feel it has a disproportionate size compared to the healthy arm.

S_07: My affected arm is distorted. I feel as if it is twisted with the palm facing upwards.

S_08: When I have a lot of pain my affected arm tends to disappear. I feel as the arm that I have is not really my arm.

S_09: Sometimes I do not recognize the thumb of the affected arm and I feel it twisted. I cannot move the wrist of the affected hand.

S_10: I do not feel any distortion of my affected arm.