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Review article

Chronic neuropathic pain is more than a perception: Systems and methods for an integral characterization

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ABSTRACT

The management of chronic neuropathic pain remains a challenge, because pain is subjective, and measuring it objectively is usually out of question. However, neuropathic pain is also a signal provided by maladaptive neuronal activity. Thus, the integral management of chronic neuropathic pain should not only rely on the subjective perception of the patient, but also on objective data that measures the evolution of neuronal activity. We will discuss different objective and subjective methods for the characterization of neuropathic pain. Additionally, the gaps and proposals for an integral management of chronic neuropathic pain will also be discussed. The current management that relies mostly on subjective measures has not been sufficient, therefore, this has hindered advances in pain management and clinical trials. If an integral characterization is achieved, clinical management and stratification for clinical trials could be based on both questionnaires and neuronal activity. Appropriate characterization may lead to an increased effectiveness for new therapies, and a better quality of life for neuropathic pain sufferers.

1. Neuropathic pain definition and problem

Pain is a complex experience of somatic mechanisms and psychological influences; hence, it is always subjective. Pain can be classified in terms of time as acute (less than 3 months) or chronic (more than 3 months) (King, 2013); or in terms of mechanism, as nociceptive, inflammatory, or neuropathic (NP) (Bennet, 2011). Recently, nociplastic pain was also added as a mechanistic descriptor for chronic pain states (Fitzcharles et al., 2021). Living with pain seriously affects all aspects of a person's life, including personal (e.g., emotions, attention, and perception), social, and professional aspects (Attal et al., 2011). Chronic pain is commonly multifactorial and frequently involves a NP component (Urch, 2011). 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" (IASP Task Force Taxonomy et al., 2011). When NP lasts for a prolonged period (more than 3 months), the neurons in the spinal cord and the brain respond with neuroplastic changes (Bannister and Dickenson, 2016). This

Abbreviations: NP, neuropathic pain; IASP, International Association for the Study of Pain; EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; PET, positron-emission tomography; HR, heart rate; EDA, electrical dermal activity; BOLD, blood oxygenation level-dependent signal; LEP, laser evoked potential; SEP, somatosensory evoked potential; LANSS, Leeds Assessment of Neuropathic Symptoms and Signs; DN4, Douleur Neuropathique en 4 points; QST, Quantitative Sensory Testing.

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maladaptive response may change the perception of pain to the point of feeling unbearable pain due to a simple caress (Bush, 2011). 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 (Costigan et al., 2009). Some pharmacological agents target these sustained pain mechanisms, focusing on preventing or altering neuronal plasticity (Cohen and Lema, 2020). 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 Fig. 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 (Michaud et al., 2007).

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 (Costigan et al., 2009). 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 (Freynhagen et al., 2006; Rolke, 2011). Patients with NP have a quality of life similar to patients with severe cardiac disease, severe mental illness (Morgan and Anghelescu, 2017), or in another study rated as "worse than death" (Jones and Backonja, 2013).

NP is present in about 7–10% of the adult population (Harstall and Ospina, 2003; Van Hecke et al., 2014), 17% of chronic pain patients, 35% of oncological patients (Grond et al., 1999), and 30% of adults that attend pain clinics (Bouhassira et al., 2008). NP is also present in the pediatric population with up to 6% of infants suffering from it (Bhatia et al., 2008). In Mexico, chronic pain is considered a public health issue (Covarrubias-Gómez et al., 2010). 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 (Harstall and Ospina, 2003). Chronic pain with NP characteristics should be treated as a separate clinical entity in Mexico, and elsewhere, given its specific demographical characteristics (Covarrubias-Gómez et al., 2008; Smith and Torrance, 2012). There is still much epidemiological work ahead to know the actual impact of chronic NP in the Mexican population.

2. The desirable characterization

The pathophysiology of NP is the fundamental problem for characterization because of the variety and complexity of the underlying mechanisms (Freynhagen et al., 2006). In most cases, NP cannot be related to specific nerves or cortical areas, because neuroplastic changes occur beyond anatomy. 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 in the short and long term (Rolke, 2011). Fig. 2 illustrates the desirable characterization method and system for NP which should be moreover integral: uniting subjective and objective interpretations.

There are several widely used methods for the subjective characterization of symptoms (Jones and Backonja, 2013; Morgan and Anghelescu, 2017). However, we also have enough evidence to state that NP is not only an abstract perception but also a physical signal mediated by neurotransmitters and synapses (Cohen and Lema, 2020; Colloca et al., 2017). Therefore, given that NP is a signal (Peng et al., 2015), it can be quantified and have an objective interpretation. Yet, characterization remains a significant gap in chronic NP research and clinical management (Dickenson and Patel, 2020; Grond et al., 1999; Xu and Huang, 2020). As described by (Finnerup et al., 2016), NP is an unsatisfied need with a considerable gap in pharmacotherapy and a great need for a simple, clinical tool that may monitor NP.

3. World-wide 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

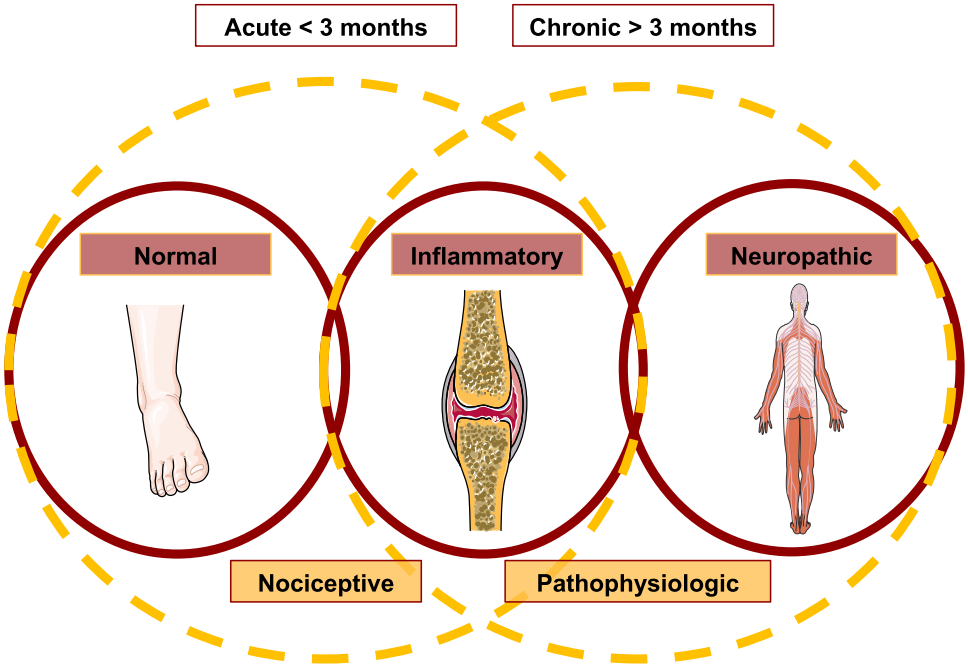

Fig. 1. Venn diagram for type of pain and chronicity. Pain from a minor foot sprain would be considered normal and nociceptive because it is signaled by tissue injury (i.e., a normal mechanism). Inflammatory pain from arthritis (center) is an example of a nociceptive mechanism because inflammation is 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. Normal pain is only acute, whereas inflammatory or NP may be acute or chronic. Medical images taken from (Smart Servier Medical Art, 2021).
Figure adapted from (Vartiainen, 2009).

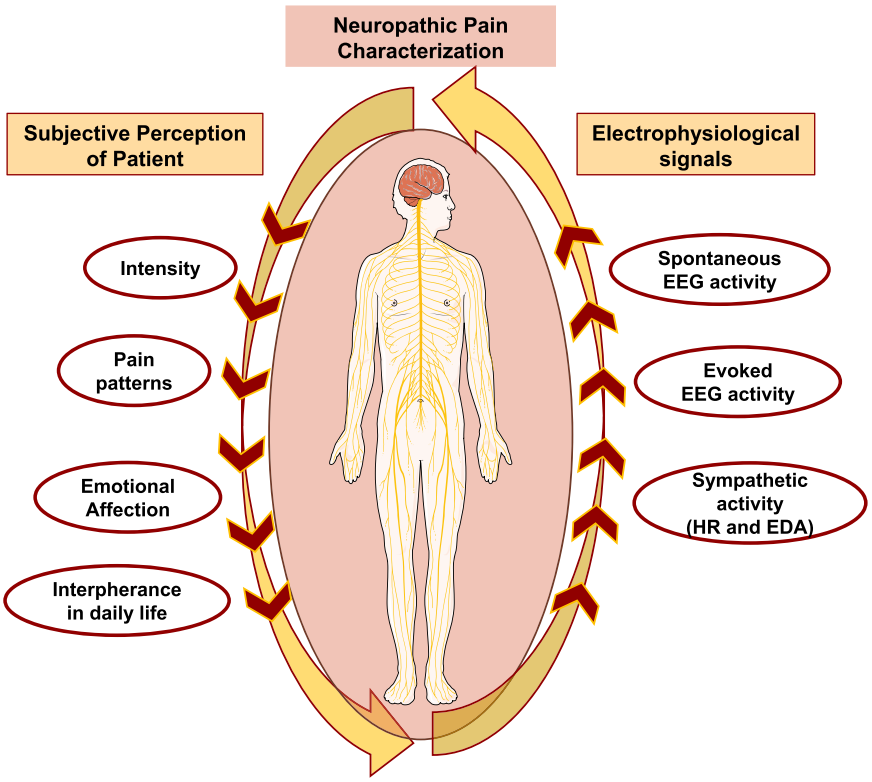

Fig. 2. Integral NP characterization. The desirable NP characterization should be integral and composed by subjective and objective information. The subjective perception of the patient may describe the intensity, pain patterns, degree of emotional affection, or the interference of daily activities due to pain. Objective information from the central nervous system may be obtained through electrophysiological signals recorded with electroencephalogram (EEG), which can be divided into spontaneous or evoked activity. Objective information from the autonomous nervous system (i.e., sympathetic activity), can also be obtained by measuring heart rate (HR) and electrodermal activity (EDA).
Body image taken from (Smart Servier Medical Art, 2021).

second-line treatments, and cannabinoids have been moved from a fourth-line to a third-line treatment option (Mu et al., 2017). Usually a combination therapy is preferred (Holbech et al., 2017) 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 (Gilron et al., 2013). There is some evidence showing that at least 45% of patients with NP are treated with two or more drugs (Ickowicz, 2009; Tarride et al., 2006). However, it does not imply that patients with a higher number of analgesics are treated better (Schneider et al., 2020). In fact, only 40–60% of patients have obtained sufficient pain relief with medications given in combination or alone (Dworkin et al., 2007). Surprisingly, one study stated that the universally used pregabalin and gabapentin are ineffective for most patients with NP (Finnerup et al., 2015). Even when newer trials seem to increase (Finnerup et al., 2018), 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 (Grupo de Consenso para el Manejo del Dolor Neuropático, 2006) interviewed seventy physicians of public and private care from different locations within the country. Fig. 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 systemic reviews and the assessment

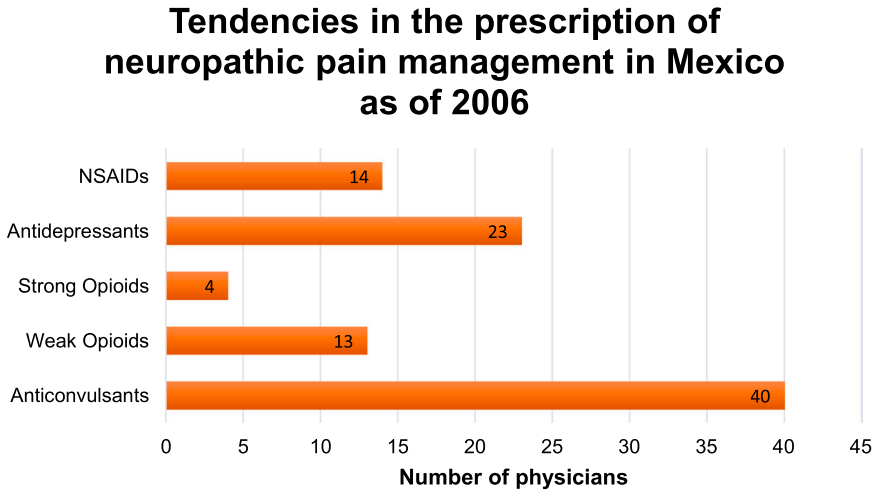

Fig. 3. Tendencies in the prescription of NP management in Mexico. Seventy physicians across the country were interviewed according to their use of first-line agents for treating NP. Anticonvulsants were the first place with 40 answers, followed by antidepressants with 23 answers.
Figure adapted from (Grupo de Consenso para el Manejo del Dolor Neuropático, 2006).

of the individual patient history.

3.1. Issues from non-integral characterization for different ages

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 (Schneider et al., 2020). Another study concluded that one out of ten geriatric patients had a problem of under- or over-treatment with pain medications (Rabenberg et al., 2019). The preceding mismanagement of treatment for NP, in addition to the vulnerability of elderly patients exposed to polypharmacy for other disorders (Hamza et al., 2019), may increase sedation, impaired balance, and thus, falls (Galicia-Castillo, 2016).

In pediatric patients, NP management and characterization, becomes even more challenging because verbalization is difficult (Dezfouli and Khosravi, 2020). Monitoring pain signs and life quality usually helps 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 (Zorina-Lichtenwalter et al., 2018). Note that, NP is dynamic, and this dynamic activity may alter white matter structurally. This particular behavior of NP could be crucial knowledge for the development years of the child because from childhood to adolescence there is a protracted maturation of the prefrontal cortex, an area highly activated in chronic NP (Delalande et al., 2020).

Even though 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 for all ages could be achieved by obtaining more information about the neuroadaptive alterations that occur in a NP state (Bannister et al., 2020) and regarding different physiological signals. Considering all life stages and syndromes, the best way to adjust treatments could be monitoring the changes in neuronal activity individually and throughout the months.

3.2. Non-pharmacological therapy for NP – an integral management

As discussed previously, pharmacotherapy does not fully treat NP in most cases. Thus, other non-pharmacological approaches have proven beneficial in the physical and psychological outcome of chronic NP patients, where the goal of treatment is to prevent, ameliorate or control symptoms. One such approach is neuromodulation, where guidelines for NP are available and pertain invasive and noninvasive techniques (Cruccu et al., 2007; Deng et al., 2015). Evidence on the effectiveness of invasive neuromodulation varies, but in general it has achieved positive effects in pain control (Hofmeister et al., 2020; Knotkova et al., 2021). In attention to the risks, complications, and high costs that invasive neuromodulation may provoke, noninvasive techniques such as transcranial current brain stimulation and transcranial magnetic stimulation are emerging as a promising methodology to reduce pain, despite their limited penetration and spatial resolution (Moisset et al., 2020; Yu et al., 2020). However, to optimize the outcome of neurostimulation methods, patient characterization and selection is primordial (Mekhail et al., 2010; Moisset et al., 2020) as it is the case for pharmacotherapy.

Exercise is also a non-pharmacological treatment option for NP (Leitzelar and Koltyn, 2021), given its wide range of established health benefits (e.g., improved sleep, cognition, anxiety, and depression). Guidelines suggest exercise should be attempted before starting opioid based pharmacological treatment for chronic pain (Dowell et al., 2016). Clinical evidence in NP patients suggests that exercise training reduced pain intensity, NP symptoms (Kluding et al., 2012; Yoo et al., 2015), and pain interference with daily activities (Yoo et al., 2015). Furthermore, routine exercise has shown to enhance peripheral nerve conduction velocity (Balducci et al., 2006; Hung et al., 2009) and intra epidermal nerve branching factor density (Kluding et al., 2012; Smith et al., 2006). Finally, physiotherapy and rehabilitative interventions, consider the psychosocial limitations, and aim to guarantee an optimal quality of life by preventing or reversing changes in trophism, contractures, and general deconditioning (Bernetti et al., 2021). In sum, a multidisciplinary approach, that comprehends pharmacological and non-pharmacological interventions is increasingly driving NP management to target different aspects of NP treatment and enhance the outcome of functional disability, pain intensity and psychological variables (Bernetti et al., 2021; Samwel et al., 2009; Shaygan et al., 2018).

4. The NP characteristics that matter

NP in most cases, has a spontaneous and an evoked component (Finnerup and Attal, 2018). 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 (Rolke, 2011). The most reported qualities of pain are burning sensation, acute stabbing, shooting, electrical discharges, or oppressive pain. Also, NP can present nonpainful paresthesia in conjunction with pain sensations (Finnerup and Attal, 2018). Table 1 states both components with their mechanisms of pain.

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) (Backonja and Serra, 2004; Tim Nash, 2011). 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. Moreover, over one type of allodynia could occur in the same patient. It has also 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 (Bowser, 2011). 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 the central and peripheral nervous system.

5. EEG as a tool to monitor central nervous system activity

The function and morphology of the brain are affected by the chronicity of NP symptoms (Bannister et al., 2020). Neuroplasticity is dynamic and unpredictable, thus neural activity may change fast and drastically for a patient, or rather, in a slow and unnoticeable process for another patient. As mentioned in Section 3.1, a NP patient would need periodic objective evaluations for proper management, requiring a simple and cost-effective system able to be used in routine clinical practice.

There are many methods to test NP, such as hemodynamic (e.g., positron-emission tomography (PET) and functional magnetic resonance imaging (fMRI)), neuroelectrical (e.g., electroencephalogram (EEG) and magnetoencephalogram) and neurochemical methods (union of receptors and modulation of neurotransmitters) (Apkarian et al., 2005). The major advantage of measuring electrical activity with EEG is temporal resolution (i.e., in milliseconds), and its major drawback is poor spatial resolution. Comparatively, fMRI has a limited temporal resolution (i.e., in seconds) but an excellent spatial resolution based on the changes in the blood oxygenation level-dependent (BOLD) signal that indicates concurrently local cerebral blood flow changes in

Table 1
Neuropathic pain mechanisms. 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.

	Mechanism	Type of altered sensation	Conducted by/ Location of sensation
Spontaneous Pain	DNA modification causes an alteration of Ca+ channel refractory time (Vardeh and Naranjo, 2017). Ectopic discharges (Devor, 2009) in dorsal root ganglion (Baron, 2006) result from an abnormal expression of Na+ channels.	**Paroxysmal pain** (e.g., shooting electrical attacks for seconds) (Baron, 2006)	Could be present anywhere in the body with NP symptoms (e.g., in trigeminal neuralgia - in the head)
		Superficial pain (e.g., ongoing burning sensation) (Baron, 2006)	Within an area of sensorial alteration in receptors of **small peripheral nerve fibers** (i.e., skin).
		Nonpainful paresthesia (ongoing sensation, e.g. ant crawling) (Baron, 2006)	**Spontaneous activity of thick Aß fibers of tactile and vibratory sensation.** These nerve fibers are less frequently affected in NP (Rolke, 2011).
Evoked pain	***From noxious stimuli.*** Decreased cellular pH after celullar damage causes neurons to be partially or totally depolarized (Huang et al., 2006; Urch, 2011). Central dorsal horn hyperexcitability is caused by central sensitization on spinal level and a decrease of intraspinal inhibitory interneurons (Baron, 2006).	**Hyperalgesia** (e.g., punctate or dynamic mechanical hyperalgesia)	Generally, **Aδ fibers** for pinprick, mechanical and heat/cold stimuli. When hyperalgesia is continuous, it is conducted by **C fibers** (Huang et al., 2006; Maihöfner et al., 2005).
	From non-noxious stimuli. May be caused by: abnormal growth of dendritic sprouts, expanding of receptive field, or intercommunication between nerve endings (Bowser, 2011). Peripheral nociceptor sensitization reduces activation threshold in receptors for heat (TRPV1), cold (TRPM8) and static mechanical allodynia (ASIC) (Baron, 2006).	**Static and dynamic mechanical allodynia** (i.e., pain from a simple touch) **Cold or heat allodynia Movement allodynia** (e.g., active or passive stretch of muscles or tendons)	**Sensitized C, Aß fibers** (Rolke, 2011;Vardeh and Naranjo, 2017) and **Aδ fibers** (Baron, 2006)

deoxyhemoglobin content (Roberts et al., 2008). fMRI is possibly the most common neuroimaging technique to study pain (Alomar and Bakhaidar, 2018), and it has revealed that the brain activates subcortical and cortical areas in different phases of the pain perception, consequently defined as the "pain matrix" (Peyron et al., 2004, 2000; Schweinhardt et al., 2006), which are also supported by PET studies (Alomar and Bakhaidar, 2018; Petrovic et al., 1999; Peyron et al., 2000). The main areas that are activated in most chronic pain conditions are the insula, secondary somatosensory cortex, and anterior cingulate cortex (Alomar and Bakhaidar, 2018; Fomberstein et al., 2013). Notably, this concept of the "pain matrix" has been challenged by evidence from fMRI responses to nociceptive stimuli which are not strictly nociceptive-specific and can be explained by multimodal neuronal processing (Mouraux et al., 2011). Clinically, fMRI has been used to study the response of NP to pharmacological treatments (Fomberstein et al., 2013), in a way it would otherwise be impossible with electrophysiological methods. For example, fMRI has detected a decrease in gray matter thickness in subcortical areas such as the amygdala (Kong et al., 2010) after the administration of morphine in chronic pain patients. In another study, a decrease in activity was reported in the posterior insula in chronic pain patients treated with pregabalin (Harris et al., 2013). Similarly, PET studies have found that the availability of opioid-receptor is significantly associated to the effectiveness of NP relief after motor cortex stimulation (Maarrawi et al., 2013). Also, both methods, PET and fMRI, have been employed to investigate the mechanism of allodynia in NP, suggesting that it activates the lateral pain system, whereas spontaneous NP is related to the emotional dimension of pain and correlates with activity changes in the medial pain system and thalamic activity (Moisset and Bouhassira, 2007). Although these methods have the capacity to assess subcortical structures that are primordial in NP pathophysiology, they have a high cost and a more complex methodology for routine clinical practice. Moreover, 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.

In this review, we will focus 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 (Spronk et al., 2011). Additionally, EEG has a much simpler methodology and lower cost, but EEG signals in their raw state do not serve for clinical interpretation, given the overlapped neuronal activity from different sources. EEG signals must be preprocessed and analyzed carefully to be useful in any clinical setting. 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. Moreover, EEG offers the possibility of analyzing brain signals according to the spontaneous and evoked components of pain (review Table 1 for pain mechanisms), which makes it ideal for NP. EEG has also been used to evaluate the function of the brain in other chronic pain syndromes such as fibromyalgia, migraine, rheumatoid arthritis, chronic pancreatitis and breast cancer (Bjørk et al., 2011; De Vries et al., 2013; González-Roldán et al., 2013; Meneses et al., 2016; Schmidt et al., 2012; Stern et al., 2006; Van Den Broeke et al., 2013). The main advances in EEG analysis for linear methods and non-linear methods are revised below.

5.1. *Linear methods: spontaneous analysis*

Most EEG studies concerning NP patients (Boord et al., 2008; Bromm and Lorenz, 1998; Pinheiro et al., 2016; Schmidt et al., 2012; Sitges et al., 2010; Stern et al., 2006) have focused on measuring spontaneous pain by requesting patients to rest either with eyes open or eyes closed. 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 (Schmidt et al., 2012; Stern et al., 2006; Vuckovic et al., 2014). Other studies (Boord et al., 2008; De Vries et al., 2013; Schmidt et al., 2012) revealed that the dominant peak in the alpha spectrum power moved to lower frequencies in patients with chronic NP. According to (Pinheiro et al., 2016), the previous results have been found mainly over frontal and parieto-occipital electrodes that correlate positively with the pain matrix (De Vries et al., 2013). Nevertheless, (Vuckovic et al., 2014) 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 (Boord et al., 2008). This interconnection is illustrated in Fig. 4, which highlights the frontal and

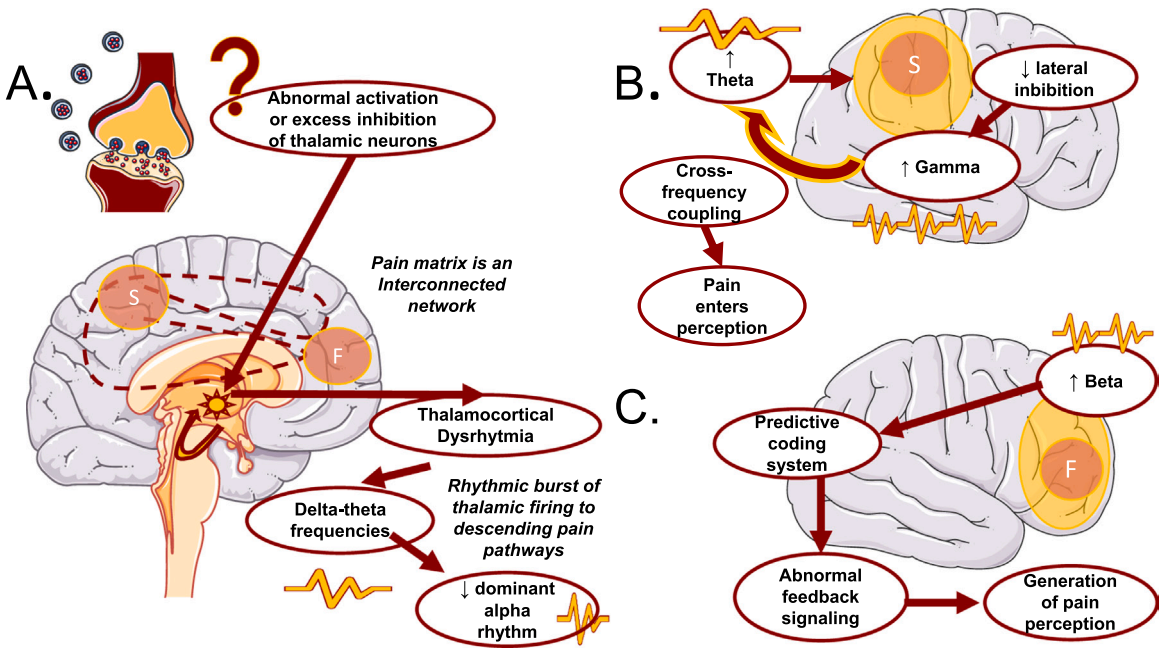

Fig. 4. Abnormal oscillatory activity in NP. Changes in electrical activity in the pain matrix and associated structures: somatosensory area (circle "S"), frontal and prefrontal areas (circle "F"), and the limbic structures (star represents the thalamus). (A) The source for the abnormal oscillatory activity is thalamocortical dysrhythmia. 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 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). Brain image taken from (Smart Servier Medical Art, 2021).

somatosensory areas of the cortex, as well as the limbic structures observed from the sagittal cut of the brain, particularly the thalamus.

5.1.1. *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 (Boord et al., 2008; Sarnthein et al., 2006). This effect along with the increase in power of theta and delta, is caused by thalamocortical dysrhythmia, a self-sustaining neuropathological mechanism that underpins the constant perception of pain (Sarnthein and Jeanmonod, 2008; Stern et al., 2006). Thalamocortical dysrhythmia is also the probable underlying mechanism of another phantom perception: tinnitus (Vanneste et al., 2019). Thalamocortical dysrhythmia is a consequence from abnormal activation or excess inhibition of thalamic neurons in the process of pain (Llinás et al., 2005; Sarnthein and Jeanmonod, 2008). 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 Fig. 4A (Alshelh et al., 2016). 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 thalamocortical dysrhythmia development (Alshelh et al., 2016). The idea that NP has a central generator was proposed in (Head and Holmes, 1911) and then further investigated in (Llinás et al., 1999). 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 Fig. 4A), and the second one relates to the emotional sensation of pain which is nonlocalizable (thalamocortical loops), and described as the moral pain of being hurt that is present in all central pain patients (Kruger and Light, 2009).

5.1.2. *Gamma oscillations*

The enhanced theta oscillations reduce lateral inhibition and increase abnormal gamma oscillations. Fig. 4B represents this effect known as the *edge effect* for the somatosensory cortex (letter "*S*") (Llinás et al., 2005). 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 (De Ridder et al., 2015). Another study suggests the theta component of thalamocortical dysrhythmia reflects traits of the stable pain state of an individual, whereas the gamma component reflects the short term modulation of pain perception (Schulz et al., 2011).

5.1.3. *Beta oscillations*

Increases of beta oscillations were observed in frontal brain areas (Sarnthein et al., 2006; Stern et al., 2006), shown in Fig. 4C letter "*F*". Beta is considered to serve as feedback signaling (i.e., the signaling of predictions) which is abnormal in chronic pain (Arnal and Giraud, 2012). 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 (Ploner et al., 2017).

5.1.4. *Alpha oscillations*

Alpha oscillations are also affected by dysfunctional thalamocortical mechanisms, which decrease the dominant alpha rhythm (Sarnthein et al., 2006; Vuckovic et al., 2014), but increase alpha power (Kim et al., 2019), observed in Fig. 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 (Kisler et al., 2020). However, the relation between enhanced alpha power and pain is not yet elucidated (Van Den Broeke et al., 2013). 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?
(Sarnthein, 2003)	Different electrode positions 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	↑ **theta band power (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 h before EEG recording	**Various neurological disorders (NP, epilepsy, and movement disorders)**
(Sarnthein et al., 2006)	60	250	17 patients with severe forms of neurogenic pain and 15 healthy controls	↑ **delta, theta, alpha and beta band power (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**
(Boord et al., 2008)	14	2048	16 patients with paraplegia (8 with NP and 8 without pain) and 16 able-bodied controls	↓ **Frequential theta-alpha peak and ↓spectral EEG reactivity** in paraplegic patients with NP	2 of 8 patients on central action medication	**NP and paraplegia patients**
(Schmidt et al., 2012)	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**
(Jensen et al., 2013)	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**
(Van Den Broeke et al., 2013)	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**

5.2. *Linear methods: evoked*

5.2.1. *Laser voked potentials (phase-locked)*

Research on the evoked component has mainly used laser to evoke pain sensation (Bromm and Lorenz, 1998; Casey et al., 1996; Di Stefano et al., 2012; Garcia-Larrea, 2002; Hatem et al., 2012; Truini et al., 2004; Valeriani et al., 2012). The laser evoked potentials (LEPs) are one of the first neurophysiological techniques to measure NP (Bromm and Lorenz, 1998; Casey et al., 1996). 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 to

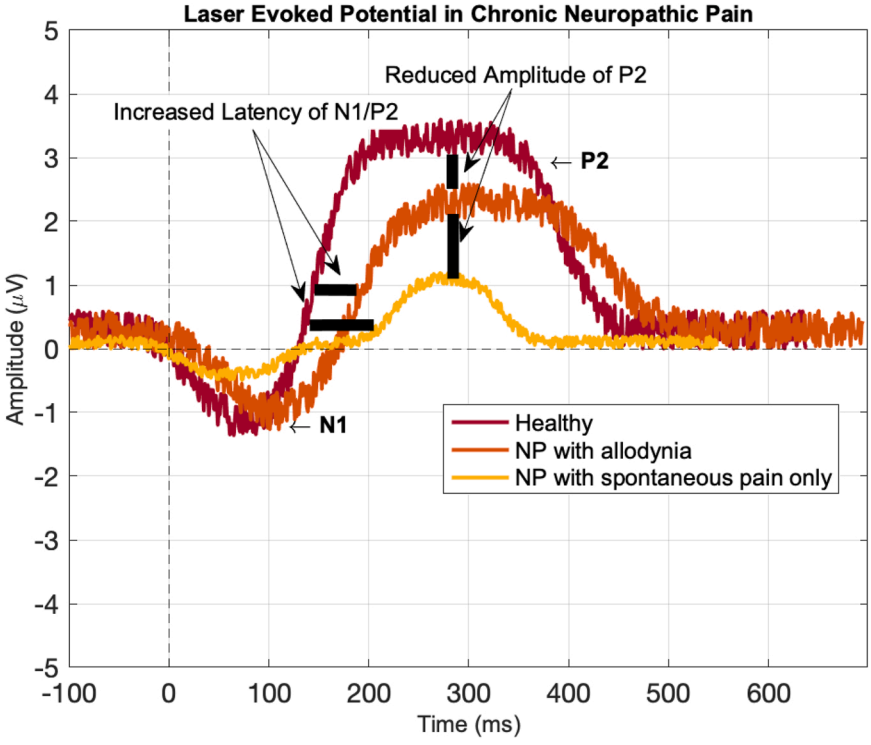

Fig. 5. Laser Evoked Potential in chronic NP with allodynia or spontaneous pain in comparison to healthy state. The alteration for components N1 (↑ latency) and P2 (↓ amplitude) in chronic NP in contrast to healthy controls (red line) is illustrated. The highest attenuation is presented for NP with spontaneous pain only (yellow line). The partial LEP preservation in a patient with NP might reflect a high probability of developing evoked pain (allodynia/hyperalgesia, orange line). Image created based on previous literature results, particularly (Garcia-Larrea, 2002). (For interpretation of the references to colour in this figure, the reader is referred to the web version of this article.)

1200 ms). 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 (Lorenz and Garcia-Larrea, 2003; Pinheiro et al., 2016). 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 (Di Stefano et al., 2012). Two significant findings in LEP components for patients with allodynia are: the reduction of amplitude from LEPs and delayed latency (Di Stefano et al., 2012; Garcia-Larrea, 2002; Truini et al., 2004). These two characteristic findings for LEPs in chronic NP are depicted in Fig. 5, the activity reflected from the LEPs originates from the lateral pain system and measures the degree of deafferentation that leads to NP (Garcia-Larrea, 2002).

In fact, 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 another study (Truini et al., 2009), the intensity of pain correlated inversely with the amplitude of the LEPs. Additionally, ultra-late responses (>700 ms) in chronic NP have been reported (Garcia-Larrea, 2002). These responses are 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 (Cruccu et al., 2010). In addition, LEP values have not been used to classify NP activity as either normal or abnormal, which impedes a proper characterization with values that define sensitivity and specificity for NP (Truini et al., 2009).

5.2.2. *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 (Sitges et al., 2010), the reaction to tactile stimulation while observing pictures (from the International Affective Picture System) was investigated. The resultant components of their study were P20, P50 and N80. 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. This contrast in the attenuation of amplitude in P50 may reflect the affective-charged state of an NP patient compared to a healthy control (Sitges et al., 2010), and supports the later abnormal emotional

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?
(Garcia-Larrea, 2002)	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	**Most patients had NP**
(Truini et al., 2009)	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**
(Veldhuijzen et al., 2006a)	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 amplitude** independent of task difficulty, **↑amplitude at frontocentral electrodes** for difficult task, **↑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**
(Sitges et al., 2010)	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 6 s followed by a blank screen for 6 s	**↓ 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	Most patients had musculoskeletal pain, but **some had NP** due to spinal cord injury or peripheral neuropathy
(Vuckovic et al., 2015)	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**

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 (Pinheiro et al., 2016). This was investigated by (Veldhuijzen et al., 2006b), who recorded SEPs from chronic pain patients (not necessarily NP) to assess whether pain decreased the performance on attention processing capacity. Pain patients had a higher reaction time response, but a higher error rate compared to healthy 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 (Lorenz and Bromm, 1997). 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 (Veldhuijzen et al., 2006b). 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 (Crombez et al., 2005).

5.2.3. Induced activity (not-phase locked)

Induced activity consisting of event related synchronization and event related desynchronization is used to study the rhythmicity of activity in a particular frequency band to an event. In patients with NP, induced activity has demonstrated that the neural reorganization occurring as a response to NP affects the activity of the motor cortex during the imagination of movements. In a recent study (Vuckovic et al., 2015), event related desynchronization and event related synchronization of imaginary movements in healthy controls, paraplegic patients without pain, and paraplegic patients with NP were studied. Paraplegic patients with NP had the largest and spatially distinctive event related desynchronization in comparison to controls and to patients without pain in theta, alpha, and beta frequency bands. Fig. 6 is an adapted figure from the results of (Vuckovic et al., 2015) and illustrates the enhanced event related desynchronization in paraplegic patients with NP for the alpha band.

Interestingly, theta event related desynchronization during motor imagination was a singular characteristic that had not been reported before in NP patients (Vuckovic et al., 2015). The enhanced activity in paraplegic patients with NP demonstrates that NP, even more than paralysis, has a global effect in brain activity which spreads beyond the painful or paralyzed limbs. These results prove that the presence of NP improves classification accuracy due to stronger and more distinct event related desynchronization. However, despite the promising results on induced activity for NP patients, the weekly practice of imagining movements of the painful body part, worsens pain (Gustin et al., 2010).

5.2.4. Other evoked methods without EEG

In a more unstandardized way, the tool for stimulating allodynia has been with a brush, and measured with fMRI (Schweinhardt et al., 2006) or with PET (Petrovic et al., 1999). Another fMRI study (Peyron et al., 2004) 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 applied to the allodynic side and activated regions in the contralateral primary and secondary somatosensory cortex.

For evoked methodologies in NP, it might be inconvenient to use laser stimuli and unstandardized brush evoked stimuli. The first method may be inconvenient by evoking pain with a painful sensation; and the second one by 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 (Petrovic et al., 1999; Schweinhardt et al., 2006). Hence, the exact amount of stimulation force or velocity was unknown.

5.3. Non-linear method: entropy

Chronic pain should be considered a cognitive state that might interfere with other cognitive or emotional states (Apkarian et al., 2004). Recently, the non-linear theory of dynamic systems has been applied to EEG to capture the macroscopic spatial and temporal cortical

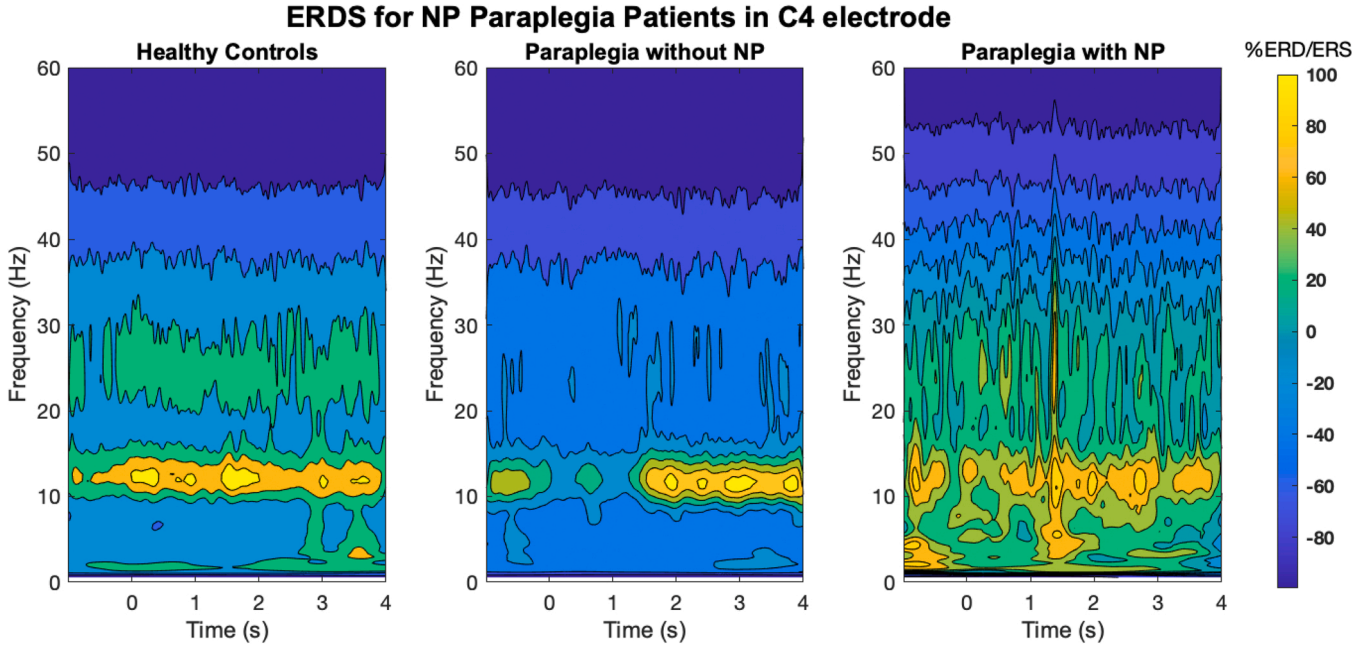

Fig. 6. ERD and ERS for NP paraplegia patients in C4 electrode for the alpha band. In t = 0 a visual cue appeared, and participants were asked to perform imaginary movements until the cross disappeared at t = 3. In healthy controls, event related desynchronization (ERD) of the alpha band is at its highest between 1.5 and 2 s. In paraplegic patients without NP (PNP), there is a clearer event related synchronization (ERS) in alpha band before the ERD which appears until 1.5 s. Paraplegic patients with NP (PWP) had the largest ERD throughout the recording and throughout frequency bands. Positive values in the color bar represent the percentage of ERD, negative values represent percentage of ERS. (For interpretation of the references to colour in this figure, the reader is referred to the web version of this article.) This image was created simulating the results of (Vuckovic et al., 2015) with data taken from a Brain-Computer Interface database (Schalk et al., 2004).

activity (Stam, 2005). A non-linear method is entropy, which quantifies the complexity and regularity of a temporal signal, to estimate the flexibility of cortical activity (Abásolo et al., 2006; Pincus, 1991). This method has been used to study physiological and pathophysiological states. A decreased entropy has been found in sleep, anesthesia, schizophrenia, Parkinson, Alzheimer, and epilepsy (Abásolo et al., 2006; Stam, 2005). For instance, a convulsion reflects an increase in the regularity of EEG, and consequently, low cortical complexity (Acharya et al., 2012). Under negative mood states, chronic pain patients showed a significant increase of multiscale entropy in the right hemisphere over the left one (Sitges et al., 2010). The authors argue that this enhanced multiscale entropy is caused by the high alertness state of waiting for a deviant stimulus in the left hand, whereas receiving a repetitive stimulus in the right hand.

We recently conducted an EEG study in 35 NP patients and stratified them in three groups according to their subjective pain experience reported on the actual pain of the Brief Pain Inventory (low = 0–3, moderate = 4–6, and high = 7–10) (Zolezzi et al., 2021). Fig. 7 illustrates the average approximate entropy across the 35 participants in the 22 electrodes for each pain severity.

In general, Fig. 7 shows more negative values in eyes closed than eyes open, probably owing to an increased cognitive demand measured by approximate entropy. In eyes open condition there is a higher demand due to the input and processing of visual stimuli. We will discuss briefly the eyes open condition for the three groups in Fig. 7. First, there is an increased approximate entropy in the occipital lobe in eyes open for low pain that may be a consequence of NP pathophysiology that involves the suppression of the resting state occipital alpha-rhythm (Ploner et al., 2006). If rhythmicity is suppressed, the irregularity increases and hence, the entropy. Second, in moderate pain for eyes open there is an overall increase in approximate entropy throughout the cortex, which may be sustained by the widespread changes of intermingled brain networks discussed previously in Section 5.1 (Vuckovic et al., 2014). Third, as pain severity increases, the irregularity of neuronal activity in NP patients shifts to frontal brain areas. This frontal shifting may be supported by the role of the prefrontal cortex in emotional processing and executive behavior for the proper psychological and therapeutic management of chronic pain (Moisset and Bouhassira, 2007). Also, the prefrontal cortex has two opposing yet leading roles in pain: (1) antinociceptive mediation of sensory stimuli at the dorsal horn, and (2) the area where induction of pain chronicity occurs (Ong et al., 2019).

There is still no information about nonlinear neuronal activity 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 nonpainful information when emotional cues are present

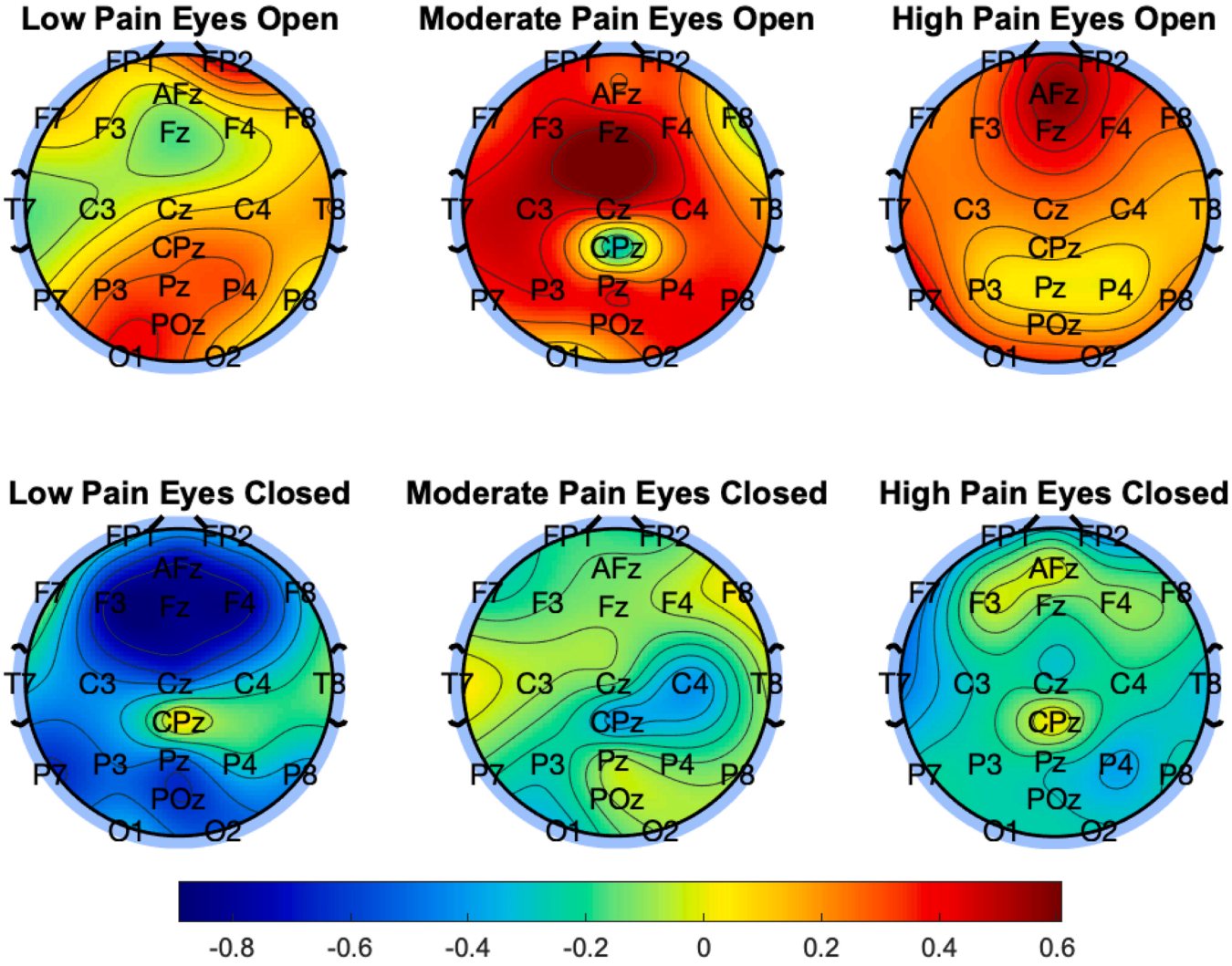

Fig. 7. Comparison of average approximate entropy for 22 electrodes in 35 NP patients according to pain severity. Approximate entropy reached the highest value for high pain in EO condition (ApEn = 0.68), and the least value for the low pain group in EC condition (ApEN = −0.84). Values are normalized in line with a z-score scale. Copyright © 2021 IEEE. Reprinted, with permission, from (Zolezzi et al., 2021).

(Sitges et al., 2010), which supports the hypothesis that negative contextual information could enhance pain feeling (Montoya et al., 2005). In chronic NP patients, entropy could be a measure of habituation, chronicity, interference with relationships, or emotional affection.

5.3.1. *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 central nervous system in the origin and maintenance of pain mechanisms (De Vries et al., 2013).
2) It proposes a biomarker for the different pain syndromes with anatomical correlations of the electrical cortical activity (Apkarian et al., 2005).
3) It promotes the use of brain information as parameters of success or failure in treatment (Del Percio et al., 2006).
4) It identifies aspects of maladaptive plasticity (e.g, the connections between brain regions and the changes in oscillations given the abnormal activity in inhibition and excitation of neurons) (Lelic, 2014).
5) It offers a viable alternative to understand the process of NP in an individualized manner with a lower cost compared to other imaging techniques (Lelic, 2014).

6. Adjuvants to EEG

The theory brain body coupling is proposed in (Klimesch, 2018), where the frequency architecture of electrophysiological signals is described and discussed. In Fig. 8, an example of its applicability is presented for an individual with a heart rate (HR) of 70 beats per minute.

With the individual HR, the frequency bands of the rest of brain and body oscillations can be obtained. These are: (1) rhythmic fluctuations in 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 (Korving et al., 2020).

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

- During respiration, 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) (Fig. 2). In addition, central nervous system 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 healthy controls (Bonnet and Naveteur, 2004). Pain descriptors and emotional words produced a higher EDA than neutral words in chronic pain patients, suggesting an enhanced effect with emotional load (Bonnet and Naveteur, 2006). Regarding HR, its variability was shown to be reduced in chronic pain (Tracy et al., 2016), and it was useful in diagnosing NP after spinal cord injury (Karri et al., 2017). We propose that measuring electrophysiological signals in parallel to EEG signals, could offer a complementary perspective. According to the theory (Klimesch, 2018), different frequency domains are associated with different

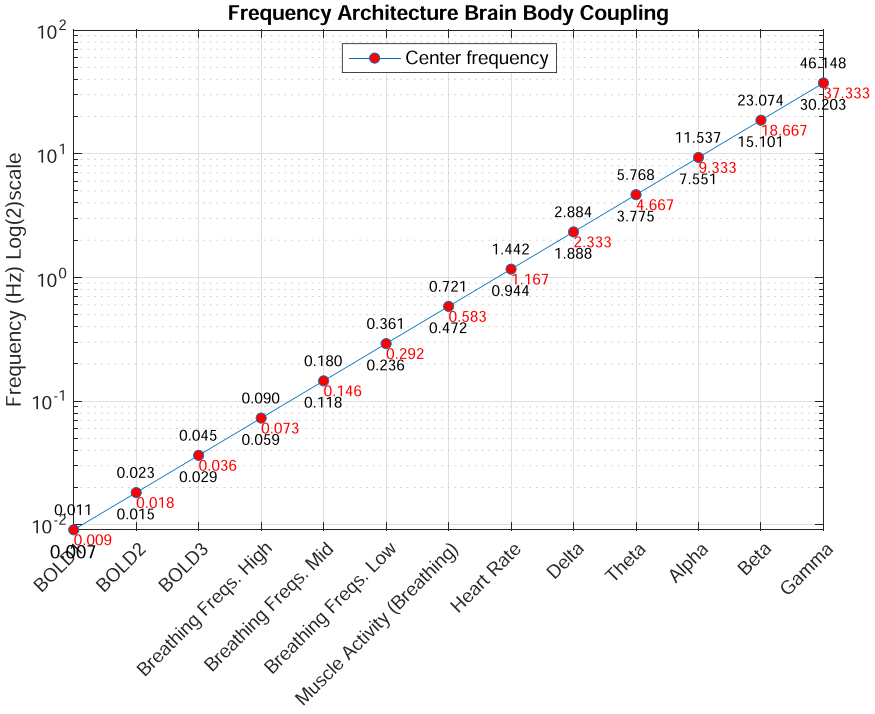

Fig. 8. Brain-body coupling theorem postulated in (Klimesch, 2018) in an individual with 70 beats per minute. Positive integers determine brain oscillations, whereas negatives ones define breathing, blood pressure, BOLD and gastric waves. Zero refers to cardiac activity at rest.

processing domains regarding cognitive and physiological functions. For a recent systemic review of physiological measures in chronic pain, consult (Korving et al., 2020).

fMRI has also been used as an adjuvant of EEG to assess alpha rhythm variations in the healthy resting state. Coregistration of EEG/fMRI allows the correlation of spontaneous electrical fluctuations with local blood flow changes in continuous brain states. A negative correlation between BOLD signal and alpha power has been found in parietal and frontal areas (Gonçalves et al., 2006; Laufs et al., 2003). As well as a positive correlation between BOLD signal in thalamic areas and alpha power (Goldman et al., 2002; Gonçalves et al., 2006). The interpretation of this correlated activity and its functional relevance has some limitations (Laufs et al., 2003), but simultaneous EEG-fMRI studies have the potential to achieve both a high spatial resolution from fMRI and high temporal resolution from EEG. This has led to identify patterns of pain and nociceptive stimulation in healthy subjects (Christmann et al., 2007; Roberts et al., 2008). Furthermore, coregistration of pain evoked potentials with EEG and fMRI could be useful for assessing the analgesic activity of drugs in experimental pain models and pain patients (Roberts et al., 2008). In such a case, NP patients could have reduced pain-evoked potential amplitudes but increased fMRI activation, contrasting with healthy or other pain inflammatory conditions. A multimodal approach of neuroimaging still requires development but could provide valuable insight into chronic pain states (Martucci et al., 2014).

7. The current subjective evaluations

As we have stated previously, even if an objective assessment of NP 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 affection, or the interference of daily activities. In this section, the primary qualitative subjective questionnaires will be stated as well as a quantitative subjective test.

7.1. Qualitative subjective

In the challenge to characterize NP, there have been several tools for the detection and evaluation of NP (Bennett et al., 2007; Jones and Backonja, 2013). A diagnostic tool differentiates from an evaluation tool for being highly sensible and capable to differentiate NP from other types of pain. The evaluation questionnaires help physicians to monitor NP that has been previously diagnosed (Morgan and Anghelescu, 2017). 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 considered, for example: changes in skin color or skin temperature. The most used diagnostic NP questionnaires are: 1) The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) 2) Douleur Neuropathique en 4 points (DN4) 3) Neuropathic Pain Questionnaire 4) ID Pain 5) Pain Detect Questionnaire; and one for evaluation, 6) Brief Pain Inventory. 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 (Bennett, 2002; Freynhagen et al., 2006; Krause and Backonja, 2003; Morgan and Anghelescu, 2017; Portenoy, 2006). Some apparent differences among the six questionnaires are summarized in the following six items:

1) LANSS contains a patient-completed questionnaire and a brief clinical assessment, which generated ambiguity in application (Backonja, 2002). Nevertheless, the validated questionnaire reported 83% sensitivity and 80% specificity (Bennett, 2001). To improve some of the criticisms concerning the clinical assessment, a self-report version of LANSS was validated, S-LANSS (Bennett et al., 2005) but with a lower sensitivity (75%) to identify pain of NP origin.
2) DN4 has seven pain discriminators and three findings from examination, where a score above 4 indicates that NP is likely. Its sensitivity and specificity are 85% and 90% respectively (Bouhassira et al., 2005).
3) Neuropathic Pain Questionnaire qualifies affective impact and exacerbating factors such as changes in weather, emotional states, or tiredness (Jones and Backonja, 2013). It has been tested to have a 66.6% sensitivity and 74.4% specificity (Krause and Backonja, 2003). The short version has a comparable sensitivity and specificity (Backonja and Krause, 2003).
4) ID Pain is a six-item screening tool that was developed to identify pain type (Portenoy, 2006). Particularly, to identify NP in a wide variety of patients (e.g., from primary care) (Jones and Backonja, 2013). In breast cancer survivors, it had a 70% of predictive validity, 86% sensitivity and 84% specificity for screening NP (Reyes-Gibby et al., 2010). To reduce misdiagnosis, it considers pain limited to articulations and subtracts one point if presenting this type of pain (−1 point).
5) Pain Detect Questionnaire was created to detect NP in chronic low back pain patients (Freynhagen et al., 2006). It has a sensitivity of 85% and specificity of 80%, which is comparable to other self-report questionnaires (Jones and Backonja, 2013; Mulvey et al., 2014). 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). It has been modified for identifying NP symptoms in knee osteoarthritis (Hochman et al., 2011).
6) Brief Pain Inventory is not a screening questionnaire, rather an evaluative self-administered questionnaire that assesses pain severity and its impact on daily function across different domains. For example, the percentage of relief from treatment, the interference of pain in walking, working, personal relationships, or enjoyment of life (Cleeland and Ryan, 1994). It was originally developed for cancer pain but it has also been used in clinical NP studies (Gimbel et al., 2003; Semenchuk et al., 2001). A modified version has been validated for painful diabetic neuropathy (Zelman et al., 2005).

In a recent reliability study with a NP population, LANSS and DN4 demonstrated 76% sensitivity (Sadler et al., 2013). In specificity, DN4 performed lower than expected (70%) compared to LANSS (94%) (Sadler et al., 2013). In patients with cancer pain, LANSS demonstrated a 76% sensitivity and 100% specificity to detect NP (Potter et al., 2003). A more recent study concerning NP in cancer pain, confirmed a higher specificity for LANSS (93.4%) than DN4 (88.4%), but a lower sensitivity (68.1% vs 87.5%) (Pérez et al., 2015). DN4 had the highest sensitivity (93%) to detect NP in spinal cord injury patients, followed by Pain Detect Questionnaire (68%), while LANSS and Neuropathic Pain Questionnaire demonstrated the highest specificity (100%) (Hallström and Norrbrink, 2011). DN4 has also demonstrated a high sensitivity (80%) and specificity in diabetic NP (92%) (Spallone et al., 2012). Contrasting the previous mentioned reliability for LANSS and DN4 to identify the NP component in other NP syndromes, the NP component of failed back surgery syndrome was less reliably identified (Markman et al., 2015). For an updated review of the strengths, limitations, and language translations of NP screening questionnaires, consult (Mathieson et al., 2015).

7.2. 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 ~80% of the peripheral nervous system and cannot be measured with conventional studies such as evoked potentials, electromyograms, or

electroneurograms (Avellanal et al., 2020). 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 (Di Stefano et al., 2012). It is quantitative because it comprises a series of calibrated stimuli and thresholds (i.e., perception and pain thresholds) for different tests. 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 (Mücke et al., 2016). In the first, 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 (Uddin and MacDermid, 2016). The first drawback of QST is that although it is quantitative, the feedback for pain intensity is based only on the patient's 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 min. 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. To counteract the wide methodologies, IASP recommended in 2013 a standardized method (Backonja et al., 2013), but new methodologies still emerge and clinicians may be prone to confusion. Fourth, mastering QST requires many hours of training to understand the different techniques for a clinical setting. Finally, only certified centers may apply QST, and full equipment could be very costly, which limits even more clinical applicability.

8. Research gaps and methodological improvements

So far, we have discussed the subjective and objective methods with advantages and disadvantages for the characterization of chronic NP. In this last section, we will propose a methodology for an integrative characterization, schematized in Fig. 9, that consists of two sessions.

The first session (see Fig. 9, First Session) would consist of the application of two questionnaires: (1) Pain Detect Questionnaire to confirm the diagnosis of chronic NP, and (2) the Brief Pain Inventory to evaluate the degree of affection in everyday life. Afterwards, the installation of the EEG equipment and measurement of vital signs would take place. Finally, the spontaneous EEG would be recorded in parallel to EDA and HR. For the second session, the EDA and HR would also be taken in parallel to the evoked component of NP assessed by EEG through the symptom of allodynia. Allodynia is the principal evoked symptom in NP patients (review Table 1: Type of altered sensation), but the measurement of allodynia has not been standardized to evaluate patients in a periodic and replicable fashion, which 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 this is not the case for mechanical allodynia (Backonja et al., 2013; Hansson et al., 2007; Walk et al., 2009). We propose an automated system where allodynia is evoked with ordinary standardized stimuli: tactile, vibration, and air (see Fig. 9, Second Session). To effectively evoke allodynia, these stimuli should be applied in the region with the worst NP symptoms marked by the patient in the Pain Detect Questionnaire and Brief Pain Inventory. For recording a SEP, each type of stimulus would consist of four levels of intensity, and each level would contain three stimuli with the same force. After each level of three stimuli, the patient would rate their pain intensity from a scale of 1–10. The stimulus intensity will ascend for the next three levels consecutively or until the patient clicks a stop button in the case of intolerable pain. In total, 12 stimuli for each type of stimulation would be recorded. Each stimulus would have different units to ascend through the levels and a specific stimulation time. For instance, the vibration stimulus should ascend in amplitude since nociceptors only respond to 250 Hz (Dyck et al., 1978). Also, every stimulus should have its particular stimulation zone, because the

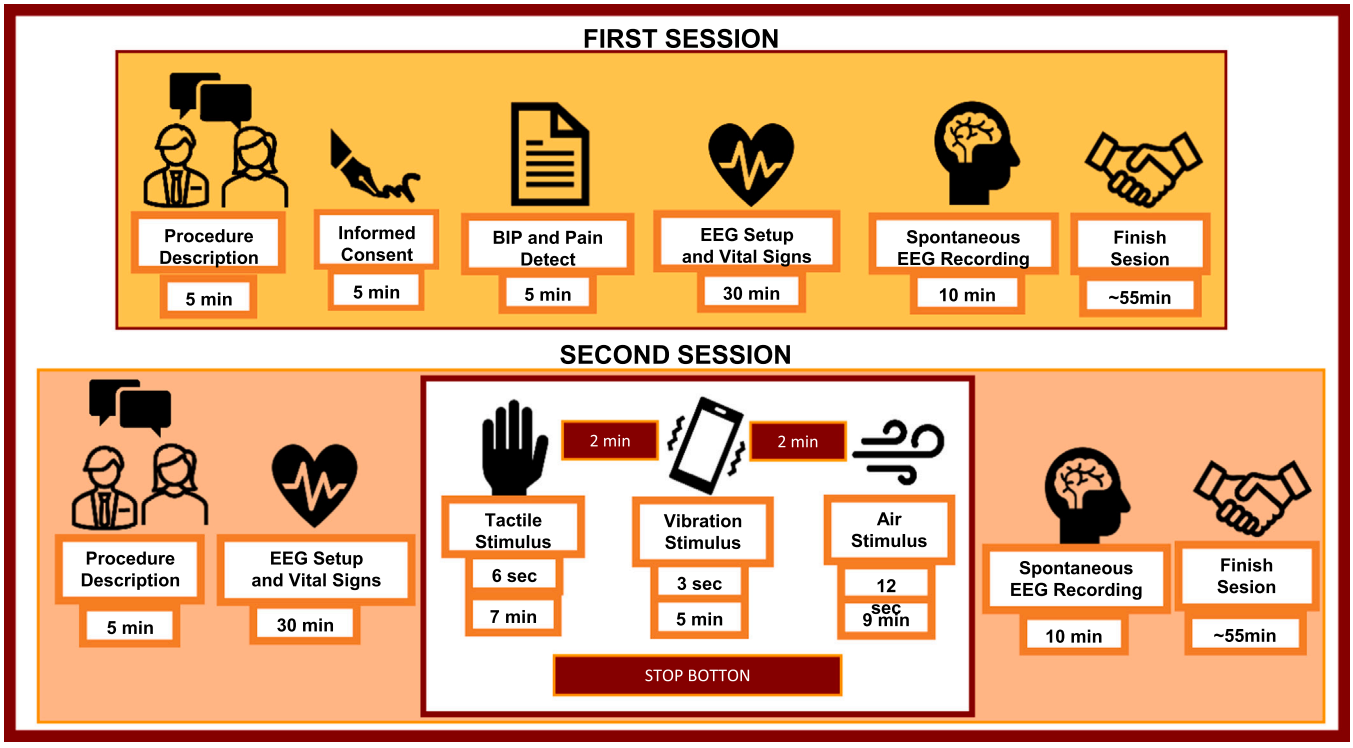

Fig. 9. Proposal for an integral methodology consisting of two sessions. First session corresponds to the baseline EEG. The second session comprehends the evoked activity recording and a post-stimuli spontaneous EEG recording. The total time for every activity is marked below it. The proposed stimulation time for tactile, vibration and air stimuli are 6s (Peyron et al., 2004), 3s, and 12 s (Chang et al., 2017), respectively. Total time for the 4 levels of stimulation with rest periods is marked in a box below the stimulation time.

character of pain depends on the A∂ and C nociceptors which depend on the type of skin (Schweinhardt et al., 2006). As discussed previously in Section 5.2.1, patients with chronic NP have delayed sensation to stimuli in EEG, so there should be 25 s between every stimulus of the same modality. To avoid excessive stimulation on the same receptors, the stimulation site should be changed after every stimulus within the predefined stimulation region (Peyron et al., 2004). After one modality of stimulation is finished, 2 min of rest between each type of stimulus is required. Finally, a post-stimuli session of spontaneous EEG should be recorded to monitor the effect of the spontaneous oscillations after being stimulated.

8.1. Stratification proposal

After subjective and objective data has been collected, stratification should be pursued since this would address the gap of the current clinical guidelines regarding the classification of NP, which affects the choice of the most appropriate treatment (Cruccu and Truini, 2017). According to (Vollert et al., 2017), recent approaches that aim to stratify NP patients are based on the specific underlying pathological mechanisms (i.e., a mechanism based therapy). Following the principle that chronic NP should be treated as a separate clinical entity for its specific socio-demographical profile (Covarrubias-Gómez et al., 2008; Freynhagen and Baron, 2009; Smith and Torrance, 2012), we propose to stratify chronic NP patients with different etiologies, but with the same NP characteristics. For instance, patients could be stratified by the fluctuation of their pain or their pain intensity. In this way, the individual NP activity of a patient could be enhanced by focusing on its nature, rather than its etiology. A recent study, stratified patients with peripheral NP based on the sensory profile of the QST. They tested the frequency of phenotypes in a population of patients with three syndromes: painful diabetic polyneuropathy, painful peripheral nerve injury, and postherpetic neuralgia (Vollert et al., 2017). Some limitations for their study were: (1) some QST parameters are mechanistically linked and are probably interconnected and (2) stratifying based on QST is not sustainable, for the drawbacks mentioned in Section 7.2. For the development of clinical trials, the overall aim would be to define patient subgroups and relate them to the efficacy of a particular drug (Bannister et al., 2020; Dickenson and Patel, 2020). In this case, stratifying based on the quantity of neuronal activity of NP (e.g., measured by approximate entropy), could bring more effective results, as is exemplified in Fig. 7. Future clinical trials could then include stratification of patients who are most likely to respond to the study drug based on their baseline neuronal activity.

9. Conclusions

In the present review, we have elucidated objective and subjective methods for the appropriate characterization of chronic NP. We established the heavy burden that an incomplete and inappropriate characterization has brought for NP patients, particularly in the management of their treatment. We stated that an appropriate characterization should be integral, considering both components of NP: spontaneous and evoked. Various objective methods based on EEG analysis and electrophysiological signals were described to record complementary information in the evolution of neuronal activity of chronic NP. To integrate the highly valuable perception of the patient, qualitative and quantitative subjective methods were also described. Finally, we proposed a prototype based on three ordinary stimuli to study the evoked NP component in EEG analysis. The complex pathophysiology of NP has made characterization equally as complex. However, we believe that approaching it integrally and stratifying according to subjective and objective data might pave the way to a better management.

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