Universidade de Aveiro
Departamento de Ciências Médicas
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Márcia de Vasconcelos Gato

Neural activity and pain variation in a spinal cord injury patient during brain-machine interface control

Atividade neuronal e variação dos níveis de dor num paciente com lesão medular durante o controlo de uma interface cérebro-máquina.

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Dissertação apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Molecular, realizada sob a orientação científica do Doutor Miguel Santos Pais Vieira, Professor Auxiliar em Regime Laboral do Departamento de Ciências Médicas da Universidade de Aveiro.

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o júri

Prof. Doutora Ana Margarida Domingos Tavares de Sousa
Professora Auxiliar em Regime Laboral, Universidade de Aveiro

Doutor Hélder Rui Cardoso da Cruz
Investigador Auxiliar, Universidade do Porto - Faculdade de Medicina

Prof. Doutor Miguel Santos Pais Vieira
Professor Auxiliar em Regime Laboral da Universidade de Aveiro

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A todos, o meu sincero obrigado.

Palavras-chave EEG, ICM, Dor Crónica

Resumo

A lesão da medula espinal está associada a uma alta prevalência de dor crónica. Vários estudos indicam que padrões específicos de atividade neuronal registada por eletroencefalografia (EEG) podem estar associados à dor, sugerindo que terapias capazes de modular a mesma possam melhorar o controlo da dor. As Interfaces Cérebro-Máquina (ICM) podem ajudar a recuperar capacidades perdidas devido a lesões neurológicas e gerar efeitos neuroplásticos benéficos, tendo potencial na neuroreabilitação. Recentemente, foi demonstrada que a utilização de uma ICM multimodal num paciente com lesão medular resultou numa redução variável nos níveis de dor. No presente estudo, foi analisada a relação entre os níveis de dor, relatados em três diferentes escalas, e os sinais fisiológicos registados por EEG num paciente com lesão medular ao longo de sessões de ICM. Os resultados indicaram que ocorreu modelação da atividade neuronal nas bandas de frequências delta e teta em dois elétrodos associados ao córtex sensoriomotor e área occipital. Nestes mesmos elétrodos verificou-se que a variação da dor estava correlacionada com atividade nas bandas de frequência delta e beta, podendo estas vir potencialmente servir como um biomarcador da dos níveis de dor.

Keywords EEG, BMI, Chronic Pain

Abstract

Spinal cord injury (SCI) is associated with a high prevalence of pain. Research indicates that specific EEG activity patterns may be associated with chronic pain, suggesting that therapies targeting EEG activity modulation could improve pain management. Brain-Machine Interfaces (BMI) may help repair capacities lost due to neurologic injury and generate beneficial neuroplastic effects, suggesting an immersive potential for neurorehabilitation. Recently, it has been shown that the use of a multimodal BMI in a patient with spinal cord injury led to a variable reduction in pain levels. In the present case study, the relation between the levels of pain, reported in three different scales, and the physiological signals, registered through EEG, in a SCI patient using a BCI, were analyzed. The results indicated that modulation of neuronal activity occurred in the delta and theta frequency bands in two electrodes associated with the sensorimotor cortex and occipital area. In these same electrodes, it was observed that the variation in pain was correlated with activity in the delta and beta frequency bands, suggesting that these could potentially serve as biomarkers of pain levels.

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List of Abbreviations

ACT	Acceptance And Commitment Therapy
ADHD	Attention-Deficit/Hyperactivity Disorder
AIS	ASIA Impairment Scale
ALS	Amyotrophic Lateral Sclerosis
ASIA	American Spinal Injury Association
BMI	Brain Machine Interface
CBT	Cognitive Behavioral Therapy
CLIS	Complete Locked-In State
CNS	Central Nervous System
CPM	Conditioned Pain Modulation
DH	Dorsal Horn
DPIS	Descending Pain Inhibitory System
DRG	Dorsal Root Ganglion
EEG	Electroencephalogram
ECoG	Electrocorticography
EMG	Electromyography
EMG	Electromyography
EOG	Electrooculography
ERD	Event-Related Desynchronization
ErrP	Error-Related Potential
FES	Functional Electrical Stimulation
fMRI	Functional Magnetic Resonance Imaging
FPS	Faces Pain Scale
IASP	International Association for the Study of Pain
ISCIP	International Spinal Cord Injury Pain
LDA	Linear Discriminant Analysis
LFOs	Low-Frequency Brain Oscillations
LIS	Locked-In State
MEG	Magnetoencephalography
NFB	Neurofeedback
NIRS	Near-Infrared Spectroscopy
NRS	Numeric Rating Scale
NS	Nociceptive-Specific
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PAG	Periaqueductal Gray
PNS	Peripheral Nervous System
RVM	Rostral Ventromedial Medulla
SCI	Spinal Cord Injury
SHC	Secondary Health Conditions
SSVEP	Steady-State Visual Evoked Potential
SVMs	Support Vector Machines
TBI	Traumatic Brain Injury
VAS	Visual Analog Scales
VEP	Visual Evoked Potential
WDR	Wide Dynamic Range Neurons
WHO	World Health Organization

1. Introduction

This dissertation aims to investigate the neural correlates of self-reported pain in a spinal cord injury (SCI) patient during multiple sessions of controlling a brain-machine interface (BMI). This interdisciplinary subject requires a thorough understanding of various concepts and techniques presented in this introduction. The first topic is a description of SCI and its evaluation methods. The second comprises the characterization of pain and how it becomes chronic, with the classification and available treatment options regarding this condition. The third section, regarding the fundamentals of BMI, includes their rationale, categorization, brief historical perspective, and applications. Since electroencephalography (EEG)-based BMIs are the most widely used BMIs, the previous section also includes a description of the basic concepts of this technique. Lastly, having defined SCI, chronic pain, and BMIs; a state-of-the-art regarding the EEG activity patterns associated with chronic pain in individuals with SCI will be detailed.

1.1.Spinal cord injury

SCI is an injury to the spinal cord characterized by temporary or permanent alterations in its function (at the motor, sensory, or autonomic level) that has an estimated yearly worldwide incidence of 40 to 80 occurrences per million people.[1,2] Traumatic injuries related to vehicle accidents, falls, sports, and acts of violence are the main causes of SCI. [2] (**Figure 1**) A widely-used method for assessing and classifying individuals with SCI, created by the American Spinal Injury Association (ASIA), is the ASIA Impairment Scale (AIS). [3] The AIS is based on motor, sensory and anorectal examinations and allows the designation of an injury severity level. There are five levels, ranging from ASIA A to E. Complete SCI, or ASIA A, is defined as the absence of all motor and sensory functions, including the sacral roots, below the site of injury. ASIA B to E levels are further classified as incomplete, with some degree of motor or sensory function activity, as described in **Table 1**.[3]

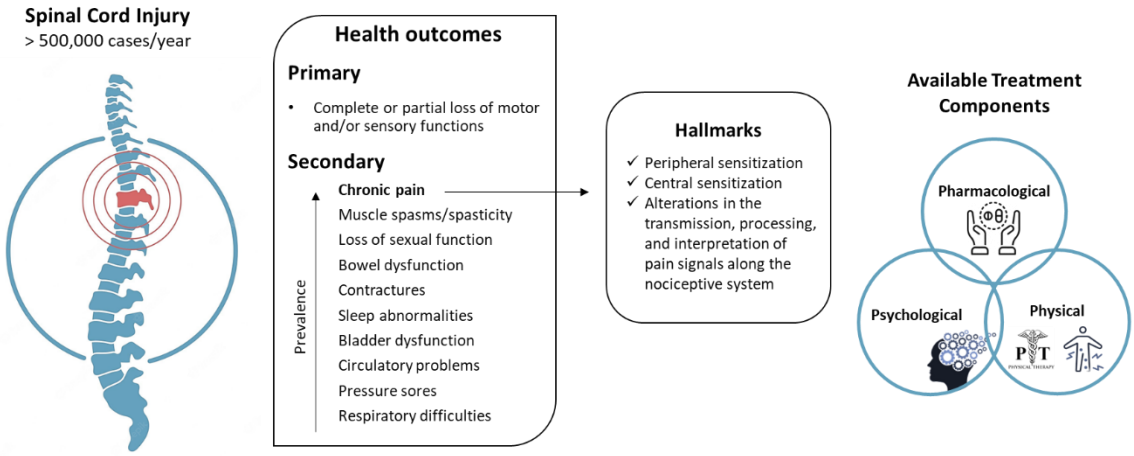

Figure 1- Spinal cord injury health outcomes and chronic pain treatment.

Following SCI, individuals are at risk of developing several health conditions that, directly or indirectly, physically or psychologically, are driven by the presence of the disability.[4] These conditions, known as secondary health conditions (SHCs), have significant impacts on many factors affecting the overall quality of life and are significant contributors to morbidity and mortality.[5] SCI-related SHCs include cardiovascular and respiratory difficulties, bowel and bladder abnormalities, pressure sores, muscle spasms, contractures, osteoporosis, loss of sexual function, sleep dysfunction, and chronic pain.[4–6] Among these SHCs, pain is the most prevalent one, affecting more than 60% of individuals with SCI. [5,7]

Currently, pharmacological and non-pharmacological options are available for the management of the different manifestations of pain. As pharmacological therapies are often non-sufficient and may lead to a variety of side effects, several research avenues are attempting to find non-pharmacological therapeutics capable of modulating/stimulating neural activity aiming to improve both primary and secondary outcomes of SCI.[8,9]

Table 1- ASIA Impairment Scale.[3]

Neurological Injury Level	Clinical Description
ASIA A Complete	No motor or sensory function is preserved in the sacral segments S4–S5.
ASIA B Incomplete	Only sensory function preserved below the neurological level (including the sacral segments S4–S5).
ASIA C Incomplete	Less than muscle grade 3 motor function is preserved below the neurological level.
ASIA D Incomplete	Muscle grade of 3 or more motor function is preserved below the neurological level.
ASIA E Incomplete/Normal	Normal motor and sensory functions.

1.2. Pain

Pain is currently defined by the International Association for the Study of Pain (IASP) as an "unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage".[10] Depending on the onset and duration, pain can be classified in acute or chronic. Acute pain typically results from a noxious stimulus and plays a crucial role as a protective mechanism of our bodies. Since the source can be usually identified and easily treated, acute pain lasts for short periods of time. Pain, however, can persist and become chronic, losing its protective role, and evolving into its own disease, even after the initial cause is resolved. Since chronic pain is induced not only from physical injuries but also by a combination of psychological, social, and physical disorders, it is difficult to identify the causes underlying this condition.[11,12]

1.2.1. Pain perception

The experience of pain is an intricate process implicating many areas of the nervous system, from the recognition of the noxious stimuli in the peripheral nervous system (PNS) to the perception of pain in the central nervous system (CNS). Nociception, which is the process by which the body detects and responds to harmful stimuli, involves four major processes: transduction, transmission, modulation, and perception. [12,13]

Transduction refers to the activation of nerve endings after being provoked by a noxious stimulus. The second process, transmission, is responsible for carrying the input from the injury site toward the spine and then up to the brain.[12,13] Once a painful trigger occurs, such as a thermal, chemical, or mechanical one, a variety of inflammatory mediators are locally released, and pain receptors, known as nociceptors, are stimulated. Upon interaction with the released substances, nociceptors generate an action potential within the afferent sensory nerve fibers, whose cell bodies are located in the dorsal root ganglion (DRG). There are two main classes of these nerve fibers: unmyelinated C fibers, which transmit pain intensity and terminate in the most superficial laminas (I and II) of the dorsal horn (DH), and fast-conducting myelinated Aδ fibers, responsible for the initial perception of pain that end in laminas I, and III-V.[14,15] Another important peripheral nerve fiber is the Aβ, which is activated by non-nociceptive stimuli such as touch. These peripheral sensory neurons comprehend the first component of the transmission system as they transmit impulses from the transduction site at their peripheral terminal to the spinal cord. In the DH, two predominant types of second-order nociceptive spinal neurons have been identified: wide dynamic range (WDR) neurons and nociceptive-specific (NS) neurons. Besides differing in their location (NS neurons are mostly present in laminas I and II and WDR on laminas III to V), they also respond to different stimuli. While NS neurons specifically respond to a noxious stimulus, WDR are primarily activated in the presence of an innocuous stimulus, brought on by Aβ fibers.[13] After synapsing, these second-order neurons (representing the second component of the transmission system) decussate at the ventral commissure and transmit projections via the anterolateral system to a variety of supraspinal regions. The anterolateral system encompasses three pathways: the spinothalamic, spinoreticular, and spinomesencephalic tracts. In the lateral spinothalamic tract, projections end in the ventral posterolateral nuclei of the thalamus. After synapsing with thalamic neurons, which form the third component of the transmission network, the impulse is delivered to the primary somatosensory cortex for additional processing and pain perception. In the spinoreticular and spinomesencephalic pathways, both pain and touch signals are sent to regions involved in memory and affective aspects of pain, such as the amygdala, hypothalamus, and periaqueductal gray (PAG).[16]

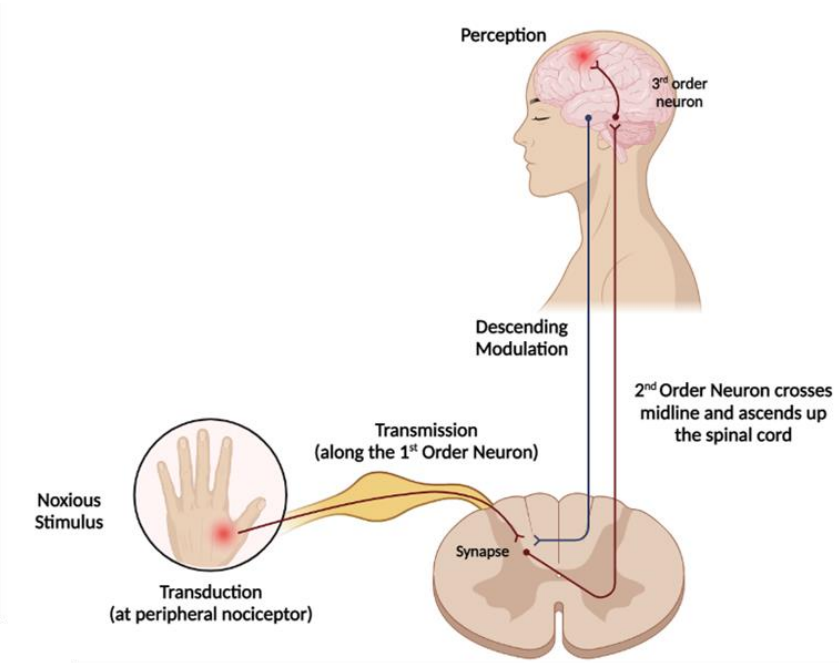

Figure 2- The non-pathological pain pathway involves the peripheral nervous system, spinal cord, thalamus, and somatosensory cortex. Pain signals are detected by nerve endings in the periphery, transmitted to the spinal cord, processed, and modulated in the brain, relayed through the thalamus, and ultimately perceived in the somatosensory cortex. Created with BioRender.com.

Modulation refers to the process by which neural activity may be altered along the transmission pathway described above. This process encompasses several mechanisms that either facilitate or inhibit pain perception, including the gate control theory, descending monoaminergic pathways, and endogenous opioid system, among others.[17] An important site of pain modulation is the DH, as it contains inhibitory interneurons capable of blocking the first synapse of the transmission pathway.[13] In 1965, Melzack and Wall proposed the gate-control theory[18] that infers that in the presence of non-noxious stimuli, such as touch or pressure, Aβ fibers stimulate the inhibitory interneurons present in the DH. This stimulation leads to the prevention of signal transmission to supraspinal regions.[13,17,19] Descending pathways refer to neural pathways that involve the transmission of signals from higher brain centers, such as the cortex and brainstem, to the spinal cord. One of the main areas involved in these pathways is the periaqueductal gray (PAG), implicated in pain control and other emotional responses. The PAG sends projections to the rostral ventromedial medulla (RVM), which in turn projects to the spinal cord, where it can inhibit the transmission of pain signals by releasing neurotransmitters. These include serotonin, capable of both antinociceptive and pronociceptive effects, and norepinephrine which exclusively inhibits pain perception by stimulating the inhibitory interneurons present in the DH.[12,14,20,21] The endogenous opioid system is a system of neurotransmitters and receptors involved in the body's natural pain-relieving mechanisms. The main substances present in this system are endorphins, enkephalins, and dynorphins, which are peptides

produced by neurons in the brain and spinal cord. These neuromodulators bind to their respective receptor along the ascending pathway inhibiting pain perception.[17,22,23]

The final stage in the nociceptive process is perception, which refers to the brain's interpretation of the pain signal. When the brain receives the signal from the transmission pathway, it activates a pain network, which includes various areas such as the thalamus, the somatosensory cortex, and the insular cortex. The stimulus' duration and intensity, the individual's previous pain experiences, and their emotional and psychological condition are all factors that can influence pain perception. For this reason, perception is considered a subjective experience since different people perceive the same stimulus differently.[13,24,25]

Several neuroimaging studies have linked many cortical areas to nociception. As a result, regions including the somatosensory, insular, and cingulate cortices—which function as a network across the perception of pain—have come to be known as the "pain matrix".[26] Some authors tend to group the brain structures according to their involvement in different aspects[27] or stages[14,28] of pain processing. For instance, some authors differentiate the structures based on their anatomical locations and, consequently, their different functions in pain perception, leading to the medial-lateral pain system. In this model, the medial structures (such as the anterior/mid cingulate cortex) are implicated in the affective and emotional aspects of pain, whereas the lateral structures (such as the somatosensory cortex) are more involved in the sensory-discriminative pain elements.[27] As for the division regarding the pain processing steps, there are essentially two groups: the nociceptive cortical matrix (first-order processing) and the second-order perceptual matrix (processing from nociception to pain perception)[14], with some authors adding a third group of structures called third-order networks (processing from immediate perception to pain memories)[28]. The nociceptive cortical matrix involves the initial detection and transmission of pain signals from the spinothalamic tract, consisting of the posterior insula, medial parietal operculum, and mid-cingulate cortex. The processing of nociceptive inputs in the brain, that results in the conscious perception of pain, involves the second-order processing matrix, which comprises the mid and anterior insula, anterior cingulate and prefrontal cortices, as well as the PAG and RVM.[14,28] Lastly, the third-order networks, which refer to structures in higher-order cortical regions beyond the conventional pain matrix, are involved in the integration of pain perception with other cognitive and emotional processes.[28]

1.2.2. From acute to chronic pain

Under normal circumstances, pain perception ends once the underlying cause is resolved, and the body has completely recovered from the tissue damage. However, continuous, or recurring nociceptive stimulation leads to several pathologic alterations in pain processing, ultimately resulting

in chronic pain.[14] The complex changes associated with this chronic state include modifications to the nociceptors' sensitivity as well as alterations in the transmission, processing, and interpretation of pain signals along the nociceptive system. The increased sensitivity of nociceptors and the high excitability of neurons are characteristics of a process known as sensitization. This process can occur at various levels, from the periphery, where the stimulus is detected, to the brain, where it is interpreted.[29] Peripheral sensitization is marked by a reduction of the pain threshold in the primary afferent neurons, amplifying the sensibility to stimuli and consequently increasing the susceptibility of an individual to experience pain from any innocuous stimuli. This process is believed to occur due to an inflammatory response at the site of the injury. At the central nervous system level, this process is called central sensitization and unlike the peripheral one, it may persist even after the stimulus is removed and the tissue has fully recovered. Central sensitization may be initially maintained by peripheral sensitization but is also strongly associated with other mechanisms such as the impairment of descending modulatory pain pathways, resulting in an increment of the pain intensity experience.[12,30] Glial cells (i.e., non-neuronal cells crucial for the homeostasis and protection of neurons) such as microglia and astrocytes, play a role in both peripheral and central sensitization.[31] Upon activation, these cells can release several substances, including cytokines, inflammatory mediators, and growth factors, which affect neuronal function in multiple ways, tipping the balance towards an exacerbated excitable sensitized state.[16,32] Another major contributor to chronic pain reported is reduced inhibitory activity in the spinal cord DH. This may result from glial activation or dysregulation along the descending modulatory pathway described in the previous sections. Both epigenetics modulation and psychological factors such as stress, anxiety, and depression have also been associated with the development and maintenance of a chronic pain state.[11,33]

Even though there are some theories and potential mechanisms reported in the literature, chronic pain is still a broad area of active research as it is a very complex and multifactorial subject.

1.2.3. Chronic Pain

Chronic pain is defined as any type of pain that persists for more than 12 weeks, and according to Siddall and his colleagues, there are three key points that might reflect how pain affects a person with SCI.[5,34] These are: its prevalence, the prognosis for the long term, and the repercussions that pain has.[34] Several studies have recognized pain as a critical element in rehabilitation and its outcomes being highly related to psychological disorders, such as depression, and therefore altering the quality of life of patients with SCI. [7,35,36]

1.2.3.1.Classification

Given the many different types of pain experienced after SCI and the subsequent amount of classification strategies described in the literature, the International Spinal Cord Injury Pain (ISCIP) has provided a standardized system to classify them **(Table 2)**. This system is organized into three tiers: the first divides pain according to its type (nociceptive, neuropathic, other pain, and unknown pain), the second into subtypes, and the last is related to the primary pain source.[37]

Table 2- International Spinal Cord Injury Pain (ISCIP) Classification.

Pain Type	Pain Subtype	Primary pain source and/or pathology
Nociceptive Pain	Musculoskeletal pain	e.g., glenohumeral arthritis, lateral epicondylitis, comminuted femur fracture; quadratus lumborum muscle spasm
	Visceral pain	e.g., myocardial infarction, abdominal pain due to bowel impaction, cholecystitis
	Other nociceptive pain	e.g., autonomic dysreflexia headache, migraine headache, surgical skin incision
Neuropathic Pain	At-level SCI pain	e.g., spinal cord compression, nerve root compression, cauda equina compression
	Below-level SCI pain	e.g., spinal cord ischemia, spinal cord-compression
	Other neuropathic pain	e.g., carpal tunnel syndrome, trigeminal neuralgia, diabetic polyneuropathy
Other Pain		e.g., fibromyalgia, Complex Regional Pain Syndrome Type I, interstitial cystitis, irritable bowel syndrome
Unknown Pain		

An injury to a somatic structure, such as the skin, muscles, tendons, bones, or joints, results in nociceptive pain.[38] Nociceptive pain is further divided into musculoskeletal, visceral and other. Recently, using the ISCIP classification system, Hunt et. al conducted a meta-analysis aiming to estimate the prevalence of chronic pain following SCI. From the studies included, the pooled prevalence of musculoskeletal pain was 56% and visceral pain about 20%. [39] Musculoskeletal pain manifests itself in areas with some intact sensibility, such as the shoulders, wrists, and back. [40,41] When chronic, this type of pain is associated with cumulative stresses over time of upper limb overuse or abnormal loading of joints.[40] Visceral pain, on the other hand, presents in the abdomen, thorax, or pelvis and is thought to be mainly originated in visceral structures.[40,41] Pain resulting from constipation, urinary tract infection, and ureteral calculus, are some examples of this class of nociceptive pain.[37]

Neuropathic pain has a prevalence of 58%, and is caused by damage to or dysfunction of the somatosensory nervous system.[38,39] Being broadly perceived as the most severe, neuropathic pain is further divided into three subtypes: at-level, below-level, or others.[7,37] This type of SCI pain may be

associated with alterations in the brain, spinal cord, and peripheral nervous system.[34] For instance, at-level pain may occur in response to damage to the cauda equina or other spinal nerve roots, which can cause peripheral pain however, if the lesion is in the spinal cord, then central neuropathic pain can arise. The nerve roots may sustain direct damage at the time of the accident or later as a result of disease, degeneration, or unstable vertebrae.[40,41] A central pain brought on by the spinal lesion, if spread below the level of injury to the nervous system, is known as below-level neuropathic pain. It frequently appears months or even years after the initial injury and is described as the most agonizing form of SCI pain.[40,42]

1.2.3.2.Existing Treatments

Chronic pain is a complex condition that requires a heterogenous treatment strategy, typically combining pharmacological, physical, and psychological elements.[43] However, for neuropathic pain, available treatments may only provide partial pain relief rather than complete remission. [44,45]

Pharmacological options often follow the World Health Organization (WHO) analgesic ladder, originally designed for cancer pain, and then adapted for chronic non-cancer pain. The ladder consists of three steps, starting with non-opioid analgesics such as aspirin or non-steroidal anti-inflammatory drugs (NSAIDs), then weak opioids like codeine, and eventually recommending strong opioids like morphine and oxycodone.[46] However, and regarding the remarkable increase in the number of deaths due to the intake of these substances, Bryce et al. proposed that these should not be prescribed to relieve chronic pain.[47,48] The first argument relies on the missing literature supporting opioids as being beneficial for these conditions, the second is that they can lead to serious adverse effects such as cognitive deficits and hormonal depression. Lastly, these narcotics and their overuse may also lead to addiction (use disorder) and further on to an opioid-overdose.[47] Also described in the ladder are the so called 'adjuvants', i.e., additional drugs that could be used in any step of the ladder. These adjuvants include anxiolytics, hypnotics, and muscle relaxants to reduce pain-related anxiety, insomnia, and muscle spasms, respectively.[46] Antiepileptic and antidepressant drugs are currently among the main classes of pharmaceuticals available for SCI-related chronic pain, with pregabalin, gabapentin, and tricyclic antidepressants having the most literature supporting their use.[48] There is increasing interest in alternative options for chronic pain relief, such as in components of the plant Cannabis Sativa, especially in cannabidiol (CBD). Nabiximols (Sativex®) is a highly standardized pharmaceutical product, containing both CBD and the Δ^9-tetrahydrocannabinol (THC) that has been assessed in various clinical trials and have shown promising results.[43,49]

Even though pharmaceuticals are the first line of treatment; SCI-related chronic pain is frequently unresponsive to this treatment since medications result in just 50% pain reduction for merely 30% of

the individuals. Besides, long-term drug therapies often lead to severe side effects such as constipation or toxicity and an increased risk of addiction or abuse. [5,44] In terms of physical treatments, options include physiotherapy[46], chiropractic care[50], massage therapy [51], acupuncture[52] and neurostimulation techniques[53]. Previous neuroimaging and neurophysiological studies have suggested that maladaptive plastic alterations are on the basis of SCI-related chronic pain mechanisms.[54] After establishing the possibility of modulating nerve activity through electricity in the late 1700s, several methods of neurostimulation have been designed to improve both primary and secondary outcomes of SCI, such as restoring motor function and reducing spasticity.[9] These non-pharmacological therapies can be both non-invasive and invasive, but it is important to note that overall, they have negligible or no side effects.[8] Noninvasive techniques stimulate the brain by focusing on various structures, for instance, repetitive transcranial magnetic and transcranial direct current stimulations target the primary motor cortex, while transcutaneous electrical nerve stimulation induces localized activity in peripheral nerves. Spinal cord and motor cortex stimulations are examples of invasive techniques.[8] Although some studies have shown that these treatments can successfully reduce pain, the effectiveness can vary depending on the patient and the particular condition being treated. Psychologically based interventions for pain management include cognitive behavioral therapy (CBT), behavioral therapy[55], acceptance and commitment therapy (ACT)[56], Mindfulness therapy[57] and biofeedback[58]. Overall, while these studies have shown modest reductions in pain compared to other interventions, they can still be valuable components of a comprehensive pain management plan, as by combining them with different therapies, individuals may achieve better pain outcomes.

1.3.Brain-machine interfaces

A BMI, also referred as brain-computer interface, is a system that translates central nervous system signals, captured by neural signal recordings such as electroencephalogram (EEG), into executable commands using computer algorithms.[59] A BMI system consists mainly of five functional components that interact with one another to optimize its efficiency[60], as summarized in **Figure 2**. The first component, signal acquisition, uses one or more methods, including EEG, magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), near-infrared spectroscopy (NIRS), intracortical neuron recording, electrocorticography (ECoG), to record, amplify and digitize the users' brain signals. Each of these methods has its advantages and disadvantages. For instance, ECoG and intracortical recordings, which involve placing electrodes directly on the surface and inside the brain tissue, respectively, provide remarkable spatial and temporal resolutions but also implicate risks associated with the procedures such as infections or seizures. MEG, which detects magnetic brain activity, also has good spatial and temporal resolutions.

On the other hand, similarly to fMRI, its equipment is sizeable, expensive, and therefore unfeasible for general use. fMRI and NIRS, which measure brain activity by detecting changes in blood flow and oxygenation levels in the brain, have good spatial resolutions but poor temporal ones. Lastly, EEG, which captures the brains' electrical activity on the scalp, has a low spatial resolution but has advantages such as its high temporal resolution, non-invasive nature, and the fact that it is relatively inexpensive, easy to use, and portable.[61,62]

The signals obtained from EEG recordings are often tainted with artifacts and noise. These can arise from electrical interference from the heart (ECG artifact), power supply noise (power-line noise), eye movements (EOG artifact), muscle tension (EMG artifact), or other physiological processes. Signal pre-processing is the second module of the system and is responsible for cleaning and preparing the raw brain signals for further analysis. This step includes several techniques such as removing noise, artifact rejection, and filtering.[60] There are two types of filtering techniques used in BMI systems: spectral and spatial. Spectral filtering, applied in the frequency domain, eliminates unwanted noise signals like slow drifts and line noise from the EEG signals. Spatial filtering, in contrast, combines signals from multiple electrodes to target brain activity in a specific location, is applied in the spatial domain, and is used to emphasize or discard signals based on their origin site.[61]

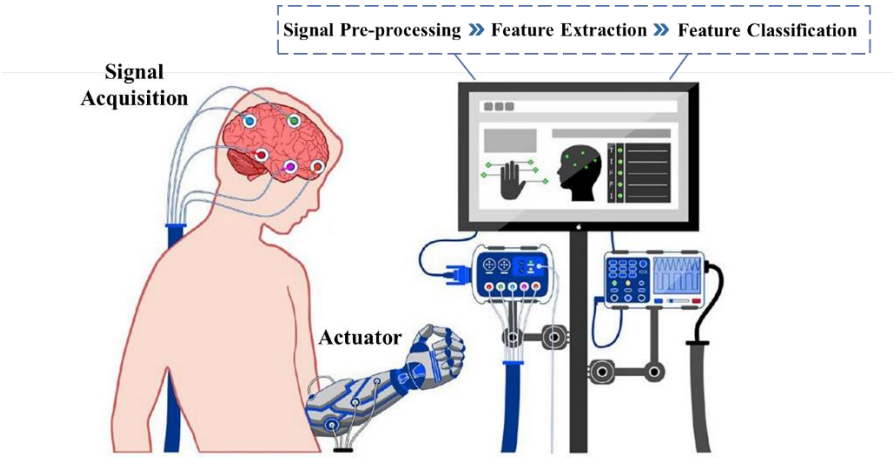

Figure 2- Main functional Components of an EEG-based BMI system. Adapted from.[63]

The following component is feature extraction, a process used to identify and separate features that represent the intention (i.e., the brain signals indicative of the user's intent or mental state) from the remaining brain impulses. Recently, Pawar and colleagues reviewed several techniques used to extract features from EEG signals for BMI. They highlighted commonly used methods such as the time-domain, frequency-domain, and time-frequency domain features. Their findings indicate that each method has its advantages and disadvantages, therefore, the best feature extraction technique highly depends on the specific application.[64] The two mostly adopted features are the time-domain and the frequency band power features, the last referring to the power of EEG signals within a

specific frequency band. Since each frequency band (delta, theta, alpha, beta, gamma) is associated with a certain type of brain activity, the power within each band can provide information about the state of the brain. [60] Once the relevant elements are extracted, they are used in the classification stage, which assigns the features to one of the predefined classes or categories. Several types of classification algorithms have been described in the literature, from linear and non-linear Bayesian classifiers to the recently developed deep learning and adaptive classifiers. Linear classifiers use linear functions to separate the feature vectors of different classes. Examples of this algorithm include linear discriminant analysis (LDA), regularized LDA, and support vector machines (SVMs). SVM and LDA are the most popular linear classifiers for EEG-based BMIs due to their computational efficiency, robustness, good performance, interpretability, easy implementation, and ability to handle non-linearly separable data. Nonetheless, the choice of the classifier should ultimately depend on the nature of the data, features, and the specific task of the BMI system. [61,65,66]

The last component of a BMI system, accountable for the final translation of the brain signals into meaningful actions, is the output device. The physical components of these devices are typically actuators that allow the user to interact with their environment. Actuators can take many forms, including haptic feedback devices[67], virtual reality environments[68], functional electrical stimulation (FES)[69], prosthetic devices, exoskeletons[70], and other types of interfaces that allow the BMI system to interact with the environment.[60]

Feedback can be included as an additional component in the BMI model, as it is often used to adjust the system's response based on the user's current brain activity. This process sustains and enhances the accuracy and speed of the intended outcome, such as communication or motor execution.[71,72] Based on whether subjects receive feedback, BMI systems can be classified as open- or closed-loop. In closed-loop, also known as feedback control systems, the feedback is provided in real-time as the subject performs the action or task. These systems allow for active adjustments of the device response based on the user's current brain activity. On the other hand, open-loop BMI is a system where no direct feedback is provided to the user. Also referred to as non-feedback or feedforward systems, these rely on a pre-defined mapping between brain activity and actions or commands.[73,74]

1.3.1. Classification

BMIs can be classified in various ways depending on different characteristics, as summarized in **Table 3**. These include the method used to generate brain responses[75], the invasiveness of the neuroimaging techniques used, how the input data is processed [76], the type of task that the user must perform to control the device[77], and the dependency on output pathways to generate and transmit control signals [76].

Based on the method used to generate brain responses, BMIs can typically be classified into active, reactive, or passive. The first two groups differ on whether the brain activity markers extracted are voluntarily generated by the user (active) or measured as a response to an external stimulus (reactive). Active BMIs thereby require the users to actively engage with the system by performing specific tasks or actions, such as motor imagery or P300, to produce responses capable of controlling the system. Reactive systems detect changes in the user's brain activity triggered by external events, such as an error or changes in the environment. Some examples of reactive BMIs include error-related potential (ErrP)-based and Hybrid BMIs. On the other hand, passive BMIs do not require the user to produce a specific brain activity instead, they drive their outputs from spontaneous brain activity. For example, a passive BMI might use brain activity associated with attention or relaxation to control the device. [75,78,79]

Different neuroimaging techniques can be used to acquire electrical brain signals for BMI systems. Based on the level of invasiveness of these methods, they can be categorized as invasive, partially invasive, or non-invasive. Invasive techniques involve the surgical placement of devices or electrodes directly into the brain. This method allows the recording of neural activity from deep within the brain, resulting in high-quality signals. However, it is associated with scar tissue build-up over time which leads to a gradual degradation of the recorded signals. [77,80] Some authors distinguish the partially invasive category as one that involves the insertion of electrodes into the brain but not as deep as invasive methods.[76] An example of such technique is ECoG, also known as intracranial EEG, where electrodes are placed on the surface of the brain (typically under the skull but above the dura mater). On the other hand, non-invasive methods capture brain activity externally, without the need to penetrate the skull. These methods are of lower quality and can be affected by noise and artifacts from external sources; however, they are able to measure the large-scale neuronal activity of the entire brain near the skull in a cost-effective and safe way. Examples of these techniques include MEG, fMRI, NIRS, and the most widely used EEG.[77,80]

BMI systems can also be classified based on how they process input data, which can be either synchronous or asynchronous. Synchronous BMI systems analyze brain activity during specific, pre-determined time frames. Advantages of this process include the anticipation of mental activity and its association with a particular cue, and the avoidance of artifacts (e.g., eye movements). As for asynchronous BMI, the subject can execute mental tasks at any time, with the system reacting to the respective mental activities. Due to the users' freedom from time restrictions, this method enables a more natural interaction between the user and the machine. However, it can also be more complex and computationally demanding, as the system must be able to react to the users' mental activity at any time.[81,82]

Table 3- Classification of BMIs and respective description based on different characteristics.

Characteristic	Classification	Description
Invasiveness	Non-invasive	Devices are placed on the scalp (e.g., EEG)
	Partially invasive	Devices are inserted in the skull on the top of human brain
	Invasive	Devices are inserted directly into the human brain by a critical surgery
Control	Active	Requires the user to actively produce a specific brain activity or pattern to control the device or computer
	Reactive	Requires external stimuli to produce specific brain activity or pattern to control the device or computer
	Passive	Use involuntary status of the brainwaves, for example on emotional states such as meditation, excitement, and stress
Synchrony	Synchronous	The user can only send commands during specific, predetermined time windows
	Asynchronous	Allows the user to execute mental tasks at any time, with the system reacting to the respective mental activities
Task Paradigms	Motor imagery	Use the brain activity associated with the imagination of movement to control a computer or external device
	External Stimulation	Use specific brain responses to external stimuli, such as visual, auditory, or somatosensory stimuli to control a computer or external device.
	ErrP	Use the brain activity associated with errors to control a computer or external device
	Hybrid	Use multiple types of brain signals, such as EEG and EMG, in combination to control the computer or external device
Dependability	Dependent	Requires the use of some muscle control to produce the neural activity used for communication or control
	Independent	Rely solely on the brain's inherent signals for communication or control
Type of application	Medical	Developed for medical reasons to help patients to communicate, grasp objects, move around and support in other daily activities. (Rehabilitation, prosthetic control)
	Non-medical	Used for entertainment, art, as well as some other areas.

BMIs can be classified according to the specific task the user must perform to generate the brain signals, also referred to as the task paradigm. The most used EEG-based BMI paradigms are motor-imagery, external stimulation, ErrP, and the hybrid paradigm.[77] The concept of motor imagery involves envisioning a movement rather than physically performing it. Studies have shown that this mental process activates the same brain regions as when an actual movement is executed.[83] This task paradigm is particularly popular in BMI research as it offers high-resolution control signals, is intuitive to use, and has applicability in a range of applications.[83–85] External stimulation-based paradigms are also commonly used in BMI due to their high accuracy and reliability. These involve influencing brain activity through external stimuli, like flashing lights or sounds, and then decoding it to control output devices. Examples of these paradigms are the Visual evoked potential (VEP), which uses visual stimuli; the P300 and steady-state visual evoked potential (SSVEP), which are based on visual evoked potentials; and Electrooculography (EOG) and Electromyography (EMG)-based BMI, which use eye movements and muscle activity, respectively, as a control signal.[77,86]

Another BMI paradigm is the error-related potential (ErrP), a component of the event-related potential (ERP), generated by the brain in response to errors, specifically when the subject's intended action does not match the response produced by the BMI system.[77,87] Lastly, hybrid paradigms refer to the combination of various physiological measures. EEG is typically included, along with others signals such as ECG, EOG, and fNIRS. This paradigm enables the use of multiple sources of information, improving the accuracy and reliability of the BMI system.[77,88]

Based on how a BMI depends on the brain's normal output pathways (i.e., peripheral nerves and muscles) to generate and transmit control signals, they can be dependent or independent. Dependent BMI systems rely on muscle control to produce neural activity that is then used for communication or control. An example of these systems is the SSVEP, which relies on gaze control and muscle activity to produce the necessary neural activity. In contrast, an independent BMI does not rely on the brain's normal output pathways for communication, being the signal generated solely by the user's intention or imagination, without the need for actual physical movement. This type of BMI allows users to communicate their mental tasks without controlling their limbs.[71,89,90]

1.3.2. History and Applications

Research on BMI systems began in the 1970s, limited by the computer capabilities of that era and the level of understanding of brain physiology.[91] In 1973 Jacques Vidal published a paper entitled "Toward Direct Brain-Computer Communication", one of the first to investigate the possibility of using brain activity to control computers, creating a direct link between the brain and technology, similar to a prosthetic device.[92] Another early attempt at this direct communication was accomplished in 1988 when Farwell and Donchin used the P300 event-related potential to allow healthy volunteers to spell words on a computer screen.[93] With the advancement in technology over time, the interdisciplinary field of BMI has evolved tremendously, with an increase in research teams interested in this area and its vast array of applications. Prashant et. al. [94] proposed four main factors that led to this improvement in the BMI research field. The noteworthy first one is related to one of the main goals of BMI, which is its potential to improve the lives of individuals with severe motor impairments (e.g., patients with locked-in syndromes and SCI). The second factor is the improved knowledge of the basis, purpose, and relationship between EEG and associated neural activity. The last two factors refer to the development and accessibility of low-cost microelectronics and the improvements in machine learning and decision-making techniques. These two factors allow BMI users to execute complex tasks via integrated circuits and further expand the potential of brain-controlled applications.[94] Since the ultimate purpose of BMI systems initially was to give people with severe motor limitations the ability to communicate and control their environment, Nicolas-

Alonso and his colleagues outlined three primary target populations that may benefit the most from BMI applications. These include Complete Locked-In State (CLIS) patients (i.e., individuals with complete paralysis), Locked-In State (LIS) patients, and people with considerable neuromuscular control (mainly speech and/or hand control).[95]

BMI applications can be classified in medical or non-medical (**Table 3**). The potential use of BMI in healthcare is vast, covering several applications such as prevention, detection, and neurorehabilitation.[96] In the prevention field, BMIs can be used to detect and prevent seizures in epileptic individuals, as well as to detect and prevent car accidents caused by drowsiness or exhaustion. For instances, Maksimenko et al. developed a closed-loop brain-stimulation algorithm implemented in a BMI system capable of controlling absence seizures in epileptic patients, leading to a 72% reduction in seizure activity and an improvement in the patients' quality of life. [97] Another area of investigation is road safety and the prevention of fatigue while driving, as it is a significant contributing factor that can lead to deadly accidents. Fatima et al. proposed a wireless EEG-based BMI system capable of providing real-time biofeedback to the driver when a drowsy state occurs. This system offers numerous benefits, such as the use of wireless communication to transfer data, eliminating therefore, the need for cables, its adaptability for use in a vehicle, and its low cost and ease of implementation.[98] BMI technologies can also be used to detect and early diagnose certain diseases or pathological states, such as epilepsy, depression [99], and attention-deficit/hyperactivity disorder (ADHD).[100] Depression is a condition that is typically diagnosed through clinical observations or self-reported information from patients. However, since BMI technologies can obtain emotional data from the users, they have the potential to diagnose the disease in an early stage, allowing for a more suited course of treatment.[99] Another condition that can be currently diagnosed and monitored through BMI systems is ADHD. Recently, Serrano-Barroso and colleagues designed a single-channel BCI headset that assessed the attention levels of both children with and without ADHD while playing a video game. The study showed that the system has the potential to be used in clinical settings as an early screening tool for attentional features, controlling their progression.[100] One crucial treatment component for those with neurological disabilities, such as stroke or SCI, is rehabilitation, that aims to help individuals to regain lost motor or cognitive functions and learn to adapt to their disabilities, leading to an improved quality of life. Neurorehabilitation has its foundations in the principles of neuroplasticity, which refers to the brain's ability to reorganize and form new neural connections in response to changes in the environment, learning, and experience.[101] BMIs offer a new and innovative approach to neurorehabilitation, providing a way to directly interface with the brain and potentially facilitate faster and more effective rehabilitation outcomes.[96] Regarding this, BMIs can be further classified into assistive and rehabilitative devices. Assistive BMIs intend to replace or compensate for lost functions in impaired individuals by using brain signals

to control external devices, allowing them to perform specific tasks such as communication or mobility.[102] This type of BMI should be easily accessible and operable by users without requiring any medical expertise, allowing them to control external devices using their brain signals whenever needed.[103] Rehabilitative BMIs, on the other hand, focus on restoring or improving impaired functions through targeted neuroplasticity-based training.[102] These BMIs are typically used during treatment sessions with certified therapists since the purpose is to produce long-term modifications.[103]

In the following sections, we will briefly explore some of the examples of assistive and rehabilitative BMIs and their applications in communication, motor, and cognitive rehabilitations. In the field of communication, assistive BMIs are designed to help individuals with communication impairments, such as those with amyotrophic lateral sclerosis (ALS), locked-in syndrome, or severe speech and motor disabilities. They allow these individuals to communicate with others using brain signals, which are then translated into text or speech output.[102] There have been several remarkable developments of assistive BMIs for communication, such as the P300-based BMI spellers[104], Eye-tracking BMIs[105], Brain Gate System[106], and most recently the Handwriting BMI[107]. The P300-based BMI spellers use the P300 wave, an event-related potential in the brain, to select letters or words from a computer screen. They are among the most widely studied BMIs for communication and have been used in various applications, including helping individuals with ALS to communicate.[104] The Eye-tracking BMIs use eye movements to control external devices, including communication aids like a high-speed text entry system in virtual reality. They are particularly useful for individuals with severe motor disabilities who are unable to use traditional input devices, such as a keyboard or mouse.[105] The Brain Gate System has been used to enable individuals with paralysis to control a computer cursor, robotic arm, or other devices using their thoughts. It has been studied extensively in both preclinical and clinical trials and has shown promising results in restoring communication and mobility to individuals with severe paralysis.[106] Lastly, the Handwriting BMI is a new assistive technology that enables individuals to communicate by writing using their brain signals. A recent study conducted by Willett et al. demonstrated the system's potential by showing that a participant with a paralyzed hand due to SCI was capable of writing messages by imagining the movement of doing so on a piece of paper. The study results were promising, as the participant was able to write at speeds comparable to those of a healthy subject using a smartphone keyboard. [107] One of the main areas of focus is motor rehabilitation, where BMI systems can be both assistive, by enabling patients to produce more reliable motor brain signals and used them to control external devices that assist with movement; or rehabilitative as they may help train persisting cortical connections to execute motor output of the motor-impaired limb.[102] An example of an assistive BMI for motor rehabilitation is the MyoPro. This system uses surface electromyography (EMG) sensors to detect muscle activity

in the arm and translate those signals into movements of a robotic arm brace. It is designed to assist individuals with upper limb paralysis due to conditions such as stroke, spinal cord injury, and multiple sclerosis.[108] As previously mentioned, rehabilitative BMIs operate by providing real-time feedback to an individual's brain signals, encouraging the brain to reorganize and relearn motor skills. These devices, which usually focus on either the upper or lower limbs, are designed based on clinical evidence that suggests the potential for neural plasticity through intensive, repetitive, task-oriented movements. This approach promotes the formation of new neural connections allowing the restoration of movement and functionality of affected body parts, even in patients with neurological disorders.[109] Examples of upper limb rehabilitation devices include the Neofect Smart Glove[110] and the Armeo Spring exoskeleton[111], developed to improve hand function, and to regain arm and hand functions, respectively. Examples of rehabilitative BMIs for lower limb rehabilitation include the ReStore Exo-Suit [112] and the ExoAtlet [113]. Both are exoskeleton devices that use advanced sensors and algorithms to provide real-time feedback and assistance to users during rehabilitation. The ReStore Exo-Suit is a lightweight and comfortable exoskeleton specifically designed for stroke rehabilitation. It is a soft, wearable device that can be used for extended periods to help individuals improve their gait and balance.[112] In contrast, the ExoAtlet is a more rigid exoskeleton designed for the rehabilitation of individuals with lower limb disabilities due to spinal cord injury, stroke, or other neurological conditions. It provides more support and stability during walking and standing to help individuals regain their mobility.[113] Another field of rehabilitation is the cognitive one where rehabilitative BMIs are designed to help individuals with cognitive impairments caused by neurological disorders such as stroke, traumatic brain injury, and Alzheimer's disease. These BMIs aim to improve cognitive function, including attention, memory, language, and executive function. One type of cognitive rehabilitation BMI is neurofeedback (NFB) training, which uses real-time monitoring of brain activity to help individuals learn to self-regulate their brain function. This type of BMI helps individuals with ADHD, traumatic brain injury (TBI), and other neurological disorders.[114]

While BCIs have primarily been developed for medical applications, there are also non-medical applications for this technology. One example is in the field of entertainment and gaming, where BMIs can be used to provide a more immersive and interactive experience for users. BMIs can also be used for enhancing human performance, such as in sports training or driving simulators. Additionally, BMIs have potential applications in the field of communication and human-machine interfaces, such as in the development of smart homes and personal assistant devices. The possibilities for non-medical applications of BMIs are vast, and ongoing research in this area is expected to lead to even more innovative uses in the future.[72,91,115]

1.3.3. EEG-based BMIs

1.3.3.1.EEG Basics

The electroencephalogram (EEG) is a non-invasive technique that uses electrodes attached to the scalp to record electrical activity in the brain. This electrical activity is produced by the movement of charged particles, across the membranes of active neurons during synaptic transmission. [116] At the scalp level, only synchronous brain activity (i.e., summation of various brain signals) can be detected. This is due to the signals' attenuation, which results from the distance between the source and the electrodes, and their spatial smoothing, which is a consequence of the head's tissues' high-volume conductance (mostly the brain, cerebral fluid, skull, and scalp).[117]

EEG recordings can be conducted repeatedly over a long period to evaluate recovery in neurorehabilitation processes. The electrode placement is crucial since the slightest change in their location may lead to alterations in the measured evoked potentials and, consequently, in the overall recovery assessment.[118] For this reason, several methods describing the locations of the EEG scalp electrodes and guaranteeing equal inter-electrode spacing have been proposed. The 10-20 system, presented in **Figure 3**, was proposed by Herbert Jasper in 1958, and is one of the most internationally recognized methods that allows electrode placement to be proportional to skull shape and size. It is called the 10-20 system because electrodes are placed at sites 10% and 20% from four anatomical locations on the scalp: the nasion and inion (front-back direction) and the two preauricular points (right-left direction).[119,120] Different methods include expanded versions of the 10-20 system, such as the 10-10 and 10-5 systems. These systems use additional electrodes between the existing system, resulting in a higher density measurement. The knowledge of these systems and the methods behind them allows for consistent and replicable EEG recordings.[121,122] When using the 10-20 system, each electrode is named using a combination of letters and numbers. The letters F, T, P, and O indicate the lobe of the brain where the electrode is placed (frontal, temporal, parietal, and occipital lobes, respectively). C denotes the central region, and z the midline section. Frontal-polar electrodes are annotated with ‘Fp’ and typically associated with activity in the prefrontal cortex. Odd-numbered electrodes are placed on the left side of the head, while even-numbered ones are on the right side.[123]

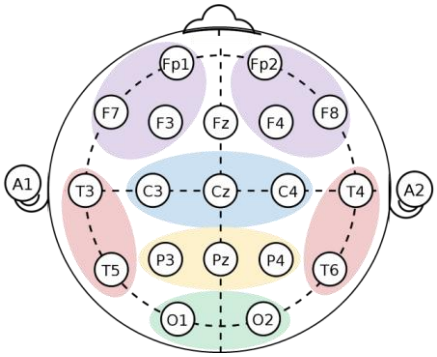

Figure 3- The 10-20 International system of EEG electrode placement. Cerebral areas are colored in purple (Frontal regions), blue (central), pink (temporal), yellow (parietal) and green (occipital).

EEG oscillations contribute to cognitive functions differently based on their location in the brain and various parameters like amplitude, frequency, phase, and coherence. This concept is grounded on the idea that distinct brain areas perform specific functions and that the frequency and coherence of EEG oscillations can provide information about the scale and organization of neural activity involved in cognitive processes.[124] For instances the cerebral cortex, i.e., the area of the brain captured by the EEG electrodes, is divided into four lobes with different functions associated with each one. The frontal lobe, which is the largest one including the prefrontal and motor cortices, is responsible not only for motor control but also for several cognitive processes, also referred to as executive functions, such as decision-making, problem-solving, working memory, and attention.[125,126] The temporal lobe, which encloses structures like the hippocampus and amygdala, is associated with functions such as auditory processing, language comprehension, and memory.[127] The parietal lobe includes the somatosensory cortex and is therefore involved in tactile processing and pain perception, also has a role in language processing and the coordination of movement and spatial awareness functions.[128,129] Lastly, the occipital lobe includes the structure of the visual cortex, being mostly responsible for processing visual information.[130] The frequency of EEG oscillations can provide insights into the size and organization of the neural activity involved in cognitive processes. For instance, low-frequency oscillations are believed to represent the activity of large-scale neuronal assemblies connecting distant brain regions, whereas high-frequency oscillations are more likely to reflect the activity of local smaller neuronal populations.[119] As for the coherence, i.e., synchronization between the EEG signals in a particular frequency band, it may provide information about the possible communication between different brain regions. When there is a high coherence in a specific bandwidth, the brain regions involved in that band may be part of a larger network supporting a specific cognitive function.[124]

There are five main types of brainwaves, i.e., the oscillating electrical voltages in the brain that produce the EEG signal, each with its characteristic frequency range and the associated state of mind. Different brain areas generate different types of oscillations simultaneously, and the unique pattern

of the brainwave activity can provide insights into an individual's cognitive and emotional states.[131] These neural oscillations are the delta, theta, alpha, beta, and gamma waves, and **Table 4** summarizes their respective frequencies, typical locations, and state of occurrence.

Table 4- EEG rhythms and their respective frequency range[132], typical brain location[133] and associated state of mind.[131,134–136]

EEG Rhythms	Frequency Range (Hz)	Typical Brain Location	Associated State of Mind
Delta (δ)	0.5-4	Frontal regions	Deep sleep
Theta (θ)	4-8	Temporal and Parietal regions	Deeply Relaxed, inward focused, Subconscious
Alpha (α)	8-13	Occipital and Parietal regions	Relaxed wakeful awareness, Passive attention
Beta (β)	13-30	Frontal and Parietal regions	Focused, Alert, Active thinking
Gamma (γ)	30-100	Various	Hyper alertness, Concentration, Integration

Delta waves have the slowest frequency range observed in EEG recordings, from 0.5 to 4Hz, and the highest amplitude, with values ranging between 20 and 200μV.[133,137] While these may be observed in other brain regions, they are most noticeable in the frontal cortex.[132,133] Delta waves are most observed during deep, dreamless, and unconscious sleep, known as non-rapid eye movement (non-REM) sleep. Abnormalities in this frequency band have been associated with certain neurological disorders, such as dementia and traumatic brain injury.[134,135,138] Theta waves, with a frequency range of 4 to 8Hz and amplitudes of over 20μV, are mainly present in the temporal and parietal lobes.[133,137] These rhythms are linked to subconscious activity and are observed during states of deep relaxation, meditation, daydreaming, and early drowsiness. They also play a role in cognitive processes such as memory formation and retrieval.[133–135] Representing the white matter of the brain are alpha waves, with a frequency between 8 and 13Hz with an amplitude ranging from 30 to 50μV.[137] These neural oscillations, primarily recorded from the posterior regions of the brain, specifically the occipital and parietal lobes, act as a bridge between the conscious and subconscious mind.[132,133] They are associated with states of relaxed awareness (without attention or concentration), good mood, peacefulness, focus, and learning new information.[135] With a frequency of 13-30Hz are the beta waves, occurring typically in both sides of the frontal and parietal lobes and with a small amplitude of 5-30μV.[132,137] These bandwidth patterns are associated with sensory perception, including sight, touch, smell, taste, and hearing. Additionally, they are commonly observed during conscious activities such as problem-solving, decision-making, and judgment.[134,135] Finally, gamma waves are the highest frequency signals, ranging between 30 and 100Hz, and with small amplitudes of less than 5μv.[137] These neural oscillations, which typically occur in various cortical sites of the brain, are associated with hypervigilance and the integration of sensory information, as well as a range of

cognitive functions such as consciousness, intellect, empathy, self-control, and cognitive tasks.[132,133,135]

1.3.3.2.EEG signatures in Chronic Pain

Currently, the benchmark for assessing the severity of chronic pain are the self-reported scales, such as the Numeric Rating and Visual Analog Scales (NRS and VAS, respectively). However, the validity of these subjective methods can be compromised by various factors, including the patient's physiological and psychological state and the examiner's propensities. As a result, there has been a growing interest in developing objective pain assessment methods, particularly in the neuroimaging field.[139] Mouraux A. et al.[140] proposed three main ideas that advocate using functional neuroimaging techniques for measuring pain objectively. The first is that this approach could allow the development of brain biomarkers that could efficiently quantify the pain severity and possible treatment outcomes. Accordingly, neuroimaging could assist in diagnosing pain based on its mechanisms, thereby enabling the prediction of individual treatment responses, and ultimately allowing for personalized treatment strategies. Lastly, by describing their effects on CNS pain circuits, neuroimaging, and electrophysiology could help discover novel pain-relieving pharmaceuticals.[140]

One of the earliest research papers on EEG activity patterns and their possible association with chronic pain was published by Gücer et al. in 1978. [141] Since then, a significant number of research papers on the potential association between specific EEG signatures, such as alterations in frequency bands and connectivity patterns, and the presence and/or intensity of chronic pain, have been published (**Table 4**). Different study designs can lead to the identification of different types of biomarkers. For instance, cross-sectional studies, which examine a population at a single point in time comparing patients with healthy participants, typically focus on identifying diagnostic biomarkers. Longitudinal studies, on the other hand, track changes in a population over time which can identify monitoring and/or, predictive biomarkers. As for descriptive studies, which seek to characterize a population or disease in more detail, biomarkers found may have both diagnostic and monitoring purposes.[142] Twenty-eight research papers that studied EEG signatures associated with various types of chronic pain are briefly reviewed in **Table 4**. Overall, the selected studies have a cross-sectional design, except four whose design was observational[143], descriptive[144–146], longitudinal/descriptive or comparitive[147–152], and a case series[153] and report[154]. The main EEG parameters analyzed in those studies were power spectra[143–146,155–165] (n = 15), peak frequency (n = 5)[143,159,160,163,166], and connectivity patterns (n=3)[149,164,167]. The analyses of power spectra revealed that chronic pain patients displayed decreased alpha power[143,155,156,160,163,167], and increased delta[146], theta[156–159,161,164,168], beta[155,158,159], and gamma[164,165] powers. Even though these results had the most evidence support, there is also evidence that chronic pain might be associated with increased

alpha[157,159,161] and decreased beta[160,165]. The main relevant finding from studies that analyzed the peak frequency of the power spectra in the averaged EEG signal was a shift towards lower frequencies in chronic pain patients compared to healthy controls. [143,159,160,163,166] Several of the studies additionally found correlations between brain activity and pain intensity. For instance, significant negative correlations were found between alpha[144,145,151,156] and low beta[165] powers. On the other hand, delta[146], theta[146,157], beta[157] , and gamma[168] powers have been shown to be positively correlated with pain intensity. Four studies[152,157,158,167] further investigated the pain matrix in patients with chronic neuropathic pain and found an overactivation in brain areas such as the thalamus, anterior and posterior insula, cingulate, somatosensory, and prefrontal cortices. Additionally, some found that this overactivation was specific for frequency ranges, such as theta and low beta [152,158,167], and that it could decrease along with pain reduction [152,157,158]. Thirteen of the included studies investigated the influence of interventions on chronic pain and how brain activity changed accordingly. Four of these studied the effect of NFB protocols on chronic pain and concluded that the treatment resulted in a reduction of pain, accompanied by a decrease of theta[147,153,162], and beta[162] powers and an increase in the alpha[147,151] frequency. The remaining studies assessed the effects of therapeutic lesions in the thalamus (central lateral thalamotomy, CLT)[157–159], DRGS coupled with tDCS[169], several pharmacological[152], such as ketamine[150], and psychological therapies[148,170], and one additionally assessed interdisciplinary multimodal pain therapies[149].

Table 4- Studies on EEG signatures associated with chronic pain. Information about the authors, design of the study, the type of pain and the associated condition, the type of intervention assessed, and the main results regarding the EEG activity of the subjects with chronic pain. (NP- neuropathic)

Author, Year	Study Design	Condition	Type of pain	Intervention	Main Results
Braden[155] 2011	Cross-sectional	SCI	NP		More relative β-wave activity Less α-wave activity
Boord[166] 2008	Cross-sectional	SCI	NP		Decrease in peak θ-α frequency
Camfferman [144] 2017	Descriptive	Mixed	Mixed		Correlation (-) between α-wave activity and pain intensity, in frontal and parietal areas
Day[148] 2021	Longitudinal descriptive	Low back pain	Mixed	Cognitive therapy (CT), Mindfulness-meditation (MM), and Mindfulness-based cognitive therapy (MBCT)	After treatments: Reduction in θ- and α -wave in the left frontal area; and in β-wave in all regions
Doruk[143] 2017	Observational	SCI	NP		Less α-wave activity Lower alpha/theta ratio Peak frequency significantly lower Correlation (+) between α-wave activity and VAS scores

Feng[145] 2021	Descriptive	Low back pain	Mixed		Correlation (-) between α-wave activity and pain intensity in central regions
Hasan[162] 2016	Randomized Controlled Trial (RCT)	SCI	NP	NFB	Decrease in β- and θ-wave activity after NFB
Heitmann[149] 2022	Longitudinal descriptive	Mixed	Mixed	Interdisciplinary multimodal pain therapy	Increase in global network efficiency at θ frequencies after intervention
Jensen[147] 2013	Longitudinal descriptive	SCI	NP	NFB (different protocols)	Decrease in pain after NFB treatment. Decrease in θ activity after NFB. Increase in α activity after NFB
Jensen[156] 2013	Cross-sectional observational	SCI	Mixed		More θ-wave activity Less α-wave activity Correlation (-) between pain intensity and α activity in frontal regions
Jensen[170] 2021	RCT	Mixed	Mixed	Hypnosis focused on pain reduction (HYP), hypnotic cognitive therapy (HYP-CT), CT, and Education (ED) control condition	Decrease in θ-wave activity after ED
Michels[157] 2011	Cross-sectional observational, Longitudinal descriptive	NP pain of various etiologies	NP	Central lateral thalamotomy (CLT)	Higher θ- and α-wave activity Correlation (+) between θ and β activity and pain intensity. After CLT: normalization of power in all frequency bands (for HPC patients), and in low-frequency bands (for LPR patients)
Oga[150] 2002	Longitudinal descriptive	NP pain of various etiologies	NP	low-dose ketamine HCl	Lower α-wave activity after ketamine Correlation (+) between ketamine-induced effects on pain relief and α-power (right central electrode)
Parker[169] 2021	RCT	NP pain of various etiologies	NP	dorsal root ganglion stimulation (DRGS) + transcranial direct current stimulation (tDCS)	Increased cortical β activity in both frontal and parietal regions during acute pain relief (after both interventions)
Patel[151] 2021	Longitudinal comparative	Mixed	Mixed	Alpha-neurofeedback (a-NFB)	Trend of increase in α state parameters such as fractional occupancy, dwell time distribution and transition probability. Correlation (-) of α state parameters with changes in VAS pain rating.
Prichep[152] 2011	Longitudinal descriptive	Root and or nerve compression or trauma	NP	Different pharmacological treatments	Higher activity levels in very narrow bands within the α- or low β-waves (for 3 Patients). Maxima activity in the θ-wave (2 Patients)
Prichep[167] 2018	Cross-sectional observational	Mixed	Mixed		Higher θ and low α-wave activity Higher θ connectivity

Sarnthein[159] 2006	Cross-sectional observational, Longitudinal descriptive	NP pain of various etiologies	NP	CLT	Higher spectral power over the whole frequency range (2–25 Hz) Reduction of θ-wave power after CLT
Simis[160] 2022	Cross-sectional	SCI	NP		Less α- and β-wave activity Decreased peak α-θ frequency. Correlation between θ-wave and DPIS activity
Stern[158] 2006	Cross-sectional observational, Longitudinal descriptive	NP pain of various etiologies	NP	CLT	Higher activity in the high θ and low β-wave frequency ranges After CLT: significant reduction in activation in cingulate and insular cortices
Ta Dinh[164] 2019	Cross-sectional observational	Mixed	Mixed		Higher θ and γ connectivity in frontal regions Decrease in global efficiency in γ frequencies
Teixeira[165] 2021	Cross-sectional observational	NP pain of various etiologies	NP		Lower β-wave activity Correlation (-) between low β power and VAS
Teixera[146] 2022	Descriptive	Low back pain	Mixed		Correlation (+) between pain intensity and relative δ- and θ-power, in central area
Vanneste[168] 2021	Cross-sectional observational	NP pain of various etiologies	NP		Higher θ- and γ-wave activity in somatosensory cortex (SSC) Correlation (+) between pain intensity and γ activity, in SSC
Vuckovic[161] 2014	Cross-sectional	SCI	NP		More α-wave activity Larger θ-wave activity in frontal and occipital regions
Vučković[153] 2019	Case series	SCI	NP	NFB	More α-wave activity associated with decrease of pain. (Some participants also showed a decreased in θ-wave activity)
Wydenkeller[163] 2009	Cross-sectional	SCI	NP		Less α-wave activity Peak theta–alpha frequency decreased
Yoshida[154] 2016	Case Report	SCI	NP	BCI	Increased β-wave activity after SMR training

Since our case-study will be based on a patient that besides chronic pain is suffering from SCI, in the next section the results from the research papers that included populations with SCI will be discussed. Two of the studies[155,160] compared SCI populations with and without pain; five of them [143,156,161,163,166], additionally compared these two groups with a group of healthy volunteers. The studies that evaluate the effect of an intervention only worked with SCI patients with chronic pain.[147,153,154,162] Although there were some contradictory findings, the most common EEG signatures found among chronic pain SCI patients was a higher power in theta bandwidths[156,161] and lower activity of the alpha

waves[143,155,156,160,163]. Three of which additionally found significant correlations between the EEG signals and other parameters such as pain intensity[143,156] and the activity of the descending pain inhibitory system (DPIS).[160] Regarding the correlation with pain intensity levels, Doruk et al. found a positive correlation between alpha activity in the occipital areas and the VAS pain scores [143]. On the other hand, Jensen et al. found a negative correlation between the alpha activity from frontal regions and the pain intensity, measured on a 0–10 numerical scale, proposed that this might be related to drowsiness or the possible involvement of frontal brain structures in the suppression of pain, meaning that the increase of alpha activity in these areas may be a result of less successful pain suppression[156]. By using conditioned pain modulation (CPM) efficiency as an index of the DPIS, Simis et. al found a correlation between the increase in theta activity and the decrease in CPM efficiency. [160] Four of the studies included, evaluated the effect of an intervention, namely NFB[147,153,162] or BCI[154] training, for the chronic pain treatment. The NFB protocols used were mostly focused on increasing the alpha activity and decreasing both theta and beta powers. [147,153,162] Yoshida et al.[154] used a BCI system with sensorimotor (SMR) feedback, which measures and provides feedback on the sensorimotor rhythm, a specific pattern of electrical activity observed over the sensorimotor cortex and associated with lower beta frequency bands. The study specifically focused on event-related desynchronization (ERD); a pattern characterized by decreased SMR amplitudes. Since all these interventions resulted in a decrease in pain levels, neurofeedback, either as a standalone intervention [147,153,162] or inserted in a BCI system [154], has the potential to be a promising approach for alleviating chronic pain after spinal cord injury.

1.4.Objectives

Based on this literature reports we hypothesized that the BMI training employed in this study could decrease the pain levels reported by our subject and consequently modulate his neural activity, ultimately leading to the identification of EEG signatures capable of identifying chronic pain biomarkers. To this end, we'll focus on the electrodes and bandwidths that are most reported in the literature.

2. Materials and Methods

2.1.Subject and Timeline of Experiment

The present case-study was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki by the World Medical Association for research involving humans and received approval from the Ethics Committee of CES- Hospital Senhora da Oliveira (no. 15/2020).

Informed consent was obtained from the participating subject, a 52-year-old male with an AIS complete T4 SCI stabilized (32 years), and a history of chronic low back pain following surgery (5 years). Data collection took place between June 2021 and July 2022 at the Hospital Senhora da Oliveira in Guimarães, Portugal. The study involved two distinct BCI training protocols, distinguished as passive and active according to the participant's control over the VR avatar. The passive protocol comprised ten training sessions over five weeks, with two sessions per week, followed by a final evaluation and a 12-week follow-up. This protocol aimed to evaluate the participant's comfort level while experiencing illusory lower limbs, without introducing additional stress resulting from low performance in real-time neural decoding feedback. Subsequently, the participant underwent an active BCI training protocol, comprising 22 sessions, followed by a final evaluation at week 41 and a follow-up 33 weeks later. The specific details and timeline of these training protocols are presented in **Figure 4**.

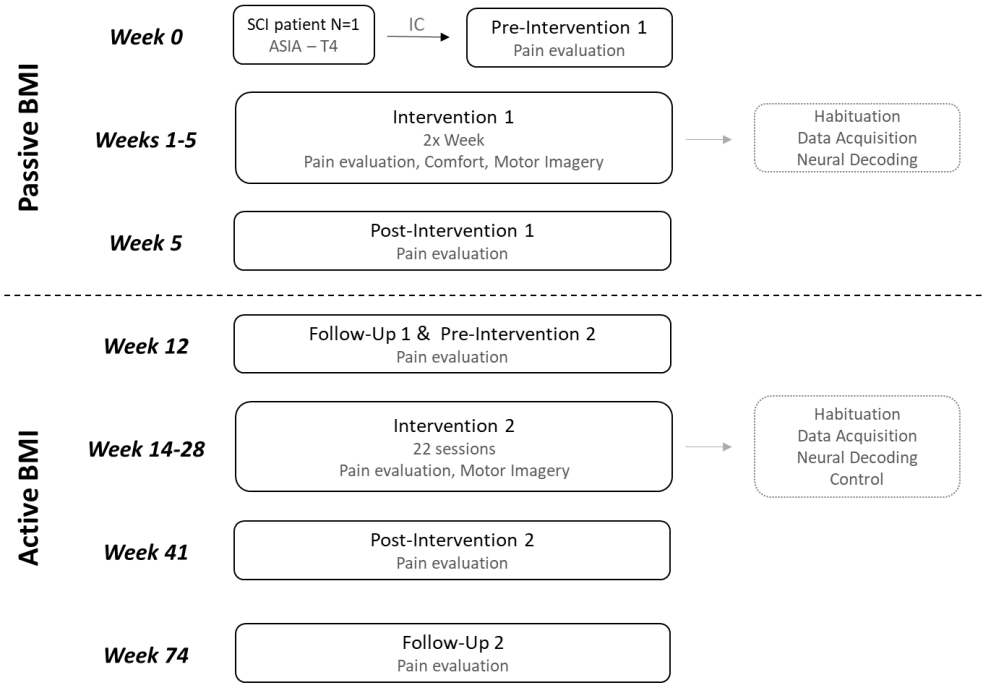

Figure 4- Timeline. The study procedures began with obtaining informed consent from the participant and conducting a pre-intervention assessment. Throughout the intervention, the participant's comfort levels with embodiment experiences, VR side effects, self-reported pain levels, and the use of thermal-tactile sleeves were assessed. The post-intervention assessment was conducted after seven weeks and included a re-evaluation of self-reported pain levels. This follow-up assessment also served as the pre-intervention assessment for the second training protocol. Notably, the active protocol differed from the passive protocol in that the participant was able to control the VR avatar using neural activity. Adapted from[171]

2.2.Sessions and Clinical Measures

The intervention consisted of 33 sessions, conducted by a team of 2-4 researchers to ensure proper equipment functioning and minimize experiment setup time. Each session lasted between 70–90 min,

which included periods of equipment setup (**Figure 5 (A)**), assessment of the participant comfort, interaction with the VR environment, and questionnaire administration. The initial period, usually lasting approximately 10 min, served to evaluate the comfort of the subject with the equipment as well as to collect information regarding pain and stress experienced at home or work between sessions. The VR interaction phase (**Figure 5 (B)**), lasting between 20-25min, consisted of three sequential phases: (a) habituation, (b) acquisition of baseline EEG data and neural activity recording; (c) online period marked by real-time neural decoding and control of the VRs avatar.

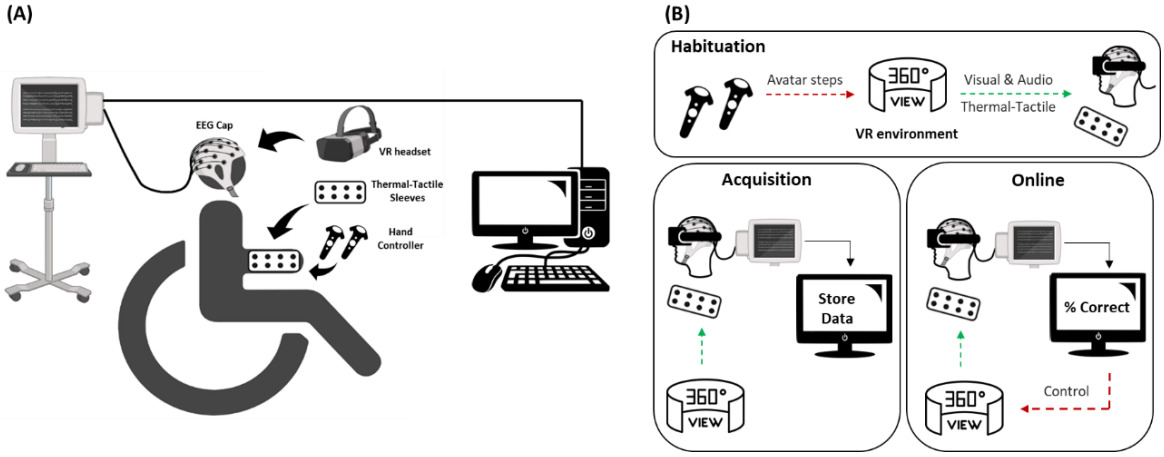

Figure 5- Setup and Session Phases. **(A)** Equipment and Setup. (**B)**VR interaction phases: Habituation, Acquisition and Online.

During the habituation phase, the subject was instructed to choose a VR scenario and interact with it using hand controllers, controlling the movements of the avatar within the VR environment. This interaction provided the participant with various types of feedback, including visual cues, audio stimulation, through the VR headset, and thermal tactile sensations, through the thermal-tactile sleeves. This phase aimed at optimizing the setup by making any necessary adjustments to the sleeves, VR environment, or wheelchair position. During the neural data acquisition phase, the subject was presented with visual cues that specifically instructed them to "Walk" (green cues) or "Stop" (red cues). For the green cues, the participant was instructed to imagine one leg rising and stepping on the ground, while for the red cues, to remain still and enjoy the scenario. After data acquisition, a common spatial filter and classifier were trained, and training proceeded when the true positive values exceeded 70% for each category. If the threshold was not met, the neural data acquisition phase was repeated. In the last phase, named as the “online” phase neural decoding was performed in real-time. As previously mentioned, for the first 10 sessions that composed the passive rehabilitation protocol, motor imagery was only used to train the participant, not providing any control of the avatar nor immediate feedback on his performance. This means that, independently of the subject’s neural activity, the avatar would move when a green visual cue (Walk) appeared, and the remain still when the red (Stop) visual cue appeared. In the active rehabilitation protocol, the

subject had actual control of the avatar and immediate feedback on his performance (i.e., upon a green cue, the avatar would still move, but different auditory feedback was delivered when neural activity encoded “walk” and “not walk” cues).

The clinical measures used were subjective pain scales administered via a questionnaire at the end of each session. These scales consisted of the Faces Pain Scale (FPS), the Verbal Pain Intensity Scale, and the Visual Analog Scale (VAS) Pain Scale. The subject was instructed to rate his pain level on each scale by indicating a number on the VAS pain scale ranging from 0 (representing ‘no pain’) to 10 (representing the ‘worst possible pain’), selecting a facial expression corresponding to their pain level on the FPS, and choosing a word on the verbal pain scale ranging from “no pain” to “unbearable pain”.

2.3.EEG Recordings and Analysis

EEG recordings were acquired using a 16-channel EEG cap (V-Amp, actiCAP; Brain Products GmbH, Gilching, Germany) placed according to the 10-20 system. Signals were recorded using the Brain Vision Recorder and analyzed using Brain Vision Analyzer, MATLAB, and Excel. In the Brain Vision Analyzer, during the data pre-processing stage, an Infinite Impulse Response (IIR) notch filter was applied, ocular movements were removed using the Gratton and Coles algorithm, and a Fast Fourier Transformation (FFT) was performed to obtain frequency spectra for further analysis. The mean power for each bandwidth (delta (0.5-3.5 Hz), theta (4-7.5 Hz), alpha (8-12.5 Hz), beta (13-30 Hz), and gamma (30.5-100 Hz) for each of the 16 channels were analyzed. EEG data was acquired in a total of 32 sessions; however, due to technical issues, four sessions (sessions 2, 26, 28 and 32) were excluded from the analysis, resulting in a final dataset of 28 sessions (**Table 5**). The acquisition period encompassed a total of 10 sessions dedicated to passive BMI training, while the remaining sessions focused on active BMI training. It is important to note that during the online period, six additional sessions (sessions 3, 4, 5, 6, 7, and 19) were not available for analysis, resulting in a reduced dataset for the online period (22 sessions in total).

Table 5- Available EEG data and respective sessions. The first 10 sessions belong to the passive BMI training protocol and EEG data was available for all sessions except session 2 (Recorded on 30th June 2021)for the acquisition period and sessions 2 and 7 (Recorded on the 21st of July 2021) for the online period. The active BMI protocol was performed in 22 sessions, three of which (Sessions 26, 28 and 32) had no available EEG records for either the recording phases (acquisition and online). For session 19 on the 19 of November 2021, EEG data recorded in the online period was also not available. All in all, the total of available data consisted of 28 and 22 sessions, for the acquisition and online periods, respectively.

BMI Protocol	Sessions	EEG Data Available	
		Acquisition	Online
Passive	1	✓	
	2	✗	
	3 to 7	✓	✗
	8 to 10	✓	
Active	11 to 18	✓	
	19	✓	✗
	20 to 25	✓	
	26	✗	
	27	✓	
	28	✗	
	29 to 31	✓	
	32	✗	
Total		28	22

2.4.Statistical Analysis

Results are presented as mean ± standard deviation. Arbitrary units (a.u.) were used as units for the different questionnaires. A z-score normalization was applied to the EEG data. This method allowed the standardization of the EEG measurements, ensuring comparability across different recording sessions. For the subsequent analysis, the data was divided into subsets based on the sessions. To investigate potential changes over time, the sessions were grouped into two sets: the initial group sessions and the final group sessions. Furthermore, considering that the acquisition data included more sessions, it was additionally categorized based on the type of BMI utilized. The first set of sessions corresponded to the passive BMI training, while the second set pertained to the active BMI training. The permutation test (with 1000 permutations) was used to assess the presence of any statistically significant distinction in these data sets. Additionally, the Mann-Kendall test was employed to identify trends, determining if there was a significant upward or downward trend. Spearman's rho coefficient and adjusted p-values were calculated between the EEG data and the variation of pain scores to investigate the possible relationship between these variables. An alpha value of 5% was considered significant for all hypothesis testing.

3. Results

In this section, the results will be presented in three different parts. First an exploratory analysis with all the available EEG data will be conducted, assessing the possible differences between the acquisition and online periods datasets. Second, the modulation of neural activity with time will be studied. Finally, the third subsection will include the results of the self-reported pain levels and their potential association with the neurophysiological signals.

3.1.Power Spectra of EEG Recordings

Power spectrums were obtained in Brain Vision Analyzer, **Figure 6 (a)**, shows a typical EEG spectrum from a time frame of a session recorded on the 15th of October 2021. After the pre-processing all data was normalized. To assess the differences between session periods, acquisition and online, only EEG data common to both was included, resulting in a total of 22 sessions. **Figure 6 (b)** presents a power spectra of electrode C4, showing alterations in the activity in different frequency ranges between the acquisition and online periods of the session mentioned above.

To ensure data consistency and reliability, after the EEG data underwent normalization, the spectral profile across all sessions were examined. This process aimed to eliminate sessions with unusual values or spectral characteristics that indicate potential errors or artifacts, enhancing the validity of the EEG data and ensuring its integrity for subsequent analyses. From the 22 sessions common to both periods five of them showed aberrant spectrum, such as outliers suggestive of noise in a specific frequency band and across multiple channels, being subsequently removed.

Afterwards, to evaluate the possible differences between the two periods, the permutation test was applied for between the means of each channel and frequency band. Statistically significant differences were found in all electrodes and frequency bands, except for the Fp1 and F4 electrodes in the delta and beta frequency bands respectively. Apart from these, all electrodes presented significantly higher power values in the delta and alpha frequencies band for the online period and theta, beta, and gamma frequencies for the acquisition period. (**Table A1**)

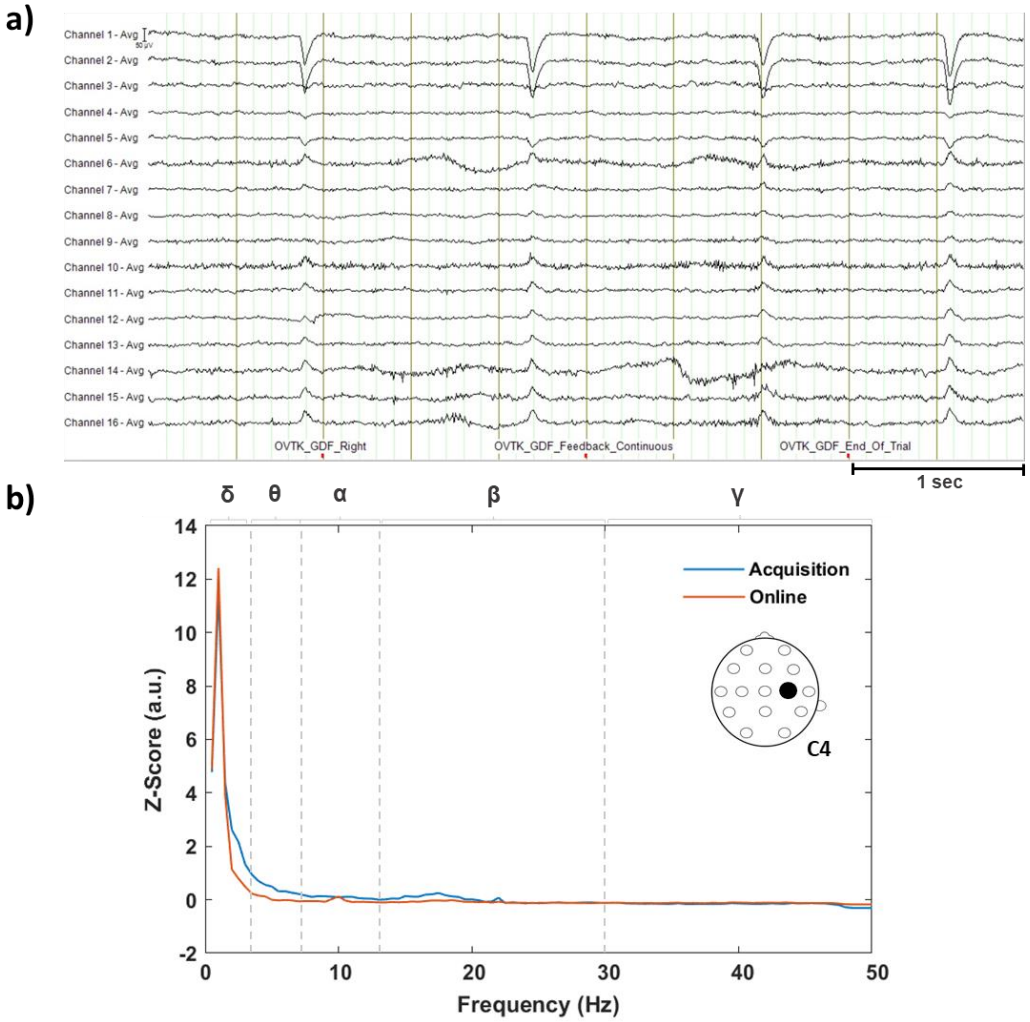

Figure 6- a) Spectra obtained in brain vision analyzer after ocular correction from session on 15 of October 2021. **b)** Spectra of the normalized power values same session between the acquisition (blue) and online (orange) period in electrode C4. Frequency bands are highlighted above with delta ranging from 0.5-3.5Hz, theta: 4-7.5Hz, alpha: 8-12.5Hz, beta: 13 to 30Hz and gamma: 30.5 to 50Hz (only for better visualization purposes, in the analysis gamma ranged between 30.5 to 100Hz).

From this point on, as the data sets are significantly different in almost all electrodes and frequency bands, the analysis of neural activity modulation and its relationship with pain levels will be done separately for the two periods. By doing so, the 28 sessions available from the acquisition period will now be taken into consideration.

3.2.Neural activity and chronic pain

Given the focus of this study on exploring the potential impact of BMI on pain and its modulation of neural activity, in the next sections we directed our attention toward electrodes located in the pre-frontal, frontal, motor, parietal and occipital regions. These brain regions are often associated with processes such as motor function and pain perception, being mentioned in most literature related to this subject. [144–146,156,161,169] Additionally, in the context of chronic pain associated with spinal cord

injury (SCI), previous research has primarily emphasized alterations in the delta, theta, alpha, and beta frequency bands [143,155,156,160,161,163] , consequently leading us to exclude the gamma bandwidth from subsequent analysis (**Figure 7b**).

3.2.1. Neural activity alterations with time

To study the possible changes of neural activity across sessions, each of the datasets (acquisition and online) were first divided in half and tested for differences between the initial vs final set of sessions. In this analysis the acquisition period includes a total of 25 sessions after three of them being eliminated in the quality control assessment mentioned above.

The first part of the sessions, i.e., the acquisition period, was divided into two subsets for analysis (**figure 7 a**). The first subset, meant to assess the possible variation of brain activity through time, disregarding other factors, was divided into two subsets: the initial 12 sessions (from June to October 2021) and the last 13 sessions (from October 2021 to April 2022). The second subset, which aimed to study if the alterations in the EEG activity through time were due to the type of BMI training, was divided into passive BMI training (9 sessions) and active BMI protocol (16 sessions). Regarding the EEG recordings from the online period, which included only 17 sessions (with only 3 from the passive BMI training), the initial set consisted of 8 sessions (June to October 2021), and the final set comprised 9 sessions (October 2021 to April 2022).

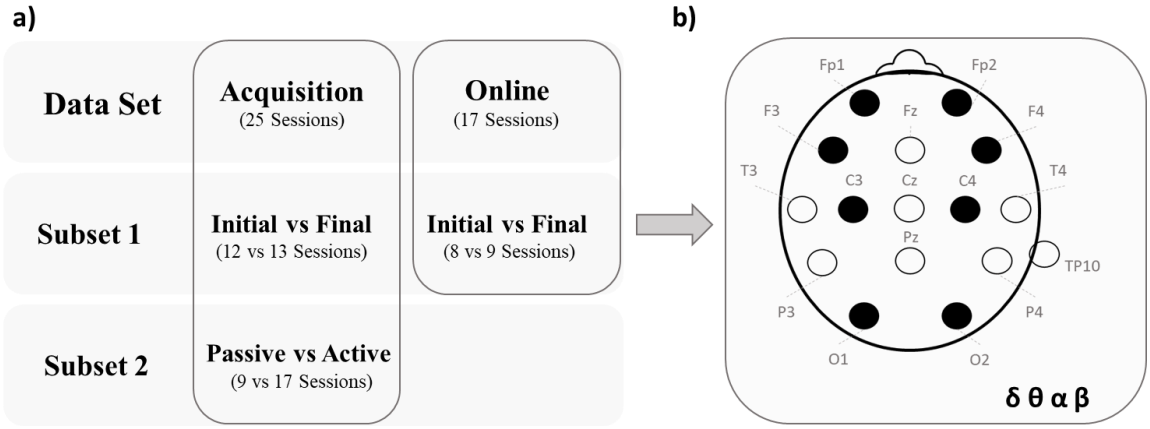

Figure 7- Overview of the studied subsets. Each data set, acquisition and online, are divided into subset 1 consisting of an initial and final group of sessions. Additionally, the acquisition data set is further grouped into subset 2 divided into passive vs active BMI training sessions. All the analysis focused on the delta, theta, alpha and beta activity in electrodes from the pre-frontal (Fp1 and Fp2), frontal (F3 and F4), motor (C3 and C4) and occipital (O1 and O2) areas.

Permutation tests were performed to evaluate the temporal changes within each channel (Fp1, Fp2, F3, F4, C3, C4, O1, and O2) and frequency band (delta, theta, alpha, and beta) for each set of comparison. After the correction for multiple comparisons only the acquisition period data showed significant results. When comparing between the initial and final sessions, two electrodes showed

significance, electrode C4 in the theta bandwidth (adjusted p-value= 0.040) and O2 in both delta and theta frequencies (adjusted p-value= 0.027 and 0.030, respectively) and electrode O1 presented a tendency towards significance in the theta bandwidth (adjusted p-value=0.056). When alterations between BMI protocols were studied, only electrode C4 showed significance in the delta frequency band (adjusted p-value= 0.032) and showing a trend towards significance in the theta band (adjusted p-value=0.053) (**Table A2**). Afterward, the Mann-Kendall test was employed to examine the nature of the observed changes in the data. This statistical test aimed to assess whether the changes exhibited a consistent trend over time or if they displayed abrupt transitions between data points. The results of the Mann-Kendall test yielded significant outcomes for all electrodes (**Figure 8**), indicating that the observed changes in the data were characterized by a continuous and statistically significant upward trend across the analyzed electrodes.

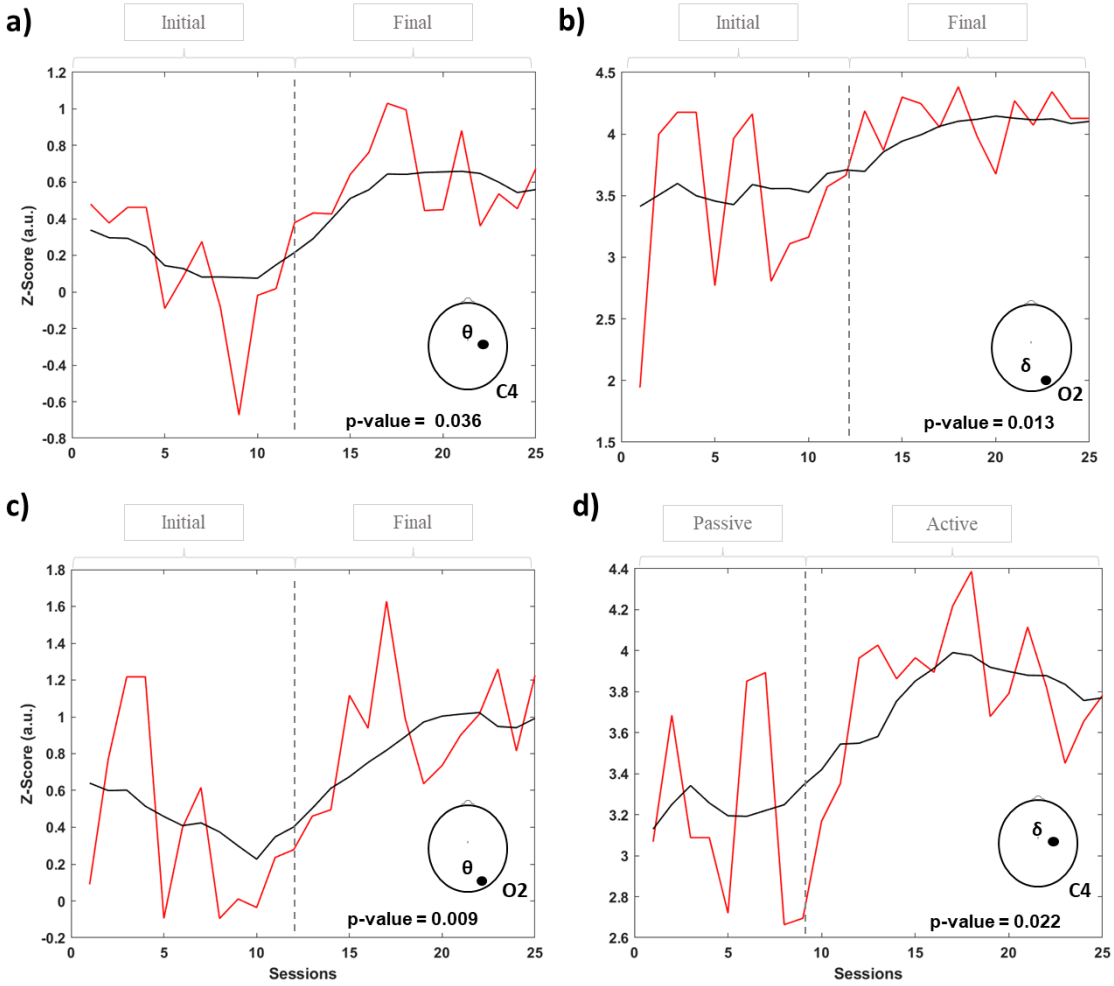

Figure 8- Alterations of neural activity from the acquisition period throughout the sessions. The Mann-Kendall test was applied between the mean values of the initial and final sessions in **a)** theta bandwidth electrode C4, and in delta **(b)** and theta **(c)** waves in electrode O2. **d)** Shows the alteration of neural activity in the delta frequency band in electrode C4 between the passive and active BMI protocol.

3.2.2. Correlation between neural activity and pain

The following section provides the results of the pain assessment using three distinct pain scales: Visual Analog Scale (VAS), Faces Pain Scale, and Verbal Pain Scale. The pain scores, collected in questionnaires administered in a total of 34 sessions (**Figure 9 (a)**), provide valuable insights into the subject's perceived pain levels. To gain a comprehensive understanding of the variations in pain levels during the intervention, mean values were computed for sessions involving the passive and active BMI protocols separately (**Figure 9 (b)**). All three scales showed a decrease in pain scores. At the pre-intervention session, the subject reported a pain score of 10 on the Faces Scale, an 8 on the VAS, and as "severe" on the verbal pain scale. During the passive BMI protocol sessions, the mean pain scores were 7.1 (Faces), 5.8 (VAS), and rated as "moderate" on the verbal scale. During the active BMI sessions, the mean pain scores were 6.7 (Faces), and 5 (VAS), and again as "moderate" on the verbal scale. These findings consistently demonstrate a reduction in pain levels, implying the potential efficacy of the BMI intervention in alleviating pain.

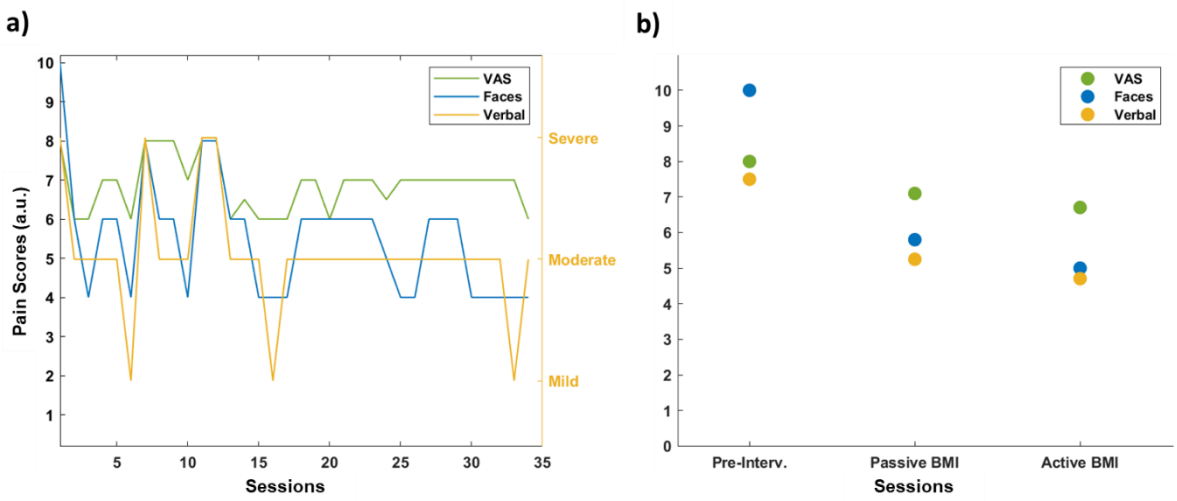

Figure 9- Overview of the pain scores. **(a)** Pain variation measured in the VAS (green), Faces (blue) and the Verbal (orange) pain scales throughout the 34 sessions. **(b)** Mean pain scores in the pre-intervention; the first 10 sessions that employed the passive BMI training protocol and the second set of sessions (17 sessions with available EEG data) that employed the Active BMI protocol.

These results prompt further investigation into whether the observed changes in pain could be associated with EEG activity. For this Spearman's rho correlation coefficients were calculated for the same electrodes and frequency bands as in the previous section, both in acquisition and online periods. To diminish the number of comparisons, we initially computed the correlation between the pain scales (VAS and Faces). Given that we observed significant results (Rho = 0.621; p-value= 8.886e-05), we chose to solely utilize the VAS scale scores, considering its widespread usage in EEG-related studies. Furthermore, to enhance the interpretability of the association between neural

activity and pain fluctuations, we elected to correlate the power values of the specific channels and frequency bands with the variations in the VAS pain scale scores.

All the rho and respective p-values obtained for all the electrodes in all selected bandwidths are listed in **Table A3**. Only two statistically significant correlations were obtained (**Figure 10**). In the acquisition period, electrode O2 showed a statistically strong negative correlation in the beta frequency band (rho= -0,515; adjusted p-value=0.028). However, from the online data, electrode C4 showed a strong positive correlation in the delta bandwidth (rho= 0.733 ; adjusted p-value= 0.026).

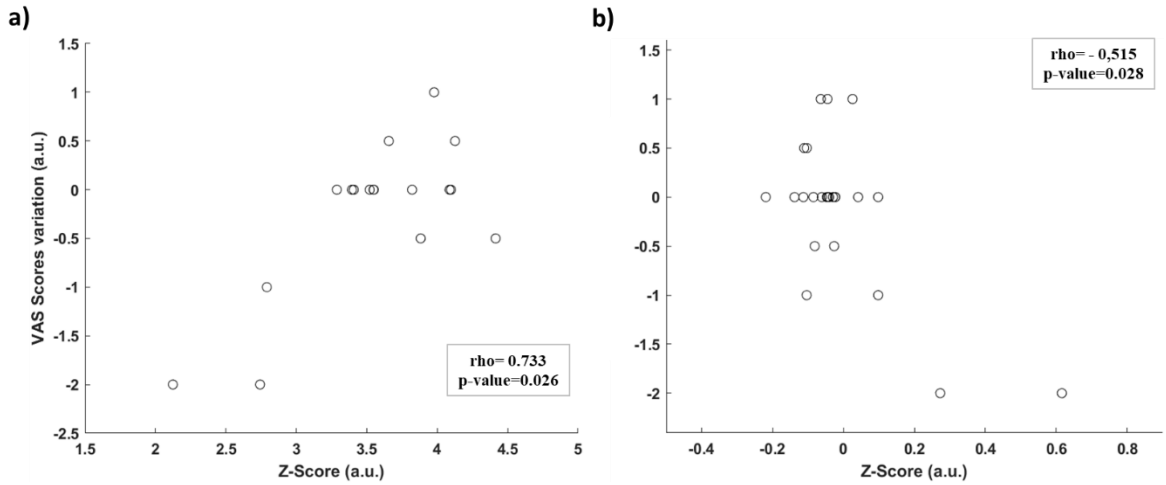

Figure 10- Spearman's rank correlation between the variation of the VAS pain scale scores and **a)** the delta frequency band in electrode C4 from the online data and **b)** the beta frequency band in electrode O2 from acquisition data.

4. Discussion

In the present study, the neural activity and self-reported pain levels of an SCI patient were analyzed during the implementation of a 14-month neurorehabilitation protocol. The analysis revealed a consistent and significant reduction in the patient's reported pain levels, accompanied by observable alterations in the EEG signal. Electrodes C4 and O2 showed plasticity in both delta and theta frequency bands. Additionally, these electrodes were strongly correlated with the variation of pain levels in the delta and beta frequency bands. These results support the notion that the implementation of a neurorehabilitation protocol combining a motor imagery-based BMI with highly immersive virtual reality scenarios resulted in a decrease in pain levels that was maintained throughout the testing period.

BMI periods and neural activity

In this study a distinct pattern of frequency bands was found between the acquisition and online periods of the BMI sessions. As previously mentioned, during the acquisition period, the avatar

moved independently while the subject received visual cues to train specific mental states with the desired actions (e.g., thinking about walking during green cues and thinking about not walking during the red cue). In the online phase, the subject received real-time feedback based on EEG activity to control the avatar's movements.

Neural oscillations in the beta and gamma frequency ranges are closely associated with conscious activities and cognitive functions.[134,135] The observed increase of activity in these frequencies during the acquisition period of the BMI training may reflect heightened cognitive engagement and attention-related processes. On the other hand, delta waves, primarily observed during sleep, have been implicated in the brain's reward systems.[172] The increase of this neural oscillation during the online period may be related to the possible enhancement of motivation/ pleasure because of the real-time feedback, particularly, when accurately performing the task and achieving the desired outcome.

Considering that this data was from an SCI patient suffering from chronic pain, the changes between the two periods might be related to shifts in the processing of sensory information, and emotional states. For instance, from the literature, most EEG signatures associated with chronic pain are increased power in theta frequencies [156,161] and decreased alpha levels [143,155,156,160,163]. This could be indicative that perhaps during the acquisition period, in which the theta activity showed higher values, the subject experienced more pain and on the other hand, during the online phase, where alpha oscillations were higher, the real-time feedback and engagement in the BMI task could have provided a distraction from the experience of chronic pain compared to the acquisition period. However, since the self-reported pain scale scores were only acquired after the intervention further studies would be needed to confirm this hypothesis.

BMI influence on neuroplasticity

The analysis of neural activity focused on four electrode groups that have been frequently implicated and shown alterations in chronic pain conditions.[144–146,156,161,169] These included electrodes in the prefrontal and frontal regions (Fp1, Fp2, F3, and F4), central electrodes (C3 and C4), parietal electrodes (P3 and P4), and electrodes in the occipital regions. Additionally, since the existing literature on SCI-related chronic pain primarily highlights changes in the delta, theta, alpha, and beta frequency bands[143,155–161,163–165,167,168], and aiming to simplify the analysis and reduce the number of comparisons, the gamma frequency band was excluded from the subsequent analysis. When assessing the alterations of neural activity with time in the selected electrodes, electrodes C4 and O2 showed significant alterations in both delta and theta frequency range.

The occipital lobe, responsible for visual processing, has been associated with heightened delta and theta oscillatory activity during cognitive tasks, suggesting its involvement in cognitive processes

beyond vision.[175] In a recent study utilizing a SSVEP-BCI, an increase in delta activity in the occipital region was observed during a mental focus task, contrasting with a 'lost-in-thought' state.[176] Building upon these findings, our results regarding the sustained increase in delta and theta oscillations in electrode O2 may shed light on the active involvement of the occipital cortex in cognitive tasks, emphasizing the significance of these neural oscillations.

Since our BCI training protocol focused on motor imagery, the possible modulation of neural activity associated with the motor cortex was reasonable. The motor cortex plays a crucial role in motor control and recovery processes. Low-frequency brain oscillations (LFOs), such as delta and theta waves, have been suggested to be related with motor recovery in stroke patients. [177,178] Considering the similarity in motor impairment between stroke and SCI, the observed alterations in delta and theta activity may indicate a potential mechanism associated with motor recovery.

These findings suggest that BMI training can potentially induce neuroplastic changes associated with cognitive processes and motor recovery. However, further research is needed to fully understand the underlying mechanisms and validate this interpretation.

BMI influence on Chronic Pain

Studies have provided evidence supporting the potential use of BCIs, including neurofeedback, as a treatment for chronic pain. [147,153,154,162] In line with these findings, our data revealed that the subject self-reported pain levels decreased throughout the intervention period. These results led us to further investigate the potential relation between neural activity and the fluctuation of pain levels, which were found to be negatively correlated in the beta frequency band of electrode O2 and positively in the delta bandwidth of electrode C4.

In the context of chronic pain, it is known that there is an imbalance between inhibitory and excitatory mechanisms, eventually leading to sensitization, i.e., increased responsiveness of neurons to pain signals, resulting in amplified pain perception. [29] One of the suggested mechanisms associated with this is the disruption of GABAergic inhibition, that has been shown to be decreased in the context of chronic pain. Beta waves are mainly produced by inhibitory interneurons, such as the GABAergic interneurons, and are conversely decreased in chronic pain states.[179,180] In this study, no significant alterations were observed regarding this frequency, however, a strong negative correlation was found between the beta wave activity in electrode O2 and the variation of the VAS pain scale. To the best of our knowledge this negative correlation has only been reported in frontal areas[160], or associated with the global power spectrum[165] (i.e., regarding all electrodes).

While there may be contradictory reports in the literature regarding EEG signatures associated with chronic pain, one of the most recurrent ones is the fact that chronic pain patients present an increased

power at lower EEG frequencies compared to patients without pain.[143,159,160,163,166] It is believed that chronic pain is associated with thalamocortical dysrhythmia. This abnormal activity in the thalamus- results in hyperpolarization of thalamic cells causing them to fire at lower frequencies, potentially explaining the association with increased delta oscillations.[159,181] In this study we found a positive correlation between the delta activity in electrode C4 and the variation of the VAS pain scale during the online BMI period, which is in line with the findings reported by Teixeira et. al[146], where the same correlation was found in central brain regions of patients with chronic low back pain. This finding further supports the hypothesis that the increases in delta activity may not have been products of pain but connected to interoceptive attentiveness or reward processes as the levels of pain experienced by our subject reduced throughout the intervention. Nonetheless, since this correlation was obtained regarding the variation of the pain values rather than the actual pain scores, further investigation is needed to confirm the validity of the relationship between the delta oscillations and their relationship with chronic pain.

Limitations and Future Perspectives

This study presents several limitations that should be considered. First, since it was a case study, i.e., with only one subject, and there is inherent variability in neural activity among individuals, the possibility to generalize the results to a larger population is limited. Accordingly, the absence of control subjects, such as healthy individuals or SCI patients with and without pain, limits the ability to compare and draw assertive conclusions about the observed neural activity alterations. Another limitation of this study is the 16-electrode setup, which may lead to spatial under sampling.[123] For this reason, these results should be considered within the associations with the electrode locations rather than the respective underlying cortical regions.

These limitations highlight the need for future studies with larger sample sizes and appropriate control groups to provide a more comprehensive understanding of the relationship between neural activity, BMI interventions, and chronic pain in spinal cord injury.

5. Conclusion

In conclusion, this study provides valuable insights into the neural activity patterns associated with a BMI intervention in an individual with spinal cord injury and chronic pain. The findings indicate potential neuroplastic changes in the delta and theta frequency bands within electrodes recording above the motor cortex and occipital areas that could be related to motor recovery and cognitive processes. Furthermore, significant correlations between the delta and beta powers in electrodes C4

and O2, respectively, and the variation in VAS pain scores were observed. Despite a small number of limitations, this study contributes to the understanding of the complex relationship between the effects of BCI in neural activity and chronic pain in reduction the context of spinal cord injury, highlighting the need for further research in this area.

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Appendix

Table A1- Permutation test results. Observed differences and respective adjusted p-values between the mean values of each electrode and frequency band in acquisition and online period.

Channel	Frequency band	Observed Difference	Effect Size	p-value	Adjusted p-value
Fp1	Delta	-3,299	-9,313	0,001	0,080
	Theta	0,896	3,100	0,001	0,040**
	Alpha	-0,595	-3,897	0,001	0,027**
	Beta	0,090	1,165	0,001	0,002**
	Gamma	0,134	3,129	0,001	0,020**
Fp2	Delta	-3,420	-11,218	0,001	0,016**
	Theta	0,936	4,134	0,001	0,013**
	Alpha	-0,492	-5,264	0,001	0,011**
	Beta	0,091	0,644	0,031	0,042**
	Gamma	0,130	4,236	0,001	0,010**
F3	Delta	-3,403	-12,380	0,001	0,009**
	Theta	0,906	3,880	0,001	0,008**
	Alpha	-0,583	-4,041	0,001	0,007**
	Beta	0,086	1,080	0,003	0,002**
	Gamma	0,139	3,233	0,001	0,007**
Fz	Delta	-3,428	-11,890	0,001	0,006**
	Theta	0,679	2,322	0,001	0,006**
	Alpha	-0,766	-2,953	0,001	0,005**
	Beta	0,088	1,211	0,001	0,003**
	Gamma	0,165	3,192	0,001	0,005**
F4	Delta	-3,108	-5,069	0,001	0,005**
	Theta	0,959	3,961	0,001	0,004**
	Alpha	-0,567	-4,415	0,001	0,004**
	Beta	0,053	0,232	0,740	0,711
	Gamma	0,128	1,885	0,001	0,004**
T3	Delta	-3,308	-9,841	0,001	0,004**
	Theta	0,878	2,198	0,001	0,004**
	Alpha	-0,546	-4,372	0,001	0,003**
	Beta	0,101	2,674	0,001	0,003**
	Gamma	0,129	3,196	0,001	0,003**
C3	Delta	-3,292	-7,526	0,001	0,003**
	Theta	0,914	3,638	0,001	0,003**
	Alpha	-0,595	-2,728	0,001	0,003**
	Beta	0,117	1,642	0,001	0,003**
	Gamma	0,126	2,282	0,001	0,003**
Cz	Delta	-3,339	-9,641	0,001	0,003**
	Theta	0,702	1,797	0,001	0,002**
	Alpha	-0,622	-3,931	0,001	0,002**

	Beta	0,096	1,658	0,001	0,002**
	Gamma	0,147	3,056	0,001	0,002**
C4	Delta	-3,039	-7,383	0,001	0,002**
	Theta	0,792	1,956	0,001	0,002**
	Alpha	-0,851	-1,868	0,001	0,002**
	Beta	0,066	0,753	0,042	0,043**
	Gamma	0,151	2,164	0,001	0,002**
T4	Delta	-3,261	-10,213	0,001	0,002**
	Theta	1,019	4,310	0,001	0,002**
	Alpha	-0,504	-4,125	0,001	0,002**
	Beta	0,073	0,849	0,007	0,011**
	Gamma	0,122	3,874	0,001	0,002**
P3	Delta	-3,269	-8,411	0,001	0,002**
	Theta	0,848	3,652	0,001	0,002**
	Alpha	-0,683	-2,170	0,001	0,002**
	Beta	0,103	1,144	0,001	0,002**
	Gamma	0,138	2,329	0,001	0,002**
Pz	Delta	-3,515	-9,698	0,001	0,002**
	Theta	0,700	2,352	0,001	0,002**
	Alpha	-0,726	-3,053	0,001	0,002**
	Beta	0,093	1,707	0,001	0,002**
	Gamma	0,164	3,719	0,001	0,002**
P4	Delta	-3,201	-7,084	0,001	0,002**
	Theta	0,762	2,070	0,001	0,001**
	Alpha	-0,757	-2,687	0,001	0,001**
	Beta	0,092	0,965	0,005	0,005**
	Gamma	0,148	2,189	0,001	0,001**
O1	Delta	-3,285	-7,251	0,001	0,001**
	Theta	0,450	0,924	0,007	0,011**
	Alpha	-0,790	-2,434	0,001	0,001**
	Beta	0,080	1,106	0,002	0,003**
	Gamma	0,175	3,089	0,001	0,001**
O2	Delta	-3,391	-9,033	0,001	0,001**
	Theta	0,413	0,904	0,012	0,010**
	Alpha	-0,753	-3,040	0,001	0,001**
	Beta	0,092	1,416	0,001	0,001**
	Gamma	0,177	3,180	0,001	0,001**
TP10	Delta	-3,290	-9,299	0,001	0,001**
	Theta	0,899	3,098	0,001	0,001**
	Alpha	-0,592	-3,813	0,001	0,001**
	Beta	0,093	1,179	0,001	0,002**
	Gamma	0,132	3,016	0,001	0,001**

Table A2- P-values and respective adjusted p-values obtained in the permutation test conducted between the initial and final sessions of both acquisition and online periods, and the passive and active BMI protocols. Statistically significant p-values before (*****) and after (******) the adjustment for multiple comparisons.

Channel	Fband	Acquisition				Online	
		Initial vs. Final		Passive vs Active		Initial vs. Final	
		p-value	adj p-value	p-value	adj p-value	p-value	adj p-value
Fp1	Delta	0.205	0.390	0.776	0.862	0.003 *	0.120
	Theta	0.201	0.402	0.643	0.780	0.051	0.255
	Alpha	0.574	0.741	0.795	0.860	0.206	0.457
	Beta	0.961	1.039	0.407	0.678	0.272	0.543
Fp2	Delta	0.067	0.223	0.298	0.567	0.007 *	0.140
	Theta	0.233	0.405	0.411	0.657	0.044 *	0.293
	Alpha	0.777	0.888	0.912	0.912	0.113	0.376
	Beta	0.130	0.273	0.026	0.148	0.161	0.402
F3	Delta	0.046 *	0.167	0.035 *	0.140	0.021 *	0.280
	Theta	0.419	0.620	0.496	0.708	0.093	0.338
	Alpha	0.635	0.770	0.411	0.632	0.362	0.579
	Beta	0.436	0.622	0.283	0.565	0.972	0.972
F4	Delta	0.013 *	0.074	0.026 *	0.130	0.945	0.969
	Theta	0.077	0.205	0.083	0.184	0.372	0.572
	Alpha	0.330	0.527	0.545	0.682	0.228	0.480
	Beta	0.101	0.224	0.016 *	0.160	0.444	0.612
C3	Delta	0.068	0.209	0.071	0.167	0.634	0.746
	Theta	0.370	0.569	0.500	0.666	0.491	0.654
	Alpha	0.696	0.819	0.900	0.947	0.918	0.966
	Beta	0.090	0.225	0.035 *	0.127	0.392	0.559
C4	**Delta**	0.002 *	0.080	0.001 *	**0.040****	0.050	0.285
	Theta	0.002 *	**0.040****	0.004	0.053	0.145	0.386
	Alpha	0.562	0.757	0.742	0.848	0.509	0.637
	Beta	0.848	0.942	0.534	0.690	0.672	0.768
P3	Delta	0.015 *	0.067	0.051	0.127	0.335	0.582
	Theta	0.098	0.230	0.304	0.552	0.086	0.382
	Alpha	0.963	1.014	0.379	0.658	0.858	0.928
	Beta	0.605	0.757	0.261	0.549	0.695	0.773
P4	Delta	0.013 *	0.065	0.003 *	0.060	0.023 *	0.184
	Theta	0.023 *	0.092	0.043 *	0.115	0.359	0.598
	Alpha	0.259	0.431	0.908	0.931	0.134	0.382
	Beta	0.505	0.697	0.711	0.837	0.532	0.645
O1	Delta	0.010 *	0.067	0.031 *	0.138	0.317	0.576
	Theta	0.007 *	0.056	0.035 *	0.117	0.021	0.356
	Alpha	0.983	1.008	0.498	0.686	0.384	0.568
	Beta	0.074	0.211	0.016 *	0.128	0.282	0.537
O2	**Delta**	0.002 *	**0.027****	0.023 *	0.153	0.205	0.482
	Theta	0.003 *	**0.030****	0.041 *	0.117	0.089	0.356

	Alpha	0.986	0.401	0.468	0.693	0.505	0.652
	Beta	0.221	0.986	0.035	0.108	0.118	0.363

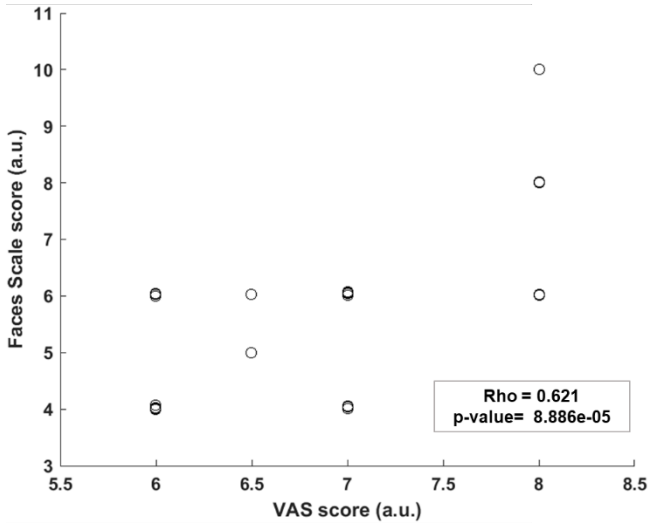

Figure A2- Spearman's rank correlation between the Faces and the VAS Pain Scale. Note that to visualize the presence of multiple data points with similar values, a slight centesimal difference was introduced to one of the variables.

Table A3- Spearman's Rank Correlations Coefficients (Rho) and correspondent p-values between the power values from the electrodes and frequency bands selected and the variation of the VAS scores.

Channel	Fband	Acquisition			Online		
		Rho	p-value	adj p-value	Rho	p-value	adj p-value
Fp1	Delta	-0.164	0.432	0.720	0.335	0.189	0.420
	Theta	-0.095	0.652	0.767	0.301	0.240	0.458
	Alpha	-0.100	0.634	0.793	0.132	0.615	0.683
	Beta	-0.160	0.444	0.710	-0.379	0.133	0.355
Fp2	Delta	-0.071	0.737	0.797	0.457	0.065	0.374
	Theta	-0.136	0.516	0.737	0.296	0.249	0.452
	Alpha	-0.118	0.573	0.790	0.281	0.275	0.440
	Beta	-0.536	0.006 *	0.076	-0.582	0.014 *	0.190
F3	Delta	0.092	0.662	0.797	0.263	0.308	0.474
	Theta	-0.165	0.430	0.748	0.134	0.608	0.532
	Alpha	-0.259	0.212	0.605	-0.225	0.386	0.695
	Beta	-0.396	0.050 *	0.287	-0.394	0.117	0.335
F4	Delta	0.097	0.645	0.782	0.331	0.194	0.408
	Theta	0.253	0.222	0.593	0.434	0.081	0.326
	Alpha	0.262	0.206	0.633	0.086	0.743	0.762
	Beta	-0.448	0.025 *	0.164	-0.566	0.018 *	0.178
C3	Delta	0.220	0.291	0.646	0.081	0.757	0.757
	Theta	0.116	0.582	0.751	0.230	0.375	0.555

	Alpha	-0.144	0.491	0.727	-0.415	0.098	0.301
	Beta	-0.518	0.008	0.079	-0.433	0.082	0.300
C4	**Delta**	0.295	0.152	0.551	0.733	0.001 *	0.032 **
	Theta	0.177	0.396	0.754	0.424	0.090	0.300
	Alpha	-0.060	0.776	0.795	-0.097	0.712	0.749
	Beta	-0.207	0.321	0.643	-0.287	0.264	0.460
P3	Delta	0.076	0.717	0.797	0.340	0.182	0.429
	Theta	0.005	0.980	0.980	0.200	0.442	0.589
	Alpha	-0.288	0.163	0.544	-0.456	0.066	0.328
	Beta	-0.243	0.242	0.606	-0.191	0.462	0.596
P4	Delta	0.333	0.104	0.417	0.665	0.004 *	0.072
	Theta	0.209	0.316	0.665	0.470	0.057	0.380
	Alpha	0.061	0.772	0.812	0.285	0.267	0.445
	Beta	0.150	0.475	0.731	0.350	0.169	0.421
O1	Delta	0.225	0.279	0.658	0.228	0.379	0.541
	Theta	0.174	0.406	0.738	0.158	0.545	0.642
	Alpha	-0.363	0.074	0.372	-0.163	0.531	0.644
	Beta	-0.565	0.003 *	0.065	-0.529	0.029 *	0.233
O2	Delta	0.345	0.091	0.405	-0.123	0.638	0.689
	Theta	0.118	0.574	0.766	-0.180	0.488	0.610
	Alpha	-0.474	0.017 *	0.134	-0.303	0.237	0.474
	Beta	-0.631	0.001 *	0.028 **	-0.456	0.066 *	0.293