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REVIEW

EEG Recordings as Biomarkers of Pain Perception: Where Do We Stand and Where to Go?

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ABSTRACT

Introduction: The universality and complexity of pain, which is highly prevalent, yield its significance to both patients and researchers. Developing a non-invasive tool that can objectively measure pain is of the utmost importance for clinical and research purposes. Traditionally electroencephalography (EEG) has been mostly used in epilepsy; however, over the recent years EEG has become an important non-invasive clinical tool that has helped increase our understanding of brain network complexities and for the identification of areas of dysfunction. This review aimed to investigate the role of EEG recordings as potential biomarkers of pain perception.

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Methods: A systematic search of the PubMed database led to the identification of 938 papers, of which 919 were excluded as a result of not meeting the eligibility criteria, and one article was identified through screening of the reference lists of the 19 eligible studies. Ultimately, 20 papers were included in this systematic review.

Results: Changes of the cortical activation have potential, though the described changes are not always consistent. The most consistent finding is the increase in the delta and gamma power activity. Only a limited number of studies have looked into brain networks encoding pain perception.

Conclusion: Although no robust EEG biomarkers of pain perception have been identified yet, EEG has potential and future research should be attempted. Designing strong research protocols, controlling for potential risk of biases, as well as investigating brain networks rather than isolated cortical changes will be crucial in this attempt.

Keywords: EEG; Electroencephalogram; Pain; Perception; Biomarker

Key Points
An increase in the delta power activity is observed in standard EEG during pain.
An increase in the gamma power activity is observed in standard EEG during pain.
EEG has potential as a biomarker of pain perception.
Investigating brain networks rather than isolated cortical changes is important in future studies.

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INTRODUCTION

The universality and complexity of pain, which is highly prevalent, yield its significance to both patients and researchers [1]. The International Association for the Study of Pain has recently changed the definition of pain to an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage [2]. Along with this definition it is underscored that pain is subjective, whilst it is currently impossible to objectively measure it.

To date, in clinical studies pain intensity is determined by the subjective ratings that participants give using numerical rating or visual analogue scales. In experimental studies researchers have attempted to record the nociceptive processing in the human brain in numerous ways, such as by using haemodynamic methods and neuroimaging techniques [3–7]. Developing a non-invasive tool that can objectively measure pain is of the utmost importance, not only as it can be used as a gold standard in clinical research to monitor for example the effectiveness of an intervention but also in order to be able to assess and diagnose presence of pain in subjects that are not able to communicate.

During electroencephalography (EEG) electrical signals are collected from electrodes placed on one's scalp [8]. These signals represent the electrical activity of the brain at the time of recording; frequency and amplitude content vary according to the subject's level of alertness, mental state, age, medication and physical health.

Fourier transform has been previously used to decompose EEG signals into non-overlapping sinusoidal frequencies with estimates of the relevant power of each frequency band i.e. delta, less than 4 Hz; theta, 4–7.5 Hz; alpha, 7.5–12.5 Hz; beta, 12.5–30 Hz; gamma, 30–40 Hz. The absolute and relative power (μV^2)/power spectral density (μV^2/Hz) for each bandwidth and electrode location are essential parameters assessed by quantitative EEG studies aiming to delineate brain function under certain tasks or conditions. Increased power or

power spectral density of a certain frequency in a certain scalp electrode denotes a dominant EEG frequency on the underlying brain location.

In a normal brain, delta frequencies represent deep sleep or unconsciousness, theta frequencies [9–11] relate to intuition, creativeness, imaginary, fantasy, recall and other introverted brain functions, and alpha frequencies denote conscious relaxation. On the other hand, low range beta frequencies (up to 15 Hz) represent focused attention, whilst faster beta frequencies are found during alertness, surroundings awareness and agitation. The less studied gamma frequencies reflect mainly higher mental activity.

Furthermore, researchers can check the synchronization of EEG brain rhythms generated by neurons within different brain regions. A commonly used linear method in this field is coherence analysis and it is based on the aforementioned spectral analysis. It is mainly used to find spatial and temporal synchronization of brain rhythms under a certain task or situation in order to unravel task- or situation-specific neural networks [12].

Traditionally EEG has been mostly used in epilepsy; however, over the recent years EEG has become an important non-invasive clinical tool that has helped increase our understanding of brain network complexities and for the identification of areas of dysfunction [13]. The aim of this systematic review of the current literature was to investigate the role of EEG recordings as potential biomarkers of pain perception.

METHODS

Protocol Registration

This review was initially registered to PROSPERO, an international prospective register database of systematic reviews that fall within health and social care. The registration number was CRD42021233903.

Literature Search Strategy

We conducted a systematic literature search in the PubMed database on 14 January 2021 using the following Medical Subject Heading (MeSH) terms: term A was "EEG" OR "electroencephalography"; term B was "pain" OR "painful". Three filters were applied: human subject, English language, full-text. We also perused the reference lists of the included papers so as to include further papers that may fall within the scope of our review.

Inclusion Criteria

1. EEG was performed at a resting state and during a painful stimulus (evoked pain).
2. A non-painful control condition (baseline or non-painful stimulus) was used for comparison.
3. Participants had a clear medical history, not suffering from chronic pain or acute pain during their participation.
4. Human adult subjects are involved.
5. Full text was written in English language.

Exclusion Criteria

1. Use of a medication that could have affected the EEG recordings (i.e. analgesics, anaesthetics etc.)
2. Primary aim of the study was other than the use of EEG recordings as potential biomarkers of pain.
3. Studies of somatosensory evoked potentials.
4. Trials with less than 10 subjects.
5. Non-original articles.
6. Duplicate articles or studies referring to the same population.
7. Withdrawal studies.

Three investigators (AL, PN and GT) independently screened the titles and abstracts to ascertain whether each study met the eligibility criteria. The full texts of the identified eligible articles were then evaluated to determine whether they should be included in the analysis. Disagreements between the three reviewers were resolved by consensus. In case of persistent

disagreement, arbitration by a fourth reviewer (PZ) settled the discrepancy.

This study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. Details of this process are illustrated in Fig. 1.

Data Collection Process

Data were extracted from each study in a structured coding scheme using Excel. Data collected included population size, demographics, handedness, position of subjects, type, intensity, side, area and duration of painful stimulation, experimental protocol, number of EEG channels that were applied, EEG findings and potential biomarkers.

Compliance with Ethical Guidelines

The article is based on previously conducted studies. Thus, there were no ethical concerns in respect to this study, nor was approval of the research protocol from an ethics committee required.

RESULTS

Search Results

The above mentioned literature search strategy produced 938 results. During the eligibility assessment 919 papers were excluded. One article was added through reference screening of related papers. Overall, a total of 20 completed studies published between 1992 and 2018 were included in our review [15–34]. The selection process is briefly illustrated in Fig. 1.

Study Characteristics

All studies where exploratory in populations of healthy young adults. The mean (± standard deviation) number of subjects per study was 24 ± 11, ranging from 10 to 43.

The most common types of painful stimulation were (i) thermally evoked pain (cold or heat stimuli) via a contact-heat thermode [23, 25, 27, 32, 34], (ii) cold stimuli, where subjects placed their hand(s) in a bucket of iced water [16, 17, 21, 26] and (iii) electrical laser stimuli [20, 28, 30]. Less common types of painful stimulation were intramuscular injection of hypertonic saline [15, 18, 22, 31], intramuscular injection of capsaicin (50 μg/0.5 ml) [19], topical application of capsaicin cream 1% [33] and pressure pain applied through a tourniquet cuff and manometer up to 600 mmHg [24]. In most studies painful stimuli were applied on the hand(s) [16, 17, 20, 21, 26, 27, 29, 30, 32].

The EEG in most studies was recorded through 64 surface electrodes [27, 29–32]. In one study EEG was recorded through 128 surface electrodes including two EOG channels (Electro OculoGram, a voltage difference between the cornea and retina monitoring human eye movements), and two mastoid reference channels using a standard EEG-cap [24]. In the remainder of the studies fewer electrodes were used. In all studies the outcomes of interest were alpha, beta, gamma, delta and theta band activity during painful stimulation.

Table 1 summarizes the main characteristics of the included studies. Detailed characteristics of the included studies are available as supplementary material.

EEG Activity

Delta Activity

An increase of the delta activity—mainly in the frontal areas contralateral to the stimulation hemisphere—was the most commonly reported EEG change during painful stimuli [16, 19, 21, 28]. Ferracuti et al. reported that the increase in delta power throughout the period of stimulation was diffuse (n = 15)—though more evident in the frontal areas—and similar in the ipsi- and contralateral leads [16]. Le Pera et al. (n = 12) also reported an increase of the delta activity but over the contralateral posterior parietal region (P4) [18]. Gram et al. (n = 39) reported an overall increase of the average delta activity across all EEG electrodes [26]. Huber et al. did report an increase for power density in

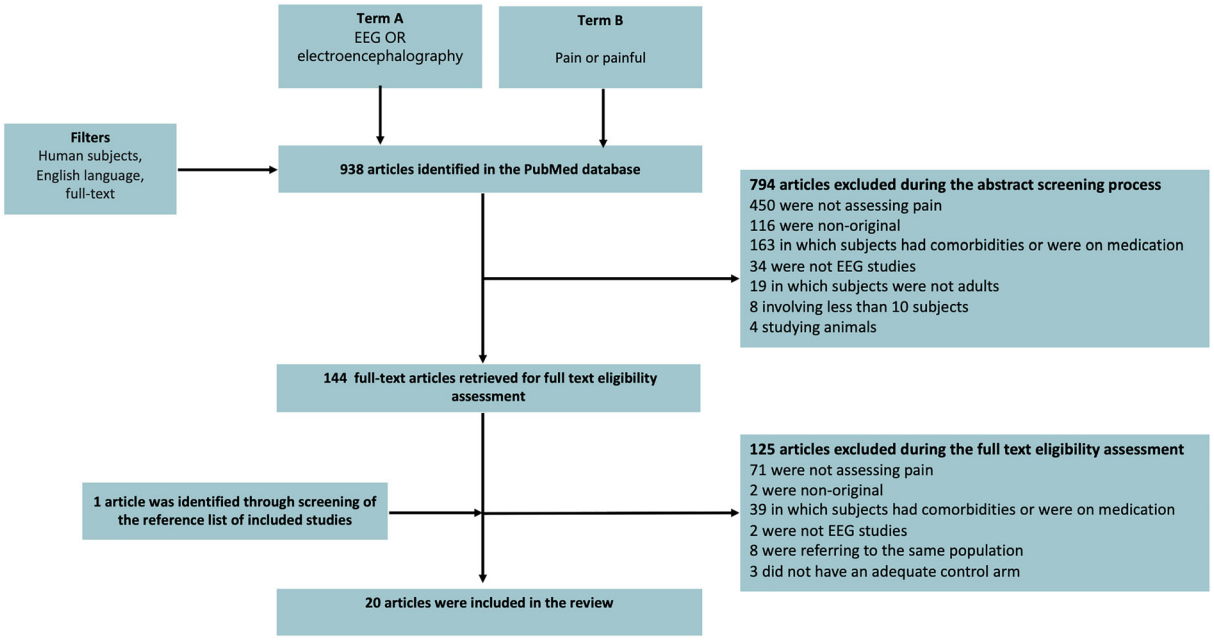

Fig. 1 PRISMA chart

the delta[2] (2–4 Hz) frequency band in all EEG leads except in the two occipital ones after tonic stimulation (defined as series of small heat pulses with a constant frequency of 30 pulses/min for 10 min) compared to baseline; however, the significance of differences was completely lost when the condition with tonic painful stimulus (1 °C above the individual pain threshold) was compared to the condition with tonic non-painful stimulus (0.3 °C below the individual pain threshold) [23].

In few studies no significant differences in the EEG changes of delta activity were found [22, 29, 34].

Theta Activity

The results on theta activity during painful stimulation are contradictory as some studies reported an overall increase in theta activity [16, 20, 27, 28, 30, 33], while others reported decrease [19, 23, 26, 34] or no significant changes [17, 21, 22, 29, 31, 32].

Alpha Activity

A decrease of the alpha activity, mainly in the parieto-occipital areas, was the most commonly reported EEG change [16, 19, 21–27, 29, 32, 34].

However, a few studies had contradictory findings as Le Pera et al. reported an increase over the parietal areas [18], Bobiloni et al. an increase over the region contralateral to the stimulation frontal area [20] and Martel et al. an increase of the region ipsilateral to the stimulation prefrontal area [33].

Beta Activity

An increase of the beta activity, mainly in the temporal areas, has been reported in almost all studies [15, 17–23, 26, 27, 33].

Interestingly, Chen et al. showed that the amplitude increase in T5 (contralateral to stimulation) was accompanied by intra- and interhemispheric coherence increase between T5 and multiple channels, whereas amplitude increase in T6 (ipsilateral to stimulation) was accompanied by coherence decrease between T6 and the centro-parietal electrodes, a finding indicating clearly that amplitude and coherence are different measures.

Only Nickel et al. [33] and Bunk et al. [34] reported a decrease of the beta power with increasing stimulus and subjective pain intensity, respectively.

Table 1 Characteristics of the included studies

Study	*N* (female)	Mean age (range)	Type of painful stimulation	Control condition(s)	Eyes	Number of electrodes	Types of analyses
Veerasarn (1992) [15]	19 (2)	26.5 (21–38)	Hypertonic saline intramuscular injection	(1) Baseline and (2) imagined pain	Closed	8	Spectral and topographic
Ferracuti (1994) [16]	15 (0)	(23–34)	Cold water (0.5–1 °C)	Baseline	Closed	8	Spectral and topographic
Chen (1998) [17]	10 (0)	27.4 (22–48)	Cold water (0.3 °C)	(1) Baseline and (2) non-painful cold	Open	9–32	Spectral, topographic, coherence/ networks
Le Pera (2000) [18]	12 (0)	26.6	Hypertonic saline intramuscular injection	(1) Baseline and (2) vibration	Closed	9–32	Spectral and topographic
Chang (2001) [19]	15 (0)	25.6 (22–28)	Capsaicin intramuscular injection	(1) Baseline and (2) isotonic saline injection	Open	9–32	Spectral and topographic
Babiloni (2002) [20]	12 (NR)	NR	Electrical repetitive stimulation	Non-painful electrical stimulation	NR	9–32	Spectral and topographic
Chang 2002 [21]	15 (0)	24.4 (22–26)	Cold water (2 °C)	Baseline	Both eyes open and closed epochs	9–32	Spectral and topographic
Chang (2003) [22]	13 (0)	25.9	Hypertonic saline intramuscular injection	Baseline	Open	9–32	Spectral and topographic

Table 1 continued

Study	*N* (female)	Mean age (range)	Type of painful stimulation	Control condition(s)	Eyes	Number of electrodes	Types of analyses
Huber (2006) [23]	20 (0)	26.9 (20–32)	Heat	(1) Baseline and (2) non-painful heat. Three levels of attention were also put into effect: attention focused, attention defocused and no control of attention	Closed	9–32	Spectral and topographic
Egsgaard (2009) [24]	40 (20)	(19–30)	Cuff pressure	Baseline	Both eyes open and closed at baseline, eyes closed during pain	More than 64	Spectral and topographic
Nir (2012) [25]	18 (9)	26	Heat	Non-painful warm	Closed	9–32	Spectral and topographic
Gram (2015) [26]	39 (18)	26.9	Cold water (2 °C)	Baseline	Open	33–64	Spectral and topographic
Schulz (2015) [27]	41 (22)	26	Heat	Baseline (visual control)	Open	33–64	Spectral and topographic
Rouleau (2015) [28]	23 (13)	23.8	Electrical repetitive stimulation	Non-painful electrical stimulation	NR	9–32	Spectral and topographic
Zhang (2016) [29]	21 (7)	25	Heat	Non-painful warm	NR	33–64	Spectral, topographic, coherence/ networks

Table 1 continued

Study	*N* (female)	Mean age (range)	Type of painful stimulation	Control condition(s)	Eyes	Number of electrodes	Types of analyses
Taesler (2016) [30]	20 (9)	26.9	Electrical single-pulse stimulation	Non-painful electrical stimulation	Open	33–64	Spectral, topographic, coherence/networks
Li (2016) [31]	43 (0)	22	Hypertonic saline intramuscular injection	(1) Baseline and (2) isotonic saline injection	NR	33–64	Spectral and topographic
Nickel (2017) [32]	39 (18)	24.3	Heat	Baseline (visual control)	NR	33–64	Spectral, topographic, coherence/networks
Martel (2017) [33]	19 (12)	29	Topical 1% capsaicin cream application	Baseline	NR	9–32	Spectral, topographic, coherence/networks
Bunk (2018) [34]	36 (18)	22.6	Heat	Non-painful warm	NR	9–32	Spectral and topographic

NR not reported

Gamma Activity

The majority of the studies that looked into the gamma activity during painful stimuli have shown an increase in power [20, 26, 27, 30–32]. The topography of these changes varied across studies as changes were shown in prefrontal, frontocentral, central and temporal regions [20, 27, 31, 32]. Moreover, the neuronal gamma oscillations, at frontal or frontocentral electrodes encoded the subjective intensity of pain, showing a positive correlation [27, 30, 32].

In their study (n = 21), Zhang et al. [29] did not find a statistically significant change in the overall gamma power but they reported gamma as one of the frequency bands that carry directed causality information from the contralateral side of the sensory region where the painful stimulus was applied to the ipsilateral side when stimulus was delivered to the right hand.

Networks

Chen et al. studied coherence changes (n = 10) and found that during painful stimulation the delta coherence showed enhancement between the temporal electrode T5 and the frontal electrodes F7, Fp1, F3, and Fz, the central electrode C3, as well as parietal electrodes P3 and Pz in the left hemisphere (contralateral to the stimulation site). In the right hemisphere, delta EEG activity showed great coherence enhancement between the frontal electrodes F8 and F4 and other sites (P4, C4, Cz). The activation was less profound in the right hemisphere than in the left hemisphere. Additionally, interhemispheric coherence increase was found from the left posterior areas to the right frontal areas as well as strong interhemispheric coherence enhancement in the central regions [17].

Taesler and Rose (n = 20) showed that during the post-stimulus interval, an increased connectivity between the area ipsilateral to the side of stimulation temporal sites T7/FT7 and an area comprising the contralateral frontotemporal and parietotemporal sites was noted [30].

Nickel et al. (n = 39) analysed the functional connectivity (calculating the debiased weighted phase lag index) and the effective connectivity (calculating the Granger causality) between the sensorimotor cortex and the medial prefrontal cortex and did not find any significant differences between tonic pain and visual control conditions.

DISCUSSION

In this systematic review, we investigated the role of EEG recordings as biomarkers of pain perception, showing that changes of the cortical activation have potential, though the described changes are not always consistent. The most consistent finding is the increase in the delta and gamma power activity. Our review can be used as a guide for future research on the topic, especially for protocol design.

The included studies involved young, healthy subjects to whom painful stimuli were applied and EEG changes were analysed. Since EEG differences between individuals, especially in the alpha frequency, can be attributed to age [35], age-wise homogenous groups is advised to be recruited.

The majority of the studies used baseline EEG for comparison after removing EEG segments that contained electro-oculographic or muscle artefacts. However, EEG can be contaminated because of altered attention, salience, pain expectation, carry-over and sensitization/habituation effects. Zhang et al. observed that the presence of a painful stimulus can induce changes in the temporal dynamics among these nodes of the pain perception network in contrast to the effects of an innocuous stimulus [29]. Some studies used additional EEG recordings in order to control for such possible contaminations. Controlling for EEG changes during non-painful stimulation or attention-related changes may strengthen the study.

A range of potential limitations of studies attempting to investigate the role of EEG recordings as biomarkers of pain have been identified, highlighting the need to control for additional parameters when analysing the recordings. Firstly, the research protocol in some studies was with eyes closed, in others with eyes open whereas in many it was not clear whether the EEG epochs that were analysed were with eyes closed or open. As a result, spectral power changes related to eyes open and eyes closed states might have influenced the findings. Moreover, handedness was not assessed in all studies and site of stimulation was not necessarily the dominant, raising another potential risk of bias. An additional potential limitation is that the scoring of pain varied significantly. Some studies asked participants to rate the pain after the painful stimulus while some asked for a continuous rating during the EEG recording, which may well lead to additional contamination due to altered attention. An interesting observation in many studies was that stimulation intensity is not the same as pain intensity and this is reflected in the EEG recordings [29, 32, 34]. A wide spectrum of painful stimuli were employed, though the most commonly used were thermal (hot or cold). However, even among those a degree of variability was noted; some studies used quantitative sensory testing equipment whilst others less precise stimuli such as iced water. Using quantitative measurements of stimulation has an advantage as it will allow for additional analyses.

In this review, all studies employed spectral and topographic analyses. As described above, potential biomarkers of pain perception are the increase in the delta and gamma power activity. However, over recent years, scalp EEG recordings have been used to estimate with various methodologies, to include coherence, inter- and intrahemispheric functional and effective connectivity. Pain is a highly dynamic process generated by a distributed network, rather than an isolated "pain cortex", where sensory stimuli and affective and cognitive variables interact to produce this unpleasant experience [36]. Novel qEEG methodologies that are able to track nonstationary, dynamic and nonlinear brain

network dynamics and the implementation of machine learning frameworks offer the means for in-depth work in this field, aiming to dissect the electrophysiological characteristics of widely distributed brain networks involved in the various aspects of pain perception.

CONCLUSION

Currently there is no robust EEG biomarker of pain perception; however, EEG has potential and future research should be attempted. Designing strong research protocols, controlling for potential risk of biases, as well as investigating brain networks rather than isolated cortical changes will be crucial in this attempt.

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Compliance with Ethics. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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