The Pain Signals: A Systematic Review on the Electroencephalogram of the Nociceptive Pain

Mahmoud Elsayed, Sim Kok Swee, Tan Shing Chiang

***Abstract*— Since the birth of modern medicine and neuroscience, scientists have been searching for a pain centre in the brain. In particular, they have been trying to find a pain biomarker in the electrical activity of the human brain. This search was not only motivated by mere curiosity but also by an immense need in medicine. Finding a brain electrical indicator or biomarker to objectively measure the sensation of pain is vital in medical practice and the pharmacological development of pain remedies. Furthermore, it has recently been observed that transient painful stimuli activate several brain parts with electrical patterns. This has prompted researchers to pursue a quest to objectively measure nociceptive pain based on biological biomarkers. In this paper, we review research in the literature that attempted to identify physical pain from a specific brain activity or correlate pain with any variations in brain rhythms. Even though a comprehensive understanding of the nature and effects of pain remains unavailable, general trends have been observed in the literature. Based on our survey, most researchers agreed on the correlation between the sensation of pain and two electrical activities: (i) an increase in Gamma power in the frontal cortex and (ii) various electrical activities in the primary somatosensory cortex (e.g., a decrease in Alpha power). Another research trend that was observed is the use of machine learning for classifying different intensities of pain-related EEG signals.**

***Index Terms*— *Pain, Physical Pain, Electroencephalogram (EEG), Human Brain,* Machine Learning.**

I. Introduction

Sensory neural receptors become activated and transmit a signal to the spinal cord when they receive a strong enough stimulus. The spinal cord can initiate an immediate reflex, such as withdrawing a hand from a hot surface or stepping away from a sharp object. Regardless of whether an immediate response is taken, the pain signal is ultimately transmitted to the brain for perception, recording, and further processing [1].

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Pain can travel to the brain through various pathways, as depicted in Figure 1. Over time, scientists have attempted to identify a specific pain center in the brain, but the search for a singular location has been unsuccessful. In the 1960s, the Gate Control Theory and Neuromatrix Theory were proposed and eventually combined to form the Pain Matrix[2] and the theory of neuromatrix [2]. This matrix comprises the brain structures and regions that collaborate to process and perceive pain. These include the thalamus, anterior cingulate cortex, somatosensory cortex, and insula [3-10]. Surface Electroencephalogram (EEG) readings have been used to identify the most relevant brain activities linked to pain signals, which are primarily associated with the somatosensory cortex [11, 12]. Studies indicate that the electrical oscillations (EEG) in the brain can reflect pain perception and sensation [13-18].

Pain is a complex and unpleasant emotion that is experienced subjectively. Although pain is often associated with tissue damage, it is not a simple reflection of sensory data. Psycho-physiological factors, such as psychological state, age, attention, and culture, significantly influence pain perception [19, 20]. Due to the subjective nature of pain, different individuals can experience varying levels of pain intensity, even when exposed to the same painful stimulus [11-21]. Given its complexity, it is challenging to develop an objective measure or evaluation system for pain. Therefore, in clinical practice, physicians rely solely on self-report pain assessments, such as the Numeric Rating Scales (NRS) and Visual Analog Scale (VAS) [22, 23].

Despite the significant role that self-report assessments play in clinical practice, they have two primary limitations. The first is that they are not suitable for certain vulnerable populations and non-communicative patients, including those with disorders affecting consciousness or speech [24]. The second limitation is that they can result in miscommunications or misjudgments [25]. This is particularly concerning for pharmacologists and medication developers who rely on accurate pain assessment techniques. Any inaccuracies in pain assessment measures can lead to inadequate or suboptimal treatment, which may result in additional clinical complications. Without a reliable measure of pain assessment, the consequences could be severe.

Pain can be classified into two types depending on how long it lasts (i.e., Acute and Chronic) [22]. Acute pain happens suddenly and due to a specific real/potential damage of a tissue such as bone, muscle, or organs. It lasts for a short period of time, between minutes and days. It is often associated with anxiety, increased heart rate, and increased blood pressure. Chronic pain is pain that lasts for a long

period of time, such as months or years. It is often caused by diseases like arthritis, osteoarthritis, and cancer [26]. Pain can also be categorised into three types based on its physiological nature, which are nociceptive, inflammatory, and pathological pain [22]. Nociceptive pain happens due to perceiving a noxious stimulus, like the example demonstrated in Figure 1. Inflammatory pain is felt on the occurrence of unavoidable tissue damage such as injury or inflammation. Pathological pain is caused by abnormal functionality in the nervous system (neuropathic pain). Unlike the other types of pain, it is not a symptom of a particular disease but rather an illness state. It could also exist without any sort of damage or inflammation (dysfunctional pain), such as what happens in conditions like fibromyalgia, temporomandibular joint disease, tension type headache, irritable bowel syndrome, and interstitial cystitis [22]. In Figure 1, the journey of pain starts by reading the sensory neuron to a noxious stimulus. The read signal gets delivered to the spinal cord to take immediate action (reflex) if needed and, subsequently, forward it to the brain for further analysis.

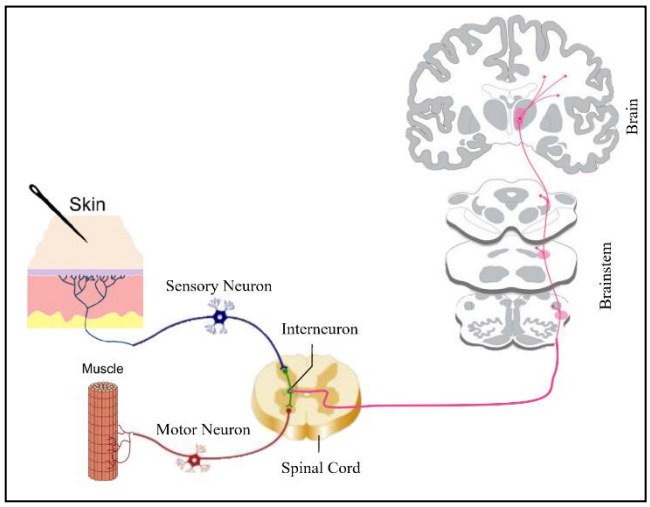

Fig 1 An example of a nociceptive pain journey to the brain.

Nociception and pain are even confused with one another. Hence, an important distinction to highlight here is the difference between nociception and pain. Nociception is the neural encoding of potential or actual damage of the biological tissue (i.e., noxious stimulation), while pain is the subjective experience of this actual or potential harm. Although nociceptive stimulation often causes pain experience, neuroscientists show that one can exist without the other [27]. For instance, in 1995, a 29-year-old construction worker was sent to the emergency room after jumping onto a 7-inch nail and pierced his boot to the other side. He experienced terrible pain and had to be sedated with opioids, only to discover later that the nail passed between his toes without penetrating his skin at all [28]. In another odd instance, another construction worker was using a nail gun when it unexpectedly discharged, clocking him in the face. He ignored the occasion, thinking nothing serious had happened; after six days of experiencing some mild toothache and a bruise under his jaw, he decided to see a doctor. The X-Ray revealed a 4-inch nail embedded in his head, penetrating his cerebral cortex [29]. These two cases have taught us a clear distinction between nociception and pain. Nociceptive pain, however, happens when the nociceptive stimulation accompanies the feeling of pain.

Nociceptive pain has three different ascending pathways or tracts through which the pain signal gets transmitted from the affected body part to the brain: the neospinothalamic tract, the paleospinothalamic tract and the archispinothalamic tract. Each tract of them originates in different spinal cord regions and ascends to transfer the signal to the brain. The type of transmitted pain signal dictates which tract the pain signal will use to reach the brain. For instance, pricking pain reaches the brain through the neospinothalamic tract, while both the paleospinothalamic and archispinothalamic tracts are taken to deliver the burning and soreness sensation resulting from tissue damage. It is also worth mentioning that more than one tract could be activated at the same time [30].

Based on our current understanding, all types of pain have a quite similar effect on the electrical activities of the brain [19], [22], [31]. Though slightly different neural networks might process them, it is still believed that the impact of the different types of pain on the surface electrical activities are highly overlapped. However, it is accurate to claim that our collective scientific understanding of the pain's effects on the brain still lacks clarity, and so does our ability to measure its intensity [2], [19, 20], [29, 30]. In this paper, we will review all the relevant findings in the literature with the hope and objective that the survey and analysis presented herewith will better understand the nature and effect of pain on the human brain.

II. Materials and Methods

When reviewing the literature, we followed strict selection and exclusion criteria which are listed below:

- Selection Criteria:
  - Population: individuals with chronic or experimentally induced pain (humans or animals)
  - Age: participants who are at least 18 years old in the case of humans.
  - Outcomes: findings related to EEG.
  - Recording device: more than four electrodes.
  - Language of publication: English
- Exclusion Criteria:
  - The study does not satisfy the selection criteria or is unrelated to the pain investigation.
  - Lack of control group.
  - Participants are unconscious or asleep.
  - Participants are diagnosed or have a history of stroke.

Figure 2 shows the breakdown of the included and excluded papers.

Although the chosen studies in the literature investigated different types of pain, we did not carry out an analysis for each type individually but rather a single analysis for all the types collectively. This is because this paper aims to find a biomarker of pain in the EEG signal. Hence, by investigating the overlaps of the different electrical indicators found in the literature to be correlated with pain, we hope to achieve this objective.

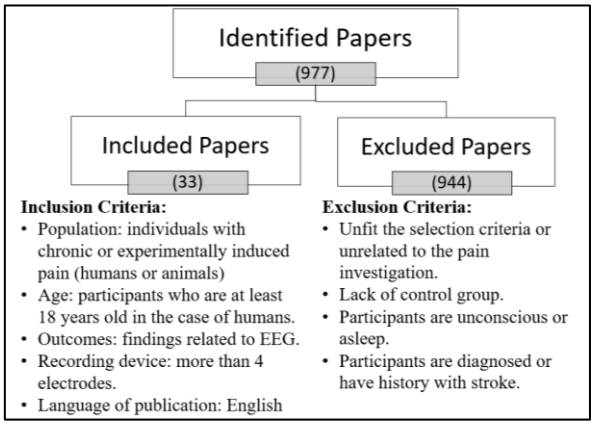

Fig 2 The breakdown of the included and excluded surveyed papers.

III. Survey

Chen and Rappelsberger [31] investigated the effect of pain on the human brain by studying the topographic amplitude and the coherence mapping of the different frequency bands of the EEG signals. A 19 gold-discs recording device was used to extract the pain signals. Their experiment had the palm ice cube test as a pain stimulator on 19 healthy participants with an age of 22.5 ± 5.5 years (mean ± Standard deviation). Eleven of them were females. Their analysis concluded that the painful stimulation resulted in an increase in EEG coherence and a decrease in EEG amplitude in the central regions of the human brain.

In another study, the possible neurophysiological underpinnings of self-injurious behaviour in women with borderline personality disorder (BPD) were investigated [16]. Seventy-six female subjects with an age range of (18-50) participated in the study. A Cold Pressor Test (CPT) stimulus was recorded through 16-channel gold disk electrodes. This study empirically proved the effect of psychological state on the physiological preceptive nature of pain. Moreover, the effect of attention on the subjective pain experience is experimentally demonstrated in [34].

Thirteen healthy male subjects participated in the experiment conducted in [35], where their EEG signals were recorded through a 32-channel device while they were intramuscularly injected with hypertonic saline. The study has found that Beta activity is positively, but Alpha activity is negatively related to the pain intensity and pain area on the skin. The difference between brain activities induced by skin pain and muscle pain was intuitively investigated in [36], where 15 healthy subjects participated in the study at the age of 25.6 ± 3.2 years. The stimulus used was Capsaicin Injection. However, the study has found an increase of Beta waves in the frontal, parietal, and occipital areas that are only induced by muscle pain with no other differences in the topographical EEG patterns. Hence, the authors concluded that the nociceptive signals fed by the muscles and skin are processed similarly with very slight differences by the same neural matrix.

Babiloni et al. [37] tested the hypothesis that the evaluation of the subject's subsequent pain intensity gets affected by the suppression of pericentral (Rolandic) Alpha power before the occurrence of the predictable painful stimulation. The hypothesis was tested on ten healthy participants with an age range of (24-32) years. The subjects experienced a CO2-leaser painful stimulus while their high-resolution EEG was being recorded during the experiment. The study concluded that anticipatory Rolandic Alpha is a good biological marker to estimate the subjective intensity of pain.

Rissacher et al. [38] demonstrated how the frequency domain of EEG could provide features that will help in the pattern recognition of pain. A CPT experiment was carried out on 15 healthy participants. A 29-electrode device was used in the recording process. They found an independent and direct relationship between the decrease in the power of the Alpha frequency band over the parietal and temporal cortices and the intensity of the pain.

The spatial and temporal identification of pain-induced Gamma oscillations in the human somatosensory cortex were achieved in [39], where a noxious lesser stimulus was applied to 12 healthy male participants to induce their EEG pain signals. The authors' analyses confirmed the correlation between primary somatosensory cortex Gamma band oscillations and the subjective intensity of pain.

In [11], it was aimed to indicate EEG features that can index cortical activities which could be related to pain nociception. Fifteen health subjects, nine males and six females, with an age of 20.1 ± 2.9 years, participated in the study. The participants were exposed to a painful cold stimulus while recording their EEG through 29-electrode recording devices. The study found that Alpha amplitudes increased over the posterior scalp and decreased over the contralateral temporal scalp during the experience of the painful stimulus. However, an increase in Gamma activity in all electrodes was observed due to the EMG artefacts. The study also indicated markers that might represent EEG features that are pain related. These markers included (a) an increase in Alpha power in the visual cortex, which is hypothesised to be related to the withdrawal of attention towards the pain; (b) an increase in Gamma band activity which is hypothesised to be related to the EMG activities generated by muscles reaction that often accompanies the painful experience.

The effect of heat stimulus on the nociceptive pathways and the brain was studied in [40]. Both EEG and fMRI images were recorded and analysed for ten healthy participants, six females and four males, with an age range of (22-35) years. The study claimed the contribution of the insula, post-central gyrus, middle supplementary motor area (SMA), pre-central gyrus, and cingulate cortex in pain processing and, thus, in the brain pain matrix or network.

The association between the leaser-evoked pain and EEG brain activities was investigated in [41] where seven healthy subjects, five males and two females, whose ages were 24 ± 6 years) participated in the study. The EEG was recorded using seven silver disc electrodes device. Unfortunately, the study could not find any direct correlation between the EEG activities in the brain and the perception of the noxious radiant heat stimuli.

In [42], the coupling of the phase amplitude between Gamma and Theta was correlated to the nociceptive pain. This was done by recording the EEG of rats while experiencing nociceptive stimulation. The scalps of the rats were exposed to 14 stainless steel screws with sockets that worked as epidural electrodes. A significant coupling between Gamma amplitude and Theta phase was found over

the parietal and frontal region was found after the nociceptive stimulation. This suggested that the coupling between Gamma and Theta was involved in the processing of nociception.

The relationship between the power of the Alpha frequency band and the subjective perception of tonic pain was demonstrated in [43], where 18 healthy subjects aged 26 ± 2.1 years old participated in the study in which they experienced an innocuous thermal stimulus. Based on the signal analysis, R. Nir et al. concluded that the Alpha frequency band power could be considered a stable, direct, and objective measure of the tonic pain subjective perception [43].

The main goal of [12] was to confirm the correlation between the painful stimulus and the Gamma band oscillation in the somatosensory cortex. The study's experiment was conducted on seven healthy participants, five males and two females, with an age of 29 ± 6 years old. The noxious radiant heat was used in the experiment as used a painful stimulus. The study found a direct correlation between the Gamma band oscillations over the somatosensory and the subjective pain intensity.

In [44], the electrocortical activities inflicted by tonic cold pain were investigated through the source analysis of EEG in its frequency domain, and to indicate potential electrocortical indices of acute tonic pain in 26 healthy subjects, 14 males and 12 females, participated in the study with an age of 25.1 ± 3.3 years old. A negative correlation was found between the subjective pain intensity and (a) Theta activities in the frontal cortex, (b) the Alpha activities in the anterior cingulate, and (c) the Beta activities in the posterior cingulate.

Twenty-three healthy subjects, nine males and 14 females, who were in an age range of (19-35) years, participated in [45]. The study aimed to develop a classification technique to decode the subjective pain sensitivity of individuals. The stimulus used in the experiment was leaser, and the classification algorithm was Support Vector Machine (SVM). The developed classifier could achieve an accuracy of 83%.

Huang et al. [24] proposed a practice-oriented and novel approach to predict pain perception by recording and analysing single-trial Leaser-Evoked Potentials (LEPs). The experiment was conducted on 29 participants with 40 LEP. They then divided the collected signals into 39 training trails and 1 test trail. They used a binary Naïve Bayes classifier to classify between the low and high pain signals. They could achieve a cross-individual classification accuracy of 80.3±8.5% and a within-individual classification accuracy of 86.3±8.4%.

Nine healthy subjects participated in [46], where the concepts of polynomial kernel SVM and fuzzy logic were used to build a classifier that estimated the pain intensity by using extracted features from the EEG signals. The EEG recording device included 32 channels, and the stimulus used was a hot thermal pad placed under the hand of the subject. The study developed a high-accuracy classifier and found that the pain intensity is directly correlated to the Alpha Power Spectral Density (PSD) and negatively correlated to the Beta PSD.

Jensen et al. [44] examined the relationship between EEG activities and pain severity in a group of patients who had a Spinal Cord Injury (SCI) and experiencing chronic pain. A total of 82 participated in the study, 64 with SCI (38 of them suffered from chronic pain), and 28 were control subjects who were healthy. The study showed that the Alpha activities were correlated to the intensity of chronic pain.

Indicating specific pre-stimulus EEG activity and connectivity patterns correlated to subsequent pain perception, a total of 23 healthy subjects participated in [47]. A 64-channel EEG was recorded during noxious stimulation that was achieved by directing an electrical current to the flexor/abductor pollicis brevis of the left hand. This study found that Gamma band power increased by 12% at frontocentral regions, and the frontoparietal connectivity decreased in the pre-stimulus EEG activities.

The EEG reaction to tonic muscle pain was investigated in [48]. The subjective pain ratings and EEG signals were recorded in three order-counterbalanced innocuous conditions from 43 males with an age of 22± 3 years. A 64-channel EEG recording device was used. The study provided evidence for the correlation between frontal-central Gamma oscillations and tonic pain intensity.

The existence of pain sensation in healthy subjects was indicated in [49] with the purpose of duplicating the exact process for patients who were non-communicative. A CPT-induced EEG effect was recorded by a 128-channel EEG recording device from 20 healthy subjects. The study concluded that pain was directly correlated with an increase in Beta frequency band power over the interhemispheric region in the brain.

Leancester et al. [50] developed a method of detecting acute pain by extracting features from EEG and combining it with some other physiological markers, such as heartbeat variations. A 16-dry electrodes cap was used as a recording device. Their experiment used a noxious cold stimulus applied on the left volar forearm of 14 healthy participants (ten males and four females) with an age range of (21-35) years. Their analyses concluded a correlation between the pain intensity with the high Gamma activities in the brain.

A total of 20 subjects, 16 females and four males, with an age of 20± 2 years, participated in [51]. Thermal stimuli were directed to the right forearm of the subjects using a contact heat-evoked potential stimulator thermode. A 256-channel EEG recording device was used. The study found that the Theta and Gamma power increased in the prefrontal and medial cortex regions. Additionally, a Beta power decrease in the contralateral sensorimotor cortex was associated with the increase in pain intensity perception. The study then applied a machine-learning algorithm to achieve a binary classification accuracy of 89.88% (low and high pain). However, The different pain intensities were classified [52] by extracting important features from the EEG signals and inputting them into a machine-learning classifier. CPT stimuli were recorded from 24 healthy subjects, 15 males and nine females, with an age range of (20-28) years, by a 28-channel EEG recording device. The finding revealed a direct correlation between the Delta and Alpha activities with the pain intensity. The accuracy of their developed SVM classifier achieved 83±5%.

A pre-clinical screening of analgesic efficacy in vivo was done in [53], which contributed to the scientific understanding of the pain electrical nature in the brain and the effects of the three tested drugs: (1) minocycline, a CNS-acting glial inhibitor. (2) EMA 401, a PNS-acting angiotensin

II type 2 receptor inhibitor; and (3) pregabalin, a CNS-acting calcium channel inhibitor. The subjects of this study were 67 rats that underwent a chronic implant of EEG electrodes over the primary somatosensory cortex. It was also found that there was a strong relationship between the power of the Theta frequency band over the primary region of the somatosensory cortex and the preceptive physical pain.

The relationship between the Alpha activity peak frequency over the sensorimotor cortex with the pain intensity while experiencing capsaicin-heat pain (C-HP) was examined in [54]. Twenty-one participants experienced capsaicin-heat pain when recording their EEG with a 64-channel recording device. The study found that the slowing Peak Alpha Frequency (PAF) in response to prolonged pain could possibly act as an objective indicator of the subjective intensity of pain.

An automated assessment technique of pain intensity was proposed in [55] by using EEG signal processing and decision tree classifiers. A 14-dry electrode cap was used as a recording device. A CPT was used as a painful stimulus on 22 healthy participants with an age of 25 ± 2 years. Seventeen of them were males. The developed decision tree classifier achieved an accuracy of 72.7%. Some other advanced algorithms of deep learning were used in [56] to achieve the classification of the different levels of pain from EEG signals. The developed classifier's accuracy was 82.8 %. The study used the dataset from [57], which consisted of 85 participants who were healthy and had different ages and genders. The subjects experienced painful heat stimuli in their right forearm. In our previous work [58], 30 subjects,17 males and 13 females, males with an age of 24 ± 3 years, participated in a CPT experiment. We found the following consistent observations in the EEG pain signals: (1) a decrease of Alpha frequency band power over the somatosensory cortex, (2) a decrease of all the electrical activities over the frontal cortex, (3) and an increase of Gamma frequency power in all the sensors' readings due to the EMG artefacts. We utilised deep learning algorithms to build a classifier to classify four different levels of pain with an accuracy of 94.83 %.

A classification accuracy of 60% was achieved in [59] by using the state-space model (SSM) and SVM. The data was collected from 51 healthy right-handed participants, 26 males and 25 females, with an age range of (20–37) using cutaneous laser stimulation and an EEG recorder with 65 electrodes.

Bayes optimised support vector machine (BSVM) was used in [60] to achieve a binary accuracy of 99.8% accuracy (pain and no-pain) and classification accuracy of 93.33% (5 different classes of pain). The data was collected from 44 healthy right-handed participants, 24 males and 20 females, with an age range of (20-28) using CPT and a 34 silver channels EEG recorder. The following regions were found to be correlated to the pain sensation: the primary and secondary somatosensory cortices; anterior cingulate; prefrontal cortex; basal ganglia, posterior parietal cortex; Posterior cingulate; primary and supplementary motor cortices.

In [61], it was found that painful stimuli significantly increased gamma power bilaterally in regions such as frontotemporal regions and decreased alpha power in the contralateral central scalp. The study used CPT and a 128-electrode EEG recorder on 14 healthy participants, six males and eight females, with an age of 23.5 ± 3.8.

A bio-inspired decision tree that achieved a binary accuracy of 92 % (pain and no-pain) and an accuracy of 86% (between 5 different classes of pain) was proposed in [62]. The data was collected using CPT and a 29-electrode EEG recorder on 23 participants with an age of 22 ± 1.4 years.

It was concluded after surveying the chronic pain literature indicating the clinical characteristics of individuals who had chronic pain as the increased Theta and Alpha power at spontaneous EEG and the low amplitudes of ERP during various stimuli [63]. According to the review paper of [19], phasic pain is often related to Alpha and Beta frequency bands over the sensorimotor cortex, while the Gamma band is often correlated to the intensity of the pain. Tonic pain, however, evoked the same type of frequencies but over the medial prefrontal cortex. Chronic pain is persistently correlated to Theta oscillations. Table 1 summarises all the correlations between different pain stimulations and the different frequency bands in the aforementioned studies.

Table 1 Summary of the relevant findings compiled from the literature.

Study	Participants	Stimuli Inducing Force	Findings
[31]	19 humans	Noxious Cold Temperature	Decrease of EEG amplitude and an increase of EEG coherence in the central regions of the human brain.
[16]	76 humans	Noxious Cold Temperature	Theta activity was significantly associated with pain ratings.
[35]	13 humans	Hypertonic Saline Injection	Alpha activity is negatively associated with the pain intensity and pain area on the skin, while Beta activity was found to have a positive correlation.
[36]	15 humans	Capsaicin Injection	Muscle pain induced a significant increase in Beta activity.
[37]	10 humans	Noxious Radiant Heat	Rolandic Alpha is directly associated with subjective pain intensity.
[38]	15 humans	Noxious Cold Temperature	A decrease in the power of the Alpha frequency band.
[39]	12 humans	Noxious Radiant Heat	Gamma band oscillations over the primary somatosensory cortex increase with the subjective pain intensity.

[11]	15 humans	Noxious Cold Temperature	Alpha amplitudes increased over the posterior scalp and decreased over the contralateral temporal scalp during the cold pain condition, in addition to increased Gamma activities in all the electrodes due to the EMG artefacts.
[41]	7 humans	Noxious Radiant Heat	No Correlations found
[42]	Rats	Noxious Radiant Heat	Coupling between Theta and Gamma can work as a pain biomarker.
[44]	26 humans	Noxious Cold Temperature	The power of Beta increases.
[45]	23 humans	Noxious Radiant Heat	The pain experience caused the appearance of Gamma oscillations at 80 Hz.
[43]	18 humans	Noxious Hot Temperature	The Alpha band is negatively correlated with the subjective perception of the pain intensity.
[12]	7 humans	Noxious Radiant Heat	Gamma band frequencies over the primary region of the somatosensory cortex increase with the subjective pain intensity.
[64]	64 humans	Spinal cord chronic pain	Increase of Alpha and Theta bands associated with the pain in the frontal cortex.
[46]	9 humans	Noxious Hot Temperature	Low PSD in the Beta band and high PSD in the Alpha band are associated with subjective pain intensity.
[47]	23 humans	Noxious Electrical current	The Gamma band power was increased by 12% at frontocentral sites, and a decrease in frontoparietal connectivity.
[48]	43 humans	Isotonic Saline and Hypertonic Saline Injection.	A correlation between the frontal-central Gamma frequencies and tonic pain intensity was found.
[50]	14 humans	Noxious Cold Temperature	Increase in high Gamma activities.
[49]	20 humans	Noxious Cold Temperature	Beta power increases over intrahemispheric
[51]	20 humans	Noxious Hot Temperature	The Theta and Gamma power increase in regions such as the prefrontal and medial cortex, in addition to the Beta power decrease in the contralateral sensorimotor cortex, is associated with the increase of pain intensity perception.
[53]	67 rats	Chronic Clinical Illness CCI	Increase in Theta waves over the primary somatosensory cortex.
[52]	24 humans	Noxious Cold Temperature	A correlation between the Delta and Alpha activities and the pain intensity was found.
[54]	21 humans	Capsaicin-Heat Pain (C-HP).	A correlation between subjective pain intensity and the slowing response of PAF to prolonged pain.
[55]	22 humans	Noxious Cold Temperature	Built a successful decision tree classifier with no observable human correlations.
[56]	85 humans	Noxious Hot Temperature	Built a successful neural network classifier with no observable human correlations.
[58]	30 humans	Noxious Cold Temperature	A decrease in the power of the Alpha frequency band over the somatosensory cortex, a decrease in all the electrical activities in the prefrontal cortex, and an increase of the Gamma power in all of the cerebral cortex.
[59]	51 humans	Noxious Cold Temperature	No correlation
[60]	44 humans	Noxious Cold Temperature	Fluctuation in the electrical activities of the following brain region: the primary and secondary somatosensory cortices; anterior cingulate; prefrontal cortex; basal ganglia; posterior parietal cortex; Posterior cingulate; primary and supplementary motor cortices.
[61]	14 humans	Noxious Cold Temperature	An Increase of gamma power bilaterally in regions such as frontotemporal regions and a decrease of alpha power in the contralateral central scalp.
[62]	23 humans	Noxious Cold Temperature	Changes in Alpha frequency band connectivity.

IV. Results

Unfortunately, the exact statistical power and effect size of the investigated studies could not be compared due to the lack of reporting them or reporting insufficient variables that did not allow us to calculate them in most cases. Additionally, the data/samples heterogeneity, different experiments protocol and quality prevented the proper conduction of meta-analysis and made them hardly comparable [65]. Moreover, it may be

obvious by now that the current scientific literature has no single unified trend that can represent the EEG activities caused by nociceptive pain [66].

The usage of deep learning or machine learning techniques has been proven to be useful in classifying the bio-signals due to the flexibility and the nonlinearity they provide [67, 68]. However, their accuracies might be, in some cases, statistically misleading as they are impacted by a number of sophisticated considerations and biases [69]. To illustrate, the accuracy of every machine learning model does not reflect the accuracy of the classification universally, but rather the accuracy of classification for only the selected data sample, and it does not explain the potential data biases. However, based on the statistical concepts, it is understood that the larger and the more diverse the pool of population the data is collected from, the more statistical power the study would have, or the more reliable the study gets. Figure 3 shows the number of participants in all the studies that experimented on humans.

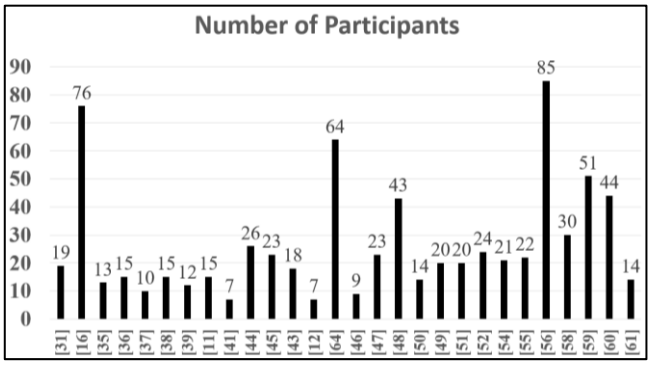

Fig 3 The number of participants in all the surveyed studies that experimented on humans.

It is important to highlight here again that the outcome variables heterogeneity averted the data standardisation, which made the meta-analysis conduction impossible to be performed. Although meta-analysis conduction is not possible, a comparison between the accuracies of the studies that used machine learning algorithms in the literature has been conducted. Table 2 presents a comparison between the accuracies of the relevant studies that were reported in the literature. Note that the accuracies shown in Table 2 do not necessarily reflect the actual performance of the algorithm or the developed system. This is because they are hardly comparable due to different experimental designs and the use of different datasets and algorithms.

The brain areas affected by the pain sensation in the surveyed studies included cerebral structures like frontal, medial, interhemispheric, contralateral temporal, somatosensory cortexes, insula, the midbrain, and parts of the limbic system. This confirms our previous understanding of the brain regions involved in the pain matrix or network. To further investigate this, the automated meta-analysis tool Neurosynth (https://neurosynth.org/) was used to narrow down the studies of the term 'pain'. It demonstrated the findings found in 516 studies [70]. Although these studies were mainly fMRI images, it was helpful to look at them as they investigated the same phenomenon of pain, and it is well-known that fMRI has better spatial resolution than EEG. Figure 4 shows the results of the Neurosynth meta-analysis [70] after being redrawn by the Analysis of Functional NeuroImages (AFNI) software [71]. Figure 4 shows three cross-sections in each of the sagittal, coronal, and axial views.

Table 2 A Comparison between the accuracies of the studies that used machine learning algorithms in the literature.

Study	Machine Learning Algorithm	Accuracy	Participants	Stimulus
[45]	SVM	83 %	23	Leaser
[24]	Decision Tree	72.7 %	22	CPT
[51]	SVM	89.88 %	20	Thermal
[52]	SVM	83 %	24	CPT
[55]	Binary Naïve Bayes classifier	83.3 %	29	Leaser
[56]	Neural Networks	82.3 %	85	Thermal
[58]	Neural Networks	94.83 %	30	CPT
[59]	SSM and SVM	60 %	51	CPT
[60]	BSVM	93.33 %	44	CPT
[62]	Decision Tree	92%	23	CPT

It was found that different stimulators were used in the literature. Below is a list of the stimulators and the number of studies that used them in the literature:

- Noxious cold temperature: 14 studies.
- Noxious hot temperature/ radiant heat: 10 studies.
- Hypertonic saline, isotonic saline, and capsaicin injections: 3 studies.
- Capsaicin-Heat Pain: 1 study.
- Noxious electrical current: 1 study
- Chronic pain: 2 studies.

Figure 5 shows the percentage distribution of the different stimulators used in the surveyed studies.

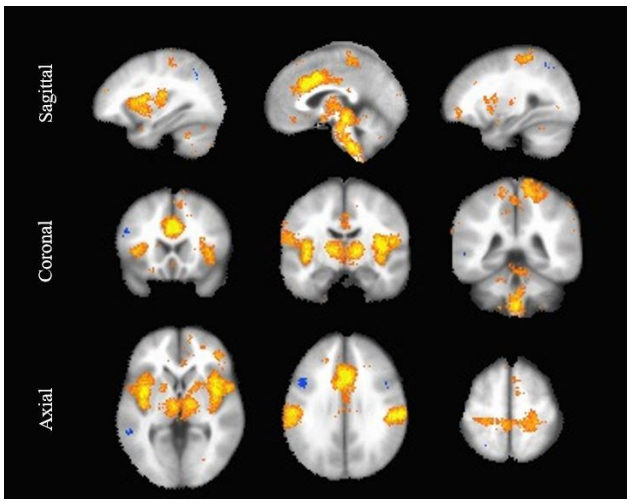

Fig 4 The brain regions activated while perceiving the sensation of pain.

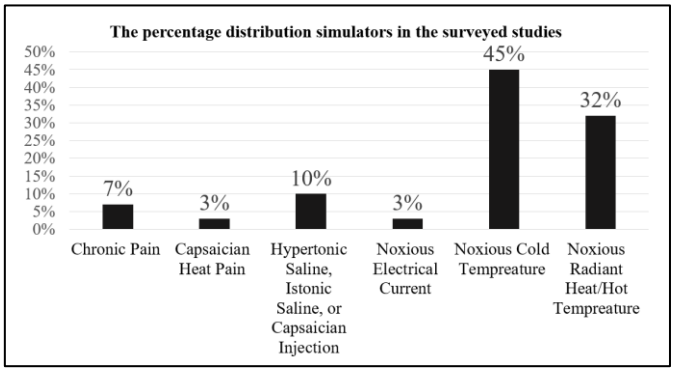

Fig 5 The percentage distribution of the different types of simulators used in the surveyed studies.

V. Discussion

Notably, there is no consistent trend in literature that links pain intensity with specific EEG activity [66]. The studies and findings presented in Section III clearly show a lot of conflicts, contradictions, and gaps in our collective scientific understanding of the brain's electrical activities inflicted by the pain sensation. Obviously, we still lack a comprehensive understanding of the electrical measures of brain activity that we can relate directly to perceptive physical pain [72]. There is also an apparent problem with the effect size of most, if not all, of the surveyed studies, as the number of participants is too small to make an induction that will be held true in representing the collective human population. Figure 6 shows the number of studies that correlate pain sensation with a frequency band in a certain brain region. There are some overlaps between the correlated frequency maps, as could be seen in [51], which was repeated in three frequency bands. For more information about the affected brain region, refer to Figure 4.

However, there were a few observed tendencies which could be summarised as correlating the perception of pain with the increase of Gamma power in the frontal cortex and variational electrical activities in the primary somatosensory cortex (e.g., the decrees of Alpha power). Unfortunately, these observed tendencies were not common in all the surveyed studies, so we cannot even hesitantly call them global trends. Moreover, there is a tendency to direct the classification of the EEG and bio-signals in general towards the machine learning direction. This is clear from the studies that have been published in the past five years. Craik et al. [67] demonstrated the efficiency and the popularity of using deep learning in EEG signal classification and realisation, while the study [68] demonstrated the success of the machine learning algorithms in generating accurate new EEG data.

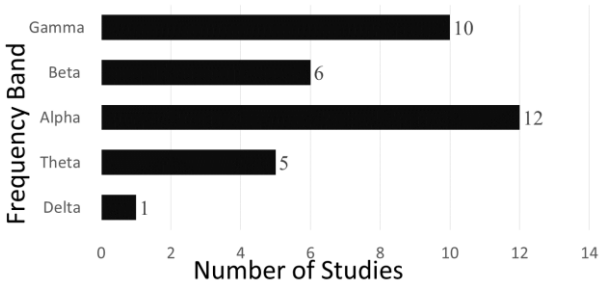

Fig 6 The number of studies that correlated the pain sensation to the different frequency bands.

Figure 7 shows the distribution of the different machine-learning techniques that have been used in the literature to identify pain and quantify its intensity. The utilisation of these machine-learning algorithms is not only restricted to the EEG analysis but includes other bio-signals too. In fact, some studies take this even step further and analyse the pain sensation through the analysis of video sequences which identify pain through the face expression [73]. Similarly, a novel approach to infant facial pain classification using a multi-stage classifier and geometrical-textural features combination was implemented in [74]. The research work reported in [75] is another example of a study that used machine learning to deal with biological signals where some machine learning techniques with low dimensional feature extraction to Improve the Generalizability of Cardiac Arrhythmia detection. All of these studies clearly demonstrate a global trend of using machine learning algorithms to investigate pain sensation and biological signals in general.

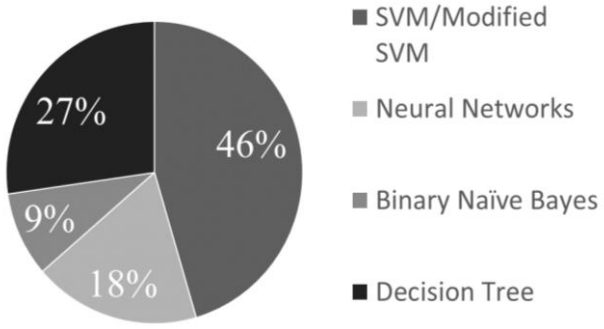

Fig 7 The distribution of the different machine learning techniques that have been used in the literature to identify the pain and quantify its intensity.

It was also observed in [58] that females and males tend to have different tolerances to pain intensity as males tend to have more tolerance to low-intensity pain and females have more intensity to high-intensity pain. However, this observation, though interesting, has not been supported by any other studies in the literature, and no EEG analysis has been made on the differences between the genders when it comes to pain sensitivity or tolerance to the best of our knowledge. There are only 19 studies out of all the surveyed papers that clearly mentioned the breakdown of the gender count of the participants. So, we added all of them. The male participants were 241, while the females were 227. Figure 8 shows this breakdown.

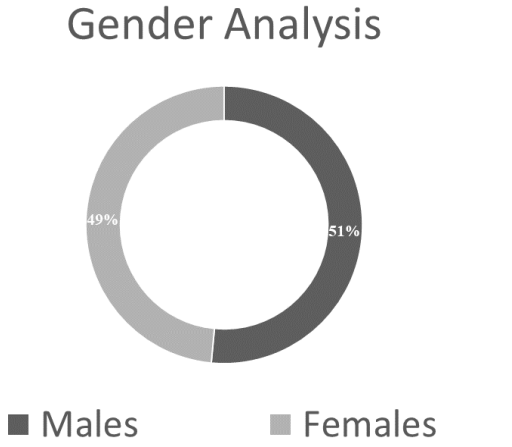

Fig 8 The number of female and male participants in the surveyed studies.

It was also found that only 25 studies clearly mentioned the age of the participants. The mean and standard deviation of all the participants was averaged to be 22.9 ± 5.2 years. This shows a clear gap in our understanding of how pain sensation might have different effects on the elderly and children.

It may be clear that we are still far from having an objective pain measure or measurement technique that could have clinical applicability or that can possibly be adapted to any therapeutic applications. Such an ambitious goal, however, requires more studies and experiments to be conducted so we can have more robust and conclusive findings than the ones that are currently reported in the literature.

The study of the nature and effects of physical pain on the human brain is extremely challenging due to the very subjective nature of the human brain and its connectivity. Any action potential produced by any part of the brain gets deflected and reflected countlessly within the skull. So, when we record the surface EEG, we get a combination of mixed-up and complex signals that originated in different parts of the brain, which makes the processing of these signals complicated.

Another factor that makes the study of pain challenging is the pain's very subjective nature. The perception of any painful stimulus intensity depends on one's subjective pain tolerance. It is possible that this subjectivity is not solely associated with the intensity of pain but also with the way it is perceived and processed in the brain. Perhaps that is why the literature cannot really reveal conclusive correlations.

The unpleasantness of any painful experience makes it difficult for researchers to recruit participants. Thus, most of the pain studies have a tiny sample size, making it tough to come up with firm, conclusive results. Furthermore, the study of pain involves many ethical complications, whether in humans or animals.

It may also be that EEG is just not accurate or powerful enough to facilitate such application and objectively measure the nociceptive pain. However, to empirically conclude whether this is the case or not, further investigations have to be done.

This review also highlights a massive problem in the fields of neuroscience and bioengineering, which is the issue of reproducibility. Little to none of the surveyed studies could be empirically reproduced due to the lack or improper reporting of the data needed to reproduce the study. This could be the biggest problem in the scientific field because if all our studies have a very small statistical effect size and are not reproducible, then all our collective efforts are deemed meaningless [76].

VI. Conclusion

This paper presents a comprehensive systematic literature review aimed at identifying pain biomarker/s in the electrical activities of the human brain. It was found that we still lack a comprehensive understanding of the brain activity measures that can be directly related to perceptive physical pain, as the literature is full of contradictory findings and gaps. However, a few tendencies were observed, such as correlating the perception of pain with an increase in Gamma power in the frontal cortex and various electrical activities in the primary somatosensory cortex (e.g., a decrease in Alpha power). Furthermore, a trend of using machine learning to classify the different intensities of EEG pain signals was found. It is clear that further clinical studies are needed to help us better understand the nature and effects of pain on the human brain.

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