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Severity Identification of Chronic Neuropathic Pain based on EEG Analysis

A thesis presented by

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Dedication

To God: my origin, my present and my end. To Saint Joseph, *Redemptoris Custos* of whom I learn to work without taking my eyes away from God. To all those who have believed in me the most: my family, Dr Luz María, Dr David and Michael. To all those who suffer neuropathic pain, specially CRPS. To Jessica, who was the first CRPS warrior I met, and whose gaze filled of suffering and happiness (at the same time) has accompanied me in the same path.

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Abstract

The lack of an integral characterization of chronic neuropathic pain (NP) has led to pharmacotherapy mismanagement and has hindered advances in clinical trials. In this study, we attempted to identify chronic NP by integrating psychometric (based on Brief Inventory of Pain – BIP), and both linear and nonlinear electroencephalographic (EEG) features. For this purpose, 35 chronic NP patients were firstly recruited voluntarily. All of the volunteers filled in the BIP; and additionally, 22 EEG channels positioned in accordance with the 10/20 international system were registered for 10 minutes at resting state: 5 minutes with eyes open and 5 minutes with eyes closed. EEG Signals were sampled at 250Hz within a bandwidth between 0.1 and 100Hz. Secondly, linear and Nonlinear EEG features were extracted from healthy and NP conditions. In addition, a database of an age matched control group of 13 healthy participants was downloaded from the Figbase open access site. As linear features, band power was obtained per clinical band considering five regions: prefrontal, frontal, central, parietal and occipital. As Nonlinear features, approximate entropy (ApEn) was calculated per channel and per clinical frequency band. The control group was used as an EEG feature reference against those in NP condition to explain power and entropy tendencies. Finally, resulting feature vectors in NP condition were grouped in line with the BIP outcome to create BIP-EEG patterns in three groups: (a) low, (b) moderate, and (c) high pain. Resulting BIP-EEG patterns were classified achieving 96% accuracy for all severities, F-score of 95% for high pain, and 94% F-score for moderate and low pain. Despite being cross validated with 5k-fold, this classifier must be tested with new patient data to discard overfitting. Statistical results showed most significant differences in EO condition for ApEn. NP severities were best identified from the control group in the full bandwidth, theta and delta. In particular, high pain was significantly different from control for all bands, except for the alpha band. Taken together, these results indicate that EEG activity of chronic NP patients shows significant differentiable neuroplastic trends with respect to the severity of pain in the spontaneous state for each clinical band. The main contribution of this work is proving ApEn as a method that effectively characterizes the different levels of chronic NP. With further characterization of NP, entropy might be an appropriate and sufficient method to monitor the experience of pain and aid physicians to achieve a better pain management and treatment for chronic NP.

KEYWORDS:

Chronic neuropathic pain; neuronal oscillations; neuroplasticity; diagnostic and evaluation questionnaires; linear and Nonlinear analysis of EEG; classification of EEG features.

ACRONYMS:

APPROXIMATE ENTROPY (APEN)

BRIEF PAIN INVENTORY (BIP)

FULL EEG BANDWIDTH 0.1-100 HZ (BW)

CENTRAL NERVOUS SYSTEM (CNS)

EYES CLOSED STATE (EC)

ELECTRODERMAL ACTIVITY (EDA)

ELECTROENCEPHALOGRAM (EEG)

EYES OPEN STATE (EO)

EVENT RELATED DESYNCHRONIZATION (ERD)

EVENT RELATED SYNCHRONIZATION (ERS)

HEART RATE (HR)

INDIVIDUAL ALPHA FREQUENCY (IAF)

INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN (IASP)

NEUROPATHIC PAIN (NP)

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

PAIN DETECT QUESTIONNAIRE (PDQ)

QUANTITATIVE SENSORY TESTING (QST)

SOMATOSENSORY NERVOUS SYSTEM (SNS)

SUPPORT VECTOR MACHINE (SVM)

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1 Chapter One: Introduction

Pain is a complex experience of somatic mechanisms and psychological influences; hence, it is always subjective. The classification of pain in terms of time has varying definitions, but generally it may be classified as acute (less than 3 months), chronic (more than 3 months)[1] or subacute (between 6 weeks and 3 months)[2]; or in terms of mechanism, as nociceptive, inflammatory, or neuropathic [3]. Living with pain seriously affects all aspects of a person's life, including personal (e.g., emotions, attention, and perception), social, and professional aspects [4]. Chronic pain is commonly multifactorial and frequently involves a neuropathic pain (NP) component [5]. The International Association for the Study of Pain (IASP) defines NP as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system (SNS)" [6]. When NP lasts for a prolonged period (more than 3 months), the neurons in the spinal cord and the brain respond with neuroplastic changes [7]. This maladaptive response may change the perception of pain to the point of feeling unbearable pain due to a simple caress [8]. The maladaptive changes include abnormal threshold to stimuli, altered sensibility in receptors, ectopic generation of action potentials, reduced inhibition, and inappropriate connectivity of neurons. These are the changes that take part in the induction of NP, but there are other mechanisms that develop later to sustain pain [9]. Some pharmacological agents target these sustained pain mechanisms, focusing on preventing or altering neuronal plasticity [10]. Definitely, chronic pain is a challenge for any physician and pain specialist due to the impact on the human body and the struggle to reach an accurate treatment.

In Figure 1, the types of pain are exemplified. Not every chronic pain is NP. For instance, chronic pain from arthritis results from a normal activation of pain pathways by inflammatory mediators surrounding a joint [11]. Likewise, not every NP is chronic. The phantom pain that may be experienced after an amputation is NP and usually lasts between one or two months [9]. Some

patients experience one type of pain predominantly when having several types of pain. For instance, low back pain with a component of NP has a higher and more severe depression, reduction in functionality, and higher values of pain severity when compared to adults with the same pain that is nociceptive or inflammatory [12], [13].

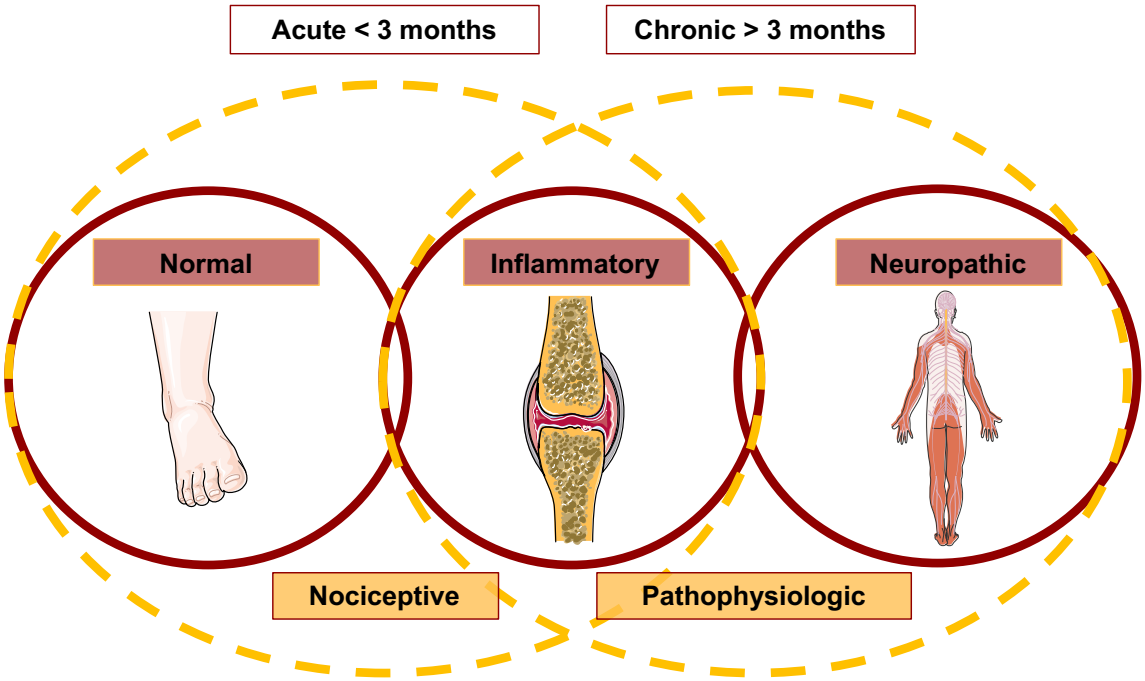


Figure 1 Venn diagram for type of pain and chronicity. Pain from a minor foot sprain would be considered normal and nociceptive because it is signaled by tissue injury (i.e., a normal mechanism). Inflammatory pain from arthritis (center) is an example of a nociceptive mechanism because inflammation is the cause of pain. Inflammation is also pathophysiologic because it involves an altered (i.e., disease) state. NP is at the right, considered only as pathophysiologic because pain is elicited by abnormal pain mechanisms in diseased neurons. Normal pain is only acute, whereas inflammatory or NP may be acute or chronic. Figure adapted from [14].

1.1 Problem Statement

Characterization is a significant gap in chronic NP research and clinical management [15]–[17], because it is based almost exclusively on the subjective perception of the patient. Since there are still no objective measures for chronic NP, the current consensus for an adequate management is based on trial and error [18]. As described by [19], NP is an unsatisfied need with a considerable gap in pharmacotherapy and a great need for a simple clinical tool that may identify and monitor

NP. It is important to address the gaps of characterization to improve the management of treatment and ultimately the life of patients suffering from chronic NP.

Patients with NP have a quality of life similar to patients with severe cardiac disease, severe mental illness [20], or in another study rated as “worse than death” [21]. NP is present in about 7% - 10% of the adult population [22], [23], 17% of chronic pain patients, 35% of oncological patients [16], and 30% of adults that attend pain clinics [24]. NP is also present in the pediatric population with up to 6% of infants suffering from it [25]. In Mexico, chronic pain is considered a public health issue [26]. If chronic pain affects between 25% and 29% of the world population, there could be approximately 28 million people suffering from chronic pain in Mexico alone [23]. However, chronic pain with NP characteristics should be treated as a separate clinical entity in Mexico, and elsewhere, given its specific demographical characteristics [27], [28]. There is still much epidemiological work ahead to know the actual impact of chronic NP in the Mexican population. Yet, a proper epidemiological study of chronic NP has also been impeded by the current inadequate characterization. The fundamental problem of characterization arises because of the pathophysiology of NP, given the variety and complexity of the underlying mechanisms [12]. In most cases, NP cannot be related to specific nerves or cortical areas, because neuroplastic changes occur unrelated to the anatomy of nerves where NP is felt. Consequently, specific symptoms or patterns of NP are almost impossible to identify through verbal reports from the patient. This hinders an adequate characterization of NP and an accurate clinical management at the short and long term [13]. Figure 2 illustrates the optimal characterization method and system for NP that should be moreover integral: incorporating subjective and objective interpretations. There are several widely used methods for the subjective characterization of symptoms [20], [21]. However, there is enough evidence to state that NP is not only an abstract perception but also a physical signal mediated by neurotransmitters and

synapses [10], [29]. Therefore, given that NP is a signal [30], it can be quantified and have an objective interpretation.

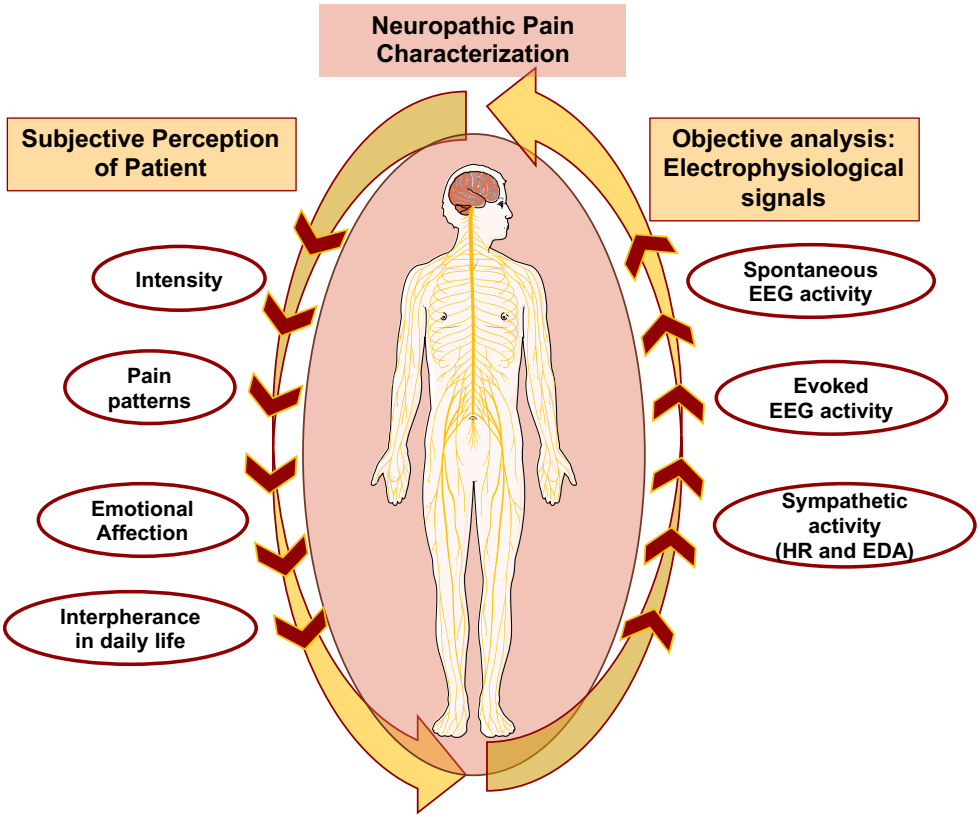


Figure 2 The desirable NP characterization. It should be integral and composed of subjective and objective information. The subjective perception of the patient may describe the intensity, pain patterns, degree of emotional affection, or the interference of daily activities due to pain. Objective information from the CNS may be obtained through electrophysiological signals, divided into spontaneous or evoked recorded with electroencephalogram (EEG); or from the autonomous nervous system, where the sympathetic activity may be measured (heart rate (HR) and electrodermal activity (EDA)).

1.3 Justification: Current gaps in Neuropathic Pain Research

1.3.1 Worldwide pharmacotherapy issues from non-integral characterization

Pharmacotherapy for NP targets specific action sites to achieve analgesic effects for different mechanisms of pain. However, when the mechanisms of pain for a patient are not characterized

appropriately, pharmacotherapy may become inefficient. According to the latest review of the Canadian Pain Society Consensus statement, the pharmacological treatment for NP are gabapentinoids (gabapentin and pregabalin), tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors as first-line agents. Tramadol and opioids are second-line treatments, and cannabinoids have been moved from a fourth-line to a third-line treatment option [31]. Usually a combination therapy is preferred [32] because of greater analgesic activity with mutual reinforcing effects of drugs, and better tolerability profile with reduced symptoms such as anxiety, depression and sleep disturbance [33]. There is some evidence showing that at least 45% of patients with NP are treated with two or more drugs [34], [35]. However, it does not imply that patients with a higher number of analgesics are treated better [36]. In fact, only 40-60% of patients have obtained sufficient pain relief with medications given in combination or alone [37]. Surprisingly, one study stated that the universally used pregabalin and gabapentin are ineffective for most patients with NP [38]. Even when newer trials seem to increase [39], recent pharmacological clinical trials for NP have failed to provide efficacy because of the poor characterization and stratification of NP. In Mexico, Guevara and colleagues [40] interviewed seventy physicians of public and private care from different locations within the country. Figure 3 shows the tendency of treatment for NP in Mexican physicians. Forty of them stated that anticonvulsants were the first line of treatment, twenty-three of them opted for tricyclic antidepressants, and the rest of them opted for either strong or weak opioids. To develop a precise judgement of first-line agents, physicians should update themselves constantly with systematic reviews and the assessment of the individual patient history.

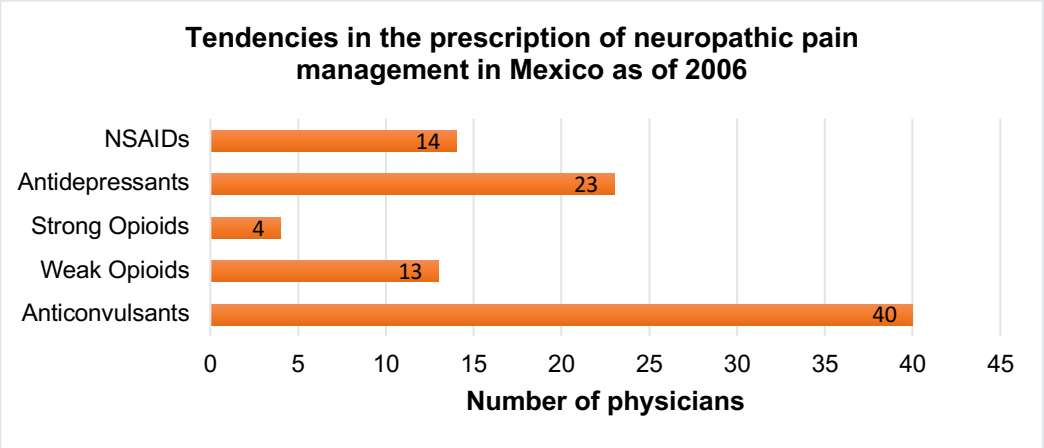


Figure 3 Tendencies in prescription of pain medicine in Mexico. Seventy physicians across the country were interviewed according to their use of first-line agents for treating NP. Anticonvulsants were the first place with 40 answers, followed by antidepressants with 23 answers. Figure adapted from [40]. NSAIDs refers to nonsteroidal anti-inflammatory drugs.

1.3.2 Issues from non-integral characterization by age group

A recent cross-sectional study in Germany revealed the deficits in NP medication for chronic NP patients. From their sample, 57% of patients had NP, but only 18% received adequate pain treatment in terms of dosage or number of pharmacological agents used [36]. Another study concluded that one out of ten geriatric patients had a problem of under- or over-treatment with pain medications [41]. The preceding mismanagement of treatment for NP, in addition to the vulnerability of older adults exposed to polypharmacy for other disorders [42] may increase sedation, impaired balance, and thus, falls [43].

In pediatric patients, NP management and characterization becomes even more challenging because verbalization is difficult [44]. Pain signs and life quality monitoring usually help in the management of pain, but this is not enough to adequately treat a child with NP. Each brain with NP may evolve differently in view of genetic, environmental, emotional, or cognitive factors [45]. Note that, NP is dynamic and this dynamicity may alter white matter structurally. The monitoring

of this particular behavior of NP could be very informative for physicians during the development years of the child. From childhood to adolescence there is a protracted maturation of the prefrontal cortex, an area highly activated in chronic NP [46].

Despite the fact that physicians have a varied pharmacotherapy selection at first, when a patient has gone over several agents for months or even years, the treatment scheme might not be changed due to a lack of understanding of the current NP state of the patient. Improved patient analgesia suitable for all ages could be achieved by obtaining more information about the neuroadaptive alterations that occur in a NP state [47]. Discussion of clinical management with neurostimulation is out of the scope of this study, but is dealt elsewhere [48]. Considering all life stages and syndromes, the best way to adjust treatments could be monitoring the changes in neuronal activity individually and across time.

1.4 Aim of the Work

In the light of the above discussion, subjective perception for the management of chronic NP has been proved to be limited to monitor the pain experience. This is because specific patterns and characteristics of NP will differ across individual experiences. The SNS responds and evolves to NP differently in view of genetic, environmental, emotional or cognitive factors [45]. Therefore, a characterization based almost exclusively on the subjective perception of the patient, given through written or verbal reports is inadequate [17]. Indeed, there is a great need of an objective tool that monitors NP [19]. As a consequence, it seems necessary to take into account both psychometric testing (the patient report) and electrophysiological measurement (neuronal plastic changes of the electrical activity of the nervous system) to characterize NP adequately. Therefore, the aim of the present work was to investigate if the level of NP could be predicted by psychometric (BIP score) and electrophysiological measurements (EEG signals). To our knowledge, only one study [49] has classified NP based on EEG features. In [49], EEG band power in eyes open (EO) and eyes

closed (EC) condition were used as features, and a support vector machine (SVM) as classifier. Their pattern recognition proposal achieved 87-90% classification accuracy. In addition, we hypothesized that adding Nonlinear EEG features in the classifier would increase prediction performance due to the better characterization of neurophysiological mechanism of NP, along with psychometric evaluation. Have in mind that disease identification in clinical applications, should be closer to 100% [49]. This is supported by previous evidence which indicates that approximate entropy (ApEn) can numerically differentiate between simple and complex cognitive states, and between control and neuropathological conditions, including schizophrenia or Alzheimer [50].

1.5 Organization of the Thesis

The thesis is divided as follows. Chapter one gave an introduction to the problem of characterization and NP management, stating the aim of the study. Chapter two exposes the general literature framework of NP with its pathophysiology, mechanisms, electroencephalographic and psychometric measurements. Chapter three introduces the research questions, hypothesis and objectives of this study. Chapter four describes the study design: sample size calculation, stratification, questionnaire election and evaluation. Chapter five defines the characteristics of the NP sample studied, experimental procedure, equipment and the data analysis methods used. Chapter six presents the results of both questionnaires and all EEG features, as well as the statistical results. Chapter seven discusses and integrates all the results with previous literature, stating the principal impacts and contributions of our study. Chapter eight concludes and presents future work.

2 Chapter Two: Framework

2.1 Chronic NP Background

To further discuss the appropriate characterization of chronic NP, its complex pathophysiology needs to be stated thoroughly.

2.1.1 Pathophysiology of NP

NP in most cases, has a spontaneous and an evoked component [51]. Therefore, in any proposed integral system to manage chronic NP, both components should be addressed. The most prominent component in NP is the spontaneous pain. This is independent of stimuli and may be continuous, similar to the pain of a limb in diabetic neuropathy; or otherwise, with intermittent attacks, as in trigeminal neuralgia [13]. The most reported qualities of pain are burning sensation, acute stabbing, shooting, electrical discharges, or oppressive pain. Also, NP can present non painful paresthesia in conjunction with pain sensations [51]. Table 1 states both components with their mechanisms of pain. The two components of NP (spontaneous and evoked pain) are described with their mechanism, type of altered sensation, and the conductor fibers or the location of sensation. Evoked pain in NP may be from noxious (i.e., dangerous) stimuli or from non-noxious stimuli. Non-noxious stimuli are further divided into three types of allodynia.

Table 1 NP components with their neurophysiological mechanism, type of altered sensation, and conduction or location characteristics.

	Mechanism	Type of altered sensation	Conducted by/ Location of sensation
Spontaneous Pain	DNA modification causes an alteration of Ca+ channel refractory time [52]. Ectopic discharges [53] result from an abnormal expression and accumulation of Na+ channels, which then results in decreased threshold of receptors.	Altered sensation to mechanic thermal or innocuous stimuli	Within an area of sensorial alteration in receptors of small peripheral nerve fibers (i.e., skin)
		Nonpainful paresthesia	Reflect the spontaneous activity of thick Aß fibers that mediate the tactile and vibratory sensation. These nerve fibers are less frequently affected in NP [13]
Evoked pain	***From noxious stimuli.*** When cellular damage is a consequence of an underlying disease, decreased pH reduces the threshold in membrane channels. Neurons are always partially or totally depolarized, which causes depolarization with more intensity and for its effect, more pain [5], [54].	Hyperalgesia	Generally, A∂ fibers for stimuli such as pinprick, mechanical and heat/cold. When hyperalgesia is continuous, it is conducted by C fibers [54], [55]
	From non-noxious stimuli. Its origin is more complex and may be caused by: (a) abnormal growth of dendritic sprouts, (b) expanding of receptive field, or (c) intercommunication between nerve endings. Over one type of allodynia could occur in the same patient. Besides, it has been reported that allodynia within a sensible area may be induced by a stimulus in another distant part of the body, as if the pain region was stimulated [56].	Mechanical dynamic allodynia	Pain evoked from a simple touch. Reflects central nociceptive sensitivity. This type of allodynia is very common and is conducted by large peripheral nerve fibers [13], [52]
		Cold allodynia	Provoked by a non-noxious cold stimulus. Conducted by large peripheral nerve fibers
		Movement allodynia	Provoked by an active or passive stretch of muscles or tendons. Conducted by large peripheral nerve fibers

These pain mechanisms are common in different diseases, and their manifestation usually varies among patients, even if the etiology is the same. This is another factor that hinders the NP characterization. For example, a diabetic patient with peripheral NP may have a different evolution and history from a cancer patient with NP. Moreover, a patient with complex regional pain syndrome can have NP in various limbs without a pattern or defined region, in contrast with

trigeminal neuralgia that occurs specifically in the trigeminal territory (i.e., face, including oral cavity) [57], [58]. The same applies in extension and intensity. Two patients with the same etiology (e.g., post-surgical NP) may present different symptoms: one may have stabbing pain in a local point, whereas the other may feel a burning sensation that extends from the thorax to the arm. This diversity supports the proposal for seeking an integral characterization, which should be independent of the etiology, and more focused on the individual neuronal activation from CNS and peripheral nervous system.

2.1.2 Neuroplasticity of the CNS measured by EEG

The function and morphology of the brain are affected by the chronicity of NP symptoms [47]. Neuroplasticity is dynamic and unpredictable, thus neuronal activity may change fast and drastically for a patient, or rather, in a slow and unnoticeable process for another patient. As mentioned previously, a NP patient would need periodic objective evaluations for proper management. The system for measuring NP objectively should also be costly effective so that it may be used in routine clinical practice. There are many methods to test NP, such as hemodynamic (positron-emission tomography (PET)) or functional magnetic resonance imaging (fMRI)), neuroelectric (electroencephalogram (EEG), magnetoencephalogram (MEG)) and neurochemical (union of receptors and modulation of neurotransmitters (MRS)) [59]. These tools have mapped effectively the activated regions of pain, specifically with fMRI [60]–[62] and PET[61], [63]. However, they have a high cost and a more complex methodology for clinical practice. In addition, hemodynamic methods do not measure neuronal activity per se, they measure the dynamics of blood flow. As neuronal activity is electrical by nature, it may be more adequate to monitor NP in terms of electrophysiology.

This following literature review focuses on EEG as it stands out as a valuable noninvasive tool that provides relevant information of the brain function during rest, sensory stimulation or

execution of cognitive tasks [64]. The major advantage of measuring electrical activity with EEG is temporal resolution, and its major drawback is poor spatial resolution. EEG has a much simpler methodology and lower cost. Raw EEG signals are not very helpful in clinical application due to the superposition of wide variety and large number of neuronal sources. EEG signals must be preprocessed and analyzed carefully to be useful in any clinical settings. This may be what is hindering the use of EEG as a monitoring tool, but it may be simplified by using graphical and intuitive interfaces for physicians. Additionally, EEG offers the possibility of analyzing brain signals according to the spontaneous and evoked components of pain (Table 1), which makes it ideal for NP. EEG has been used to evaluate the function of the brain in chronic pain syndromes such as fibromyalgia, migraine, rheumatoid arthritis, neuralgia, chronic pancreatitis and breast cancer [65]–[67]. The main advances in EEG analysis for linear methods and Nonlinear methods are revised in the following section.

2.2 Subjective and Objective Tools for the Assessment of Chronic NP

2.2.1 EEG Measures

For EEG analysis, there are spontaneous and evoked methods. These may be divided into linear and nonlinear measures. Spontaneous measures will be explained through the pathophysiology perspective of neuronal oscillations. Additionally, the evoked method may be phase locked or non-phase locked.

2.2.1.1 What does the EEG measure?

EEG reflects particularly the summation of excitatory and inhibitory postsynaptic potentials at the dendrites of ensembles of neurons with parallel geometric orientation [68]. In order for the neuronal synapses to occur, neurotransmitters activate ion channels in the cell membrane, which lead to ion flow into and out of the cell. This electrical field generated by the flow of ions is too weak coming from a single neuron to be measured from an EEG electrode several centimeters

away. As neuronal activity becomes synchronous across hundreds, thousands, or tens of thousands of neurons, the electrical fields generated by individual neurons sum, and the resulting field becomes powerful enough to be measured from outside the head. It has been estimated that between 10,000 and 50,000 neurons, mainly in superficial cortical layers, dominate the EEG signal [69].

2.2.1.2 Neurobiological Mechanism of Oscillations

An oscillation is a rhythmic alternation of states, which can occur in time or in space. Particularly for the brain, the term oscillation refers to rhythmic fluctuations in the excitability of neurons or ensembles of neurons. Neuronal oscillations are observed on many spatial and temporal scales and have been linked to many neurobiological events ranging from long-term potentiation to conscious perception [70]–[72]. There are many factors that modulate the frequency, amplitude and phase of neuronal oscillations but there is one primary physiological mechanism that produces them. This mechanism involves the interaction between inhibitory (GABAergic) interneurons and excitatory pyramidal cells. The alternating balance of excitation and inhibition is thought to dominate the oscillations of EEG [68].

The main theory that states oscillations as cause for cognition, denotes interregional oscillatory synchronization as the mechanism that underlies the transmission of information across neuronal networks, where synchronization-mediated connectivity is crucial for perceptual and cognitive processes [73]. This means that spatially disparate neuronal networks cooperate and transfer information more efficiently when they are phase synchronized.

2.2.1.3 Linear Analysis – Power and Synchronization

One-dimensional signal analysis is linear and refers to frequency or time-frequency domain [74]. The term “power” indicates the squared length of the complex vector. It is an estimate of the amount of energy at a certain point in time in a particular frequency band. Thus, changes in the

amplitudes of power (increase or decrease) are frequency band specific. The synchronization of local neuronal networks is the most likely neurobiological event that contributes the most to an increase in time-frequency power. For instance, 10,000 neurons oscillating at 8 Hz would lead to *synchronous* field potential oscillations, that would generate a field potential powerful enough to be detected in the alpha band by scalp electrodes [68]. This is may be the reason why power is referred to as synchronization in a usual way. An increase of power may reflect a change in local synchronization strength or a change in the number of neurons that are synchronized.

2.2.1.4 Nonlinear Dynamics and Analysis

The theory of deterministic chaos contrasts with the traditional "Newtonian" physics that focuses on "linear" systems. In linear systems, small perturbations of the system do not grow with time. Although this systems may have nonlinear equations involved, they either have closed-form solutions or some sort of workable linear approximation [75]. Nonlinear dynamical systems that are capable of *self-organization* are open, dissipative, and subject to strong non-equilibrium constraints. Neuronal systems at some levels have been shown to exhibit various nonlinear behaviors [76]. Deterministic chaos theory states that nonlinear systems are governed by few variables that can result in apparently random time series. If the parameters of a nonlinear differential equation are "pushed" beyond a certain threshold value, small perturbations in the measurement of the initial state can result in an exponential deviation of the behavior of the system as a function of time, despite a small initial difference between the states. Consequently, it has been proposed that EEG waveforms are not as a sum of sine waves but a chaotic pattern [76]. Beginning in the mid 1980s, scientists began to apply chaos theory to the human EEG. Since then, chaos has been applied to EEG in two main ways, (1) estimating the dimension of attractors that have been reconstructed from experimental time series by delay-time embedding, and (2) estimating the largest Lyapunov exponent of an experimental time series [50]. The mathematical description of a dynamical system consists of two parts: **the *state*** ("snapshot" of the system at a

given moment) and the ***dynamics***. The "snapshot" of the system is given by the ***state vector***. The vector is of length *n,* where *n* is the number of variables necessary for a complete description of the current status of the system. The ***dynamics*** is the set of rules by which the state of the system evolves over time. State space determines the hypothetical space of *n* dimensions formed by *n variables* of the state vector [77]. Point attractors represent a cessation of dynamical behavior, which in the case of the EEG would be upon death [75].

2.2.2 Linear Measures in Chronic NP: Analysis of Spontaneous Activity

Most EEG studies concerning NP patients [65], [67], [78]–[81] have focused on measuring spontaneous pain by requesting patients to rest either with EO or EC. The analysis of the spectrum of EEG manifests that patients with chronic NP have an increased power at rest in theta, beta, and delta bands [65], [67], [82]. Other studies [66], [67], [83] revealed that the dominant peak in the alpha spectrum power moved to lower frequencies in patients with chronic NP. According to [81], the previous results have been found mainly over frontal and parieto-occipital electrodes that correlate positively with the pain matrix [83]. Nevertheless, [82] argues that the observed changes in EEG power are widespread and correspond to multiple changes in an interconnected network of somatosensory, limbic, and associative structures that receive inputs from multiple nociceptive pathways [78]. This interconnection is illustrated in Figure 4. It highlights the frontal and somatosensory areas of the cortex, as well as the limbic structures observed from the sagittal cut of the brain, particularly the thalamus.

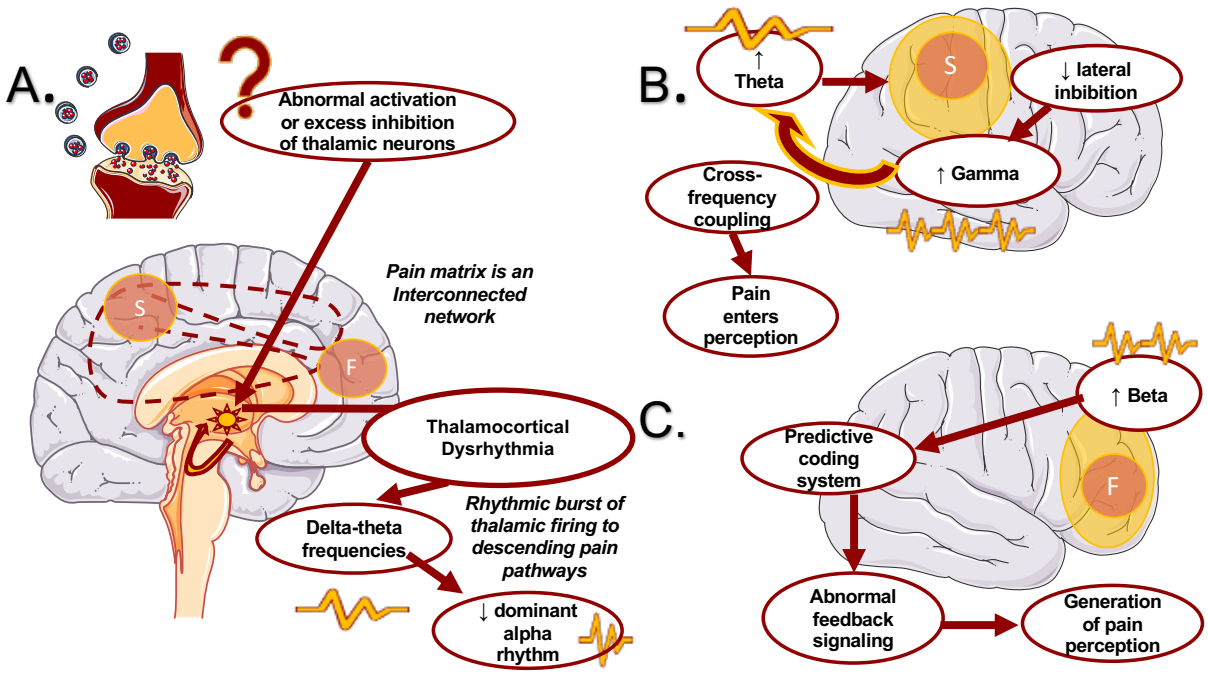


Figure 4 Abnormal oscillatory activity in NP. Changes in electrical activity in the pain matrix and associated structures: somatosensory area (circle "S"), frontal and prefrontal areas (circle "F"), and the limbic structures (star represents the thalamus). (A) The source for the abnormal oscillatory activity is thalamocortical dysrhythmia (TCD). Thalamic firing is an input to descending pain pathways whose input terminates again in the thalamus (loop arrow). The changes in alpha oscillatory activity are depicted in (A) as a consequence of the abnormal oscillatory activity from slow-frequency ranges. (B) The cross-frequency coupling between gamma and theta (*edge effect*) allows pain to enter perception. (C) Increased beta activity predominantly in frontal areas generates perception and is feed forwarded to other brain structures (predictive coding system).

2.2.2.1.1 Theta and delta oscillations

Complementary information of the NP experience may be retrieved from the different frequencies of brain activity. There is evidence showing that EEG spectrum moves towards the theta frequency range [66], [84]. This effect along with the increase in power of theta and delta is caused by thalamocortical dysrhythmia (TCD), a self-sustaining neuropathological mechanism that underpins the constant perception of pain [65], [85]. TCD is also the probable underlying mechanism of another phantom perception: tinnitus [86]. TCD is a consequence from abnormal activation or excess inhibition of thalamic neurons in the process of pain [85], [87]. It is described

as a rhythmic burst of thalamic firing at infra slow frequencies in the ascending pain pathway that inputs the somatosensory thalamus, as depicted in Figure 4A [88]. The change along pain pathways is associated with modified whole-brain network connectivity. Note that the network and oscillatory changes do not occur during an acute painful stimulation in a healthy patient. Therefore, it is believed that only chronic NP may cause network changes that are based in long-term processes, such as astrocyte activation, synaptic modulation, and TCD development [88]. The idea that NP has a central generator was proposed in [89] and further investigated in [90]. The presence of this theta activity provided by thalamic neurons has revealed two electrical components of the pain sensation in central pain patients. The first component localizes the pain experience in the physical body (somatosensory cortex, letter "*S*" in Figure 4A), and the second one relates to the emotional sensation of pain which is non localizable (thalamocortical loops), and described as the moral pain of being hurt that is present in all central pain patients [91].

2.2.2.1.2 Gamma oscillations

The enhanced theta oscillations reduce lateral inhibition and increase abnormal gamma oscillations. Lateral inhibition refers to the low-frequency activation (theta oscillations) of corticocortical inhibitory interneurons, by reducing lateral inhibitory drive (dysinhibition), which can result in high-frequency (gamma oscillations) coherent activation of neighboring cortical modules (shaded in yellow). Figure 4B represents this effect known as the *edge effect* for the somatosensory cortex (letter "*S"*) [87]. It results in a persistent cross-frequency coupling between theta and gamma. This is presumed to be the step where the pain perception enters consciousness through the global workspace [92]. Another study suggests the theta component of TCD reflects traits of the stable pain state of an individual, whereas the gamma component reflects the short term modulation of pain perception [93].

2.2.2.1.3 Beta oscillations

Increases of beta oscillations were observed in frontal brain areas [65], [84], shown in Figure 4C letter "*F"*. Beta is considered to serve as feedback signaling (i.e., the signaling of predictions) which is abnormal in chronic pain [94]. The predictive coding system states the brain is not only a passive receiver, but also a generator and optimizer of resources in which sensations are compared with previous experience. If prediction errors arise, perception may be generated, and feed forwarded. Thus, the predictive coding system poses pain as a result of prediction errors, rather than from nociceptive information [95].

2.2.2.1.4 Alpha oscillations

Alpha oscillations are also affected by dysfunctional thalamocortical mechanisms, which decrease the dominant alpha rhythm [82], [84], but increase alpha power [96], observed in Figure 4A. The role of synchrony at alpha also plays a role in the prediction and contextual coding. High alpha-band activity may relate to particular features of chronic NP [97]. However, the relation between enhanced alpha power and pain it is not yet elucidated [98]. The individual methods and results of the previously mentioned spontaneous EEG studies with chronic NP have been summarized in Table 2.

Table 2. EEG studies concerning spontaneous activity in patients suffering from chronic pain and NP.

Study	Electrodes	Sampling Frequency (Hz)	Number of patients	Results	Limitations	NP or other disorders?
[99]	Different electrode position for each disorder. ***For pain: Fz, Pz and C4***	**1024**	17 in total, of which: (1) 7 had central neurogenic pain, (2) 3 had epilepsy and, (3) 7 had movement disorders	↑ **Power in the theta (4–8 Hz)** Peaks in the theta and beta band (14–30 Hz), indicated phase correlations of oscillatory events	Patients were given anxiolytic Bromazepam 4-5 hours before EEG recording	**Various neurological disorders (NP, epilepsy and movement disorders)**
[84]	**60**	**250**	17 patients with severe forms of neurogenic pain and 15 healthy controls	↑ **Power delta, theta, alpha and beta (2-25 Hz)** in frontal central electrodes, ↓ **mean peak frequency**	9 of 15 patients on central action medication; after surgical procedure, only 7 patients were available for EEG analysis	**NP only**
[78]	**14**	**2048**	16 patients with paraplegia (8 with NP and 8 without pain) and 16 able-bodied controls	↓ **Frequential theta-alpha peak and reduced spectral EEG reactivity** in paraplegic patients with NP	2 of 8 patients on central action medication	**NP and paraplegia patients**
[67]	**60**	**1000**	37 chronic pain patients (of which, 18 had NP and 19 did not) and 37 healthy controls	**Ratings of pain intensity showed strong correlations in EEG power**, psychopathology was related to peak frequency	Results were not significant or positively correlated to previous findings	**Chronic pain with either NP or no NP**
[100]	**19**	**250**	54 patients with spinal cord injury (SCI) (38 with chronic pain, and 16 without) and 28 healthy controls	↑ **theta and ↓ alpha power in SCI with chronic pain, ↑ alpha activity in frontal electrodes associated with more pain severity**	All data recordings were repeated: (1) using only participants with no centrally acting drugs and (2) using only men	**Pain was a consequence of SCI**
[98]	**64**	**2000**	19 patients, 8 with persistent pain and 11 without pain who were treated for breast cancer	↑ **overall alpha amplitude** in pain patients. No significant correlation between pain intensity and the overall alpha amplitude	Small sample size, results of alpha activity may be due to chance	**The persistent pain after breast cancer treatment is considered *at least partly* of peripheral neurogenic origin**

2.2.2.2 Linear Methods: Evoked Activity

In evoked methods, phase-locked activity corresponds to phase-aligned with the time=0 event and will be observed both in time-domain averaging and time-frequency domain averaging. Non-phase-locked activity (also called "induced") is time-locked but not phase-locked to the time=0 event.

2.2.2.2.1 Laser Evoked Potentials (Phase Locked)

Research on the evoked component has mainly used laser to evoke pain sensation [79], [101]–[106]. The laser evoked potentials (LEPs) is one of the first neurophysiological techniques to measure NP [79], [106]. This technique activates selectively nociceptors of A∂ and C fibers of the superficial layers of the skin. There are two components after the sensation perceived from the laser: the first is stabbing or tingling, mediated by A∂ (observed in the EEG before 700 ms); and the second one lasts longer: it is diffuse, burning, and mediated by C fibers (*ultra-late potentials* observed from 750-1200ms). The electrical cortical activity in distinct electrodes (usually centroparietal), is analyzed with the amplitude and latency of LEP components in the milliseconds after the stimulus [81], [107]. LEP components consist primarily of: (1) N1, which is generated in the primary somatosensorial cortex, and in the insular cortex bilaterally, (2) N2 generated in insular networks, and (3) P2 which originates from the anterior cingulate cortex [101]. Two significant findings in LEP components for patients with allodynia are: the reduction of amplitude from LEPs and delayed latency [101], [102], [104]. These two characteristic findings for LEPs in chronic NP are depicted in Figure 5, the activity reflected from the LEPs originates from the lateral pain system and measures the degree of deafferentation that leads to NP [102].

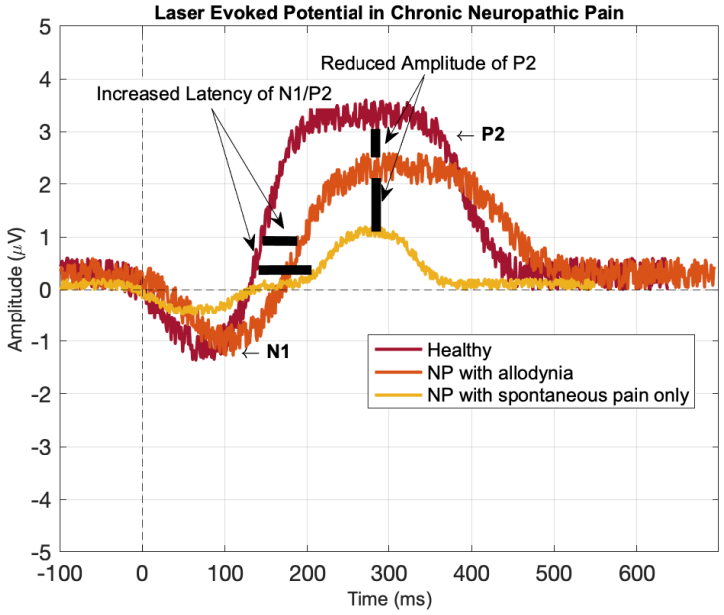


Figure 5. Laser Evoked Potential in chronic NP with allodynia or spontaneous pain in comparison to healthy state. The alteration for components N1 (↑ latency) and P2 (↓ amplitude) in chronic NP in contrast to healthy controls (red line) is illustrated. The highest attenuation is presented for NP with spontaneous pain only (yellow line). The partial LEP preservation in a patient with NP might reflect a high probability of developing provoked pain (allodynia/hyperalgesia, orange line). Image created based on previous literature results, particularly [102].

Actually, the true hyperalgesia and allodynia from NP are never accompanied by increased LEPs. Attenuated responses of LEPs could be a consequence of pain habituation and supports NP pathophysiologic mechanisms. In a more recent study [108], the intensity of pain correlated inversely with the amplitude of the LEPs. Additionally, ultra-late responses (>700 ms) in chronic NP have been reported [102]. This response is supported by the slow-conducting and intermingled network of multiple synapses that input and modulate the signal for NP. In earlier years, LEPs were considered to be the most reliable and sensitive neurophysiological test to diagnose NP, but their availability is limited because few neurological centers are equipped with a laser stimulator [109]. In addition, LEP values have not been used to classify NP activity as either normal nor abnormal, which impedes a proper characterization with values that define sensitivity and specificity for NP [108].

2.2.2.2.2 Somatosensory Evoked Potentials (Phase-Locked)

Other methodologies applied to measure the evoked activity in chronic pain patients are the somatosensory evoked potentials (SEPs) to visual (e.g., images) or tactile stimulation. The evoked potential studies discussed below have been summarized in Table 3 in Annex 1. In [80], the reaction to tactile stimulation while observing pictures (from the International Affective Picture System) was investigated. The resultant components of their study were P50, N80, and P20. Patients were instructed to ignore tactile stimulation, and to pay attention to the images that displayed pleasant and unpleasant situations. Healthy controls displayed an attenuation in P50 amplitude only during unpleasant pictures, whereas chronic pain patients showed an attenuated P50 amplitude in both situations over the primary somatosensory cortex. In sum, this activity may reflect the affective-charged state of an NP patient compared to a control [80], and supports the later abnormal emotional processing that occurs because of NP. Another component that has been studied for SEPs is P300, which is related to an increase of attention due to the assignation of brain resources to the processing of pain [81], [110]. In an earlier study, SEPs were recorded from chronic pain patients (not necessarily NP) to assess whether pain decreased the performance on attention processing capacity [110]. Pain patients had a higher reaction time response, but a higher error rate compared to controls. Task performance for these chronic pain patients implied to be poorly controlled and more impulsive, which provides evidence that pain reduces accuracy in tasks [111]. These results conclude that there is a deficit in the allocation of attention resources, but not on the capacity of resources. In other words, patients are hardly free from directing their attention towards pain [110], [112]. This attentional demand not only exists in the anticipation of pain, but also when pain is continuous (as for most NP patients), and not only to pain stimuli but also to innocuous deviant stimuli. This behavior may be explained by the model of hypervigilance in chronic pain, which makes patients excessively attentive, and more vulnerable to distraction from any somatic sensation [113].

2.2.2.2.3 Induced Activity (Not-Phase Locked)

Induced activity consisting of event related synchronization (ERS) and event related desynchronization (ERD) is used to study the rhythmicity of activity in a particular frequency band to an event. In a recent study [114], ERD and ERS of imaginary movements in healthy controls, paraplegic patients without pain (PNP), and paraplegic patients with NP (PWP) were studied. PWP had the largest and spatially distinctive ERD in comparison to controls and to PNP in theta, alpha, and beta frequency bands. This implies that the neuronal reorganization affecting the SNS in chronic NP, also affects the cortical processing of the motor cortex during the imagination of movements. Figure 6 is an adapted figure from the results of [114] and illustrates the enhanced ERD in PWP for the alpha band. Participants were instructed to imagine hand or lower limb movements using a sequence of visual cues. The cues comprised at t = 1 s, a readiness cue (a cross +) which remained on for 4 s. At t = 0 s an initiation cue, presented as an arrow, was displayed for 1.25 s, pointing to the left, to the right, or down, and corresponded to imagination of the left-hand waving (LH), right-hand waving (RH) and tapping with both feet (F), respectively. Participants were asked to continue to perform imaginary movements until the cross disappeared from the screen (3 s after the initiation cue appeared) [114]. The enhanced activity in PWP demonstrates that NP, even more than paralysis, has a global effect in brain activity which spreads beyond the painful or paralyzed limbs. However, despite the promising results on induced activity for NP patients, the weekly practice of imagining movements of the painful body part, worsens pain [116].

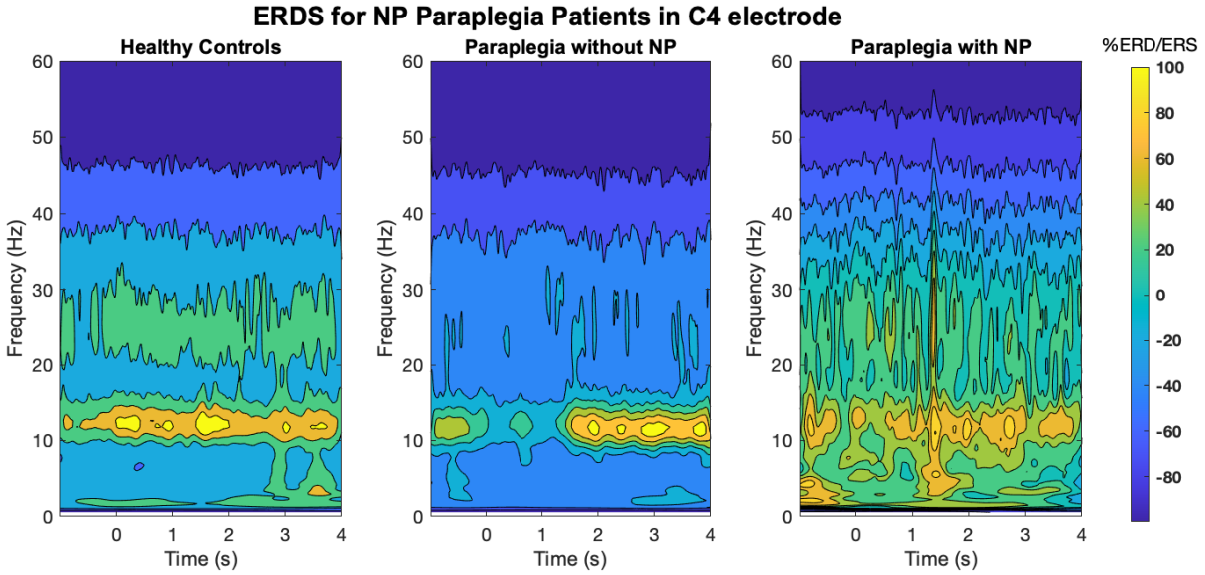


Figure 6. ERD and ERS for NP paraplegia patients in C4 electrode for the alpha band. In t=0s a visual cue appeared, and participants were asked to perform imaginary movements until the cross in the screen disappeared at t=3s. In healthy controls, ERD of the alpha band is at its highest between 1.5-2s. In PNP, there is a clearer ERS in alpha band before the ERD which appears until 1.5 s. PWP had the largest ERD throughout the recording and throughout frequency bands. This image was created simulating the results of [114] with data taken from a Brain-Computer Interface database [115]. Positive values in the color bar represent the percentage of ERD, negative values represent percentage of ERS.

2.2.2.2.4 Other evoked-based methods without EEG

In a more unstandardized way, the tool for stimulating allodynia has been with a brush, and measured with fMRI [62] or with PET [63]. Another fMRI study [60] used a frozen bottle as stimulus. The "*cold rubbing*" did not evoke pain while applied in the normal side of NP patients, but evoked pain when it is applied to the allodynic side and activated regions in the contralateral primary and secondary somatosensory cortex. For evoked-based methodologies, there could be drawbacks either laser or unstandardized brush evoked stimuli. The first method may be evoking pain with a painful sensation; and the second one is using an *"approximate velocity*" (3-4 cm/s) and an "*approximate force*" (100-150 mN) to apply the brush stroke, as authors reported in their work. Hence, force or velocity are not quantified.

2.2.3 Nonlinear EEG Analysis in Chronic NP: Entropy

Chronic pain should be considered a cognitive state that might interfere with other cognitive or emotional states [117]. Recently, the Nonlinear theory of dynamic systems has been applied to EEG to capture the macroscopic spatial and temporal cortical activity [118]. A Nonlinear method is entropy, which quantifies the randomness and regularity of a temporal signal, to estimate the degree of the dynamical changes through time in cortical activity [119], [120]. This method has been used to study physiological and pathophysiological states. A decreased Sample and Spectral entropy has been found in sleep, anesthesia, schizophrenia, Parkinson, and epilepsy [118], [119]. For instance, a convulsion reflects an increase in the regularity of EEG, and consequently, low cortical randomness [121]. Under negative mood states (while observing unpleasant images), chronic pain patients showed a significant increase of Multiscale entropy in the right hemisphere over the left one [80]. There is still no information about brain randomness and the affective modulation of pain processing in chronic NP patients, but entropy could be ideal for exploring these questions given their dynamic nature. Chronic pain patients might be characterized by an abnormal processing of non-painful information when emotional cues are present [80], which supports the hypothesis that negative contextual information could enhance pain feeling [122]. In chronic NP patients, entropy could be a measure of habituation, chronicity, interference with relationships, or emotional impact.

2.2.4 Limitations of EEG to measure Neuroplasticity of the CNS

The principal disadvantage of EEG to measure neuroplastic brain changes is the limited spatial precision at the electrode level due to mixing of projections: (1) from source activities and (2) from volume conduction through the skull/scalp. Besides, EEG cannot measure all neuronal events. In fact, most of the events in the brain are not measurable with the EEG or all other brain-imaging techniques (single-unit recordings, local field potentials, voltammetry, fMRI). No single brain imaging technique can record most of the events in the brain, but different techniques are more

appropriate for measuring certain kinds of brain events [123]. Particularly, because maladaptive plasticity occurs in the neuronal level, and EEG cannot measure the changes happening at this microscopical unit. However, for the brain to perceive NP chronically, a change has occurred at a larger scale and maladaptive plasticity has altered many neurons, which can be measured to some degree with the EEG.

2.2.5 Clinical Applicability of EEG

The clinical applicability of EEG for the management of chronic NP patients is based on the following six key points:

1) It helps diagnose with precision based on objective parameters about the role of CNS in the origin and maintenance of pain mechanisms [83].
2) It proposes a biomarker for the different pain syndromes with anatomical correlations of the electrical cortical activity [59].
3) It promotes the use of brain information as parameters of success or failure in treatment [124].
4) It identifies aspects of maladaptive plasticity: (a) the connections between brain regions, and (b) the changes in oscillations given the abnormal activity in inhibition and excitation of neurons [125].
5) It offers a viable alternative to understand the process of NP in an individualized way with a lower cost compared to other neuroimaging techniques [125].

2.2.5.1 Adjuvants to EEG

In [71], the theory of brain-body coupling is proposed, where the frequency architecture of electrophysiological signals is described and discussed. In Figure 7, an example of its applicability is presented for a person with HR of 70 beats per minute.

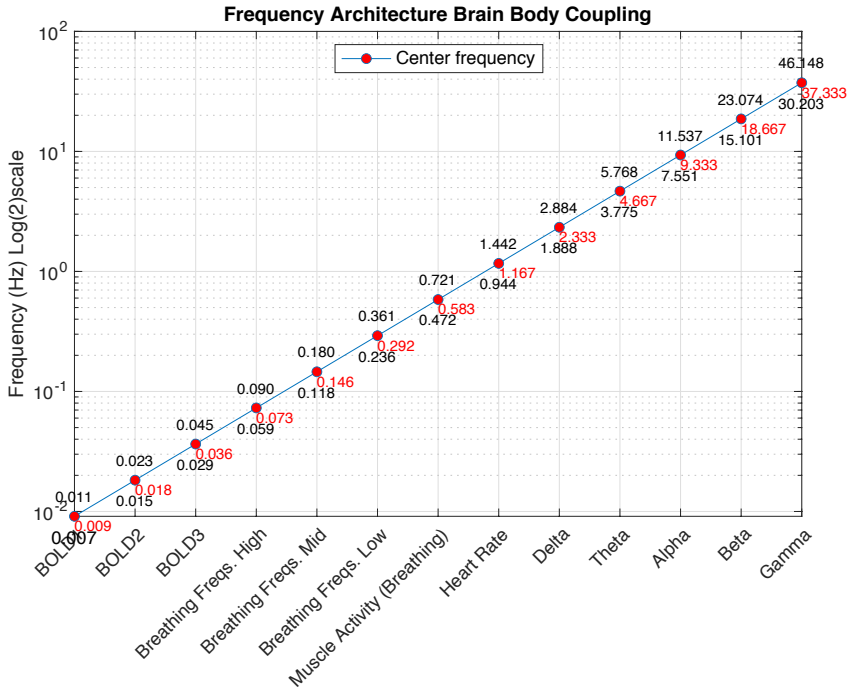


Figure 7. Brain-body coupling theorem postulated in [71] **for a person with 70 beats per minute.** Positive integers determine brain oscillations, whereas negatives ones define breathing, BP, BOLD and gastric waves. Zero refers to cardiac activity at rest.

With the individual HR, the frequency bands of the rest of brain and body oscillations can be obtained. These are: (1) rhythmic fluctuations in the blood oxygen level dependent (BOLD) signal, (2) breathing frequencies, (3) blood pressure waves, (4) gastric waves, and (5) neuronal oscillations: delta, theta, alpha, beta, and gamma. In line with this theorem, recording other electrophysiological signals besides EEG may be of extreme relevance in NP, given that the brain and other body oscillations are a single system [126].

This theorem demonstrates that resonance of a biosignal is harmonized with other ones, and then, the same information to design clinical neuro-technology may be obtained from different sources. For instance,

- During respiration, heart rate (HR) increases at inhalation and decreases at exhalation.

- HR presents a clear tendency 10:1 frequency ratio relative to breathing rate owing to energy demands and emotional regulation.
- Gastric waves explain 8% of alpha band modulation of EEG signals, and 15% of BOLD variance is explained by gastric phase.
- Slow frequency that modulates the envelope of the EMG signal is originated from neural mechanisms of motor control and resonance frequency of body parts.

Regarding characterization of NP, sympathetic nervous system information can be collected from other electrophysiological sources such as HR or electrodermal activity (EDA) (Figure 2). In addition, CNS information may also be retrieved by estimating individual frequency bands of EEG from HR, to avoid analyzing in typical approximations applied in previous studies (see frequency bands in Table 2). In this respect, there is still no literature regarding chronic NP and EDA or HR, however there are few with chronic pain. EDA in chronic pain patients with depression was found to be lower than controls [127]. Pain descriptors and emotional words produced a higher EDA than neutral words in chronic pain patients, suggesting an enhanced effect with emotional load [128]. Regarding HR, its variability was shown to be reduced in chronic pain [129], and it was useful in diagnosing NP after spinal cord injury [130]. We propose that measuring electrophysiological signals in parallel to EEG signals, could offer a complementary perspective. According to the theory [71], different frequency domains are associated with different processing domains regarding cognitive and physiological functions. For a recent systematic review of physiological measures in chronic pain, consult [126].

2.2.6 Psychometric Diagnostic and Assessment Questionnaires

As stated previously, even if an objective assessment of neuropathic pain is available, the subjective perception of the patient is still essential for proper characterization and management. The information that can be retrieved from the patient cannot be obtained from any other source, as for example: the fluctuation of pain, the emotional impact, or the interference of daily activities.

In this section, the primary qualitative subjective questionnaires will be stated as well as a quantitative subjective test.

2.2.6.1 Qualitative subjective

In the challenge to characterize NP, there have been several tools for the detection and evaluation of NP [21], [131]. A diagnostic tool differentiates from an evaluation tool for being highly sensitive and capable to differentiate NP from other types of pain. The evaluation questionnaires help physicians to monitor NP that has been previously diagnosed [20]. These tools are qualitative, because they are based on the subjective perception of the patient about his or her symptoms. In some questionnaires, the presence or absence of physical signs are also taken into account, for example: changes in skin color or skin temperature. The most commonly used diagnostic questionnaires are: 1) The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) 2) Douleur Neuropathique en 4 Questions (DN4) 3) NP Questionnaire (NPQ) 4) ID Pain 5) Pain Detect Questionnaire (PDQ); and one for evaluation, 6) Brief Pain Inventory (BIP). All of them coincide in the questions about symptoms, showing a quality of these, such as: “stabbing, prickling, pins and needles, electrical discharges or shots, burning, pain evoked by a slight caress, or numbing” [12], [20], [132]–[134]. There are some apparent differences among the six questionnaires. They are the following six items:

1) LANSS has 95% specificity for the diagnosis of NP, which makes it the highest of all questionnaires [135].
2) DN4 has higher precision in patients with spinal cord injury [136] and diabetic patients [137].
3) NPQ qualifies affective impact and exacerbating factors such as changes in weather, emotional states, or tiredness [21], [134].

4) ID Pain is the best tool for identifying NP in a wide variety of patients, particularly from primary care. To reduce misdiagnosis, it considers pain limited to articulations and subtracts one point if presenting this type of pain (-1 point) [21].
5) PDQ was created for assisting physicians in the primary care to determine the level of NP in patients with lumbar pain [12]. It is the only questionnaire that considers four fluctuation patterns of pain. Additionally, it considers pain irradiation which adds two points supporting the diagnosis of NP (+2 points).
6) BIP is useful for the evaluation of NP because it highlights the impact of NP in daily life and across different domains. For example, the percentage of relief from treatment, walking, working, personal relationships, or enjoyment of life [138].

2.2.6.2 Quantitative subjective

The only validated quantitative subjective test is the Quantitative Sensory Testing (QST) from the German Research Network for NP. QST measures the small nociceptive nerve fibers that account for approximately 80% of the peripheral nervous system, and cannot be measured with conventional studies such as evoked potentials, electromyograms, or electroneurograms [139]. QST has been used to test treatment efficacy for NP, but it cannot give a definite evidence for NP, because other types of pain (e.g., inflammatory pain) can reflect changes in the QST [101]. It is quantitative because it comprises a series of calibrated stimuli and thresholds (i.e., perception and pain thresholds) for different tests. The instrumentation with the different types of stimuli for QST is shown in Figure 8. During the evaluation, thirteen parameters are assessed to determine, and quantify the function of the somatosensory nervous system. Stimuli are applied by using two methods: (1) method of levels, and (2) method of limits [140]. In the first one, predetermined stimuli are applied repeatedly under, and above the threshold of pain detection. Then, the intensity of the following stimuli is increased or reduced systematically, until the patient identifies it as painful. The patient may then stop the stimulus by pressing a button which involves the time of

reaction [141]. The first drawback of QST is that although it is quantitative, the feedback for pain intensity is based only on the patient opinion. Thus, it is still subjective, as happens with questionnaires. A second drawback is time, since the duration of the QST is approximately 30-90 minutes. Third, there are a vast number of methodologies available for different diseases, which makes it even more complicated to adapt to clinical practice, where time and simplicity are crucial [142]. Fourth, only certified centers may apply QST, and full equipment could be very costly, which limits even more clinical applicability. The final drawback is that mastering QST also requires many hours of study, and training to understand the different techniques to apply them in a clinical setting.

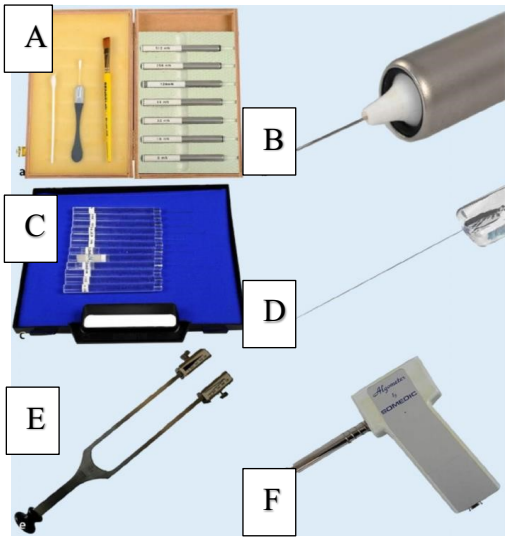


Figure 8 Instrumentation of QST. A) Mechanical testing: set for testing the mechanical pain sensitivity, consisting of: stimulators (pinpricks) of different intensity and a Q-tip, cotton swab and a brush. B) A needle stimulator of the mechanical testing set. C) Von Frey filaments (optic fiber filaments with a rounded tip) to evaluate the mechanical threshold. D) The filaments are fiber optic cables with rounded tips. E) Tuning fork of 64 Hz at a scale of 8/8 (Rydel-Seiffer) to evaluate the vibration detection threshold. F) Digital algometer of pressure to determine the pain threshold to pressure[140].

3 Chapter Three: Research Questions, Hypothesis and Objectives

3.1 Research Questions

For this project, the main research question was the following:

Is it possible to quantify and qualify neuroplastic changes due to chronic NP by means of noninvasive neuroimaging techniques such as electroencephalography based on the outcome of a psychometric measurement?

If so, two other secondary questions were:

1) What are the differences in spontaneous EEG activity among patients with chronic NP at a low, moderate or high pain severity?
2) Is the resulting EEG analysis (with linear and Nonlinear features) sufficient to monitor the patient pain experience, and thus be able to eventually assess the patient's neurophysiological severity of NP?

3.2 Null and Alternative Hypotheses

3.2.1 Null

The null hypothesis was the following:

Even with neuroplastic changes, EEG activity does not show significant differentiable patterns with respect to pain severity since EEG technique, being a noninvasive method, does not reflect the dynamics of the neural networks in the SNS.

3.2.2 Alternative

The alternative hypothesis was the following:

Due to the neuroplastic changes, spontaneous EEG activity will show significant differentiable patterns with respect to the severity of pain, since the cortical electrical activity is a reflection of the dynamics of the neuronal networks in the SNS that are considerably affected with greater severity level of pain.

3.3 General Objective

The general and particular objectives were:

To characterize the neuroplastic changes reflected in electrical activity caused by the degree of alteration of the SNS in patients with different NP severities.

3.4 Particular Objectives

1. To stratify the sample of patients based on the BIP actual pain outcome: low (0-3), moderate (4—6) and high (7-10).

2. To study the neuroplastic tendencies given the degree of effect on the SNS in the different neuronal oscillations, through the analysis of the baseline neuronal electrical activity.

3. To improve the identification of NP severity by including nonlinear EEG features (ApEn) in previous tested pattern recognition proposal based on linear features and classifiers.

4 Chapter Four: Study Design

This study design is **cross-sectional** because it investigates a specific population through a sample (patients with chronic NP) at a specific point in time [143]. All participants had a common variable, in this case chronic NP, and multiple variables that they did or did not share such as pain severity, age, or sex.

4.1 Sample Size

The sample size was calculated in line with Eq (1), with a two-tailed Z normal distribution to evaluate similarity between a control group (null hypothesis) and the NP group (alternate hypothesis). Calculations were performed in MATLAB R2020a (The Mathworks, Inc., Natick, MA, USA) with the Statistics and Machine Learning Toolbox.

$$Power = \phi\left[z_{\propto} + \frac{(\mu_0 - \mu_1) * \sqrt{n}}{\sigma} \right] \quad (1)$$

Note that for Eq (1), the power depends on four factors: $\propto$, $|\mu_0 + \mu_1|$, σ, and *n.* Thus, to compute the power with this formula, an expected value from the control group (μ_0 with its variance σ) and from the NP group (μ_1) is necessary. To solve for *n,* see Eq (2) where 1-ß is the power and $\propto$, is the significance level:

$$n = \frac{\left(z_{1-\propto/2} + z_{1-ß} \right)^2 \sigma^2}{(\mu_0 - \mu_1)^2} \quad (2)$$

The parameter to estimate significant differences between the groups was the individual alpha frequency (IAF) value, an EEG biomarker taken from the analysis of the alpha band and from electrodes O1 and O2. The IAF is modulated by lifestyle, diet, exercise, sex, age, and many other factors. Moreover, it can be affected by neuropathologies such as tinnitus and NP by the mechanism of TCD, as mentioned earlier in the Section 2.2.2.1.4. To approximate the unknown value of the IAF of patients with NP, data from patients with tinnitus was taken from a database of Neuroengineering and Neuroacoustics Research Group of Tecnológico de Monterrey. The extraction of the IAF from the database is exemplified in Figure 9. It has been established that

[86], [90], [144]–[146] neurological mechanisms between tinnitus and NP patients are similar, since both of them are phantom perceptions. IAF for the control group was also calculated from this database. The mean and standard deviation of the IAF were calculated from previous calculated IAFs for each patient. The results were a mean of 10 Hz and standard deviation of 1 Hz from 15 healthy subjects, 7 men and 8 women, with a mean age 38+-10.2. These results support those found in another group for healthy patients from ages 20-80 years reported in [71] and in [147]. On this basis, μ_0 (mean of the null hypothesis) was established as 10 Hz, and the σ at 1 Hz. For patients with tinnitus, the resulting IAF was calculated from 65 patients of tinnitus (40 women and 25 men, mean age 54.92+-11.79) and resulted in 9.5 Hz (μ_1, mean of the alternate hypothesis), which is also supported by the results of another NP study [85].

The power of a test shows how likely it is that a statistically significant difference will be detected based on a finite simple size *n,* if the μ_1 of the IAF in NP subjects differs from the mean of the control group under the null hypothesis (μ_0). If the power is low (less than 80%), then it is unlikely to find a significant difference even if real differences exist between the true mean μ of the group being studied and the null mean μ_0 [148].

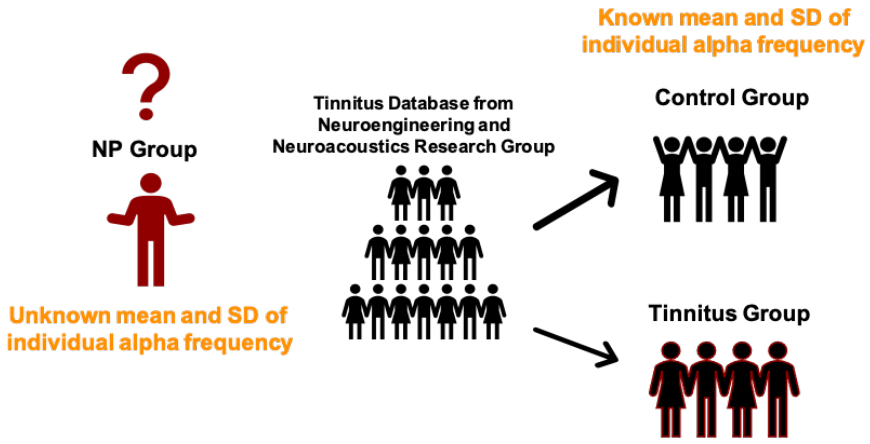


Figure 9. Diagram for the expected value of chronic NP. Since the calculation of sample size requires an expected parameter of a known value for the studied sample, a known parameter from EEG analysis was taken from the database of Tinnitus from the Neuroengineering and Neuroacoustics Research Group. The parameter was the mean and standard deviation of the alpha individual frequency, an individual measure that has been characterized to be altered with the same mechanism as NP.

Therefore, to calculate the sample size for this study, and considering a power between 0.8 and 0.9, the following parameters were applied in the Eq. (1), $\mu_0 = 10$, $\mu_1 = 9.5$, $\propto = 0.05$, $and\ \sigma = 1$. According to Eq (2), for a power of 0.8, ß=0.2 and $\propto$= 0.05, n=32, meaning that 32 NP patients are needed to reach significant differences between NP and a control group. For a power of 0.9, ß=0.1 and $\propto$= 0.05, n=43.

Figure 10 compares the power at different number of patients for the hypothesis parameters specified above. Two red lines in Figure 9 delimit the values between 32 and 43. As long as the number of patients stay within this range, the false positives would be 20% or less. As it can be seen, the higher the number of patients, the greater the power of the study. In conclusion, the objective was to recruit between 32 and 43 patients with chronic NP.

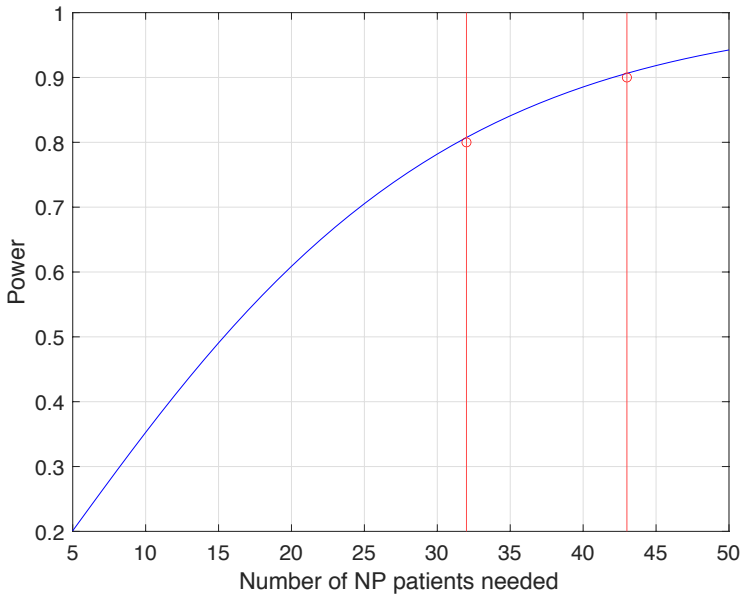


Figure 10 Power vs sample size. The blue line shows the different powers reached with the numbers of patients. The two red lines delimit the power between 0.8 and 0.9 with a significance level of alpha 0.05, which is ideal for a study not to contain too many type II errors (false positives). For the power of 0.8, the number of patients was 32 and for the power of 0.9 the number of patients was 43.

4.2 Questionnaire Election

The Spanish version of the questionnaires used [12], [149] are found in Annex 2 NP Questionnaires: PDQ and BIP. The two questionnaires have an anatomical map, where the patient marks the site with the greatest pain with an X. See Figure 11, image at the right. These two questionnaires are the following:

1) The **PDQ** is a NP **diagnostic tool**. This questionnaire was chosen because it specifies four different patterns of pain fluctuation. These patterns can be important information for subsequent analysis of EEG signals (Figure 11, image at the left). In addition, pain qualities are used with various adjectives that can help the patient respond, for example: burning, tingling, sudden pains, electric shocks or numbness.
2) The **BIP** is a NP **assessment tool**. This second questionnaire was chosen, since the patient reports the impact that NP causes in his or her daily life. For example, the patient

responds the degree of pain relief relative to individual treatment and the effect of pain on work, mood, ability to walk, or relationships.

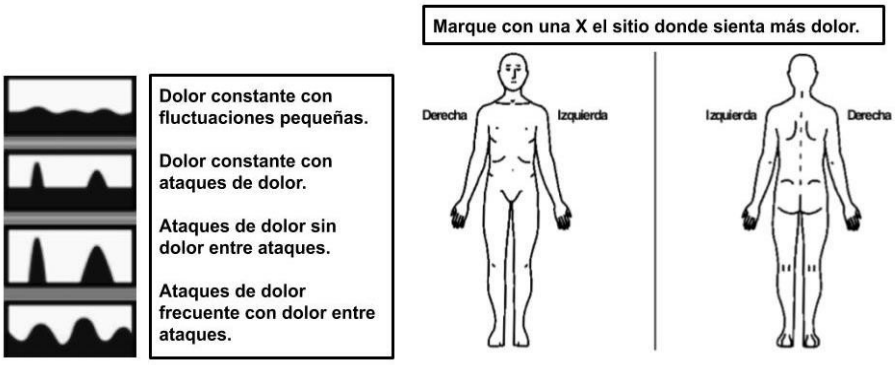


Figure 11 Questionnaire fluctuations and anatomic map. At the left, diagram depicting fluctuation patterns of pain experience (PDQ). At the right, anatomical map to mark the most painful site (BIP).

4.3 Sample Stratification

In a stratified sample, the population is taken and segregated by strata or groups. The principle of stratification is to divide the population so that the individuals of each stratum have greater similarity between them, and the variability between subjects is reduced to increase the power of the study [150]. In this experiment, the proposed stratification for the groups depended on the severity of pain marked in the “actual pain” reported in the BIP, which has a scale from 0 to 10 [138]. In Figure 12, the variable NP is broken down in strata with the number of respective groups. For our study we considered three classes: (a) low pain = 0-3, (b) moderate pain= 4-6, and (c) high pain = 7-10. This division is hypothesized to have an increase intergroup variability while having less intragroup variability. The final groups with their respective sample size are defined in Section 6.1.2. Stratification makes an important difference in terms of the underlying neuroplastic mechanism. Different mechanisms involve different areas of the cortex. This entails a different neuronal dynamic that can be measured in function of the effect of chronic NP in the SNS. For instance, when dividing the sample by severity of pain, changes related to the emotional processing centers like the limbic system, or the frontal cortex were expected.

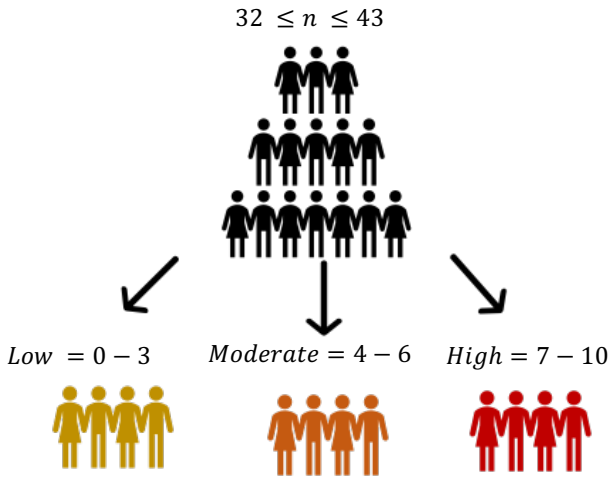


Figure 12 Diagram of stratification of sample. Exemplifies the stratification based on the number of patients for each stratum.

4.4 Questionnaire Evaluation, Outcomes and Scores

In this section, the scores for each questionnaire and their respective evaluation are described.

4.4.1 PDQ

The questionnaire consists of nine items in total, seven of these are questions about the quality of NP symptoms. The questionnaire is completed by the patient and does not require any physical examination. The first five questions are about the severity of pain and have a score of 0 to 5 (0 = never, 1 = very light, 2 = light, 3 = moderate, 4 = intense, 5 = very intense). See Figure 14A. Question 6 is about the pain fluctuation with a score from -1 to 2, depending on the selected pain fluctuation. Question 7 refers to the radiation of pain, with an answer of yes or no, and with a score between 2 and 0 respectively (see Figure 14B). A total score between -1 and 38 can be calculated from the nine items, with a greater probability of having NP with higher scores. A score less than or equal to 12 indicates pain with a modest probability of being NP, greater than or equal to 19 means that there is a 90% probability that NP exists. A value between 12 and 19 indicates that the result is borderline. See Figure 14C.

4.4.2 BIP

Pain measurement in BIP is divided into two categories: severity and interference with function. The severity category consists of four pain items, as previously mentioned in the Section 4.3. The category of functionality is divided into seven items: general activity, mood, ability to walk, normal work, relationships with other people, rest and enjoyment of life. Each item is measured on an 11-point scale from 0 to 10, where 0 is no pain or no interference, and 10 is worst pain or complete interference. See Figure 13, to visualize two questions of each category.

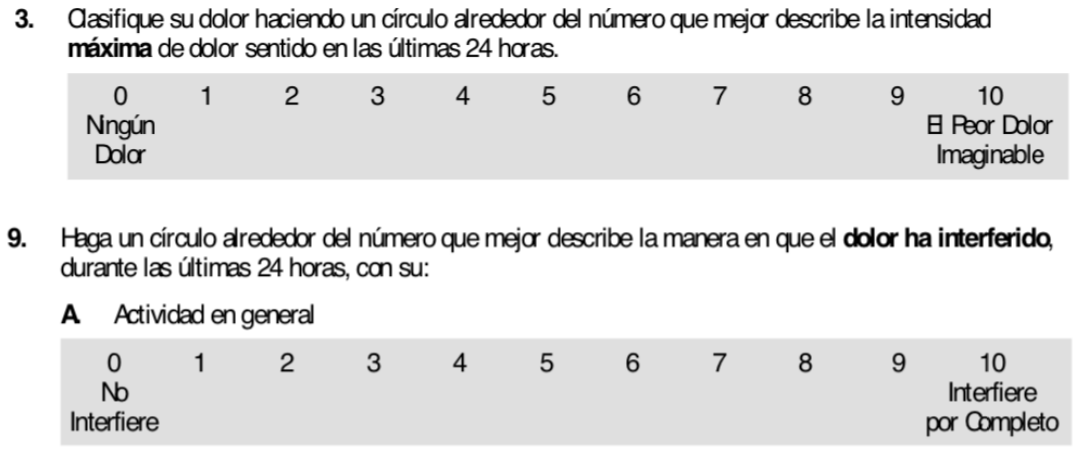
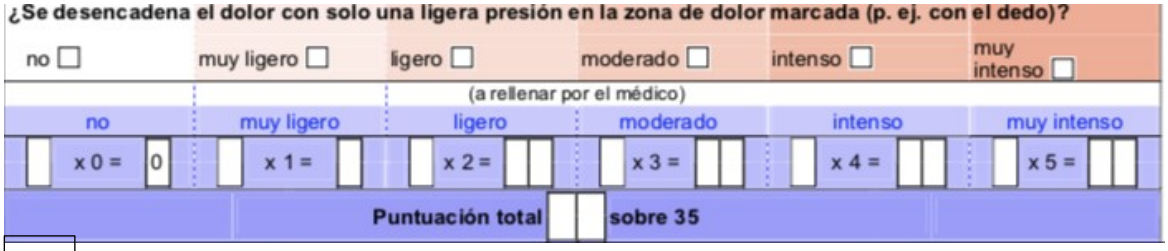
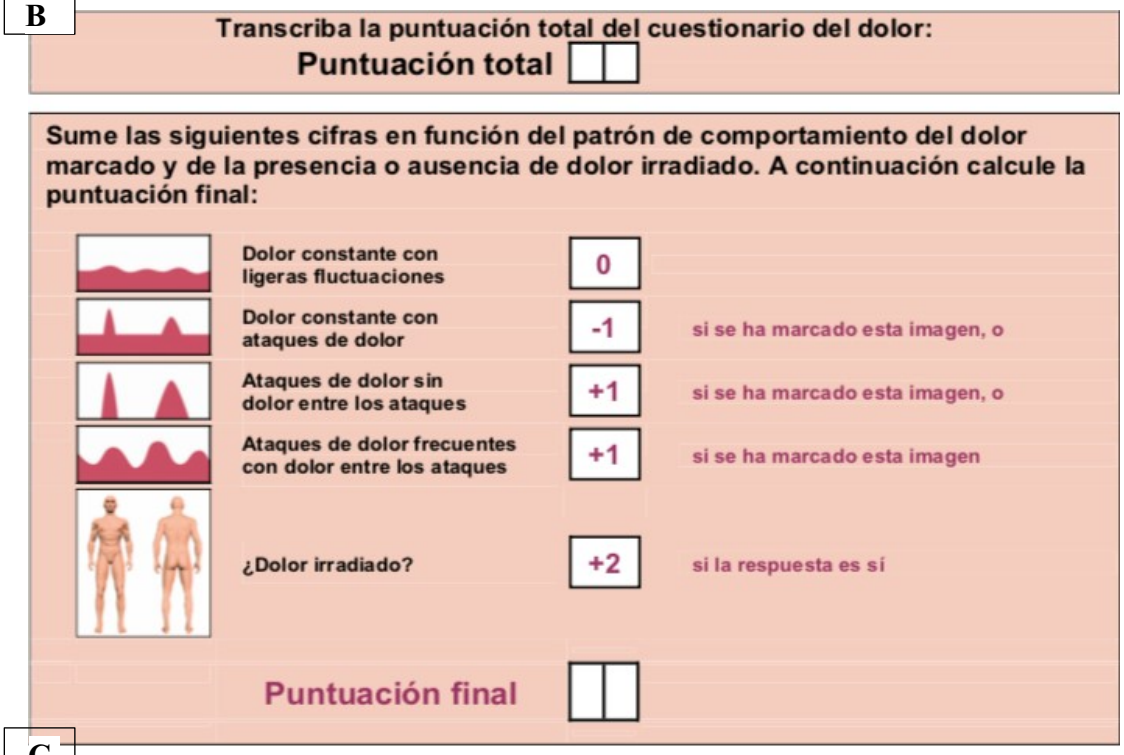


Figure 13 Two questions of BIP. Questions correspond to one of each category in the questionnaire. Both are evaluated from 0 to 10. A) Severity of pain. B) Interference and function.

A



B



C

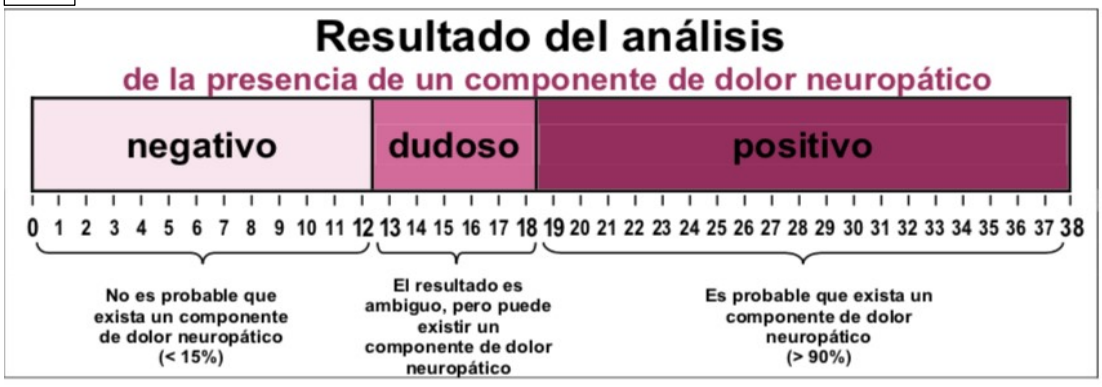


Figure 14 Score of PDQ validated in Spanish. A) The score of the quality of symptoms. B) Depicts the score for the fluctuations of pain and irradiation. C) The result of the total score which if it is >=19 there is a 90% probability to have NP.

4.5 Feature Extraction: Selection of EEG Analysis Methods

4.5.1 Linear Method: Time-frequency based analysis: Absolute Band Power

The linear method selected was absolute band power. Analyzing EEG data as a signal that contains frequency as a prominent dimension provides many opportunities to link EEG data to experimental manipulations, ongoing subject behavior and patient groups [68]. There are three major advantages of using time-frequency based approaches. The first advantage is that results concerning time-frequency-based analyses can be interpreted in terms of neurophysiological mechanisms of neuronal oscillations. Oscillations seem to be a fundamental neuronal mechanism that supports a synaptic, cellular and the overall brain function as a system across multiple spatial and temporal scales [151]. The second advantage is that until now, oscillations are arguably the most promising bridge linking multiple disciplines with neuroscience such as: biophysical computational models, in vitro single-cell recordings, intracranial EEG, scalp EEG and MEG. The third advange is more practical and statistical. EEG data captures a dynamic and multidimensional space with a diverse array of information concerning the brain processing, can be used and analyses from different methods that could answer a variety of questions. Thus, there are many task-relevant dynamics in EEG data that can be retrievable using only time-frequency based approaches [123]. Some limitations of these analysis include: the decrease of temporal precision resulting from time-frequency decomposition (although fMRI temporal precision will almost always be worse), and the wide array of analysis that exist that may lead to suboptimal application of the analysis chosen.

4.5.2 Nonlinear Method: Approximate Entropy

In a brain with NP that has maladaptive plasticity (i.e., a dynamical model), it may be said that several neurons have no pre-defined meaning: they specialize, during the learning phase, in a manner which is often unexpected [152]. The reason is because propagation of activity in

excitatory networks is simple and predictable, it converges toward the same end. In contrast, when an inhibitory interneuron at the beginning of the chain is activated, it suppresses the activity of the target neuron. Consequently, the third interneuron in the chain will be less suppressed by the second interneuron, and the activity of the third neuron may increase. This process is called disinhibition [70]. Thus, networks built from both excitatory and inhibitory elements can self-organize and generate complex properties. In fact, NP may arise from disinhibition and long-term depression of GABAergic interneurons [153]. Interneurons have also been proposed as a gate of pain transmission to higher brain areas [154]. Given the nonlinearity of a brain with NP caused by maladaptive plasticity, it was proposed to calculate the randomness of the system measured with entropy in the EEG. Various entropy algorithms [76] have been developed in the past two decades to explore the nonlinear dynamics of physical systems, for example the Kolmogorov and Renyi entropy have been widely used [155]. Specifically, to characterize chaotic behavior in time series data of the human system, different types of entropy have been applied, such as: approximate entropy (ApEn) [120], sample entropy [156], and multiscale entropy [157].

In this study, ApEn was used as the measure of Nonlinearity for its properties and clinical applications concerning biological signals. The development of ApEn was motivated by data length and noise constraints commonly encountered in heart rate, EEG, and endocrine hormone secretion data sets [158]. Thus, ApEn is relatively unaffected by noise, it is finite for composite, stochastic and noisy deterministic processes [159], and it detects changes in underlying episodic behavior undetected by peak amplitudes[160]. The key of ApEn for clinical utility is the capacity to preserve order even in composite systems, because most biological time series are likely comprised of mixed processes with both stochastic and deterministic components. For these properties, ApEn has been used to understand brain function in brain disorders [161], [162] or in healthy subjects [163], [164], given the complex and dynamical characteristics of cerebral systems. However, it has still not been used for the analysis of chronic NP.

Mathematically, ApEn is part of a general development as the rate of entropy for an approximating Markov chain to a process [165]. Unlike Shannon entropy, that calculates the predictability based on the probability distribution of amplitude values observed in the signal, ApEn is not predicated on the underlying distribution of the data, rather it is based on sequence recurrence. ApEn quantifies the predictability of subsequent amplitude values of data series (e.g., the EEG) based on the knowledge of the previous amplitude values. Accordingly, in a regular time series, the ApEn would be zero. With increasing irregularity, even knowing the previous values, the prediction of the subsequent value would be unachievable and ApEn would increase. The ApEn value of an entirely irregular data series depends on the length of the epoch and on the number of previous values used for the prediction of the subsequent value [166].

4.5.3 Selection of Classifier: Support Vector Machine

There are four fundamental approaches in machine learning: supervised, unsupervised learning, semisupervised, and reinforcement learning. Classification is a supervised learning method, which categorizes input data to output data based on many input-output example pairs during the training phase [167]. In this way, features related to samples from patients with NP can be used to train a decision function that generates labels when encountering new patients. Once the decision function (i.e., the classifier) is created based on the previous features, it can then automatically classify unseen observations using the patterns established in the training. Types of machine learning algorithms that can perform classification are support vector machines (SVMs), decision trees, naïve bayes, and deep learning networks. SVMs have become a widely used tool for classification in brain disorder research, particularly in neuroimaging [167], [168]. The decision function of SVMs is more precisely an optimal “hyperplane” that separates the observations belonging to each class based on the features from those observations. To solve classification problems, SVMs utilize a technique called the “kernel trick” as depicted in Figure 15. By means of this kernel trick, the input data (in a Nonlinear lower dimension space) is

transformed to a higher dimension space where data may be linearly separable. However, there are many cases where data is not linearly separable and other Nonlinear kernel functions may be used. These functions are discussed in Section 5.4.1.4. The hyperplane can then be used to determine the most probable label for unseen data as seen in the right side of Figure 15.

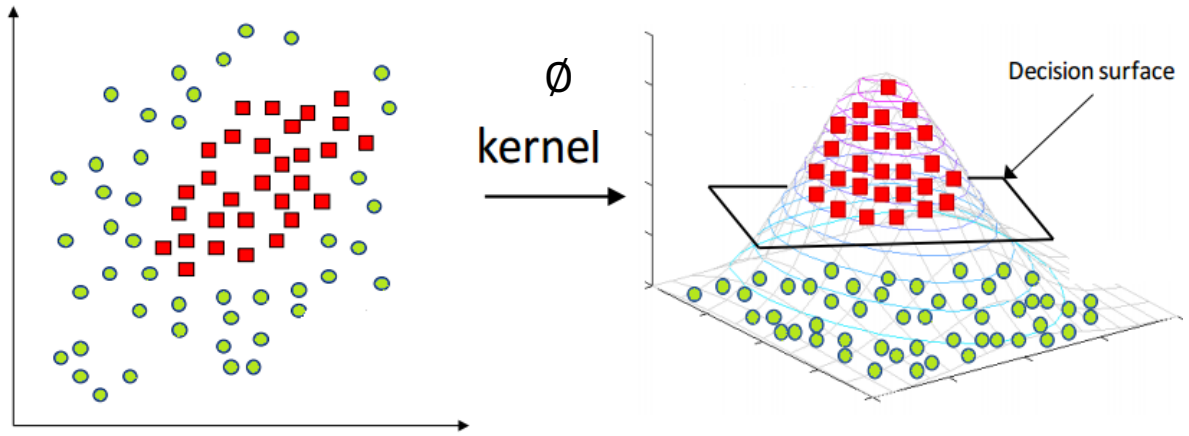


Figure 15 Kernel Trick in SVM. Different SVM algorithms use different types of kernel functions expressed as Ø.

The power of SVMs is the ability to learn data classification patters with balanced accuracy and reproducibility. Thus, while working with SVMs, two complementary aims have to be considered: (1) maximizing the percentage of correct labels (i.e., optimizing its accuracy) and (2) ensuring that the classifier is generalizable to new data (i.e., optimizing its reproducibility). Reproducibility is assured by the degree of information that features reflect of a particular class, whereas accuracy is bound by the number of unique examples used to train the model. The power and popularity of SVMs compared to other classifiers, comes from its ability to achieve high accuracies that are generalizable even when dimensionality of the feature space exceed the number of observations, which is a common occurrence in neuroscience research [167]. Besides offering this balance performance, SVMs offer versatility, referring to the many different kernel functions available. A third advantage is that they are nonparametric, so SVMs do not assume prior knowledge of the distribution of the data. Another advantage is robustness, which guarantees SVMs will perform well in the presence of outliers or extreme data points. Nonetheless, SVM are also susceptible to overfitting precisely to the increased chance of model selection bias [169].

5 Chapter Five: Materials and Methods

5.1 Neuropathic Pain Patients Sample

For this study, 35 chronic NP patients (8 men and 27 women) with a mean age of 44±13.98 were recruited. In order to participate, the patient authorized and signed the informed consent. The place where the EEG recordings were held is described in the informed consent in Annex 3: Informed Consent. Patients were recruited from social media. As a means to sign up and collect the patient's clinical history about their pain they filled a Google Forms. Afterwards, an ID number was given to them with which they answered the PDQ in a second Google Forms (see Figure 16). Since patients were not taken from a specific pain doctor or pain center, only those that passed the total score of PDQ with a minimum of 12 points were included. In this way, all patients that had preliminary signed up, but did not have NP were excluded. Three patients were excluded for having a different type of pain.

Figure 16 Google Forms for the PDQ. This questionnaire was answered to confirm eligibility for the study after the patient had preliminary signed up.

5.1.1 Inclusion Criteria

After an extensive literature review the following inclusion criteria were established under the supervision of pain specialist Dr. Fernando Cantú. The inclusion criteria were the following:

(1) Age above 18 years old

(2) Chronic NP for more than 3 months

(3) Long-term treatment for the last 3 weeks at least

(4) Absence of a major psychiatric disorder (i.e., schizophrenia, major depressive disorder, bipolar disorder)

(5) Absence of a neurological disorder (i.e., epilepsy, tinnitus)

For ethical reasons, patients were allowed to continue with their medication. Some other EEG studies with NP have been undertaken under the same condition. For instance, one study established that patients taking co-analgesic treatment (anticonvulsants and antidepressants) needed to have that specific medication treatment for at least 4 weeks prior to registration [58]. Moreover, the sub chronic dose (25 mg, > 15 days) of amitriptyline (an antidepressant given for NP) has no effect on the P3 component in patients with NP [170]. Finally, no significant differences were found between NP patients with or without central drugs (opiates and antidepressants) in EEG studies at rest condition and analyzing the signals in the bandwidth: 2-18 Hz [84].

5.1.2 Exclusion Criteria

The exclusion criteria were:

(1) Any type of acute or chronic pain other than NP

(2) Recent brain or neurological injury (seizures, tumor or infarct) that may affect the outcome of the EEG

5.1.3 Suspension Criteria

At any time, the patient was free to stop participating in the study. None of the patients that had agreed to be in the study dropped out.

5.1.4 EEG Recordings

EEG recordings were held at a doctor's office (see Annex 3: Informed Consent). The Sanitary Protocol established in Annex 5: Health Guidelines for Medical Units, was based on the health protocol for the safe restart of activities in medical units of the Health Secretariat of Mexico City [171]. This protocol was followed strictly in view of the COVID19 safety measures. Some of these measures can be seen in the Figure 17.

A **B**

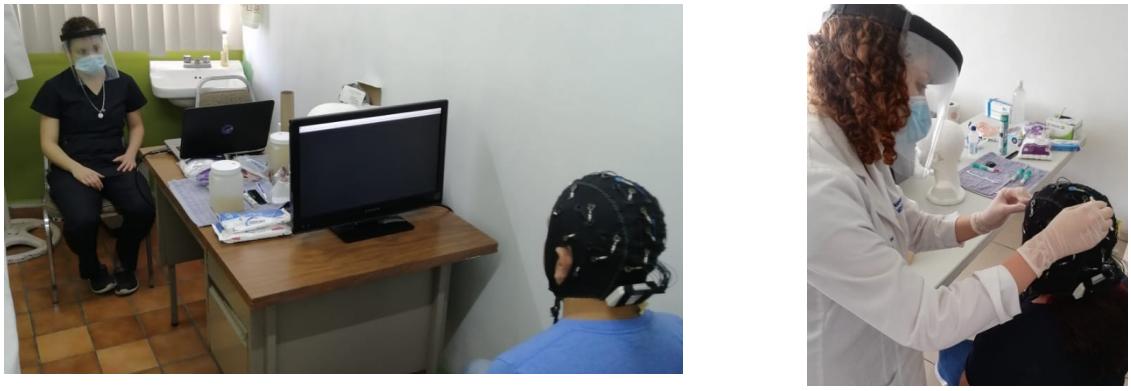


Figure 17 Sanitary safety measures for COVID. (A) shows a patient that is already in the EC segment of the session. (B) The application of the EEG cap was done with latex gloves trying to keep the distance with the maximum effort while wearing mask and face shield at all times.

5.1.5 Clinical History and Demographical Data

The clinical history was taken through a Google Forms when signing up for the study. The clinical history included general demographical questions and information regarding the patient NP condition, including major neurological or psychiatric diseases. The specific questions are listed in Annex 4: Patient profile questions. Some questions were multiple choice, the options are enumerated below the question.

Once patients had filled their profile and clinical history, they had preliminary signed up for the study. The next step was to confirm eligibility by answering the PDQ. Non eligible patients were those who obtained a score less than 12 (in a range between 0 and 38), see exceptions in Section 6.1.1. The questionnaire outcome was confirmed by the clinical history of the patient. In Figure 18A, the frequency of the pharmacological treatment of patients is illustrated. Twelve patients (n=12) were not taking any type of medication, eighteen patients (n=18) were taking centrally acting drugs for over a year, two patients (n=2) were on cannabidiol derivatives (CBD), and three (n=3) took nonsteroidal anti-inflammatory drugs (NSAID) for pain attacks. In Figure 18B, the etiology of the NP patient sample is illustrated. The causes for NP in the studied sample were

spinal cord injury (31%), peripheral neuropathy (23%), diabetes (17%), trigeminal neuralgia (9%), CNS disorder (6%), and other (14%). None of these patients had a severe mental disorder, neurological disorder (beside NP), or had suffered from traumatism, cerebral infarct or CNS tumor.

5.1.6 Informed Consent

Written informed consent for study participation was obtained at the beginning of the EEG session, before the patient answered the BIP (see Annex 3: Informed Consent). All screening evaluations (in this case clinical history and PDQ) had to be completed and reviewed to confirm that patients met all eligibility criteria prior to recruitment. This study was approved by the Clinical Investigation Ethics Committee of TecSalud with the following number: P000369-DN-RespElectro-CI-CR005.

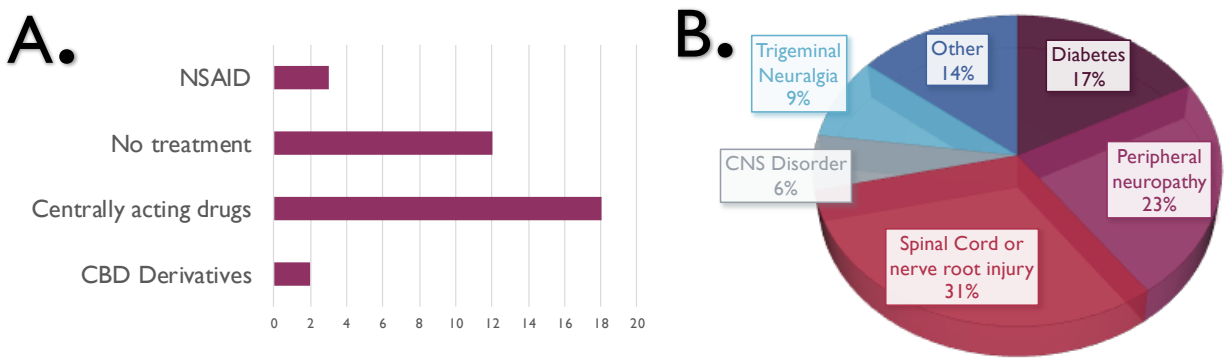


Figure 18 Current drug treatment and etiology of the NP studied sample. (A) Centrally acting drugs refer to anticonvulsants (pregabalin, gabapentin) or tricyclic antidepressants (amitriptyline) that are commonly prescribed for NP. NSAID (Nonsteroidal Anti-Inflammatory Drug, e.g., aspirin, ibuprofen and naproxen) were used by 3 patients, while CBD (Cannabidiol Based Derivatives) were used by 2 patients. The majority of the patients that had no current treatment, had previously been also in centrally acting drugs. (B) The most common etiology in this sample was spinal cord or nerve root injury (31%) followed by peripheral neuropathy (23%). The CNS (Central Nervous System) disorders in the sample were: Lyme disease (n=1) and CRPS (Complex Regional Pain Syndrome) (n=1).

5.1.7 Control group

For the control group, a database was downloaded from open access Figshare site [172]. The database contained 13 healthy individuals (the majority were women, although the precise number was unclear, with a mean age = 38.277 +- 15.64). The healthy control subjects were examined for many psychiatric conditions and were found to be normal.

5.1.8 Control group equipment and recording conditions

Data acquisition hardware included a 19-channel electro-gel cap interfaced with a Brain Master Discovery amplifier. The 19 recording sensors were placed over the scalp (Fp1, F3, C3, P3, O1, F7, T3, T5, Fz, Fp2, F4, C4, P4, O2, F8, T4, T6, T8, Cz and Pz). The amplifier was attached to the computer system through a universal serial bus (usb) port. The EEG cap with 19 sensors covered the whole scalp according to 10–20 electrode placements, which were standard with a link-ear (LE) reference. The sampling frequency was 256 samples per second. EEG recordings were conducted during eyes closed (EC) and eyes open (EO) conditions for 5 min each. During EO, the participants were instructed to sit relaxed with minimum eye movement [173].

5.1.9 Comparison with NP Sample

There are several similarities that validate the comparison between this control database and the chronic NP sample from this study: (1) the number of subjects in the control group (n=13) is comparable to the number of patients in each NP severity group, (2) age and sex are similar, (3) the recording conditions were 5 min EO and EC, (4) sampling rate was 256 Hz while for NP was 250 Hz, and (5) electrode number (19 vs 22) and location (10-20 electrode placement with Cz as reference) were comparable.

5.2 Recording Systems and Equipment of Chronic NP Sample

5.2.1 EEG System

Ten minutes of spontaneous EEG data were recorded using 24 electrodes positioned according to the International 10/20 System (Figure 19C). Figure 19A shows the mBrainTrain cap with 24 Ag/AgCl electrodes (M1 and M2 were used as ground electrodes and Cz as the reference). The amplifier in use was the Smarting mBrain which has a wireless bluethooth v2.1 communication (Figure 19B). The input impedance is 1G Ohms. The input referred noise is less than 1 μV. It has a resolution of 24 bits. The temporal resolution is determined by the sampling rate of the system, which was 250Hz (250 samples per second). The bandwidth was between 0.1-100 Hz, with a flat frequency response of 0-133 Hz. OpenViBe software was used to implement the experimental paradigms and record the EEG signals. Electrode impedances were kept below 5 kΩ. Right and left mastoid electrodes were used as ground electrodes and Cz as the reference electrode.

Figure 19 Laboratory Resources of the Neuroengineering and Neuroacoustics Research Group. (A) MBrainTrain cap with 24 Ag/AgCl electrodes. (B) Smarting device used for communication between electrodes and recording device by means of bluethooth. (C) Topographic map for the 24 channels positioning according to the 10/20 system. Two mastoid electrodes (M1 and M2) were averaged and used as ground, and Cz was the reference electrode.

5.3 Experimental Procedure

5.3.1 Recording Session

Patients sat in an upright position. The first five minutes, they were asked to keep their eyes opened and fixed on a white cross in a dark background of a monitor 50 cm away. At the end of the first 5 minutes, the cross disappeared, and patients closed their eyes for the last 5 minutes until a beep marked the end of the recording. A simplified diagram for the procedure followed for the recording session is depicted in Figure 20.

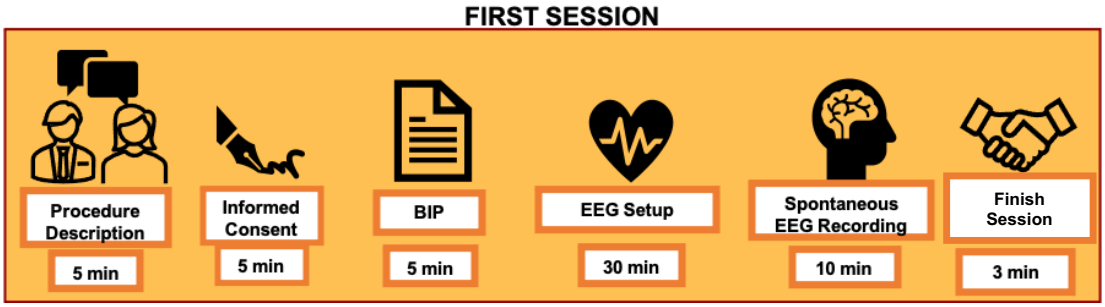


Figure 20 Methodology for the Recording Session. First, the procedure is explained to the patient thoroughly. Second, the informed consent is signed. Third, the BIP is answered. The PDQ that was answered previously is explained again to the patient. Fourth, the EEG cap is installed along with the measurement of heart rate with a pulse oximeter. After everything is set, the spontaneous EEG Recording paradigm starts. Finally, the session ended in approximately 55 min and a monetary contribution was given.

5.4 Data Analysis

5.4.1 Signal Analysis

In this section, the signal analysis methods used for preprocessing, feature extraction and data processing are described thoroughly. Signal preprocessing and processing was performed in MATLAB R2020a (The Mathworks, Inc., Natick, MA, USA).

5.4.1.1 Preprocessing of Raw EEG signals

EEG data contains signal and noise. Appropriate preprocessing is needed to attenuate the noise in the data. Noise pertaining to artifacts might be easier to remove. However, even with preprocessing, some noise might remain because it may be mixed with the signal. It is a trade-off between signal and noise: removing a lot of noise may remove signal as well, and leaving as much signal in the data, means to leave noise as well. In other words, there is tolerance for some noise in order to retain as much signal as possible [174].

5.4.1.2 Preprocessing Methods

EEG raw signals were preprocessed using EEGLAB toolbox (v.19.1.1) for MATLAB (R2020a) software. Signals were firstly filtered by a 6th-order Butterworth high-pass filter with a cut-off frequency at 0.1 Hz to remove very low frequency artifacts. Then, transitory artifacts were rejected using the Artifact Subspace Reconstruction [175]. After that, muscular, ocular, cardiac, line noise, or channel noise artifacts were removed by Independent Component Analysis supported by ICLabel [176].

5.4.1.3 Feature Extraction

To estimate the electrical activity in neuronal frequency bands, a linear and nonlinear method were applied as illustrated in Figure 21. Before feature estimation, EEG signals were divided into one-minute segments. Afterwards, ApEn and absolute band power was estimated per segment as follows. On one hand, ApEn was calculated for the 22 electrodes, and for six frequency bands: delta (0.1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz), gamma (30-100 Hz) and broad bandwidth (Bw) (0.1-100 Hz). On the other hand, absolute band power was calculated for five bands (delta, theta, alpha, beta and gamma), and for the following five regions, averaging the EEG electrodes over each region: prefrontal (AFz, Fp1, Fp2), frontal (F7, F3, Fz, F4, F8), central (T7, T8, C3, C4, Cz, CPz), parietal (P7, P3, Pz, P4, P8), and occipital (POz, O1, O2). As a result, 157 features ([22 electrodes × 6 bands] + [5 regions × 5 bands]) were extracted, yielding 350

observations (35 patients × 10 EEG segments). The dimensionality of the resulting feature vector was 157. Finally, data was normalized in z-score scale with center 0 and a standard deviation of 1.

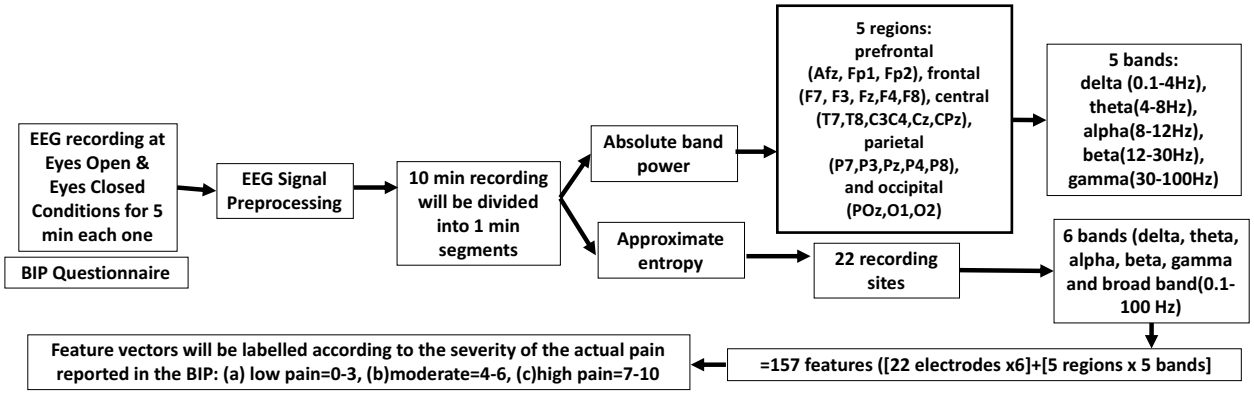


Figure 21 Pipeline of Signal Analysis and Feature Extraction. Resulting feature vectors were 157 features per 350 observations.

5.4.1.3.1 Band filtering

To filter segments into the five clinical bands and the broadband, six filters were designed (for ApEn). For power, only the five clinical bands were used. The filters were 8th-order bandpass Butterworth filters with the lower and higher frequency of each band specified in the previous section. The sampling rate was 256 samples per second.

5.4.1.3.2 Absolute Band Power Estimation

Absolute band power was calculated to estimate the level of neuronal synchrony according to *Eq.* (3), where *n* is each data point of *N* (segment of 60 s x 256 Hz, N=15360) and x is the amplitude value of the filtered signal,

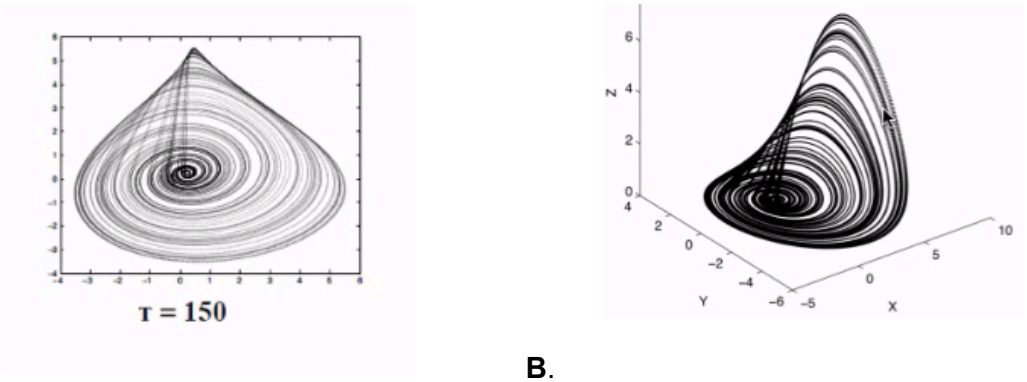
$$y[n] = \frac{1}{N}\sum_{i=1}^{N} x_i^2[n] \quad (3)$$

5.4.1.3.3 Approximate Entropy Estimation

ApEn is estimated from the uniformly sampled time-domain signal by reconstructing the phase space. ApEn measures the likelihood that runs of patterns that are close of m observations remain close on next incremental comparisons. Thus, two input parameters are needed: the pattern length *m* and tolerance factor *r*; *r* is a tuning parameter (a.k.a. similarity criterion) used to identify the meaningful range in which fluctuations in data are similar [163]. For a given system, there usually is significant variation in ApEn over the range of *m* and *r* [177]–[179]. ApEn results in a unitless number varying from 0 to 2, where 2 corresponds to a random time series and 0 to a perfectly regular time series [180]. It is computed as follows: (1) the first sequence of length *m* is compared to all sequences of the same length point by point, the sequences for which all points are within *r* of their corresponding point (in the original sequence) are counted, (2) this is repeated for all sequences of length *m+1,* (3) the natural logarithm of the ratio between the amount of similar sequences for m+1 and the resulting amount from *m* long sequences is calculated, (4) the process is repeated for all sequences, (5) the results of all logarithms are added and normalized for *N,* the total number of data samples and *m* [163]. Thus, the ApEn was calculated as $approxEnt = \phi_m - \phi_{m+1}$ in line with *Eq*. (4) with the Predictive Maintenance Toolbox.

$$\phi_m = (N - m + 1)^{-1} \sum_{i=1}^{N-m+1} \log (N_i) \quad (4)$$

A value of ApEn was computed for each segment and each channel. In order to reconstruct the phase-space, a delayed reconstruction $Y_{1:N}$ for N data points with dimension *m* and lag τ is needed. For the appropriate τ and sufficient dimensions, the embedded dynamics (Figure 22A) are diffeomorphic to the original state-space dynamics (Figure 22B), meaning that they have qualitatively the same topology and have the same dynamical variants (see Figure 22).



A. **B.**

Figure 22 Taken's Theorem. (A) Embedded dynamics and (B) Original space dynamics. The Taken's Theorem states that, whenever reconstructed appropriately, embedded dynamics and original space dynamics are diffeomorphic, because they share the same topology and dynamics. Adapted from [77].

The delay-coordinate embedding is used to "reinflate" the data in a reconstruction space [77]. First, for the uniformly sampled univariate time signal $X_1=(x_{1,1},x_{1,2},...,x_{1,N})^T$, the time series is reconstructed according to *Eq*. (5) [181],

$$X_{1,i}^r = \left(X_{1,i}, X_{2,i}, \dots X_{1,i} + (m_1 - 1,)\tau_1\right), i = 1,2, \dots, N - (m_1 - 1,)\tau_1 \qquad (5)$$

where X is the one-minute segment (60s*256 Hz) and *N* is the length of the time series (600s*256Hz), τ_1 is the lag, and m_1 is the embedding dimension for X_1. It can be demonstrated, based on the Whitney embedding theorem, that a reconstruction of the full state vector at each data point can be done by delay-time embedding each point in a higher dimensional space (Figure 22). The delay for the phase space reconstruction is estimated using Average Mutual Information (AMI). For reconstruction, the time delay is set to the first local minimum of AMI. AMI is computed as (6) [181],

$$AMI(T) = \sum_{i=1}^{n} p(x_i, x_{i+T}) log_2 \left[\frac{p(x_i,x_{i+T})}{p(x_i)p(x_{i+T})}\right] \qquad (6)$$

where, N=15360, the length of the time series and *T*=1: MaxLag. If lag is too small, then the state vectors would be reconstructed from lagging on data points that are nearly identical [75]. This

would lead, to a diagonal line as the entire reconstructed attractor in the m-dimensional embedding space [182].

The embedding dimension was estimated using the False Nearest Neighbor (FNN) algorithm [183]. For a point *i* at dimension *d,* the points X_i^r and its nearest point $\mathrm{X}^{r*}{}_i$ in the reconstructed phase space $\{\mathrm{X}^{r*}{}_i\}, i = 1{:}N$, are false neighbors if (7)

$$\frac{\sqrt{R_i^2(\mathrm{d}+1) - R_i^2(\mathrm{d})}}{R_i^2(\mathrm{d})} > DistanceThreshold \tag{7}$$

where, $R_i^2(\mathrm{d}) = \| \mathrm{X}_i^r - \mathrm{X}_i^{r*} \|^2$ is the distance metric. When results were computed, dimension was *m=3* for the control group, as well as NP patients in EO and EC. The lag was calculated for each subject and condition. Previous references held that EO has an increased dimension than EC, but it wasn't the case in this study [75]. Additionally, previous theoretical studies indicate that filtering a time series prior to estimating its dimension increases the dimension estimate because it increases the randomness of system dynamics [184]. Furthermore, if the dimension is increased beyond the minimally required value it has the effect of emphasizing the noise contamination in the EEG signal dynamics [185]. For actual EEG data, it would appear that the longer the data length, the higher the estimated dimension [75]. It can be demonstrated that the optimal number of previous values used for the prediction of the subsequent value (m) depends on the number of data points N (in our case 60s x 256Hz, N=15360 for each segment). According to [186], the number of data points should range between 10^m and 30^m. Nonetheless, the value for (m) is typically chosen as m=2 or m=3 , which are in accordance with the theoretical implications of [177]. The number of within range points at point *i* was calculated by *Eq.* (8),

$$N_i = \sum_{i=1, i \neq k}^{N} 1(\| Y_i - Y_k \|_\infty < R) \tag{8}$$

where one was the indicator function, and R was the radius of similarity (*r,* the similarity criterion); *r* was calculated as 0.2*variance(X), where X is a 60 s segment of a specific channel and subject in either EC or EO (60s x 256 Hz, N= 15360). These values have been demonstrated to produce

good statistical reproducibility for time series of length N > 60 [120]. To normalize *r* with this approach gives ApEn a scale invariance, so it remains unchanged under uniform process magnification, reduction, or constant shift to higher or lower values [159].

5.4.1.4 Classification

As classifier, a support vector machine (SVM) with a quadratic kernel function was selected as it had the best performance compared to the linear, cubic, and gaussian kernels tested. In most machine learning methods including SVM, there are three essential stages to SVM analysis: (i) feature selection, (ii) training and testing the classifier, and (iii) performance evaluation.

5.4.1.4.1 Stage 1: Feature Selection

Only the feature vector of the NP group was used for the classifier. The control data was not used. The feature vectors were labelled according to the severity level of the actual pain reported in the BIP. Three classes were considered: (a) low pain = 0 – 3, (b) moderate pain = 4 – 6, and (c) high pain = 7 – 10. The feature vector that served as an input for the SVM was the data resulting from the linear and nonlinear analysis, depicted in Figure 21. Scaling is important in the algorithm of SVM because the distance between the data points is used to calculate a hyperplane to spatially separate training data of different classes [187]. For this reason, the vector was normalized in z-score scale as previously mentioned. The number of features for power was reduced in the preprocessing stage by averaging the electrodes across regions based on the relevance that certain brain regions have on the mechanisms of neuronal oscillations (Section 2.2.2). Also, feature selection was incorporated in the classifier itself during the training phase. This type of feature selection is called embedded method and it is applied when using the kernel functions. Instead of relying on the feature vector directly, kernel functions allow to train the SVM using a Gram matrix (i.e., *kernel* matrix) which has the value $k(x_n, x_m)$, on *(n, m)* element, where $\{x_n\ x_m\}(k = 1, \ldots . N)$ is training inputs (Gram matrix is symmetric and should be positive

semidefinite) [188]. This matrix maps the raw data to a higher dimensional feature space. The following were the kernel functions tested in this study:

- Gaussian kernel *Eq. (9)*, is a general-purpose kernel, used when there is no prior knowledge about the data, it is known that $\exp(k(x_n, x_m))$ is a valid kernel function, if $k(x_n, x_m)$ is a kernel function. This kernel has infinite dimensionality.

$$k(x_n, x_m) = \exp\left(\frac{\|x_n - x_m\|^2}{2\sigma^2}\right) \quad (9)$$

- Polynomial kernel *Eq. (10),* for the linear kernel $d = 1$, for cubic $d = 3$ and for quadratic $d = 4$.

$$(x_n, x_m) = (x_i \cdot x_j + 1)^d \quad (10)$$

5.4.1.4.2 Stage 2: Training and Testing the Classifier

Features are furthered referenced by coordinates based on their relationships to each other and form the "support vectors" [167]. Regardless of the SVM's level of dimensionality (number of features), classification is often linear (the hyperplane is straight and not curved). The SVM aims to maximise the distances between input data points belonging to the different NP severities, which are closest to the hyperplane, and are called support vectors. Thus, the aim of SVMs is to minimise the classification error while maximising hyperplane margins. This may create Nonlinear barriers between the classes, which is the basis for the suitability of SVMs in Nonlinearly separable datasets. To classify the three classes, one versus one was used as multiclass method. The one versus one approach uses a hyperplane to separate between every two classes, which breaks down the multiclass problem to multiple binary classifications. Permitting misclassification can be achieved using what's referred to as a soft margin, which relies on the use of slack variables represented by ε [167]. The average error across all of the five partitions was reported as ε (errors caused by allowing the classifier to misclassify, or having a soft margin). A penalty factor C, called the "soft-margin constant," is also introduced with the soft-margin approach to incur a penalty on

slack variables. This parameter serves to control the trade-off between hyperplane complexity and training errors (i.e., regularization).

5.4.1.4.3 Stage 3: Evaluating SVM performance

To validate the performance of model, a cross-validation 5-Fold was chosen (k = 5). Datasets were split into five randomly chosen folds of roughly equal size. One subset was used to validate the model trained, using the remaining subsets. This process was repeated five times such that each subset was used exactly once for validation.

For each class, accuracy, sensitivity, specificity, precision and F-score were calculated. Accuracy *Eq.* (11) refers to the number of correctly classified data observations, for instance those correctly labeled as high pain and those correctly labeled as not high pain. Sensitivity *Eq.* (12) measures the proportion of positives that are correctly identified, for example those patients with high pain were identified correctly as high pain. Specificity *Eq.* (13) refers to the proportion of negatives that are correctly identified, meaning that those that had moderate or low pain were not identified as high pain. Precision *Eq*. (14) is the positive predictive value in classifying data points. F1 Score *Eq.* (15) is a metric that measures how precise and robust (i.e., does not miss any significant number of observations) the classifier is. In the following equations, *TF= true positives, FP= false positives*, *TN=true negatives,* and *FN=false negatives.*

$$Accuracy = \frac{TP+TN}{TP+FP+FN+TN} \quad (11)$$

$$Sensitivity = \frac{TP}{TP+FN} \quad (12)$$

$$Specificity = \frac{TN}{TN+FP} \quad (13)$$

$$Precision = \frac{TP}{TP+FP} \quad (14)$$

$$F1 = \frac{2 \times Sensitivity \times Precision}{Sensitivity+Precision} \quad (15)$$

5.5 Statistical Analysis

First, from the resulting feature vectors, ApEn from all of the electrodes and severity levels were grouped according to two conditions: EO or EC. Likewise, power data was grouped in those conditions. Secondly, a Shapiro-Wilk normality test was performed to test data normality.

ApEn estimates for both conditions were non-normal, therefore a Kruskal Wallis test was applied for each band in EC and EO. A multiple comparison Nemenyi test after Kruskal-Wallis was used to compare groups in ApEn with the Tukey procedure (significance value=0.05).

5.5.1 Justification for Analysis of Kruskal-Wallis

The Kruskal-Wallis test is the non-parametric equivalent for the one-way analysis of variance (ANOVA), and it is used for testing whether samples originate from the same distribution. It may be used for comparing two or more independent samples of equal or different sample sizes [189], [190]. This is important since the number of electrodes for control and NP were different. If the p-value from the Kruskal-Wallis test is lower than 0.05, at least one group is different from the others. Some have stated unambiguously that equal variances are required for a Kruskal-Wallis test. However, as long as Kruskal-Wallis is used to essentially compare groups, homoscedasticity is not required [193]. A Levene's test was performed to test equality of variances in ApEn and obtained a pvalue=6.395e-06 which concludes unequal variances, but as mentioned previously it is not required. If medians were to be compared, for example, then the Kruskal-Wallis test would require homoscedasticity. When observations represent very different distributions, as in the case of this study, the result from Kruskal-Wallis should be regarded as a test of dominance between distributions. If the interpretation of results can be done in terms of dominance of one distribution over another, then there are indeed no distributional assumptions [194]. Actually, in the biological statistics domain, using Kruskal–Wallis is an advantage in cases with heterogeneity of variance [195].

For power values, each frequency band in either EO or EC showed a normal distribution, yielding a higher value than 0.05 in the Shapiro-Wilk test. Therefore, before using a one-way ANOVA test to compare the groups, equality of variances was tested in each frequency band, which is also an assumption for ANOVA. A Tukey test was performed as a post-hoc analysis (significance value=0.05)..

6 Chapter Six: Results

6.1 Questionnaire Outcome

6.1.1 Pain Detect

As stated previously, the PDQ was used as a screening questionnaire to confirm the presence of NP in each patient. A score higher than 12 was needed as an inclusion criterion. Figure 23 shows the PDQ results for the 35 patients. Only four patients who had results lower than 12 were included. Two patients (one who scored 5 and the second one scored 9) had recently gone in remission. However, we decided to include them for the high possibility of observing longterm NP consequences, (2) one patient had undergone a surgical procedure one month before to alleviate the NP, and (3) the patient who scored 10 reported in the recording session that he always answered pain questionnaires lightly. He also reported to experience a lot of pain while driving and walking. The most frequent score (n = 4) was 24, followed by 13 and 17 (n = 3). The highest score (x = 31) was from a patient suffering from Complex Regional Pain Syndrome (CRPS), the most painful NP syndrome reported [191].

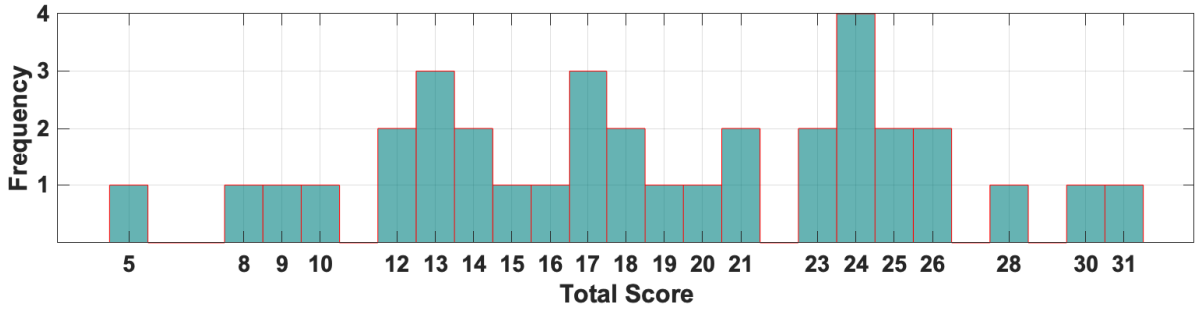


Figure 23 PDQ Results for the 35 patients. PDQ results depicted in a histogram. The score with the most frequency of patients was 24 (n=4), followed by 13 and 14 (n=3). The minimum score was 5 and the highest 31. Most of the scores stay between 12 and 26.

6.1.2 BIP

The BIP is an integrative questionnaire, and outcomes show the complexity and variety of an NP condition for a particular patient. The most important advantage of the BIP is that it gives insight into NP effect on daily activities. In Figure 24, it can be seen that NP affects relationships and sleep the most. After quantifying the BIP Actual Pain score (first column of Figure 24), the sample size for each NP severity group was stratified as follows: 10 patients for the low pain group, 12 patients for the moderate pain group, and 13 for the high pain group.

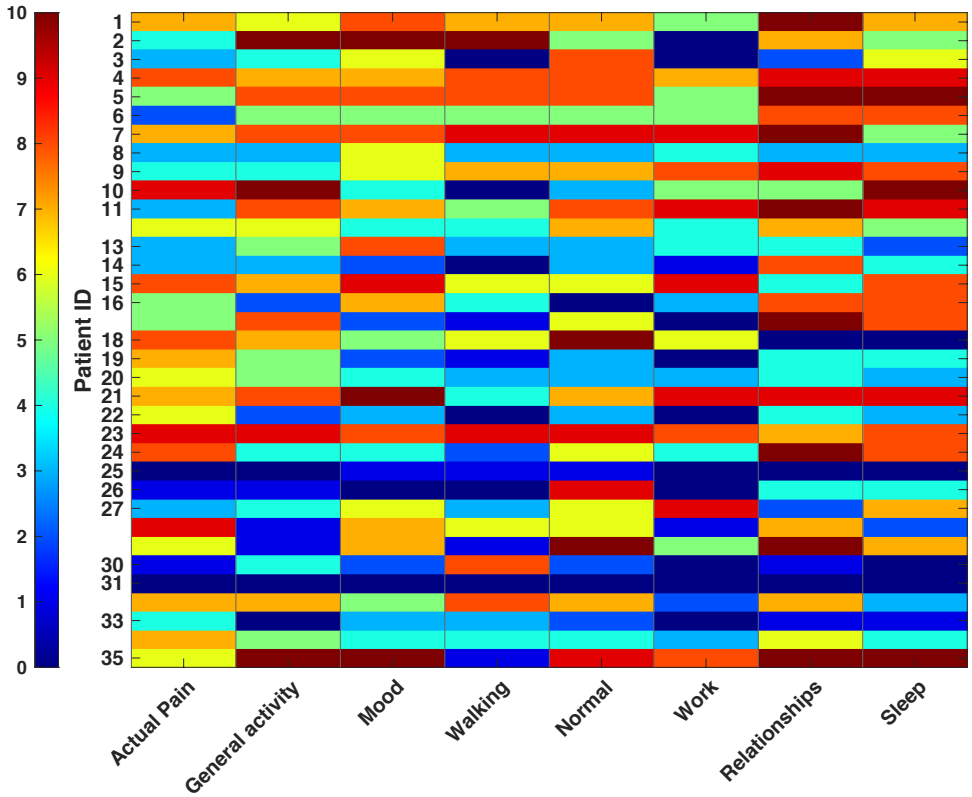
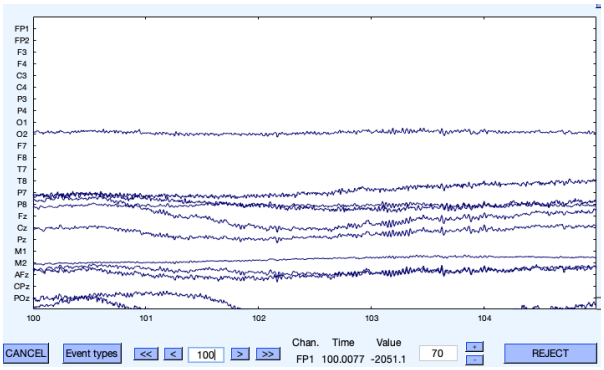


Figure 24 BIP Results for the 35 NP patients. The color bar in the far left illustrates the scores by colors (score ranges from 0-10). Some patients did score a 0 (darkest blue) or a 10 (darkest red). The columns of walking and work had the most rectangles in dark blue. Relationships and sleep have the darkest shades of red.

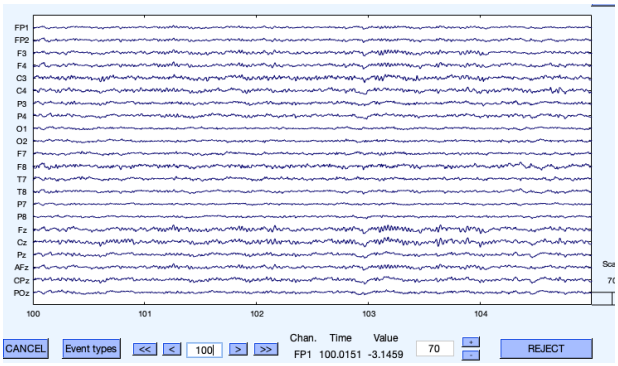
6.2 EEG Preprocessing: Noise reduction

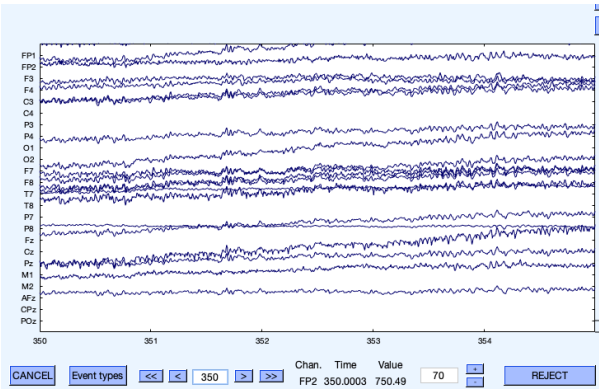
In Figure 25, an example of raw signals (not preprocessed) versus preprocessed signals is shown for the patient ID8.

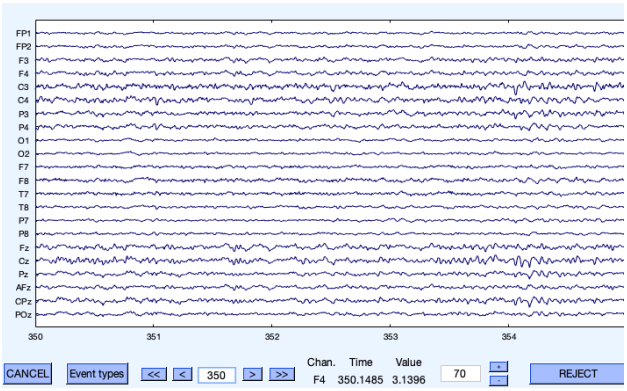
A. Raw: 100 seconds



B. Preprocessed: 100 seconds







C Raw: 350 seconds

D Preprocessed: 350 seconds

Figure 25 Comparison of raw and preprocessed EEG signals. A and B are windows of 100 seconds. C and D are windows of 350 seconds. In all the cases, the voltage scale is of 70uV per row.

6.3 EEG Processing to characterize neuroplastic changes due to NP

In this section, the ApEn of each electrode, as well as the band power across regions will be displayed in graphs to give an insight into the EEG characterization of NP based on linear (band power) and nonlinear (ApEn) features. Mean ApEn is displayed on topographical plots per level of severity for all of electrodes (22 for NP and 19 for control). Mean EEG band power is displayed in three dimensions: regions (prefrontal, frontal, central, parietal and occipital), severity, and power amplitude. These results from power and ApEn may help explain the central tendencies of the abnormal increased neuronal power or randomness expected from neuronal plastic changes owing to the different NP severity levels.

6.3.1.1 Eyes Open Control

For control in EO (Figure 26), theta reached the highest power for all bands. Alpha power in EO had reduced power compared to alpha-power in EC, which is supported by the results of [192].

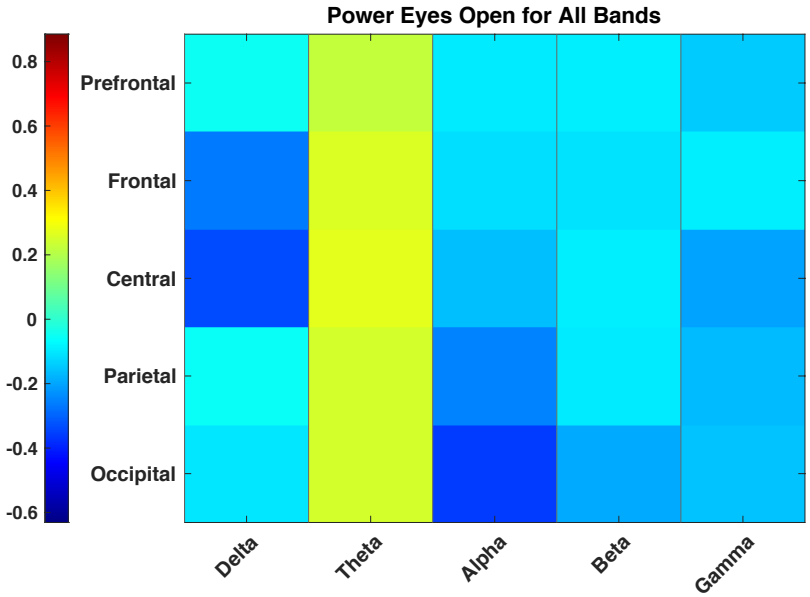


Figure 26 Power EO in All Bands and Regions for the control group. The band that displayed the highest power was theta. Delta showed decrease in power for central and frontal region, while alpha showed a decreased power for the occipital region.

6.3.1.2 Eyes Closed Control

In Figure 27, for the control group in EC, the highest power is seen in delta (frontal and central region) and alpha (occipital and parietal). However, there is also some gamma and beta activity that was not present in EO. These results are in line with [192], where the dominant alpha power was found to be at the posterior area with a frontal extension much more evident in EC than EO state, which can be seen here in the darker yellow shade corresponding to the alpha band over the occipital region.

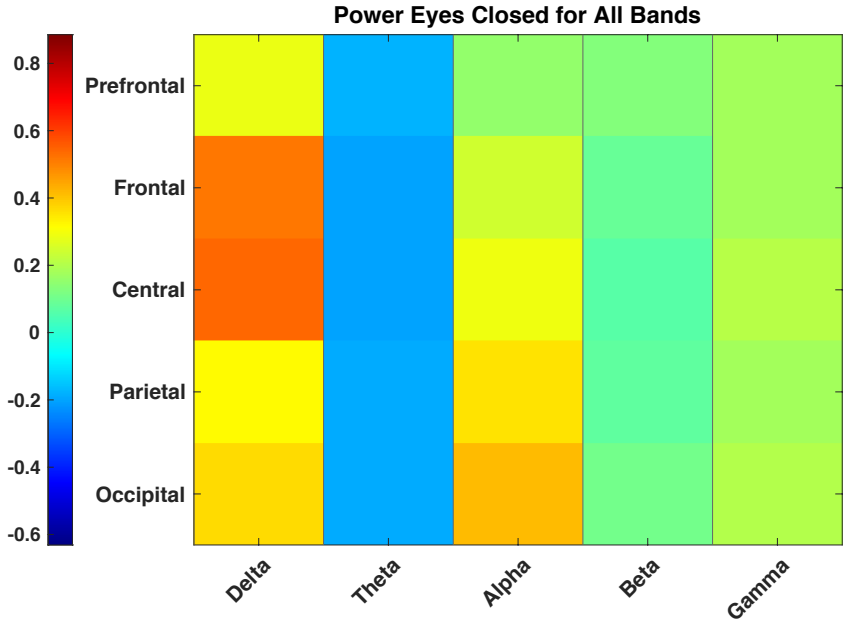


Figure 27 Power EC in All Bands and Regions for the control group. Delta in frontal and central regions showed the highest power. Followed by the alpha-power in occipital, parietal and central regions. Beta and gamma also showed a higher activity than for EO.

6.3.1.3 Eyes Open NP

In Figure 28, gamma was more enhanced than in the control group across all regions in all severities, particularly for low pain in central regions and moderate pain in occipital and parietal regions. In second place, delta for low pain (particularly for prefrontal, frontal and central regions) had an increased power. Finally, beta for moderate pain had an increased power as well, specifically in the prefrontal region. Conversely, beta presented decreased power for prefrontal, frontal, parietal and occipital regions in low pain. For alpha and theta, power remains in values below 0.2.

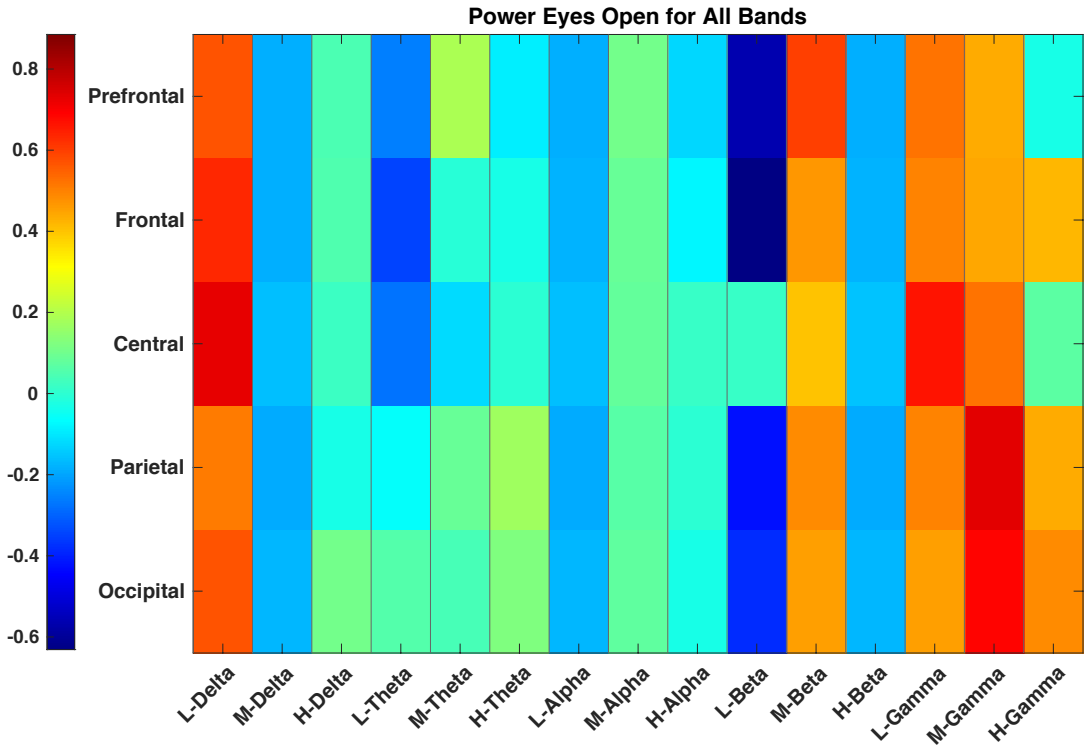


Figure 28 Power EO for All Bands and Regions for the NP group. Gamma bands showed the highest power for all severities of pain, but low and moderate severities had a higher power than high pain in the gamma band. The second highest power was seen in delta low pain. Beta also displayed some high activity in moderate pain. In the x-axis, the labels for each column are according to severity and band: *L*- low pain, *M*- moderate pain and *H*-high pain.

6.3.1.4 Eyes Closed NP

In Figure 29, almost all frequency bands are show a decrease power ranging from [-0.4 -0.6], but there are a few bands that show some enhanced power. These exempted bands are beta and gamma in high pain, delta and theta in moderate pain, and alpha in low pain. For theta, there is increased power that only happens for the prefrontal and frontal regions in moderate pain. The results of [193] show an increased power in EC comparing controls with NP. The majority of bands in all NP severities of Figure 29, have a power in the ranges of [-0.2, -0.6], whereas in the control group the range goes from [0.2, 0.3] approximately (Figure 27).

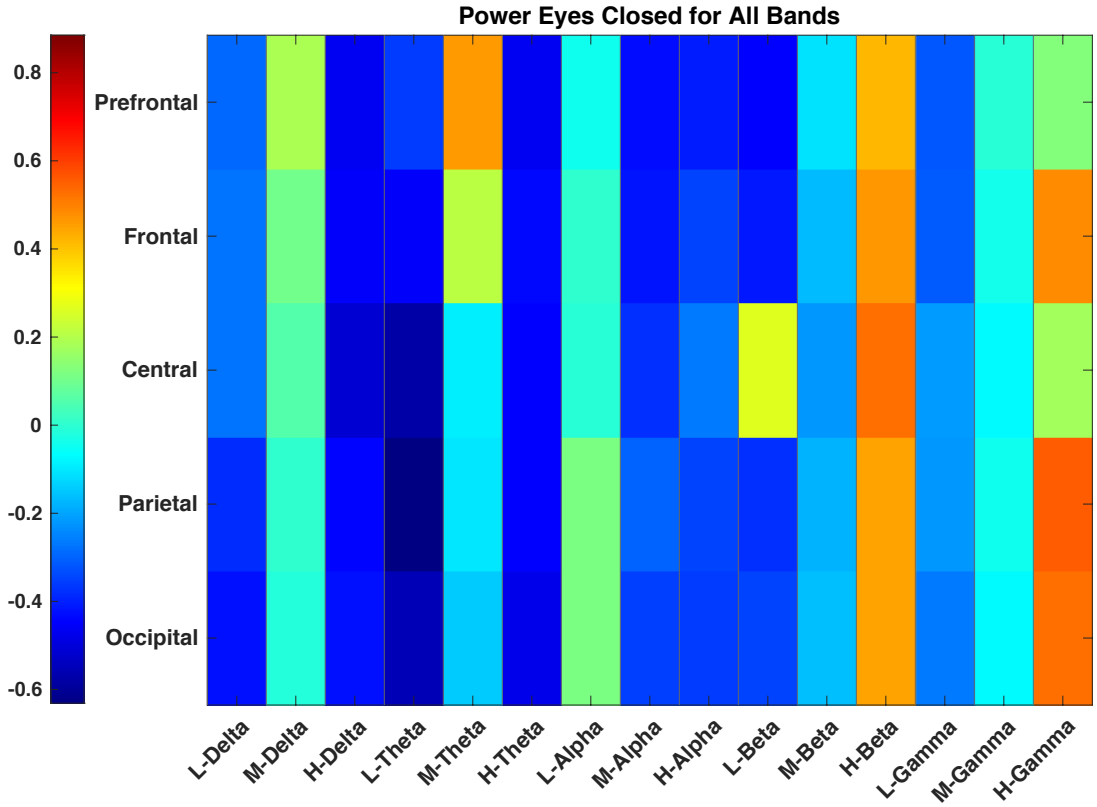


Figure 29 Power in EC for all bands and regions in the NP group. The highest power was found in beta band in high pain and gamma band for high pain. There is focalized enhanced power in prefrontal and frontal regions for moderate pain for the theta band. In the x-axis, the labels for each column are according to severity and band: *L*- low pain, *M*- moderate pain and *H*-high pain.

6.3.1.5 ApEn

Up to now, there has not been another NP study that has analyzed EEG signals based on ApEn. In some cases, absolute band power was inversely proportional to ApEn since band power increases when the level of synchronized neuronal activity increases as well. In contrast, ApEn decreases when the regularity of EEG signals increases, that is, the neuronal synchronicity.

6.3.1.5.1 Delta band

In Figure 30, ApEn in delta for control group is higher in EC than EO. Thus, there is more randomness in theta band during EC in a healthy state. This is confirmed with the power results

of Figure 27 in which there was less synchronization (i.e., decreased power) in EC (i.e., more randomness) for theta compared to other bands. Delta in EO for all NP severities (topoplots to the right) resembles that of the control group. However, a higher ApEn can be observed in NP, particularly in EC for all NP severities compared to the control group. High pain is characterized by more signal randomness in the left hemisphere.

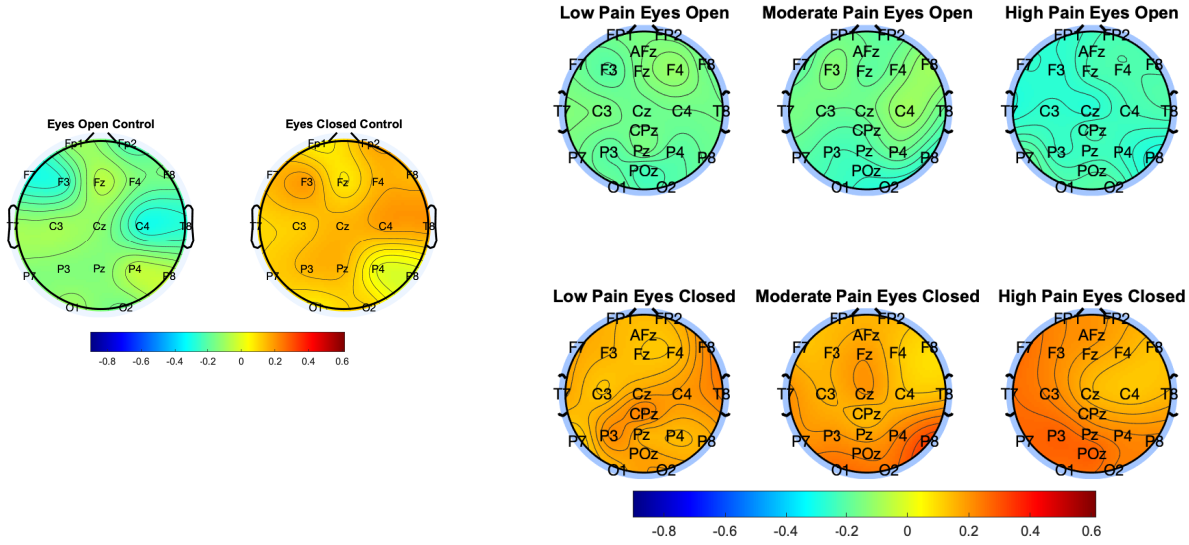


Figure 30 ApEn for delta band in control and NP groups. ApEn for EC in the control group showed a higher ApEn than EO (topoplots to the left). For the NP group (topoplots to the right), there is increased ApEn for all severities in EC compared to EO. This increase of ApEn seems to happen in unison for all severities, since it is generalized without any particular region having more ApEn. This may reflect the role of delta as a global processing mode.

6.3.1.5.2 Theta band

In Figure 31, the opposite of what is observed in delta band occurs in theta: the highest ApEn is seen in EO instead of EC, particularly around electrodes F7, F3 and T8. This is supported by the findings of [192] that described a radical reduction of theta field power (possibly an increase of ApEn) from EC to EO. EO from the low NP severity has a slightly decreased ApEn compared to the EO of the control group. Low pain severity in EC resembles the control group in EC. However, in moderate pain there is an enhanced signal randomness over right parietal and occipital

electrodes. As pain increases to high, the enhanced ApEn expands predominantly in central and parietal electrodes.

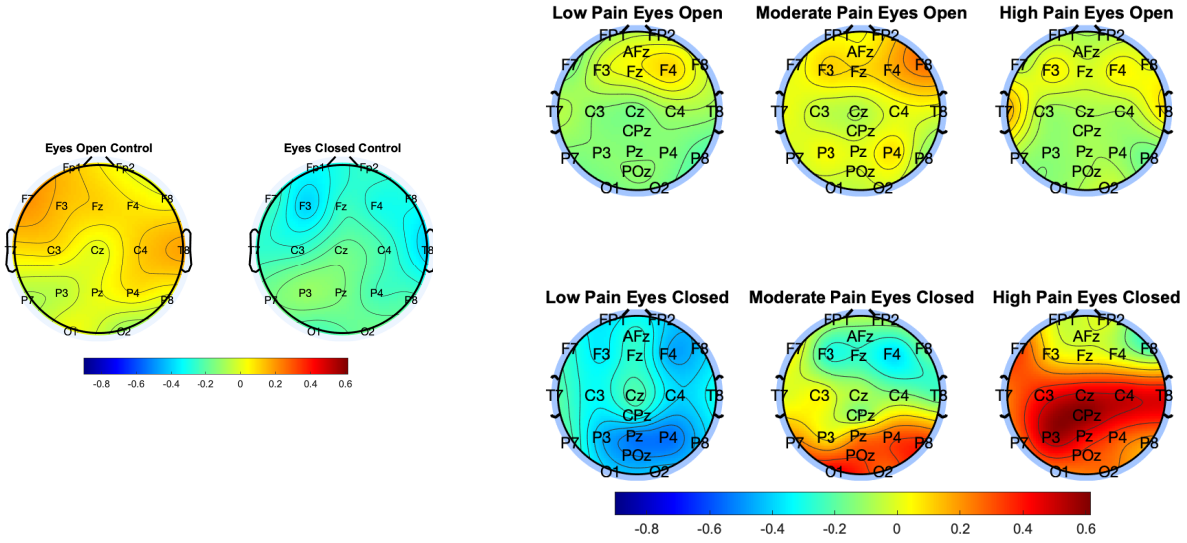


Figure 31 ApEn for theta band in control and NP groups. There is increased ApEn for the control group in EO as compared to EC (topoplots to the left). The increased of ApEn in the control group occurs slightly over the left frontal electrodes and right central electrodes. For the NP group (topoplots to the right), ApEn stays almost on a neutral level in all three severities in EO. Except for some frontal areas that increase marginally their ApEn as in moderate pain. In EC, there is decreased ApEn in low pain, whereas there is an enhanced ApEn in moderate pain for occipital and left central/parietal electrodes. In high pain, central, parietal, occipital and frontal areas have more ApEn compared to other severities.

6.3.1.5.3 Alpha

In a previous study in healthy participants, the dominant alpha power was found to be at the posterior area with a frontal extension much more evidently in EC than EO state [192]. In Figure 32, a posterior extension of alpha ApEn in EC is observed for the control group (topoplots to the left, yellow area). Furthermore, ApEn is enhanced in EO (more desynchronization or randomness) in some frontal electrodes (Fp1, F3, Fz), parietal (P3, P7, P4 and P8) and in O1 electrode. In the NP groups (Figure 32, topoplots to the right), there is an intensely enhanced ApEn for low and moderate NP in EO. This may point out towards the alpha desynchronization that occurs in EO

state in healthy individuals [192]. However, this enhanced generalized ApEn in EO is not present in the control group or in high pain. In high pain for EO, there is a decrease in ApEn or a plausible increase in synchronization (manifested by the blue region) primarily in central and parietal electrodes. For low and high pain in EC, there seems to be a decrease ApEn overall compared to the control group. This with the exception of moderate pain, where parietal and occipital electrodes have an increased ApEn or increased desynchronization.

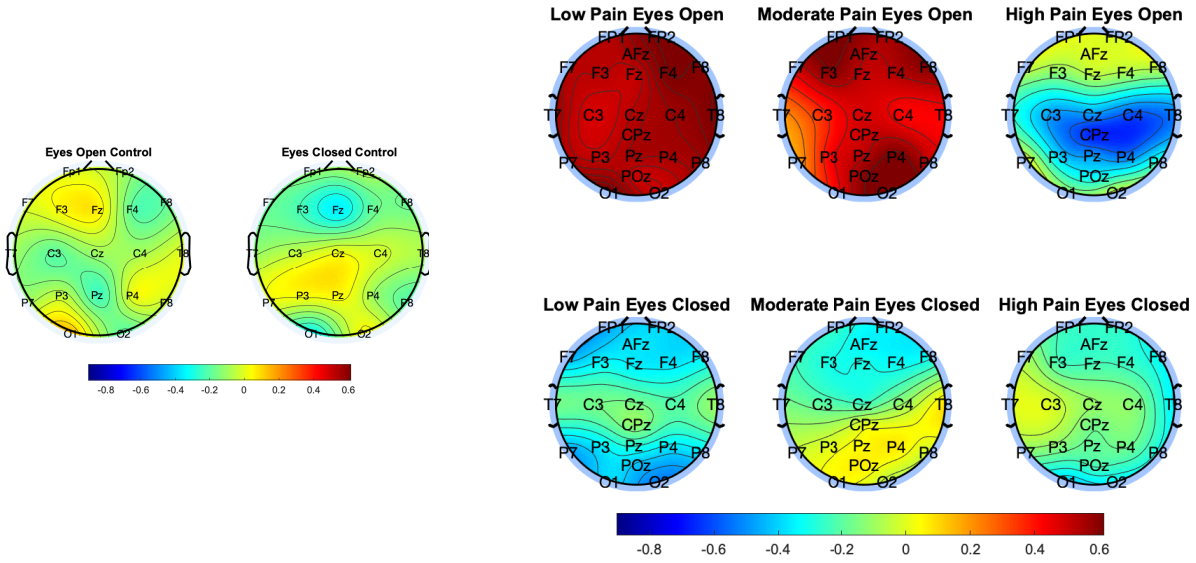


Figure 32 ApEn for alpha band in control and NP groups. ApEn for the control group (topoplots to the left) is enhanced in EO in some frontal electrodes (Fp1, F3, Fz), parietal (P3, P7, and P8) and in O1 electrode. ApEn for EC in the control group has more ApEn over central (Cz) and parietal electrodes (P7, P3, Pz). For the NP group (topoplots to the right), low and moderate pain in EO have a remarkable generalized increased ApEn as compared to other severities. High pain in EO has a decreased ApEn in central and parietal electrodes, particularly in CPz. For all severities in EC there is an overall decreased ApEn, except for moderate pain where parietal and occipital electrodes have a slightly increased ApEn.

6.3.1.5.4 Beta

In Figure 33 (topoplots to the left), the ApEn of the control group has an increased ApEn over the prefrontal electrodes and Fz in EO. The latter is supported by another study, of healthy participants, where beta-2 field power was limited mainly to the prefrontal area [192]. In the NP

groups (Figure 33, topoplots to the right), there is an increase of ApEn mainly in EO for low and high pain over prefrontal and frontal electrodes. In EC, there is a generalized decrease in ApEn, particularly for moderate pain in prefrontal and frontal electrodes. The localization of the decreased or increased ApEn is in line with other studies that argue also for prefrontal and frontal areas of beta activity in NP [65], [84].

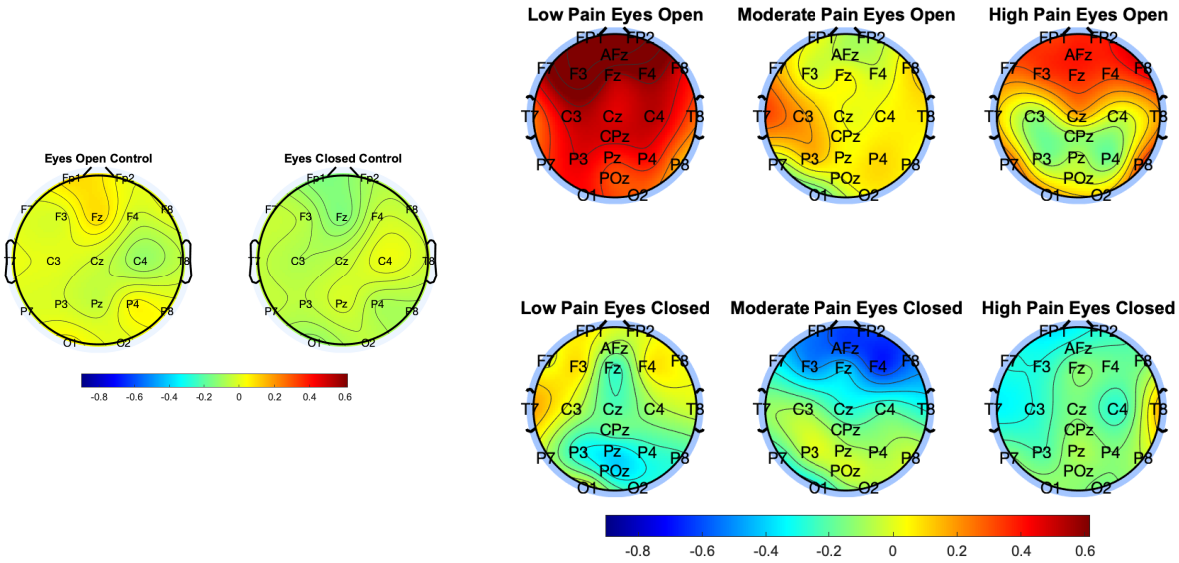


Figure 33 ApEn for the beta band in the control and NP groups. Beta band for the control group (topoplots to the left) showed a neutral ApEn ranging approximately between [-0.1 and 0.1]. Only with a slightly increase of ApEn over the prefrontal cortex (Fp1 and Fp2 electrodes) and the frontal Fz electrode. For the NP groups (topoplots to the right), the only severity that shows a significant and overall Increase of ApEn is the low pain in EO. High pain in EO has increased ApEn in the prefrontal and frontal electrodes. Moderate pain in EO has a slight increase over the T7 and C3 electrodes. In the other hand, all three severities in EC are relatively neutral. Moderate pain in EC has significant decrease of ApEn in the prefrontal and frontal electrodes.

6.3.1.5.5 Gamma

In Figure 34 (topoplots to the left), an increase of ApEn in EO as compared to EC is observed for the control group. The highest ApEn in EO is localized over the F3 electrode, but also F4, Cz and C4. In EC, ApEn remains below 0. The previous findings of the control group is supported by [192], that reported gamma localized in the prefrontal area in healthy participants. For the NP

group (Figure 34, topoplots to the right), high pain had the highest ApEn. The increased ApEn was generalized with a specificity of central, parietal and occipital electrodes in EO. High pain in EC had the same distribution, but with a lower intensity of ApEn. In low pain for EO, there was increased ApEn in the right frontal hemisphere. For moderate pain, the increased ApEn occurs over the left frontal hemispheres for both EC and EO.

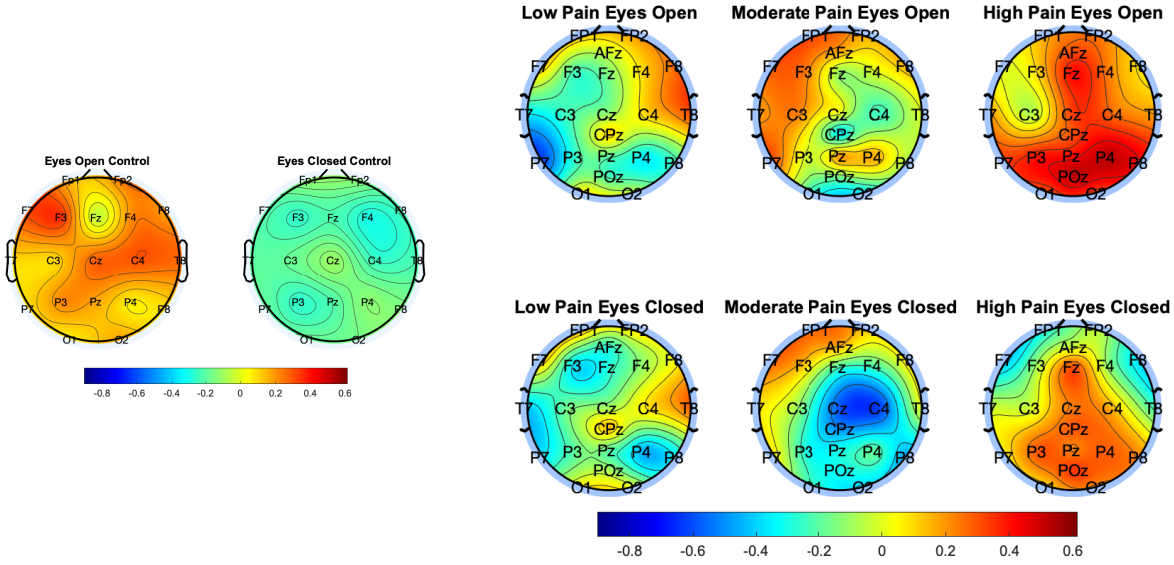


Figure 34 ApEn for the gamma band in the control and NP groups. The control group (topoplots to the left) in EO had an increased ApEn over the frontal electrodes F7 and F3, as well as F4, Cz and C4. ApEn for EC remained around -0.2 throughout the scalp. For the NP group (topoplots to the right), the highest increase of ApEn occurred for high pain in EO. In EC for high pain, there was also an increase of ApEn almost with the same distribution but with a less degree. In moderate pain (both EO and EC), the enhanced ApEn occurred in the frontal left electrodes. Meanwhile for low pain, this enhanced ApEn was only slightly enhanced in frontal and temporal right electrodes for EO.

6.3.1.5.6 Broad Bw

In Figure 35 (topoplots to the left), for EO in the control group, there is a modest increase of ApEn compared to EC particularly for T7 and C3. ApEn for EC is mainly below zero. For the NP group (topoplots to the right), Figure 35 shows the ApEn of the full Bw in NP with more negative values for EC than EO. In EO, there is increased ApEn in the occipital lobe for low pain. In moderate pain, there is an overall increase in ApEn throughout the cortex. As pain severity increases to

high pain, the irregularity of neuronal activity in NP patients shifts from posterior to frontal brain areas. There is also a remarkable decrease in ApEn for low pain in EC.

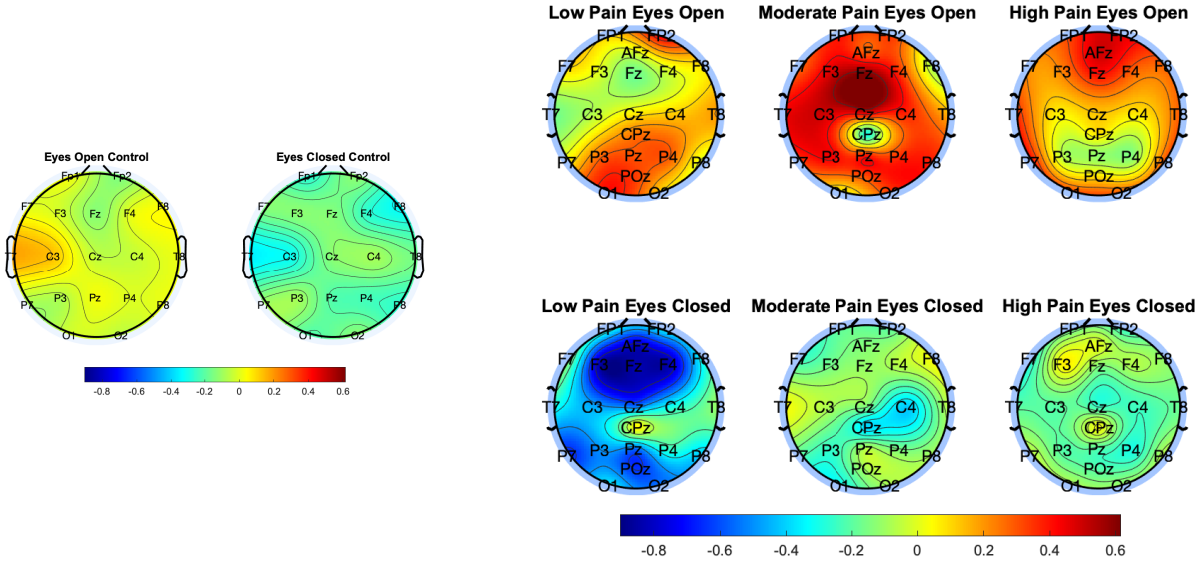


Figure 35 ApEn for the BW band in the control and NP groups. In the control group (topoplots to the left), an enhanced ApEn in EO is observed for T7 and C3 with a generalized increased ApEn for all the electrodes. For EC, ApEn ranges in the values below zero. In the NP group (topoplots to the right), for EO low pain has increased ApEn in the occipital/parietal electrodes. Moderate pain in EO is enhanced generally but also focally in a greater degree for Fz and Cz. In EO for high pain, the increased ApEn is observed in the prefrontal cortex. In EC, there is a prominent decrease in ApEn for low pain mainly in the frontal and prefrontal electrodes.

6.3.2 Statistical Results

In this section, the statistical results for ApEn and power are reported in each frequency band for every combination of groups. Firstly, normality using the Spearson-Wilk test for both conditions (EC and EO) was assessed (Figure 36). All computations were done in RStudio(1.2.5033), an integrative development environment for R, the programming language for statistical computing and graphics (https://www.rstudio.com/). Hereinafter, “High” for high pain, “Mod” for moderate pain, “Low” for low pain, while referring to the comparison of NP groups, are used as abbreviations.

Despite the apparent normality shown in the QQ-plot for ApEn in EC (Figure 36B), the Shapiro-Wilk normality test for EC had a p-value = 0.0058, which is lower than 0.05 and hence it is significantly different from a normal distribution. For EO, the p-value was 8.381e-11. Concluding that both data sets for ApEn are non-normal. Therefore, for every band, the Kruskal-Wallis rank sum test was done separating the data in EO and EC.

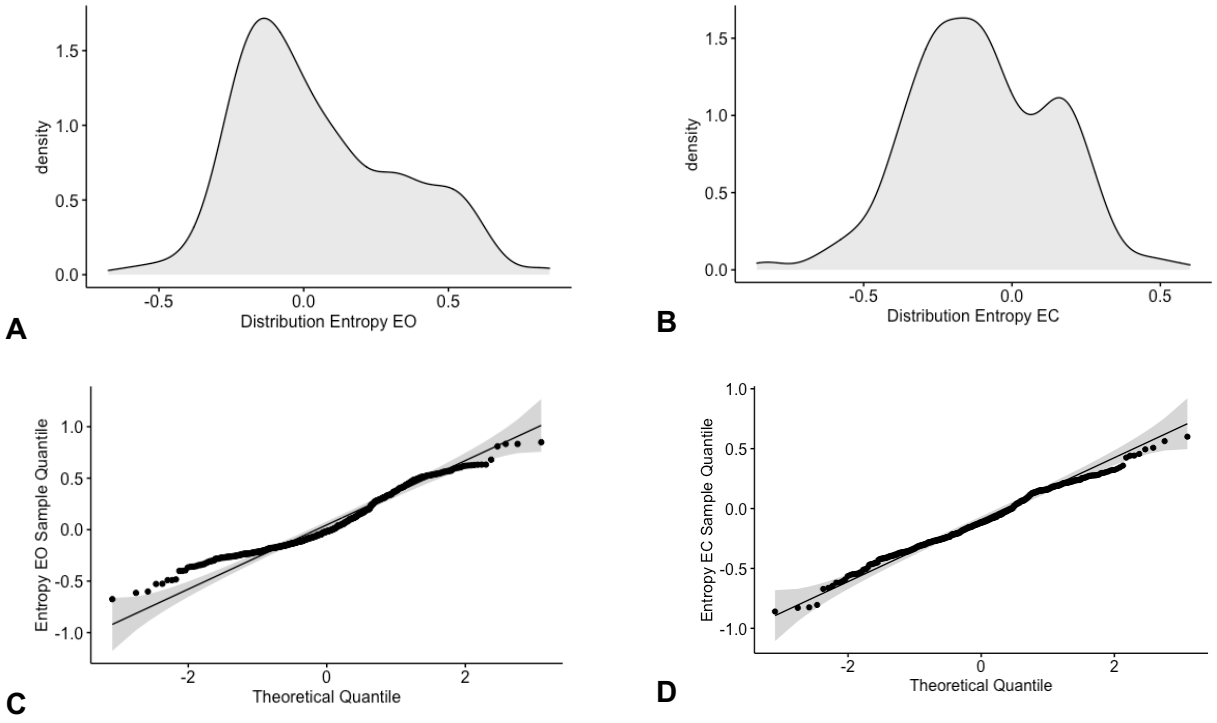


Figure 36 Distribution for ApEn of EO and EC for all severities and bands. (A) Distribution of ApEn values across all severity groups (including control) for EO state. (B) Distribution of ApEn values across all severity groups (including control) for EC state. (C) and (D) are the qq-plot for each of the respective data. These graphs prove visually that neither of the two datasets have a normal distribution.

6.3.2.1 ApEn Delta Statistical Results

For delta, the most differentiable state was EO (Figure 37). Almost all groups proved to be different (Control-High p-value=7.1e-14, Control-Low p-value=0.00094, Control-Mod p-value=4.3e-06, High-Low p-value=0.00019, High-Mod p-value=0.01850) except for Low-Mod. For EC, only Control-High (p-value=1.5e-05) and Control-Mod (p-value=0.021) showed significant difference.

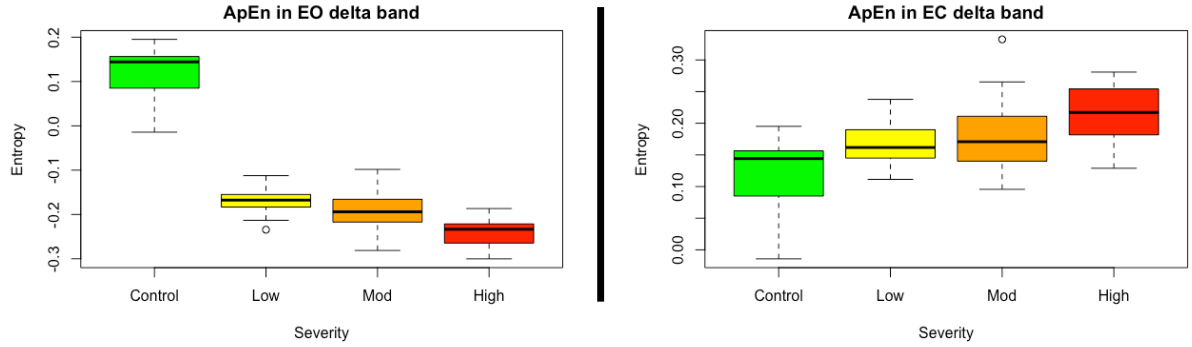


Figure 37 Boxplots for ApEn in delta band in EO and EC. Boxplots for the mean of all the electrodes. All values are normalized with z score of mean 0 and standard deviation of 1.

6.3.2.2 ApEn Theta Statistical Results

By observing Figure 38, theta band was atypical in the sense that both EC and EO exhibited the same number of differentiable groups between states. In EC, the combinations that differed significantly were the following: Control-High (p-value=9.7e-06), Control-Mod (p-value=0.018), High-Low (p-value=1.0e-11) and Low-Mod (1.9e-06). In EO the groups that were significantly different were High-Control (p-value=3.8e-06), Low-Control (p-value=0.0020), Control-Mod (1.0e-11) and Low-Mod (0.0017).

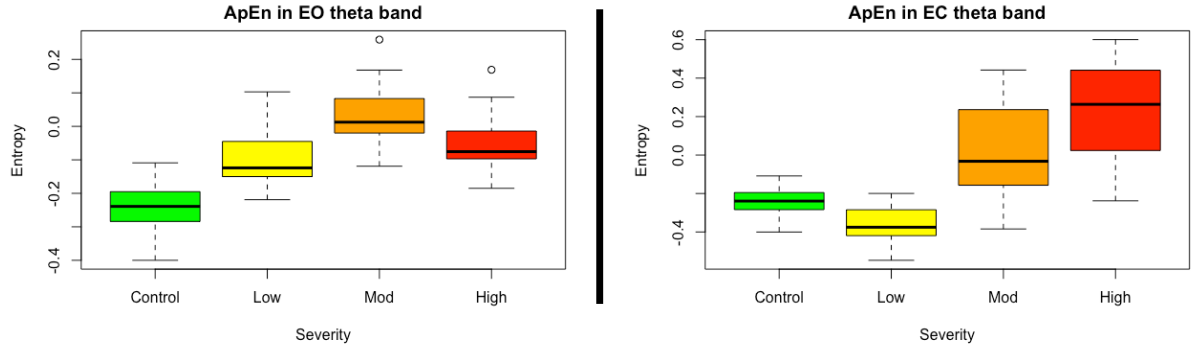


Figure 38 Boxplots for ApEn in theta band in EO and EC. Boxplots for the mean of all the electrodes. All values are normalized with z score of mean 0 and standard deviation of 1.

6.3.2.3 ApEn Alpha Statistical Results

Alpha band was most differentiable for EO and exhibited significant differences in: Control-Low (p-value=2.7e-07), Control-Mod (p-value=3.3e-05), High-Low (p-value=2.0e-10) and High-Mod

(p-value=8.6e-08). For EC, Control-Low (p-value=2.2e-05) and Low-Mod (p-value=0.00017) where significantly different. The difference in the distribution between groups may be observed in Figure 39.

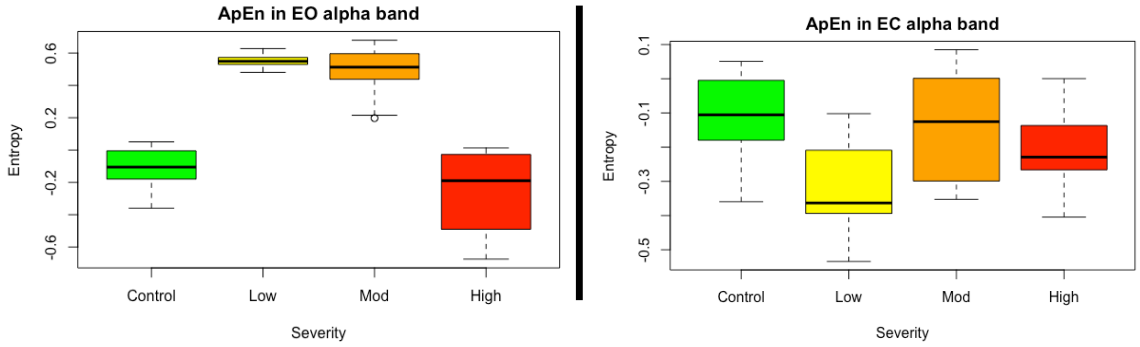


Figure 39 Boxplots for ApEn in alpha band EO and EC. Boxplots for the mean of all the electrodes. All values are normalized with z score of mean 0 and standard deviation of 1. Outliers in the distributions are represented with a circle.

6.3.2.4 ApEn Beta Statistical Results

Beta band was significantly different for EC in Control-High (p-value=0.01), Control-Mod (p-value=0.00054), and Low-Mod (p-value=0.0123). In EO, beta band exhibited significant differences in Control-High (p-value=0.0025), Control-Low (p-value=3.0e-11), High-Low (p-value=0.0023), Low-Mod (p-value=5.6e-06). The boxplots of Figure 40 illustrate these results.

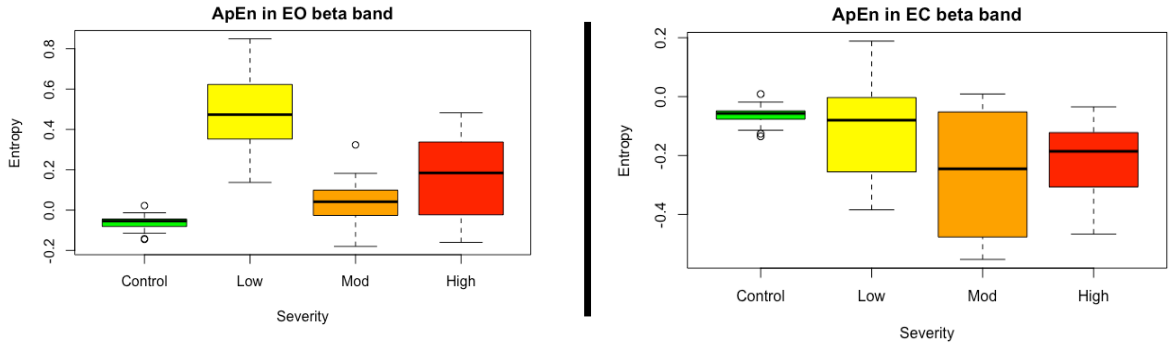


Figure 40 Boxplots for ApEn in beta band EO and EC. Boxplots for the mean of all the electrodes. All values are normalized with z score of mean 0 and standard deviation of 1. Outliers in the distributions are represented with a circle.

6.3.2.5 ApEn Gamma Statistical Results

Gamma band was most differentiable for EO and exhibited significant differences in Control-High (p-value= 8.9e-09), Control-Mod (p-value=0.0145), High-Low (1.9e-05), and High-Mod (p-value=0.0084). This can be explained by observing the boxplot of EO in Figure 41 as the low and moderate groups have a more similar distribution compared to the rest. In EC, Control-High (p-value= 0.006) and High-Mod (p-value=0.027) were significantly different.

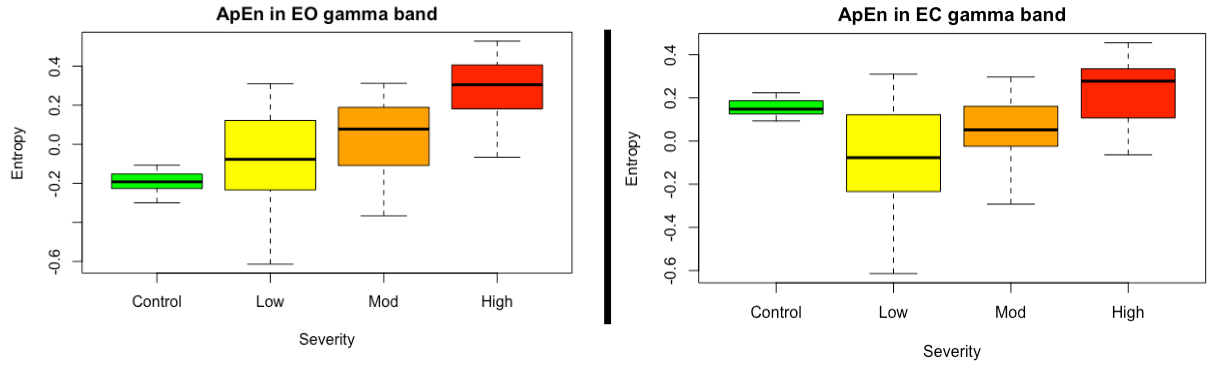


Figure 41 Boxplots for ApEn in gamma band EO and EC. Boxplots for the mean of all the electrodes. All values are normalized with z score of mean 0 and standard deviation of 1.

6.3.2.6 ApEn Bw Statistical Results

In EC, the significant differences were found in all the combinations of low: Control-Low (p-value=0.01), High-Low (p-value=3.8e-05) and Low-Mod (p-value=3.0e-05). For EO, the statistically significant difference was found mostly for the control group vs all pain severities (Control-High p-value=2.6e-06, Low-Control p-value=0.00083, Mod-Control p-value=9.2e-10), including the combination of the NP groups Low-Mod (p-value=0.035). The differences between distributions may be perceived in Figure 42.

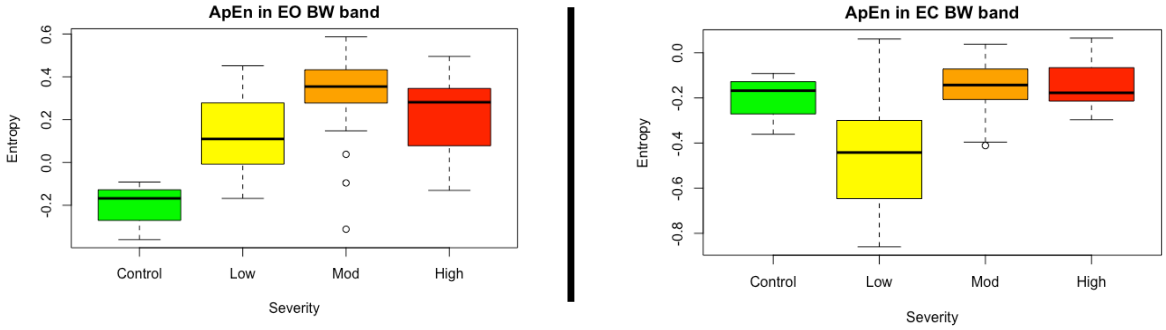


Figure 42 Boxplots for ApEn in Bw band EO and EC. Boxplots for the mean of all the electrodes. All values are normalized with z score of mean 0 and standard deviation of 1. Outliers in the distributions are represented with a circle.

6.3.2.7 Power Statistical Results

The calculation for statistical power results were the same as for ApEn. First, a visual inspection for EO and EC was done separately with the data from all severities. This is depicted in Figure 43. For power, both distribution plots and quantile-quantile plots look fairly non normal. The Shapiro-Wilk normality test proved this true with a p-value = 0.0075 in EC, meanwhile for EO the p-value= 0.0043. Concluding that both data sets for power were also non-normal.

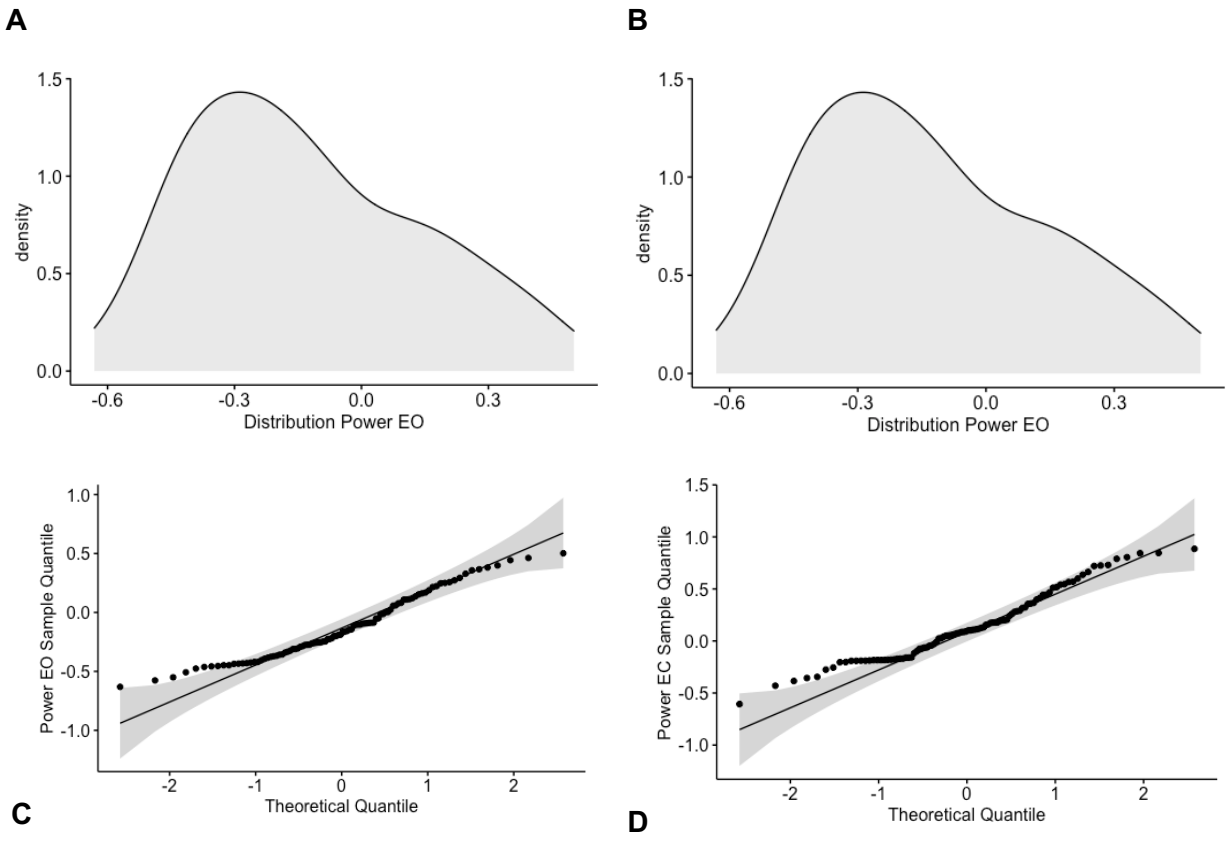


Figure 43 Distribution of Power in EO and EC for all severities and bands. (A) Distribution of power values across all severity groups (including control) for EO state. (B) Distribution of power values across all severity groups (including control) for EC state. (C) and (D) are the qq-plot for each of the respective data. These graphs prove visually that neither of the two datasets have a normal distribution.

6.3.2.8 Comment on Statistical Results of Power for All Bands

Even though the Shapiro test returned a non-normal result, normality was confirmed for each band in EO or EC state, before the Kruskal-Wallis test. Surprisingly, all bands in either EO or EC were normal. Consequently, before performing an ANOVA on each of the frequency bands, a Levene's test was done to test the equality of the variances. Most bands (either in EO or EC) had a p-value over 0.05 which proved equal variances. For instance, the Levene's test returned a a pvalue= 0.575 and 0.644 for beta and gamma respectively, which concludes equal variances.

Afterwards, the ANOVA and a Tukey procedure was performed as a post-hoc test to compare the groups in each band. There were no bands with statistically significant differences between groups in either EC or EO state. The only results that approximated a statistically significant result were in beta and gamma band in EO (see boxplots of Figure 44). For the beta band, Low-High (p value= 0.053) and Mod-High (pvalue=0.079) had close significant results. For the gamma band, the combination of groups that approximated the most to being significant were Low-High (pvalue=0.068) and Mod-High (p=0.088). Note that both band distributions are partially similar. For instance, the high pain group had the maximum power values in both bands. Low and moderate distributions are both below control. Lastly, most of the boxplots have roughly the same mean and interquartile range between the bands.

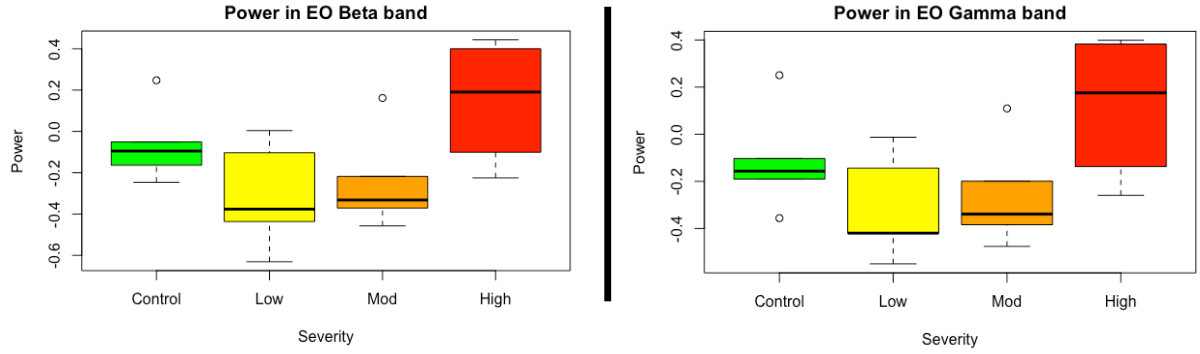


Figure 44 Boxplot for beta and gamma power in EO. Boxplots for the mean of the five regions. All values are normalized with z score of mean 0 and standard deviation of 1. Low and moderate pain have a similar distribution between beta and gamma. Control and high pain have also a similar distribution between the bands. Outliers in the distributions are represented with a circle

6.3.3 Feature Extraction Results

The previous study [49] that classified NP based on EEG features in EO and EC, achieved 87-90% of classification accuracy. We hypothesized that Nonlinear EEG features would increase classifier performance closer to 100% for clinical applications, due to a better characterization of the nonlinearity of NP. First, the two most differentiable features among the three classes are presented. Figure 45 shows the relationship of these two variables that come from the two

different methods of analysis: power and ApEn. The feature ranked in the first place was power in the prefrontal region in the beta band. The second place was ApEn in the Fz electrode for the Bw band. Particularly, lower values of power have increased values of ApEn. Besides, the scatterplot distinguishes that moderate (blue dots) and high (green dots) are clustered better than the low (red dots). This means that high and moderate are better classified than low pain for these specific features. The results for the classifier with the added Nonlinear features were the following.

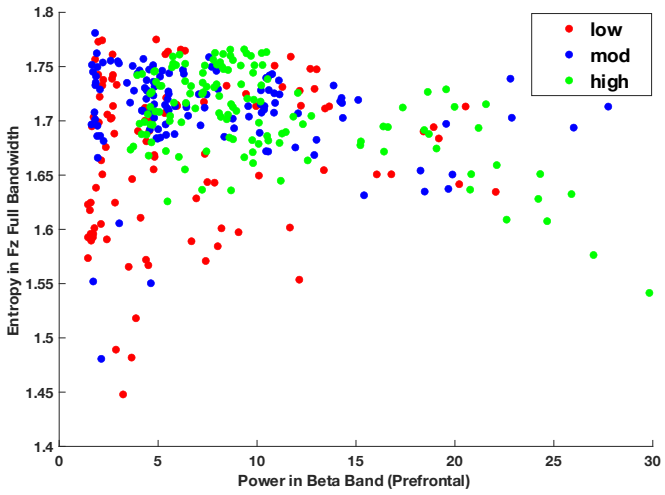


Figure 45 Scatterplot for the first two ranked features. ApEn in Fz in the full Bw is represented in the y-axis, and power in the prefrontal region for the beta band is presented in the x-axis. Low pain is represented in red, moderate in blue and high in green.

6.3.3.1 Differentiation among NP severity levels: Classification outcomes

As explained in Section 5.4.1.4.1, four types of kernels for SVM were tested and their resulting accuracies were the following: for the quadratic kernel 96.6%, the linear kernel 84.9%, the cubic kernel 95.1% and the gaussian kernel 86.3%. The quadratic kernel was selected for achieving the highest accuracy. In Figure 46, the resulting confusion matrix of the 3-classes SVM-based classification with the quadratic kernel is presented. As can be seen, the 3 levels of NP severities were identified at least in a 93% and misclassified at most 6%. In Figure 47, accuracy, sensitivity,

specificity, precision and F-score for each class are illustrated. The F score for high pain was 95%, while for moderate 94% and for low pain was 96%. Specificity for low pain was 98%, while for moderate and high was 97%. Sensitivity was 95% for high pain, and 94% for moderate and low pain. Precision was 96% for low pain, 93% for moderate pain, and 93% for high pain.

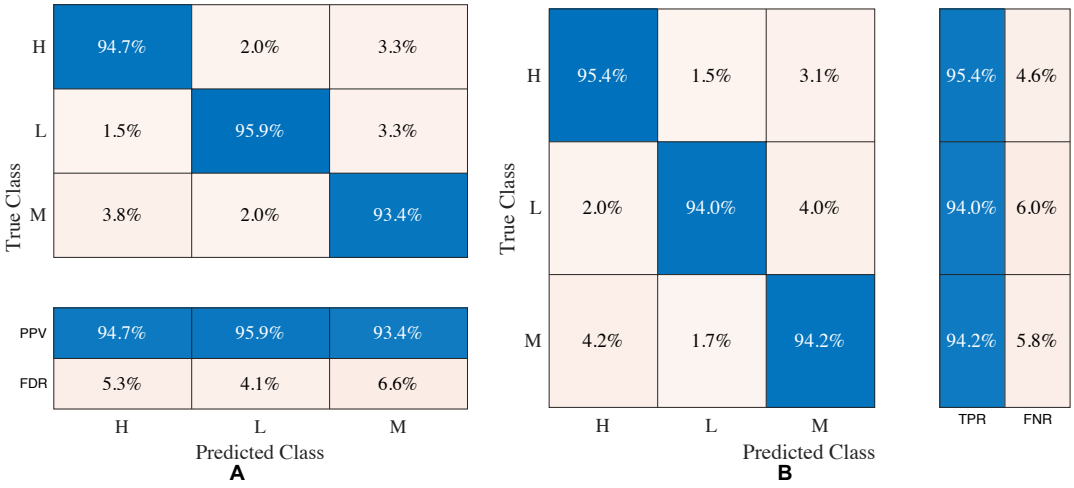


Figure 46 Positive predicted values and false discovery rates of the SVM confusion matrix. (A). True positive rates and (B) false negative rates of the SVM confusion matrix.

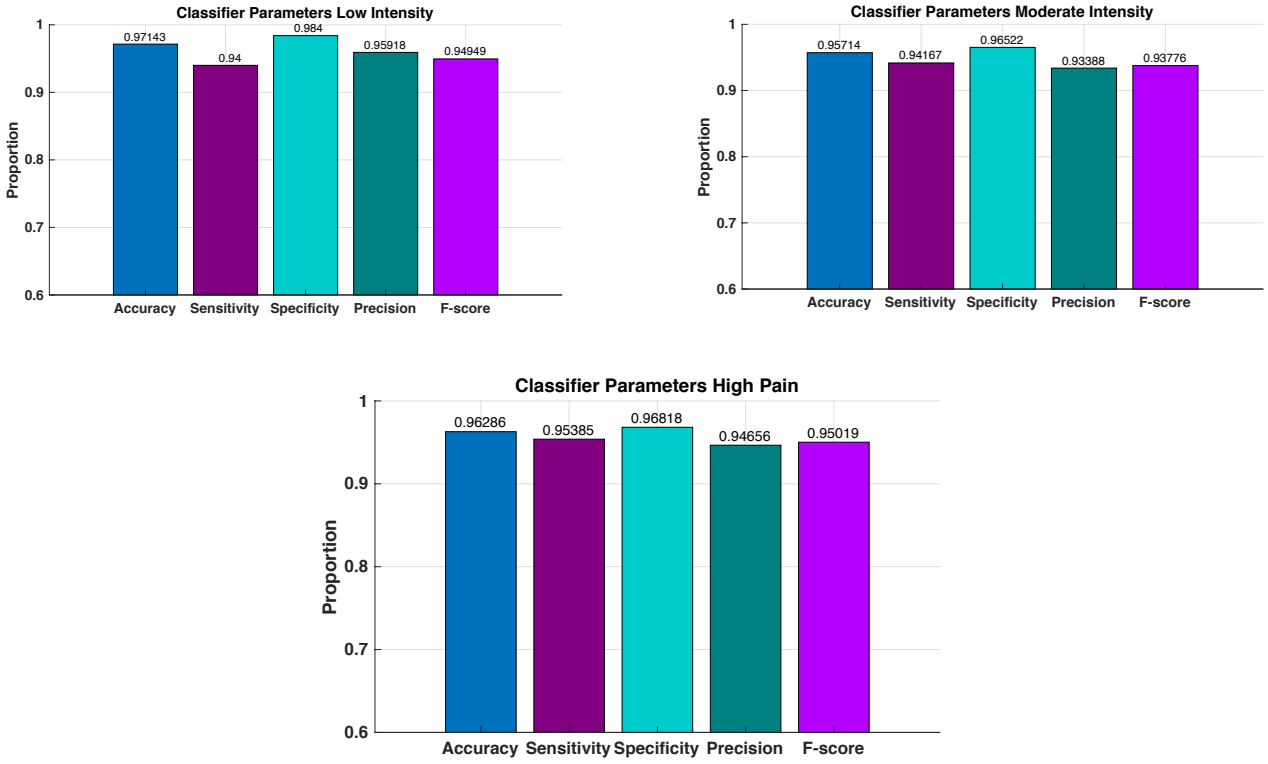


Figure 47 Classifier scores for each level of NP severity. Low pain achieved an accuracy of 97% and a specificity of 98%. Moderate pain reached an accuracy of 96% and a specificity of 97%. High pain achieved an accuracy of 96% and a specificity of 97%.

7 Chapter Seven: Discussion

7.1 Neuroplastic Tendencies by Severity

In this section, the NP severities by bands will be addressed with an integration of the neurophysiological and statistical results that have been reported. Power from brain oscillations is a highly complex circumstance. In general, power modulations might be related to the overall activity of neuronal populations [194] or to the degree of spike synchronization [195]. Oscillation frequency might be related to the neuronal networks involved and their extension [196], or the excitation-inhibition balance in the background neuronal activity [197]. Therefore, neuronal oscillations at different frequencies may reflect diverse neuronal populations and/or network states [196], functionally relevant for cognitive task performance [198]. There are some genetic factors that take part on EEG signals [199], but possibly the main effect on EEG is the difference between EC and EO states at rest [192]. EO is different from EC state, since the Default Mode Network (DMN) is active in the resting brain and deactivated during tasks (EO) [200]. In EO, there is a greater cognitive demand given the visual input. For this purpose, both states were studied. Consequently, the higher cognitive demand imposed by NP, the greater deactivation of DMN [201]. Some of the assumptions proposed to explain the differences observed in ApEn are based on the neurophysiological theory behind EEG band power studies. The relationship between ApEn and power is still not defined, but the following discussion will give particular intuitions of this relationship. Yet, only enhanced responses (of power or ApEn) have a strong impact on down-stream processes. If there is a successful binding and dynamic selection of responses, then there is a signal relayed which in fact could be the signal leading to the perception of chronic NP [202]. A previous work [192], stressed the necessity for EEG studies to define not only the spectral information but also the spatial characteristics of the subjective experience, since the spatial nature may manifest the underlying co-activity in structure-function relations. The spatial and spectral nature of the results are herein discussed. Results are summarized in Table 4.

Table 4. Results summarized by frequency bands and groups.

	Control	Low Pain	Moderate Pain	High Pain
Delta	↑ ApEn in EC compared to EO control ↓ Power in EC for control group	↑ Power compared to other pain severities in parietal, central and frontal regions	↓ ApEn than control group	ApEn in EO was significantly different from all groups
Theta	ApEn in EO was significantly different from all other groups	↓ ApEn compared to control in EO ↑ Power in EO for all regions (slight increase) ↓↓ Power in EC for all regions	↑ Power in EC compared to low and moderate pain ↑↑↑ Power in EO for the prefrontal region ↑↑ ApEn in EO for parietal and occipital electrodes	↑ Power in EO for the occipital and parietal electrodes ↑↑↑ ApEn in EO for the occipital, central and parietal electrodes
Alpha	Control was not differentiated from high pain only in this band	↓↓ Power in EO for all regions ↑↑↑ ApEn in EO for all electrodes	↑ Power in EO for all regions ↑↑↑ ApEn in EO for all electrodes	↑ Power in EO for central and parietal regions ↓ Power in EC for central and parietal regions ↓↓ ApEn in central and parietal electrodes
Beta	-	↓↓ Power in EO for all regions except the central region that has ↑ power ↑ ApEn in EO	↑↑↑ Power in EO across all regions	↑↑↑ Power in EC across all regions, particularly for central region
Gamma	↓↓ Power in EO for all regions ↑ Power in EC (slight increase)	↑↑↑ Power in EO	↑↑ ApEn in EO for prefrontal and frontal electrodes ↑↑ Power in EO for parietal and occipital regions	ApEn in EO was significantly different from all groups ↑↑ Power in EO for frontal, parietal and occipital regions ↑↑↑ ApEn overall electrodes except C3
Bw	ApEn in EO was significantly different from all severities of pain	↑↑ ApEn in EO for the occipital electrodes	↑↑↑ ApEn in EO for the frontal, central, parietal and occipital electrodes	↑↑↑ ApEn in EO only in prefrontal and frontal electrodes

7.1.1 Delta

Delta (with theta and alpha) is one of the global processing modes. These three bands have been hypothesized to integrate cortical sites by synchronizing coherent activity and phase coupling across widely spatially distributed neuronal assemblies [151]. Delta oscillations are considered the most ancient oscillatory mode, compared to higher frequency oscillations. Accordingly, delta dominates the EEG spectrum of lower vertebrates, particularly reptiles, the direct evolutionary ancestors of mammals. In 1958, [203] proposed a principle stating that delta oscillations in humans are more pronounced in conditions that are associated with diminished activity of the 'higher', or more advanced 'nervous arrangements'. These conditions include: (a) earlier developmental stages, (b) deep sleep; and (c) pathological states [204]. NP is an example of a pathological state as it decreases alpha, a higher nervous arrangement.

7.1.1.1 Control

The statistical results of delta in EO show that all possible combinations revealed a true difference between all NP groups and control (Control-High, Control-Mod and Low-Control). Thus, delta in EO might effectively differentiate the NP neuroplastic changes from a healthy state. The increased ApEn in EC compared to EO (Figure 30), may be related to the primitive neurophysiological role of delta. In other words, the increase randomness might be given from the constant screening of internal and external stimuli in search for potential threat or reward [199]. Meanwhile alpha is associated with a conscious percept oscillation, delta is associated with an unconscious percept oscillation [205], [206]. There is an increase of ApEn in EC for the control group (Figure 30), at the time that there is decrease of power (desynchronization) in Figure 26.

7.1.1.2 Low Pain

Delta was not significant in EO for Low-Mod pain. The reason that Low-Mod was not a differentiable combination may be that neuroplastic changes involved in the delta band, do not severely change from a low to moderate NP (see Figure 30, low pain and moderate pain). This

may also be a consequence of the neuroplastic changes happening in the delta band from emotional processing [207], [208]. It is possible that there are more changes in emotional processing from a control to a higher pain severity than from control to low pain state. Convergently also, delta power in EO (Figure 28) was highest for low pain in the parietal, central and frontal regions, which are all involved in emotional processing and somatosensory perception [122].

7.1.1.3 Moderate Pain

Delta was significantly different in EO for Control-Mod and Mod-High (Figure 37). Similarly, in EC, Mod-Control was significant. In moderate pain, the increase in delta oscillations may characterize the salience system that pays attention to the NP as a relevant percept over other percepts, because the brain has not fully adapted to NP [209].

7.1.1.4 High Pain

Delta was also significantly different in ApEn EO between all groups for high pain (Control-High, Low-High and Mod-High). In the boxplot of Figure 37, it can be observed that the groups of NP have a much lower ApEn than the control group. This lower ApEn value may be due to the increase of delta activity (more synchronization) in NP that has TCD as a background and the ongoing subconscious percept of pain. Delta power for EC (Figure 29) was only relatively increased in high pain. However, neurons also adapt as neuroplastic changes increase [210], which may be the reason that power in EO (Figure 28) is not as increased for high pain as compared to low pain in delta.

7.1.2 Theta

EEG theta oscillatory activity (4–8 Hz) appears to be functionally involved in higher brain functions including the integration of working memory [211], executive control, and focused attention [212].

Furthermore, the TCD proposes that the increased theta activity in pathological states is the normal resting-state alpha [90]. Hence, there is increased power in theta and less power in alpha compared to a healthy state.

7.1.2.1 Control

In EC, Control-High and Control-Mod, showed a significant difference (Figure 38). This may be due to neuroplastic changes that have not occurred severely in low pain as have for other severities, leaving low pain almost as a "control state" for theta band. However, in EO (Figure 38) there were significant differences in control between all severities of NP (Control-High, Control-Low and Control-Mod). This confirms that ApEn characterizes NP in the theta band appropriately, as others have reported repeatedly for power analysis in NP [78], [84], [85].

7.1.2.2 Low Pain

Low-Mod and High-Mod represented a significant difference in EC (Figure 38). In the other hand, for EO Control-Low and Low-Mod were significant. In Figure 31, the decreased ApEn in low pain compared to control in EO may reflect more synchronization. However, power was only slightly increased (little greater than 0) for theta in EO (Figure 28). In EC (Figure 29), theta was highly desynchronized (decreased power) in all regions.

7.1.2.3 Moderate Pain

There was significant difference found from Control-Mod and Low-Mod for ApEn in EO and EC (Figure 38). For ApEn in EC, there is increased signal randomness in posterior areas (Figure 31). The results for power in EC show a slight increase in power across all regions compared to low and high pain severity (Figure 29). Moderate pain shows an increased power in the prefrontal area for EO (Figure 28), which supports a previous study that found increase workload in frontal electrodes for theta [212].

7.1.2.4 High Pain

It seems that high pain in theta band might represent a neuroplastic tendency for high severity NP since it is differentiable from control and low. However no significant difference was found between High-Mod in neither EC nor EO, which might indicate that theta activity does not suffer significant neuroplastic changes from moderate to high pain (Figure 38). In Figure 28, power was enhanced in EO for high pain in the occipital and parietal electrodes. Additionally, Figure 34 (gamma ApEn) supports the assumption that theta is a means of nested gamma oscillations. The gamma topoplots illustrate an increased level of ApEn surrounding the same areas as theta for high pain in EC (Figure 31), which is known as the edge effect in TCD theory [87]. Whether gamma and theta are actually correlated in our study still needs further investigation. Nevertheless, their location and intensity give intuition of what has been previously reported.

7.1.3 Alpha

Alpha oscillations characterize the resting state neuronal activity in EEG of humans [198], [213]. There are some implications that the primary function of alpha oscillations is the synchronization of internal mental processes [201]. Since Berger [214], many have reported alpha as an “idling rhythm”, measuring decrease in alpha power upon task performance [215]. For instance, in the somatosensory cortex (S1), watching painful situations suppressed somatosensory alpha oscillations [216]. Others have hypothesized alpha as a baseline for specific brain structures associated with the attentional system [205], during the processing of emotional arousing stimuli [217]. For instance, attention toward constant NP may deactivate the cortex as if it were performing a task [110], [112]. Alpha synchronization in the central/parietal region may reflect top-down control during perception of painful stimuli [218], [219], whereas alpha desynchronization reflects bottom-up release of this inhibitory control [213]. Hence, recent studies point towards a direct and active role for alpha frequency band rhythmicity in attention and consciousness, rather than the idling view that was previously thought [220].

7.1.3.1 Control

Alpha band statistical results were significantly different in EC only in Control-Low (Figure 39). This might suggest that even though NP poses an altered environment for alpha oscillations, there is no difference in the randomness of alpha during EC. In Figure 39 in EO, significant differences were found in Control-Low and Control-Mod. Alpha was the only band in which control was not differentiated from high pain. The reason may be related to neuroplastic changes occurring in the attentional system, where high pain may adapt to a control state attentionally or emotionally [205]. Note, the similarity between the distributions of control and high pain in the boxplot of Figure 39.

7.1.3.2 Low Pain

Low pain was significantly different in the following combinations for EC: Control-Low and Mod-Low. For EO, significant differences were found in Control-Low and High-Low (Figure 39). In fact, alpha desynchronization seen in Figure 28 for power in EO, might be the release of bottom-up inhibitory control that results in alpha desynchronization (plausibly more randomness) [213]. Hence, the generalized increase of ApEn in alpha band for low pain (Figure 32) may reflect the disorder in underlying neuronal networks towards a new way of perceiving sensory processes [221].

7.1.3.3 Moderate Pain

In EC, Low-Mod was significantly different. In EO, two combinations were significant: Control-Mod and High-Mod. Moderate pain follows in some way the narrow variability distribution as low pain (Figure 39) and perhaps also its same neurophysiological explication given above. Besides the generalized enhanced ApEn in EO (Figure 32), there is also some increase of alpha power (Figure 28) in moderate pain. This may be associated with the internal mental processes. If an internal mental process is active (such as pain rumination), inhibition of sensory perception and decreased attention to the external world follows [201].

7.1.3.4 High Pain

Alpha behaved unexpectedly for high pain. Power in EO (Figure 28) showed a slight increase of synchronization in the central and parietal regions, and a decrease of ApEn for these same regions (Figure 32). By the literature exposed previously, desynchronization in alpha band was expected for high NP. However, synchronization in central and parietal regions has been reported to reflect top-down control during perception of painful stimuli [218], [219]. Therefore, in high pain alpha synchronization may reflect the inhibition of painful stimuli, serving as an active inhibitory mechanism that gates sensory information by means of cognitive relevance [222]. In EC, there was decreased power for high pain (Figure 29), which could be attributed to lower attentional spans [198],[206].

7.1.4 Beta

Beta is a very prominent signal in the human sensorimotor cortex, generally associated with motor functions [196]. Other functions for beta oscillations have been found such as, top-down control [72] or serving as a large-scale link of neuronal interactions [223]. Recent studies have suggested a correlation between GABA concentrations and the power of beta band oscillations at rest [224]. GABAergic interneurons are behind the GABA concentrations, which play a crucial role in pain perception and processing [225], [226]. In fact, beta oscillations could represent an index of the GABAergic component of pain [227]. Even though some studies have reported an increase of beta activity in neurogenic pain [65], [85], lower beta power is explained by the brain inhibition that is a consequence from deficiency of GABA which leads to NP [228]. Furthermore, beta has been recognized as a characteristic oscillation in chronic pain, because it provides prediction signals via descending feedback connections, which hold the theory that chronic pain arises from prediction errors rather than nociceptive input [95], [229]. Beta power is maximal when the predicted perception presents.

7.1.4.1 Low pain

For low pain in EC the only significant difference occurred between Low-Mod. In the other hand low pain was significantly different for all groups in EO: Low-Mod, High-Low and Control-Low. This can be confirmed by observing the boxplot of Figure 40, where low pain has the highest ApEn. In the case of low pain, there is a decrease in power across all regions, except for the central region where there is increase in power (Figure 28). These changes occur in parallel to an increase in ApEn (Figure 33) in EO. Whether this activity comes from a decreased brain inhibition [228], from prediction errors [95], [229], or both is still to be determined.

7.1.4.2 Moderate pain

In EC, moderate pain was significant for Control-Mod and Low-Mod. In EO only Low-Mod were significantly different. In the boxplot of Figure 40, moderate pain has a very similar ApEn as in the control state. In the boxplot of power in EO (Figure 44), Mod-High was in the borderline of having a significant difference. Moderate pain seems to reduce the variability of beta power distribution as compared to the low pain state, this might be due to the increase of power in EO across all regions for moderate pain (Figure 28).

7.1.4.3 High pain

In Figure 40, high pain was significantly different in EC for Control-High only. In EO, Control-High and High-Low were significantly different. This is a very appropriate differentiation, because high pain is accurately reflecting a neuroplastic change that differs particularly from the lower severity and the control state which can be seen in the difference of ApEn (Figure 33). Also, for power in EC high pain has a generalized increased synchronization, particularly for the central region (Figure 29). Thus, supporting previous results concerning beta band as an optimal feature to predict central NP [49].

7.1.5 Gamma

Gamma band is also related in the pathogenesis of TCD. Gamma networks desynchronize and theta networks synchronize during encoding and retrieval [230]. Lower γ oscillations (as GABAergic EEG marker) have been found in pain controlling regions [225], such as the prefrontal cortex [231]. In the theory of predictive coding, prediction errors of perception induce error-related responses primarily in the gamma band (followed by an increased in beta) [94]. Gamma-band activity decreases, when the expected perception is fulfilled [232]. Gamma activity is believed to be a neuronal basis underlying the integration of sensory information into a coherent perception [233]. On a cellular level, it has been reported that gamma oscillations trigger synaptic transmission potentiation, which might further result in neuropathic pain generation after nerve injury and other aspects of the conscious pain experience [202], [234].

7.1.5.1 Control

The gamma band for EC reflected a significant difference only for Control-High. However, in EO the significant difference was found with Control-High and Control-Mod (Figure 41). In general, a decrease of power is observed in control in EO (Figure 26) with a slight increase of power in EC (Figure 27). The lower synchronization in EO compared to NP groups, might be due to the lack of interregional communication compared to NP groups. In NP, synchronization in gamma is needed to integrate sensory information in the coherent perception of pain [233].

7.1.5.2 Low Pain

Significant differences were found only in EO between High-Low only. In Figure 34, a generalized decrease of ApEn in EO can be observed compared to control group. This is confirmed with the boxplot of Figure 41 where there are decreased ApEn values. Additionally, this decrease of ApEn in EO is at the same time accompanied by an increase of power in the low NP severity (Figure 28).

7.1.5.3 Moderate Pain

In EC, High-Mod displayed a significant difference, while for EO the significant differences were found for Control-Mod and High-Mod. In the boxplots of Figure 41, moderate pain has a slightly higher ApEn than low pain, but still decreased ApEn compared to high pain. The increase of ApEn occurs primarily in the prefrontal and frontal electrodes for EO (Figure 34). The latter supports the results of other studies [235], [236] that describe higher pain ratings associated with stronger frontal and prefrontal gamma oscillations. The increase in gamma oscillations can also be observed in power for EO (Figure 28), but particularly for parietal and occipital regions. The continuous increase of gamma might be a reflection of synaptic transmission potentiation, which increases as pain increases [202], [234].

7.1.5.4 High Pain

In EC, two combinations were significant: High-Mod and Control-High. In EO, the significant differences were found for all group combinations involving high NP: Control-High, High-Low and High-Mod (see boxplots of Figure 41). This could also manifest gamma band as a neuromarker for high NP. It has been reported that for almost all brain regions, gamma power rises as that region desynchronizes with gamma activity elsewhere in the brain, establishing gamma as a largely **asynchronous** phenomenon [230]. In NP, there is an enhanced gamma power in EO for frontal, parietal and occipital regions (Figure 28) at the same time that we see an enhanced ApEn in EO (Figure 34). If gamma is a largely asynchronous phenomenon, then there could be enhanced gamma power (more synchronization), at the same time that there is increased ApEn (more desynchronization or randomness).

7.1.6 Bw Band

7.1.6.1 Control

The statistical results showed significant differences between the control group and all severities of pain in EO: Control-High, Low-Control, Mod-Control (Figure 42). This might mean that the full

Bw is another frequency band in which the neuroplastic tendencies for NP are effectively differentiated from the healthy state. In Figure 35, the difference in ApEn can be clearly observed. Control in EO and EC ranges from a generalized neutral state [0-0.2], while all severities of pain have localized areas with higher ApEn values [0.4-0.6].

7.1.6.2 Low Pain

For EC, the significant differences were found in all the combinations of low: Control-Low, High-Low and Low-Mod (Figure 42). Moreover, in Figure 35 there is an increased ApEn in the occipital lobe in EO for low pain that may be a consequence of the suppression of resting state occipital alpha-rhythm, which occurs in NP and is manifested predominantly in the occipital lobe [237]. If rhythmicity is suppressed, the irregularity increases and hence, the ApEn.

7.1.6.3 Moderate Pain

Moderate pain was significantly different for Low-Mod (in EC) and Control-Mod (in EO). For EO there is an overall increase in ApEn throughout the cortex with the highest ApEn localized between the frontal, central and parietal electrodes (Figure 35), where the sensory qualities of NP are processed. Besides, the generalized increased of ApEn may be due to the widespread changes of intermingled brain networks in the processing of pain [82].

7.1.6.4 High Pain

As pain severity increases, the irregularity of neuronal activity in NP patients shifts from posterior (low pain) to central parietal (moderate pain), to frontal brain areas in high pain (Figure 35). This frontal shifting may be supported by the role of emotional processing and executive behavior of the prefrontal cortex in the proper psychological and therapeutic management of chronic pain [238]. It is plausible that as NP increases, its sensory attributes (i.e., location and type of sensation) processed in somatosensorial cortex (CPz and central electrodes) are not processed anymore and coping abilities are the priority. Accordingly, the prefrontal cortex has two opposing yet leading roles in pain: (1) the location where top-down processing modulates pain in the dorsal

horn to the CNS, and (2) the area where induction of pain chronicity occurs [239]. In this frequency band, the significantly different combinations were Low-High (in EC) and Control-High (in EO).

7.2 Discussion and Limitations of Classifier

The results of the SVM classifier in this study reached a classification accuracy of 96% per class and above a 90% for the other scores in each class. These results were validated with cross-validation of 5k-fold. However, even with cross validation, there is still a possibility of overfitting from the SVM whenever exposed to unseen data. Thus, this model needs to be proven with new patient data to assure that there is no overfitting. Overfitting might happen when there is a generalization error due to an increased variance and low bias [168].

Some drawbacks of the model proposed might have been: (1) an inadequate number of observations vs features (at least 5 observations per 1 feature), this could result in less proportion of sample training data relative to dimensionality of features, (2) an increased number of features includes noise (high variance may result from modeling the noise in the training data), (3) not an adequate feature selection process. In this study, features were reduced in preprocessing by averaging and features were selected by the kernel function in the embedded method. However, other methods for feature reduction in the preprocessing stage could have been implemented, such as: (1) removing features with near-zero variance and (2) removing significantly correlated features that may contribute complexity to the model [167]. Also, in the classifier stage, wrapper methods may be implemented to reduce features, the most common in traditional SVM is recursive feature elimination, which removes features by recursively ranking them among increasingly smaller subsets of features through cross validation. This could have assured results with less chance of overfitting. If after applying this model to new data, overfitting is detected, then observations can be increased to 2,100 (60s x 35 patients) by segmenting EEG recordings in 10s rather than 60s. Even though the results of the classifier are not definite, the statistical results prove that ApEn can significantly differentiate among NP severities. For this reason, if the

model has a poor performance with new data, an improvement of it would be pursued. The classification based on NP severity and spectral bands might be informative because the interaction between the bands causes NP to persist. The results of another study, using a data-driven classification by means of SVM learning, show that theta, beta and gamma-frequency bands are important in differentiating between neuropsychiatric disorders and healthy control subjects in confirmation of the TCD model [240].

7.3 Limitations of Study

The limitations of the study include: (1) the relatively small sample size, (2) the fact that other cognitive processes are occurring in the brain besides NP which could also be responsible for the activity observed in the EEG, and (3) there is still not enough known to explain with conviction the changes observed in ApEn. Even though the ApEn discussion was based in the neurophysiology behind the power results of the literature, some ApEn activity might not coincide entirely with the assumptions made. That is, for some bands, for some locations and for some severities, ApEn was in fact inverse, but not always. In more than one case, a positive correlation was observed.

7.4 Contributions and Impact

- This is the first NP study that investigated NP by performing a parallel EEG analysis based on an integral proposal: uniting objective data (EEG features) with subjective criteria (BIP questionnaire).
- This is the first study that proves differentiable significance between NP severities using Nonlinear features.
- This study proves that different NP severities have diverse patterns of neuronal electrical activity that may reflect neuroplastic tendencies. For instance, higher pain severities differentiated most from control and low pain states. In some bands, there were no significant differences between closer severities of NP (High-Mod or Control-Low). Hence,

NP severity alters neuroplastic changes as severity increases. The only band that did not differentiate between control and high was the alpha band.

- This is the first study to compare ApEn and power. The comparison helps us advance in the questioning of our current understanding of neuronal activity and neuronal synchronization.
- It was also proven that the different conditions of EO and EC, modify the electrical activity in chronic NP with respect to different neuronal oscillations.

8 Chapter Eight: Conclusion and Future Work

8.1 Conclusion

The aim of this investigation was to identify chronic NP severity by fusing psychometric (on the basis of the Brief Inventory of Pain – BIP), and both linear (power) and nonlinear (ApEn) electroencephalographic (EEG) features. Particularly, whether the level of NP severity could be differentiable by patients' report (BIP) along with the analysis of EEG. For this purpose, we stratified the sample of patients based on the severity of pain (low, moderate and high pain), to evaluate the neuroplastic changes reflected in the neuronal electrical activity caused by the degree of involvement of the SNS. Our results show that ApEn is an attribute that significantly characterizes the different levels of chronic NP. Therefore, we prove our alternative hypothesis. Namely, that the EEG activity of chronic NP patients shows significant differentiable trends with respect to the severity of pain in the spontaneous state. Thus, the cortical electrical activity is a reflection of the dynamics of the neuronal networks in the SNS that are affected considerably with the greater severity of pain. Neuroplastic tendencies of NP were best identified from the control group in the full BW, theta and delta in EO. In particular, high pain was significantly different from control for all bands, except for the alpha band. Finally, our results show that the most utilized method for EEG analysis (power) did not yield any statistically significant results between the NP severities or control group. The latter points out that NP research could be extended to a deeper level by using ApEn to analyze EEG signals. With further characterization of NP, ApEn might be a very appropriate and sufficient method to monitor the experience of pain and aid physicians to achieve a better pain management and treatment for chronic NP.

8.2 Future Work

8.2.1 ApEn and Power

For future work, testing the classifier with new data is primordial. Generalization of the method is also desired. For that purpose, a larger sample is necessary, including both genders, a larger range of ages, and different clinical histories. Additionally, after the discussion of our results, we see the need to research the relationship between ApEn and power more profoundly. Some of the questions that have arisen are the following:

What is the correlation between the synchronous electrical activity measured as power and the signal irregularity measured as ApEn in chronic NP? Is this relationship dependent on pain severity or frequency band? If there is correlation, is there causality? What is behind the increased ApEn? Is it global desynchronization or local synchronization? How does alternating between EO and EC change the processing of NP in ApEn analysis?

We propose to answer these questions by signal simulation and linear regression models. Afterwards, the connectivity between the frequency bands will be investigated, because of the dynamic environment needed to integrate the perception of NP. This can be done by researching phase-amplitude and cross-frequency coupling that occurs between theta–gamma and theta–beta oscillations [240]. Recent research suggests that phase-amplitude coupling reflects with better precision the physiological mechanism for effective communication in the human brain [241]. Cross-frequency coupling might be important for the integration via low-frequency coherence of distributed, local, and high-frequency activity [242]. All these questions are highly important in NP research and have been poorly addressed specially with EEG.

8.2.2 Evoked domain

For a much deeper understanding of NP, the evoked component needs to be studied as well. Allodynia is the principal symptom in NP patients, but the measurement of allodynia has not been standardized to evaluate patients in a periodic and replicable fashion, as would be needed for an

objective evaluation of NP. The QST has calibrated tools in other domains of sensation such as temperature, pressure or pinprick, but it is not the case for mechanical allodynia [142], [243], [244]. After the present discussion, we consider that a system where allodynia is evoked with ordinary stimuli: a caress, vibration and air is necessary. These stimuli would be applied in the most painful peripheral area that was marked by the patient in the subjective evaluation. There would be three blocks, one for each stimulus and four ascending levels for each block. Each stimulus will have different units to ascend through the levels. Each level contains three stimuli with the same force. Every stimulation should have its particular stimulation zone, because the character of pain depends on the A∂ and C nociceptors, and on the type of skin. As discussed previously, patients with chronic NP have delayed sensation to stimuli in EEG, so there should be 25 seconds between every stimulus, even if they are the same modality. After the evoked EEG, a post-stimuli session of spontaneous EEG should be recorded, to monitor the affection of the spontaneous oscillations after being stimulated. Figure 45 describes the spontaneous recording session, plus the evoked session proposed in this section.

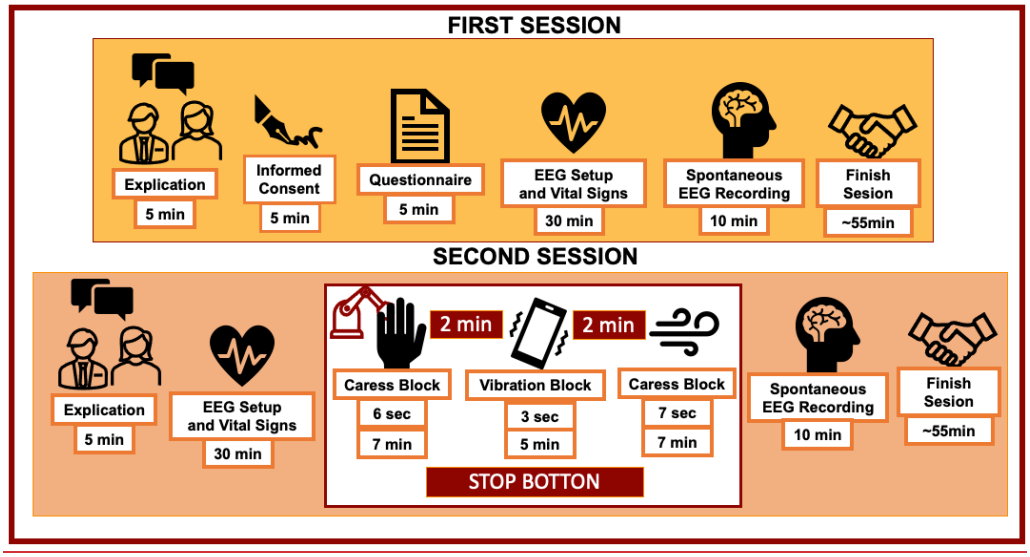


Figure 48 Integrated method of spontaneous and evoked measurement sessions. The first session was described in Figure 18 in our methodology. The second session comprehends the evoked activity recording and a post-stimuli spontaneous EEG recording. The total time for every activity is marked below it. The proposed stimulation time for tactile, vibration and air stimuli are 6s [60], 3s, and 12s [245], respectively. Total time for the 4 levels of stimulation with rest periods is marked in a box below the stimulation time.

8.1 Ethics Committee

This study was submitted to the Ethics Committee of CEIC TecSalud in April 2020. It was approved with the following number: P000369-DN-RespElectro-CI-CR005.

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8.3 Work in process of publication

Table 5: Papers submitted for publication.

Type of paper	Authors	Title	Journal	Date of Submission	Current Status
Review Article	Daniela M. Zolezzi, Luz Maria Alonso-Valerdi, David I. Ibarra-Zarate	Chronic neuropathic pain is more than a perception: systems and methods for an integral characterization	Neuroscience and Biobehavioral Reviews	March 8, 2021	Under review
Congress – Full contributed paper	Daniela M. Zolezzi, Luz Maria Alonso-Valerdi, Norberto Emmanuel Naal-Ruiz, David I. Ibarra-Zarate	Identification of Neuropathic Pain Severity based on Linear and Nonlinear EEG Features	43rd Annual International conference of the IEEE Engineering in Medicine and Biology Society (EMBC)	May 1, 2021	Under review
Database of raw EEG data	Daniela M. Zolezzi, Luz Maria Alonso-Valerdi, Norberto Emmanuel Naal-Ruiz, David I. Ibarra-Zarate	Chronic Neuropathic Pain EEG Raw data in EC (5 min) and EO (5 min)	Mendeley Data	May 17, 2021	Under review

The work described in this thesis is only a first approximation to the objective characterization of chronic NP with linear and nonlinear EEG analysis. Much more work is needed for this characterization to be applicable in daily clinical practice and eventually help physicians in the management and treatment of chronic NP patients.

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Annex 1: Table 3

Table 3. EEG studies concerning analysis of evoked activity in patients with chronic pain and NP.

Study	Electrodes	Sampling Frequency (Hz)	Number of patients	Stimuli	Results	Limitations	NP or other disorders?
[102]	**19**	256	54 patients: 42 with central NP and (2) 12 with lateralized pain of non-organic origin	Blocks of 20-30 stimulus repetitions of laser stimuli applied to the dorsum of the hand	**↓ amplitude of N1 and P2 in hyperalgesia/allodynia and spontaneous pain ↑ latency for both groups of pain, patients with allodynia presented ultra-late responses (>700 ms)**	The presence or absence of medication from patients **was not declared**	**The vast majority of patients had NP**
[108]	**Not clear about their electrode placement. Only Cz was reported**	Not stated	40 NP patients: (1) 19 patients with NP in hands and (2) 21 without NP in hands	10 - 20 trials of laser stimuli applied to the dorsum of the hand	**↓ LEP amplitude in patients with NP in hands, pain intensity correlated inversely with LEP amplitude**	Mean age (62.8) might bias the results [33]	**Only NP**
[170]	**Midline electrodes: *Fz, Cz, Pz, and Oz***	250	14 patients with chronic pain and 30 healthy controls	Task stimuli consisted of: (1) pressing the right-hand button when a blue rectangle appeared (easy), and (2) subjects had to compare each rectangle with the preceding one (difficult)	**For chronic pain patients in contrast to healthy controls: ↓reaction times, ↑error rate in difficult task, ↓ P1 independent of task difficulty, ↑amplitude for difficult task at frontocentral electrodes, ↑P3 amplitude by irrelevant stimuli**	Diversity of clinical features of the chronic pain patients	**Given the diagnoses reported in the study, at least 8 patients from 14 had NP**
[80]	**32**	1000	19 patients with chronic pain and 21 healthy controls	560 somatosensory stimuli were applied to the index finger in a random series (480 frequent, 80 deviant). Pictures (pleasant and unpleasant) were presented for 6s followed by a blank screen for 6s	**↓ theta and beta band power in pain patients** viewing pleasant images **↓ P50 amplitudes of ERPs in chronic pain when viewing pleasant images ↑ entropy in P4 electrode in chronic pain**	72.2% of patients were taking and 52.6% of patients were taking and anxiolytics	**The majority of patients had musculoskeletal pain, but some had NP due to spinal cord injury or peripheral neuropathy**
[114]	**61**	1000	Three groups: (1) 10 paraplegic patients with central NP, (2) 9 paraplegic patients without NP, (3) 9 healthy controls	Participants imagined hand or lower limb movements. There were 60 trials of each movement (right hand, left hand, feet), giving a total of 180 stimuli	**↑ largest and spatially distinctive ERD for NP patients** in theta, alpha and beta band and in centro-parietal region	It was not possible to separate the effect of paralysis and NP (all NP patients were paraplegic)	**Paraplegic patients and NP with paraplegia**

Annex 2 NP Questionnaires: PDQ and BIP

painDETECT

CUESTIONARIO DEL DOLOR

Fecha: Paciente: Nombre: Apellidos:

¿Cómo valoraría el dolor que siente **ahora**, en este momento?

0 1 2 3 4 5 6 7 8 9 10

Ningún dolor — Máximo dolor

¿Cuál ha sido la intensidad del dolor **más fuerte** que ha sentido en las últimas 4 semanas?

0 1 2 3 4 5 6 7 8 9 10

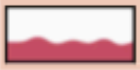
Ningún dolor — Máximo dolor

¿**Por término medio**, cuál ha sido la intensidad de su dolor en las últimas 4 semanas?

0 1 2 3 4 5 6 7 8 9 10

Ningún dolor — Máximo dolor

Marque con una cruz la imagen que mejor describa el curso de su dolor:

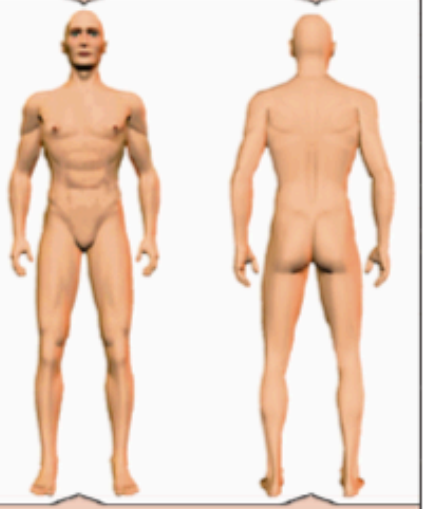

Dolor constante con ligeras fluctuaciones ☐


Dolor constante con ataques de dolor ☐


Ataques de dolor sin dolor entre los ataques ☐


Ataques de dolor frecuentes con dolor entre los ataques ☐

Marque su **principal zona de dolor**



¿Se irradia el dolor hacia otras partes de su cuerpo? sí ☐ no ☐

Si la respuesta es sí, indique con una flecha la dirección hacia la que se irradia el dolor.

¿Tiene una sensación de quemazón (p.ej. como por roce de ortigas o al tocar la lejía) en la zona de dolor marcada?

no ☐ muy ligera ☐ ligera ☐ moderada ☐ intensa ☐ muy intensa ☐

¿Tiene una sensación de hormigueo o cosquilleo (como una corriente eléctrica) en la zona de dolor marcada?

no ☐ muy ligera ☐ ligera ☐ moderada ☐ intensa ☐ muy intensa ☐

¿Le produce dolor cualquier ligero roce (p.ej. la ropa o las sábanas) en esta zona?

no ☐ muy ligero ☐ ligero ☐ moderado ☐ intenso ☐ muy intenso ☐

¿Tiene ataques de dolor repentinos, como descargas eléctricas, en la zona de dolor marcada?

no ☐ muy ligeros ☐ ligeros ☐ moderados ☐ intensos ☐ muy intensos ☐

¿En alguna ocasión le produce dolor el contacto del frío o el calor (p.ej. el agua de la ducha) en esta zona?

no ☐ muy ligero ☐ ligeros ☐ moderado ☐ intenso ☐ muy intenso ☐

¿Tiene una sensación de entumecimiento (adormecimiento) en la zona de dolor marcada?

no ☐ muy ligera ☐ ligera ☐ moderada ☐ intensa ☐ muy intensa ☐

¿Se desencadena el dolor con solo una ligera presión en la zona de dolor marcada (p. ej. con el dedo)?

no ☐ muy ligero ☐ ligero ☐ moderado ☐ intenso ☐ muy intenso ☐

(a rellenar por el médico)

no	muy ligero	ligero	moderado	intenso	muy intenso
☐ x 0 = 0	☐ x 1 = ☐	☐ x 2 = ☐☐	☐ x 3 = ☐☐	☐ x 4 = ☐☐	☐ x 5 = ☐☐

Puntuación total ☐☐ **sobre 35**

R. Freynhagen, R. Baron, U. Gockel, T.R. Tölle, CurrMed ResOpin Vol 22, 2006, 1911-1920

painDETECT

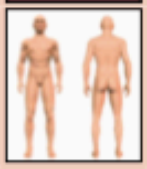
Puntuación del cuestionario del dolor

Fecha: Paciente: Nombre: Apellidos:

Transcriba la puntuación total del cuestionario del dolor:

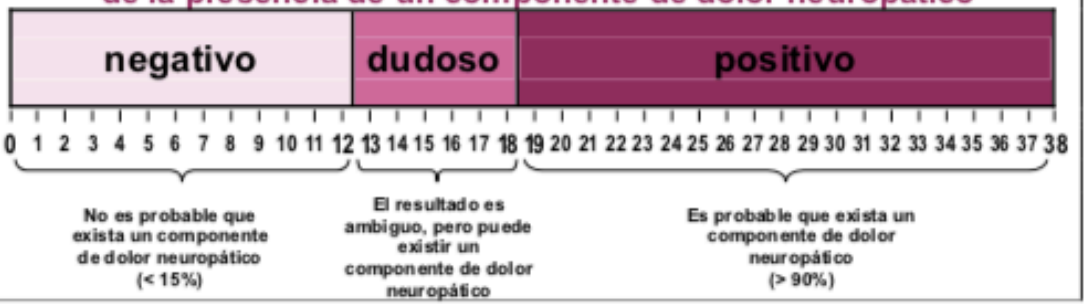
Puntuación total ☐☐

Sume las siguientes cifras en función del patrón de comportamiento del dolor marcado y de la presencia o ausencia de dolor irradiado. A continuación calcule la puntuación final:

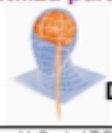
	Dolor constante con ligeras fluctuaciones	0
	Dolor constante con ataques de dolor	-1 si se ha marcado esta imagen, o
	Ataques de dolor sin dolor entre los ataques	+1 si se ha marcado esta imagen, o
	Ataques de dolor frecuentes con dolor entre los ataques	+1 si se ha marcado esta imagen
	¿Dolor irradiado?	+2 si la respuesta es sí
	Puntuación final	☐☐

Resultado del análisis

de la presencia de un componente de dolor neuropático



Este cuestionario no sustituye el diagnóstico médico.
Se utiliza para analizar la presencia de un componente de dolor neuropático.



DFNS

pain

R. Freynhagen, R. Baron, U. Gockel, T.R. Tölle, CurrMed ResOpin Vol 22, 2006, 1911-1920

Cuestionario Breve para la Evaluación del Dolor

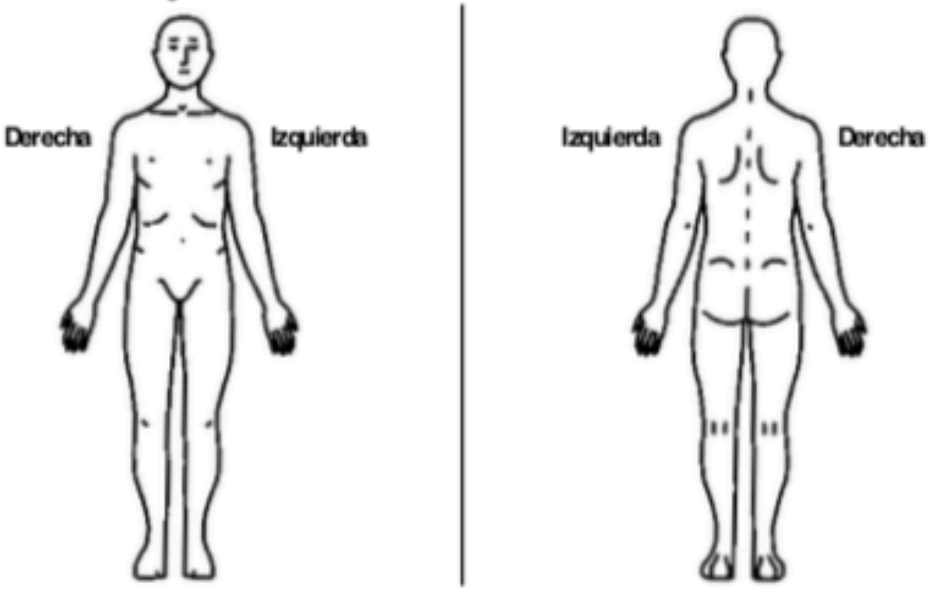
Fecha: _____ /_____ /_____ Hora: _____

Apellido:_____ Nombre:_____

1. Todos hemos tenido dolor alguna vez en nuestra vida (por ejemplo, dolor de cabeza, contusiones, dolores de dientes). ¿En la actualidad, ha sentido un dolor distinto a estos dolores comunes?

   1. Sí 2. No

2. Indique en el dibujo, con un lápiz, donde siente el dolor. Indique con una "X" la parte del cuerpo en la cual el dolor es más grave.



3. Clasifique su dolor haciendo un círculo alrededor del número que mejor describe la intensidad **máxima** de dolor sentido en las últimas 24 horas.

0	1	2	3	4	5	6	7	8	9	10
Ningún Dolor										El Peor Dolor Imaginable

4. Clasifique su dolor haciendo un círculo alrededor del número que mejor describe la intensidad **mínima** de dolor sentido en las últimas 24 horas.

0	1	2	3	4	5	6	7	8	9	10
Ningún Dolor										El Peor Dolor Imaginable

5. Clasifique su dolor haciendo un círculo alrededor del número que mejor describe la intensidad **media** de dolor sentido en las últimas 24 horas.

0	1	2	3	4	5	6	7	8	9	10
Ningún Dolor										El Peor Dolor Imaginable

6. Clasifique su dolor haciendo un círculo alrededor del número que mejor describe la intensidad de su dolor **actual**.

0	1	2	3	4	5	6	7	8	9	10
Ningún Dolor										El Peor Dolor Imaginable

7. ¿Qué tratamiento o medicamento recibe para su dolor? _____

_____

8. ¿En las últimas 24 horas, cuánto **alivio** ha sentido con el tratamiento o con el medicamento? Indique con un círculo el porcentaje que mejor se adapta a su alivio.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Ningún Alivio										Alivio Total

9. Haga un círculo alrededor del número que mejor describe la manera en que el **dolor ha interferido**, durante las últimas 24 horas, con su:

A. Actividad en general

0	1	2	3	4	5	6	7	8	9	10
No Interfiere										Interfiere por Completo

B. Estado de ánimo

0	1	2	3	4	5	6	7	8	9	10
No Interfiere										Interfiere por Completo

C. Capacidad de caminar

0	1	2	3	4	5	6	7	8	9	10
No Interfiere										Interfiere por Completo

D. Trabajo normal (ya sea en casa o afuera)

0	1	2	3	4	5	6	7	8	9	10
No Interfiere										Interfiere por Completo

E. Relaciones con otras personas

0	1	2	3	4	5	6	7	8	9	10
No Interfiere										Interfiere por Completo

F. Sueño

0	1	2	3	4	5	6	7	8	9	10
No Interfiere										Interfiere por Completo

G. Capacidad de diversión

0	1	2	3	4	5	6	7	8	9	10
No Interfiere										Interfiere por Completo

Annex 3: Informed Consent

Before the restrictions and circumstances imposed by the current COVID-19 pandemic, it was proposed that patients would be **recruited** from two Tec Salud centers:

(1) Pain management center of the Zambrano Helión Hospital in San Pedro Garza García, NL, Mexico
(2) Eugenio and Eva Garza Lagüera Center for Medical and Diagnostic Specialties (CEM) in Santa Catarina, N.L. Mexico (*this center has been closed throughout the pandemic*)

EEG recordings were also meant to be in those preestablished centers. However, as the pandemic advanced, it was neither possible (entrance was strictly supervised) or safe to ask patients to assist a hospital without any urgent necessity. **In view of this situation and by recommendation of Dr. Fernando Cantú,** patients were recruited through social media. In order to control the influx of patients, a private doctor's office in Guadalupe, NL was borrowed to us. This establishment was closed during the pandemic and only opened for the 35 NP patients that we recruited. Three patients or four at maximum were seen in a day. The doctor's office was located in the following address: Lic. Amador Garza Sepúlveda 2303, 25 de Noviembre, 67174, Guadalupe, NL.

The following Informed Consent is written in Spanish, as was given to the patients of the study.

Centro de estudio: Hospital Zambrano Hellion
Domicilio: Batallón San Patricio 112 Col. Real de San Agustín CP 66278, San Pedro Garza García, Nuevo León, México
Número telefónico de oficina: Centro del Manejo de Dolor, 8888-0000 Extensión 5491
Número telefónico de atención las 24 horas: 8888-0911
Hospital donde se verán eventos adversos serios del protocolo: Hospital Zambrano Helión

Comité de Ética e Investigación de la Escuela de Medicina del Instituto Tecnológico y Estudios Superiores de Monterrey
Persona de contacto: Dr. Víctor Lara Díaz
Domicilio: Av. Ignacio Morones Prieto 3000, Sertoma, 64710 Monterrey, NL
Número telefónico: (+52) 81 88882275

Coinvestigadores médicos con especialidad en dolor **Centro de Manejo de Dolor, Hospital Zambrano Hellion, Tec Salud**	**Dr. José Miguel Guerra** Anestesiólogo con subespecialidad en dolor Núm. Cédula Médico General: 6883518 Núm. Credencial Anestesiología: 9405751
	Dr. Fernando Cantú Flores Anestesiólogo con subespecialidad en dolor desde el 2001. Núm. Cédula Médico General: 1336326 Núm. Credencial: en proceso de renovación.
Coinvestigadores secundarios del área de ingeniería **Tec de Monterrey**	**Dra. Luz María Alonso Valerdi** Interfaz cerebro-computadora y registro de bioseñales. SNI: Nivel 1
	Dr. David Isaac Ibarra Zárate Procesamiento de señales y neuroacústica. SNI: Nivel 1

CARTA DE CONSENTIMIENTO INFORMADO

Dirigido a: Pacientes con Dolor Neuropático Crónico

Título del estudio:

"Caracterización de la Respuesta Electrofisiológica del Dolor Neuropático para Monitorear la Experiencia de Dolor"

Investigador Principal: Lic. Daniela Montemayor Zolezzi
Investigadores Secundarios: Dra. Luz María Alonso Valerdi -- Dr. David Isaac Ibarra Zárate
Fecha de aprobación por el Comité de Ética: XX/XX/XX
El siguiente consentimiento informado es aprobado por el Comité de Ética de la Escuela de Medicina del Tecnológico de Monterrey para cualquier persona involucrada en un estudio de investigación patrocinado por la universidad.

Introducción:
Estimado(a) Señor/Señora:
Usted ha sido invitado a participar en el presente proyecto de investigación, el cual es desarrollado por la Escuela de Ingeniería y Ciencias del Tecnológico de Monterrey en colaboración con los especialistas de dolor de la Escuela de Medicina Tec Salud. Ambas sesiones del estudio se realizarán en el Hospital Zambrano Hellion en San Pedro Garza García. Las sesiones serán en el día y hora que el paciente decida, durante el horario (9:00 am a 6:00pm) que permanece abierto el Centro de Manejo de Dolor en el Zambrano.

Si Usted decide participar en el estudio, es importante que considere la siguiente información. Siéntase libre de preguntar cualquier asunto que no le quede claro.

Objetivos y Justificación de Investigación: El objetivo de la investigación es identificar el dolor neuropático crónico por medio de electroencefalografía para monitorear la experiencia de dolor y el grado de afectación del sistema nervioso somatosensorial. La electroencefalografía es una herramienta que detecta la electricidad emitida por el cerebro por medio de electrodos. Posteriormente, esta señal puede ser analizada para encontrar patrones que den parámetros objetivos sobre el dolor neuropático en una persona. En México y en todo el mundo, el dolor es un reto por su carácter subjetivo. Debido a la carencia de una medida objetiva para el dolor neuropático, los tratamientos son tan variados que los fármacos de primera línea varían con la opinión de cada especialista. En este estudio, el objetivo es clasificar a los pacientes por la naturaleza del dolor, es decir, por su intensidad o tiempo con dolor. Una vez divididos, se analizará el dolor neuropático en su componente espontáneo. Además de la actividad eléctrica como medida objetiva, se tomará la percepción del paciente sobre su dolor por medio de cuestionarios como medida subjetiva. Como último objetivo, se compararán ambas medidas, la objetiva y subjetiva, para proporcionar al médico una perspectiva integral sobre el estado de afectación del sistema nervioso somatosensorial en un paciente.

Criterios de elegibilidad: Le pedimos participar en este estudio porque usted forma parte de la población de dolor neuropático crónico mayor a 3 meses, su edad está entre el rango de 18 y 60 años, ha tenido un tratamiento estable por al menos las últimas 3 semanas, existe una ausencia de un desorden psiquiátrico mayor y su NP crónico está en al menos una de las cuatro extremidades.

Procedimiento:
El protocolo consiste en dos sesiones. Durante este semestre solamente registraremos la primera sesión.

Instrumentos utilizados:

- **Electroencefalograma (EEG)**: gorra que detecta la electricidad emitida por el cerebro por medio de electrodos.

- **Prototipo**: para las estimulaciones usaremos un prototipo automático y calibrado que tiene un botón de paro que usted puede parar en el momento que lo desee.
- **Pulsímetro**: aparato pequeño que mide la frecuencia cardíaca desde un dedo de la mano.

Su participación consistirá en:

- La primera sesión **durará máximo 50 min,** pero pueden durar menos. En la primera sesión, se explicará el procedimiento de todo el protocolo.
- Después, le entregaremos el **consentimiento informado** para que lo firme si está de acuerdo. Si procede a firmar el consentimiento, posteriormente le pediremos que **conteste dos cuestionarios sobre el dolor y el impacto que tiene en su vida**.
- Cuando termine, tomaremos su frecuencia cardíaca con un pulsímetro en su dedo índice y comenzaremos con la instalación del equipo.
- El registro de EEG de la primera sesión durará tan sólo 10 minutos, en los que permanecerá sentado en una posición cómoda con los ojos cerrados por cinco minutos y con los ojos abiertos por 5 minutos. Se le proporcionará un cubre ojos para su comodidad.
- En la segunda sesión, pasaremos directo a la instalación del equipo y se le colocará de nuevo el pulsímetro que será retirado en un minuto. Una vez terminada la instalación del equipo de EEG, comienzan los bloques de estimulaciones. Son cuatro bloques para tres diferentes estímulos: caricia, vibración y aire. Durante los estímulos le pediremos que mantenga los ojos cerrados y le brindaremos de nuevo el cubre ojos para su comodidad.
- El primer estímulo será una ligera caricia sobre su brazo o pierna, dependiendo de la región que usted nos haya marcado en el cuestionario. Esta caricia será una tela que pasa por su brazo y poco a poco ira subiendo de intensidad. En cualquier momento, usted tiene la opción de detener las estimulaciones con un botón, el cual parará el estudio completamente. En el caso que esto sucediera, usted puede seguir con la siguiente modalidad de estímulo si lo desea, y si no, podemos dar por terminada la sesión. Entre cada estímulo y cada cambio de sensación habrá un pequeño descanso. El segundo estímulo es la vibración que será aplicada en la palma de su mano o la planta de su pie. El tercer estímulo será aire que proviene de un pequeño ventilador a 10 cm de su piel. El tiempo transcurrido durante las estimulaciones son 20 min aproximadamente en total.
- Terminada la sesión de estimulación, se le tomará un último EEG en reposo.

Sobre medicamentos: Usted puede seguir tomando sus medicamentos como es costumbre. El régimen terapéutico que lleva nos lo indicará el médico y su historial clínico.

Beneficios: Después de las dos sesiones, le entregaremos $300 pesos en efectivo como mínimo para saldar los gastos de transporte y estacionamiento. Adicionalmente, una vez terminada la investigación, se le darán a conocer los resultados de su estudio. En particular, se le explicará por medio de mapas y gráficas el grado de afectación del dolor neuropático en su sistema nervioso. Aunque esto aún no sea un beneficio directo sobre su dolor, será una herramienta que ayude a su médico a tomar mejores decisiones en base a su tratamiento.

Por medio del presente hacemos constatar la total garantía de recibir respuesta a cualquier pregunta y aclaración ante cualquier duda acerca de los procedimientos, riesgos, beneficios y otros asuntos relacionados con la investigación.

Confidencialidad: Toda la información que usted nos proporcione para el estudio será de carácter estrictamente confidencial, será utilizada únicamente por el equipo de investigación del proyecto y no estará disponible para ningún otro propósito. En la investigación, no se identificará al paciente con nombre, manteniendo la confidencialidad de la información relacionada con su privacidad. Se usará la abreviatura: ID1, ID2, ID3… Los resultados de este estudio serán publicados con fines científicos, pero se presentarán de tal manera que no podrá ser identificado(a).

Participación Voluntaria/Retiro: Su participación en este estudio es absolutamente voluntaria. Usted tiene la libertad de retirar su consentimiento en cualquier momento y dejar de participar en el estudio, sin que por ello se creen prejuicios para continuar su cuidado y tratamiento.

Nos comprometemos a proporcionarle información actualizada obtenida durante el estudio, aunque ésta pudiera afectar la voluntad del sujeto para continuar participando.

Riesgos e inconvenientes: Los riesgos involucrados en el estudio son mínimos. Todo el equipo que entre en contacto directo con su piel es estéril y en ningún momento se generará una lesión o herida sobre la piel o cuero cabelludo. El mayor inconveniente respecto a esto, pudiera ser una irritación menor del cuero cabelludo al retirar el gel que se aplicó para los electrodos. Aun así, el gel se puede retirar fácilmente de su cabello con un lavado adecuado. En la modalidad caricia del prototipo, pudiera causar incomodidad la fricción de la tela con su brazo, pero si llega a ser muy incomodo puede oprimir el botón de paro y podemos aplicar una crema como Neosporin. Si alguna de las preguntas de los cuestionarios de dolor, lo hiciere sentir incomodo(a), tiene el derecho de no responderla.

Costos: Los costos fueron sufragados por el grupo de investigación de Neuroingeniería y Neuroacústica del Tecnológico de Monterrey. Dentro de los costos, se encuentran $2000 pesos de material de apoyo para el equipo de EEG (vendas, mallas) y material de limpieza. El equipo de EEG y el pulsímetro son parte del equipo que ya ha sido comprado por el grupo antes de este proyecto. El costo para los materiales del prototipo fue $14,575.90 pesos, mismo que se sufragó con el presupuesto del Grupo de Neuroacústica en el mes de febrero 2020.

Contacto: Si usted tiene alguna pregunta, comentario o preocupación con respecto al proyecto, por favor comuníquese con la investigadora responsable del proyecto: Lic. Daniela Montemayor Zolezzi, al siguiente número de celular 8116289000 en un horario de 6:00 am a 16:00 hrs o al correo electrónico: a01039052@itesm.mx.

Si usted tiene preguntas generales relacionadas con sus derechos como participante de un estudio de investigación puede comunicarse con el Dr. Víctor Lara Díaz de Tec Salud, al número (+52) 81 88882275, de 9:00 am a 16:00 hrs.
No firme este formato a menos que usted haya tenido la oportunidad de hacer preguntas y de que haya obtenido respuestas satisfactorias a todas sus preguntas.

SUS DERECHOS NO SON AFECTADOS BAJO NINGUNA LEY DE PROTECCIÓN DE LA INFORMACIÓN.

¿A quién poder contactar si tengo preguntas sobre mis derechos?

Este Consentimiento ha sido revisado por Comité de Ética en Investigación de la Escuela de Medicina del Instituto Tecnológico y de Estudios Superiores de Monterrey y el Comité de Investigación de la Escuela de Medicina del Instituto Tecnológico y de Estudios Superiores de Monterrey.

Si tiene alguna preocupación o queja acerca de este estudio o sobre cómo se está realizando, o alguna pregunta con respecto a sus derechos como un participante de investigación, usted puede comunicarse al (01) 81 88882107

Declaración de la persona que da el consentimiento

Por la presente doy mi consentimiento para ser objeto de esta investigación. Afirmo que se me ha dado:

A. Una explicación de los procedimientos que deben seguirse en el proyecto, con indicación de los que son experimentales.

B. Respuestas a las preguntas que he hecho.

Entiendo que:

A. Mi participación es voluntaria y puedo retirar mi consentimiento y dejar de participar en el proyecto en cualquier momento. **Mi negativa a participar no dará lugar a ninguna sanción.**

B. Al firmar este acuerdo, no renuncio a ningún derecho legal o liberación al Instituto Tecnológico y de Estudios Superiores de Monterrey ni a sus agentes de responsabilidad por negligencia.

Nombre del paciente _____

Fecha (dd/mm/aa) _____

Firma del paciente_____

Testigo 1

Nombre: _____

Dirección: _____

Relación con sujeto de investigación: _____

Firma: _____

Testigo 2

Nombre: _____

Dirección: _____

Relación con sujeto de investigación: _____

Firma: _____

Este consentimiento se extenderá por duplicado, quedando un ejemplar en poder del sujeto de investigación

Resumen de Protocolo

Fecha: _____

Gracias por ser parte de este experimento.

Antes de leer este documento ya debe de haber firmado el consentimiento informado. Si no es así solicítelo al investigador. A partir de este momento se debe guardar confidencialidad acerca del estudio.

1. Se debe de tener en cuenta algunas cosas para que la adquisición de los datos sea de buena calidad, se le dará una hoja donde se explica que debe de hacer durante el experimento, es necesario que usted como participante las tenga presente.
2. Se hará adquisición de información de ondas cerebrales. Esta es una muy pequeña actividad eléctrica que el cerebro y produce como efecto secundario de la interacción de las neuronas, debido a que es muy pequeña se trata de que en el lugar a efectuarse el experimento exista la menor cantidad de fuentes de ruido eléctrico, por lo cual por favor no debe de llevar su teléfono celular ni otro aparato electrónico consigo.
3. Por favor intente moverse lo menos posible, la fricción con la alfombra o con la silla puede causar estática eléctrica, aún en pequeñas cantidades, la estática es mayor que las ondas cerebrales, además si el ruido eléctrico generado por los músculos es mayor a las ondas eléctricas que se desean detectar. Usted tendrá momentos y espacios para descansar.

4. Si usted tensiona los músculos de su cara, pierna, cuello, o hombros, causará una gran cantidad de ruido eléctrico. Por favor tampoco apriete sus dientes. Trate de mantenerse en estado de relajación muscular, prestando la atención necesaria para realizar las acciones solicitadas durante el experimento, no se preocupe por su rendimiento, lo hará bien. Preocuparse solo elevará la tensión muscular y generará datos sin la calidad deseada.
5. Si usted toca los electrodos en su cabeza, puede afectar el contacto entre el electrodo y la piel. Inclusive un pequeño desplazamiento de los electrodos puede afectar la adquisición de los datos, si algún electrodo es incómodo para usted, por favor infórmele al investigador. En general, la incomodidad es mínima y conforme pasen los minutos dejará de sentir la presencia de los electrodos.
6. Durante los periodos de descanso, los investigadores podrán revisar y ajustar los electrodos si es necesario, además podrán darle instrucciones sobre qué debe de hacer durante el resto del experimento, por favor atienda las instrucciones que se le sean dadas.
7. Informe al investigador a la brevedad si alguno de los estímulos comienza a causar más dolor de lo soportable y siéntase con la confianza de parar.
8. Usted tiene la posibilidad de contactar a cualquier médico residente en el piso, o a su médico de cabecera si se ve en la necesidad de asistencia médica.
9. Gracias por su paciencia. Si usted tiene alguna duda sobre el experimento o por favor **notifíquele al investigador de inmediato**, ellos se asegurarán de que usted pueda comprender y llevar a cabo el experimento.

¡Muchas gracias, ahora los investigadores darán una explicación del experimento, recuerde seguir las instrucciones!

Annex 4: Patient profile questions

(a) Full Name

(b) Age

(c) NP cause

1. Diabetes
2. Peripheral Neuropathy
3. Trigeminal Neuralgia
4. Spinal cord or nerve root injury
5. Central Nervous System Disorder (i. e., CRPS, Lyme disease)
6. Other

(d) Time elapsed with chronic NP

(e) Current drug treatment (choose all that apply)

1. Pregabalin
2. Amitriptyline
3. Tramadol
4. Gabapentin
5. CBD derivatives
6. Other
7. I do not take any medication currently.

(f) If you answered yes, how long have you been in that current drug treatment?

(g) Have you had any procedures to manage your pain? (Select all that apply)

1. Infusions
2. Nerve blocks
3. Any type of surgery
4. Other

5. I have not had any procedures.

(h) Do you attend with regularity to a psychological or emotional therapy for pain management?

(i) If your answer was yes, please write down the name of your therapy.

(j) Do you suffer from any other pain condition like arthritis, migraine or fibromyalgia?

(k) Do you suffer from a major mental disorder? (i.e., schizophrenia, bipolar disorder, post-traumatic stress disorder or dissociative disorders)

(l) Do you suffer from any other neurological condition? (i.e., epilepsy, Alzheimer, tinnitus)

(m) Have you suffered from a severe neurological traumatism or a brain-infarct?

Annex 5: Health Guidelines for Medical Units

The following health guidelines are based on the health protocol for the safe restart of activities in medical units of the Health Secretariat of Mexico City [171].

- At the entrance of the workplace, 70% alcohol-based gel will be applied to the hands of the researchers, participants and companions before entering the office.
- The temperature of each person entering the unit will be measured with an infrared thermometer.
- Prior to the experimental procedure, participants will be sent a COVID19 symptom questionnaire and will also ask if they have been in recent contact with people sick with the virus.
- Only researchers wearing masks, gowns and face shields will be allowed to enter the office. Regarding the participants, they can only enter if they wear a mask.
- At the beginning, between each participant, and at the end of the experimental sessions, surfaces, materials and electronic devices will be thoroughly cleaned.
- Electronic devices will be cleaned with alcohol-free disinfectant wipes with the following ingredients:
    - Water, Isopropyl Alcohol, Dipropylene Diamine Laurylamine, Propylene Glycol, Fragrance, Glycerin, Sodium Cocoamphoacetate, Hydrogenated Castor Oil, Citric Acid, Benzalkonium Chloride, Tetrasodium EDTA, Emulsifier.
- Investigators should avoid being in front of the participant during the EEG recordings and maintain a healthy distance at all times.

The cleaning of the doctor's office should be done in the following order:

1. Cleaning will start from the least used places towards the most used places, and from top to bottom.

2. Cleaning of surfaces will be done in one direction only to avoid passing through areas that have already been disinfected.

3. Cleaning of the surfaces will be done with a cloth with water and detergent.

4. After cleaning a surface, the cloth will be rinsed with clean water and disinfected.

The disinfectant substances recommended in [171] are the following:

- Chlorine solution 0.1% (1000 ppm) at least, which is obtained by adding 25 ml of sodium hypochlorite (4% commercial chlorine) in 1 liter of water.
- Compounds based on isopropyl alcohol or ethyl alcohol at least 60-70% alcohol.

At the end of the experimental procedure with each participant, the waste will be deposited in a bag with chlorinated solution. The place should be ventilated by opening a window if possible, for better air flow.