Investigating the Role of an Embodied Avatar in Virtual Reality on Pain Alleviation, the Sense of Embodiment, and Brain Waves in Patients with Chronic Pain

by

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Declaration of Committee

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Ethics Statement

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Abstract

For about two decades, many studies have shown the effectiveness of Virtual Reality (VR) as an alternative intervention for pain reduction in patients with acute and chronic pain. One of the possible mechanisms of VR effect is associated with Sense of Embodiment (SoE). To uncover the underlying brain mechanisms of VR analgesia, in this thesis, I am exploring if having an avatar in VR reduces pain through activation of SoE using Electroencephalography (EEG). To address this, I ran an exploratory pretest-posttest pilot study on a VR intervention called Virtual Meditative Walk (VMW) with and without an avatar. 14 participants with Chronic Pain (CP) (> 18) were recruited and used VR. Subjective pain score, and EEG signals were recorded before and after the intervention. Also, SoE scores were collected after VR. To analyze the data, alpha and theta Power Spectral Density (PSD) and Peak of Theta-Alpha Frequency (PTAF) for subjects across conditions were calculated. Results showed a higher but insignificant pain reduction and SoE trend in the Avatar group. The EEG analysis also demonstrated an increase in alpha in time for both conditions, with a significantly lower post-Rest frontal alpha for the Avatar group. The PTAF was also significantly higher for the Avatar group. Overall, the Avatar group showed promising but inconclusive results in terms of pain reduction and SoE, with some differences in brain activity observed in the EEG analysis. This study is a step toward understanding the role of an avatar in VR analgesia and designing more effective VR scenarios for patients with CP.

Keywords: Virtual Reality; Chronic Pain; Sense of Embodiment; Electroencephalogram, EEG; VR.

Dedication

To the kingdom of Science,
And to its true guardians.
Shall no one invade this wondrous realm with money, greed, or fame.

To our front-line warriors against COVID;
Doctors, Nurses, and all medical staff.
We owe you a lot!

To my brave people,
For Women, Life, Freedom.

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List of Acronyms

ACC Anterior Cingulate Cortex. 11, 16, 24

AE Avatar Embodiment. ix, 46, 47, 55, 56

ANCOVA Analysis of Covariance. xiii, 49, 54, 58, 59, 60, 129, 131

ANOVA Analysis of Variance. 48, 49, 54, 55

AR Augmented Reality. 2

BIID Body Integrity Identity Disorder. xi, 22

BMBIs Brief Mindfulness-Based Interventions. 14

CBT Cognitive Behavioral Therapy. 13, 14

COPCs Chronic Overlapping Pain Conditions. 12

CP Chronic Pain. iv, 1, 2, 3, 4, 5, 7, 12, 13, 14, 15, 17, 19, 20, 23, 25, 26, 27, 29, 34, 36, 37, 38, 39, 41, 45, 48, 64, 65, 67, 68, 107

CRPS Complex Regional Pain Syndrome. 2, 25, 26, 29

EDA Electrodermal Activity. 17, 39

EEG Electroencephalography. iv, xi, 1, 3, 4, 5, 10, 29, 30, 31, 32, 33, 34, 36, 37, 38, 40, 41, 42, 43, 44, 48, 52, 56, 61, 63, 65, 66, 67, 68, 69, 70, 103, 104, 105, 106, 107

ERP Event-Related Potential. 30

FA Focused Attention. 13

FFT Fast Fourier Transform. 44

fMRI functional Magnetic Resonance Imaging. 10, 11, 16, 24, 26

GCT Gate Control Theory. xii, 8, 10, 16

HMD Head Mounted Display. 16, 28, 37, 40, 41, 69, 103, 108

HMDs Head Mounted Displays. 15, 104

IASP International Association for the Study of Pain. 6, 37

ICA Independent Component Analysis. 43

ICD-11 International Statistical Classification of Diseases and Related Health Problems. 12, 37

IK Inverse Kinematic. 40

IPQ Igroup Presence Questionnaire. ix, 46, 47, 48, 55

KSS Karolinska Sleepiness Scale. 38

M1 Primary Motor Cortex. 24, 26, 27, 32

MBSR Mindfulness-Based Stress Reduction. 13, 14, 17, 39, 45, 64

NRS Numerical Rating Scale. 45, 46, 52, 54, 128

NSAIDs Non-Steroidal Anti-Inflammatory Drugs. 12

OM Open Monitoring. 13

PAG Periaqueductal Gray. 16

PFC Prefrontal Cortex. 33

PLP Phantom Limb Pain. 2, 9, 10, 22, 23, 25, 26, 27, 28

PMC Premotor Cortex. 24, 33, 65

POV Point of View. 40

PPC Posterior Parietal Cortex. 23, 24

PRS Pain Reduction Score. xiii, 4, 45, 47, 48, 54, 56, 57, 61, 64, 67

PSD Power Spectral Density. iv, xiii, 44, 45, 48, 49, 50, 56, 57, 58, 59, 62, 130

PTAF Peak of Theta-Alpha Frequency. iv, xiii, 3, 5, 34, 48, 49, 59, 60, 67, 70

RCT Randomized Controlled Trial. 16, 17

RHI Rubber Hand Illusion. 3, 4, 22, 24, 33

ROI Regions of Interest. 48

rsEEG resting state EEG. 30

rTP right Tempro-Parietal Cortex. 24

S1 Primary Somatosensory Cortex. 16, 18, 19, 24, 26, 27, 32

S2 Secondary Somatosensory Cortex. 16, 18, 24, 32

SCI Spinal Cord Injury. 25

SF-MPQ Short-Form McGill Pain Questionnaire. 45, 46

SFU Simon Fraser University. 36, 37

SNRIs Serotonin-norepinephrine reuptake inhibitors. 12

SoA Sense of Agency. 4, 21, 23, 27, 47

SoE Sense of Embodiment. iv, ix, xi, xiii, 3, 4, 5, 21, 23, 24, 27, 28, 29, 33, 36, 39, 45, 46, 47, 48, 55, 56, 57, 61, 63, 64

SoL Sense of self-Location. 4, 21, 23, 24, 33, 47

SoO Sense of Ownership. xi, 4, 21, 22, 23, 27, 28, 33, 47

SPL Superior Parietal Lobe. 23

TPJ Tempro-Parietal Junction. 18, 24

TSS Tiredness Symptoms Scale. 38

VE VR-embodiment. 1, 2, 3, 4, 14, 15, 19, 20, 21, 27, 28

VMW Virtual Meditative Walk. iv, xii, 4, 16, 17, 38, 39, 45, 64

VR Virtual Reality. iv, viii, ix, xii, 1, 2, 3, 4, 5, 12, 14, 15, 16, 17, 19, 20, 23, 27, 28, 29, 30, 31, 32, 33, 36, 39, 40, 41, 42, 43, 44, 45, 46, 47, 52, 54, 56, 59, 64, 65, 67, 68, 69, 70, 103, 104, 105, 106, 107, 108, 128

Allons-y!

Chapter 1

Introduction

[1] If we consider our world constant, for each of us, our brain is a super powerful graphic card, generating a virtual reality (a representation of the actual reality) for us. This way, there will be 8 billion different perspective machines constantly perceiving and discovering the world. So, what makes Virtual Reality (VR) (as in its everyday use in today's technology) impressive is that the perceived *actual reality* can be modified this time. By providing different sensory inputs, this reality can change, bend, and tweak as far as 8 billion imagination engines can go. This feature makes VR, one of the best laboratory environments for the brain. We can test specific and controlled scenarios without compromising reality's integrity or crossing ethical boundaries.
VR has been used in research for about 40 years as a powerful therapeutic clinical tool for rehabilitation, physical therapy [17], and psychological disorders [86]. It has also shown promising results as an alternative medication for pain alleviation, especially Chronic Pain (CP) treatment [116]. Nevertheless, as for many things in nature, the effectiveness might be apparent, but the responsible underlying mechanisms are complicated and challenging to be isolated from other coinciding events. Hence, little is known about it. We know it works, but we do not know why. One of the theories offered to characterize VR pain alleviation is VR-embodiment (VE). VR-embodiment theory suggests that the effectiveness of VR-analgesia is due to the changes in one's body representation in VR. In this thesis, I will explore the effect of this aspect of VR (i.e. VR-embodiment) on CP patients. In doing so, I will also explore the effect of VR analgesia on brain mechanisms using Electroencephalography (EEG).

Pain is a subjective experience and usually emerges when signals rise by a noxious stimulus and activate the peripheral nociceptors, integrate within the brain [173]. This might cause an automatic

[1]The content of this chapter ,as a part of my thesis proposal, has been partially peer-reviewed as part of the introduction of a protocol paper in the Journal of Frontiers in Virtual Reality (Virtual Reality in Medicine), for the research topic of Novel Applications of Virtual and Mixed Reality in Pain Research and Treatment [140]. Therefore, this writer acknowledge that some passages in this chapter have been quoted verbatim from the original paper.

response; if I burn my hand by putting it over a fire, I will rapidly remove it. However, sometimes, the pain sensation might arise and persists for a long time (i.e. more than three months) regardless of the existence of painful external stimuli; this type of pain is called Chronic Pain (CP) [217].
With a prevalence of about 20% in North America and about 10% worldwide, CP stands among the top 10 causes of disability [251]. As a serious health problem, CP is inadequately managed by the healthcare systems, raising concerns about the standards of care in treating it. These considerations mainly question the effectiveness, overuse, and safety of medicinal therapies such as opioids [223]. In response, non-pharmacologic interventions have become popular in CP management [219]. Despite the usual methods, these non-chemical treatments aim to address more than just biological aspects of pain. They manipulate affective, cognitive, behavioural, and socio-cultural dimensions of pain. Virtual and Augmented Reality (VR/AR) interventions are among such non-medicinal methods.

About 40 years after developing the first Virtual Reality (VR) system [36], in the 2000s, research on VR for pain began with Hunter G. Hoffman's work by designing a video game for severe burn patients [120]. Since then, VR has shown compelling potential as a non-pharmaceutical pain treatment[158]; agreed on an effect termed "analgesia." Yet, few studies have explored the underlying mechanism of VR in pain, especially in Chronic Pain (CP) treatment. Among these few studies, some suggest the theory of VR-embodiment (VE) as an explanation for this phenomenon.
Studies have suggested that body image can be distorted in people with chronic pain, especially in some types of CP such as Complex Regional Pain Syndrome (CRPS) or Phantom Limb Pain (PLP) [237, 197, 166] . The *body-image* is a sense and representation (or an image) that one has of their body in terms of its characteristics [94], giving them a sense of "Embodiment" [148]. Another concept closely related to *body-image* is *body-schema*. *body-schema* refers to an unconscious cortical capacity manipulating the "performance of the body," such as updating the position of body parts in space. [166, 90] According to Melzack [188], a pre-wired neuro matrix (i.e. body-self neuromatrix) stores this *body-schema* as a representation of our body in the brain (a.k.a. body matrix [196]). It is yet unknown how exactly the pain is projected into the *body-image* [166]; however, mediums such as VR, which can manipulate the body representation, might help us understand this relation.
Cognitive scientists supporting VR-embodiment believe that VR defines a new mapping of our body matrix. The virtual avatar in VR replaces the image of one's real body with a virtual body representation. Our brain makes a new mental model based on the virtual avatar to gain the sense of agency and ownership in the VR environment and to predict expected inputs from that virtual environment [221]. They proposed that our body representation changes in VR by adjusting to new sensory signals from the virtual world. As a result of body matrix modulation, pain perception is manipulated, leading to pain reduction [181].
Some research has studied the effect of body illusion and VR-embodiment on perceived pain and pain threshold by altering an embodied avatar's synchronization [177], colour [175], size [222], and

transparency [176]. Martini and his team believed that the cause of VR-embodiment is similar to Rubber Hand Illusion (RHI), a phenomenon known as *proprioceptive drift* [176]. In *proprioceptive drift*, our sense of body position and orientation can become distorted over time, and the perceptual system might favour the visual sensory inputs over proprioception to resolve the sensory conflict between the incongruent visuotactile inputs [181]. As we adapt to these conflicting signals, our brain may gradually adjust our perception of our body's position and orientation, leading to a feeling of "drift" or displacement. Martini and colleagues assessed the effect of synchronous and asynchronous stimulation in RHI in VR. Their result showed that the heat pain threshold increases only when there is a Sense of Embodiment (SoE) towards an avatar (i.e. in synchronous condition). They claimed that we might be able to modulate pain threshold by inducing body ownership [177]. Studies investigating the VR-embodiment in pain examined the effect of virtual body parts modulation on pain and pain threshold. However, these studies have been mostly conducted on healthy subjects and acute (heat/cold-induced) pain, and there are fewer studies on CP patients[116, 181]. Despite the encouraging result, VR pain treatment studies have a limited evidence level and high risks. Some of the risks are due to the use of uncontrolled and not-previously-tested VR interventions, and lack of neurological evidence. Therefore, there is a need for a new study to analyze the VR-embodiment effect on VR analgesia for CP patients by adding an embodied avatar to a previously studied VR environment. Due to the biopsychosocial nature of CP [101], Questionnaires were the most used assets for evaluating CP and different dimensions of embodiment. However, since surveys are subjective and dependent on a participant's interpretation of questions, there is a need to combine those methods with neurophysiological measurements[158].

Electroencephalography (EEG) is one of the non-invasive brain imaging methods able to address this problem. Running EEG studies are relatively cheap, more accessible and portable, and have a high temporal resolution. To better exlore the effect of VR-analgesia I used EEG in my study.
EEG signal waveform is conventionally categorized into five main bandwidth ranges: Delta (δ: up to 4 Hz), Theta (θ: 4-8 Hz), Alpha (α: 8 -15 Hz), Beta (β: 15-30 Hz), and Gamma (γ: $>$ 30 Hz).
Theta brain signal is most prominent in the frontal regions. This signal is associated with alertness, efficient processing of cognitive and perceptual tasks, and concentration. It is most dominant during learning and working memory. This brain wave has also been observed during the encoding of sensory stimuli, including noxious stimuli [77, 169]. It is suggested that this waveform frequency is related to the subjective pain intensity rating [230]. Also, the power of the Peak of Theta-Alpha Frequency (PTAF) may shift towards lower frequencies in the presence of CP [42].
Alpha oscillation originates from the occipital lobe during wakeful relaxation. This oscillation has observed to be higher with eyes closed and reduces after eyes opening, in drowsiness, and sleep [168]. This oscillation often reflects the inhibitory mechanism in the thalamocortical network [211]. In a study on participants moving in a VR environment using brain imagery, Alchalabi and his team found that the subjective feeling of ownership was related to a more substantial central frontal and

central parietal alpha oscillation (i.e. μ ERS) [18].

It is known that VR can be a powerful alternative method for CP alleviation. However, there is a need to better investigate the underlying mechanisms of VR analgesia. For that, I aimed to investigate the virtual embodiment's effect on pain alleviation among CP patients. At the same level, we want to explore how this embodied illusion affects patients' brain signals.

1.1 Objectives and Hypotheses

In the previous section, we discussed that changes in the sensation of embodiment might alter the subjective pain which can be correlated with the changes in the EEG signals. In the pilot study conducted for this thesis I explored how brain oscillations change during VR analgesia in people with CP. Specifically, I concentrated on the effect of having an embodied avatar in VR (VR-embodiment), on patients' pain levels and brain signals by asking the following research question:

"How does having an embodied avatar in a VR environment (VMW) affect Chronic Pain (CP) patients' Sense of Embodiment (SoE), perceived pain and neural activity."

The following main hypotheses are the main focus of this pilot exploratory pretest–posttest experimental study:

Hypothesis 1:*Participants in the embodied group (witha an avatar) will show greater pain reduction level (i.e. Pain Reduction Score (PRS)) after the VR session than participants in the control group (without an avatar).* The use of embodied avatars in VR has been associated with increased subjective pain threshold [177] and decreased pain severity[119]. Similarly, for CP participants, I hypothesize that the participants experiencing an embodied avatar in their VR intervention will report a greater Pain Reduction Score.

Hypothesis 2: *Participants in the embodied group (with an avatar), will show greater Sense of Embodiment (SoE) Score after the VR session, than participants in the control group (without an avatar).* Previous research has suggested that using an embodied avatar might enhance the Sense of self-Location[156], Sense of Ownership [181], and Sense of Agency [18] as different dimensions of SoE. Therefore, it is possible that using an embodied avatar in virtual reality could lead to an increased subjective SoE.

Hypothesis 3:*Participants in the embodied group (with an avatar), will show higher α-power after the VR session than participants in the control group (without an avatar).* Literature on RHI and VR-embodiment suggest that an increase in the sensation of embodiment can be correlated

with higher central frontal and central parietal Alpha oscillation [18]. The increase in alpha power has been observed upon seeing a virtual body only in comparison to an non-avatar object [155]. I hypothesize that greater embodiment in our VR environment with an embodied avatar may be associated with greater alpha band activity in the central and parietal cortex, which are responsible for processing and integrating sensory information from the body.

Hypothesis 4:*Participants in the embodied group (with an avatar), will show lower θ-power after the VR session than participants in the control group (without an avatar).* Pain has been associated with increased EEG theta band activity in the brain, particularly in the frontal and central regions [212]. I hypothesize that adding an avatar to the VR environment will lead to a lower theta band activity compared to the control condition.

Hypothesis 5:*Participants in the embodied group (with an avatar), will show higher PTAF after the VR session, than participants in the control group (without an avatar).* For different types of CP, the PTAF has been correlated with the presence of pain [212]. Boord et al. observed a shift-to-lower-frequencies in the theta-alpha peak frequency among CP patients. This effect was assumed to be connected to thalamocortical dysrhythmia [42]. Therefore, I hypothesize that this peak value will shift towards higher frequencies for the treatment group with an embodied avatar.

1.2 Contribution

In this thesis I aimed to investigate how VR analgesia affects Chronic Pain. Through an exploratory, experimental pilot study we explored the effect of using an embodied avatar in a meditative VR enviroment on pain and SoE amongst CP participants. We also investigated the changes in EEG oscillations before and after the VR intervention. To this point, this is the first study inquiring about the effectiveness of having an avatar in VR using EEG for CP population. The results and takeaways from this pilot study will be a foundation for and be utilized in future follow-up studies with a larger population.

In the following chapters, I will first review the definition and existing literature on Chronic Pain (CP), Virtual Reality (VR), and Electroencephalography (EEG) with regard to the purpose of the study. In the second chapter, the methods and materials of the study are provided by detailing the design of the VR application, study procedure, and analysis plan. After reporting the study results in chapter 4, we will discuss the implication of the results in addition to takeaways and implications for the future study procedure. Eventually, alternative possibilities and the limitations of the study will be reported.

Chapter 2

Literature Review

2.1 Chronic Pain

2.1.1 Pain

Pain is a primitive and evolutionary survival mechanism, not only for an individual's survival [243] but also for the species. Pain is defined by the International Association for the Study of Pain (IASP) as "An unpleasant sensory and emotional sensation associated with actual or potential tissue damage, or described in terms of such damage" [217]. In other words, it warns of injury that should be avoided or treated [188]. So, by the definition, if one burns their finger, the following pain grabs their attention, and the visuomotor system gets activated and they move their finger to escape from the painful source [40]. Pain promotes the body's healing process and immune system's activity and forces the person to rest. Also, the memory of such pain would hopefully prevent them from burning their finger again. [196] Simple on the surface, this definition is thought by many to be inadequate.

Pain is not a clear-cut phenomenon; it is highly subjective [173]. Moreover, many factors can alter pain; the biological perception of pain can be influenced by different social, behavioural, and cultural factors [40]. Gatchel et al. proposed the 'biopsychosocial' model to address this multidimensionality [100]. This model looks at pain as an interrelationship of two viewpoints: an objective physiological or pathological change and a subjective experience when the mind-body is bound up with the social factors and adds to our pain [101, 40]. It should therefore be no surprise that understanding the pain mechanisms, experience, and management has become a challenging mystery in medicine.

In order to better understand pain mechanisms and pain management methods, various theories and categories have been proposed. In a broader clinical setting, chronic and acute pain are the most common categories of pain [23, 40]. Acute pain is the sudden and usually temporary pain that is provoked by adverse chemical, thermal, or mechanical stimuli, such as surgery, injury, illness,

or infection [138, 23, 77]. Albeit unpleasant, acute pain is a purposeful biological warning signal. Chronic Pain (CP), on the other hand, can be persistent and does not always have a protective function which makes it the primary reason why patients seek pain treatment [138]. It usually serves no useful purpose and "*is* the disease" [196].
Pain can be categorized in many forms. It is **highly** subjective. And, there is no single solution to alleviate it. In order to find a customized pain alleviation solution, first we need to explain how it forms. In the following subsections of this section, I review some of the recent theories on pain explaining how pain works as a multi-dimensional phenomenon, before focusing on chronic pain to provide a baseline for my research.

2.1.2 Pain Theories

To study pain, it is important to distinguish the difference between pain as an unpleasant sensory and emotional experience and the "neural process of encoding the noxious stimuli" (aka. nociception) [162].

A potentially harmful -not necessarily painful- stimuli (noxious stimuli) can be detected by the sensory receptors (nociceptors) distributed in our body's skin and deep tissues [35]. These nociceptors have protein receptors with high activation thresholds that are sensitive to chemicals released by tissue cells when damaged in different mechanical, thermal, and chemical states such as inflammation, pressure, temperature, etc. [40, 138]. If activated, the detected severity is transduced into electrical activity and evokes action potential propagated through nociceptive afferent neurons extending through the dorsal horn of the spinal cord [138, 77]. This action potential can be carried via slow, small-diameter, non-myelinated C fibre nerves (for dull and slow-burning after pain) or rapidly conducting myelinated Aδ afferent fibres (for the initial sharp pricking pain) [70]; each conveys distinct modalities. These fibres are demonstrated in Figure 2.1. In the dorsal horn of the spinal cord, the primary fibres synapse with secondary afferent neurons and cross the midline [196]. Then, through the ascending pathways, nociceptive signals would be transmitted from the spinal cord to the higher center, contra-laterally [138].
Figure 2.2 shows the three main ascending pathways, from which the spinothalamic tract is the most prominent in the spinal cord. Secondary afferent neurons traveling along the spinothalamic tract terminate in nuclei located in the thalamus before reaching higher brain centers. Some pain signals also ascend in the spinomesencephalic tract and the dorsal column pathway. And, some others relay the signal through the spinoreticular tract in which the signal projects to the reticular formation of the brainstem before reaching the thalamus and hypothalamus area and projects throughout the brainstem.
When the signal terminates in the brain, the perception of pain from the noxious signal would, then, be possible. Evidently, pain is not simply a direct product of the activity of nociceptive afferents,

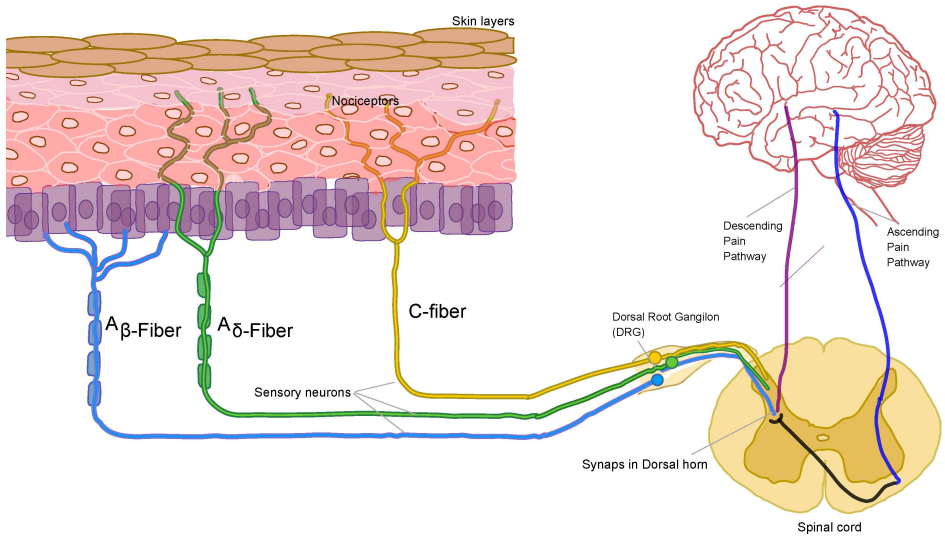

Figure 2.1: The nerve fibres [138].

and many factors can alter the signal through this path before it reaches the end. However, this raises another question: How is the pain so subjective?

In the 1960s, Melzack and Wall [190] made one of the most revolutionizing discoveries in pain research: Gate Control Theory (GCT). The theory suggests that an embedded regulatory system in the central nervous system is modulating the pain perception in the brain and is determining the degree to which the noxious signal relays through the ascending pathways. Figure 2.3, shows a simple schematic for the GCT. A "gate" mechanism in the dorsal horn of the spinal cord (where the primary afferent synapse to the secondary afferent neuron) is influenced by smaller nociceptive (C and Aδ) fibres, larger non-nociceptive (Aβ) fibres, and descending "Central control" signals from the brain [35, 40]. In the dorsal horn, a small inter-neuron acts as a gate. This inhibitory (Opioid) middle neuron is activated by fast, myelinated non-nociceptive afferent neurons (Aβ fibres) carrying senses such as deep touch, and normally inhibits the projection neuron (i.e.secondary afferent neuron's synapse). It also inhibits, albeit not directly, non-myelinated nociceptors (C-fibres). Thus, based on this theory, after noxious stimuli (such as heat) contact, first, Aδ fibres relay the initial sharp nociceptive signals to the brain. After removing the stimuli, the C-fibres are responsible for carrying the dull sensation of pain resulting from burnt cells on the tissue. Now, by activating Aβ fibres, like rubbing the pain area, the non-nociceptive stimuli activates the inhibitory inter-neuron resulting in the activation of the projection neurons, or as Melzack and Wall named, T-cells. As a result, it reduces the sensation of pain [190, 138].
This theory not only described a pain regulation process involving neurons with different firing,

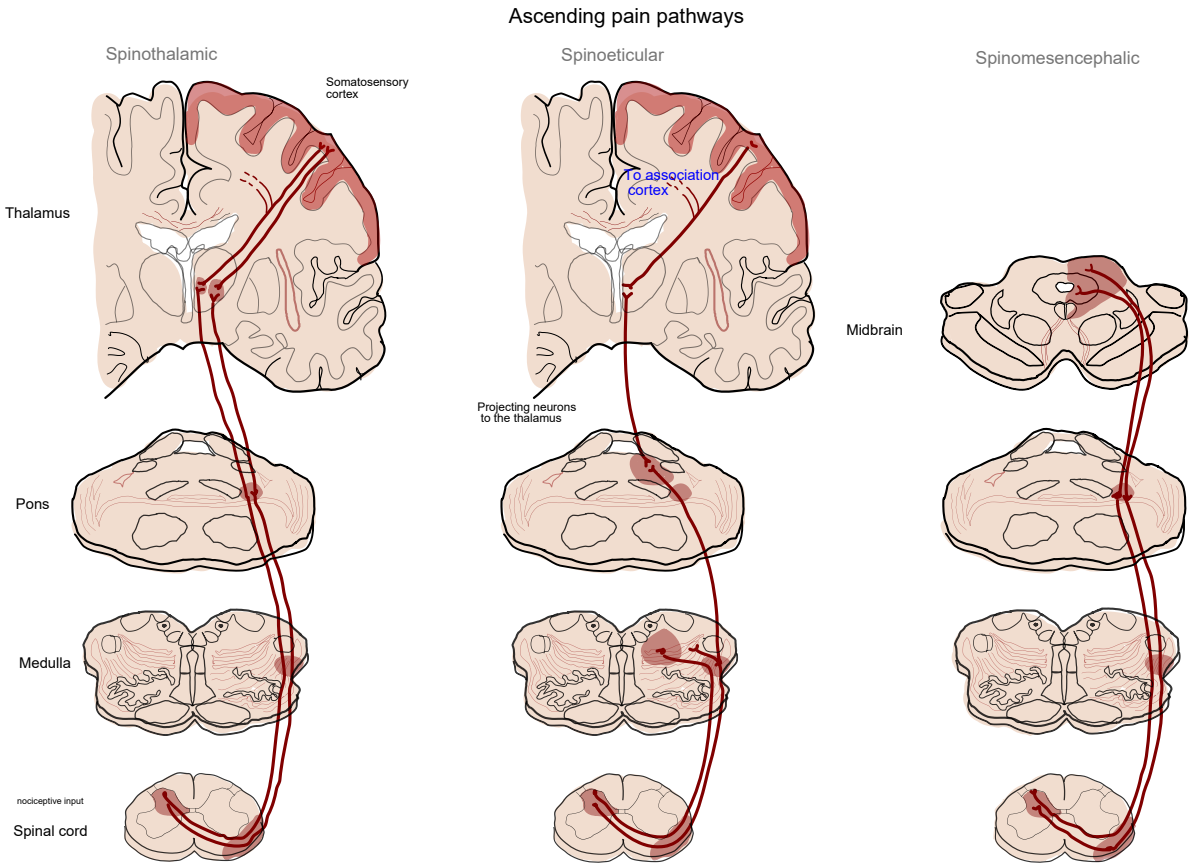

Figure 2.2: The ascending pain pathways [138].

but also described how attributes such as magnitude, type, previous experiences with pain, and attention affect the transmission of sensory nociceptive signals at the synaptic level [190, 40]. This was mostly done by providing feedback input from a central regulatory system to the gating system. They also suggested the replacement of the concept of "pain center" as a single "terminal center", with a more dynamic action system. The theory was a great step towards understanding pain variability and subjectivity [187]. However, this theory was unable to fully explain the conditions such as chronic pain or Phantom Limb Pain (PLP); a persistent pain that emerges from the body parts that no longer exists [40].

The multiple aspects of pain (such as visual and cognitive mechanisms), especially in conditions such as Phantom Limb Pain (PLP), -in which the pain occurs with no stimuli and no mapped body part to the pain- can question the direct relationship between pain and nociceptive sensory signal. Additionally, the activation of different areas of the cortex was observed in neuroimaging studies conducted when experiencing pain [129], which led researchers to the idea that there is no single "pain center" on the cortical level. In 1989, Melzack proposed that more widespread areas of the

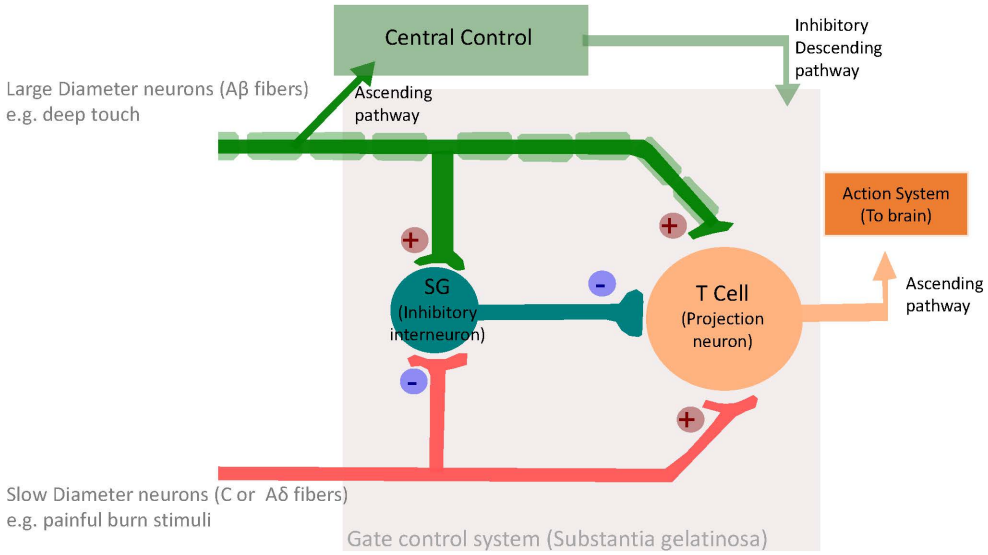

Figure 2.3: The GCT schematic [190, 138].

brain must be involved in this process[185]. He observed that in conditions such as Phantom Limb Pain (PLP), the limbs are felt "real" as a part of "self", and can be experienced even without any painful or physical input or stimulus [186].

He proposed the concept of "*body-self neuromatrix*"; a widespread network of neurons distributed through many areas of the brain.=[189]. He suggested that this body-self neuromatrix (a.k.a. *neuromatrix*) is a pre-wired network of neurons — which can also be modified by the sensory inputs— that consists of thalamus-cortex and cortex-limbic system loops. In this neuromatrix, body input signals go through *processing and synthesis cycles* and influence the formation of specific synaptic patterns (a.k.a *neurosignature*). The neurosignatures, as the out-flow result of the neuromatrix, can 1)be projected to different brain areas (*sentient hubs*) and result in awareness, or 2) activate other patterns.

Based on Melzack's proposal, the perception of bodily unity is formed by a neurosignature pattern containing the entire body. This could explain the multi-dimensionality of the body-self experience (e.g. having sensory and affective dimensions) by assuming that "portions of the neuromatrix [which contributes as a portion of the total neurosignature] lie in the sensory projection areas of the brain"[189]. Similarly, the neurosignature for pain experience is determined by the synaptic architecture of the neuromatrix, and this neurosignature can be modulated and triggered by sensory inputs (i.e. noxious stimuli) or cognitive events (e.g. stress)[189, 188].

With the advent of neuroimaging techniques (e.g. Electroencephalography (EEG), functional Magnetic Resonance Imaging (fMRI)), more and more studies aimed to find the underlying neurological mechanisms of pain. In these studies, some of the cortical structures were frequently observed to

be more activated than others in response to the nociceptive stimuli; including primary (S1) and secondary (S2) somatosensory cortices, insula, Anterior Cingulate Cortex (ACC), thalamus, and pre-frontal cortex[63, 208]. Taken from Melzack's neuromatrix theory, the collection of these structures was named as *Pain Matrix*[196]. Researchers observed that in Pain Matrix's structures, the magnitude of changes in the neural responses was often correlated with the magnitude and the modulation of a pain stimulus[126, 216].[1] Moreover, the Pain Matrix was considered as a network with some structures specifically responsible for processing the affective (e.g. ACC), and some for physical (e.g. somatosensory cortices) dimensions of pain [77]. This model became a fundamental assumption for some other psychological studies to interpret the data[149]. For example, in a study by Eisenberger et al., they found a similar activation pattern of ACC to physical pain in patients who were socially excluded from the group. They very cautiously reported and concluded that "social pain is analogous in its neurocognitive function to physical pain"[80]. As Iannetti & Mouraux and Mano & Seymour critiqued, such conclusions must be taken cautiously as many brain regions such as ACC [259] show similar activation patterns to both painful and non-painful conditions (a.k.a. functional multiplicity problem) [126, 173].
In 2014, Kucyi et al. looked at pain processing as a process of communication between brain cognitive networks encoded by a *Pain Connectom*, which is in fact "dynamic over multiple timescales". By employing a multi-variant analysis[2] he showed the pain-attention interactions through analyzing the three main brain-wide networks: 1) Salience Network, 2) Default Mode Network, and 3) Anti-nociceptive system. However, discussing the details of the study is beyond the scope of the literature review [150]. Later in 2015, Mono et al. suggested that to find the correct answer we may need to change the perspective; either we are looking with a wrong glass, or from a wrong direction.[3]They suggested that researchers should employ data-driven approaches to investigate the underlying mechanisms of pain, more frequently[173].

As any other biological system, *Degeneracy* has fundamentally contributed to the development and evaluations of the human brain [78]. Degeneracy is —as Barrett articulated— the ability for distinct representations(e.g. different sets of neurons), to generate a model of a common category (e.g. [Pain]) "in the same context" (i.e. many-to-one mappings of structure to function) [29]. Although many pain-specific neurons have been identified in the brain [126] the pattern of neural connectivity between (or even within) individuals is not fixed. Research to find the underlying

[1]These changes can often be captured by recording the neural activity of the brain which is explained in more detail in section 3 of this literature review.

[2]Multivariate pattern analysis (or "brain decoding") approaches to functional neuroimaging allow researchers to identify the information and activation patterns arising from different brain regions.

[3]"either the macro-scale resolution of fMRI is not able to adequately resolve heterogeneous micro-scale neuronal processing units (anatomy), or we haven't defined the psychological processes (functions) correctly"[173].

brain circuits and pain bio-markers continues; from the level of identifying pain-specific neurons and RNA sequencing, to identifying the connections between large brain areas in time scales, to finding the patterns that may now be visualized due to the technological advances that can help us control the environmental factors and target the pain and analyze it with higher precision. All, to find the best tailored treatment for pain, specifically chronic pain [161].

2.1.3 Chronic Pain

Chronic Pain (CP) is prevalent in 10% of the population worldwide making it one of the top 10 causes of suffering and disability [255, 123]. As mentioned in the previous section, given the complexity of how pain is processed, this experience can be modulated by natural, social, psychological, and emotional influences, internally or externally [101, 77]. Targeting one or multiple of these dimensions, medical and non-medical alleviating methods have been proposed to reduce the perceived pain and make it more manageable. In the following section, I briefly discuss these two categories with a focus on Virtual Reality (VR) as the main goal of this thesis.

Pharmacological methods

The International Statistical Classification of Diseases and Related Health Problems (ICD-11) classifies CP as pain that "persists or recurs for longer than 3 months", into 6 main categories[6]. In each condition (even considering the most common types of chronic pain such as low back pain, osteoarthritis, or migraine), the pain arises from different peripheral and biological processes, with different pathological and physiological symptoms. This variety makes the development and prescription of medical treatments a challenge [161].
In Canada, analgesic medical treatments for chronic pain stand amongst the top 10 standard-of-care solutions for people suffering from chronic pain[215]. Numerous medications have proven to be effective in chronic pain treatment. Non-opioid analgesics such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), antidepressants, and Serotonin-norepinephrine reuptake inhibitors (SNRIs), and opioids such as Codeine —individually or in combination— should be effective in relieving different symptoms and managing CP [204]. Such customization in treatment requires a thorough understanding of pain mechanisms [4] and a well-established patient-physician communication [204]. The lack of such communication and skills, in addition to other health-care barriers may add to the suffering of CP patients[105].
Additionally, concerns have recently evolved about the standard of care for CP, mainly question the overuse, and safety of medicinal therapies such as opioids. Although opioids are consistently termed the most effective treatment for CP, long-term opioid treatments have recorded harmful

[4]some factors might complicate the process of medication, such as the frequent co-occurrence of different chronic conditions (aka. Chronic Overlapping Pain Conditions (COPCs)) [161].

side-effects and there is a risk of abuse and opioid disorder[223, 161, 204, 77]. These issues suggest a need for substitute non-pharmacological strategies for CP treatment.

Non-Pharmacological methods

Given the drawbacks of the current pharmacological treatments and the insufficiency of their effectiveness in reducing pain, researchers have been exploring the non-chemical alternatives -to be used as a separate modality or as a multi-modality treatment method- for pain alleviation. Some of these methods proven for substantial pain reduction include physical therapy [81], neuro-modulatory interventions such as brain stimulation using tDCS[16], Neurofeedback, Biofeedback, Cognitive Behavioral Therapy (CBT), mindfulness meditation, and the use of technological interventions such as Virtual Reality [161, 77, 116]. For my thesis, I focus more on mindfulness meditation and virtual reality methods and their analgesic capability, discussed in the following sections.

Mindfulness Meditation

We can define mindfulness as a "non-judgmental" awareness of the present experience in which the person reaches the state of a "detached observant" towards their thoughts, experience, and their sensation [132]. One of the ancient Buddhist texts, Sellatha Sutta (The Dart), analogizes the experience of physical feelings or thoughts as a combination of two darts; "a bodily and a mental feeling". For an "untaught worldling", these darts would hit one after the other when you experience sorrow, death, joy, or pain. In contrast, the inscription illustrates a Buddhist as "a man [who] were pierced by a dart, but was not hit by a second dart following the first one" [250]. So, in the case of pain perception the sensation, and the feelings are distinct as two "separate events": the sensory aspect of pain (first Dart), and the pain experience (second Dart). One may become the "detached observant" by carefully paying attention to present moment experience and distinguishing these two darts[132, 66]. Such state of mind can be gained by practicing mindfulness meditation exercises [133, 66].

There are different meditation practices[66] usually classified based on the way they focus one's attention: Focused Attention (FA) in which the cognitive ability is gained by sustaining attention on a single object (such as breath, part of the body, or pain), and Open Monitoring (OM), in which the practitioner openly monitor all aspects of the experience [112].

While FA might provide distraction from pain sensation [137] and may be associated with pain threshold sensitivity and reduced hypersensitivity, OM practices are perceived as mindfulness meditations [112].

The mechanisms fully explaining the mindfulness meditation have yet to be recognized. Nonetheless, various mindfulness meditation practices were found effective for attuning pain sensation [97, 113, 268]. One of the most studied approaches is an 8 to 10-week Mindfulness-Based Stress Re-

duction (MBSR) practice [135]. In an early longitudinal study in the 1980s by John Kabat Zinn et al., a total of 90 participants with various Chronic Pain (CP) conditions underwent five consecutive 10-week cycles of training on stress reduction or relaxation programs; 6 days per week at least 45 minutes per day. In addition to assessing participants' pain levels, the researchers followed up with participants a few times for a year and a half after the study. They observed that the program was successful in reducing subjective pain and related pain symptomologies such as negative *body-image* and mood. Moreover, this improvement is sustained over future follow-ups [135].
The effect of an 8-weeks MBSR practice, has been evaluated in many studies and compared to other pain management practices, such as CBT [49]. However, these usually intensive practices are time-consuming, require highly-trained therapists, and are usually delivered in specialty settings (e.g., pain clinics); Shorter practices of mindfulness meditation might also be effective in pain reduction.
A more recent study by Zeidan et al. evaluated the thermal-stimuli-evoked pain in a shorter form of practicing mindfulness meditation (4 sessions of 20 minutes). They compared the pain among four groups who did different activities: mindfulness meditation, sham mindfulness, placebo condition, and listening to audiobooks. Although the result showed pain intensity and unpleasantness reduction in all groups compared to the control, they showed that mindfulness meditation was significantly more effective in reducing sensory processing when down-regulating painful stimuli [268].
The effect of even shorter ($\approx$ 30 minutes) intervention or Brief Mindfulness-Based Interventions (BMBIs) has also shown a reduction in pain intensity sensation in some studies. Although, this effect may depend on various factors such as the nature of pain, duration (less or more than 5 minutes), the mindfulness technique, and the practitioner's experience level [183].

Virtual Reality

The use of technologies such as biofeedback and neurofeedback systems can also be an alternative treatment for pain alleviation as well. Virtual Reality (VR) has also shown potential as a non-pharmaceutical alternative for pain (aka. VR-analgesia) over the past 20 years [116]. In the next section of this literature review, I focus on this technology for CP alleviation, starting with a brief introduction to VR before getting to the details about its effectiveness.

2.2 Virtual Reality

As introduced in the first chapter, this thesis focuses on evaluating the effectiveness of VR-embodiment (VE) for Chronic Pain (CP) alleviation. In the *Virtual Reality* section of my literature review, I first introduce the VR technology before getting to the two main approaches explaining the underlying mechanisms of VR-analgesia. I first discuss the VR distraction approach for VR-analgesia by reviewing some primary and recent studies. Second, we explore the phenomenology

of embodiment and body ownership before reviewing the relevant experiments and literature on VR-embodiment and CP, crucial for justifying the design of the experiment in the methodology chapter of this thesis.

2.2.1 VR

In the 1980s, Jaron Lanier founded the VPL company and coined the term Virtual Reality (VR) by commercializing the first display products that could display an alternative computer generated reality. The VR paradigm has evolved from the early stage of projecting computer graphics on large screens to CAVE-like systems with 360 degrees of freedom to newer technologies employing high-resolution Head Mounted Displays (HMDs). The definition of VR that I use in this thesis is Immersive VR, a 3D computer-graphical designed, interactive VR environment being projected through VR-HMDs [36, 247].
Given VR interventions' unique ability to modulate sensory inputs and simulate a virtual world for the audience, researchers employed this medium for purposes other than a mere tool of game, including the field of pain analgesia [116].

2.2.2 VR for Pain

About 40 years after developing the first Virtual Reality (VR) system in the 1990s, Diane Gromala and Yacov Sharir designed the first VR work specifically for CP at the Banff Centre for Arts and Creativity: Dancing with the Virtual Dervish [198]. In this VR experience, they transformed MRI data into a 6-degree-of-freedom VR, which resulted in a short time analgesic effect.
Leveraging VR for pain reduction and management was introduced at the beginning of the 21st century. Since then, it has been shown to be an effective tool for patients experiencing pain in different medical conditions and during various medical procedures [116]. Researchers have studied different aspects and factors in VR design and implementation that might affect its effectiveness in pain reduction. Although the exact mechanism through which VR functions to reduce pain remains unknown, most proposed mechanisms attribute the impact of VR to attention distraction [158] or VR-embodiment [181] approaches. In the following sections, I discuss each of these theories briefly. These sections may help the reader better understand the reason for choosing the two study conditions that we compare in Chapter 3.

VR Attention distraction

According to the Attention Distraction Theory, the VR analgesic effect is primarily due to its significant ability to distract a person's attention [158, 116]. They hypothesized that based on the multiple-resource theory [31], VR could compete with patients' pain over the limited amount of the brain's attentional resources. Therefore, instead of pain, patients' attention would be attracted to the VR environment[106, 73].

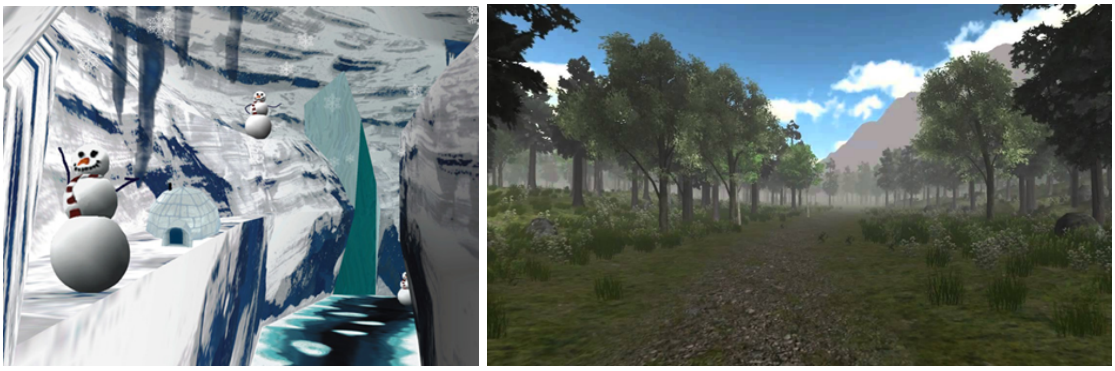

Figure 2.4: (left) A scene from the Snoworld VR environment designed for burn patients by Hoffman and colleagues [120]. (right) A scene from the VMW VR environment design by Gromala and colleagues [115].

Leveraging VR for pain -and more specifically acute pain- treatment was initiated by Hoffmans's team in 2000 by designing the SnowWorld (Figure 2.4(Left)). SnowWorld is a VR application during which patients float through a snowy path and can shoot snow toward objects such as snowmen by pointing the HMD towards the objects. Their study on adult burnt patients during a painful physical procedure showed a reduction in subjective pain rating after using the VR video game [120].
A few years later, in 2004, by designing an fMRI-compatible VR HMD, Hoffman's team conducted an fMRI study on fourteen participants during the SnowWorld VR intervention while applying "painful" thermal stimuli to participants' hands [121]. They observed that brain activity decreased in the VR scenario over the brain regions associated with the processing of pain (thalamus, insula, the Anterior Cingulate Cortex (ACC), and somatosensory cortex (i.e. S1,S2)).In another fMRI study a few years later, they also found out that the analgesic effectiveness of VR, as a non-pharmaceutical treatment, is comparable to a medium dosage of opioids [122]. Gold et al. analyzed the neurobiology of VR and pain by referring to Melzak's Gate Control Theory (GCT) (see section 2.1.2 for more information) [106]. They believed that VR modulates pain perception "directly and indirectly by engaging mainly attention, but also emotion, concentration, memory, and other senses such as visual and auditory," thus modulating the complex pain perception system. He hypothesized that by shifting attention from the medical procedure to VR environment, the perigenual ACC activates, which is known as a mediator for attentional and emotional processes. Activation of ACC projects and activates the Periaqueductal Gray (PAG), which can cascade signalling events through the descending pain pathway (i.e. "Central control"), producing analgesia [158, 106].

Although VR for pain attenuation has been studied for more than 20 years, most of the Randomized Controlled Trial (RCT) studies on attentional distraction have been conducted in the past three to four years. These studies were predominantly targeting acute pain in the fields

of burn treatment[102, 240], venipuncture (or intravenous procedures)[108, 75], emergency room procedures[109], labour[179], dental procedures[214], post-stroke[20] and post-cancer treatments[25], surgery[53], and pediatric pain [75, 107, 108], primarily hiring interactive games and VR environments. However, only a few RCT studies have focused on the effectiveness of VR as a distractive medium amongst Chronic Pain (CP) patients [157, 76].
In addition to the aforementioned interactive VR environments, physical rehabilitation using VR is another approach towards designing VR application for indirect pain alleviation. Some VR applications, such as Lumapath, researched by Tong et al., have hired this method to reduce chronic and acute pains and increase patients' range of motion. However, this category of VR applications is not in the scope of my thesis [248].

As I mentioned in section 2.1.3, meditation is one of the non-pharmaceutical methods that can be employed for CP treatment. Given this idea, another approach to design VR environments employed by researchers was using VR environments for mindfulness meditation practices [194, 99, 98]. Gromala et al. conducted one of the first studies on using mindfulness meditation in VR for CP patients [114, 241, 115]. By combining an immersive VR environment with pain control mindfulness practices (Mindfulness-Based Stress Reduction (MBSR)), they designed a VR application named Virtual Meditative Walk (VMW) (Figure 2.4) [115]. In this application, a vocal coach guides CP patients through mindfulness practices, directing their attention inward.
They utilized patients' Electrodermal Activity (EDA) as a bio-feedback manifested in an environmental fog with its thickness correlated with patients' CP intensity. A user study, over 13 CP participants by Gromala et al. showed that VMW was more effective in reducing perceived pain than the non-VR control condition, in which participants only listened to the Mindfulness-Based Stress Reduction (MBSR) practices [115]. In my study protocol, I also used the VMW VR environment. Therefore, the detail of this application is further discussed in Chapter 3, section 3.2.2.
Trost et al. have also recently studied walking in nature in a VR environment. They utilized an interactive VR intervention replicating the sense of walking among adults with Spinal Cord Injury (SCI) neuropathic pain. Their 2-week intervention reduced pain intensity and improved patients' mood and affect [252, 118].
A more recent study by Hu et al. compared the cortical process of two groups of healthy subjects before, during, and after 10-minute interoceptive breathing awareness practices. Participants were assigned to either the Virtual Reality Breathing (VRB) or Traditional Mindfulness Breathing (TMB) group. In each group, after the functional Near-Infrared Spectroscopy (fNRIS) initial pre-test, they experienced three sessions of fNIRS, breathing and 5-minute pre-fNIRS, 20-trials of thermal Quantitative Sensory Test (tQST), and breathing and 5-minute post-fNIRS. Participants' pain sensation was collected during the tQSTs. Following the study session, participants were asked to continue using the at-home breathing technique for 7 days, 3 times per day (See Figure 2.5 (right)), and a similar protocol were employed on the seventh day. The VR design was

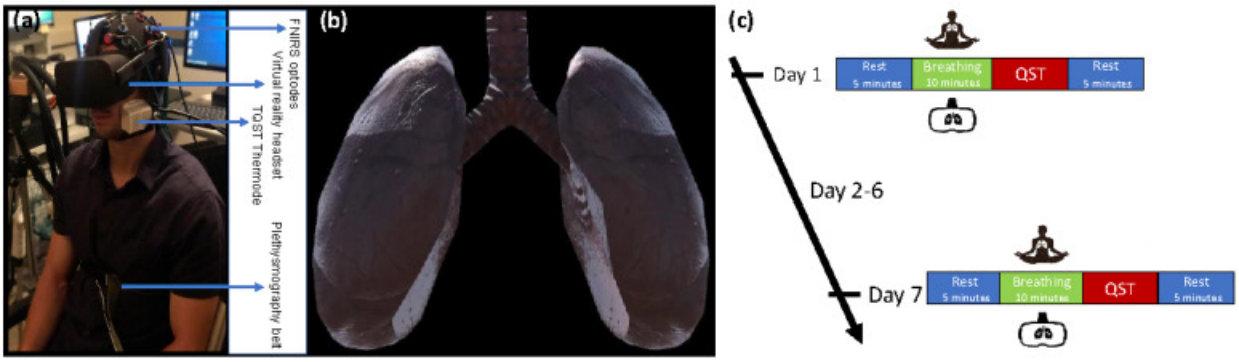

Figure 2.5: (left) The virtual 3D model of lunge and fNIR setup for the study by Hu et al. (right) The schematic of the study protocol designed and proposed by Hu et al.. [124].

a 3D-modeled lung synchronized with participants' inhaling and exhaling cycles while they could listen to their breathing via headphones (see Figure 2.5 (left)). Similarly, the TMB group was asked to imagine their breathing [124]. While participants in both groups showed an increase in their pain threshold without any group difference, 3 of their reported findings are of importance to my thesis: [131, 50].

- Primary Somatosensory Cortex (S1) region was activated in both groups at both visits. However, this activation has decreased for TMB group, while it increased amongst VBRs.

- The activation of aPFC has been reduced for both groups over a week. Also, this trend of less activation was correlated with an increase in participants' pain threshold. PFC is known for its role in attention control and emotional processing. In a study by Zaidan et al., they observed the default-mode-related (medial PFC) deactivation during the attention to the breath practices [267].

- They found activation in the right Tempro-Parietal Junction (rTPJ), right Dorsolateral Prefrontal Cortex (DLPFC), and visual cortex for the VRB group, and deactivation of TPJ and auditory cortex for TMB.
  TPJ responds consistently to sensory inputs that are novel and salient, regardless of sensory modality [72]. It, also, acts as a multi-sensory international hub encoding self-location. TPJ activated during the experimental changes in self-location in the presence of visuo-tactile and visuo-vestibular conflicts [127]. More specifically rTPJ plays a role in maintaining the internal representation of verticality [84, 139]. Kucyi et al. also found out that rTPJ encodes the prolonged salience of pain and might be part of the salience/ventral attention network and other regions implicated in salience/pain-related processing (e.g., insula, S2) [151]. Its activation is also coupled with "sensory-discriminative and affective-motivational aspects of pain."
  Additionally, DLPFC plays a role in "top-down modulatory control over early visual attention processes" [266] and cognitive control adjustments [44].

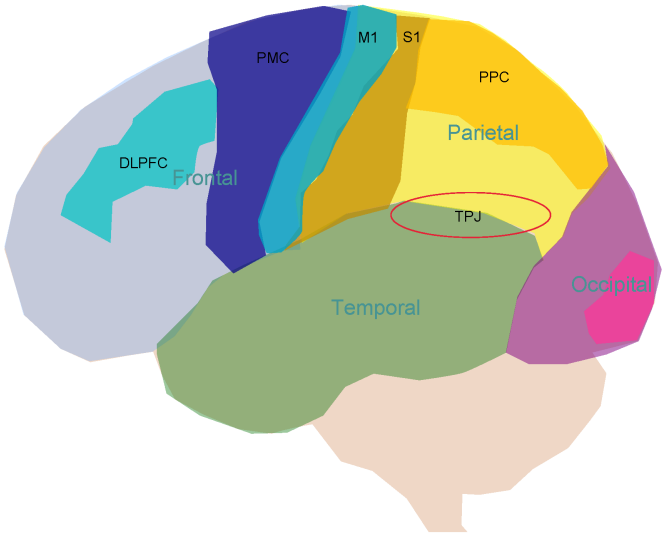

Figure 2.6: A schematic of the brain lobes and regions.

More specifically Lorenz et al. observed that the magnitude of DLPFC activity significantly affects the relationship between pain intensity and unpleasantness, and anterior insula activation [165], which itself plays a crucial role in predicting the pain intensity of an impeding painful stimuli [263].

Hu et al. proposed that VRB and TMB conditions might result in an increase in the participants' pain threshold through two different methods. They suggested that VR experience provides a "3D-extroceptive experience" and activates visual-auditory activation that diminishes the functional connection with S1, and weakens the pain process of S1. While in the TMB condition, aPFC modulates PMC which increases the functional connectivity between PMC and S1. This increases the introspective processing of breathing which consequently inhibits S1's role in pain processing [124]. However, given the limitations of their study such as the lack of a nonintervention control group or the VR design, these results - however partially- might not fully picture the brain mechanisms of a meditative VR for CP reduction. Nevertheless, I refer to some of these findings in the next section regarding the VR-embodiment.

To summarize, for over two decades (from 2022!), VR has shown great potential to -at least partially- replace traditional pharmaceutical pain treatments, especially in the field of acute pain and in the short term. This has been achieved by either directing attention outward (using interactive, engaging VR "games", or inward using meditative environments. However, there are a few points that can be raised:

- Most of the studies on VR applications are often on lab-designed prototypes or commercial applications not specifically designed for pain treatment. Therefore, no standardized design methods and mechanisms exist to develop VR environments for pain treatment. This variation in design[27] may jeopardize the validity of research and the reproducibility and comparability of study results.

- The lack of not-publicly-accessible and clinically proven VR applications makes it harder for the end users to benefit from it in at-home settings. Additionally, as most of the studies were single-session experiments, it is yet to be discovered if VR distraction effects persist beyond the therapy session and if it benefits long-term use.

- In this section, I reviewed the literature on VR attentional distraction. Although some methods tend to provide a sensory-exteroceptive and some introspective experience, not enough research studies are conducted comparing the effectiveness of these two methods on pain reduction.

- Moreover, there are few studies on VR for attention distraction quantitating participants' experience using biological or neurological data. Although there might not be a clear-cut picture of CP brain mechanisms, having neurophysiological measurements in addition to the subjective pain assessment can help us better understand the brain mechanisms for both VR and pain[5].

VR-Embodiment

In a review by Matmala-Gomez et al., they claimed that the effectiveness of VR as a distractive medium might be due to the "lack of embodiment and a virtual body" in the VR scenarios. They reviewed studies on VR-embodiment, showing how body representation provides subjects with Sense of Presence and how manipulating those bodies (parts) can modulate pain perception [181]. Researchers believe that VR provides one with visuotactile sensory feedback. The feedback alters an individual's sense of presence which might play an essential role in pain perception. Riva et al. suggested predictive coding as an explanation of how VR-embodiment works by changing the "internal model" of the *body-image* in the brain'[221].
In this section, I briefly reviewed the theory of VR-embodiment. For this, I first define embodiment and discuss its relation to CP, before discussing the theory of VR-embodiment. This section is specifically important for justifying the use of avatar in the study protocol I propose in Chapter 3.

[5]I also wanted to add that given Hu et al.'s study and the studies I review in the VR-embodiment section, distraction and VR-embodiment might even be the two sides of the same coin. But, indeed much more detailed VR and neuroimaging studies are required to get a better picture of such hypothesis, which is way beyond the scope of my Master's thesis!

Embodiment

How can I understand that *this is me*? How do we accept that the body we are "feeling" is "our body"? How do we see our self the "cause" of an "action"? Descartes and Spinoza questioned the mind-body (embodiment) relation 500 years ago: "What is the relationship between a mind and its body—the one that it seems to inhabit, feel, control or otherwise be uniquely involved with?"[207, 110]. Yet, ever since, despite being used by many authors in various ways, "Embodiment" has been defined differently based on context and use [142]. Regarding that, there have been interesting philosophical debates on how to define and structure this concept (I suggest reading Gallager et al. articles [94, 90], Thomas Metzinger's book [191], and their argument regarding this matter [92, 192]). To limit the definition of embodiment to the immediate "subject of experience, unextended in time" and dependant to the brain experience, in 2000, Gallagher coined the term *minimal-self*. He believed this minimal-self awareness involves two components of agency and ownership [89].

For my thesis, I used the common definition of previous literature on VR-embodiment; The brain's capability to construct a "mental representation of one's body" [178, 181] as a non-conceptual somatic, form of knowledge [163]. Shawn Gallagher provided a framework to separate the two aspects of Embodiment; 1) *body-image* as "an intentional content of consciousness that consists of a system of perceptions, attitudes, and beliefs about one's own body," and 2)*body-schema* as "an automatic system of processes that constantly regulates posture and movement, that functions without the necessity of perceptual monitoring [90]." For example, in the scenario of picking up a cup, our attention (related to the function of *body-image*) might be on the cup, its location or our desire to drink coffee rather than paying attention to the movement of our arm and mussels towards it. The smooth movement of our body results from the automatic motor function related to the *body-schema* [89].

We can define the Sense of Embodiment (SoE) as an "ensemble of sensations that arise in conjunction with being inside, having, and controlling a body [142]." Kilteni et al. classified the properties of SoE (our embodied experience) into three sub-components: Sense of Ownership (SoO),Sense of Agency (SoA), and Sense of self-Location (SoL) [89, 142, 163]. SoO reflects the sensation of having and belonging to a body (i.e., *this is My Body*), SoA refers to the experience of having control over the body in causing an action (i.e., *I am the doing this action*), whereas SoL is the sense of *being there* and locating inside one's body [142].

But how do we relate these two concepts? Recently, Ben David and Ataria proposed a *body-image/schema-ownership/agency* model to define the relationships between these two concepts used by Gallagher and other researchers [34]. As shown in Figure 2.1, based on the level of consciousness (*body-schema/ body-image*) processes (*feeling/knowing*) each of these components. The model, then, divides the Agency and Ownership into two sub-components, the *Sense/Judgment of Agency and Ownership*, respectively. Nevertheless, in relative literature, *body-image* is the term commonly used instead of a distinction between *body-image/schema*, and the *SoO/ SoA* instead of

	Ownership	**Agency**
Body Schema (Sense)	BIID	schizophrenia
Body Image (Judgment)	Anaroxia	PTSD

Table 2.1: The *body-image/schema-ownership/agency* model by Ben David et al [34]. The model explains the etiology and pathology of different conditions based on the relation between *body-image/schema-ownership/agency* and their effect on one another. For example in the BIID condition, it is known that patients gradually lose the feeling of ownership over a body part. So, first, we can identify the source of the problem as a decrease in the SoO in *body-schema* level (horizontally). Consequently, the problem in the *body-schema* level results in a contradiction on the *body-image* level (vertically). Patients' limb ownership perception decreases while the perception of agency remains unchanged.The *body-image*, then, adapts using a top-down process. Patients might correct the mismatch by either decreasing the agency (e.g. stopping using that limb) or, increasing the ownership (e.g. by engaging in activities such as sports).

Judgment of Agency/Ownership.

We usually experience the presence of both *body-image* and *body-schema* because, first, these two cognitive systems are linked, work synchronously together, and shape each other[91]. Second, our body is always there! However, in some cases, *body-image/body-schema* dissociation might manifest in neural degeneration, dysfunctional multi-sensory integration, or brain damage (such as in Body Integrity Identity Disorder (BIID), Anorexia, hemineglect, and some types of chronic pain such as Phantom Limb Pain (PLP)) [39, 34, 90]. For example, in the same paper mentioned before, Ben David and Ataria explained that in the phantom limb phenomenon, [in the *body-schema* level] one's SoO towards their body parts exist while, in fact, the limb is no longer there [34].
However, it is challenging to study the dissociation between *body-image* and *body-schema*; As Longo et al. put it well, such experiments "would involve comparing one condition in which a participant has a body and another in which they do not" [163]. Therefore, researchers rely on producing bodily illusion experiences by manipulating the multi-sensory input. For example, by stimulating the afferent sensory inputs, we can generate body ownership illusion during the Rubber Hand Illusion (RHI) experiment [163, 43].
During the RHI, the experimenter applies a tactile stimuli (stroked with a paintbrush) to both subjects' left hand (hidden out of sight) and the visible rubber hand with a paintbrush, while they see a lifelike rubber left hand in front of themselves. If the stroke happens synchronously, the subject experiences the rubber hand as their own with an illusion of ownership towards the rubber hand. In their study, when Botvinick and Cohen asked the participants to point to their left hand, they usually pointed toward the rubber hand. Also, when they applied the strokes asynchronously and in different directions, participants did not experience the illusion of ownership anymore [43].
Ramachandran et al. showed that a similar visuotactile illusion could also be employed to help

Phantom Limb Pain patients [218, 71]. In a study called *Mirror Box*, they used a mirror perpendicular to the patient to reflect the normal hand on the phantom one so that they could see the other hand in the mirror. Patients "felt" their arm was "resurrected" and "plugged in again" after "seeing" the movement of the reflection of the normal hand in the mirror [218]. Their PLP has also been controlled or resolved after four weeks of using the *Mirror Box*.

In this subsection, I reviewed some of the related concepts in the embodiment theory to my thesis. I defined the two fundamental constructs of embodiment (i.e. *body-image* and *body-schema*), and its sub-components (i.e. SoO, SoA, and SoL). In the following sections, however, I might use the term‘ body representation’ as a reference to the general, neuronal representation of the body.
We also learned that bodily illusions could be generated to modify embodiment components through multi-sensory manipulation. Bodily illusions can be used to study the dissociated *body-schema* and *image* and help us solve those disorders, specifically CP. The VR technology allows us to generate these illusions unlimitedly, more effectively, and with a greater degree of freedom. However, concerning my thesis topic, I first need to review how distorted body image might affect CP.

Embodiment in the Brain
In the previous section, I generally reviewed two complex constructs maintaining the ongoing bodily experience; *body-schema*, as the generally unconscious bottom-up sensory-motor and organizational processes, and *body-image* as a sometimes conscious, higher-order, top-down bodily representation which is the constitute of perception, attitudes, and beliefs [22, 104]. However functionally distinct, these two constructs are not mutually exclusive, and based on Gallagher's co-construction model, they maintain a strong interaction to construct a body representation [93]. Integrating these top-down and bottom-up processes to provide a full bodily sensation is complex and requires the integration of visual, vestibular, proprioceptive [6], and efferent motor inputs (i.e. interoceptive) bodily signals.
Incongruency in data and failure to coordinate those input signals may elicit an abnormal Sense of Embodiment in body parts. Such incongruencies have been observed after brain injuries, vascular stroke, or deafferented patients [164]. For example, Wolpert et al. described a patient with *Asomatognosia* injured on her Superior Parietal Lobe (SPL) [264]. This patient reported that her right arm and leg would drift and then fade (i.e. *proprioceptive drift*) unless she was able to see them

[6]Proprioception comes from the Latin word proprius (meaning own) + English word -ceptive (as in perception). It refers to the way we feel our "self" (i.e. body parts) in space. This provides feedback on the body's own actions by sensing one's own limbs and trunk position and movement, and the sense of effort, force, and heaviness, signaled by receptors in muscles, joints, skin, etc.. The proprioception has usually been associated with the activation of Posterior Parietal Cortex (PPC) [213, 104]. We can induce the illusion of this sensation by stimulating primary muscle spindles with different frequencies. Surprisingly, such illusions might position the limb in an arrangement physically impossible to reach or move to [104]!

(i.e. *visual capture*) [104].

It might be a naive approach if we want to pinpoint regions in the brain responsible for processing bodily information. The complex task of maintaining the body representation requires a harmonic implication of several brain areas. Nevertheless, Premotor Cortex (PMC) and Posterior Parietal Cortex (PPC) (aka. Somatosensory association cortex) has been shown to have a crucial role in integrating such multi-sensory inputs. PPC and PMC are suggested to be involved in perceiving the SoE [164]. It is suggested that these regions transform and *re-reference* sensory-motor signals gathered from different references, and generate a representation of the body - as a whole- in space. This would allow individuals to move and interact with the environment [104, 164, 127]. In order to better understand the underlying mechanism of embodiment, some brain studies investigated the *proprioceptive drift* in RHI experiments and associated it with the activation of PMC, PPC, and right posterior Insula. Lesion of right Tempro-Parietal Cortex and PPC has also, been associated with disorders such as Somatoparaphrenia [7] in some patients [156, 104]. Ionta et al., inspired by a previously designed "out-of-body-experience (i.e. full-Body-RHI)" [156, 155], ran an fMRI study on healthy participants [127]. They experimentally manipulated the SoL by changing the participant's perspective. They observed that TPJ activity was different between the synchronous and asynchronous stroke conditions only when a virtual body was seen and suggested that the activity of TPJ might reflect the SoL.
Giummarra et al. suggested that in specific conditions (e.g. when the visual and proprioceptive or auditory sensory inputs are incongruent), the multisensory neurons in PPC and PMC favour the visual input as it has more "spatial acuity" over others. During this *visual capture*, our proprioception drifts from the *felt* position to *seen* [104]. The RHI can be an example of bottom-up (*body-schema*) and top-down (*body-image*) interplay. Giummarra et al. conjectured that for a given generated movement command, not only is the command is being sent to the efferent neurons for action, a series of expected sensory outcomes would be predicted based on the internal body-representation template of the body in the space. In case of any incongruent information between the expected and sensory outcomes, this template would then be adjusted. For example, in the case of amputation, the *forward model* exists while following the deafferentation; there might not be a sensory *feedback* to contradict and correct the "template," so the patients falsely perceive the movement of their limb [104]. This conceptual phenomenon is also referred to as *predictive coding* in literature [221].
The limb ownership illusion in RHI has also been associated with the activation of the Primary Somatosensory Cortex (S1), Secondary Somatosensory Cortex (S2), Primary Motor Cortex (M1) [166, 197], Anterior Cingulate Cortex (ACC), and cerebellum[8] [79]. S1, S2, and M1 might be

[7]"Somatoparaphrenia is a delusional belief whereby a patient feels that a paralyzed limb does not belong to his body [95]".

[8]Plays a role in representing the automatic, real-time *body-schema*

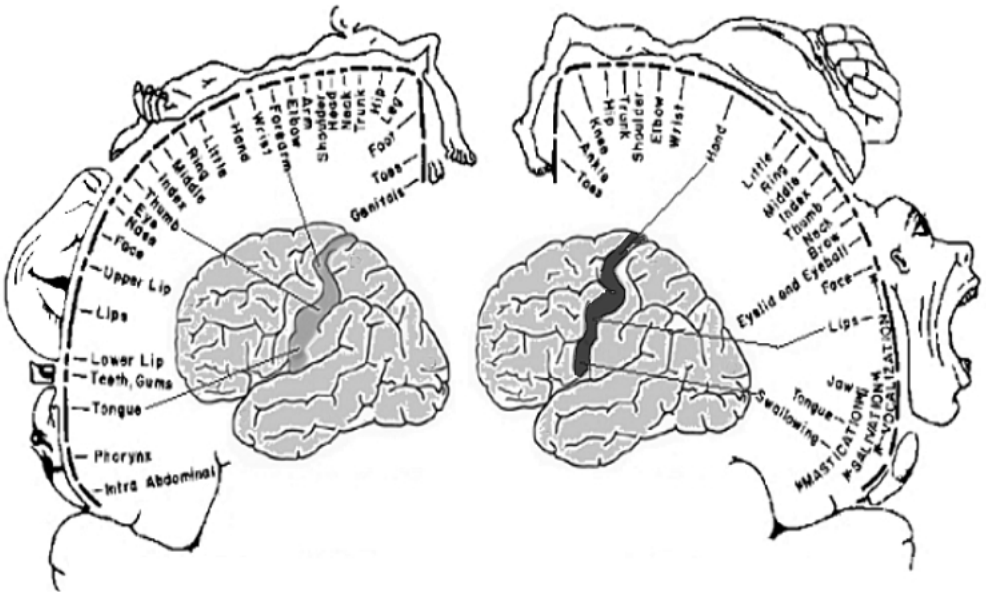

Figure 2.7: Somatotopic map of the body.(left) Somatosensory , (right) Motor homunculuse [88, 206].

amongst the most studied regions representing the body in the brain, especially in pain and CP studies [253, 170], given the importance of the topographic body-part mapping (a.k.a. somatotopic map, figure 2.7) proposed by Penfield et al. in the 19th century [170].

To summarize the section, the body representation in the brain is based on an ongoing and successful integration of multi-sensory signals on a brain-wide matrix of regions. Incongruent signals might cause dissociation between *body-image*/*body-schema* and result in conditions such as Somatoparaphrenia, Asomatognosia, and types of CP such as PLP, SCI, and CRPS. [197, 104]. This dissociation is often known as distortion in *body-image* or *body-schema* which I discuss in the next section.
Additionally, I discussed some of the possible brain regions associated with processing the body-representation, mainly regions responsible for processing and integrating the sensorimotor signals. Although, the exact construct of *body-image* and *body-schema* is under ongoing investigation! The question remains about how such dissociation might affect CP, which I discuss in the next section.

CP and distorted body-image
Our brain is plastic. This process allows the brain to re-organize and form new neural connections during the memory and learning processes, recovering from brain injury and healthy aging. For example, brain plasticity allows the body representation to re-organize and adapt to the new sensory (i.e. bottom-up) signals and update the *body-image*. So, when we roller skate, the representation of

our legs can extend to the skates after the first few minutes. So, we can ride it without thinking about it as an alien accessory [104]. However, sometimes, this reorganization in neural connection causes disorders such as chronic pain [71].
Studies on phantom limb pain shed light on the link between distorted body representation and pain [85]. In some people with PLP, the limb extends to other regions [218, 71]. Studies on the brain re-organization amongst PLP patients observed cortical changes in the regions related to the process of sensorimotor signals from the lost limb, and the scale of these changes has been strongly related to the severity of PLP [154, 71]. This reorganization may likely happen after a chronic loss of feedback signal from the deafferented limb, accompanied by a shift in the limb's region towards the neighboring regions in the primary motor and sensory cortex. Consequently, these changes might "cause central excitability" and impact cortical and sub-cortical connectivity, including affecting the thalamocortical inhibitory system [197, 154, 71]. Lotez and Moseley suggested that this remapping might occur due to "structural changes like axonal sprouting" or activation of connections between areas responsible for representing different body parts, which were usually suppressed[166]. However, correlation does not necessarily bring causation and similar brain changes have also been observed among people with amputation and without pain. [171, 59].
Lotez and Moseley claimed that the experience of pain might lead to cortical reorganization, but it does not always necessarily cause it. However, the presence and magnitude of pain, chronically, might reinforce the reorganization. They argued that changes in GABAergic and cortical inhibitory systems [9] might lead to increased cortical excitability, which can lead to cortical reorganization. For example, it has been observed that after treatments such as mirror therapy or deep brain stimulation for CRPS or PLP, the change in body representation results in lower perceived pain [154, 67]. Moreover, normalization in the structure of S1 has been observed upon pain elimination. [197].

The changes in many cortical regions have been investigated regarding Chronic Pain. For example, a recent tDCS study by Kikkert et al. used fMRI to analyze brain activity in participants with PLP. They stimulated S1 and M1 cortices while the participants were asked to move their phantom hand. The results showed that the stimulation caused the phantom limb disappearance and reduced the PLP sensation while reducing the activity of primary motor and sensory cortices [141]. Similar cortical activation was also reported during mirror therapy plus motor imagery for PLP [154]. Nevertheless, it might be wrong to assume that there is a simple relation between the remapping and the sensation of Phantom Limb Pain as the inter-regional connections between brain regions (cortical and sub-cortical) are not one-directional and simple. So, we cannot conclude that the remapping of a single cortical region occurs exactly due to the changes in one body part, and more studies on network-wide relations on PLP is required [171].

[9]Inhibitory neurons have the ability to reduce the activity of specific neurons, such as pyramidal neurons in the cortex [58].

In addition to S1 and M1, changes in insula connectivity have also been reported in some CP conditions such as Fibromyalgia (FM) [254]. Insula appears to be involved in the central processing of internal bodily signals and contributes to the brain's salience network.
Scandola and colleagues found that FM patients often feel like their bodies are strange and unfamiliar. Although there is no clear connection between pain and bodily sensations, their study on 60 women with FM condition revealed that in addition to body representation, motor imagery was also affected by pain. Furthermore, the more severe the impairment in motor imagery, the more the participant's daily functioning was impacted. They suggested that the results might show that body representation and motor imagery impairments are part of FM's clinical presentation [228].

Lengenhagger et al. claimed that pain reduction followed by S1, M1 activation during mirror therapy is highly influenced by how much ownership and agency patients feel towards the movement of the intact limb [154]. They suggested that wearing a prosthetic limb after an amputation might mitigate PLP in a similar way as brain imagery; by increasing the SoA and SoO through sensory feedback. The result of a survey by Bekrater-Bodmann et al., over 2383 prosthesis users reported that with an increase in SoO towards the prosthesis, the sensation of the phantom limb and PLP decreases [33], and the phantom limb eventually fades or merges with the sensation of the prosthesis [154]. Using a prosthesis has also increased the excitatory activity and cortical reorganization in M1 and S1. [167].
Using a prosthesis may correct bodily-representation of the absent limb in the *body-schema* by utilizing the same motor patterns employed for regular body movements. Integrating the prosthesis into the *body-image* can help prevent cortical reorganization and ultimately lessen the severity of PLP.

In summary, it is suggested that the severity of some types of CP is related to the degree of distortion in their body representation. We do not exactly know the causality sequence between distorted body image and pain, nor have we fully identified the underlying mechanisms of it. However, correcting that representation by utilizing treatments such as mirror therapy, prosthesis, or Virtual Reality can effectively reduce pain.

VR-Embodiment and pain
Without a full picture of how body representation associates with pain and how VR affects it, it is difficult to pinpoint the mechanism of VR-embodiment and VR analgesia. However, studies have observed pain reduction by improving the body representation through "bodily illusions[181]." We can generate an illusion of the body by using a rubber hand, a mirror, or a virtual avatar. Many studies in VR-embodiment have also reported analgesia (usually induced pain) by experiencing Sense of Embodiment [247, 181, 116].
Some researchers have assimilated the effectiveness of VR-embodiment to prosthesis limb, especially

in conditions such as PLP[154, 104]. Visual and sensory feedback from the virtual world, simulating sensorimotor signals, alters the perception of the body, creating an illusion of embodying the virtual body. For the case of amputation, by seeing and moving the missing limb in VR replicating the missing body part, "re-embodying a functional body" can help regenerate the neuronal pathways that had been degenerated due to the loss of motor and sensory feedback from bottom-up pathways (see the previous section)[154, 104].
Riva et al. theorized VR-embodiment underlying mechanism using the *predictive coding* (see section Embodiment in the brain and De-Wit et al. [61]) theory. They believed that VR acts in two levels. First, through a *"body swapping phase"*, a virtual body (i.e. avatar) replaces the sensory inputs (i.e. *body-schema*) and improves the "disturbed body." Then, through a *"frame shifting phase"*, the content of the body in "memory" (i.e. *body-image*) would be reorganized and updated. They explained that the level of effectiveness in VR might be due to the similarity of VR and the human brain's function. VR predicts and provides the sensory feedback from the virtual world, similar to how brain expects such feedback from the *actual* world[221].

The Sense of Embodiment in VR can be induced by leveraging an avatar (completely or partially as a limb). Synchronous stimulation (i.e. visuotactile correlation) of the visual body part and the use of avatar synchronous with participant's movement (i.e. visuomotor correlation) have shown to significantly influence SoE and increase pain threshold amongst participants![177, 181, 110, 103]. Surprisingly, even the mere seeing of an avatar without any movement or stimuli has been observed to have an analgesic effect amongst participants when participants report a high level of ownership [181].
For example, Martini et al. have reported an increase in participants' pain threshold in the condition of synchronous tactile stimuli in VR compared to observe-only conditions. Additionally, they observed that a subjective SoO was crucial for that analgesic effect. Another recent study by Hunter Hoffman found that using an avatar (even with a non-human body) reduces pain intensity among participants [119].
Many studies have evaluated the effect of different features of the limbs on participants' induced pain (usually heat) level, including color, size [182], and transparency [176, 180]. Moreover, they mostly observed a reduction in the pain threshold by increasing the SoE. Also, they commonly utilized an HMD with a real-time hand tracking system rendering the body(part) with synchronous movement as participants' and providing a motor control [181], and It appears that a real-time simulation of the painful body part is required and crucial for an effective analgesic effect [247, 110].
However, the positive result has not always been observed, and some studies reported negative correlation, or even contradictory results [247]. For example, Martini et al. and Gomez et al. evaluated the effect of transparency on pain sensation [176, 180]. Martini et al. recorded participants' pain threshold over 24 healthy participants by increasing the heat pain. They found that the more transparent virtual body negates the participants' feelings towards the body. Consequently, decreasing

the feeling of embodiment would result in a lower pain threshold [176]. In a-cautious-contrast, Gomez et al. applied two sets of changes (size and transparency) on the virtual limb for two sub-population of CP; Peripheral Nerve Injury(PNI) and CRPS conditions. First, they found that the increase in transparency was correlated with a decrease in subjective pain in CRPS but an increase in PNI patients. They also found that changes in size slightly increase pain ratings amongst CRPS patients [180]. They concluded that embodiment in VR *can* decrease pain ratings in chronic arm pain. However, the type of pain must be considered for choosing the strategy to decrease pain more effectively [181].
As Gomez et al. stated in their review, it is safe to say that given different pathologies in different types of CP, one solution does not fit all types of pain. If we consider that in some types of CP the body-representation has been disturbed due to neural changes or damage, it might be inaccurate to compare the effect of a Virtual Reality on induced acute pain level during an experimental condition, with CP. Therefore, there might be a need for more studies on VR for CP-specifically to build a more reliable foundation with a magnifying focus on each type of CP (with a customized VR) in addition to the CP as an umbrella condition [181]. Nevertheless, we can see through the literature that modulating and having an embodied body part or an avatar has a role in pain alleviation amongst CP patients.

Following the previous studies, in this thesis, I am interested in exploring how observing an avatar in VR affects pain and SoE. However, most previous studies only relied on subjective reports of Sense of Embodiment and pain level. What I was interested in this *pilot-study* was to explore how observing an avatar changes CP patients' pain with regards to avatar embodiment in VR and see how those changes affect the underlying brain activity.

2.3 Neural Oscillations

To better understand how VR for CP alleviation works, we need to see how it is processed and affects the brain. To do so, we can leverage neuroimaging techniques to "capture" those processes in the brain. Given the inconvenience and unethicality of opening the skull, utilizing non-invasive techniques has been extensively recruited by neuro researchers. Electroencephalography (EEG) is one of those non-invasive methods to record cortical activity. I chose to use EEG for my study given its relatively low cost and portability. However, there are some limitations including EEG's low spatial resolution and noisy signals. In this section, I first set a foundation for this method before reviewing the literature related to the question of my thesis as VR for CP alleviation. The objective of this section is to justify the EEG indicators that I used for my hypotheses in Chapter 1. Moreover, to fulfill the exploratory purpose of my study, I investigate those EEG signals further in Chapter 4.

The action potential in firing neurons triggers depolarization and hyper-polarization across other brain neurons by propagating electrical current through axons. The generated electrical potential difference can be recorded from the scalp surface using EEG electrodes. However, the current of a single neuron would attenuate given the brain morphology, the orientation of neurons, synchrony of the firings, etc. Therefore, the potential of a single or a few neurons cannot be sensed through the skull. What EEG detects and amplifies from the surface of the skull is a small potential oscillated by the synchronous firing of a group[10] of neurons (usually pyramidal neurons[11]) in the cerebral cortex that has not been canceled and has passed through multiple skull layers [246, 225].

EEG records the electrical brain activity directly from the scalp surface in real-time, so it has a very high temporal resolution. The signal can detect the changes in neural firing with millisecond precision. Therefore, researchers can record individuals' Event-Related Potential (ERP) as their response to a stimulus or task [246]. However, in order to investigate the baseline neurophysiological activity, resting state EEG (rsEEG) can be recorded. This type of EEG recording is usually performed for 2 to 10 minutes, before/after a task or an intervention or for comparing the resting state activity of different groups [246, 225]. For my study, I performed rsEEG to capture the brain activity before and after the VR intervention. The reasons are twofold. First, I was interested to see how different embodiment conditions in VR change brain activity over time. Second, there was no specific task or stimulus in the VR. In fact, given the VR intervention's essence as "a meditative walking through a forest," it would not be feasible to isolate the audio-visual stimuli and distractors for participants.

The EEG sensors record the postsynaptic potentials in a format of a time series of voltage power in μV. The signal in the time domain is a composition of various sinusoidal waves (resulting from neural oscillation) with different amplitudes and phases. We can then decompose these time-series frequencies and transfer them to the frequency-domain using Fourier transform to understand the power of constitutional waves. Researchers have evaluated the association of different frequency components extracted from these signals with different neuronal processes. Researchers have investigated underlying neural processes associated with different cognitive states and behaviours by analyzing the power or amplitude of different frequency bands in EEG signals. [32] Five most common frequency components, which are commonly referred to as frequency bands are: δ (1-4 Hz), θ (4-8Hz), α (8-12Hz), β (12-30Hz), and γ(>30Hz) [54, 225]. For this thesis, I mostly focus on alpha and theta oscillation bands.

[10] About 10,000 to 50,000 neurons/mm^3 [246]

[11] This is because pyramidal cells are perpendicular to the cortical surface [159].

2.3.1 Alpha

We can posit that alpha is the most studied brain oscillation, as it was the first oscillation observed by Hans Berger. Alpha is the predominant rhythm in EEG, primarily observed over the occipital region amongst participants at rest (but not tired or asleep) with their eyes closed. The alpha brain oscillation is usually considered between the frequency of (8-12Hz). However, this value might change and should be considered individually as a range calculated relative to a center that changes with age. [144, 32, 77].

It has been observed that the power of this oscillation drops with the eyes open, and during sleep and it increases with drowsiness. So, traditionally it was believed that alpha represents wakefulness, the visual process, and a cortical "ideal" state during relaxation and lack of cognitive process [32, 152]. Further studies, however, suggested that alpha might reflect the inhibition and excitation of cortical and sub-cortical networks. And that it plays a role in inter-network connections and process modulation [145, 32].

It has been observed that attention to external stimuli or objects, such as visual stimulation, sensory-motor task or movement, would decrease alpha power [32]. In contrast, during memory or arithmetic calculation, an increase in alpha power [12] has been observed [168]. It is suggested that maybe the alpha increase, in fact, indicates top-down cortical inhibitory process, and this oscillation work as a "filter" to inhibit non-essential distractors in order to perform a task [145] and to increase efficiency [32]. For example, during an attention-directed task towards auditory sensors, researchers observed an increase of alpha in the occipital lobe, which is known to be active in processing visual stimuli (as a "task-irrelevant" region) [169, 130]. Similarly, alpha power improvement has been observed amongst the meditators after mindful breathing sessions, and this relation was not correlated with their experience level [45, 152], and even after a meditative VR intervention [87].

Magosso et al. investigated the changes in attention by comparing the power of alpha oscillation in an arithmetic cognitive task and an immersive VR[168]. In the VR scenario, participants were first presented with a CAVE-like VR in the shape of an airplane interior with two levels of immersion, a presented picture and another in which they could move inside the airplane. Their EEG waves were collected after each scenario. As illustrated in figure 2.8, alpha power dropped initially in VR. However, it increased to the resting-state value after the immersive VR intervention. In comparison, in the arithmetic task, the alpha power increased after the task was over (figure 2.8 (right)). Such "returning to normal" was not observed in the VR. Although the parieto-occipital lobe might be

[12] Alpha-Event-Related Synchronisation (ERS) has been observed. Time-locked and not phase-locked capturing of EEG in response to an event or stimuli might result in Event-Related Synchronisation (ERS) or Event-Related Desynchronization(ERD). The frequency oscillation is dependent too the number of synchronous neurons activated at the same time. Therefore, the synchronous short-lasting activation of neurons might overweight the asynchronous activities. Therefore, ERD can be considered as an activated level of cortical neurons (firing with different frequencies) and can be considered as a measure for cortical excitability [209].

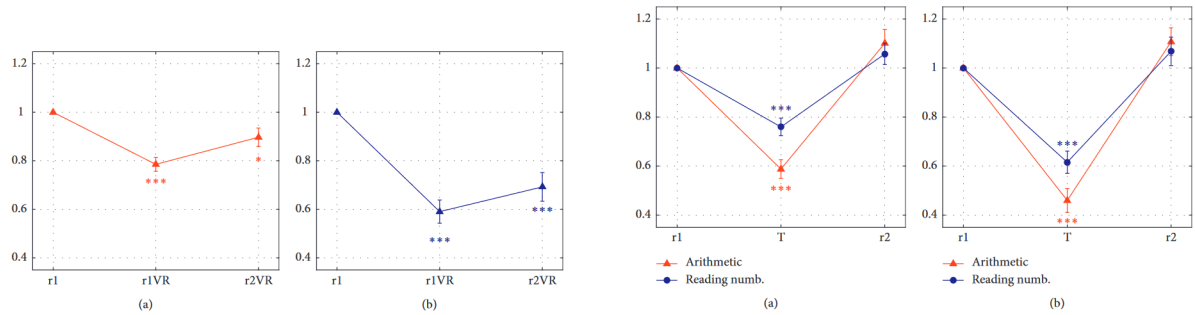

Figure 2.8: The result of VR study by Magosso et al. [168]. (left) Alpha suppression over fronto-central(a);parieto-occipital(b). r1: initial resting state without VR, r1VR: static immersion in VR r2VR: static immersion in VR after interactive exploration. (right) Alpha suppression over fronto-central(a);parieto-occipital(b). r1: initial relaxation, T: task (arithmetic task or reading numbers task) r2: final relaxation. Asterisks represent the significant result of t-test with the reference value of eye-open resting state as 1.

involved in the spatial processing of stimuli, they suggested that maybe after the sense of presence and immersion towards the VR environment, the "attention-grabbing" feature of the intervention partially declined.

As mentioned in the previous section, the Central and Parietal lobes have a crucial role in bodily sensorimotor signal integration and have been studied in the research on the Embodiment. Alpha oscillation over the sensorimotor area (i.e. S1, S2, M1) has also been associated with Embodiment aspects, including somatosensory and motor processing, and body awareness [13].
In a study by Alchalabi et al., they examined the changes in alpha activity during motor imagery and walking in VR. They conducted the study on healthy subjects with 2 conditions, one with congruous action of an avatar with the participant's aim in VR and another with manipulated movement in VR in which the avatar was stepping in the opposite direction as "done" or "imagined" [18]. They reported a significant alpha suppression in the central and parietal area upon incongruent input information when the imagined/done action was not aligned with the seen action by the avatar. At the same time, they observed an increase in alpha activity in frontal regions

[13]A frequency type of 8-13Hz over the motor cortex is commonly known as μ-rhythm. In literature sometimes -maybe incorrectly- alpha and μ-rhythm are used interchangeably [96]. Contrary to alpha oscillation, opening or closing the eyes does not change the activity of the μ-rhythm showing the different origin of this EEG component, than the occipital lobe. This "arch-shaped rhythm", has been observed to be suppressed in the presence of motor activity, imagery, and observation, and is suggested to be connected to the activity of mirror neurons [96]. In the literature of my thesis, some studies on embodiment have reported the connection of alpha [130, 154, 168] and some other μ-rhythm [18] with visuo-tactile conflict, immersion, brain imagery, and observing a 3rd person embodied avatar. Nevertheless, alpha has also been reported as an index for cortical inhibition and excitation making it a better candidate as I aimed to *explore* the effect of avatar in resting state EEG [145]. Additionally, accurately distinguishing μ from alpha was beyond the aim of my thesis.

amongst the modified version, which was not observed amongst the non-modified group. They suggested that this change might be related to the complex "error-monitoring loops and cognitive control." A violation of the sense of agency might result in changes in internal body representation and frontocentral activation which might be related to the mirror neurons in the frontal cortex. Moreover, they reported a significant correlation between these changes in front-central alpha and the subjective Sense of Ownership. However, given their topographical reports, during the epoch, after observing the avatar's action, there was an alpha power decrease across scalp electrodes. The group did not compare the significance of the last epoch with do/imaging and the action ones. Therefore, we do not know if there was a remained difference in alpha activation between the two groups.

Similarly, Lenggenhager et al. investigated the role of alpha oscillation in visuotactile stimulation on full-body RHI experiment by changing participant Sense of self-Location, seeing the synchronous and asynchronous application of a stimulus on a bodied and object model and monitoring the drift in their position. They observed an alpha suppression in the sensorimotor cortex and PMC during the visuotactile conflict in the asynchronous condition. Furthermore, this suppression was only observed when participants observed an avatar. They suggested that this alpha suppression is caused by the cortical excitation over the centro-parietal region and could be connected to the "multisensory bodily conflict." Although the activation of the frontal cortex (i.e. medial Prefrontal Cortex(mPFC)) was not significant between the conditions, the correlation analysis between the neuronal activation changes between the two groups and the amount of drift in participants' location found significance in PFC and mPFC. They suggested that the activation of mPFC (decrease in alpha over the region) might indicate the "robustness" of self-representation (normal SoL) while lower (i.e. inhibited) mPFC activation (higher alpha over the region) might be associated with illusory of self-location and results from the changes in bodily self.

The relation between alpha oscillation and the SoE has been studied mostly in replications of RHI. Nevertheless, most of these studies focus on cortical changes concerning perceiving a stimulus or different embodied/non-embodied avatar hand, and non have evaluated the longer-lasting effect of embodying an avatar or a rubber hand on brain oscillations and cortical reorganization. For example, those changes can be studied in several epochs after stimuli or in a resting-state EEG after a longer use of an embodied avatar. In a VR study of the sense of presence using different immersion levels, Clemente et al. found an increase in frontal alpha activity in conditions with a higher sense of presence [52]. Moreover, Studies on embodying prosthetic limbs [46, 265] have recorded a reduction in the connectivity on the sensorimotor network for alpha frequency and an overall increase of alpha after a few months of use of a "sensorized" prosthesis [111]. However, previous literature lacks the effect of the short-term change of Sense of Embodiment on EEG alpha oscillations. However, given the effect of visuotactile conflict mentioned in previous studies and its relation with SoE dimensions, I expected to see an increase in alpha related to the increase in the SoE amongst the avatar group.

2.3.2 Theta and PTAF

Theta oscillation falls between the frequency range of 4-8Hz. Although it can be recorded from all over the scalp, it is observed specifically in the cortical and hippocampal regions [48], and it can be mostly detected from frontal and prefrontal cortex. It is known to represent the "online" hippocampal state and been correlated with memory retrieval and formation and are dominant during light sleep, heavy relaxation, daydreaming, or drowsiness [205, 146]. The frontal increased theta has been recorded during concentration and after 4 days of meditation [152]. Also, higher theta was shown to be related to higher subjective pain [230].

While there have been some cases in research that contradict this, the majority of studies concur that in the continuous resting state EEG recordings of patients with CP, there is an increase in the power of theta and beta oscillation [211]. Ploner et al. suggested that this increase could be attributed to irregularities in neural activity caused by thalamocortical dysrhythmia (TDC) [212, 260]. The thalamocortical circuit plays an important role in transmitting sensory and inhibitory signals to the cortex. TDC is also observed in many other disorders, such as Parkinson, epilepsy, depression, central tinnitus, and autism [235]. In TCD, the normal rhythmic firing of neurons in the thalamus and cortex becomes disrupted [14], leading to an ongoing theta-range activity of thalamus and high-frequency (gamma) oscillations in the cortex. In the case of chronic pain, this causes an abnormal balance in the pain-matrix [261, 212].

Such abnormal activity of theta and slow waves, can also be projected in, and decrease the Peak of Theta-Alpha Frequency [212] value. In 2008, Boord et al. conducted a resting state study on 16 participants with chronic Neuropathic Pain (NP) compared to healthy control group. They found that the PTAF in all recording sites decreases in the presence of NP. Since then, many studies have recorded the shifts of PTAF towards lower frequencies in the presence of different types of CP and have been suggested as a possible biomarker candidate for it [212, 160, 60].

2.4 Summary

In this chapter, I reviewed the literature in three main categories: chronic pain, VR, and EEG. Although theories have evolved, our understanding of brain mechanisms is still limited.

In order to mitigate the pain, CP patients may use different techniques and medications. These have raised concerns regarding the resistance and overuse of medications such as Opioids. This is why technological advances such as VR as an alternative solution for controlling and treating CP are becoming popular in scientific and clinical settings. Although VR has shown promising results in pain treatment, it is necessary to understand how this technology works to design more effective VR intervention for CP patients. Our knowledge of the brain mechanisms of VR in pain

[14] in chronic pain it is usually caused by neuronal deafferentation

(esp. Chronic Pain as a multidimensional condition in the biopsychosocial framework) is in its infancy and requires further investigation. One of the theories proposed to define the underlying mechanisms of VR-analgesia for CP patients is VR-embodiment. Research shows that the body representation is distorted in some CP conditions. This theory identifies VR as a means of reinforcing the reorganization of the body-representation (body-image and body-schema) during the predictive-coding process. This theory is tightly coupled with the concepts such as embodiment, Sense of Embodiment, and bodily illusions. The sense of bodily-illusion and Sense of Embodiment can be induced using an avatar. Therefore, it is essential to investigate the role of having an avatar in VR pain alleviation for CP if we want to design a more effective VR application for CP patients. Therefore, I look into the effect of having an embodied avatar in VR for CP patients in this study. Most of the VR experiments are lacking neurophysiological evidence. Additionally, there was no previous study in VR for CP exploring the effect of embodiment by collecting neurophysiological data. In my investigation, I therefore utilized the EEG neuroimaging method to explore the changes in the brain signal induced by an avatar.

Chapter 3

Methodology

In this chapter, I addressed the designed protocol for my study. Throughout the chapter, I first discuss my participants, their demographic distribution, and the criteria I chose to recruit them. Then, the study design, including the detail of the VR application and the EEG protocol is presented. Finally, in the data processing and statistical section, I review the instruments I used to assess pain, Sense of Embodiment (SoE) and EEG. I review the pipeline we chose for data cleaning and discuss my data analysis plan for each measure.
The contents of this chapter have been peer-reviewed and published in the format of a protocol paper in the Journal of Frontiers in Virtual Reality (Virtual Reality in Medicine) for the research topic of Novel Applications of Virtual and Mixed Reality in Pain Research and Treatment [140]. Therefore, this writer acknowledges that some passages in this chapter have been quoted verbatim from the original paper.

3.1 Participants

In this pilot study, the total of fourteen participants (12 female) diagnosed with CP were recruited. Recruitment was carried out from three pain clinics in the Vancouver area and by contacting a database of participants with CP conditions in the Pain Studies Lab, SFU.
The designed flyers were distributed amongst the CP patients in the clinics. Therefore, they voluntarily attended the study; Their attendance was anonymous, and it did not affect their treatment procedure. After the initial contact through email, participants were informed about the inclusion/exclusion criteria and the study detail by sharing the consent form and the Edinburgh handedness inventory as a pre-screening questionnaire (see Appendix 1) [200]. In case of further eligibility, they were asked to send us back the pre-screening questionnaire, their age, and their gender. Handedness scores over 40 (indicating right-handedness) were confirmed for the study; all volunteers passed the pre-screening test. The Edinburgh questionnaire is a 20-item tool assessing the participants' laterality. The score can be calculated as follow:
Laterality Quotient = (R-L)/(R+L) $\times$ 100. Where L and R are the number of left or right, respec-

tively.
In the follow-up emails, participants were instructed about the restriction they needed to consider on the day of the study (see sections 3.1.1 and 3.1.2), the study location, and the necessity of providing their COVID-19 vaccine card before attending the study. They were also asked to contact us to reschedule (even on the day of the study) in case of insufficient sleep or violating the caffeine/nicotine/alcohol abstain (see section 3.1.2).
To mitigate the chance of having unobserved differences between the groups due to confounding variables related to participants' differences, assignments to either control or treatment group happened quasi-randomly [195]. Participants were assigned to groups by considering their age and sex, using the group matching workflow in R [24, 1].

3.1.1 Inclusion criteria

Considering the age distribution of patients with CP in Canada [232], participants older than 18 years old of age diagnosed with CP (>3 months) consistent with the IASP pain taxonomy and ICD-11[231] criteria were recruited by medical doctors from LifeAgain Musculoskeletal Pain Clinic, AT Pain Solutions clinic, Initium Center for Pain Medicine clinic, amongst Dr. Owen Williamson's patience, and from the previous volunteer list of the Pain Studies Lab.
All participants provided written informed consent before entering the study. They all visited the Pain Studies Lab at SFU in person. The visit was limited to the same late morning hours (10 am. - noon) to exclude the influence of circadian wakefulness in the brain activity of participants and on the EEG data [37, 74, 249]. Through initial contacting emails, participants were instructed to abstain from caffeinated beverages and food hours before the recording session to eliminate the caffeine-induced alpha [30] and theta reduction in EEG [69, 244]. They were also asked to self-report any caffeine dependence or withdrawal. Similarly, they were asked to abstain from nicotine for at least 4 hours before the study to avoid the effect of nicotine use or withdrawal on EEG signals [74]. Participants were able to read and speak English. They had normal or corrected-to-normal eye vision and normal hearing to reach the immersion level and prevent motion sickness using the Head Mounted Display (HMD) in the virtual environment. Considering the study design, they were expected to physically be able to sit-stay unmoved for about 20 min and have not been diagnosed with migraines. Finally, all participants were right-handed due to the difference in neural activity signature and laterality [55]. As mentioned in the previous section, participants' handedness was assessed using the Edinburgh inventory for assessment of handedness before the day of the study.

3.1.2 Exclusion criteria

We excluded participants with any history of significant brain injury, medical or surgical illness, neurological disease, drug or alcohol abuse, and any diagnosis of epilepsy or seizure activity [152]. Individuals with CP may experience severe pain or heightened sensitivity in the absence of their

prescribed medication. Therefore, following a previous study protocol on this population the usage time, dosage, and type of their medication such as Opioids that bias results were carefully noted initially and considered as an exclusion criterion if they were used prior to the study[1] [42, 244].
Participants with a handedness score < 40 were also excluded from the study. Finally, possible changes in vigilance were minuted throughout the recording sessions for the possible slowing of dominant occipital rhythm (Alpha), and EEG files with any sign of drowsiness were either excluded or the corresponding parts were cut from the data during the cleaning process.
On the day of the study, participants were also asked about their level of tiredness and quality of sleep using the common indexes; The 10-item Tiredness Symptoms Scale (TSS) and the 14-item Karolinska Sleepiness Scale (KSS) (see Appendix 1) [74].
The TSS survey offers a means of assessing the "physical and emotional" signs of fatigue during the evaluation. Participants indicated the presence or absence of symptoms with binary responses (yes = 1, no = 0), which were then tallied to generate a score. Scores exceeding 8 were considered ineligible for analysis [2]. The KSS scale is a commonly employed tool comprising 10 items for assessing self-reported sleepiness levels. Research has demonstrated a positive correlation between KSS scores and increased EEG alpha and theta oscillation power[74, 136]. Likewise, we removed data from participants who reported a KSS score greater than 7 [238].

3.2 Study Design

3.2.1 Procedure

The study occurred in a single session and took about 1.5 hours on average. Figure 3.1 demonstrates the study procedure. Also, the detailed script used in the study is provided in Appendix 2. Upon arrival, after a brief introduction to the study, patients were instructed to read and sign a consent form containing the study process, potential benefits, and participants' rights. After signing the consent form, all participants were asked to fill in questionnaires (*pre-intervention*) to measure their pain level (see section 3.3.1). This questionnaire gathered data regarding participants' general CP level, medication, and tiredness. We gathered participants' medication (dosage and type) and pain history to consider them an exclusion criterion if required (see section 3.1).
Next, participants were comfortably positioned on a reclining chair in the study room, outfitted with the EEG cap, and instructed to begin the study. It is worth noting that the use of an embodied avatar was not mentioned in the introductory section to prevent participant bias.
The study session took about 25 minutes overall. Participants were assigned to one of the two conditions in a quasi (pseudo) randomized order. They experienced Virtual Meditative Walk (VMW)

[1]Given the sample size of this pilot study, it was not feasible to isolate the effect of medication on the result, therefore we would exclude those participants.

[2]In the analysis the impact of these scores were evaluated by considering them as a covariate.

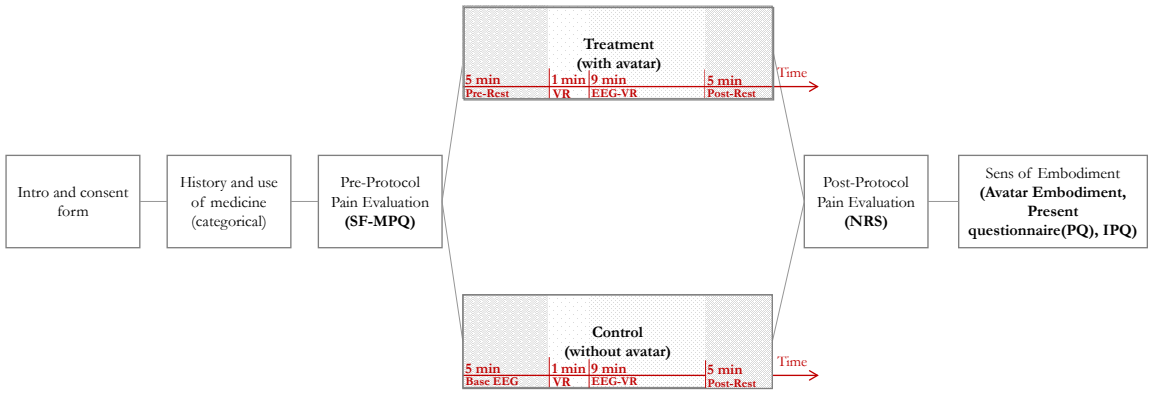

Figure 3.1: The study procedure.

without an avatar in the control condition. While in the treatment condition, they had a virtual avatar in the VR environment synchronized with their movement and consistent with their gender skin colour (see section 3.2.2).

We evaluated participants' pain levels for the *post-intervention* assessments. We also collected a Sense of Embodiment (SoE) questionnaire in that part.

As it was essential to have parity in all sessions, a script was prepared for each step of the process, including the answers to the possible questions from participants and the headset setup. The script can be found in Appendix 2.

3.2.2 VR Design

Virtual Meditative Walk

The Virtual Meditative Walk (VMW) was developed and customized based on Chronic Pain (CP) patients' needs in the Pain Studies Lab [115, 114]. This VR system is implemented by the Unity3D game engine [12]. During the intervention, participants are guided through a mindfulness meditation protocol via a vocal coach as they appear to "walk" or glide forward through a forest. Based on prior studies, the forest was designed to provide a non-disturbing and safe environment [115]. Figure 2.4 depicts a scene from the VMW virtual environment. In the original version, the forest's fog density slowly changes based on the patient's Electrodermal Activity (EDA). Although designed to function in a more ambient way than a graph, we nevertheless removed the fog and disabled the EDA capturing feature to eliminate any potential attentional distractors that may violate the validity of the study. The meditation protocol is based on a well-studied Mindfulness-Based Stress Reduction (MBSR) technique by Jonh Kabat-Zinn [134]. MBSR is a scientifically validated form of meditation often used to manage chronic pain (see section 2.1.3 for more information). Considering the hypersensitivities of CP patients, we decided to limit our intervention to 10 minutes as the

(a)

(d)

Figure 3.2: The VMW environment for each of the conditions:(a) no-Avatar, (b) avatar condition.

average duration of previous studies that used VR to reduce or manage chronic and neuropathic pain [172].

Implementation

The VR intervention ran on Oculus Quest 2 HMD, commercially available and commonly used for VR [11]. This lightweight headset does not require a prior room setup and uses an embedded hand-tracking system, making it suitable for our study. The VR headset was calibrated for the study based on the participants' Pupillary Distance (PD) values. This customization would prevent a blurry 3D environment and avoid motion sickness in the VR environment. Moreover, they could wear their eyeglasses without a metallic frame (which would interfere with the EEG signal quality). Figure 3.2 illustrates the Virtual Reality application. (A) Shows the Point of View (POV) of the control condition patients: They "walk" or float through a forest during their POV intervention. (B) Shows the treatment condition POV: patients would see a 3D animated avatar with their skin colour and gender-matched with the participants.
During the meditation, participants were asked to lie on a reclining chair (aka. zero gravity). This sited position was chosen to give them a sensation of gliding throughout the forest. Considering their initial position, we set the avatar in the same sited position for the treatment group, on an exact model of the reclining chair. For the avatar used in the treatment condition, we synchronized their body movement with participants' movements using Inverse Kinematic (IK) and animated using Unity's Animation Rig library [13]. Unity's IK feature lets us determine the relative position and orientation of the joints (as a chain) to a target point (i.e. patient's wrist). By knowing the

relative placements of the joints and by capturing the target point as the wrist's locations, we could estimate the movement of the virtual arms. However, the reverse operation might only partially match with users' movement.
To capture the position of the wrist and get a correct estimation of the participants' actual hand size and poses, we used Oculus Quest 2 built-in hand-tracking feature, which uses inside-out infrared cameras [5]. Additionally, the avatar's skin colour and gender were modified based on the participant's gender during the study setup on the day of the study.

3.2.3 EEG Design

Protocol and setup

The monopole EEG signals were captured using an 8-channel Enobio EEG recording system manufactured by Neuroelectrics (Massachusetts, United States) with Geltrode electrodes. Geltrodes are wet EEG electrodes with an Ag/AgCl coated core that require the use of conductive electrode gel that could be used in scalp areas with or without hair, with a sampling rate of 500 Hz [8, 10]. The average life of Ag/AgCl coated electrodes is 30 times of use [9]. Therefore, considering the number of participants for this study, the new set used in this study could hold a good-quality signal for all participants. The Enobio system was chosen because of reasons including 1) reasonable signal quality, even using dry electrodes [56], 2) fast application[51], 3) previous studies on people with CP (Fibromyalgia) [257, 256] and elderly adults [15], and 4) being approved by the Food and Drug Administration (FDA).
We used Neoprene Headcap to install and fixate the electrodes. Figure 3.3 shows the spatial distribution of the electrodes based on the standard 10–10 international system configuration with the following electrode distribution: F3, F4, C3, C4, P3, P4, O1 and O2, with the online reference placed on the right earlobe(CMS/DRL). The electrodes were positioned in a way that the HMD would not interfere with the EEG collection.
The data collection happened in a dark room with its door closed and shielded against sound and stray electric fields with controlled temperature to increase the signal-to-noise ratio [74]. Computers and monitors (except the VR HMD) were kept no closer than 1.5-meter from patients to reduce the noise and all electrical devices were connected to the sockets equipped with ground contact. Participants were also instructed to remain still and relax, avoid eye blinks and movements [even during the resting-state EEG capturing with Eyes Closed (EC)], and relax jaw muscles during recording (see Appendix 2 for more information on the instructions). Alpha waves are largest at posterior electrode sites when the subjects are tired; therefore, we asked them to be well-rested on the day of the study. They were asked to wash their hair the day before the study, and we cooled and reduced the room's humidity to 15 degrees to reduce skin impedance caused by residue or sweat respectively [210].
The EEG recording occured in three sessions for each condition: a 5-minute *pre-Rest*, a 9-minute

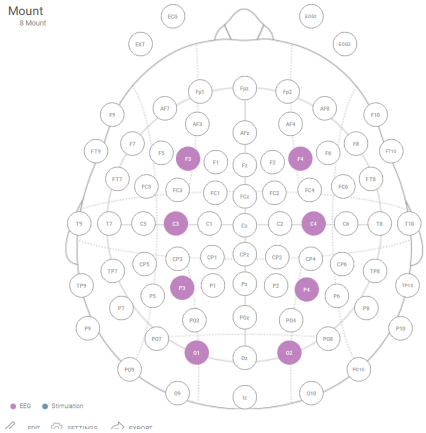

Figure 3.3: The EEG setup from the Neuroelectric application [8]. Purple cites indicate the electrode position.

subsequent *EEG-VR*, and a 5-minute *post-Rest*(see section 3.2.1). We defined the EEG protocol in NIC2 software. Specific keys were defined to mark changes in the participants' cognitive state (eg. drowsiness), electrode pop-s, signal loss, transient losses, and movement during the study. Electrodes impedance was not accessible through the NIC2 application directly. However, the NIC2 application provided us with a real-time measurement of the signal quality considering 4 main types of artifacts: Line noise, Main noise, Drift noise, and Offset. A Quality Index (QI) was calculated as a relative-weighted average of 3 prior artifacts (with the Drift artifact exempted) using the formula below:

$$\tanh\left(\sqrt{\left(\frac{Offset(t)}{WeightOffset}\right)^2+\left(\frac{MainNoise(t)}{WeightMainNoise}\right)^2+\left(\frac{LineNoise(t)}{WeightLineNoise}\right)^2}\right)$$

with WeightOffset = 280mV, WeightLineNoise = 100μV, and WeightMainNoise = 250μV. For all participants, we kept the noise QI below 0.7. Also, by monitoring the detailed noise types, we could adjust the cap position and electrodes or add more gel based on the noise type in real-time. For example, a bad offset quality could be resulted from band electrode contact with skin and could be solved by adding more gel underneath the electrode [14].

Preprocessing and cleaning pipeline

Figure 3.4 shows the EEG data pre-processing and cleaning pipeline. Data was pre-processed using the EEGLAB toolbox [62]. NIC2 software can record the signals in multiple formats with 24-bit resolution. For this study, we used **.easy* files as they were written in ASCII codes and were human-readable, while formats such as **.nedf* were in binary format.
We used the EEGLAB Matlab toolbox to clean the raw EEG signals. Neuroectrics has published an EEGLAB plugin to import EEG data without any loss in precision. Also, EEGLAB provides an

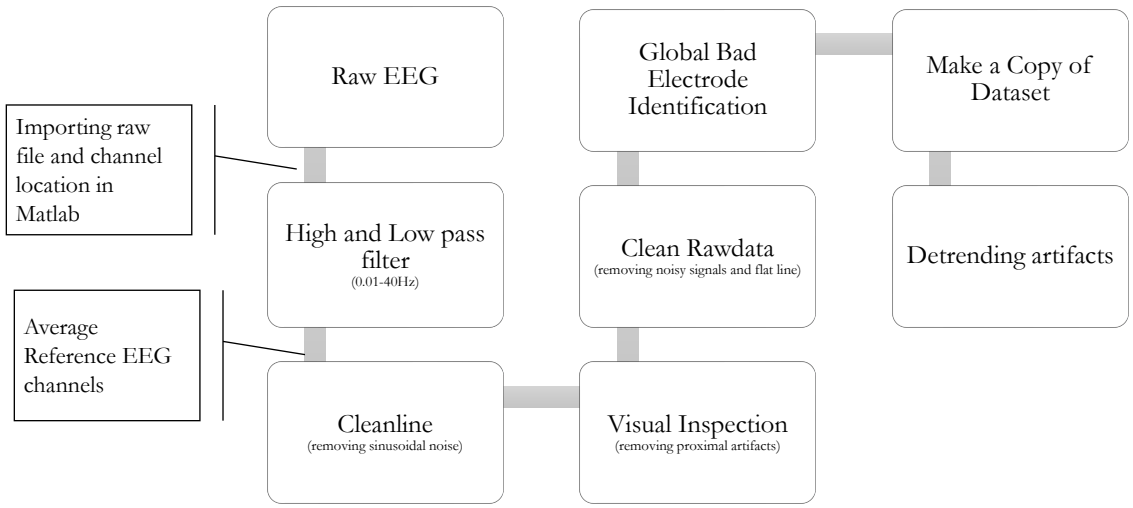

Figure 3.4: The preprocessing and data-cleaning pipeline for EEG in EEGLAB.

interactive graphic user interface (GUI), alloweing us to process EEG data interactively. For each EEG session per individual, after importing the raw recorded EEG signals to the EEGLAB, we imported the location file and set the locations. The NIC2 application for Neuroelecrics band-pass filters the signals from 0.01-40 Hz while collecting the EEG. However, after removing the DC offset from the data, we applied a notch filter for the 60 Hz frequency (North American electrical line noise) and an FIR band-pass filtered from 1-40 Hz. We chose 40 Hz, as video monitors usually have a refresh rate of 50-120 Hz.

Given the small number of scalp electrodes, using Independent Component Analysis (ICA) to identify components such as eye-blink and movement was impossible. We used multiple EEGLAB plugins to remove artifacts. First, we used "CleanLine" to remove sinusoidal noises and normalize the log spectrum by detrending; the plugin estimates and removes sinusoidal (e.g. line) noise from channels using multi-tapering and a Thompson F-statistic. Artifacts were removed using visual inspection (to remove eye movements and muscle artifacts) [225]. Time intervals of 400ms around data points with signal jumps exceeding ± 80 μV for resting EEGs and ± 100 μV for EEG-VR were marked for rejection. Additionally, artifacts caused by the muscle tension (electromyography), skin potential (changes in the skin impedance) due to the pressure or sweat, movement or blocking (disconnection of the cable) that filters have not removed were marked for rejection; Such artifacts are characterized by their low frequency (>200ms) and high amplitude (>100 μV). Also, artifact propagation through all channels could be considered as a reason for rejection marking. Bad channels (sensors with not usable signals for the process) were also marked using the EEGLAB plug-in "Clean Rawdata," which marks data looking for noisy signals, flat lines, and excessively large amplitudes. Finally, the signals were detrended using SIFT plugin for pre-processing.

It is worth noting that for this thesis as we collected a resting state recording in which the power spectrum is assumed as stationary (i.e. constant) over time, and we only looked at the spectrum in the frequency domain averaged, not how it changes over times.

Spectral Analysis

We used the Fieldtrip toolbox in Matlab to analyze and process the data. Fieldtrip provides tools for preprocessing, processing, and analyzing neuroimaging data, especially EEG data in Matlab. However, as it could not accept **.easy* files (i.e. raw data), we used EEGLAB for preprocessing. Additionally, the Fieldtrip toolbox provides analysis methods based on more recent research studies, such as built-in non-parametric permutation-based statistical analysis [203]. For the process, we followed the method used in some previous EEG for VR and resting state studies [87].
For each participant, preprocessed data files were included in their folders. Each participant was assigned a separate Matlab structure (i.e. p00.m), storing their treatment condition and the file's location. After importing all signals, each time-series EEG recording was segmented into non-overlapping epochs of 1 second[3]. The Power Spectral Density (PSD)s were then calculated using the Fast Fourier Transform (FFT) [4]. For this study, as we were looking for the amplitude of frequencies, we used the power spectrum; the squared absolute of the Fourier transform [159]. After extracting the power spectrum, we can no longer retain the phase information [4]. In FFT, we assume that our signal is stationary. However, this might not be a correct assumption. We applied Welch's periodogram method to increase the resolution and sensitivity by averaging consecutive FFTof small signal windows (5-second Hanning windows), with 50% overlap[5]. Hanning taper smoothing would also reduce the signal discontinuity at the start and the endpoints. The average PSDs across these windows were then calculated, generating the final PSD estimate for each electrode for each person. These procedures are embeded in the *ft_freqanalysis* function of the FieldTrip toolbox (see Appendix 3 for the Matlab code). These calculations were applied to signals from all three *pre-Rest, post-Rest,* and *EEG-VR* sections. Therefore, for each condition, per person, we would have 8 (for each channel, in case non is rejected as a bad channel) power spectrum.
After extracting the PSDs per channel, we selected the Frequency of Interest (ROI) for theta (4-8

[3]Although this data was a resting state and not an ERP study, epoching data would decrease The variance of the spectral estimate by the square root of the number of epochs. For example, with N=16, the estimate's variance will be 4 times smaller than with 1 epoch. This can help with increasing the signal-to-noise ratio in our process.

[4]FFT is a technique that changes our signal's representation from time-domain to frequency-domain spectra. It separates the time series signals into cosine and sine components for all frequencies. The output of the Fourier transform gives a complex coefficient for each frequency, which is calculated using Euler's formula: $Me^ik = (cos(k) + isin(k))$ and $e^i\pi = -1$ .The real component of the signal corresponds to the cosine component, while the imaginary component corresponds to the sine component. This complex number represents both the amplitude and phase of the signal [54, 2].

[5]The length of this windows sets the frequency resolution of the frequency-domain output (e.g. 4-second window, gives 0.25Hz resolution)

Hz) and alpha (8-13 Hz) sub-bands using the *ft_selectdata* function (see Pre-Post_PSD function in Appendix 3). We would then calculate PTAF and alpha and theta powers from these power spectrum signals, which are discussed in the next section.

3.3 Data Processing And Statistical Approaches

The following section discusses the measures used and evaluated for this thesis. In the next chapter (Chapter 4), for each measure, I addressed the descriptive statistics prior to inferential report. However, since the descriptive statistical methods (Mean, Median, etc.) are similar amongst all measurements I did not provide them in the "statistical analysis" section for each measure (sections 3.2.1 and 3.3.2). Also, due to the unnormal distribution of data, the need for prior knowledge about the data population under the null hypotheses, and our small sample size (for the pilot study), we used non-parametric statistics to compare data. This analysis was performed using Matlab, and the code is provided in Appendix 3.

3.3.1 Primary Measures

As discussed in the literature review section (2.2.2), research has indicated that incorporating an avatar into a virtual environment can lead to an elevation in both pain threshold [176] and pain intensity [119].
One of the objectives of this study was to validate and reinforce the previous findings in research by examining if the outcomes of this pilot-study are consistent with them. As a result, our primary focus was to examine how including a virtual avatar in VMW, as a Mindfulness-Based Stress Reduction intervention, affected participants' subjective experience of CP and their Sense of Embodiment. We were curious to see whether it results in pain alleviation and/or an improvement in the SoE of patients with CP, and whether there is any relationship between these two factors. Therefore, the primary evaluation criteria are twofold:

Pain

To measure the pain outcome, we followed the pain rating scales used by researchers previously. We used the self-reported Short-Form McGill Pain Questionnaire (SF-MPQ) by Melzack [184]. SF-MPQ is a 15-item (11 sensories; 4 affective) self-administrative questionnaire, with a Visual Analog Scale (VAS) question to assess the present index [see Appendix 1 for the questionnaires]. This well-known questionnaire specifies the different dimensions of patients' pain. We adopted the questionnaire by replacing VAS with Numerical Rating Scale (NRS), for participants' ease of use and the consistency of pain reports with previous similar studies [87]. Participants were also asked to specify their pain intensity after the VR session (20 min after the start of the session) on an NRS scale. The difference between the pre- and post- reported NRS values ($preNRS - postNRS$) was considered as the Pain Reduction Score (PRS) and was used as our index.

Scoring
SF-MPQ questions were scored as follows: The adjectives were ranked based on the pain intensity:

- 0 = none
- 1 = mild
- 2 = moderate
- 3 = severe

Therefore, the score for each of the sub-components will be evaluated as follows:

- Sensory Sub-score ($Q : 1 - 11$) : [0 33]
- Affective Sub-score ($Q : 12 - 15$) : [0 12]
- Numerical Rating Scale ($Q : 16$) : [0 10]
- Present Pain Intensity($Q : 17$) : [0 5]
- Total McGill Pain Score: [0 45]

Sense of Embodiment

The second outcome will be the SoE score. For this study, two different indices were presented to participants as an SoE questionnaire (See Appendix A). We customized and used the Igroup Presence Questionnaire (IPQ) [7, 236] and the Avatar Embodiment (AE) [128] questionnaires.
The IPQ is a measure used to assess the level of presence felt by individuals in a VR environment[233, 234]. It consists of three sub-categories: Spatial Presence, which measures the physical presence of participants in the VR through questions Q15, Q18, Q21, Q22, and Q25; Involvement, which gauges the level of attention given to the VR environment through questions Q13, Q19, Q23, and Q26; and Experienced Realism, which evaluates the perception of realism in the VR through questions Q14, Q16, Q17, and Q24. In addition, there is a general item called "sense of being there" (Q20), which is not part of any sub-scale but has a strong correlation with all three factors, particularly with Spatial Presence [7].

Scoring
After assigning a numerical value of 0-6 to each response, we then determined the value of each sub-scale using the following calculation:

- SP = mean(Q15, Q18, Q21, Q22, -Q25)
- INV = mean(Q13, Q19, -Q23, Q26)

- REAL = mean(-Q14, Q16, Q17, Q24)

We can then generate a "presence profile" using these 3 values and compare the scores amongst the two groups (see Appendix D).

For the second measure, the Avatar Embodiment (AE) index was utilized to assess a patient's Sense of Embodiment (SoE), with a focus on key aspects of embodiment, including Sense of Ownership (SoO), Sense of Agency (SoA), Sense of self-Location (SoL), Tactile Sensation, External Appearance, and Response to external stimuli[128]. This 25-item questionnaire was designed to evaluate the sense of embodiment during VR, and we were able to customize the questions based on the VR details. However, as we were specifically comparing the conditions of no-Avatar and Avatar, many of the questions related to SoO, Tactile Stimuli, External Appearance, and Response could have been confusing for participants and might have interfered with our results. Therefore for questions such as "It seemed as if my [body-part] was touching the [stimuli]" were removed. As can be seen in Appendix 1, the final questionnaire we used has 19 items.

Scoring
The only category with no assigned question was Tactile Stimuli. For the rest of the dimentions we scored as follows:

- SoO = $Q9$
- SoA = $((Q4 - Q5 + Q6 + Q7)/4)$
- SoL = $((Q1 - Q2 + Q3)/3)$
- Appearance = $((Q4 + Q10)/2)$
- Response =$Q11$
- SoE = $(SoO * 2) + (SoA * 2) + (SoL * 2) + Appearance + Response$

Statistical analysis

As mentioned above, we would have three primary measure: PRS (preNRS-postNRS), IPQ indexes, and SoE score from AE questionnaire. The variables in this pilot study would not conform to a normal distribution due to the small sample size.
For each of the PRS and SoE we had one indipendant variables, with 2 between subjects levels: the Avatar and non-Avatar groups. To compare the results between these groups, we utilized the Mann-Whitney U test. The Mann-Whitney U test (or the Wilcoxon Rank Sum Test) inspects if two data sets are comeing from the same population. This means that our null hypotheses for the primary criteria form as follows:

H0_PRS: The participants' PRS probability distribution will be similar in both conditions.

H0_SoE: The participants' SoE probability distribution will be similar in both conditions. Additionally, we conducted a Spearman correlation test to examine the relationship between the PRS and SoE scores. We also created a scatter plot to check the linear relationship between the two variables [83, 143].

For the non-parametric comparison of IPQ indices, we had a between × within design; 2 levels of treatment condition by 4 levels of IPQ dimensions. To extract the interaction effect between the two groups, we performed a factorial permutation test using the *ezPerm*, R package [82, 202], which provides an easy non-parametric alternative for the repeated measures Analysis of Variance (ANOVA).

3.3.2 Secondary Measures

Similarly, we explored the effect of the proposed treatment on (*pre-Rest* - *post-Rest*) resting-state brain signals among the two groups by investigating the effect of adding a virtual avatar on EEG brain oscillations. Based on previous literature, we studied the changes in the power of brain oscillations between two groups. We specifically chose the average of theta (θ) Power Spectral Density (θ-PSD) recorded at pain-related regions [42]; frontal, central, and parietal areas, and the average of Alpha (α) Power Spectral Density (α-PSD) recording at the centro-parietal regions in which α oscillation was previously reported to be related to SoE [152, 18]. Additionally, the PTAF, which has been used as an indicator of the presence of CP, was calculated as the peak power frequency between 4 and 13 Hz during the 9-min EEG-VR and (*pre-Rest* - *post-Rest*) resting-state interval over all electrodes [212].

α-PSD and θ-PSD

As mentioned in section 3.2.3 we used the the Fieldtrip function, *ft_selectdata*, to extract the PSD values of the regions of interest for α-PSD and θ-PSD vlues [262]. In Appendix C: CalculatePower.m you can find out the code for extracting alpha and theta PSDs for each channel per participant; For each participant, we extracted the value over Regions of Interest (ROI) channels. This power were then normalized for each channel per subject following the work of wang et al., using the following formula:

$$P_relative = \frac{\sum_{f=f_1}^{f=f_2} P(f)}{\sum_{f=f_L}^{f=f_H} P(f)}$$

where $[f_L, f_H] = [2, 45]$ and $[f_1, f_2]$ is determined by the sub-band frequency selected [262]. These alpha values for each channel were then averaged regionally. Therefore, for each participant, we would have 4 values per region: pre_θ, post_θ, pre_α, and post_α.

PTAF

Generally, there are two commonly employed techniques for computing Peak of Theta-Alpha Frequency (PTAF) (or Peack of Alpha frequency (PAF)). One is to calculate the frequency for maximum value of the spectrum within the 8-12 or 9-11 Hz range [42]. The second method involves the calculation of the Center of Gravity (weighted frequency), which is calculated using the following equation:

$$PTAF = \frac{\Sigma(a_f \times f)}{\Sigma a_f}$$

Where $a_f$is the amplitude of frequency$f$, and$f$ is -for this study- the frequencies between$4 - 13Hz$ range, per $(0.25Hz)$ [60]. The gravity, could provide a more stable method for estimating the peak of alpha in case of multiple local extremums [144]. However, since all PSD average values (per electrode) had a single peak point, we decided to use the first method following the previous studies [42].

Statistical analysis

α-PSD and θ-PSD,and PTAF values all have similar structure in our data set:

1. They are not following normal assumption
2. We have a *pre-Rest* - *post-Rest* comparison between two groups. Therefore, a 2 Variables, 4 levels, between + within subjects(pre-post) design.

pre-Rest - *post-Rest* data can be examined through various means, including: (1) analyzing the final scores alone using Analysis of Variance (ANOVA) (assuming that there is no significant difference between the *pre-Rest* results), (2) analyzing the difference scores, (3) examining the percentage change scores, (4) performing Analysis of Covariance (ANCOVA) by considering the *pre-Rest* variable as a covariate and the *post-Rest* as the dependent variable, (5) employing blocking by initial scores (a.k.a. stratification), and (6) analyzing it as repeated measures [41, 82].
For this study, we first compared the mean difference between the two groups for the *pre-Rest* data. If the difference were non-significant, we would compare the *post-Rest* values using one-way ANOVA. Otherwise, we would use ANCOVA. ANCOVA was chosen as it was suggested that this method is the preferable approach for examining pretest-posttest data, as evidenced in previous studies (e.g., [82, 68]) [147, 82].
We also compared the power spectrums for the interaction of the group×time (*pre-Rest* - *post-Rest*) effect, using a non-parametric, permutation based method [3].

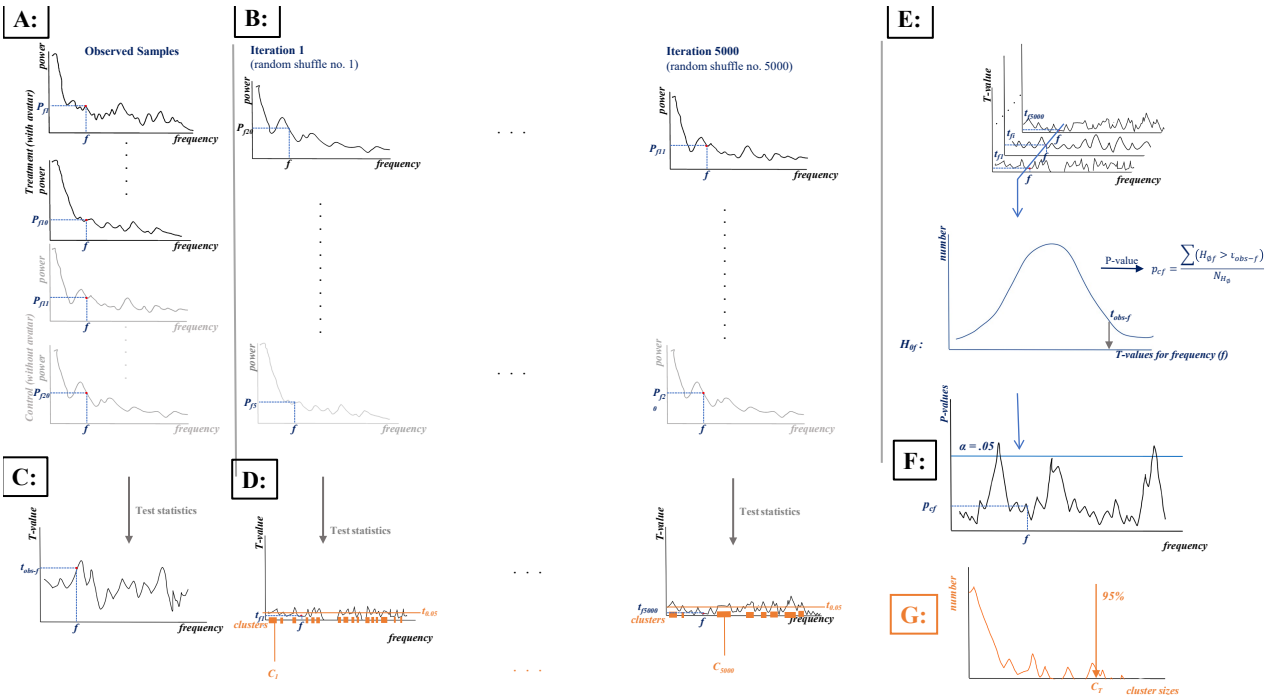

Figure 3.5: The permutation based statistics schema for processing power spectrum density of EEG. The dataset containing the observed power spectrum data for each participant (A), shuffles for the number of iterations (B). The test statistics will be calculated for each frequency on the actual data (C) and the random iterations (D). From the random iterations, we can then generate a normal distribution for the frequency of f, and calculate the p-value for that frequency f using the observed t and the randomly generated normal distribution (E). All p-values over all frequencies generate a distribution of p-values. The frequencies corresponding to p-values with the confidence level of 95% can be considered significant (F), if the cluster size is also found to be significant(G).

Permutation based statistics

Here I provided an intuition of permutation based rationale for comparing power spectrum between the two groups [174, 54][6] using the *ft_freqstatistics* function; the Matlab code is provided in the appendix 4. Figure 3.5 shows the process. For each frequency of f, we will make a pool of corresponding power values from avgPSDs for each of the participants($P_{f1} \dots P_{f14}$). These power values were then be randomly permuted and assigned to two groups (i.e. treatment and control) using Mont Carlo sampling, for all frequencies, for 5000 iterations. In each iteration, we ran the test statistic comparing the two conditions (t_{fi} is the calculated t-value for frequency of f ini^{th} iteration). Since the data is randomly shuffled over two groups (i.e. control and treatment), it is

[6]This might be different from evaluating the interaction effect [203] in which we compared two groups using the subtraction of the pre-Rest from post-Rest values.

expected for each iteration to have a near-zero distribution of t_{fi} over all frequencies. After all iterations, we will empirically estimate a null distribution for each of the frequencies f using t_f values derived from permutations ($H_{01} \dots H_{0f}$, where H_0 is the histogram of $t_f s$). From these H_0 distributions a right-tail permutation p-value will then be calculated for each frequency f to evaluate the significance of t_{obs-f} using below formula:

$$P_{cf} = \frac{\sum(H_{\varnothing f} > t_{obs-f})}{N_{H\varnothing}}$$

where "$N_{H\varnothing}$" is the number of permuting iterations: 5000. Having the p_{cf}values for all frequencies gives us a distribution. The comparison value (t_{obs-f}) for frequencies, with $p_{cf} s$ values higher than ($\alpha = .05$), can be considered as significant. Therefore, the null hypothesis can be confidently rejected for those frequencies. To correct the multiple comparisons problem in the permutation testing, we will employ a cluster-based correction, with($\alpha_{error} = .05$). In each iteration, from the distribution of $t_{fi}(s)$ overall frequencies, clusters of frequencies with t-values greater than $t_{0.05}$ will be selected. Cluster-level statistics will then be calculated by summing the t_f values in each cluster. The same clustering operation will be applied to observed values (i.e. t_{obs-f}). Then, for each iteration, the greatest sum will be selected as the cluster-level value for that iteration (C_i). After all iterations, a histogram of C_i values will be generated, and the C value corresponding to the 95 percentiles of the histogram will be selected as a threshold C_T. We can suggest that clusters in the observed data, clusters with cluster-level statistics greater than C_T, can be counted as meaningful compared with the confidence level of 95%.

In this chapter I presented the detail of the protocol designed for this study. In the following sections, the results of the statistical analysis is reported follwing by a discussion of the results.

Chapter 4

Results

As indicated in Chapter 3, given the limited sample size and non-normal distribution of the collected data, We employed non-parametric statistical tests (refer to section 3.3). We utilized R and Matlab to compute the effect of each dependent variable and the interaction between them. The code for executing these statistical analyses is available in Appendix C segment.
In this section, following the same order of measurements in Chapter 3, I report the results of the statistical analysis the gathered data by comparing the main changes between our two groups (i.e. the Avatar and no-Avatar) and reporting the significance of the interaction within subjects (i.e. the time within the pre-test/post-test).
Table 4.1 presents the demographic characteristics of all participants also table4.2 represented the descriptive statistics for each group. Ten out of the 14 participants who were initially enrolled were included in the data analysis. The EEG data collected from participants 11, 7, and 3 were excluded from the analysis as they contained excessively noisy signals. The only male participant in the Avatar group was excluded from this process. Accordingly, the data collected from Participant 10 was also removed from the analysis to ensure the homogeneity of the samples in terms of gender differences. As a result, the final sample consisted of 10 participants, all of whom were female.

4.1 Primary Measures

4.1.1 Pain

The effect of the VR intervention between the two groups was compared. Using the pain ratings collected form Numerical Rating Scale (NRS), we first compared the effect of Time (pre-test, post-test) between the two groups. As can be seen in figure 4.1, there was a decrease in the pain score in both groups after experiencing the VR intervention with or without Avatar. The Avatar group showed a decrease in scores from the pre-test (Mean = 5.40, SD = 1.81, SE = 0.36) to the post-test (Mean = 3.00, SD = 1.41, SE = 0.36), while the no-Avatar group also displayed a reduction in scores from pre-test (Mean = 4.2, SD = 2.68, SE = 0.36) to post-test (Mean = 2.6, SD = 1.81, SE = 0.36). A permutation test using the *ezperm* R function was conducted within the groups (pre-test

Table 4.1: Participants' demographic characteristics

No	Age	Sex	CP etiology	Pain duration (years)	Medication	Other treatments	SF-MPQ score
1	21	F	FM-arm, BP	10	NSAID	-	11
2	64	F	RA-joints	5	non-NSAID	-	22
3	52	M	RA-shoulders & knees, NP	4	TA	Physiotherapy, Massage, acupuncture and cup	23
4	59	F	RA	0.6	NSAID	Physiotherapy, Massage	21
5	35	F	RA	8	O	Physiotherapy, Surgery	17
6	75	F	AP	25	-	Exercise, Massage, Heat	26
7	63	F	RA	2	-	Exercise	23
8	56	F	RA, BP	10	NSAID, DMARD	-	20
9	39	F	MP	30	O, D, NSAID	Physiotherapy, Massage, IMS, Neurofeedback, cooling lotions, THC/CB-D/CBN	21
10	74	M	OA, SCI, BP	25	NSAID, non-NSAID	sugar water shots. Heat	7
11	57	F	BP	30	-	Injection	15
12	60	F	BP, AC	1	non-NSAID	Wix	18
13	54	F	BP	2	NSAID	Physiotherapy, Massage	33
14	27	F	BP, NP	5		Physiotherapy, Massage	17

FM: Fibromayalgia, RA: Rheumatoid arthritis, OA: osteoarthritis, BP: Back Pain, AP: Abdominal Pain, NP: Neck Pain, AC: Adhesive Capsulitis, SCI: Spinal Cord Injury, B: benzodiazepines, A: antiepileptic drug, NASID: Nonsteroidal Anti-Inflammatory Drug, DMARD: Disease-Modifying Antirheumatic drugs, TA: Tricyclic Atnidepressiva, D: Diuretics, SF-MPQ: Short Form of McGill Pain Questionnaire, O: Opioid

Table 4.2: Controlled measures in group assignment

	no-Avatar (control)	**Avatar**
N	7	7
Male/Female (Percentage)	1/7 (14.27%)	1/7 (14.27%)
Age (Mean SD)	52.28	52.43
SF-MPQ (Mean SD)	20	19.25

and post-test), revealing a significant effect of Time on the data with a p-value of .004.

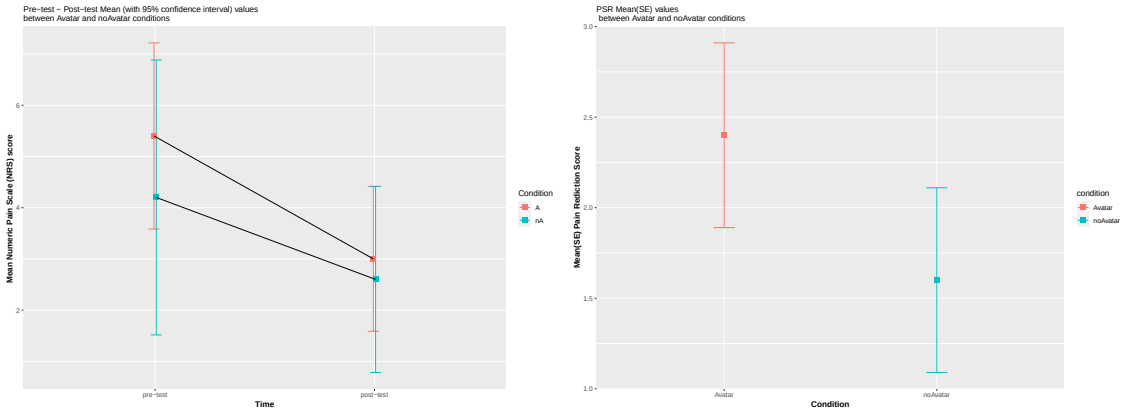

Figure 4.1: The Pain score difference between the control(no-Avatar) and treatment(Avatar) group (right) over time (pre-test and post-test), and (left) difference between the two groups.

There was a significant difference between the initial pain scores for the pre-test after applying a one-way Analysis of Variance (ANOVA) between two groups F (1,6) = 21.664, p= .003. Since the p <.05, we employed an Analysis of Covariance (ANCOVA) to remove the effect of this difference and only analyze the intervention's effect on the post-test scores. Therefore, the effect of VR on the post-test was evaluated by considering the pre-test scores as a covariate. After testing for ANCOVA assumptions (i.e. Linearity, Homogeneity, Homogeneity of variances of residuals, and removing Outliers) with F (1,7) = 0.439, p = .529, no significant difference was observed between the two groups (see Appendix D.1).

Additionally, a Pain Reduction Score (PRS) value was calculated for each participant by subtracting their post-test Numerical Rating Scale (NRS) pain score from the pre-test. Based on the error bar plot for the mean number of PRS illustrated in figure 4.1, the average pain reduction was more among the participants who experienced Avatar in their VR intervention. The error bars in the graph also represent the test's confidence interval. It implies that 95% of the participant scores are in the range of the bar. Descriptive statistics, by Mean = 1.60, SD = 1.14, SE = 0.50 for the no-Avatar (i.e. control), and Mean = 2.40, SD = 1.14, SE = 0.50 for Avatar (i.e. treatment) group, also demonstrate an overall improvement in the mean of Pain Reduction Score.

As PRS scores were not following the normality assumption and the two groups of samples were

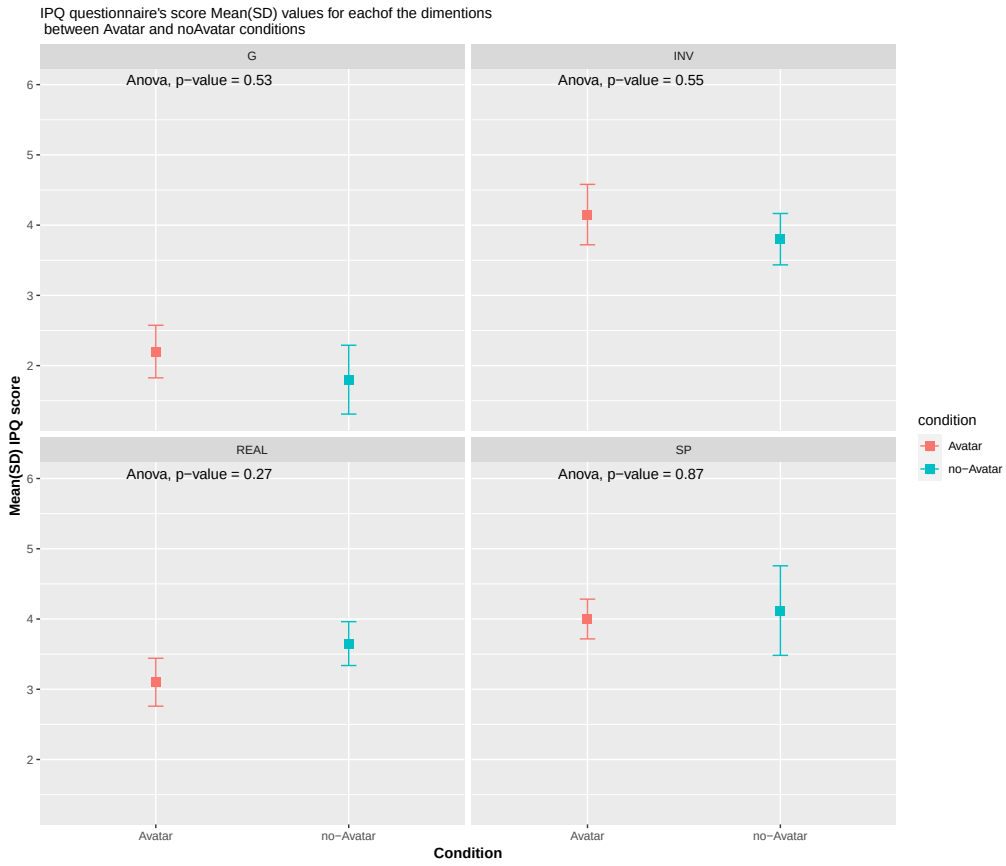

Figure 4.2: The IPQ score difference between the control(no-Avatar) and treatment(Avatar) groups.

independent, we ran a Mann-Withney-Wilcoxon test (also referred to as the Wilcoxon rank sum test or Mann-Whitney U test) for the inferential analysis. The test showed no significant difference ($W = 17$, $p = .385$) for the pain reduction score between the Avatar and the no-Avatar group.

4.1.2 SoE-IPQ

The first measurement related to Embodiment was the IPQ evaluating participants' sense of presence in the environment. It included four sub-scores: Spatial Presence, Involvement, Experienced Realism, and a general sense of presence. Figure 4.2 demonstrates the average of different dimensions of the Igroup Presence Questionnaire (IPQ) index. After running the one-way ANOVA test to investigate if there is any significant difference between the two groups, with $p > .05$, we could not confidently reject the similarity of score distributions between the two groups.

4.1.3 SoE-AE

The Avatar Embodiment (AE) score was calculated as mentioned in section 3.3.1. As can be seen in the error-bar plot of figure 4.3, on average, participants in the Avatar group reported a slightly

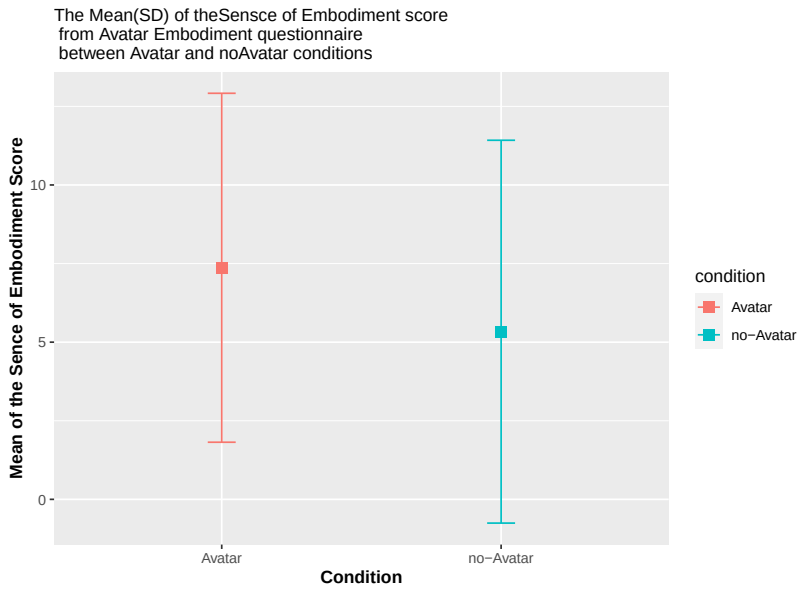

Figure 4.3: The Avatar Embodiment score difference between the control(no-Avatar) and treatment(Avatar) groups.

higher overall SoE score (Mean = 7.36, SD = 5.54, SE = 2.48) through the Avatar Embodiment (AE) questionnaire than those who did not have any Avatar in their VR experience (Mean = 5.33, SD = 6.08, SE = 2.72).
However, the Mann-Withney-U test showed no significant difference between the two groups (W = 15, p = .676).

4.1.4 Pain-SoE correlation

For further analysis, first, the correlation between AE and PRS scores were calculated for each group. As can be seen in the scatter plot in figure 4.4, there was a negative correlation for each group. Given the small sample size, the *Spearman* correlation method was used with a correlation coefficient of r(5) = -0.97,p = .004 for no-Avatar and the r(5) = -0.1,p = .87 for the Avatar condition. Additionally, the correlation coefficients were compared between the two groups *cocor* R package [65] to see if there is any significant difference between the groups. We found a significant difference between the two groups as the null hypothesis of coefficient similarity was rejected with z = -1.992, p-value = .046.

4.2 Secondary Measures

We analyzed the EEG signals in the next step. The PSD was calculated per participant (see Appendix D.3), electrode, and time. Next, alpha and theta oscillations as 2 sub-frequencies were selected and the normalized alpha and theta values for person and each electrode were calculated

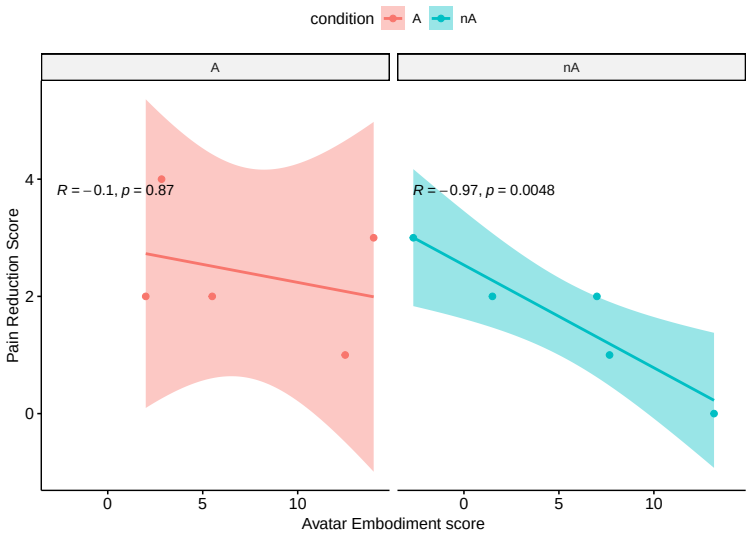

Figure 4.4: The correlation between SoE and PRS scores in each group.

using the formula in chapter 3. Normalizing the values in this way could help in accounting for individual variability among participants and assist in managing and regulating the impact of artifacts. We statically analyzed these values in R. The corresponding Matlab and R codes are provided in Appendix section. Figure 4.5 shows the log-normal average PSD over all electrodes, all participants per group.

In this section we first present for hypotheses analysis following by the exploratory analysis of data.

4.2.1 Alpha

To analyze alpha values, we grouped electrodes into 4 regions; Frontal, Central, Parietal, and Occipital. This way, we could first better understand the signal patterns across different regions, and secondly, by reducing the number of tests performed, we could increase the statistical power and limit the risk of type 1 error.

Across participants, there was an observable trend of increasing alpha values for all electrodes in each region between *post-Rest* and *pre-Rest*. Figure 4.6 (left) illustrates this trend for each group. The alpha power for the Avatar group increased from (M = 0.52, SD = 0.10) in *pre-Rest* to (M = 0.56, SD = 0.13) in *post-Rest*. Similarly, for the no-Avatar group, there was an increase from (M = 0.46, SD = 0.17) to (M = 0.52, SD = 0.16) between the two time points. Initially, the effect of time and condition[1] was analyzed using a permutation test in R, with a p-value of .037. However, as there was a significant difference between the *pre-Rest* values $p < .05$, we analyzed the effect of

[1]the repeated measure permutation test using *ezPerm* function confidently rejected the similarity in the probability distribution of *pre-Rest* and *post-Rest* conditions.

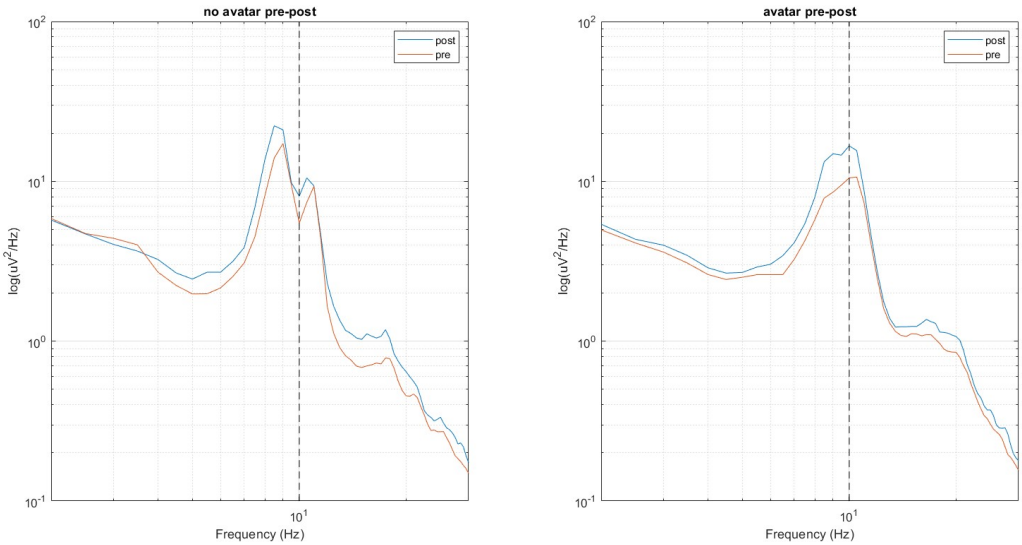

Figure 4.5: loglog plot for average PSD for both groups.

the intervention on *post-Rest* values. Upon analyzing the *post-Rest* differences using ANCOVA, no significant effect of condition was observed between the two groups (figure 4.6 (right))
The comparison between the alpha power for each region is provided in Appendix D.4. We saw a significant difference in the Frontal region when comparing the *post-Rest* values. The mean of normalized α-PSD has increased from (M = 0.39, SD = 0.19) to (M = 0.47, SD = 0.15) in no-Avatar condition between the two time points, while for Avatar, there was an increase from (M = 0.44, SD = 0.08) in pre to (M = 0.50, SD = 0.14) in post. We compared the *pre-Rest* powers between the two groups using *ezPerm*. Since the difference was significant, after adjustments of *pre-Rest* values, we ran an ANCOVA to compare the effect of the intervention on *post-Rest* values. As can be seen in figure 4.7, the Avatar condition had significantly lower power in comparison to the no-Avatar group $F(1,6) = 7.31$, $p < .05$, with a medium effect size.

4.2.2 Theta

The normalized PSD for theta was computed and divided into four regions, similar to alpha power. We observed a trend of increased mean theta scores in the no-Avatar group and decreased mean theta scores in the Avatar group across all regions (see Appendix D.5). However, we did not find any significant difference in the effect of the intervention on *post-Rest* results using ANCOVA in any of the regions analyzed.

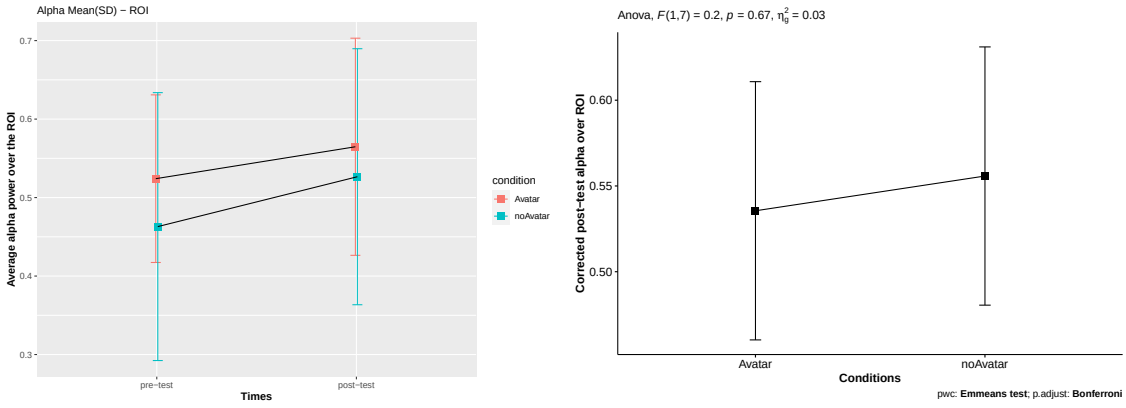

Figure 4.6: Alpha changes over the regions of interest (ROI) (Frontal, Central, and Parietal cortex). (left) the average values for each group between *pre-Rest* and *post-Rest*. For both groups the average value have significantly increased from *pre-Rest* to *post-Rest*. (right) the ANCOVA results between two groups.

4.2.3 PTAF

The analysis code for Peak of Theta-Alpha Frequency (PTAF) calculation in Matlab (FieldTrip) and statistical procedures in R are provided in Appendix C.2.1 and C.3.1 respectively. The PTAF scores were extracted by calculating the frequency of the peak powers in the range of theta-alpha oscillation (4-13 Hz) over all scalp channels. Similarly, we ran an ANCOVA test to calculate the effect of VR on the *post-Rest* PTAF after controlling for *pre-Rest*'s (see section 3.3.2) between the two conditions. The assumptions were checked: There was a linear relationship between *pre-Rest* and *post-Rest*. The homogeneity of regression slopes was not statistically significant, $F(1, 6) = 0.308$, $p = .599$. And, the Shapiro-Wilk and Levene's tests were not significant ($p > .05$).
Figure 4.8 shows the differences between the two conditions. After applying adjustments for *pre-Rest* score, there was a statistically significant difference in *post-Rest* between the conditions, $F(1, 5) = 8.06$, $p < .05$. Although we only had 2 groups, we applied a post-hoc analysis with a Bonferroni adjustment using the *emmeans* package in R. The mean PTAF score was significantly greater in Avatar condition (9.37 +/- 0.0712) compared to the no-Avatar (9.04 +/- 0.0932), $p < .05$.

4.2.4 Data Exploration

After performing statistical analysis based on the hypotheses, we delved deeper into the data to better understand the observed changes.

Interaction Effect

The interaction effect between of time×condition was compared for the PSD values by applying a between-subject non-parametric permutation test over the subtraction of *post-Rest* from *pre-Rest* (see Appendix C.2.4). To find all possible clusters, the test was ran over the frequency window

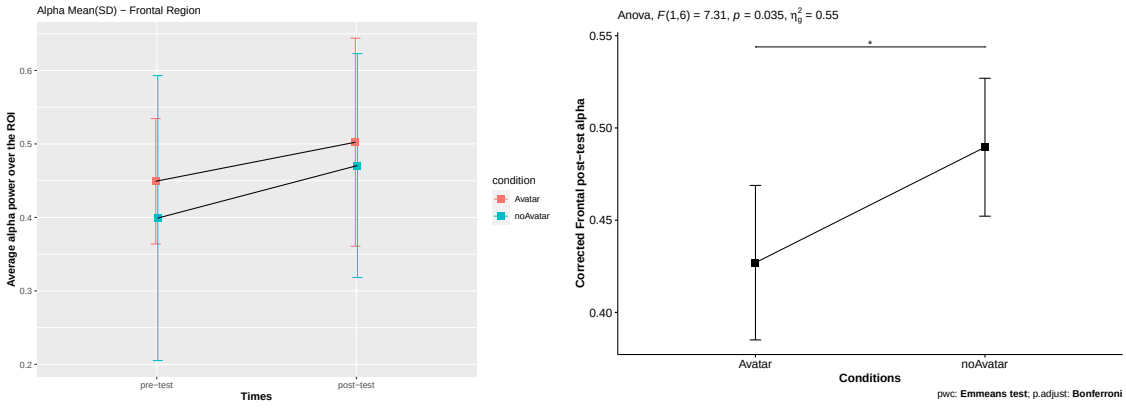

Figure 4.7: Alpha changes over Frontal region. (left) the average values for each group between *pre-Rest* and *post-Rest*. (right) the ANCOVA results between two groups. The asterisk shows the significant different between the two groups.

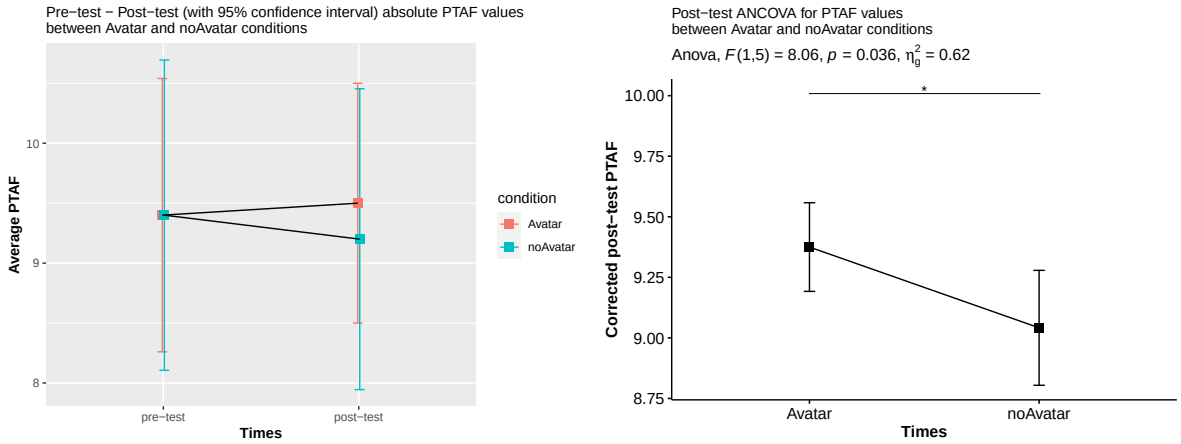

Figure 4.8: The Post-test comparison of ANCOVA for the *post-Rest* PTAF values between Avatar and no-Avatar conditions after being adjusted for *pre-Rest*.

of 2-30Hz over all 8 channels. However, during the process of averaging using FieldTrip toolbox, channels F3, C4, and P3 were discarded. The permutation tests then revealed a difference between the Avatar and no-Avatar condition. The test identified two positive clusters in the observed data over the channel *P4*, and after the cluster-based correction, one cluster over 12.5-18Hz was identified. Figure 4.9 shows the topo-graph of power, changing over the identified frequency.

Since some channels were missing from the permutation-test comparison, we further analyzed the normalized power of the overlapping frequency range (i.e. 13-20 Hz, aka. lower beta) for our four brain regions. Using ANCOVA, we found significantly lower values for *post-Rest* after controlling the *pre-Rest*. For the Parietal beta, there was a rising trend for both conditions with significant differences of $F(1,6) = 7.27$, $p = .036$ in *post-Rest*. In contrast, over the Central electrodes, we saw a slight decrease in the average beta values for the Avatar group and a subtle increase for

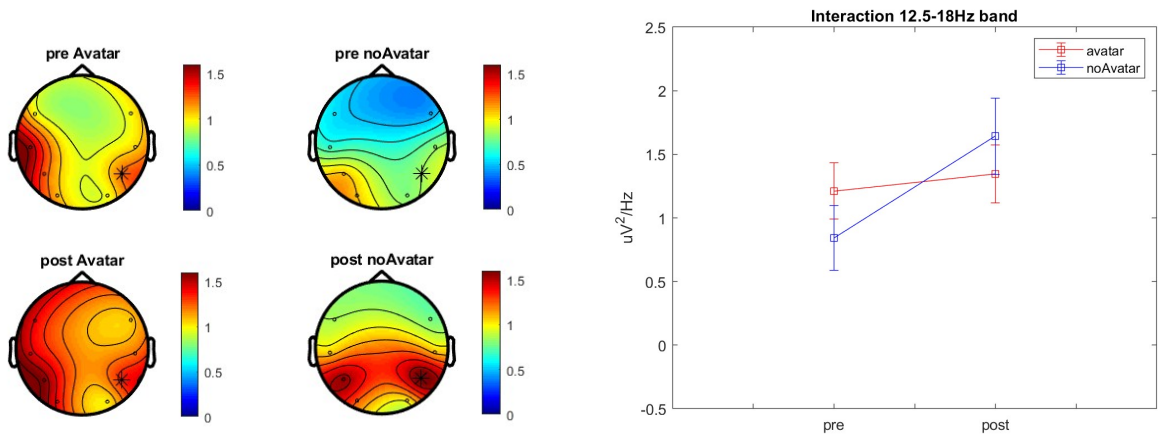

Figure 4.9: (left) The topo-plot for eeg electrodes for 12.5 - 18 Hz. The color bar shows the average PSD ($\mu V^2/Hz$) values for each group. The asterisk shows the channel (P4) with a significant cluster of difference between the two groups, after permutation-based test. (right) The average power of the frequency band 12.5-18 Hz, over time, between the two groups over the channel P4.

the no-Avatar with the *post-Rest* values for no-Avatar groups significantly higher than the Avatar $F(1,6) = 69.42$, $p < .001$(Figure 4.10).

Correlations

Finally, we looked to see if the EEG changes from *pre-Rest* to *post-Rest* in each brain region were related to the reported pain and SoE using the Spearman correlation. We looked for the changes in the normalized oscillations band power between pre- and post-Rest for each group. The correlation between the EEG difference and the behavioural measurements are presented in table 4.3. We also compared to see if the difference in correlation between the two conditions is significant.

In the Frontal region, the result showed a marginally significant positive correlation of $\rho = .87$ between Δtheta and PRS values, while there was a non-significant negative correlation for Avatar. However, the difference between these coefficients for the two conditions was significant $p < .05$. For alpha changes in the Frontal region and SoE, the coefficients of -.7 and .8 for no-Avatar and Avatar group, respectively, were not significant. However, between the two conditions, the difference was significant.

For the Central region, alpha had a significant perfect positive correlation of 1 with the reported SoE, while in the no-Avatar group, there was a non-significant negative correlation with $\rho = -.8$. In the same region, we found a positive correlation of $\rho = .9$ between low-beta changes and the reported SoE in the no-Avatar group.

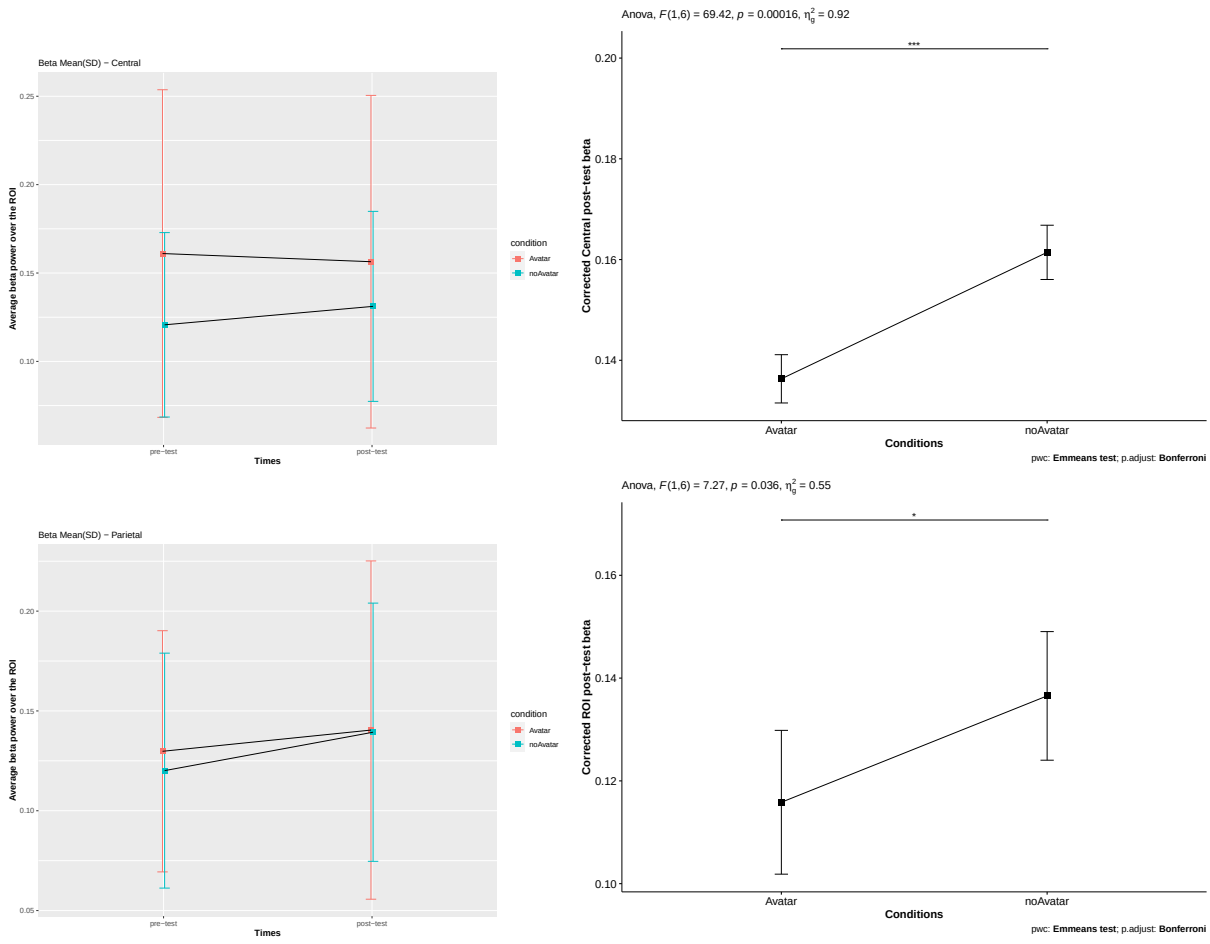

Figure 4.10: Normalized beta PSD average over (top)Central and (bottom)Parietal regions, (left) over time and (right) the corrected post-Rest values between the conditions.

			Δtheta	**Δalpha**	**Δlow-beta**	**Δptaf**
	Frontal					
no-Avatar		SoE	-0.8	-0.7 ζ	-0.1	0.5
		PRS	°0.87 ϑ	0.56	0.15	0.36
Avatar		SoE	-0.7	0.8 ζ	-0.3	-0.3
		PRS	-0.66 ϑ	0.71	-0.36	-0.36
	Central					
no-Avatar		SoE	-0.5	-0.8 ε	0.9*	-0.67
		PRS	0.61	0.66	-0.89	0.68
Avatar		SoE	-0.9	1* ε	-0.2	-0.45
		PRS	-0.56	0.15	-0.46	0
	Parietal					
no-Avatar		SoE	-0.5	-0.2	0.9*	-0.53
		PRS	0.61	0.15	°-0.87	0.44
Avatar		SoE	-0.1	-0.2	-0.2	°-0.87
		PRS	-0.41	0.56	-0.41	0.43
	Occipital					
no-Avatar		SoE	0.7	0.2	0.5	0.31
		PRS	-0.66	-0.36	-0.3	0.22
Avatar		SoE	-0.1	0.1	-0.3	-0.67
		PRS	-0.35	0.61	-0.35	-0.21

Table 4.3: Correlation coefficients for each brain region and condition, between reported pain and SoE and the EEG oscillations power difference. **Δ: postRest-preRest values, * p-value < 0.05, ° p-value marginally significant p = .58, cells with matched symbols(ζ, ε, and ϑ) had significant between-subject difference.**

Chapter 5

Discussion

For this thesis I ran an exploratory pilot-study using a pre-post experimental design to investigate whether the use of an embodied avatar would result in a greater reduction in pain levels compared to a group that did not use an avatar.
The study aimed to provide an explanation for the observed effects of the avatar on pain reduction. Although significant results and the trends were observed, it is important to interpret the outcomes of this *pilot study* very cautiously.

In Section 2.2, I elaborated on how literature has shown promising results in using VR for pain and CP alleviation [116]. Similarly, in this study, I observed that the subject of the study (re: meditative VR environment, Virtual Meditative Walk (VMW)) proved to be significantly effective in reducing the participants' subjective pain regardless of the group. It can be argued that, apart from the novelty of VR, this pain reduction for both groups might be due to the meditative effect of VMW, which uses MBSR practices for managing CP [87]. It was observed that the reported Pain Reduction Score (PRS) for the group with an avatar was higher compared to the no-Avatar group. However, the difference was not statistically significant. So, despite seeing the trend in our results, I cannot confidently [1] reject the first null hypothesis. This lack of significance might root in mainly the population size of this pilot study which I will discuss further in the limitation section.
Similarly, we did not find any significant difference between the reported SoE between the two groups.

For the analysis of the neuronal activity, I initially hypothesized that the alpha power would be significantly higher in the avatar group compared to no-Avatar (see Chapter 1). Our data analysis showed a significant increase of alpha over all brain regions from *pre-Rest* to *post-Rest* in both groups. We also observed lower post-Rest alpha in the Avatar group over the frontal electrodes (see

[1] p-value $< .05$

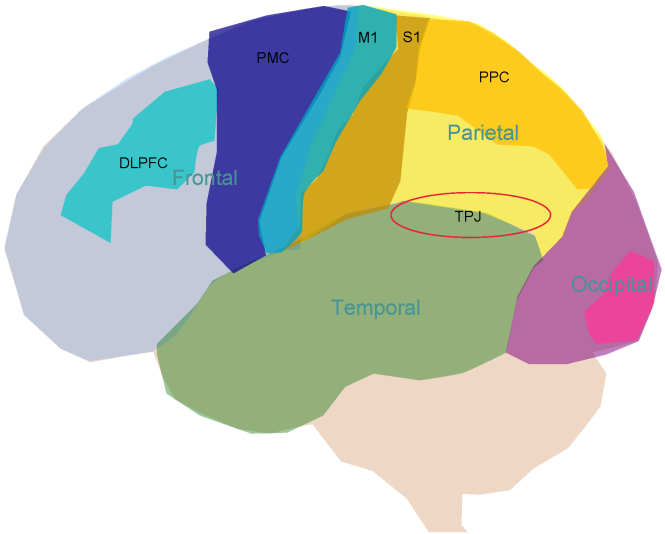

Figure 5.1: A schematic of the brain lobes and regions.

Appendix D.7).

As reviewed in Chapter 2, the alpha rhythm is known to be an indicator of top-down cortical inhibitory processes [168]. These processes in CNS are often inhibitory signals from the cortical (especially frontal lobe) towards the sub-cortical area [145]. Alpha brain oscillation has been observed to increase during mindfulness meditation regardless of the meditator's previous experiences [152]. Our EEG data, similar to previous VR studies on meditative applications for CP [87, 124], showed an increase in frontal and central alpha power in the frontal over time, which may be related to an increase of inhibitory activity during the meditation.

On the other hand, an Alpha decrease, can reflect cortical activation, excitation, and directed attention toward external stimuli [152, 209]. For example, alpha power over the centro-parietal region is known to be related to sensory and motor signal processing during movement or motor imagery [18] and was observed to decrease during the asynchronous (i.e. incongruent) stimulation of avatar in VR [155]. Our pilot study showed a trend of lower *post-Rest* alpha in almost all regions, with a significantly lower frontal alpha value (or higher frontal activation) than the no-Avatar group.

The frontal lobe is primarily known to have an executive function, such as planning and reasoning. It also plays a role in processing attention, memory, and motor commands as the PMC and supplementary motor area are located in this lobe (see figure 5.1) [131, 50]. Activation of these regions (i.e. decrease in alpha oscillation) has been observed during the visuotactile conflict [18, 155]. Additionally, studies have shown an increase in the activation of the Dorsolateral Prefrontal Cortex (DLPFC) during predictive coding error.

According to Zanto et al., the DLPFC plays a role in cognitive control and has the ability to regulate early visual attention processes in a "top-down" manner. Borsnan et al. also suggest that the DLPFC is involved in cognitive control adjustments. It has been shown that DLPFC activity is positively correlated with the observational prediction error [47] and is thought to have a role in the cognitive control processes that help to reduce prediction error by adjusting the strength of the predictive signals or updating the model to better match the incoming sensory input [19]. DLPFC activation also affects the activation of anterior insula [165], which is known to play a role in predicting the pain intensity of an impeding painful stimuli [263]. In the study by Lenggengager et al., they suggested that the mPFC activation can reflect the processing of multi-sensory conflict in the process of resolving the changes in the embodiment [155]. Although neither the sample size nor the spatial resolution of our EEG devices was sufficient to reach a compelling conclusion, the significantly lower alpha in the frontal lobe might be influenced by and represent the activation of the frontal lobe, which may represent the status of processing the changes in the body-representation and *body-image* after using an avatar in the treatment group. This might reflect the engagement of cognitive control processes helping to reduce the prediction error and update the brain's model of the world to better match the incoming sensory input.

In our supplementary analyses, we found a significantly lower *post-Rest* average of low-beta (13-20Hz) oscillation [38] over the Parietal and Central regions between the two conditions.
Beta band oscillation is typically associated with sensorimotor rhythms, with a beta ERD during the movement planning or even the observation of movement followed by a relative rebound [258]. Additionally, beta oscillation has been related to the function of working memory and executive control in the frontal lobe [229, 28]. However, more recent studies are considering beta oscillation as a mechanism for *brain-wide* signaling between distant brain regions regarding the prediction of body movement top-down mechanisms[2] in the predictive coding framework [38, 242, 21]. For example, in the visual coding and processing of a stimulus, it is suggested that alpha and beta synchronization can be an indicator of top-down mechanisms such as spatial attention. The beta band, then, augments bottom-up (feed-forward) gamma band (>30Hz) oscillations improving the impact of the stimulus [220, 193, 245]. According to Betti and colleagues, the beta rhythm observed in motor circuits could serve as a timing mechanism for predicting external stimuli [38].
The observed lower *post-Rest* alpha and beta in the avatar group, compared to the no-Avatar condition, could be the result of a reduction in top-down processing in predictive coding due to the changes in the embodiment. However, further investigation on changes in other oscillation frequency ranges such as gamma oscillation might be required. Such exploration was not possible in the process of this study because of the high-pass frequency of 40Hz during the cleaning process.

[2]Top-down processing refers to the influence of prior knowledge and expectations on the processing of incoming sensory information. Bottom-up processing, on the other hand, refers to the processing of sensory input [220].

Another hypothesis of this study was regarding the changes in the theta activity conjecturing a higher theta oscillation for the Avatar group after the intervention.
It is suggested that the thalamocortical dysrhythmia (TDC) caused by abnormal activity of the thalamus in some types of chronic pain (and many other disorders) might be manifested in an increase in theta activity [212, 160]. Among patients with CP, the therapeutic thalamic lesion has been shown to effectively reduce overactivation in the pain matrix and alleviate pain in some patients [244, 160]. The thalamocortical network plays a crucial role in transmitting modulatory inhibition signals from the thalamus to cortical regions, and the "abnormal contextual feedback processes" is suggested to be a pathological signature in CP [212, 57]. However, not all studies have shown a similar increase in theta power for Chronic Pain. Moreover, the "how" question of this brain-wide dynamic remains unanswered. [211, 212]. In our study, contrary to the initial hypothesis, I did not find any significant changes in theta power between the two conditions.

An increase in the theta activity may shift the dominant peak towards the lower powers [211]. Another central hypothesis of my study was the shift of PTAF towards higher frequencies for the avatar group. I observed a significant change from pre to post Peak of Theta-Alpha Frequency (PTAF) over all channels with a significantly higher PTAF for the avatar condition.
Primarily, PTAF has been shown to reflect changes in neuronal activation, synchronization, and some network-wide dynamics. It has been suggested as a bio-marker for conditions such as Autism and Alzheimer's disease [239, 64]. PTAF changes have also been observed amongst various types of Chronic Pain conditions; it has been observed that the dominant peak of theta-alpha frequency shifts towards the lower frequency in the presence of pain [42, 226, 160, 199]. As a result, the PTAF has been suggested as a candidate for CP bio-marker [60].
Given the nature of the peak frequency, it is clear that if the coherence between different brain regions increases in higher frequencies, it might be reflected in an increase in PTAF [201]. Factors such as age, physical activity, cognitive load, and attention might affect this peak value [125, 117, 227, 224].
Although given the study results, our initial null hypothesis was confidently rejected, there was no significant correlation between the subjective PRS values and the PTAF. The lack of correlation between these two values, might be resultant of many factors including the limited data points. The increase in PTAF might also result from the changes in the brain dynamics with regards to the use of avatar in VR.

5.1 Limitations and future work

During this pilot-study we also identified some of the possible limitations in order to provide a foundation for future EEG studies on VR for CP.

One of the major limitations of the pilot study was the sample size. Although the sample size was comparable to many previous VR studies [172], it violates the reliability and power for an EEG study [153]. Therefore, studies with larger sample sizes are suggested to be conducted. A larger sample size not only will increase the power, confidence, and effect size of statistics, but also will provide the researchers with the freedom to evaluate more measures in their design. In the method paper published for the protocol of this study, we suggested the recruitment of 60 participants in order to have more reliable results. However, during the recruitment process, we encountered some of the challenges in participant recruitment.

As a part of recruitment criteria for this study, we excluded patients with CP who had a history of brain injury or neuropsychaitric disorders. A 2021 study on the Canadian CP population in Newfoundland reported a comorbidity rate of about 60 percent for CP conditions and different types of mental illnesses. Therefore, the use of those criteria for sampling method, might actually jeopardize the validity and reliability as the sample might not fully represent the CP population. Although participants were able to take their medication, we asked them to absent caffeine and nicotine intake before the study (see Chapter 3). However, caffeine and nicotine might also be used as a CP management method, consciously or unconsciously [26] and not taking them might exacerbate participants' pain, which might eventually bias our data. Therefore, I suggest that for future studies, with larger sample sizes, we control the use of caffeinated food and beverages as a covariant, and not as an exclusion criterion to have a better picture of CP population.

Chronic Pain is known to be an umbrella term for many different types of pain that lasts for more than 3 months [217], which might originate from different pathologies. In this study, given the limited financial and time budget, we conducted the study on CP patients. Although our demographic data suggests that the majority of participants had arthritis, we suggest that for future studies to have a more heterogeneous sample, we specify the types of pain (such as PLP, CRPS, SCI, and Rheumatoid Arthritis). By specifying the pain type, we can also customize the designed VR for the target population as well as control the environmental variables in the VR intervention.

In this study we observed that both groups reported a significant pain level reduction. Although, we cannot eliminate the novelty effect of VR for them, as the majority of participants have not had a previous experience in VR. Therefore, VR evaluation is suggested to take place after a specific dosage of treatment as a Longitudinal study. However, it is worth mentioning that the dosage in longitudinal studies needs to be controlled.

Additionally, We can prevent some of the limitations of this study by adding control groups (including healthy controls and outside VR, CP controls) to control the placebo effect of VR. Moreover,

running double-blinded experiment sessions, with a randomized sample (using methods such as stratification) is suggested. These methods can prevent selection biases amongst participants and provide us with more reliable data.

During the data cleaning process of this study, the EEG data in *EEG-VR* had a low signal-to-noise ration due to the head movements and the weight of VR HMD on the electrodes. Therefore, we could not include them in the statistical analysis. Following some of the current EEG and Brain-Computer Interface (BCI) studies in VR, we suggest the use of caps with more electrodes for future studies. Alternatively, the research team can utilize new VR headsets with built-in EEG electrodes. With a higher number of electrodes, the bad channels can be interpolated using the neighbors, ICA can be used in the process of data cleaning, and the spatial resolution of EEG would increase.
In this study we only analyzed the power and the peak of frequency as the indices. However, for future analysis of data of this pilot study, or the future study, other measures such as spindles or the dynamics of these changes can also be considered. Such analysis was above the scope and the skill of this thesis.
Finally, the use of different neuroimaging techniques such as fMRI is suggested for future studies. The use of such neuroimaging methods would give us a better spatial resolution providing a better understanding of the brain-wide connectivity and interactions.

Chapter 6

Conclusion

In this thesis, we asked, "How does having an embodied avatar in a VR environment (VMW) affect Chronic Pain (CP) patients' Sense of Embodiment (SoE), perceived pain, and neural activity." We proposed a protocol to investigate the effect of having an avatar in VR for chronic pain patients using Electroencephalography.

We found that in both groups, the VR intervention reduced pain. However, we did not find a significant difference in pain reduction level or the sense of embodiment.

The observed changes in EEG alpha and theta oscillations were contrary to our initial hypotheses, with a significantly lower alpha in the frontal region and no significant difference in theta. We also observed a significantly lower beta activity for the Avatar group. While it may not be possible to come to a conclusive deduction, the observed changes could be due to the process of resolving the changes in the bodily sensory conflicts caused by the embodied avatar. Additionally, the PTAF was lower for the Avatar group, which might result from the reduction of the sensation of pain in that group. However, further studies with a larger population are required to establish a conclusion and confirm these findings.

This pilot study also allowed us to identify the limitations of the design and implementation of the proposed protocol for future studies.

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Appendix A

Questionnaires

Writers note: the following questionnaires are not designed for this project and are standard questionnaires. Also, the reference to each of them is provided in Chapter 3.

Questionnaire 0 – Edinburgh handedness inventory questionnaire

Have you ever had any tendency to be left-handedness?

YES *NO*

Please indicate your preferences in the use of hands in the following activities by putting + in the appropriate column. Where the preference is so strong that you would never try to use the other hand absolutely forced to, put ++. If, in any case, you are really indifferent, put + in both columns. Some of the activities require both hands. In these cases, the part of the task, or object, for which hand preference is wanted is indicated in brackets.

Please try to answer all the questions, and only leave a blank if you have no experience at all with the object or task.

		Left	Right
1	Writing		
2	Drawing		
3	Throwing		
4	Scissors		
5	Toothbrush		
6	Knife (with a fork)		
7	Spoon		
8	Broom (upper hand)		
9	Striking Match (match)		
10	Opening box (lid)		
11	Comb		
12	Hammer		
13	Screwdriver		
14	Tennis Racket		
15	Cricket bat (lower hand)		
16	Golf Club (lower hand)		
17	Rake (upper hand)		
18	Dealing cards (card being dealt)		
19	Threading needle (needle of thread according to which is moved)		

20	Knife (without fork)		
I	Which foot do you prefer to kick with		
ii	Which eye do you use when using only one?		

Leave these spaces blank

L.Q.	
DECILE	

Questionnaire 1 – Pain score (SF-MPQ) **age:**

For each of the Pain Dimensions mentioned below, circle the response that best characterizes the intensity of your feeling.

1. **Throbbing**

☐ *None* ☐ *Mild* ☐ *Moderate* ☐ *Severe*

2. **Shooting**

☐ *None* ☐ *Mild* ☐ *Moderate* ☐ *Severe*

3. **Stabbing**

☐ *None* ☐ *Mild* ☐ *Moderate* ☐ *Severe*

4. **Sharp**

☐ *None* ☐ *Mild* ☐ *Moderate* ☐ *Severe*

5. **Cramping**

☐ *None* ☐ *Mild* ☐ *Moderate* ☐ *Severe*

6. **Gnawing**

☐ *None* ☐ *Mild* ☐ *Moderate* ☐ *Severe*

7. **Hot burning**

☐ *None* ☐ *Mild* ☐ *Moderate* ☐ *Severe*

8. **Aching**

☐ *None* ☐ *Mild* ☐ *Moderate* ☐ *Severe*

9. **Heavy**

☐ *None* ☐ *Mild* ☐ *Moderate* ☐ *Severe*

10. **Tender**

☐ *None* ☐ *Mild* ☐ *Moderate* ☐ *Severe*

11. Splitting

☐ *None* ☐ *Mild* ☐ *Moderate* ☐ *Severe*

12. Tiring-exhausting

☐ *None* ☐ *Mild* ☐ *Moderate* ☐ *Severe*

13. Sickening

☐ *None* ☐ *Mild* ☐ *Moderate* ☐ *Severe*

14. Fearful

☐ *None* ☐ *Mild* ☐ *Moderate* ☐ *Severe*

15. Punishing-cruel

☐ *None* ☐ *Mild* ☐ *Moderate* ☐ *Severe*

16. On a scale of 0-10, my pain level is (now):

No pain

0	1	2	3	4	5	6	7	8	9	10

Worst Possible Pain

17. How do you describe your current pain intensity?

☐ *No Pain* ☐ *Mild* ☐ *Discomforting* ☐ *Distressing* ☐ *Horrible* ☐ *Excruciating*

Questionnaire 2 – Pain and medication assessment for CP pain

Please fill in the following table about your pain localization and use of medications. Also, please enter the category of the medication that you are using if you are aware of it, otherwise, please let the researcher know and they will help you with that section.

What is your Chronic Pain duration?:

Pain localization	Pain side	Medication (or other treatment inc. Meditation or physiotherapy	Dosage per day	NM (Neuro-active medication)	B (Benzodiazepines)	AT (Antiepileptic drugs)	TA (Tricyclic Antidepressant nt)	O (Opioids)	Constant pain(~6/10), or Constant and proxy-small(~3/10) pain, or Exclusively(~8/10) pain attack and how long?

Questionnaire 3 – Sleep and Tiredness assessment (Tiredness Symptoms Scale (TSS) and Karolinska Sleepiness Scale (KSS))

Please circle which of the following levels best indicate your current level of sleepness:

- **Extremely alert**
- **Very alert**
- **Alert**
- **Rather alert**
- **Neither alert nor sleepy**
- **Some signs of sleepiness**
- **Sleepy, but no effort to keep awake**
- **Sleepy, but some effort to keep awake**
- **Very sleepy, great effort to keep awake, fighting sleep**
- **Extremely sleepy, can't keep awake**

At this moment I notice

(1) heavy head	• **YES**	• **NO**
(2) sore eyes	• **YES**	• **NO**
(3)watering eyes	• **YES**	• **NO**
(4) heavy eyelids	• **YES**	• **NO**
(5) heavy legs	• **YES**	• **NO**
(6) general weakness	• **YES**	• **NO**
(7) feeling cold	• **YES**	• **NO**
(8) sensitivity to noise	• **YES**	• **NO**
(9) yawning	• **YES**	• **NO**
(10) loss of interest	• **YES**	• **NO**
(11) poor concentration	• **YES**	• **NO**
(12) irritability	• **YES**	• **NO**
(13) little desire to speak with others	• **YES**	• **NO**
(14) urge to move around	• **YES**	• **NO**

Questionnaire 4 – Pain Numeric Rating Scale

On a scale of 0-10, my pain level is (now):'

No pain											Worst Possible Pain
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Questionnaire 5 – Sense of Embodiment in Avatar

For each of the statements below, circle the response that best characterizes your experience during the experiment, where: (-3) = strongly disagree, (-2) = disagree, (-1) = somewhat disagree, (0) = neither agree nor disagree, (+1) = somewhat agree, (+2) = agree, (+3) = strongly agree.

While I was in Virtual Meditative Walk, there were moments in which…

1. I felt as if my body was located in the forest

Strongly disagree	*-3*	*-2*	*-1*	*0*	*1*	*2*	*3*	*Strongly agree*

2. I felt out of my body

Strongly disagree	*-3*	*-2*	*-1*	*0*	*1*	*2*	*3*	*Strongly agree*

3. I felt as if my (real) body were drifting toward a virtual one or as if a virtual body were drifting toward my (real)body.

Strongly disagree	*-3*	*-2*	*-1*	*0*	*1*	*2*	*3*	*Strongly agree*

4. The movements in the virtual world were caused by my movements. (How much have you sensed yourself as the agent of the movements in the VR)

Strongly disagree	*-3*	*-2*	*-1*	*0*	*1*	*2*	*3*	*Strongly agree*

5. I felt as if the(a) virtual body was moving by itself

Strongly disagree	-3	-2	-1	0	1	2	3	*Strongly agree*

6. I felt as if the movements of the virtual hands were influencing my own movements.

Strongly disagree	-3	-2	-1	0	1	2	3	*Strongly agree*

7. I felt like I could control the virtual body(my body in VR) as if it was my own.

Strongly disagree	-3	-2	-1	0	1	2	3	*Strongly agree*

8. It felt as if my (real) body was turning into a 'virtual' body.

Strongly disagree	-3	-2	-1	0	1	2	3	*Strongly agree*

9. I felt as if a virtual body was my body

Strongly disagree	-3	-2	-1	0	1	2	3	*Strongly agree*

10. At some point, it felt as if my real body was starting to take on the posture or shape of the virtual body that I saw.

Strongly disagree	-3	-2	-1	0	1	2	3	*Strongly agree*

11. I felt that my own body was warmed by the sun in the forest.

Strongly disagree	-3	-2	-1	0	1	2	3	*Strongly agree*

12. In the VMW I had a sense of "being there"

Strongly disagree	-3	-2	-1	0	1	2	3	*Strongly agree*

13. In VMW I was not aware of the real world surrounding while navigating in the virtual world? (i.e. sounds, room temperature, other people, etc.)?

Strongly disagree	-3	-2	-1	0	1	2	3	*Strongly agree*

14. How real did the virtual world seem to you?

Completely real	3	-2	-1	0	1	2	3	*Not real at all*

15. I had a sense of acting in the virtual space, rather than operating something from outside

Strongly disagree	-3	-2	-1	0	1	2	3	*Strongly agree*

16. My experience in the virtual environment seemed consistent with my real-world experience.

Strongly disagree	-3	-2	-1	0	1	2	3	*Strongly agree*

17. How real did the virtual world seem to you?

About as real as an imagined world	-3	-2	-1	0	1	2	3	indistinguishable from the real world

18. I did not feel present in the virtual space.

I did not feel	-3	-2	-1	0	1	2	3	*Felt present*

19. I was not aware of my real environment.

Strongly disagree	-3	-2	-1	0	1	2	3	*Strongly agree*

20. In the computer-generated world, I had a sense of "being there"

Strongly disagree	-3	-2	-1	0	1	2	3	*Strongly agree*

21. Somehow I felt that the virtual world surrounded me.

Strongly disagree	-3	-2	-1	0	1	2	3	*Strongly agree*

22. I felt present in the virtual space.

Strongly disagree	-3	-2	-1	0	1	2	3	*Strongly agree*

23. I still paid attention to the real environment.

Strongly disagree	-3	-2	-1	0	1	2	3	*Strongly agree*

24. The virtual world seemed more realistic than the real world. (even for a short time that I was in the VR)

Strongly disagree	-3	-2	-1	0	1	2	3	*Strongly agree*

25. I felt like I was just perceiving pictures.

Strongly disagree	-3	-2	-1	0	1	2	3	*Strongly agree*

26. I was completely captivated by the virtual world.

Strongly disagree	-3	-2	-1	0	1	2	3	*Strongly agree*

age:

gender:

chronic pain duration:

Appendix B

Study Procedure Script

Writers Note: This study procedure script is the exact script used to communicate with participants. This script was submitted as a part of the ethics application for the study, inspired from the materials submitted for ethics application in which we used the templates provided by SFU/UBC ethics board such as
"https://open.library.ubc.ca/soa/cIRcle/collections/ubctheses/24/items/1.0102587" or
"https://www.sfu.ca/research/sites/default/files/2021-04/Consent" ,as well as previous consent forms and script practices in the Pain Studies Lab.

B.1 Pre-day setup

- Sanitizing the lab area
- Checking the power cable shields (foams)
- Remove unused (extra) digital devices from the study room (including phones)
- Turn off the computers in the study room (if on)
- Send the Reminder email the day before and the morning of the study
- Use the air purifier in the study room
- Pre-setup the EEG and VR devices in the study room
- Sanitize the HMD, the cap, the surfaces (desks, chairs), pens (mark the pencil holders as sanitized and used)
- Copy the study procedure, the questionnaires, and the consent forms (2x) and put them in a clean folder
- Provide masks and wipes
- Put a mirror in the study room (for patients to see what is happening during the EEG setup)
- Check for the shower access and the kit (comb + towel + shampoo)

B.2 Greetings

- Asking participants to wait in the waiting room until you accompany them to the study room
- Greetings
- Introducing the researchers and the pain lab. Offer them water and mask and ask if you can take their coat

- Reminding/ Ensuring them about the COVID safety protocols
  - Social distancing
  - Frequent sanitizing the devices
  - Vaccinated researchers
  - Air purifiers
  - Disinfected HMDs
  - Their vaccine cards
- Ask for their concerns regarding the COVID safety protocols
- Let them know that they can ask any question anytime they want
- Let them know that they are free to go without consequences at any stage throughout the day
- Smile, Listen, Keep distance
- If any one is accompanying them, ask them to wait in the waiting area, and offer them coffee or tea or water

Hello! Welcome to the pain studies lab and thanks for volunteering for our study. I hope you have found it here easily. My name is Pegah. I emailed you earlier, and I am the main researcher in this project. I am a masters student at the Pain Studies Lab, and here with me is X my fellow researchers who will help me with the study today. Would you like me to take your coat?
Before starting the introduction to the study, I want to ensure you that all researchers in the PSL are fully vaccinated. We are following BC protocols for COVID-19, by sanitizing all surfaces, and equipment including VR headsets and EEG devices, wearing masks, and maintaining social distancing.
Also, we have special air purifies in the research rooms which can clean air born viruses up to 99.
Regarding the protocols, May I see you proof of vaccine so that we can further continue the study process?
Do you have any question from me?
Please feel free to ask your questions from me or my co-worker, any time! Also, at any stage of today's study you are free to withdraw without any consequences or need for explanation.
(If the participant has any companion) So, since the study room does not have enough space, concerning the COVID safety protocols, I should ask you to stay here for the duration of the study. We can offer coffee, water or tea. So, feel free to use the waiting area and help yourself.

B.3 Pre-test

1. An introduction to the step, what we are going to do
2. Asking participants about the restrictions they were asked to consider
   - Alcohol avoidance

Nicotine avoidance

Sleep

Coffee and caffeinated food

Washing hair

No hair products

Washed

Dried

3. Check the right size for the EEG cap (The research Assistant will cover this section while the main researcher setup the room)

4. Walk participants through the consent form

Introduce the researcher team

Study purpose

No mention of embodiment in VR and avatar

Study process

Overall duration and the steps of the study

How long each step is estimated to take

Let them know about the gel and ask them about their preferred cleaning option

Confidentiality

Different parts of the consent form to sign

Remind them of their right to leave the study without any explanations

Remind them of their right to ask any question at any step of the study

Give them time and pen to read and sign the consent form

Give them a copy of the consent form

Explain the questionnaires

Let them fill the question forms

Remind them of the process, the next step and guide them to the study room

So, here is the timeline for today's session. We expect that the study will take about 1.5-2h, totally. The first part was the greeting and protocol description, which we have already done! Next is the consent form and filling some questionnaires regarding your demographic and pain-specific information which my friend X will help me with. Then we will go to the study room for the blue (main) section which takes about 25 to 30 minutes given the headset setup. After that, my friend will ask you to fill another set of questionnaires and then the study will be over and we will thank you with 50CAD compensation for your time (which is invaluable and is much appreciated).
Before we start, I need to ask if you have followed the instructions (re: I mentioned in the email). Have you abstained any Alcoholic beverage or food (with any percentage), nicotine, and caffeine for the past 12 hours? Have you had a restful sleep last night (from 6-8 hours)? Have you washed and

dried your hair and avoided the use of any hair product (such as wax, gel, spray, oil) or conditioner? I also need to kindly ask you to take off any hair pin or clips, earring, and necklace if you have (we will keep them safe in this box and will return them to you right after the study).
Finally, can I check these caps for size to see which one fits your head better?
Thank you so much! I will leave to setup the cap. My friend X will continue with the consent forms and the questionnaires and then accompany you to the study room.
So, here is the consent form that we emailed you earlier. In today's study we are aiming to see the effectiveness of Virtual Reality on your pain level and brain signals using EEG. Are you familiar with VR?
(if no) Virtual Reality is basically a 3D, computer graphical environment. You will wear a headset [show them the headset] and the lenses(show the googles) in this headset will display that graphical environment for you. The environment that we are showing you today is specifically and carefully designed for chronic pain patients and provides you with a series of mindfulness meditation practices.
What about EEG, have you ever had an experience of taking EEG?
(if no) EEG, is a non-invasive form of recording your brain signals using electrodes. You will put on a cap with attached electrodes to it. Those electrodes will record your EEG signals. This process involves no pain, only wearing the cap for the duration of the study might be a bit uncomfortable, and we apologize for that in advance. We will then measure the changes of these signals to see if the VR environment was effective. [(if they ask)Collecting your EEG signals does not mean that we are reading your mind.]
Do you have any question so far?
So, when we go to the study room, we will setup the EEG cap for you. There, to improve the signal quality, we will insert a conductive gel beneath the electrodes. This means that your hair will become a bit greasy after the study. The gel does not damage your hair. However, when the study is done, we can provide you with a paper towel and a comb for your hair or a shampoo and towel to wash it (this will be your decision). Here is the kit of comb, towel and shampoo and you can wash your hair in a shower room inside the building (we can assist you with washing process, if you wish). Do you think if you are okay with that? Do you have any question regarding that part?
Okay, so after EEG setup, we will ask you to lie down on a reclining chair and will record your EEG. My friend will repeat this procedure for you, so do not worry if you forget it: So, we will record your EEG in 3 phases. First, with your eyes closed 5 minutes. Then, we will help you to put on the VR headset [show them the headset and how to put that on) and record it for about 9 minutes in the VR environment.Then we will take off the headset and take another eye-closed, 5 minutes of EEG, similar to the first one. Then there will be other round of questionnaires, and the study will be over.
Any question so far?

So, here [show them the contact info], you can find the name and the contact information of the principal investigator, Dr. Gromala, and the main researcher, Pegah Kiaei (whom you met). Your participation is totally voluntarily. You can ask us to withdraw the study at any point without providing any excuse. If you decide to withdraw from participating at any time during the study, you just need to inform one of the researcher about your decision. You do not need to provide ANY reason or explanation. Your data collected up to that point will be discarded. If you decide to withdraw anytime after participation, you can inform us by contacting us through email or phone

call within 2 weeks. Your collected data will be discarded.
Apart from that, all your data will be kept locked or in password-protected computer files. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law.
[if they ask how you keep the data] We will assign your data record a unique number as a participant in this study. Only this number will be used on any research-related information collected about you during the course of this study, so that your personal info [i.e., your name or any other information that could identify you] as a participant in this study will be kept confidential.
Information that has your identity will be kept by the Principal Investigator. Other data collected from questionnaires will be stored securely for 5 years from the time it is being collected, and then the data will be disposed. All physical paper questionnaires and consent forms collected will be shredded and all electronic data will be completely deleted from the storage devices. If you have any concerns about your rights as a research participant and/or your experiences while participating in this study, you may contact the SFU Office of Research Ethics at this number.
To our knowledge, the study does not have any side effects for you. However, if you are not used to virtual environments, in case your real movement does not properly be synced with your movement inside the virtual environment, you may experience mild nausea. We have done our best to decrease the chance of this phenomenon happening by slowing down the movement in the virtual environment as much as we could. If you experience the onset of any adverse symptoms, please immediately notify Us, and the experiments will be stopped right away. There will be no negative consequences at all for withdrawing early from the experiment.
So, this is the part of the consent form that you need to sign. Here is the optional section to put your initials in. if you are consenting that[the first one] we can use your anonymized, de-identified data for our database shared with other researchers if they request from SFU. if you are interested in participated in any of the future studies [point the second one], if you are willing to let us contact you later for further follow-up questions [point the last one]. And here is the part to sign for participation in the study.
Okay, so, please take your time if you need to read the consent form and sign it, and feel free to ask me any question. You can find a clean pen from that case. Also, here is your copy of the consent form. You can keep it for the further questions and contact number.

(From this section the research assistant will continue the procedure)

[Collect the consent form] Thank you. So, here is the pretest questionnaire. I want you to fill that for us, and then we can go to the study room.
the questionnaire includes some information about your pain in average during the past two weeks (the last 2 questions is however, assessing your current pain). In this box you need to put how long you've had CP condition, and then are there any medications or treatments that you use for your pain? (Ask about the detail based on the chart) and the last page is assessing your sleep and tiredness. [if they miss, ask them about their age, pronoun, chronic pain duration, coffee/nicotine user]
Okay, next, we will go to the study room to setup the EEG and VR and run the study. It will take about 20 – 30 minutes in total. Please come with me.

B.4 Set-up

- Close the door after entering the room (also close the door separating the study room with the main room to reduce the walking/outside noises.)
- Ask participants to sit on the reclining chair
- Describe the study procedure in detail for the participants.
- In each step inform them of what you are doing (e.g. I am now putting the cap on your head)
- Ensure participants about the cleanness of the devices
- Setup the EEG device

  Put the cap on participant's head

  Apply gel underneath the electrodes (note: Geltrodes are placed on the cap before)

  Attach the electrode cables to the cap

  Apply gel on earlobe electrodes and put the on the right ear

  Connect the EEG device to the computer (i.e. Enobio 8 NECBOX)

  Turn the device on

  Check for the quality of each electrode(Keep the scale under 100 *micro*)

  60Hz power frequency

  Save both .nedf and .easy files

  Adjust the cap and electrodes if needed.
- Remind the of the study step ahead (ask them to close their eyes and sit relax+ all cautions)
- Turn off the light in the study room (to reduce the noise)
- Keep checking the quality of the signal during the study. Mark the movements if observed.
- Remind them to stay still and awake if needed - Mark the section to remove later
- Record any symptom of drowsiness and sleep and try to make sound to keep them awake + Mark those section to remove later
- After the 5-minute resting state, remind them of the next step and what they should expect in VR
- Setup the HMD
- Adjust the electrodes in case of bad quality

B.5 Collection Process

So, as I said before, we are going to capture your EEG 3 times today. This is the first part. Now, I want to ask you to lie back and close your eyes for 5 minutes. I will be sitting there, but we cannot move or walk in the room while you are here. And I would need to turn the lights off as well. I want you not to move your neck or head during the recording session as much as possible. Also, try to keep your jaw muscles relax, do not crunch your teeth, smile, yawn, or move an do not speak, unless you want to let us know that you are uncomfortable or you want us to stop the study. I want you to lie back, keep your head steady, relax your muscles (do not move your hand or, body or legs), close your eyes and (please do not roll your eyes I know its super hard, but as much as is possible for you. You can let me know to stop at any time. Let me know when you are ready so we can start. when this 5 minute is over, I will let you know, and you can open your eyes and move. Then, we will setup the VR headset. During the recording, If I Lose the signal or anything goes wrong, I will softly touch your shoulder first, as a signal before modifying anything.
Before VR: So, I am going to put the VR HMD now. This section will take about 10 minutes. In the VR environment, you will see an animated forest. After the application starts (when you see the picture in the headsets) you will have about 1 minute to look around, move your head, etc. After that- I will let you know when- you need to lie back again, similar to the previous section (with the steady head and neck, and muscle relaxation) But, this time, I want you to fix your gaze in the VR and just look forward. Try not to move your head (I know this might be a challenge) but, try to relax generally. After the session is done, I will let you know, and we will take off the headset. Also, do not be afraid if anything goes wrong in the VR, or if it stops working(goes black), I will take care of that, please continue on staying relax. When the VR is done, the last part is similar to the initial part. We want you to lie back, fix your head, relax your muscles (do not move your hand or, body or legs), close your eyes and please do to roll your eyes as much as it is possible for you. Please let me know if you have any questions or concerns.
The Vr section is over, please Stay relaxed and close your eyes while I am taking the HMD off.
Thank you so much for your patience. We are done now with this part. How do you feel? So let me help you take the HMD and the cap off.
As you probably noticed you have gel on your hair. So, do you prefer us guide you the shower room to wash your hair. Or, just comb them. It is your choice. My friend can accompany you back to the main room for the post -test

- Help them taking off the HMD
- Save the EEG captured (parallel)
- Remove the EEG Cap
- urn off the EEG device
- Take off the cap(parallel)

  Careful about the wiring

  Detach the Sensors amd electrodes

  Put the electrodes in a basket and wash the electrodes with water and soft toothbrush

  Clean the cap with a wipe (will be washed afterwards)

- Check for data being saved
- Offer them Comb or hair shampoo and towel based on their choice

B.6 Post-test

1. (informally-on way to the main room) So, how your experience in VR [for the first time-for those who have been there for first time]. Did you enjoy it? Would you like to try VR later, again?
2. Ask them how they feel and how was the experience (informally)
3. So, this part will also take place for about 5 minutes. I'll ask you to fill some other questions regarding your experience in VR.
4. Can I offer you tea, coffee or water?
5. Inform them about this section of the study

   What is the procedure?

   How much will it take

   Ask them if they want some water, tea or coffee, if they want to walk a little bit

   Give them the questionnaires and ask them to fill it
6. Here are the questionnaires.
7. If avatar section- ask them about how they feel about the avatar and the VR environment

   If they would like to do that again

   If they feel better

   If the process was tiring, painful? If they were uncomfortable during the process

   Take note of those parts.

   How was your experience in the VR, or the process of taking your EEG? Do you think you would try using VR some other time? How did you find the avatar? How real did you find it?
8. Asking if we can put their name in our future participants list
9. So, are you willing to participate in our lab's future studies?
10. If so, can I have your consent on that?
11. Also, do you wish to be contacted regarding the results?
12. If so, put their name in the list
13. If they want to be contacted regarding the result?

B.7 Compensation

1. Thank you So very much for giving us your valuable time. I know it probably was not easy coming this far to the Surrey campus. I wonder if you have a parking receipt or expenses that I can compensate you for?
2. Here is $50 as our thank for your time and contribution. Also, can you please sign this form so I can get reimbursed from the school?
3. Ask them for the parking ticket
4. Give the money (the packet with an envelope) in addition to the parking ticket
5. Sign the compensation form
6. Attach the ticket to the form
7. Bring them their coat

B.8 Goodbye

1. Any question and concerns?
2. It was nice meeting you, we appreciate your participation in the study. Is there questions and concerns that WE CAN Help you with? Feel free to email me
3. Help them to find the out door in mezzanine

B.9 Clean Up

1. Clean the cap
2. Clean the room
3. Return the air purifier to the room and turn it on
4. Organize questionnaires
5. Immediately enter the data
6. Collect and pack the cleaned, dried, electrodes
7. Sanitize the room
8. Wash the cap with water (mildly)
9. Collect the compensation form - and Scan the ticket and the form
10. Collect any water bottle, coffee cup, tissue from the lab
11. Put participant's name in the excel sheet- if volunteered for the future

Appendix C

Codes

Writers note: The following codes are not fully mine and are modified for this study, learned from the tutorials provided in the FieldTrip toolbox website https://www.fieldtriptoolbox.org/citations/. Pages are separately cited throughout the text.

C.1 FieldWork pipeline for data process

C.1.1 PSD calculation

```
  function PrePost_PSDs(Subjectm)

if nargin == 0
  disp('Not enough input arguments');
  return;
end
eval(Subjectm);
outputdir = subjectdata.subjectdir;
%######################################################## ABIT OF PREPROCESS
%importing cleaned data
cfg_import = [];
cfg_import.reref='no';
cfg_import.derivative = 'no'; %correct for the 1/f dropoff
cfg_import.dataset = subjectdata.pre_dir;
p00_pre = ft_preprocessing(cfg_import);
cfg_import.dataset = subjectdata.post_dir;
p00_post = ft_preprocessing(cfg_import);
p00_pre.elec.type = 'eeg1010';
p00_post.elec.type = 'eeg1010';
%Detrending the dataset
cfg_d           = [];
cfg_d.channel   = 'all';
cfg_d.demean    = 'yes';
cfg_d.polyremoval = 'yes';
cfg_d.polyorder = 1;        % with cfg.polyorder = 1 is equivalent to
    cfg.detrend = 'yes'
p00_pre = ft_preprocessing(cfg_d, p00_pre);
p00_post = ft_preprocessing(cfg_d, p00_post);
cfg_e = [];
cfg_e.length = 2;           % epoching to Xs windows (1s epochs, 1Hz
    resolution)
cfg_e.overlap = 0.5;        % with no overlap
p00_pre_reref = ft_redefinetrial(cfg_e, p00_pre);
p00_post_reref = ft_redefinetrial(cfg_e, p00_post);
%######################################################## PSD CALCULATION
cfg_pow = [];
cfg_pow.output   = 'pow';
cfg_pow.channel  = 'all';
cfg_pow.method   = 'mtmfft';
cfg_pow.tapsmofrq = 1;      % amount of spectral smoothing through
    multi-tapering.
```

```
    cfg_pow.foi      = 2:0.5:30;
    cfg_pow.taper    = 'hanning'; %hanning window
    cfg_pow.t_ftimwin = 2;
    cfg_pow.keeptrials = 'no';
    cfg_pow.toi      = '50%';    %the times on which the analysis
                                 % windows should be centered (in seconds), or a
                                     string
                                 % such as '50%' or 'all'. Both string options
                                 % use all timepoints available in the data, but
                                     'all'
                                 % centers a spectral estimate on each sample,
                                     whereas
                                 % the percentage specifies the degree of overlap
                                     between
                                 % the shortest time windows from cfg.t_ftimwin.
    p00_pre_h        = ft_freqanalysis(cfg_pow, p00_pre_reref);
    p00_post_h       = ft_freqanalysis(cfg_pow, p00_post_reref);
                                 % the output for ft_frequencyanalysis (power) is
                                     uV^2
                                     https://www.fieldtriptoolbox.org/workshop/
                                 %oslo2019/timefrequency
    p00_post_h.powspctrm =
        (p00_post_h.powspctrm./(1/p00_post_h.cfg.t_ftimwin(1,1)*1.5));%
        calculating PSD fro power (uV^2) > (uV^2/Hz)
    p00_pre_h.powspctrm =
        (p00_pre_h.powspctrm./(1/p00_pre_h.cfg.t_ftimwin(1,1)*1.5));
                                 % PSD = Power value/(f xWf)
                                 % Wf is the correction value for each window
                                     (window function)
                                     https://www.onosokki.co.jp/English/
                                 %emm_back/emm9.htm
                                 % PSD is typically a skewed distribution, with
                                     most of the power concentrated at lower
                                     frequencies.
                                 % Taking the logarithm of the PSD can help to
                                     normalize the distribution,
                                 % making it easier to compare power across
                                     different frequency bands.
                                 % the use of log transform is suggested for
                                     highlighting the spectral
                                 % component bands and is suggested for wide
                                     ranges.
%     p00_post_h.powspctrm = 10*log10(p00_post_h.powspctrm); %log transform of
    power values 10*log_{10}(\muV^{2}/Hz)'
%     p00_pre_h.powspctrm = 10*log10(p00_pre_h.powspctrm);
%      figure; ft_multiplotER([], p00_pre_h,
    p00_post_h);legend('pre','post');xlabel('Frequency (Hz)');ylabel('absolute
    power (uV^2)');
    save([outputdir filesep '_pre_Hanning'],'p00_pre_h');
    save([outputdir filesep '_post_Hanning'],'p00_post_h');
    clear cfg*
```

```
end
```

C.1.2 Band frequency calculation

```
% we pass one of the data structures to the function and retreive alpha or
% theta value for each of the elements.
function band_relative = CalculatePower (spectrumStruct, type)
    if nargin == 0
      disp('Not enough input arguments');
    return;
    end
    try
        band_relative = [];
        fn=fieldnames(spectrumStruct); % the name of the field the struct should
            be 1x(number of subjects in that condition)
        freqNorm = [4 30]; % frequency range used to normalize the spectrum from
            the overall
        if type=="alpha"; FOI = [8 13]; else; FOI = [4 8]; end
        if type=="alpha"; ROI = {'F3'}; else; ROI = {'F3'}; end% these elctrodes
            can change based on the desired ROI
        for i=1:6
               subject(i) = spectrumStruct(i).(fn{1});
               % subject(1).powspectrum has 8 rows of value, each for one
                   channel. therefore,
               % data is averaged over trials for each channel
               % get the frequency band of interest (FOI)
               cfg = [];
               cfg.channel       = ROI;
               cfg.avgoverchan   = 'no';
               cfg.avgoverfreq   = 'no'; % calculate the mean for the band
                   oscillation
               cfg.avgoverrpt    = 'no'; % average over trials for each channel
               cfg.frequency     = FOI;
               band_average = ft_selectdata(cfg, subject(i)); % averaging the
                   power of interest over ROI, and for FOI frequency range

               % get the frequencies for the range
               cfg = [];
               cfg.channel       = ROI;
               cfg.avgoverchan   = 'no';
               cfg.avgoverfreq   = 'no';
               cfg.avgoverrpt    = 'no';
               cfg.frequency     = freqNorm;
               spectrum_average  = ft_selectdata(cfg, subject(i));

               % normalize the ROI power value for each channel by dividing the
               % band average by the spectrum average in each channel per person
```

```
                    band_relative_power =
                        sum(band_average.powspctrm,2)./sum(spectrum_average.powspctrm,2);
                        % compute relative power per trial, per channel
                    band_relative = cat(1,band_relative,mean(band_relative_power));
                        %average the relative power over all electrodes
                end
            catch
                    disp(['Something was wrong with Subject' int2str(i) 'computing
                        their' type '! Continuing with next in line']);
            end
        end
```

C.1.3 PTAF calculation

```
%% PTAF.m
function ptaf = PTAF(spectrumStruct)
if nargin == 0
     disp('Not enough input arguments');
    return;
end
    try
        ptaf = [];
        fn=fieldnames(spectrumStruct); % the name of the field the struct should be
            1x(number of subjects in that condition)
        FOI = [4 13];
        ROI = {'O1','O2','P3','P4','F3','F4','C3','C4'};
        for i=1:6
            subject(i) = spectrumStruct(i).(fn{1});% subject(1).powspectrum has 8 rows of
                value, each for one channel. therefore,
            cfg = [];
            cfg.channel    = 'all';
            cfg.avgoverchan = 'yes';
            SOI_overallchannels = ft_selectdata(cfg, subject(i)); % averaging the power
                of interest over all channels, over ROI requency range

            % calculating the gravity frequency (see Klimesch et al. 1999)
            frequencyIndex = nearest(SOI_overallchannels.freq, FOI);
            powervalues   =
                SOI_overallchannels.powspctrm(frequencyIndex(1):frequencyIndex(2));
            frequencies   = SOI_overallchannels.freq(frequencyIndex(1):frequencyIndex(2));
%               ptaf(i)       = sum(abs(frequencies.*powervalues))/sum(abs(powervalues));
    % this calculates the frequency gravity (not the power avarage)
            maxp = max(powervalues);
             ptaf(i) = SOI_overallchannels.freq(find(SOI_overallchannels.powspctrm ==
                 maxp));
        end

    catch
```

```
            disp(['Something was wrong with Subject' int2str(i) 'computing PTAF !
                Continuing with next in line']);
    end
end
```

C.1.4 Permutation test

```
    %ref:https://www.fieldtriptoolbox.org/workshop/madrid2019/tutorial_stats/
    %#3-compute-a-multivariate-anova-to-test-the-drug-effect-on-the-entire-power-spectrum
    cfg_s = [];
    cfg_s.operation = 'subtract';
    cfg_s.parameter = 'powspctrm';
    avatar_d = ft_math(cfg_s, grandavg_post_a,grandavg_pre_a);
    no_avatar_d = ft_math(cfg_s, grandavg_post_nA,grandavg_pre_nA);
    figure; ft_singleplotER([], avatar_d, no_avatar_d);legend('post-A','post-nA');

    cfg_i = [];
    cfg_i.channel        = 'all';
    cfg_i.frequency      = foi_contrast;
    cfg_i.avgovergfreq   = 'no';
    cfg_i.method         = 'ft_statistics_montecarlo';
    cfg_i.statistic      = 'ft_statfun_indepsamplesT';
    cfg_i.correctm       = 'cluster';
    cfg_i.clusteralpha   = 0.05;
    cfg_i.clusterstatistic = 'wcm';
    cfg_i.clusterthreshold = 'nonparametric_common';
    % cfg_i.minnbchan      = 2;
    cfg_i.tail           = 0;
    cfg_i.clustertail    = cfg_i.tail;
    cfg_i.alpha          = 0.05;
    cfg_i.correcttail    = 'alpha';
    cfg_i.computeprob    = 'yes';
    cfg_i.numrandomization = 5000;
    % cfg_i.neighbours     = neighbours;
    design = zeros(1,avatar_group_size + noAvatar_group_size);
    design(1,1:avatar_group_size) = 1;
    design(1,(avatar_group_size+1):(avatar_group_size + noAvatar_group_size)) = 2;
    cfg_i.design = design;
    cfg_i.ivar  = 1;
    interaction_effect = ft_freqstatistics(cfg_i, avatar_d, no_avatar_d);

    signegmask = (interaction_effect.negclusterslabelmat==1) &
        interaction_effect.mask;% this only works if there is any actual result
    foilimneg = interaction_effect.freq(sum(signegmask,1) > 0);
    foilim = [min(foilimneg) max(foilimneg)];
```

C.2 R Codes for statistical analysis

Writers note: The following R codes are not fully mine and are modified for this study, learned from the tutorials provided in the https://www.datanovia.com/en/lessons/ancova-in-r/lhbikos.github.io/ReCenterPsychStats/ANCOVA.html website. R packages are separately cited throughout the text.

C.2.1 Pain and Embodiment questionnaires

```
#reading dataset and installing packages
#install.packages("nycflights13")
#install.packages("ez")
library(ez)
library(plyr)
library(dplyr)
library(readxl)
library(tidyverse)
library(rstatix)
library(broom)
library(plotly)
library(ggpubr)
setwd("W:/thesis/dataAnalysis")
DataSPSS <- read_excel("DataSPSS.xlsx")
#View(DataSPSS)
## ----------------------------Questionnaires data
    analysis----------------------
####################################
# ============================== PAIN
# ============================== pre-post nrs
DataSPSS %>%
  filter(!row_number() %in%c(3,7, 10,11)) %>%
  select(condition, PrePain, PostPain) -> prepost_pain
# View(prepost_pain)
prepost <- data.frame(Subject = rep(1:length(prepost_pain$PrePain), times =
    2),
                      Condition = as.factor(rep(prepost_pain$condition, times =
                          2)),
                      Time      = factor(rep(c("pre-test","post-test"), each =
                          (length(prepost_pain$PrePain))), levels =
                          c("pre-test","post-test")),
                      NRS       = c(prepost_pain$PrePain,
                          prepost_pain$PostPain), stringsAsFactors = TRUE)
# View(prepost)
temp <-ezStats(data = prepost,
               dv = NRS,
               wid = Subject ,
               within = Time ,
               between = Condition
)
ezPerm(data = prepost,
```

```
      dv = NRS,
      wid = Subject ,
      within = Time ,
      between = Condition
)
pd <- position_dodge(0.02) # move them .03 to the left and right
temp%>%
  ggplot(aes(x=Time, y=Mean, group=Condition, colour = Condition)) +
  geom_errorbar(position=pd,width=.1, aes(ymin=Mean-SD, ymax=Mean+SD)) +
  geom_point(position=pd,shape=15, size=3) +
  geom_line(position=pd, colour = "black") +
  theme(axis.title= element_text(face = "bold"))+
  theme(
    legend.position="right",
    plot.title = element_text(size=11)
  )+
  ggtitle("Pre-test - Post-test Mean (with 95% confidence interval) values
      \nbetween Avatar and noAvatar conditions")+
  ylab("Mean Numeric Pain Scale (NRS) score ")+
  xlab("Time")
## ancova
prepost_pain %>% anova_test(PostPain ~ condition*PrePain)
ggscatter(
  prepost_pain, x = "PrePain", y = "PostPain", color = "condition", add =
      "reg.line")+
  stat_regline_equation (
    aes(label = paste(..eq.label.., ..rr.label.., sep = "~~~~"), color =
        condition)
  )
model <- lm(PostPain ~ PrePain + condition, data = prepost_pain)
model.metrics <- augment(model) %>%
  select(-.hat, -.sigma, -.fitted)
shapiro_test(model.metrics$.resid)
model.metrics %>% levene_test(.resid ~ condition)

toremove <- model.metrics %>%
  filter(abs(.std.resid) > 2) %>%
  as.data.frame()
sn <- which(model.metrics$PrePain %in% toremove$PrePain )
prepost_pain <- prepost_pain %>%
  filter(!row_number() %in% sn)
res.aov <- prepost_pain %>% anova_test(PostPain ~ PrePain + condition)
get_anova_table(res.aov)
# ============================ psr
DataSPSS %>%
  filter(!row_number() %in% c(3,7, 10,11)) %>%
  select(condition, PSR) -> psr
psr$subjects <- rownames(psr)
DataSPSS %>%
  filter(!row_number() %in% c(3,7, 10,11)) %>%
  summarize(Mean = mean(PSR[condition == "A"]),
```

```
            Median = median(PSR[condition == "A"]),
            SD = sd(PSR[condition == "A"]),
            Min = min(PSR[condition == "A"]),
            Max = max(PSR[condition == "A"])) -> psr.stats
DataSPSS %>%
  filter(!row_number() %in% c(3,7, 10,11))%>%
  summarize(Mean = mean(PSR[condition == "nA"]),
            Median = median(PSR[condition == "nA"]),
            SD = sd(PSR[condition == "nA"]),
            Min = min(PSR[condition == "nA"]),
            Max = max(PSR[condition == "nA"])) ->psr.stats[2,]
row.names(psr.stats) <- c("Avatar", "noAvatar")
ezStats(data = psr,
        dv =  PSR,
        wid = subjects ,
        between = condition
)
library(rstatix)
wilcox_test(
  psr,
  PSR ~ condition,
  p.adjust.method = "bonferroni",
  paired = TRUE,
  alternative = "two.sided",
  conf.level = 0.95,
)->psr_Mannwhitney
psr_Mannwhitney
```

C.2.2 Alpha and theta analysis

```
## ------------------------------------EEG data
    analysis---------------------
###################################
# ============================ alpha
library(readr)
library(emmeans)
library(ggpubr)

x1 <- as.double(read_csv("pre_alpha_na.csv", col_names = FALSE)$X1)
x2 <- as.double(read_csv("post_alpha_na.csv", col_names = FALSE)$X1)

x3 <- as.double(read_csv("pre_alpha_a.csv", col_names = FALSE)$X1)
x4 <- as.double(read_csv("post_alpha_a.csv", col_names = FALSE)$X1)
alpha.powers <- data.frame(
  subject  = as.factor(c(1:length(x1),
                         1:length(x1),
                         (length(x1)+1): (length(x1)+length(x3)),
                         (length(x1)+1): (length(x1)+length(x3)))),
  condition = as.factor(c(rep("noAvatar", times = length(x1)*2 ),
```

```
                      rep("Avatar", times = length(x3)*2 ))),
  time     = factor(c(rep("pre-test", times = length(x1)),
                      rep("post-test", times = length(x2)),
                      rep("pre-test", times = length(x3)),
                      rep("post-test", times = length(x4))),
                    levels = c("pre-test","post-test")),
  values   = c(x1,x2,x3,x4)
)
nan_subjects <- unique(as.numeric(alpha.powers[alpha.powers$values ==
    "NaN","subject"]))
alpha.powers <- alpha.powers %>%
    filter(!subject %in% nan_subjects)
#View(alpha.powers)
temp <- ezStats(data = alpha.powers ,
                dv =  values,
                wid = subject,
                within = time ,
                between = condition
)
names(temp)[4]<-"values"
pd <- position_dodge(0.02) # move them .03 to the left and right
temp%>%
  ggplot(aes(x=time, y=values, group=condition, colour = condition)) +
  geom_errorbar(position=pd,width=.1, aes(ymin=values-SD, ymax=values+SD)) +
  geom_point(position=pd,shape=15, size=3) +
  geom_line(position=pd, colour = "black") +
  theme(axis.title= element_text(face = "bold"))+
  theme(
    legend.position="right",
    plot.title = element_text(size=11)
  )+
  ggtitle("Alpha Mean(SD) - ROI")+
  ylab("Average alpha power over the ROI")+
  xlab("Times")
#################################################################
# comparing the two effect of time using ANCOVA
#################################################################
#################################################################
# The ANCOVA code is from the following source:
#  https://www.datanovia.com/en/lessons/ancova-in-r/
lhbikos.github.io/ReCenterPsychStats/ANCOVA.html
#################################################################
#################################################################
# Load and prepare the data
# Check assumptions:
# **Linearity assumption
prevalues <- c(x1,x3)
postvalues<- c(x2,x4)
prepost_alpha <- data.frame(pre = prevalues, post = postvalues, condition =
    as.factor(c(rep("noAvatar", times = length(x1)), rep("Avatar", times =
    length(x3)))))
```

```
prepost_alpha <- prepost_alpha %>%
  filter(!row_number() %in% nan_subjects)
# **Homogeneity
prepost_alpha%>% anova_test(post ~ condition*pre)
# the interaction should not be statistically significant
# **Normality of residuals
model <- lm(post ~ pre + condition, data = prepost_alpha)
# Inspecting the model + removing details
model.metrics <- augment(model) %>%
  select(-.hat, -.sigma, -.fitted)
# Assess normality of residuals using shapiro wilk test
shapiro_test(model.metrics$.resid)
# if the test does not return a significant value, the normality, we can
    assume normality of residuals
# **Homogeneity of variances
# The variance of the residuals should be equal for both groups. > use
    Levenes test:
model.metrics %>% levene_test(.resid ~ condition)
# insignificant levens = homogeneity of the residual variances
# **Outliers
remove <- model.metrics %>%
  filter(abs(.std.resid) >2) %>%
  as.data.frame()
index <- which(model.metrics$pre %in% remove$pre )
# if there are outliar we will remove them
prepost_alpha <- prepost_alpha %>%
  filter(!row_number() %in% index)
res.aov <- prepost_alpha %>% anova_test(post ~ pre + condition)
get_anova_table(res.aov)


adjustedgraph <- prepost_alpha %>%
  emmeans_test(
    post ~ condition, covariate = pre,
    p.adjust.method = "bonferroni"
  )
adjustedgraph
get_emmeans(adjustedgraph)# Display the adjusted means of each group
adjustedgraph <- adjustedgraph %>% add_xy_position(x = "condition", fun =
    "mean_se")
ggline(get_emmeans(adjustedgraph), x = "condition", y = "emmean") +
  geom_errorbar(aes(ymin = conf.low, ymax = conf.high), width = 0.05) +
  geom_point(shape=15, size=3)+
  stat_pvalue_manual(adjustedgraph, hide.ns = TRUE, tip.length = FALSE) +
  labs(
    subtitle = get_test_label(res.aov, detailed = TRUE),
    caption = get_adjustedgraph_label(adjustedgraph)
  )+
  theme(axis.title= element_text(face = "bold"))+
  theme(
    legend.position="right",
```

```
    plot.title = element_text(size=11)
  )+
  ylab("Corrected ROI post-test alpha")+
  xlab("Conditions")
  # Permutation based analysis of the two groups
ezPerm(data = alpha.powers ,
       dv = values,
       wid = subject ,
       within = time ,
       between = condition
)
alpha.powers$channel= rep("ROI", times = length(alpha.powers$values))
write_csv(alpha.powers,"21Feb/alpha-regions-posttest-pretest.csv", append =
    TRUE)

chanavgsd <- read_excel("21Feb/alpha-regions-posttest-correctedancova.xlsx")
#View(chanavgsd)
chanavgsd$channel <- factor(chanavgsd$channel, levels =
    c("Frontal","Central","Parietal","Occipital"))

pd <- position_dodge(0.1) # move them .03 to the left and right

chanavgsd%>%
  ggplot(aes(x=channel, y=mean, group=interaction(condition, time), color =
      time)) +
  geom_errorbar(position=pd,width=0.5, aes(ymin=mean-sd, ymax=mean+sd))+
  geom_point(position=pd, size=2, aes(color = time, shape = time)) +
  geom_line(position=pd, aes(linetype = condition,color = time)) +
  theme(axis.title= element_text(face = "bold"))+
  theme(
    legend.position="right",
    plot.title = element_text(size=11)
  )+
  ggtitle("The average (Mean (SD)) alpha power (for freq 8-13Hz) values \n
      for each brain region between the 2 groups")+
  ylab("Power Mean(SD) (for freq 8-13Hz)")+
  xlab("Channels") +
  geom_label(aes(label = P, y = -18),color = "black", show.legend = FALSE)+
  geom_text(aes(label = star, y = -19), color = "blue", show.legend = FALSE,
      size = 15)
```

C.2.3 PTAF analysis

```
// PTAF.r
library(emmeans)
x1 <- as.numeric(read_csv("pre_ptaf_na.csv", col_names = FALSE))
x2 <- as.numeric(read_csv("post_ptaf_na.csv", col_names = FALSE))
x3 <- as.numeric(read_csv("pre_ptaf_a.csv", col_names = FALSE))
x4 <- as.numeric(read_csv("post_ptaf_a.csv", col_names = FALSE))
```

```
ptaf.freq <- data.frame(
  subject   = as.factor(c(1:length(x1),
                         1:length(x1),
                         (length(x1)+1): (length(x1)+length(x3)),
                         (length(x1)+1): (length(x1)+length(x3)))),

  condition = as.factor(c(rep("noAvatar", times = length(x1)*2 ),
                         rep("Avatar", times = length(x3)*2 ))),

  time      = factor(c(rep("pre-test", times = length(x1)),
                       rep("post-test", times = length(x2)),
                       rep("pre-test", times = length(x3)),
                       rep("post-test", times = length(x4))),
                     levels = c("pre-test","post-test")),
  values    = c(x1,x2,x3,x4)
)
# View(ptaf.freq)
temp<- ezStats(data = ptaf.freq ,
        dv = values,
        wid = subject ,
        within = time ,
        between = condition
)
ezPerm(data = ptaf.freq ,
       dv = values,
       wid = subject ,
       within = time ,
       between = condition
)
pd <- position_dodge(0.02) # move them .03 to the left and right
temp%>%
  ggplot(aes(x=time, y=Mean, group=condition, colour = condition)) +
  geom_errorbar(position=pd,width=.1, aes(ymin=Mean-SD, ymax=Mean+SD)) +
  geom_point(position=pd,shape=15, size=3) +
  geom_line(position=pd, colour = "black") +
  theme(axis.title= element_text(face = "bold"))+
  theme(
    legend.position="right",
    plot.title = element_text(size=11)
  )+
  ggtitle("Pre-test - Post-test (with 95% confidence interval) absolute paf
      values \nbetween Avatar and noAvatar conditions")+
  ylab("Average PAF")+
  xlab("Times")
#################################################################
#################################################################
# The ANCOVA code is from the following source:
#  https://www.datanovia.com/en/lessons/ancova-in-r/
lhbikos.github.io/ReCenterPsychStats/ANCOVA.html
#################################################################
#################################################################
```

```
library(ggpubr)
pre <- c(x1,x3)
post<- c(x2,x4)

prepost_ptaf <- data.frame(pre = pre, post = post,
                        condition = as.factor(c(rep("noAvatar", times =
                            length(x1)),
                                                rep("Avatar", times = length(x3)))))
prepost_ptaf %>% anova_test(post ~ condition*pre)
model <- lm(post ~ pre + condition, data = prepost_ptaf)
model.metrics <- augment(model) %>%
  select(-.hat, -.sigma, -.fitted) # Remove details
head(model.metrics, 3)
shapiro_test(model.metrics$.resid)
model.metrics %>% levene_test(.resid ~ condition)
remove <- model.metrics %>%
  filter(abs(.std.resid) > 1.5) %>%
  as.data.frame()
index <- which(model.metrics$pre %in% remove$pre )
prepost_ptaf <- prepost_ptaf %>%
  filter(!row_number() %in% index)
res.aov <- prepost_ptaf %>% anova_test(post ~ pre + condition)
get_anova_table(res.aov)

# Pairwise comparisons (no need)
adjustedgraph <- prepost_ptaf %>%
  emmeans_test(
    post ~ condition, covariate = pre,
    p.adjust.method = "bonferroni"
  )
adjustedgraph
get_emmeans(adjustedgraph)
adjustedgraph <- adjustedgraph %>% add_xy_position(x = "condition", fun =
    "mean_se")
ggline(get_emmeans(adjustedgraph), x = "condition", y = "emmean") +
  geom_errorbar(aes(ymin = conf.low, ymax = conf.high), width = 0.05) +
  geom_point(shape=15, size=3)+
  stat_pvalue_manual(adjustedgraph, hide.ns = TRUE, tip.length = FALSE) +
  labs(
    subtitle = get_test_label(res.aov, detailed = TRUE),
    caption = get_adjustedgraph_label(adjustedgraph)
  )+
  theme(axis.title= element_text(face = "bold"))+
  theme(
    legend.position="right",
    plot.title = element_text(size=11)
  )+
  ggtitle("Post-test ANCOVA for ptaf values \nbetween Avatar and noAvatar
      conditions")+
  ylab("Corrected post-test PTAF")+
  xlab("Times")
```

C.2.4 Correlation - pain/SOE

```
#install.packages("cocor")
library(cocor)
v <- data.frame(psr= psr$PSR, soe = soe$SOE, condition = soe$condition)
v%>%ggscatter(x = "soe", y = "psr",color = "condition", group = "condition",
              add = "reg.line", conf.int = TRUE,
              cor.coef = TRUE, cor.method = "spearman",
              xlab = "Avatar Embodiment score", ylab = "Pain Reduction Score") +
                  facet_wrap(~condition)
noavatar <- subset(x, condition == "nA")
naco<- cor.test(na$soe, na$psr, method = "spearman",exact = FALSE)
avatar <- subset(x, condition == "A")
aco<- cor.test(a$soe, a$psr,method = "spearman", exact = FALSE)
n<-5
cocor.indep.groups(r1.jk, r2.hm, n, n, data.name=c("noAvatar", "avatar"),
                   var.labels=c("psr", "soe", "psr", "soe"),test = "all")
```

Appendix D

Graphs

D.1 Pain-NRS

Graph D.1 illustrates the ANCOVA results between the two groups for NRS ratings.

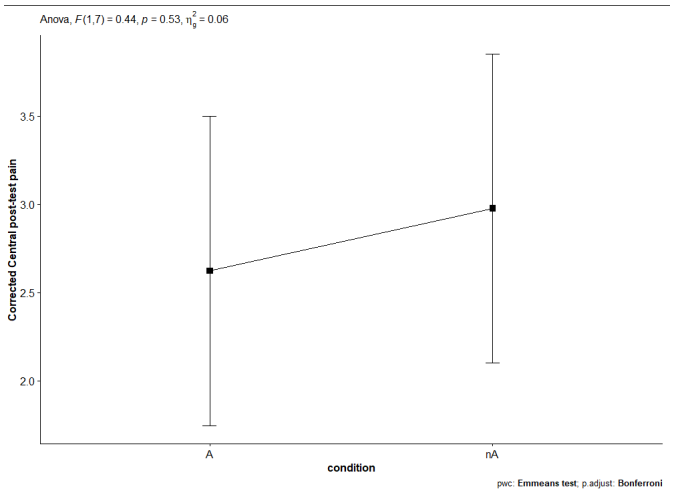

Figure D.1: The comparison between the post-test pain scores, by considering the pre-test as a covariate (ANCOVA).

D.2 IPQ

Figure D.2 illustrates participants' average score for IPQ dimensions (i.e. INV, REAL, and SP) in Avatar and noAvatar groups. This photo is provided as an appendix for consistency with reporting structure of previous studies using this questionnaire to assess presence in VR.

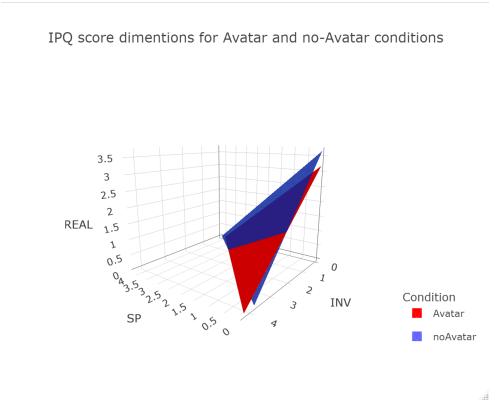

Figure D.2: The IPQ score difference between the control(no-Avatar) and treatment(Avatar) groups.

D.3 Power Spectrum Density

The collection D.3 shows the extracted log(PSD) for all participants, for all channels. As you might observe, some sections are blank due to the removal of that channel in the preprocessing stage.

D.4 Alpha power

The collection in figure D.4 demonstrates the alpha power between the two groups over time in addition to the difference resulting from ANCOVA comparison.

D.5 Theta power

The collection in figure D.5 demonstrates the theta power between the two groups over time in addition to the difference resulting from ANCOVA comparison.

D.6 Topo plots

Following are the topo-plots of average theta, alpha, and beta frequencies for the two conditions.

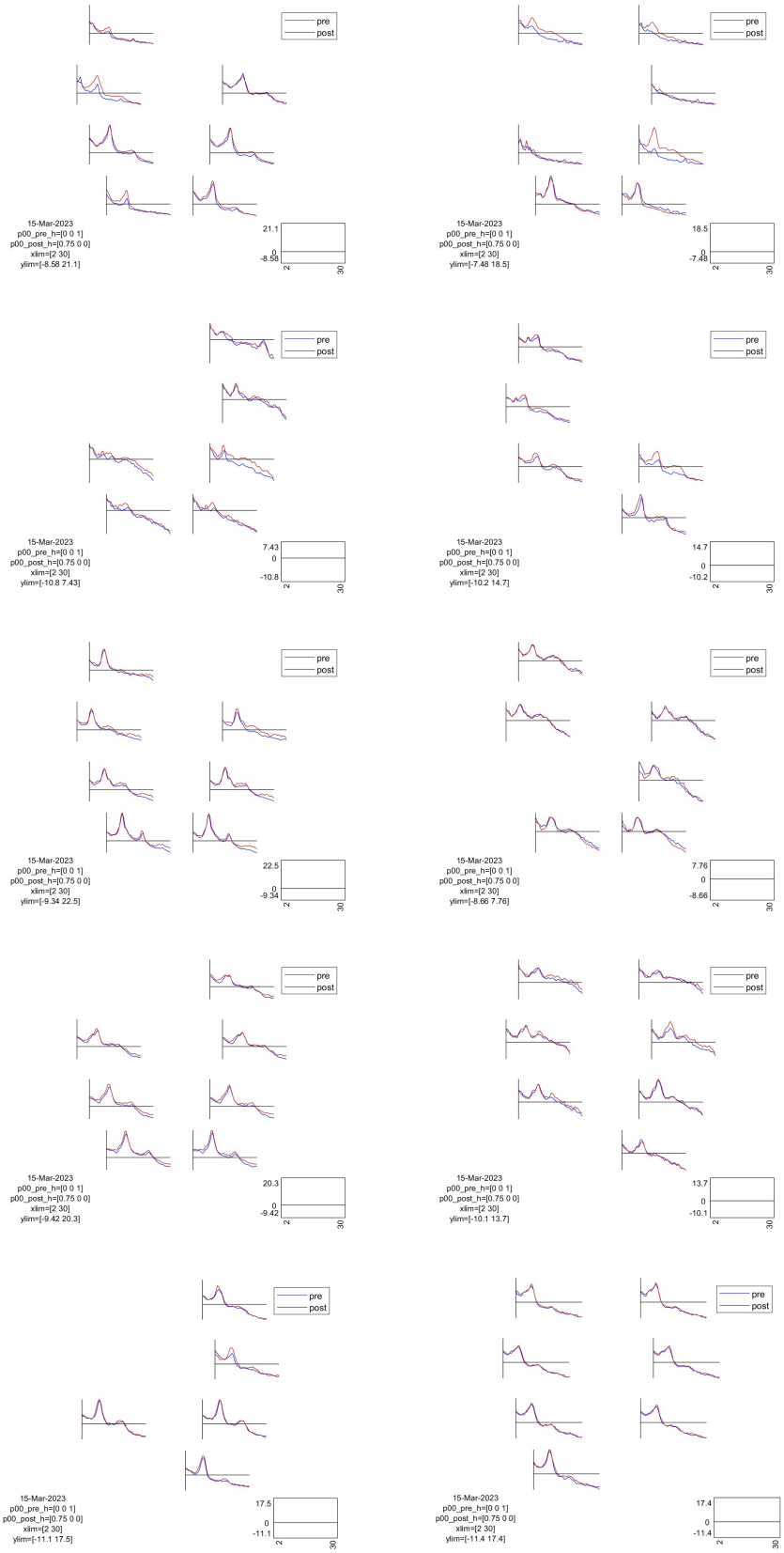

Figure D.3: Log(PSD) for all participants. In all plots, the unit for the x-axis is (Hz), and for the y-axis is $log(\mu V^2/Hz)$.

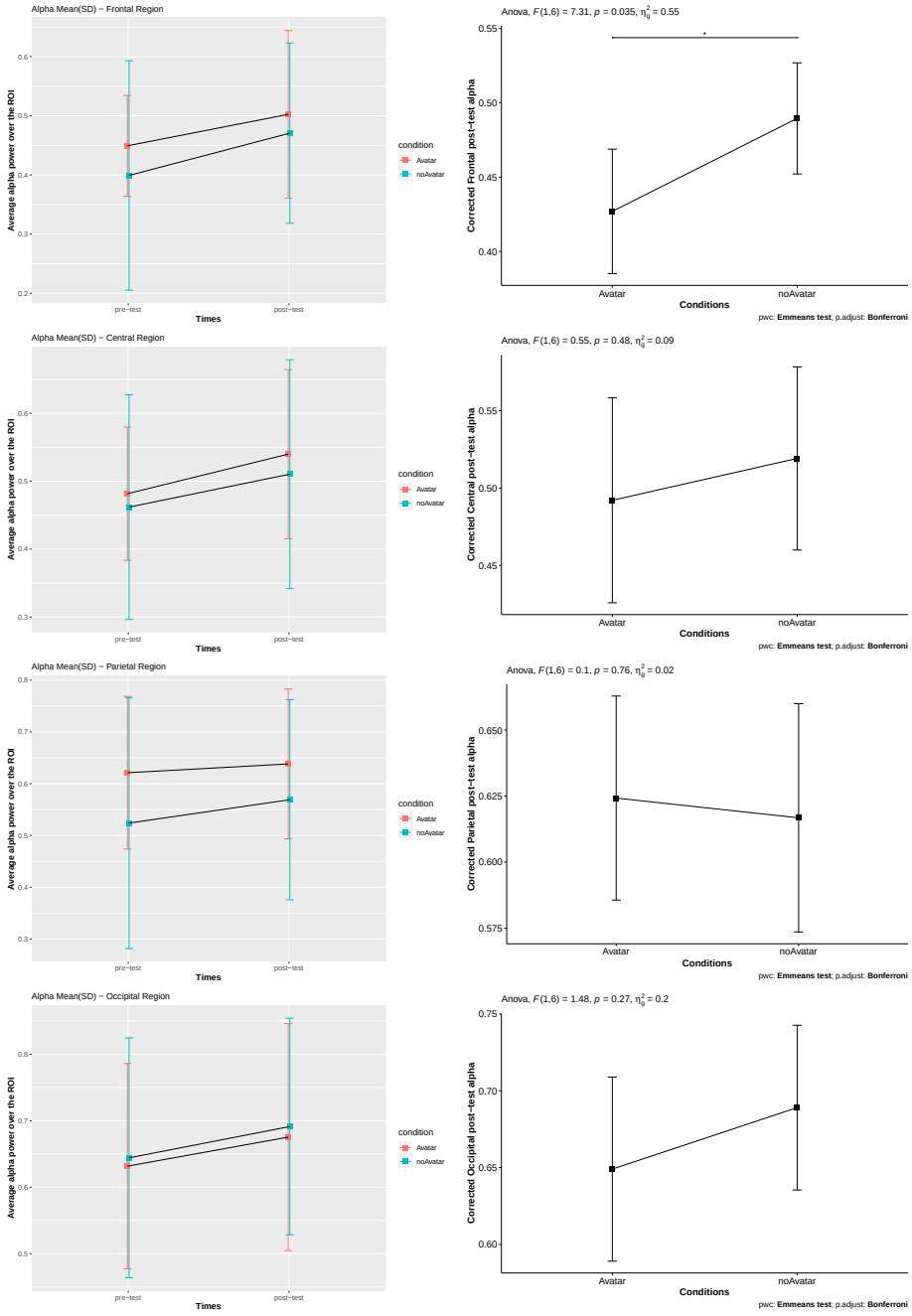

Figure D.4: Normalized alpha for each electrode across conditions. Order from the first row: Frontal, Central, Parietal, and Occipital. Asterisk shows the significance between groups resulting from ANCOVA test.

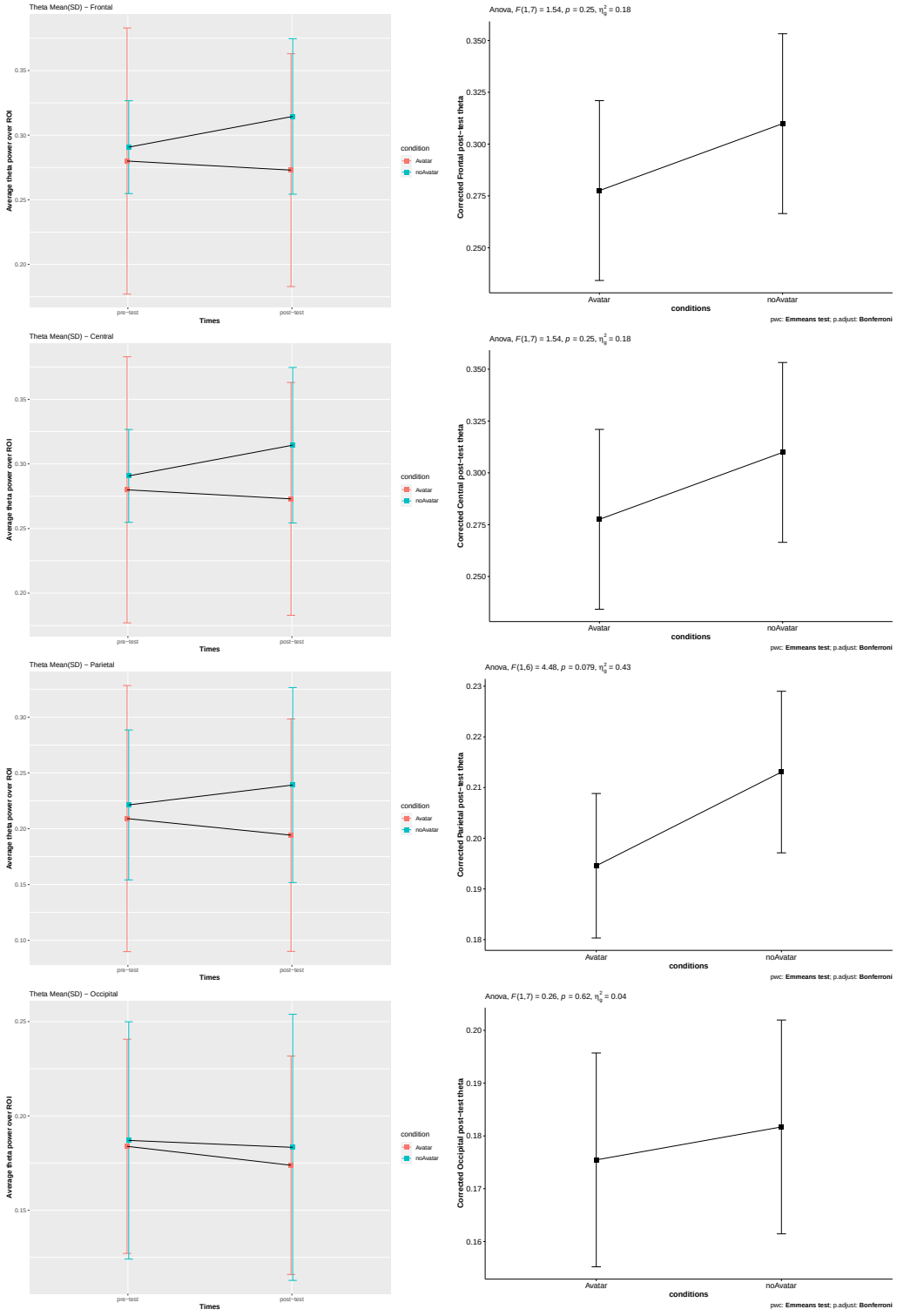

Figure D.5: Normalized theta for each electrode across conditions. Order from the first row: Frontal, Central, Parietal, and Occipital.

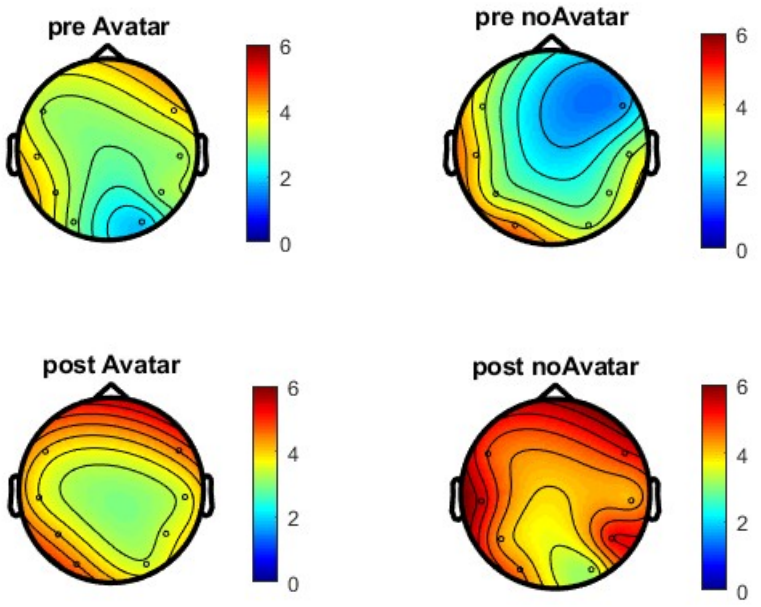

Figure D.6: The topo-plot for theta power, amongst two groups (avatar and no-Avatar) in pre and post-test. The color bar shows the average power in $\mu V^2/Hz$.

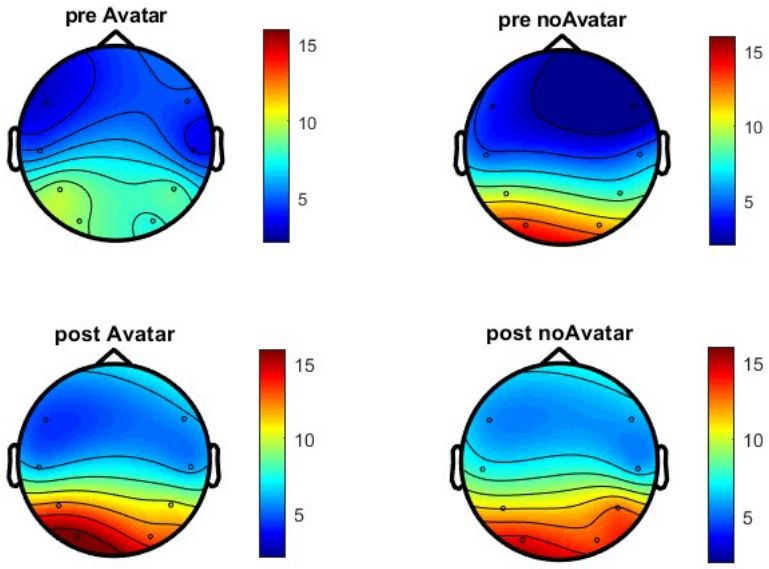

Figure D.7: The topo-plot for alpha power, amongst two groups (avatar and no-Avatar) in pre and post-test.The color bar shows the average power in $\mu V^2/Hz$.

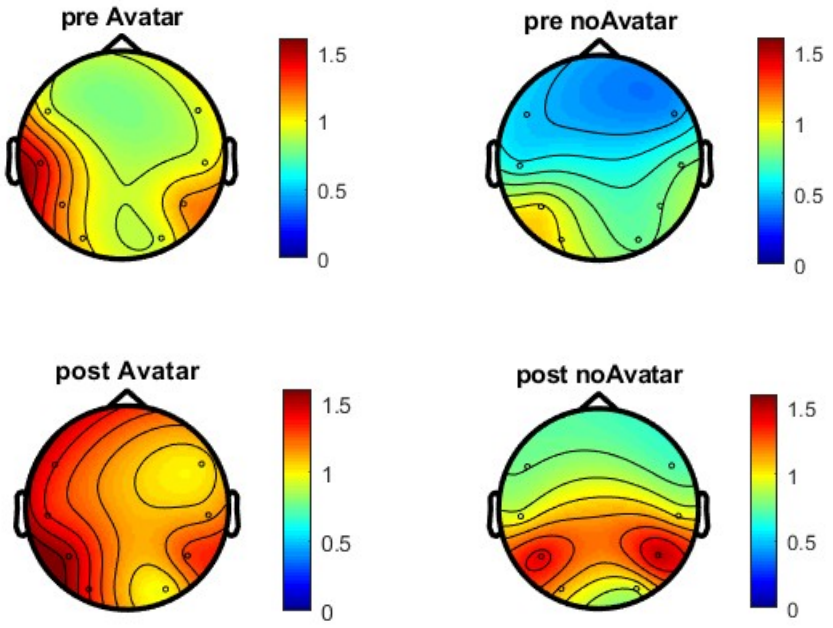

Figure D.8: The topo-plot for beta power, amongst two groups (avatar and no-Avatar) in pre and post-test.The color bar shows the average power in $\mu V^2/Hz$.