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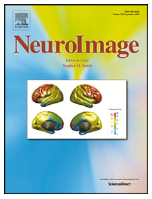

Review

Resting-state electroencephalography (EEG) biomarkers of chronic neuropathic pain. A systematic review

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ABSTRACT

Diagnosis and management of chronic neuropathic pain are challenging, leading to current efforts to characterize 'objective' biomarkers of pain using imaging or neurophysiological techniques, such as electroencephalography (EEG). A systematic literature review was conducted in PubMed-Medline and Web-of-Science until October 2021 to identify EEG biomarkers of chronic neuropathic pain in humans. The risk of bias was assessed by the Newcastle-Ottawa-Scale. Experimental, provoked, or chronic non-neuropathic pain studies were excluded. We identified 14 studies, in which resting-state EEG spectral analysis was compared between patients with pain related to a neurological disease and patients with the same disease but without pain or healthy controls. From these heterogeneous exploratory studies, some conclusions can be drawn, even if they must be weighted by the fact that confounding factors, such as medication and association with anxio-depressive disorders, are generally not taken into account. Overall, EEG signal power was increased in the θ band (4-7Hz) and possibly in the high-β band (20-30Hz), but decreased in the high-α–low-β band (10-20Hz) in the presence of ongoing neuropathic pain, while increased γ band oscillations were not evidenced, unlike in experimental pain. Consequently, the dominant peak frequency was decreased in the θ-α band and increased in the whole-β band in neuropathic pain patients. Disappointingly, pain intensity correlated with various EEG changes across studies, with no consistent trend. This review also discusses the location of regional pain-related EEG changes in the pain connectome, as the perspectives offered by advanced techniques of EEG signal analysis (source location, connectivity, or classification methods based on artificial intelligence). The biomarkers provided by resting-state EEG are of particular interest for optimizing the treatment of chronic neuropathic pain by neuromodulation techniques, such as transcranial alternating current stimulation or neurofeedback procedures.

1. Introduction

From a large French pain centre database, the estimated prevalence of chronic pain was about 30% in adult population (Chenaf et al., 2018). Chronic pain impairs the quality of life of patients, particularly due to the limited efficacy or side effects of analgesic drugs, and also results in a high economic cost to society. In clinical practice, the diagnosis and management of chronic pain is based on subjective elements reported by patients. Beyond patient interview and examination, the investigation of pain may involve techniques measuring sensory thresholds (quantitative sensory testing), recording electrophysiological potentials (microneurography or nociceptive evoked potentials) or assessing neuroimaging changes (functional magnetic resonance imaging or positron emission tomography) in response to nociceptive stimuli. Because these techniques use painful stimuli, they are more relevant to understanding provoked pain (hyperalgesia or allodynia) than continuous spontaneous pain. In fact, spontaneous pain should rather be assessed by resting-state recordings, using functional neuroimaging or neurophysiological techniques, such as magnetoencephalography (MEG) or electroencephalography (EEG). Temporal resolution is significantly better for neurophysiological techniques than for functional neuroimaging, and EEG is more commonly used, easier to perform, and less expensive than MEG. Although these techniques can only assess correlates of continuous pain, which is a symptom essentially accessible by questioning patients, expectations are high as to the possibility of EEG to provide biomarkers of chronic pain. A biomarker is a measurable and objective indicator of a biological state or condition: regarding pain, a valid biomarker should be based on pattern recognition of brain activity correlated with pain (Levitt and Saab, 2019), which could help to make its diagnosis more objective and also improve its prognosis, for example by

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predicting the response to an analgesic procedure (Mackey et al., 2019; Ploner and May, 2018; Reckziegel et al., 2019; Van der Miesen et al., 2019).

Concerning the assessment of pain by EEG, different types of studies should be distinguished. First, there are studies based on provoked pain protocols, comparing EEG recordings between a control condition and a condition with pain caused by nociceptive stimulation. This type of study is often performed in healthy controls (HC). However, the EEG changes associated with acute provoked pain, particularly in HC, are not necessarily relevant as biomarkers of chronic pain (Mouraux and Iannetti, 2018; Reckziegel et al., 2019). Therefore, these studies will not be considered in the literature review performed in this work.

On the other hand, chronic pain encompasses a range of different conditions with specific pathophysiological mechanisms and therapeutic management. The three main mechanisms at the origin of chronic pain are known to be nociceptive, nociplastic, and neuropathic. Neuropathic pain is defined according to the International Association for the Study of Pain as "*pain caused by a lesion or disease of the somatosensory nervous system*" (Scholz et al., 2019) and is considered one of the most difficult painful conditions to treat (Baron et al., 2010). Specific therapeutic approaches are recommended for the treatment of neuropathic pain (Moisset et al., 2020). In this context, more objective data would be useful to identify profiles of patients more prone to respond to specific treatments in order to make therapeutic decisions less random.

The objective of our study is therefore to define the resting-state EEG biomarkers that could be specifically associated with chronic neuropathic pain. We studied the changes observed in the different EEG frequency bands and associated with the presence of this type of pain, also examining the correlation between these changes and the intensity of pain. Only two EEG reviews have been published in the area of chronic pain. The first, by Pascoal-Faria et al. (2015), was restricted to spinal cord injury. The other, by Pinheiro et al. (2016), addressed all types of chronic pain indiscriminately. The present review includes updated studies relating specifically to neuropathic pain, discusses the localization of observed regional pain-related EEG changes, and outlines the perspectives offered by advanced techniques of EEG signal analysis. Such an analysis of literature data in this area is not currently available to our knowledge.

2. Methods

2.1. Search strategy and information sources

We followed the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) 2021 guidelines (Page et al., 2021). A complete search of the literature published in French or in English until January 2022 was conducted in PubMed Medline and Web of Science. The following search terms were used: "((electroencephal*[tiab] OR EEG[tiab]) AND (chronic) AND (pain) AND (neuropath*))" with the filters: restriction to English or French, experimentation on human. The research was equally conducted in the reference list of included articles and relevant reviews about EEG and pain. A protocol was not prepared and this review was not registered.

2.2. Eligibility criteria

An article was included if resting-state scalp EEG was assessed in a group of patients with pain (PwP) having chronic (>3 months) neuropathic pain compared to a control group of HC or disease-matched patients without pain (PwoP). Non-controlled studies were discarded. The primary objective of the studies was not taken into account, i.e. studies were included even if EEG investigation was not the primary endpoint but only a secondary objective measure. In contrast, articles dealing with acute pain, provoked pain or chronic non-neuropathic pain were excluded, as well as studies based on invasive EEG or MEG. Experimental pain in non-human models, e.g., in primates or rodents were also excluded from the review. Finally, only spontaneous resting-state EEG data were analysed, while dynamic EEG responses to various tasks or cues were not taken into account.

2.3. Selection and data collection process

Two independent reviewers (T.M. and B.B.) performed the research, reading first the title and the abstract, then the full text if relevant. After this first step, they grouped the articles meeting the inclusion criteria and reached a consensus on which to include. In the event of disagreement, a third reviewer was consulted (J-P.L.) to decide whether or not to include the article in the review.

2.4. Collected items

We collected the following data: study design, demographic and clinical characteristics of the included populations, and detailed characteristics of the EEG recordings, including the number of electrodes, methods of quantitative analysis, differences observed between PwP and controls in the different frequency bands (delta-δ, theta-θ, alpha-α, beta-β, gamma-γ), anatomical location, and the correlations between EEG data and pain intensity.

2.5. Study risk of bias assessment

The Newcastle-Ottawa scale (NOS) (Wells et al., 2022) was used to assess risk of bias in the included studies by two independent reviewers (T.M. and B.B.). NOS is a scale rating nonrandomized studies on a total score of 9 stars, from 0 star: low-quality rating to 9 stars: excellent-quality rating. The scale includes three sections: "selection" section including four items, each rated on one star for a total maximum of four stars; "comparability" section including one item rated on two stars; "exposure" section including three items, the first one being rated on two stars and the others on one star for a total maximum of four stars.

2.6. Analysis

The included articles were too heterogeneous to perform a meta-analysis. The primary endpoint of our study was the report of changes in the various EEG frequency bands according to chronic pain. Our secondary endpoint was the correlation between EEG changes and pain intensity.

3. Results

3.1. Literature search and included articles

From PubMed Medline and Web-of-Science databases, 497 articles were initially identified using our search terms (Fig. 1). Twenty-four articles were retained after reading the titles and abstracts and their full text was read. Then, seven articles were excluded because they did not investigate neuropathic pain or used non-eligible EEG procedures. Two studies investigating EEG in patients with chronic pain were excluded because of a debatable origin of pain. One study (Vuckovic et al., 2018), in which 31 patients with spinal cord injury were recruited (including 11 patients with neuropathic pain and 10 patients who later developed pain), was discarded because the EEG variables were not detailed according to frequency bands. Conversely, two studies were retained following a consensus between the reviewers, even if some patients had non-neuropathic pain: the first (Boord et al., 2008), in which two patients had 'musculoskeletal pain'; the second (Jensen et al., 2013b), in which four patients had 'chronic nociceptive pain'. However, the reviewers considered that the number of patients with a definite diagnosis of neuropathic pain was sufficiently high and predominant in these two studies to reasonably include them in the analysis.

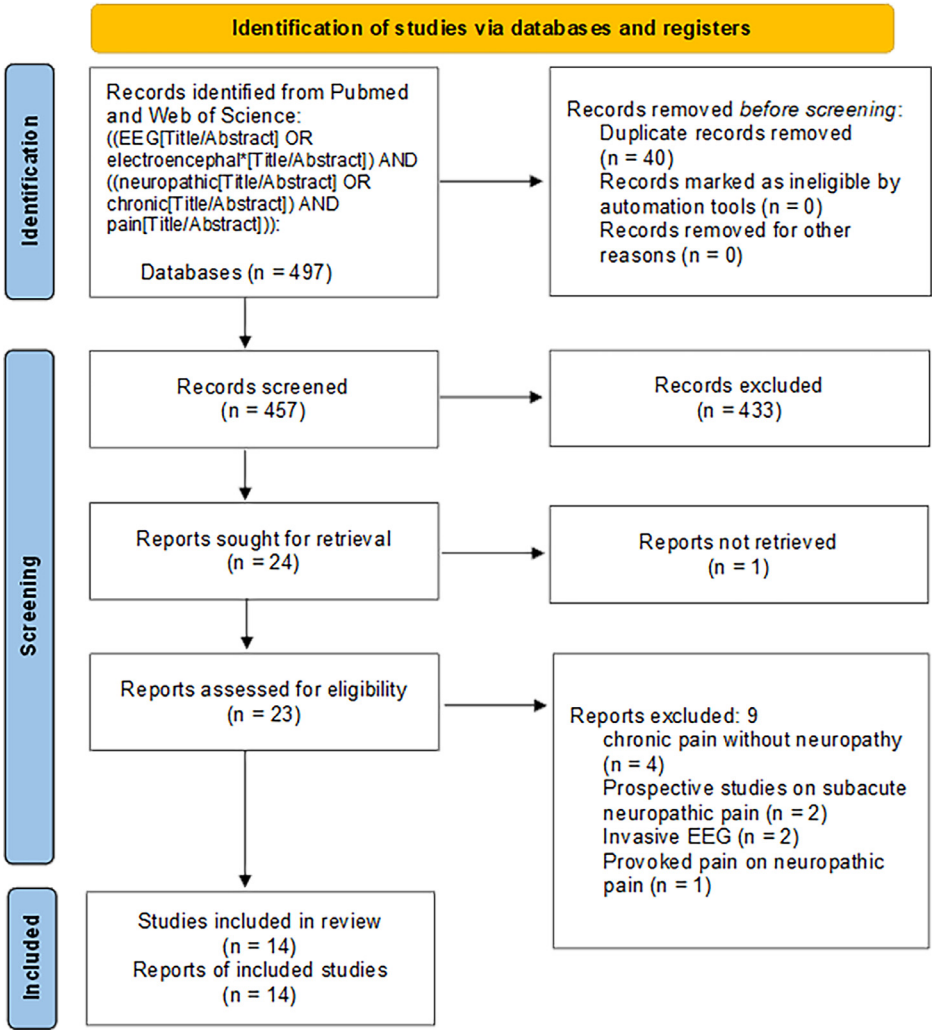

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection.

Finally, 14 articles were included in this review (Fig. 1). The included studies investigated several EEG variables as markers of pain with a cross-sectional design, while three studies were clinical trials in which resting-state EEG was recorded before and after a pain-relieving surgery (Michels et al., 2011; Sarnthein et al., 2006; Stern et al., 2006), from which we only analysed data from preoperative EEG recordings.

Among the included studies, four studies of patients with spinal cord injury (Boord et al., 2008; Jensen et al., 2013b; Vuckovic et al., 2014; Wydenkeller et al., 2009) were previously included in the review of Pascoal-Faria et al. (2015) and five studies (Boord et al., 2008; Sarnthein et al., 2006; Stern et al., 2006; Van den Broeke et al., 2013; Vuckovic et al., 2014) were previously included in the review of Pinheiro et al. (2016).

3.2. General characteristics of the studies

Table 1 shows the general characteristics of the 14 included studies, and Table 2 details the data analyses and quality assessment. Six studies investigated central neuropathic pain due to central nervous system disorder (multiple sclerosis in one study (Krupina et al., 2020) and spinal cord injury in five studies (Boord et al., 2008; Jensen et al., 2013b; Simis et al., 2021; Vuckovic et al., 2014; Wydenkeller et al., 2009) and included three groups: PwP, PwoP, and HC. Eight studies compared EEG data between only 2 groups (mainly PwP vs. HC) in various conditions of neuropathic pain: mixed (central and peripheral) in three studies (Michels et al., 2011; Sarnthein et al., 2006; Stern et al., 2006) and exclusively peripheral in the remaining five studies (including orofacial pain, lumbar radiculopathy, and post-herpetic neuralgia) (Di Pietro et al., 2018; Levitt et al., 2020; Teixeira et al., 2021; Van den Broeke et al., 2013; Zhou et al., 2018). A total of 241 patients with neuropathic pain were included in these 14 studies (ranging from 8 to 38 patients per study). In all studies, both men and women were included, excepting one with only women (Van den Broeke et al., 2013). The mean age ranged from 35 to 63 years old. Pain location was variable, affecting any part of the body, the limbs, or the head.

Regarding EEG acquisition and analysis, the number of electrodes varied from 14 to 128 (14-19 electrodes in four studies (Boord et al., 2008; Jensen et al., 2013b; Krupina et al., 2020; Levitt et al., 2020), 30-32 electrodes in three studies (Di Pietro et al., 2018; Simis et al., 2021; Wydenkeller et al., 2009), 60-64 electrodes in six studies (Michels et al., 2011; Sarnthein et al., 2006; Stern et al., 2006; Teixeira et al., 2021; Van den Broeke et al., 2013; Vuckovic et al., 2014), and 128 electrodes in one study (Zhou et al., 2018)). Automated artefact rejection was used in 11 studies, while visual-based artefact rejection only was applied in the remaining three studies (Di Pietro et al., 2018; Jensen et al., 2013b; Simis et al., 2021). The duration of resting-state EEG recording ranged from 1 to 24 minutes, usually divided into epochs of 1 to 5 seconds for signal analysis (not detailed in three studies (Sarnthein et al., 2006; Stern et al., 2006; Vuckovic et al., 2014)). Recordings were made with eyes closed (EC) in all cases, and a condition of EEG recording with eyes open (EO) was added in four studies (Boord et al., 2008; Levitt et al., 2020; Stern et al., 2006; Vuckovic et al., 2014).

Table 1
Demographic and clinical characteristics

Study	Population: number (men/women), mean age $_{\text{years old}}$ ± SD			Pain condition	Pain location	Pain treatment		
	Patients with pain	Patients without pain	Healthy controls			AE	AD	OP
Sarnthein et al., 2006	15 (9/6), 62.1 ± 10.1	-	15 (7/8), *nr*	Neuropathic pain (various causes)	Various	Yes	Yes	Yes
Stern et al., 2006	16 (7/9), 63.0 ± 10.0	-	16 (8/8), 56.0 ± 12.0	Neuropathic pain (various causes)	Various	Yes	Yes	Yes
Boord et al., 2008	8 (7/1), 35.3 ± 11.3	8 (8/0), 33.5 ± 10.3	16 (15/1), 34.3 ± 10.7	Spinal cord injury	Various	Yes	Yes	Yes
Wydenkeller et al., 2009	16 (11/5), 46.9 ± 14.9	9 (8/1), 47.3 ± 17.4	25 (19/6), 47.0 ± 15.0	Spinal cord injury	Various	Yes	Yes	Yes
Michels et al., 2011	23 (13/10), 57.7 ± 7.4	-	15 (8/7), 62.0 ± 6.0	Neuropathic pain (various causes)	Various	Yes	Yes	Yes
Jensen et al., 2013	38 (27/11), 51.2 ± 12.0	16 (15/1), 49.0 ± 12.8	28 (18/10), 44.6 ± 14.0	Spinal cord injury	*nr*	Yes	Yes	Yes
van den Broeke et al., 2013	8 (0/8), *nr*	11 (0/11), *nr*		Neuropathic pain after breast cancer treatment	*nr*	No	No	No
Vuckovic et al., 2014	10 (7/3), 45.2 ± 9.1	10, (8/2), 44.4 ± 8.1	10 (7/3), 39.1 ± 10.1	Spinal cord injury	*nr*	Yes	*nr*	*nr*
Di Pietro et al., 2018	20 (7/13), 50.1 ± 4.4	-	20 (7/13), 42.2 ± 2.9	Orofacial neuropathic pain	Orofacial	Yes	Yes	Yes
Zhou et al., 2018	14 (10/4), 64.0 ± 6.9	-	16 (10/4), 65.2 ± 7.9	Post-herpetic neuralgia	Various	Yes	Yes	Yes
Krupina et al., 2020	12 (3/9), 36.6 ± 3.2	12 (4/8), 42.9 ± 2.8	12 (4/8), 40.3 ± 4.0	Multiple sclerosis	Lower and upper limbs	No	No	nr
Levitt et al., 2020	20 (9/11), 54.2± *nr*		20 (9/11), 54.1 ± *nr*	Chonic lumbar radiculopathy	*nr*	*nr*	*nr*	No
Simis et al., 2021	29 (25/4), 36.3± 13.9	10 (6/4), 38.6 ± 13.6		Spinal cord injury	Lower or upper limbs or thoracolumbar	*nr*	*nr*	*nr*
Teixeira et al., 2021	12 (12/0), 54.4 ± 8.0	-	10 (10/0), 56.3 ± 15.6	Peripheral neuropathic pain (various causes)	Lower limb	Yes	Yes	yes

AD: antidepressants; AE: antiepileptic; nr: not reported; OP:opioids.

Table 2
Characteristics of EEG recordings.

Study	Number of electrodes	Duration of EEG recording (EEG epoch analysis)	Correction for multiple analyses	Artefact removal	NOS-Selection /4	NOS-Comparability /2	NOS-Outcome /3	NOS-Total /9
Sarnthein et al., 2006	60	5 min EC (~244 sec)	No	Visual inspection, BSS procedure, and ICA for ocular and muscle artefacts	2	1	3	6
Stern et al., 2006	60	5 min EC and EO (pooled data)	No	Visual inspection, BSS procedure, and ICA for ocular and muscle artefacts	2	1	3	6
Boord et al., 2008	14	1 min EC and EO (2-sec epochs)	No	ICA for ocular artefacts	0	1	3	4
Wydenkeller et al., 2009	30	~117 sec EC (2-sec epochs)	No	Threshold rejection and ICA for ocular artefacts	2	2	3	7
Michels et al., 2011	60	7.5 min EC (~5-6min, 5-sec epochs)	FDR	Visual inspection and ICA for ocular, muscle and heartbeat artefacts	1	0	3	4
Jensen et al., 2013	19	2 min EC (2-sec epochs)	No	Visual inspection for ocular and muscle artefacts	0	0	3	3
van den Broeke et al., 2013	64	1 min EC (4-sec epochs)	No	Visual inspection for muscle artefacts and Gratton-Coles method for ocular artefacts	0	0	3	3
Vuckovic et al., 2014	61	3 × 2 min EC and EO	FDR	Visual inspection, threshold rejection, and ICA for ocular artefacts	1	1	3	5
Di Pietro et al., 2018	32	5 min EC (2-sec epochs)	No	Visual inspection	2	1	3	6
Zhou et al., 2018	128	20 min EC (~400 sec, 2-sec epochs)	No	Spline interpolation, threshold rejection, and ICA for ocular and muscle artefacts	2	2	3	7
Krupina et al., 2020	16	3-4 min EC (4-sec epochs)	FDR (for correlation analysis only)	Visual inspection and threshold rejection for ocular and muscle artefacts	1	1	3	5
Levitt et al., 2020	16	Every 60 sec for 5 min EC and EO (1-sec epochs)	Bonferroni	Visual inspection and SVM procedure for ocular and muscle artefacts	3	2	3	8
Simis et al., 2021	32	20 min EC (5-sec epochs)	No	Visual inspection	2	1	3	6
Teixeira et al., 2021	64	24 min EC (2-sec epochs)	Bonferroni	Channel interpolation and ASR procedure for ocular and muscle artefacts	2	2	3	7

ASR: artefact subspace reconstruction; BSS: blind source separation; EC: eyes closed; EO: eyes open; FDR: false discovery rate; ICA: independent component analysis; NOS: Newcastle Ottawa Scale; SVM: support vector machine.

Table 3
Definition of the EEG variables extracted from included studies.

Term	Abbreviation	Unit	Definition
Absolute spectral power	aSP	μV^2 (or dB)	Integral of all of the power values in a given frequency range
Relative spectral power	rSP	%	Percentage of the aSP in a given frequency range from the total aSP summed over all the frequency bands studied
Power spectrum density	PSD	$\mu V^2/Hz$	Distribution of EEG signal power over frequency in a frequency range
Normalized power spectrum density	normalized PSD	%	Average value of all the PSD values measured at each frequency point in a given frequency range and normalized by the total aSP
Dominant peak frequency	DPF	Hz	Frequency at which the PSD is the highest in a given frequency range

The EEG spectral analysis variables reported in the reviewed studies are presented in Table 3. The absolute spectral power (aSP) in a frequency band is defined as the integral of all of the power values within this frequency band and expressed in μV^2 or converted to dB. The relative spectral power (rSP) is the percentage (%) of the aSP in a given frequency band, from the total aSP summed over all the frequency bands studied. The power spectrum density (PSD), in $\mu V^2/Hz$, represents the distribution of EEG signal power over frequency, i.e. reflects the 'voltage content' of the signal at a certain frequency. The PSD value for a frequency band usually represents the average value of all the PSD values measured at each frequency point in the band, and can be normalized (in %) by the total aSP. The dominant peak frequency (DPF) is the frequency (in Hz) at which the PSD is the highest in the considered spectrum. Finally, regarding between-group statistical analysis, a correction for multiple analyses was performed in five studies (Krupina et al., 2020; Levitt et al., 2020; Michels et al., 2011; Teixeira et al., 2021; Vuckovic et al., 2014), but not in the others.

3.3. Quality assessment

The total NOS score ranged from 3 to 8, with a mean of 5.5 (Table 2). In some studies, cases and controls did not match for gender or age and overall the HC population was insufficiently described. Similar results were found for the "selection", "comparability", and "exposure" sections. Studies were mainly exploratory and some identical patients were included in three studies (Michels et al., 2011; Sarnthein et al., 2006; Stern et al., 2006).

3.4. Primary endpoint: pain-related changes in EEG frequency bands

Results of quantitative EEG analysis in the frequency domain between PwP and PwoP or HC are presented in Table 4 for the 14 studies included. In these studies, pain-related changes have been reported in any or all of the following frequency bands: δ (<4Hz), θ (~4-7Hz), α (~8-12Hz), β (~13-30Hz), and γ (>30Hz), with the exception of two studies which only considered a whole broad band from 1-2 to 25-40Hz (Sarnthein et al., 2006; Zhou et al., 2018). The cortical anatomical locations of the observed changes are presented according to the different frequency bands in Table 5, when the EEG activities differed between PwP and controls.

3.4.1. Delta band

EEG in the δ band was assessed in seven studies but a pain-related change in this frequency band was only found in a study of patients with multiple sclerosis (Krupina et al., 2020) with a significant increase in aSP and DPF in PwP compared to HC and a significant decrease in rSP in PwP compared to both PwoP and HC.

3.4.2. Theta band

EEG in the θ band was assessed in 10 studies. Pain-related changes in this frequency band were not significant in only two studies (Levitt et al., 2020; Simis et al., 2021). In PwP compared to controls (PwoP and/or HC), a significant increase in PSD (Di Pietro et al., 2018; Michels et al., 2011; Stern et al., 2006; Vuckovic et al., 2014), aSP (Krupina et al., 2020), and/or rSP (Jensen et al., 2013b; Krupina et al., 2020) was found in the θ band in six studies. In one study (Wydenkeller et al., 2009), a shift of the DPF in the θ band towards a lower frequency was observed in PwP. In two other studies (Boord et al., 2008; Simis et al., 2021), a lower DPF in the whole α-θ frequency band (4-13Hz) was reported in PwP compared to HC (Boord et al., 2008) or PwoP (Simis et al., 2021). The increase in θ activities was widely located in the left hemisphere (fronto-centro-temporo-parietal regions) in four studies (Di Pietro et al., 2018; Jensen et al., 2013b; Michels et al., 2011; Stern et al., 2006), but more bilateral in one study (Vuckovic et al., 2014) or even restricted to the mid-temporal region of the right hemisphere (Krupina et al., 2020).

3.4.3. Alpha band

EEG in the α band was assessed with EC in 8 studies, while recordings with EO were considered in one study (Levitt et al., 2020) and with both EC and EO conditions in another study (Vuckovic et al., 2014). In the latter study, PSD changes in the α band were observed in PwP in EO but not in EC condition. The influence of eye closure should be further taken into account when describing changes observed in the α band in future studies. The following section presents the results of EEG recordings with EC only.

Pain-related changes in the α band were not significant in only one study (Wydenkeller et al., 2009). In the remaining seven studies, the results were controversial. In PwP compared to HC, an increase of PSD in the α band was found in three studies (Di Pietro et al., 2018; Michels et al., 2011; Stern et al., 2006), but a decrease of aSP (Jensen et al., 2013b; Simis et al., 2021) or rSP (Jensen et al., 2013b; Krupina et al., 2020) was found in three studies. In one of these latter studies, a positive correlation was found between EEG signal power in the α frequency band and the intensity of pain, i.e. more α power was associated with more pain (Jensen et al., 2013b). In addition, one study showed a larger median α amplitude in PwP (Van den Broeke et al., 2013). Both the increase in PSD/amplitude (Di Pietro et al., 2018; Michels et al., 2011; Van den Broeke et al., 2013) and the decrease in aSP/rSP (Jensen et al., 2013b; Simis et al., 2021) in the α band were located in large bilateral cortical regions, mostly fronto-centro-parietal.

3.4.4. Beta band

EEG in the β band was assessed in 10 studies. Pain-related changes in this frequency band were not significant in five studies (Di Pietro et al., 2018; Jensen et al., 2013b; Levitt et al., 2020; Vuckovic et al., 2014; Wydenkeller et al., 2009). In the remaining five studies, results were again controversial, since PSD was mildly increased in two studies from the same research group (Michels et al., 2011; Stern et al., 2006), as well as aSP or rSP in a third study (Krupina et al., 2020), while aSP and/or rSP were decreased in the remaining two studies (Simis et al., 2021; Teixeira et al., 2021). In fact, some differences were observed between the low-β band (~13-20Hz) and the high-β band (~20-30Hz), at least regarding the cortical location of the pain-related changes. They were observed in the anterior cingular cortex and left fronto-temporo-parietal region (Di Pietro et al., 2018; Stern et al., 2006) for low-β band activities, and in the posterior parieto-occipital region (Krupina et al., 2020; Simis et al., 2021; Stern et al., 2006; Teixeira et al., 2021) for high-β band activities. Finally, one study showed an increased DPF in

Table 4
Main quantitative EEG results. In each frequency band, comparisons between patients with pain (PwP) and patients without pain (PwoP) or healthy controls (HC).

Study	EEG variables	δ	θ	α	Low β	High β	γ	Correlation with pain intensity
Sarnthein et al., 2006	PSD and DPF (EC)	↑ for PSD and ↓ for DPF vs. HC (2-25 Hz)					*NA*	*NA*
Stern et al., 2006	PSD (EC and EO pooled)	*NS* (2-4 Hz)	↑ vs. HC (4-6 and 6-9 Hz)	Mild ↑ vs. HC (9-12 Hz)	↑ vs. HC (12-16 Hz)	Mild ↑ vs. HC (16-30 Hz)	*NA*	*NA*
Boord et al., 2008	DPF (EC and EO)	*NA*	↓ vs. HC, but *NS* vs. PwoP in EC condition (4-13Hz)		*NA*		*NA*	*NA*
Wydenkeller et al., 2009	PSD and DPF (EC)	*NS* (2-6 Hz)	↓ for DPF vs. PwoP and HC. *NS* for PSD (6-8 Hz)	*NS* (8-12 Hz)	*NS* (12-30 Hz)		*NA*	No correlation between θ–α DPF and pain intensity score (assessed in the two weeks before the EEG recording session)
Michels et al., 2011	PSD (EC)	*NA*	↑ vs. HC (4-7 Hz)	↑ vs. HC (7-13 Hz)	Mild ↑ vs. HC (13-30 Hz)		Mild ↑ vs. HC (30-48 Hz)	Positive correlation between PSD in the θ (r=0.44) and β (r=0.43) bands (in cingulate, prefrontal, orbitofrontal and insular areas) and pain intensity score (assessed before the EEG recording session)
Jensen et al., 2013	aSP and rSP (EC)	*NS* (2-3.5 Hz)	↑ for rSP vs. PwoP and HC. *NS* for aSP (4-7 Hz)	↓ for aSP and rSP vs. PwoP and HC (8-12 Hz)	*NS* (13-21 Hz)		*NA*	Positive correlation between aSP or rSP in the α band and pain intensity score (assessed during the EEG recording session) at three frontal cortical locations: FP1 (r=0.41), FP2 (r=0.36), and F8 (r=0.39)
van den Broeke et al., 2013	Median amplitude and centre of gravity (EC)	*NA*	*NA*	↑ for amplitude vs. PwoP. *NS* for centre of gravity (7-13 Hz)	*NA*		*NA*	No correlation between α amplitude or centre of gravity and pain intensity score (assessed the day of EEG recording session or averaged over the past 3 months)
Vuckovic et al., 2014	PSD and DPF (EC and EO)	*NA*	↑ for PSD vs. PwoP, but *NS* vs. HC in EO condition. *NS* in EC condition (4-8 Hz) ↓ for DPF vs. PwoP and HC (4-24 Hz)	↑ for PSD vs. PwoP, but *NS* vs. HC in EO condition. *NS* in EC condition (8-12 Hz)	*NS* (16-24 Hz)		*NA*	*NA*
Di Pietro et al., 2018	PSD (EC)	*NA*	↑ vs. HC (4-8 Hz)	↑ vs. HC (9-12 Hz)	*NS* (13-25 Hz)		*NA*	Positive correlation between PSD in the α band (in right temporal area, r=0.60) and the β band (in right central and parieto-occipital areas, r=0.53 and 0.57) and pain intensity score (assessed in the week before the EEG recording session)
Zhou et al., 2018	aSP (EC)	*NS* (1-40 Hz)					↑ vs. HC (40-70 Hz)	Positive correlation between aSP in the γ band (r=0.70) and pain intensity score (assessed the day of EEG recording session)
Krupina et al., 2020	aSP, rSP, and DPF (EC)	↑ for aSP and DPF (left frontal region) vs. HC but *NS* vs. PwoP. ↓ for rSP vs. PwoP and HC (0.5-4 Hz)	↑ for aSP and rSP vs. PwoP and HC. *NS* for DPF (4-8 Hz)	↓ for rSP vs. PwoP and HC. *NS* for aSP and DPF (8-13 Hz)	↑ for aSP and rSP vs. PwoP and HC. *NS* for DPF (13-20 Hz)	↑ for aSP and rSP vs. PwoP and HC. ↑ for DPF (left posterior (temporo-parieto-occipital) region) vs. HC (20-30 Hz)	*NA*	No correlation between aSP in the δ, θ, α, low or high β bands and pain intensity score
Levitt et al., 2020	PSD (EO)	*NA*	*NS* (4-8 Hz)	*NS* (9-12 Hz)	*NS* (13-30 Hz)		*NS* (31-50 Hz)	*NA*
Simis et al., 2021	aSP, rSP, and DPF (EC)	*NS* (1-3.9 Hz)	*NS* (4-7.9 Hz). ↓ for DPF vs. PwoP (4-13 Hz)	↓ for aSP (fronto-centro-parietal region) vs. PwoP (8-12.9 Hz)	*NS* (13-19.9 Hz)	↓ for aSP (parietal region) vs. PwoP (20-30 Hz)	*NA*	Negative correlation between aSP in the α band (central region, r^2=0.23) and low β band (frontal region, r^2=-0.16) and pain intensity score (assessed before the EEG recording session)
Teixeira et al., 2021	aSP and rSP (EC)	NS (2-4 Hz)	NA	NA	↓ for aSP and rSP vs. HC (13-20 Hz)	↓ for aSP vs. HC, but NS for rSP, (20-30 Hz)	NA	Negative correlation between aSP in the low β band (r=-0.93) and pain intensity score (assessed in the two weeks before the EEG recording session) only in the subgroup of patients with pain intensity ≥3/10, at the edge of significance in the high β band (r=-0.80)

aSP: absolute spectral power, DPF: dominant peak frequency; EC: eyes closed; EO: eyes open; NA: not assessed; NS: not significant change; PSD: power spectral density; rSP relative spectral power; or : significant increase or decrease regarding EEG signal analysis for PwP compared to PwoP or HC.

Table 5
Main quantitative EEG results: Cortical location when frequency band activity was increased or decreased in patients with pain versus control.

Study	θ	α	Low β	High β	γ
Stern et al., 2006	↑ left parieto-temporal (peri-insular)	Mild ↑ bilateral insular	↑ bilateral anterior cingulate, left dorsolateral prefrontal and insular	Mild ↑ left occipital	
Michels et al., 2011	↑ left fronto-centro-temporo-parietal	↑ bilateral fronto-central			
Jensen et al., 2013	↑ left parietal and bilateral occipital	↓ bilateral frontal			
van den Broeke et al., 2013		↑ bilateral parieto-occipital			
Vuckovic et al., 2014	↑ bilateral widespreadly, except central region (Eyes Open condition)	↑ bilateral widespreadly (Eyes Open condition) and only frontal region (Eyes Closed condition)			
Di Pietro et al., 2018	↑ left fronto-centro-temporal	↑ right frontal, left centro-temporal, and bilateral parietal	Mild ↑ bilateral fronto-centro-temporo-parietal, mostly on the left		
Zhou et al., 2018					↑ bilateral dorsolateral prefrontal, medial prefrontal, median and anterior cingulate, cerebellum
Krupina et al., 2020	↑ right mid-temporal (and also bilateral prefronto-temporal)		↑ right temporal (and also bilateral prefronto-temporal)	↑ bilateral parieto-occipital (and also bilateral prefronto-temporal)	
Simis et al., 2021		↓ bilateral fronto-centro-parietal		↓ bilateral parietal	
Teixeira et al., 2021				↓ right posterior	

the high-β band in PwP with multiple sclerosis compared to HC, in a posterior cortical region of the left hemisphere (Krupina et al., 2020).

3.4.5. Gamma band

EEG in the γ band was assessed in only three studies. No pain-related change was reported in one study (Levitt et al., 2020), while an increase in PSD (Michels et al., 2011) or aSP (Zhou et al., 2018) was reported in the other studies. In this last study, the increase in aSP in PwP compared to HC was located in bilateral prefrontal and anterior cingulate cortices (Zhou et al., 2018).

3.4.6. Overall changes

In two studies, changes in a broad frequency band were assessed without considering the specific EEG rhythms: one study did not reveal any significant change in the 1-40Hz band (Zhou et al., 2018), while the other showed an increase in PSD and decrease in DPF in the 2-25Hz band (Sarnthein et al., 2006). Such a decrease in DPF was also reported by Vuckovic et al. (Vuckovic et al., 2014) in a broad 4-24Hz band.

3.5. Secondary endpoint: correlation between EEG changes and pain intensity

Correlations between pain intensity and EEG spectral analysis are detailed in Table 4. This type of analysis was performed in nine studies and the absence of any correlation was observed in three studies (Krupina et al., 2020; Van den Broeke et al., 2013; Wydenkeller et al., 2009). In other studies, pain intensity scores were positively correlated with increased EEG activities (PSD or aSP/rSP) in the θ (Michels et al., 2011), α (Di Pietro et al., 2018; Jensen et al., 2013b), whole β (Di Pietro et al., 2018; Michels et al., 2011) or γ (Zhou et al., 2018) frequency band in various cortical regions. Conversely, a negative correlation was found between aSP values and pain intensity scores in two studies concerning the α (Simis et al., 2021) and low-β (Simis et al., 2021; Teixeira et al., 2021) bands.

4. Discussion

This is the first systematic review of EEG studies performed in patients with chronic neuropathic pain in order to highlight potential EEG biomarkers of ongoing pain. While no substantial change was found in δ and γ bands, PwP had a significant increase of PSD or aSP/rSP in the θ band, but with a shift of the DPF towards a lower frequency in this band (Fig. 2). The increased PSD in the θ band was mainly observed in the left hemisphere and may be positively correlated with the intensity of ongoing pain (Michels et al., 2011). Results were more controversial regarding α and β frequencies. In the α band, PSD appeared to be increased but aSP/rSP to be decreased, with either positive (Jensen et al., 2013b) or negative (Simis et al., 2021) correlation between aSP/rSP and pain intensity in the frontal or central cortical region, respectively. In the β band, PSD and aSP/rSP were increased in three studies, with positive correlation with pain intensity in two studies (Di Pietro et al., 2018; Michels et al., 2011). Conversely, aSP/rSP were decreased in two studies (Simis et al., 2021; Teixeira et al., 2021), associated with negative correlation with pain intensity preferentially observed for EEG activities in the low-β band. The changes in low-β band activities appeared to be located in more anterior cortical regions than those in the high-β band. The posterior cortical changes in EEG activities could be further associated with a DPF increase in the high-β frequency band (Krupina et al., 2020).

Thus, neuropathic pain is possibly associated with a shift of the DPF towards a lower value in a broad frequency band from θ to low-β (4-15Hz), but towards a higher value in the high-β frequency band (20-30Hz) (Fig. 2). Regarding PSD, values appeared to be increased in the θ frequency band, and possibly in the high-β frequency band, while aSP/rSP could be decreased in the α to low-β frequency band in the context of neuropathic pain. However, these conclusions should be taken with caution because the studies were few, based on small samples with heterogeneous methodology and variable clinical pain profiles, particularly with respect to the exclusive nature of neuropathic type of pain, and also because possible confounding factors were not taken into ac-

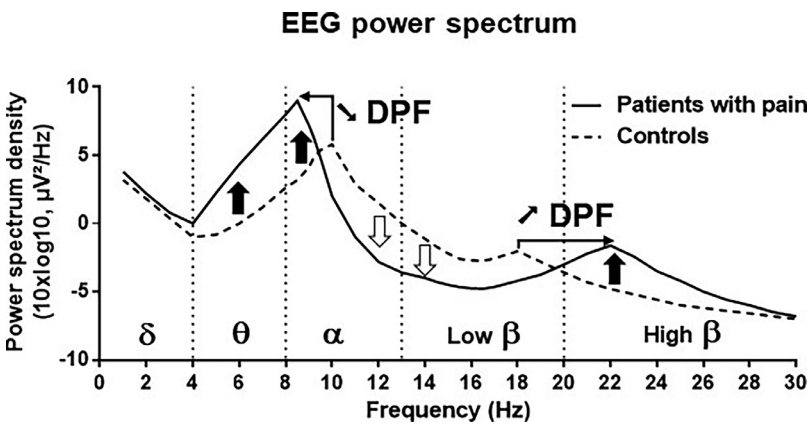

Fig. 2. Illustrative comparison of the EEG power spectrum in patients with chronic neuropathic pain versus controls without pain. In patients with chronic neuropathic pain, the power spectrum density is usually increased in the θ band and also in the low-α and high-β sub-bands (black arrows), but decreased in the high-α–low-β band (white arrows). The dominant peak frequency (DPF) is shifted towards a lower frequency in the θ - α band and a higher frequency in the whole β band.

count, such as the variety of analgesic medication taken (cf. Table 1) or the influence of psychiatric comorbidity (e.g., anxiety or depression).

4.1. Increased oscillations in theta band

Thus, patients with chronic neuropathic pain have increased θ oscillations, which may normalize after thalamotomy (surgical lesion of the central lateral nucleus) indicated for the treatment of pain (Sarnthein et al., 2006), at least in the cingulate cortex (Stern et al., 2006) or even in a more widespread anterior (fronto-central) cortical region, correlated with pain relief (Michels et al., 2011). Increased θ activities were also reported in patients with various types of chronic non-neuropathic pain (Case et al., 2018; Fallon et al., 2018; Pinheiro et al., 2016; Ta Dinh et al., 2019). Although there is a multitude of θ oscillators, mainly related to cognitive processing, including spatial memory and learning (Colgin, 2013), the mechanism of pain-related changes in the θ band could fit into the theory of thalamocortical dysrhythmia. This theory suggests that abnormal nociceptive input produces burst activities in the thalamus at θ frequency transmitted to the cortex (Jeanmonod et al., 2001).

A few studies did not report an increase in θ activities in the resting-state EEG of patients with neuropathic pain (Levitt et al., 2020; Schmidt et al., 2012; Simis et al., 2021). However, in one of these studies performed in 39 patients with spinal cord injury (Simis et al., 2021), the resting-state EEG data were analysed not only according to the presence or absence of chronic pain, but also to the efficiency of a conditioned pain modulation (CPM) protocol, as a marker of the descending pain inhibitory controls. Although no changes were found in the θ activities related to the presence of spontaneous pain, an increase in rSP in the θ band was observed in patients with low CPM efficiency, with a significant correlation between these two phenomena: the higher were θ activities, the lower were pain inhibitory controls. This study suggests that even if increased θ oscillations do not directly correlate with the presence of pain, they do at least correlate with a reduced efficiency of central pathways to control pain.

4.2. Decreased activities in the alpha band and downshift of dominant peak frequency

In chronic neuropathic pain, a decrease in α activities could be associated with the increase in θ activities (Jensen et al., 2013b; Krupina et al., 2020), leading to a shift of the DPF towards lower frequencies in the whole θ–α band (Boord et al., 2008; Simis et al., 2021). Such a result was also reported in EEG studies of patients with chronic non-neuropathic pain (De Vries et al., 2013; Vanneste et al., 2017; Villafaina et al., 2019), as well as in MEG studies of PwP (Kim et al., 2019; Lim et al., 2016; Walton et al., 2010). In experimental pain, these changes were associated with an increased sensitivity to develop more severe pain (Furman et al., 2020, 2018) and were located in the central cortical region contralateral to painful stimuli (Chouchou et al., 2021).

However, the decrease of α activities in PwP remains debatable, since several studies included in our review rather found a concomitant increase in PSD in the α and θ bands (Di Pietro et al., 2018; Micoulaud-Franchi et al., 2015; Stern et al., 2006; Vuckovic et al., 2014). This discrepancy could be explained by a relative increase in EEG activities in the lower part vs. the higher part of the α frequency band (Fig. 2). In fact, as for the β band, two α sub-bands could be distinguished: a low-α band (8-10Hz) corresponding to a diffuse relaxed state of rest in EC condition, but alert with overall tonic vigilance, and a high-α band (10-12Hz), linked to the perceptual and cognitive processing of sensorimotor integration (Babiloni et al., 2014). Indeed, the α rhythm is one of the main operators of the brain involving a multiplicity of thalamocortical loops and pacemakers (Başar, 2012; Schürmann and Başar, 2001). In any case, it seems that a shift in EEG activity towards lower frequencies in the whole θ–α band is a major biomarker of the presence of chronic neuropathic pain, as evidenced by DPF analysis. As mentioned above, this downshift is considered a hallmark of thalamocortical dysrhythmia, reflecting the weight of θ oscillators compared to α changes in chronic neuropathic pain state (Vuckovic et al., 2014).

4.3. Beta oscillations

As for the α band, neuropathic pain-related changes are controversial for the β band, likely reflecting the multiplicity of brain sources in this frequency band. Actually, the β band can be mainly divided into a low-β band (~13-20Hz) associated with an idle state of the sensorimotor network and a high-β band (~20-30Hz) related to more complex cognitive processes including attentional, cue anticipation, and mood (e.g., anxiety and excitation) (Barone and Rossiter, 2021; Betti et al., 2021; Kilavik et al., 2013; Pomper et al., 2013).

In PwP, low-β activities were found to be reduced in relation to increased pain intensity (Simis et al., 2021; Teixeira et al., 2021), while increases in low-β activities, particularly in anterior cortical regions (Di Pietro et al., 2018; Michels et al., 2011; Stern et al., 2006), are not correlated with the intensity of pain. Regarding activities in the high-β band, one study showed increased aSP/rSP and DPF in this frequency band in PwP, particularly located in a posterior parieto-occipital region (Krupina et al., 2020). In non-neuropathic pain conditions, other studies also reported reduced activities in the low-β band and/or increased activities in the high-β band, e.g., in patients with chronic jaw pain (Wang et al., 2019), pain related to sickle cell disease (Case et al., 2018), or fibromyalgia (Vanneste et al., 2017).

Overall, literature data regarding pain-related EEG changes in the β band is consistent with a relative decrease in low-β activities associated with a relative increase in high-β activities in the context of chronic neuropathic pain (Fig. 2). This is further supported by several studies show-

ing pain relief in patients with chronic neuropathic pain treated by EEG-based neurofeedback techniques aimed at reinforcing aSP/rSP in the low-β band and/or reducing aSP/rSP in the high-β band (Hasan et al., 2016; Hassan et al., 2015; Jensen et al., 2013a, 2016; Vuckovic et al., 2019).

4.4. Gamma oscillations

It is well known that γ oscillations are related to the GABAergic inhibitory control system, which is likely disturbed in PwP. Therefore, it was not surprising to observe an association between γ oscillatory activities and various aspects of pain, such as pain perception (Gross et al., 2007), pain intensity (Schulz et al., 2015), or attentional aspects of pain (Tiemann et al., 2010). However, these classical data were mainly obtained in the context of experimental pain in HC (Heid et al., 2020; Lyu et al., 2022), or at least related to provoked pain. There are only rare results showing a significant increase in γ oscillations correlated with continuous pain, e.g., in patients with chronic back pain (May et al., 2019). In our literature review, this finding was reported in only two studies in patients with chronic neuropathic pain (Michels et al., 2011; Zhou et al., 2018). Interestingly, Zhou et al. (2018) showed that increased γ oscillations correlated with anxiety as a component of the pain syndrome rather than pain itself. In fact, anxiety may be associated with diffuse muscle tension and γ oscillations recorded by scalp EEG are highly sensitive to muscle artefacts (Chouchou et al., 2021). It is difficult to overcome this problem and affirm that γ activities are indeed of cerebral origin and not linked to scalp or cervical muscle contractions, even on intracerebral EEG (Mussigmann et al., 2021). However, there is no doubt that an enhancement of γ oscillations elicited by nociceptive stimuli as compared with non-nociceptive stimuli can be observed using intracerebral EEG, especially in the insular cortex (Liberati et al., 2018a). The significance of these γ oscillations remains to be defined, since they are evoked by thermo-nociceptive stimuli but not mechano-nociceptive stimuli (Liberati et al., 2020) and their magnitude are dissociated from the intensity of pain perception (Liberati et al., 2018b). It remains possible that increased γ oscillations may be related to some conditions of provoked nociception rather than to continuous neuropathic pain. Therefore, data is lacking to support γ oscillations as a candidate biomarker of chronic neuropathic pain, unlike other pain conditions (May et al., 2019).

4.5. Correlation between ongoing pain intensity and EEG variables

A change found in an EEG variable between a group of PwP and a group of HC or even PwoP does not inherently have a causal value with the presence of pain nor provide information on the different aspects of pain (i.e. sensory, cognitive (attentional), emotional, functional, physical or disability components). Unfortunately, very little detailed clinical data are reported in EEG studies beyond the pain intensity scores. Therefore, at least the correlations between these scores and EEG variables are important to define specific biomarkers of pain of clinical value (Levitt and Saab, 2019).

Disappointingly, pain intensity scores positively correlated with increased EEG activities (PSD or aSP/rSP) in all possible frequency bands, i.e. θ (Michels et al., 2011), α (Di Pietro et al., 2018; Jensen et al., 2013b), whole β (Di Pietro et al., 2018; Michels et al., 2011) or γ (Zhou et al., 2018) bands, while negative correlations were also found in the α (Simis et al., 2021) and low-β (Simis et al., 2021; Teixeira et al., 2021) bands. No definitive conclusion can therefore be drawn from these results.

4.6. Anatomical location of EEG changes according to frequency band

In most of the studies included in our review, the number of electrodes was insufficient compared to recommendations (Michel and Brunet, 2019) to provide accurate location of pain-related EEG changes according to cortical anatomy. However, some hypotheses on specific brain regional changes related to pain seem to emerge from our review of the literature. First, the increase in θ activities appeared to be preferentially located in the left hemisphere (Di Pietro et al., 2018; Jensen et al., 2013b; Michels et al., 2011; Stern et al., 2006). Second, the changes in α activities appeared to be more widespread but rather located in fronto-centro-parietal regions (Di Pietro et al., 2018; Jensen et al., 2013b; Michels et al., 2011; Simis et al., 2021; Van den Broeke et al., 2013; Vuckovic et al., 2014). Third, the changes in β activities appeared to be located in anterior or left-sided regions in the low-β band (Di Pietro et al., 2018; Stern et al., 2006), as for the α or θ bands, while the changes were clearly more posterior in the high-β band (Krupina et al., 2020; Simis et al., 2021; Stern et al., 2006; Teixeira et al., 2021). The lateralization, preferentially to the left, of pain-related EEG changes in brain oscillations from θ (~4-7Hz) to low-β (~13-20Hz) frequencies, could be put into perspective with the analgesic efficacy of certain neuromodulation techniques such as repetitive transcranial magnetic stimulation (rTMS). For the treatment of pain with rTMS, the optimal stimulation frequencies range between 5Hz (in the θ band) and 20Hz (in the β band) (Lefaucheur, 2016). In addition, in terms of stimulation sites, the preferred targets are left dorsolateral prefrontal cortex or the left precentral gyrus in cases of diffuse pain (Lefaucheur et al., 2020; Lefaucheur and Nguyen, 2019). This is consistent with most of the results found in our study, i.e. (pre)fronto-central changes, although some data instead locate pain-related EEG changes, particularly θ overactivation, in a region encompassing the temporal, temporo-parietal, or even insular cortex (Jensen et al., 2013b; Krupina et al., 2020; Michels et al., 2011; Stern et al., 2006). In fact, the posterior insula is the main cortical centre for the integration of nociceptive information and a target for rTMS neuromodulation still under evaluation for the treatment of patients with chronic neuropathic pain (Dongyang et al., 2021).

Region-specific changes may also explain the divergent results obtained between studies in a given frequency band, for example regarding pain-related increase or decrease in EEG activities in the α or β frequency bands. Also, future studies will necessarily have to take into account the location of changes in EEG activity according to the different frequency bands, and analyse their relationship with the clinical symptomatology of patients, concerning the presence of spontaneous pain and other aspects of the pain syndrome. This will require a large number of electrodes and advanced signal analysis techniques in order to correctly interpret the results based on what is known about the dynamic pain connectome (Kim and Davis, 2021).

4.7. Comparison between chronic neuropathic and non-neuropathic pain

This review addressed the question of EEG biomarkers of neuropathic pain as a relatively homogeneous clinical entity. However, such EEG biomarkers might not be specific for the neuropathic origin of pain and more related to chronic pain regardless of its origin.

A number of EEG or MEG studies have focused on patients with fibromyalgia or chronic low back pain. Some results of these studies have already been discussed in this review. For example, several studies have shown an increase in θ activities in PwP compared to HC (Fallon et al., 2018; Kisler et al., 2020; Lim et al., 2016; Ta Dinh et al., 2019; Vanneste et al., 2017) in non-neuropathic pain syndromes. Other results relate to a decrease in DPF in the θ-α band (De Vries et al., 2013), an increase in α activities (Kisler et al., 2020; Meneses et al., 2016; Vanneste et al., 2017; Wang et al., 2019), or conversely a decrease in α activities (González-Villar et al., 2020; Kim et al., 2019). The reduced α activities were associated with a more severe pain intensity and observed in the posterior cingulate cortex and the precuneus (González-Villar et al., 2020). In the β band, changes in EEG activities were variable in the context of non-neuropathic pain, as in the neuropathic pain studies included in this review, probably depending on the cortical locations and differences between low- and high-β frequency sub-bands.

Thus, the EEG changes observed in patients with chronic pain of non-neuropathic origin are very similar to those observed in patients with neuropathic pain and highlighted in this review. Therefore, we can assume that even if EEG biomarkers of chronic pain could be defined, they would probably not be able to identify the pathophysiological mechanisms underlying a given pain condition.

4.8. Information provided by EEG studies of provoked pain

Based on magnetic resonance imaging data, a similar network-level signature on whole-brain functional connectivity was recently shown between chronic low back pain and experimentally induced tonic pain, but not phasic pain (Lee et al., 2021). However, as mentioned in the introduction, the acute changes produced in brain activities by phasic or tonic noxious stimuli are not necessarily similar to the changes associated with chronic spontaneous pain and are therefore of limited relevance to the understanding of chronic pain syndromes, especially if painful stimuli are applied in HC.

The data provided by experimental pain studies have been previously reviewed (Lenoir et al., 2020) and can be briefly summarized as follows. First, there are differences in EEG changes secondary to phasic noxious stimuli of short-duration compared to long-lasting tonic pain. Indeed, painful stimuli in the millisecond range cause changes primarily in the sensorimotor central cortex, while the prefrontal cortex engages if the pain is prolonged for several seconds or minutes (Misra et al., 2017). Overall, the intensity of acute provoked pain was correlated with a decreased EEG power in the α band, particularly in the frontal region, and the low-β band, particularly in the sensorimotor central region, but with increased γ oscillations and even θ activities, particularly in the prefrontal region (Misra et al., 2017; Nickel et al., 2017; Schulz et al., 2015). Thus, taking into account in particular preferential changes in the α and γ bands than in the θ band, the modulation of EEG activities produced by noxious stimulation appear markedly different from that associated with spontaneous continuous pain. This reinforces the idea that the results obtained in experimental pain cannot be transposed in the context of chronic pain. Indeed, chronic pain results from dysfunctional communication between either hyperactive or hypoactive brain regions involved in the dynamic pain connectome (Kim and Davis, 2021), including the neural structures ensuring nociceptive information processing, the pain inhibitory control pathways, and even the salience network involved in the selection of stimuli to be actively brought to our consciousness (Otti et al., 2013). Acute provoked pain, which relates to the primary activation of nociceptive sensory afferent pathways is far from being representative of all the changes potentially induced in brain oscillations linked to long-term maladaptive neuronal plasticity and pathological network interactions, which are present in chronic pain.

Apart from provoked pain experiments, it also is possible to use various provocative conditions, such as movement or mental imagery (Fardo et al., 2015), to modulate pain sensations in PwP and better characterize pathological changes. These studies attempt to explore how chronic neuropathic pain interrelates to dynamic brain activation patterns during a given mental task or sensorimotor processing. Thus, different signatures in the changes observed between provoked and spontaneous EEG recordings may help to better understand some underlying pathophysiological mechanisms associated with chronic neuropathic pain beyond the resting state.

4.9. Prospects for technical developments concerning EEG analyses in the frequency domain

The spectral analyses used in the studies included in this review were relatively 'sketchy'. Various types of more complex and refined analyses could have been performed. For example, the difference in EEG reactivity between EC and EO conditions is an interesting physiological approach to analyse various brain functions (Barry et al., 2007). It has only been performed in two studies involving patients with chronic neuropathic pain (Boord et al., 2008; Vuckovic et al., 2014), showing a reduced reactivity in a broad EEG band between EC and EO states, particularly in the parieto-occipital region (Vuckovic et al., 2014). Thus, the value of the EC/EO ratio according to the different frequency bands and cortical locations ('spectral' and 'spatial' factors) remains to be further studied in the context of neuropathic pain.

Spectral analyses can be performed within a given frequency band, according to different recording conditions or sites, and also between different frequency bands (cross-frequency analyses). Frequency bands other than the canonical ones may also be considered, e.g., the whole $\theta-\alpha$ band, or the low- and high-β and α sub-bands, with the calculation of α/θ, low-β/high-β, or low-α/high-α ratios of EEG activities. For example, in a resting-state MEG study of patients with chronic back or leg pain (Witjes et al., 2021), PwP had no change in aSP or DPF values in the whole α band, but an increase in low/high-α power ratio compared to HC. The strategy of analysing cross-frequency band activity ratios should be further developed in EEG studies of pain, especially as these ratios are increasingly used to design EEG-based neurofeedback protocols for neuropathic pain treatment (Bismuth et al., 2020).

Beyond demonstrating EEG changes in a frequency band, knowing in which cortical regions these changes are located is a major challenge in defining and understanding pain biomarkers. In this field, different types of EEG signal analysis are relevant, such as source localisation or functional connectivity studies.

Intracranial EEG source localisation is commonly determined from low-resolution brain electromagnetic tomography (LORETA), including its 'standardized' variant (sLORETA). The value of this approach to identify the spatiotemporal dynamics of the brain sources in experimental (provoked) pain studies has been recently reviewed (Völker et al., 2021). Conversely, in the context of ongoing chronic pain, data are scarce.

Using a sLORETA approach in a series of 77 patients with chronic pain of radicular or myofacial/musculoskeletal origin, Prichep et al. (Prichep et al., 2018) found a significant $\theta-$low-α overactivation in various brain regions, known to be involved in nociception and pain processing (Garcia-Larrea and Peyron, 2013), particularly in the left hemisphere. In another series of patients with pain related to sickle cell disease, increased θ activities were found in the prefrontal cortex and left operculo-insular region, while β activities were decreased in the precuneus (Case et al., 2018).

Functional EEG connectivity, e.g., through the coherence method, has been studied to investigate the dynamic interaction between various brain structures involved in chronic pain (Ploner and May, 2018). For example, an increased connectivity in the θ and γ bands in frontal areas was reported in a large series of 101 patients with chronic pain of various origins (Ta Dinh et al., 2019).

Connectivity and source localization or microstate analyses were combined in studies of patients with fibromyalgia (González-Roldán et al., 2016; González-Villar et al., 2020; Lim et al., 2016), but not in the context of neuropathic pain to our knowledge. On MEG recordings, Kim et al. used a spatial filtering (beamforming) technique to optimally extract the signal in areas of interest corresponding to the nodes of the nociceptive pathways, default mode and salience networks that form the dynamic pain connectome (Kucyi and Davis, 2015). In a series of 33 PwP related to multiple sclerosis, they found abnormalities in cross-network functional coupling in multiple frequency bands, particularly between the salience network and the other networks, depending on whether pain was neuropathic or not (Kim et al., 2020). In a larger series of patients with neuropathic pain, they found an increased SP in the α band with a lower DPF in various nodes of the dynamic pain connectome (temporoparietal junction and posterior insula) in resting-state MEG, but with some gender-related differences (Fauchon et al., 2021). This increased MEG activity in the α band was located in the ascending pain pathways in a subset of patients with neuropathic features of chronic back pain due to ankylosing spondylitis (Kisler et al., 2020). Unfortunately, this type of study has never been performed on resting-state EEG.

New developments for the decoding and classification of EEG signal changes are based on artificial intelligence algorithms, including machine learning models (Saeidi et al., 2021). These models were applied in experimental pain studies (Misra et al., 2017) and rarely to EEG data from neuropathic pain patients. First, Vuckovic et al. (Vuckovic et al., 2018) showed that learning classifier systems were accurate (>85%) to identify patients with pain or at risk of developing pain secondary to spinal cord injury. Second, Levitt et al. (Levitt et al., 2020) showed that a learning program could differentiate resting-state EEG data between PwP (lumbar radiculopathy) and gender-matched HC with an accuracy >70%, while PSD, coherence, and phase-amplitude coupling analyses could not. A third study, combining sLORETA, lagged phase coherence, cross-frequency coupling, and a machine learning program to analyze resting-state EEG data from a large series of 50 patients with chronic neuropathic pain (compared to 50 HC) was recently published (Vanneste and De Ridder, 2021). In particular, the machine learning system was able to differentiate PwP from HC with an accuracy > 85% solely based on brain activity of three regions of interest: somatosensory cortex (including θ and γ bands) and pregenual and dorsal anterior cingulate cortices (including α and θ or β band, respectively).

5. Therapeutic perspectives of the use of EEG biomarkers of pain

Beyond the objective of defining objective biomarkers for the diagnosis of neuropathic pain, the characterization of the cerebral brain rhythms associated with pain as well as their cortical location could be the theoretical basis for the development of therapeutic techniques of neuromodulation. These techniques include transcranial magnetic or electrical stimulation and EEG-based neurofeedback protocols, the optimization of which to treat chronic pain depending on a better understanding of brain network dysfunctions linked to pain. The use of EEG also offers great prospects as a tool to differentiate responders from non-responders to these various therapeutic techniques and therefore to select candidates for these treatments and monitor their efficacy.

5.1. Non-invasive transcranial stimulation

Regarding rTMS, we previously mentioned that the 'classic' protocol for the treatment of pain was based on stimulation frequencies between 5 and 20Hz (Lefaucheur, 2016), which was consistent with the broad frequency band (θ-β) in which the EEG changes are found in the context of neuropathic pain. However, to our knowledge, resting-state EEG has never been studied to assess the treatment of chronic pain with rTMS, e.g., to show post-treatment changes or to correlate these changes or baseline EEG data with the analgesic efficacy of this treatment.

In contrast, using the TMS-EEG technique, changes in TMS-evoked potentials (TEPs, N100-N120) were observed after rTMS in two studies of experimental cold-induced pain in HC (Che et al., 2019; Ye et al., 2022). The rTMS protocols consisted of theta burst stimulation (TBS) and 10Hz-rTMS delivered to the left dorsomedial (Che et al., 2019) or dorsolateral (Ye et al., 2022) prefrontal cortex. Analgesic effects were associated with TEP changes in the bilateral fronto-central region in the first study (Che et al., 2019) and in the contralateral prefrontal and ipsilateral insular cortices in the second study (Ye et al., 2022). However, beyond the measurement of TEP amplitudes and latencies, the TMS-EEG technique also allows the assessment of different regional changes in EEG activities, time-locked to the TMS pulse with minimized TMS-induced artefact: area under the curve of the rectified EEG signal (mean field power), TMS-related cortical oscillations in the canonical frequency bands, or source localization and cortical activity connectivity (Farzan et al., 2016; Tremblay et al., 2019; Julkunen et al., 2022). These approaches could produce biomarkers of EEG changes in intracerebral connectivity associated with neuropathic pain with a very high temporal discrimination, allowing for example the development of closed-loop rTMS protocols.

Another approach of non-invasive neuromodulation is low-intensity transcranial electrical stimulation (Antal et al., 2017), including various techniques such as transcranial direct current stimulation (tDCS) (Lefaucheur and Wendling, 2019) and transcranial alternating current stimulation (tACS) (Antal and Herrmann, 2016). This latter technique is particularly appealing since it can modulate brain oscillations in a frequency-specific manner (Herrmann et al., 2016; Tavakoli and Yun, 2017; Vosskuhl et al., 2018). In fact, tACS induces periodic current into the brain, able to generate fluctuations in axon membrane potential, which can synchronize endogenous oscillations in terms of frequency and phase ('entrainment' phenomenon). The main challenge of this technique is to produce prolonged after-effects, lasting beyond the time of 'entrainment' stimulation. Lasting effects relate to the occurrence of synaptic plasticity processes (Korai et al., 2021) and are necessary to consider the therapeutic application of a non-invasive brain stimulation procedure, not involving the surgical placement of an implanted pulse generator (Lefaucheur, 2009).

In the domain of chronic pain, only two tACS studies have been published to date to our knowledge. First, Ahn et al. (Ahn et al., 2019) assessed the effect of one session of tACS performed at α frequency (10Hz) and 1mA intensity for 40 minutes over bihemispheric prefrontal areas (F3-F4, with a 'return' electrode over Pz) in a series of 20 patients with chronic low back pain. After active α-tACS compared to sham stimulation, these authors found a significant increase in PSD in the α band in the somatosensory cortical region, α activities being reduced at baseline. The restoration of α oscillations in the somatosensory region after α-tACS was correlated with pain relief.

Second, Bernardi et al. (Bernardi et al., 2021) applied a tACS protocol performed at 1-2mA with repeated sessions (5 sessions of 30 minutes per week for two weeks) in a series of 15 patients with fibromyalgia. The frequency of stimulation was either 4Hz (θ-tACS) or 30Hz (β-tACS), according to the EEG frequency band (1-10Hz or 10-30Hz) in which the greatest decrease in SP was found in PwP compared to HC at baseline. The anode was placed over the scalp region in which this greatest decrease was found, while the cathode was placed over the ipsilateral mastoid. In addition, each tACS session was followed by 60 minutes of physical exercise. Thus, 11 patients received high-frequency β-tACS (30Hz) over fronto-central targets and only four patients received low-frequency θ-tACS (4Hz) over centro-parietal targets, showing that θ activities were often increased in this region in patients with fibromyalgia at baseline. Overall, following tACS, EEG activities were found to increase in the low-α band (8-10Hz), correlated with pain relief and improvement of various other clinical aspects.

The therapeutic development of tACS depends on the targeted frequency and electrode placement ('spectral' and 'spatial' specificities) (Hohn et al., 2019). It is evident that EEG studies will be needed to optimize the definition of these parameters (Cancelli et al., 2016), especially if one considers an individualized/personalized approach, and also to assess the effects. Later, if a tACS protocol demonstrates significant analgesic efficacy, it will be time to determine whether repeated sessions (even performed at home) or chronic stimulation using implanted device (Khatoun et al., 2019) will be the best solution, depending on the duration of the effects obtained, the intensity used, and the local tolerance of scalp stimulation.

Finally, in this area, one of the most promising strategy should be to use tACS or other periodic/oscillating neuromodulation techniques in a closed-loop system, which includes online measurement of neural activity to trigger or adjust the stimulation parameters to the current brain state (Thut et al., 2017; Zrenner et al., 2016). Such closed-loop systems are being developed for implanted deep brain stimulation (Guidetti et al., 2021) but still require systematic evaluation for therapeutic cortical stimulation techniques (Beuter et al., 2014). Various attempts to develop closed-loop tACS techniques have been published (Brittain et al., 2013; Ketz et al., 2018; Mansouri et al., 2019; Stecher et al., 2021; Zarubin et al., 2020), but not yet in the pain domain.

5.2. EEG-based neurofeedback

Obviously the EEG changes related to chronic pain should serve as a benchmark for the development of EEG-based neurofeedback techniques for pain treatment. This is certainly one of the most direct applications of the future definition of EEG biomarkers for chronic pain. So far, very few EEG-neurofeedback studies have been published in the area of neuropathic pain treatment. Interestingly, the EEG targets of these neurofeedback studies correspond well to the conclusions that we drew from the analysis of the resting-state EEG studies in patients with neuropathic pain: namely an increase in EEG power in the θ and high-β bands with a shift of the DPF towards lower frequencies in the θ–α band and towards higher frequencies in the whole β band.

Indeed, in patients with chronic neuropathic pain (secondary to spinal cord injury or MS) attempts have been made to decrease aSP/rSP in the θ and high-β bands (Hasan et al., 2016; Hassan et al., 2015; Jensen et al., 2013a, 2016; Vuckovic et al., 2019) and/or to reinforce aSP/rSP in the low-β band (Hasan et al., 2016; Hassan et al., 2015; Jensen et al., 2013a, 2016). Maybe also reinforcing α activities could be interesting (Hasan et al., 2016; Hassan et al., 2015; Jensen et al., 2013a, 2016; Vuckovic et al., 2019). A few studies were published in the domain of non-neuropathic pain (fibromyalgia), with the aim of upregulating low-β activities and downregulating θ and even high-β activities (Caro and Winter, 2011; Kayiran et al., 2010).

In these studies, the EEG recording electrodes and therefore the targeted regions were located at various cortical sites (vertex, central, temporal, or parietal locations). Notably, good pain relief was obtained by modulating EEG activities in the central sensorimotor area (Kayiran et al., 2010; Vuckovic et al., 2019). In a study still in progress, we have proposed to use an EEG-neurofeedback procedure to relieve chronic neuropathic pain by increasing either the low-β/high-β ratio or the α/θ ratio at a central cortical location (Bismuth et al., 2020), which is consistent with the findings of this review.

Finally, it was recently shown that a neurofeedback training aimed at inhibiting θ (4–8Hz) and high-β (20–30Hz) activities and reinforcing α (9–12Hz) activities and based on a single channel EEG recording located in the central sensorimotor area (C4) could produce widespread significant effects on various cortical structures involved in pain processing (Hasan et al., 2021). This study, performed on five paraplegics suffering from chronic neuropathic pain, benefited from a source localization analysis by sLORETA and mainly showed a decrease in θ activities in different regions of the frontal lobe linked to the analgesic effects of neurofeedback.

Using EEG biomarkers provided by source localization or other techniques to predict or evaluate neuromodulation techniques, such as neurofeedback is surely the main challenge for future studies (Micoulaud Franchi et al., 2020). Defining which EEG rhythm to modulate and where to modulate it in order to produce an optimal analgesic effect in a given individual is the key to the future success of this type of therapeutic strategy.

6. Conclusions

Although the studies are relatively heterogeneous, the literature data analysed in this review suggest that ongoing neuropathic pain intensity is positively correlated with the amount of EEG activities in a broad θ-low-α band and also possibly in the high-β band, while a negative correlation is likely with EEG activities in a broad high-α-low-β band. Based on these spectral changes, the DPF is shifted towards a lower frequency in the θ-α band and towards a higher frequency in the β band in patients with chronic neuropathic pain. Thus, EEG analyses in the frequency domain could provide reliable biomarkers of ongoing neuropathic pain.

However, these results are based on group comparison (between PwP and HC or PwoP) and do not ascertain a causal correlation of the EEG changes with specific aspects of the pain syndrome. In future studies, it will be important to take into account various clinical factors, such as: (i) the intensity of pain during the EEG recording, which is rarely measured, in contrast to that chronically experienced during the previous days or weeks; (ii) the various aspects of the multifaceted pain syndrome: cognitive, emotional, physical…; (iii) the variable clinical profiles of chronic neuropathic pain syndromes, which may include nociceptive or nociplastic aspects in the context of mixed pain; (iv) the cause of neuropathic pain, particularly in the context of central neuropathic pain, such as in MS, in which brain damage can alter EEG activities regardless of the presence of pain; (v) the influence of analgesic drugs on cerebral activities, which is potentially major, while this confounding factor is very rarely taken into account, in particular for the matching of control PwoP with PwP; (vi) the influence of psychiatric comorbidities, such as anxiety or depression.

Another major issue in the interpretation of the results is the analysis of the cerebral anatomical correlates of the observed EEG changes. These changes can occur in all of the regions involved in the pain connectome and not just in the nociceptive sensory-discriminative areas (i.e. the posterior insular cortex and the secondary somatosensory area). Thus, by considering a network modulation effect, one could explain the efficacy of certain non-invasive stimulation techniques which apply to certain nodes of brain networks such as the central sensorimotor region. For example, by targeting sensorimotor rhythms in the central region, one could produce a relaxed state, associated with positive emotional environment without anxiety if the low-β/high-β ratio is increased, and maintain a state of quiet alertness and mindfulness, if the α/θ ratio is increased (Bismuth et al., 2020). This could help decrease the central transmission and sensitization of nociceptive information in the brain of patients with chronic neuropathic pain. Other approaches to be developed are multi-site network-targeted neuromodulation strategies (Fischer et al., 2017), with the objective to modulate concomitantly or sequentially the brain activities at different nodes or central hub regions (Vlasov and Bifone, 2017) of the dynamic pain connectome.

Thus, research in this field must develop along various axes, opening up broad perspectives and challenges. In any case, if quantitative EEG signal analyses can provide objective pain biomarkers complementary to the subjective reports of pain made by the patients, it will be necessary to establish the clinical correlates of these EEG features, according to the sensory, emotional and cognitive components of the pain, to ensure their specificity, reliability, and relevance.

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