**Clinical Use of Electroencephalography in the Assessment of Acute Thermal Pain**

**Abstract**

**Keywords**

**Introduction**

Emerging from activation of a wide cortical network, the subjective feeling of pain is hard to interpret using a spatially-driven approach. As of now, no practically implementable system has successfully been able to decode and predict pain clinically [1, 2]. Beside its spatial component, pain is accompanied by complex temporal–spectral patterns of brain activity [3]. In order to detect such subtle changes in neural activation, a neuroimaging device must have the capacity to record at the millisecond scale, far beyond the spend of functional Magnetic Resonance [2] -- not to mention its high cost and limited portability. The use of electroencephalography (EEG) has therefore been suggested for the investigation of a dynamic cerebral biomarker of pain [4]. EEG portability, low cost and safeness makes the tool well suited for clinical application to vulnerable population [2]. Patients with severe and profound intellectual disability would benefit from the implementation of an tool that could objectively assess pain without reliance on verbal report [5]. In particular, the variability in verbal ability and difference in pain response have limited the application of pain assessment tools to children with developmental disabilities [6]. This review aims to address the potential use of electroencephalographic features as biomarkers of acute experimental pain. Aiming for homogeneity of stimulation, only studies using thermal, e.g. heat or cold, stimulations will be addressed. We will also review whether electroencephalography (EEG) combined with machine learning could ultimately be used as an objective tool in acute pain diagnosis.

**Methodology**

In order to provide an overview of current electroencephalographic studies using thermal stimulation in their experimental design, a literature search in PubMed was performed. To do so, combinations of the following terms were used: “EEG”, “Electroencephalography”, “Acute”, “Pain”, “Tonic”, “Noxious”, “Thermal”, “Stimulation”, “Brain”, “Activity”, “Cold”, “Subjective” and “Perception”. A filter for human populations was also applied and only studies published between 2009 and 2019 were kept. After screening abstracts, we solely kept studies using a thermode for heat stimulation, thus eliminating laser and electrical stimuli or other kind of eclectic devices. A total of 20 experimental studies primarily investigating cerebral features of thermal heat pain including healthy participants were identified. As for studies investigating cold stimuli, the focus was kept on the ones using bath immersion in their experimental design and in which cold immersion was not used as a conditioning stimulus. Studies examining the impact of analgesics on noxious cold sensation were also eliminated. As a result, only 3 experimental studies investigating cerebral features of cold stimulation that have pain as their primary outcomes were identified. The aim of these inclusion and exclusion criteria is to reduce confounding variables by seeking homogeneity of stimulation.

**Cerebral features of thermal heat stimuli**

Event-related potentials (ERPs) have been widely studied in pain research [7-13]. Researchers make use of “the signal change evoked in response to a stimulus event to elucidate the timing, intensity and spatial location of the underlying brain activity” [10]. A specific kind of ERPs, especially used in thermal pain investigation, is the contact-heat-evoked potential (CHEP). CHEPs are obtained through rapidly delivered, noxious heat stimulations known to activate both Aδ- and C-fiber nociceptors [14]. The formation of a negative-positive complex having effects from approximately 200ms to 550 ms post stimulation has been commonly recorded around the central electrode (Cz) [7-13, 15]. High and low-resolution source localization have revealed altered activity in orbitofrontal, cingulate, insular, motor, sensory and cerebellar regions following the N2P2 complex formation [7-13]. Further findings have suggested that the N2 and P2 components might reflect different elements of the pain experience [9, 12]. Particularly, the P2 component has been temporarily linked to increased activation of the frontal-central cortices [9, 12, 13]. The P2 component is hypothesized to be linked with higher cognitive processes such as pain expectancy and motor preparation [9, 13]. Despite all these findings on pain-evoked potentials, they are restricted to a time-locked period and can hardly be extended into a longer time window post stimulation [16]. Researchers have hence suggested to investigate tonic noxious stimuli since they are thought to best mimic the mechanism involved in clinical pain [17-19].

Longer lasting stimuli require time-frequency analyses, as “cortical responses are not phase-locked as are pain-evoked potentials” [18]. One especially investigated feature of continuous EEG is spectral power. In order to analyze the spectral power, the recorded data has to be transformed from the time domain to the frequency domain using a fast Fourier transformation or a wavelet analysis [20]. The data is then characterized by a curve of the power amplitude plotted against the frequency range of interest [17] Alpha frequencies (8-12 Hz) have yielded a growing interest in pain research for being the predominant wave band observed in primary sensory regions [21]. It has also been suggested that alpha rhythm modulation could represent altered mechanisms of cortical synchronization in clinical populations with cognitive-motor deficits [18]. Decreased alpha power around the midline has been commonly observed during noxious stimulations, particularly in the contralateral sensorimotor areas [19, 22-25]. Ongoing suppression was further linked to decreased blood-oxygen-level dependent (BOLD) response and higher pain evoked potentials, both suggesting less cortical deactivation [10]. These observations suggests that decreased alpha power during noxious stimulation is linked with increased activity in areas involved in sensorimotor processing [25]. Whether alpha suppression is linked to subjective pain ratings, stimulus intensity or both, is a common topic under investigation. Increased subjective pain perception has been associated with decreased power of alpha rhythms at temporal and central electrodes [18, 19, 22, 24, 25]. Attention and expectancy have further been found to modulate alpha responses, suggesting that alpha rhythms may be involved in top-down processes [19, 25, 26]. Interestingly, increased stimulus intensity has additionally been linked to decreased alpha and beta power over sensorimotor areas [23, 26, 27]. This consistent decrease in cortical inhibition linked to both pain and stimulus intensity is thought to reflect the dynamic adjustment of the pain response to both internal and external stressors [24, 25].

A sub-feature of alpha spectral power widely investigated in pain research is the peak frequency. The peak frequency is the highest power–density point within the investigated frequency range [17]. In the search for an objective pain biomarker, peak alpha frequency (PAF) has been pointed out as a single-featured correlate of tonic experimental pain [17, 21]. Both the PAF recorded at baseline and during noxious-stimulation have been associated with subjective pain ratings [17, 21]. Nir et al. (2010) found a positive relationship between PAF and subjective pain scores [28], while Furman et al. (2018) recently found the inverse relationship [17, 21]. The later study incorporated a capsaicin prolonged pain model known to induce central sensitization which might explain why these results resemble chronic pain findings more than experimental ones [21]. However, as pain perception and arousal are intimately intertwined, it is hard to rule out the possibility that an arousal state might partially explain variability recorded in the PAF [17]. A single feature predictor might not be ideal to capture all subtleties of the pain experience.

Investigating power spectra of other frequency bands, researchers have aimed at differentiating cerebral features of pain from those of nociception. As briefly mentioned above, decreased beta power (14-29 Hz) in sensorimotor regions has been observed in several studies during noxious stimulation [15, 22, 23, 26, 27]. This decreased in beta power was associated with both stimulus intensity [23, 26, 27] and subjective pain ratings [15, 22].

Regarding subjective pain ratings, gamma power (30-100 Hz) recorded over widespread cortical areas has repetitively been associated to pain perception [15, 23, 25, 27, 28]. Increased gamma power over frontal regions has particularly been linked to higher pain sensation [15, 23, 25, 27]. Indeed, gamma frequencies are thought to be independent of stimulus location [23] and robust towards cognitive modulation [25]. Consequently, gamma bands might rule the cognitive-affective component of pain rather than sensory-discriminative one.

Similarly, increased theta power (3-7 Hz) in medial prefrontal cortices (mPFC) and central regions was associated with increased pain perception [11, 15]. Interestingly, less localized decrease in theta power has also been associated with increased pain perception [22, 24]. A plausible hypothesis would be that theta rhythms help carry the sensory information from the Rolandic region to the anterior cingulate cortex (ACC) and insula [24], explaining why they have been observed rostrally and caudally around the longitudinal fissure [22]. Consistently, intracranial coherence analysis has demonstrated that phase locking partially contributes to increased theta power observed in medial prefrontal areas including cingulate and caudate regions [15]. Granger causality analysis has further revealed changes in connectivity of the contralateral somatosensory cortex and the medial frontal areas during high level of pain [24]. Theta bands are thought to facilitate these changes in network connectivity, helping carry the information from sensory inputs to cognitive-affective centers [24].

Lastly, the role of delta bands (0.5-3.5 Hz) in pain perception has also been investigated [11, 19, 22, 24]. Delta power in parietal and occipital lobes was found significantly higher during noxious stimulation than during innocuous stimulations [19]. Nevertheless, increased delta power has been observed to some extend in non-painful thermal stimulations, suggesting that this feature might not be specific to pain but rather to stimulus intensity [11]. Additionally, decreased delta power around the longitudinal fissure has also been associated to increased stimulus intensity [22, 24]. These discrepancies overall suggest that delta power might not be the most robust and predictive feature of tonic thermal pain.

**Cerebral features of thermal cold stimuli**

A limited number of studies have investigated changes in cerebral activity elicited by noxious cold stimulation [29-31]. Aiming to develop pain models that best mimic clinical pain, interest has been given to cold stimulations. The cold pressor test (CP) is a tonic experimental model where participants are asked to immerse their hand or forearm in cold water [31]. The immersion can last from seconds to minutes, providing a broad recording window. Shao et al. (2012) have recorded brain activity during a 10 min immersion in cold water at 10 °C [30]. They found reduced power of lower frequencies and enhanced power of higher frequencies when the participant’s hand was immersed in a bath of 10 °C compared to room temperature [30]. Source localization revealed that increased high frequencies power, notably from 18-30 Hz, was significant in widespread cortical regions including the frontal and cingulate cortices during cold immersion [30]. Additionally, activity in the frontal, parietal and cingulate cortices were linked to decreased power of lower frequencies ranging from 4 to 18 Hz [30]. The activity in prefrontal (4-8 Hz) and cingulate regions (8-18 Hz) was further correlated with both pain intensity and unpleasantness ratings [30]. Similarly, Gram et al. (2015) recorded brain activity during immersion of the hand in cold water at 2 °C [31]. They investigated dynamic and static indices of spectral power during a 2 min period of stimulation [31]. Similarly to Shao et al. (2012), they found increased power of higher frequencies and decreased power of lower frequencies during cold stimulation compared to resting state [31]. Interestingly, while the relative power of theta bands (4-8 Hz) decreased during cold stimulation, theta absolute power increased [31]. The dynamics of theta bands were further correlated to continuous pain ratings under CP, resembling findings of thermal heat pain [11, 31]. A recent study by Levitt et al. (2017) has investigated cerebral synchrony and connectivity during a 20 second hand immersion in cold water [29]. They found an increase power at the frontal electrode in the theta band (6-7 Hz) and a wide decrease in caudal power (3-30 Hz) localized at the occipital lobe [29]. These modulations in power were referred to as frontal synchrony and caudal asynchrony [29]. Functional connectivity between frontal (Fz) and caudal (O1) electrodes revealed increased coherence in the theta band (4-8 Hz) [29]. This enhanced fronto-caudal connectivity possibly reflects involvement of the cerebellum in nociceptive processing [29]. Overall, cerebral activity during noxious cold stimulation revealed dynamic modulation of frontal theta rhythms thought to be linked with the affective-motivational aspect of pain.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | | **Cerebral Regions** | | | |
|  | | Frontal Activity | Temporal Activity | Central-Parietal Activity | Occipital Activity |
| **Pain Evoked Potentials (Eps)** | N2P2 complex | **Activation of orbitofrontal, prefrontal or cingulate regions**  (Lev, Granovsky, & Yarnitsky, 2010, 2013; Mayhew, Hylands-White, Porcaro, Derbyshire, & Bagshaw, 2013; Meng et al., 2013; Reches et al., 2016; Wang et al., 2016) | **Activation of insular regions**  (Mayhew et al., 2013; Meng et al., 2013; Reches et al., 2016) | **Activation of sensorimotor regions, including S1, S2 and M1**  (Kisler et al., 2017; Lev et al., 2010, 2013; Mayhew et al., 2013; Meng et al., 2013; Wang et al., 2016) | **Activation near cerebellum**  (Mayhew et al., 2013 |
| **Power Spectra** | Delta (0-3.5 Hz) | **Increased delta power**  (Reches et al., 2016) | **Increased delta power contralaterally**  (Reches et al., 2016) | **Decreased delta power over sensorimotor regions**  (Huishi Zhang et al., 2016)  **Increase delta power over parietal region**  (Giehl, Meyer-Brandis, Kunz, & Lautenbacher, 2014; Reches et al., 2016) | **Increased delta power caudally**  (Giehl et al., 2014) |
| Theta (4-7 Hz) | **Increased frontal theta power**  (Levitt, Choo, Smith, LeBlanc, & Saab, 2017; Misra, Wang, Archer, Roy, & Coombes, 2017; Shao, Shen, Yu, Wilder-Smith, & Li, 2012) |  | **Decreased theta power over sensorimotor regions**  (Bunk et al., 2018a; Huishi Zhang et al., 2016; Reches et al., 2016) |  |
| Alpha (8-12 Hz) | **Decreased alpha power over cingulate region**  (Shao et al., 2012)  **Increase alpha power over frontal area**  (Huishi Zhang, Sohrabpour, Lu, & He, 2016) | **Decreased alpha power bilaterally**  (Nir, Sinai, Moont, Harari, & Yarnitsky, 2012) | **Decreased alpha power over sensorimotor regions**  (Bunk et al., 2018b; Giehl et al., 2014; Huishi Zhang et al., 2016; Nickel et al., 2017; Peng et al., 2014; Shao et al., 2012) |  |
| Beta (13-29 Hz) | **Decreased low beta (12-18 Hz) power over cingulate region**  (Shao et al., 2012)  **Increased high beta power (18-30 Hz) over frontal and cingulate regions**  (Shao et al., 2012) | **Increased beta power in temporal, insular and parahippocampal regions**  (Shao et al., 2012) | **Decreased beta power over sensorimotor region**  (Bunk et al., 2018b; Mancini, Longo, Canzoneri, Vallar, & Haggard, 2013; Misra et al., 2017; Nickel et al., 2017; Schulz et al., 2015; Shao et al., 2012) | **Increased beta power near cerebellum** (Shao et al., 2012) |
| Gamma (30-100 Hz) | **Increased frontal gamma power**  (Misra et al., 2017; Nickel et al., 2017; Peng, Hu, Zhang, & Hu, 2014; Schulz et al., 2015) |  |  |  |

Table 1: Modulation in Cortical Activity Associated with Principal Examined EEG Features

DISCUSSION

In general, thermal noxious stimulations seem to modulate activity over frontal [7-12, 15, 23-25, 29, 30] and sensorimotor regions [7-13, 15, 19, 22-27, 30]. Studies using phasic stimuli measured the N2P2 complex [7-13], which is thought to reflect brief stimulation of the A-delta and C fibers. Source localization has associated activity of the sensorimotor and frontal cortices to the N2P2 response [7-12]. Spectral analysis over longer noxious stimulations have consistently revealed changes in cerebral activity over frontal [11, 15, 23-25, 27, 29, 30] and central regions [11, 15, 19, 22-27, 30]. On the one hand, researchers found decreased spectrum power over the central sulcus, extending from high theta to low beta bands but predominant in the alpha band [11, 15, 19, 22-27, 30]. Alpha bands being often linked to cortical inhibition, this decreased power over central regions might possibly reflect activation of the sensorimotor cortices to noxious stimulation [25, 32]. On the other hand, recent studies have shown an increasing relationship between frontal rhythms and pain intensity thought to be independent of stimulus location and attentional resources [23, 25]. Notably, gamma and theta rhythms recorded over frontal cortices seem to facilitate connectivity between sensory and affective regions [15, 23, 25, 27, 29]. A recent predictive coding framework has linked gamma rhythms to feedforward processing of sensory information, ultimately merging into the subjective feeling of pain [33]. In contrast, alpha and beta oscillation are thought to reflect top-down control of primary areas, dynamically adjusting the sensory gate and responsiveness [3, 34]. The specific location of elicited brain activity might not be as important as originally thought. Mouraux et al. previously demonstrated that activity in the so-called pain matrix is indeed multimodal and can be equally activated by salient stimuli of other modalities [35]. This attempt to localize activity in cortical regions previously associated with the pain matrix has impeded the functional significance of neuroimaging results [36].

A few studies mentioned above have investigated the use of machine learning in pain classification using some of the features mentioned above [11, 15, 28]. In pain research, machine learning algorithms have been used to identify spatiotemporal patterns of brain activity that discriminate between two conditions, e.g. pain or no pain, and could ultimately serve for making prediction on untested data [1]. Regarding brief noxious thermal stimulation in the order of milliseconds, Reches et al. (2016) have classified high and low pain responders using Brain Network Analysis (BNA) as a tool [11]. The BNA algorithm uses graph representation to depict the evolution of network dynamics in time, location and frequency [11]. The features used included a combination of pain evoked potentials (EPs) and spectral power [11]. The BNA algorithm comprises a group level pattern recognition that extract co-occurring EPs peaks across subjects to obtain a reference brain network model (RBNM) [11]. Once the RBNM is computed, each subject’s network dynamics during thermal stimulation is compared to the RBNM and a similarity score is obtained [11]. At high stimulus temperature (49 and 52 C), complex networks were revealed by increasing activity and expending connectivity between the nodes of the network [11]. The RBNMs obtained at these high temperatures were effective in classifying high and low pain responders reaching an accuracy of 87-93 % when assessed at 52 °C [11]. High responders, scoring over 4 on a 0-10 numerical pain scale, demonstrated higher similarity score to the RBNM than low responders [11]. However, the short period of stimulation limits the application of these findings to clinical pain.

Investigating noxious stimulation in the order of seconds, Misra et al. 2016 have used machine learning to classify subjects into high and low pain groups [15]. Event-related spectral perturbations were computed at each frequency band and time. Significant domains of activity were found in the medial prefrontal cortex and sensorimotor areas when computing the difference between high and low pain states [15]. Increased power of gamma and theta bands in the prefrontal cortex and decreased power of beta bands in sensorimotor regions served as features for pain classification [15]. Using the leave-one-out approach, high and low pain subjects were classified. The highest accuracy (89.58%) was obtained using the Gaussian kernel support vector machine model (Gaussian SVM), implying that a nonlinear decision boundary is better suited than a linear one for such classification problems [15]. In order to determine which feature contributed the most to the classifier accuracy, Misra et al. ran the classifier using one feature at the time and obtained accuracies of 68.52%, 76% and 75.93 % for theta, beta and gamma bands respectively [15]. When gamma and beta bands were taken together as features, the maximum leave-one-out accuracy obtained was 87.5 % [15]. This suggests an overlap in frontal activity accounted for by the theta and gamma bands.

Vijayakumar et al. trained a random forest (RF) model to predict pain scores during thermal stimulation in the order of minutes [28]. RF models use multiple decision trees to search for the best feature that splits the dataset into several leaf nodes returning a majority class [28]. Using the leave-one-out classification approach, Vijayakumar et al. trained the classifier on 25 subjects using power spectrum of independent components along with the corresponding discrete pain score as data points. The accuracies obtained were 95.33% for a two-way classification and 89.45 % for a 10-way classification [28]. Ignoring one frequency band at the time, they found that the gamma band contributes the most to the 10-way classifier accuracy— dropping by 10% when the gamma band is ignored [28]. Their results suggested that “the alpha band had the highest variance across subjects… and showed a reduction in relative importance as the resolution of the pain score was made finer” [28]. Interestingly, the classifier accuracy suffered regardless of which frequency band was ignored, suggesting that all frequency bands contribute to pain classification.

LIMITATIONS

While spectral features currently dominate the landscape, Salomons et al. have highlighted the importance of supplementing current features with techniques that allow to investigate network dynamics [37]. Given the absence of specialized nociceptive brain tissue, entropy measures and causal inference could be key in understand how the flow of information dynamically merge into the conscious experience of pain [38].

A universal pain biomarker would ideally operate as well on non-verbal and verbal populations including children and adolescents suffering from intellectual disabilities. Nonetheless, the studies discussed in the present review were mostly performed on young adults in their twenties and thirties. Adolescents frontal circuitry is known to be different from the adult brain; the later not fully developed until the third decade of life [39]. These difference in frontal myelination might impede the translation of the previous findings into pediatric care units.

CONCLUSION

In summary, thermal noxious stimulations provoke changes in activity over frontal and central regions. This caudal-rostral modulation in cerebral activity reflects the flow of information between sensory-discriminative and affective-motivational components of pain. Further studies should supplement spectral findings with causality measures in order to understand how noxious information is actively encoded in the brain. The investigation of network dynamics has potential to improve our understanding of functional circuitry beyond preestablished anatomical landmarks.

REFERENCES

1. Rosa, M.J. and B. Seymour, *Decoding the matrix: Benefits and limitations of applying machine learning algorithms to pain neuroimaging.* PAIN, 2014. **155**(5): p. 864-867.

2. Levitt, J. and C.Y. Saab, *What does a pain 'biomarker' mean and can a machine be taught to measure pain?* Neurosci Lett, 2018.

3. Ploner, M., C. Sorg, and J. Gross, *Brain Rhythms of Pain.* Trends in cognitive sciences, 2017. **21**(2): p. 100-110.

4. Ploner, M. and E.S. May, *Electroencephalography and magnetoencephalography in pain research-current state and future perspectives.* Pain, 2018. **159**(2): p. 206-211.

5. Zwakhalen, S.M., et al., *Pain assessment in intellectually disabled people: non-verbal indicators.* J Adv Nurs, 2004. **45**(3): p. 236-45.

6. Temple, B., et al., *Pain in people with developmental disabilities: A scoping review.* Journal on developmental disabilities, 2012: p. 73-86.

7. Lev, R., Y. Granovsky, and D. Yarnitsky, *Orbitofrontal disinhibition of pain in migraine with aura: an interictal EEG-mapping study.* Cephalalgia, 2010. **30**(8): p. 910-8.

8. Lev, R., Y. Granovsky, and D. Yarnitsky, *Enhanced pain expectation in migraine: EEG-based evidence for impaired prefrontal function.* Headache, 2013. **53**(7): p. 1054-70.

9. Meng, J., et al., *Pain perception in the self and observation of others: an ERP investigation.* Neuroimage, 2013. **72**: p. 164-73.

10. Mayhew, S.D., et al., *Intrinsic variability in the human response to pain is assembled from multiple, dynamic brain processes.* Neuroimage, 2013. **75**: p. 68-78.

11. Reches, A., et al., *A novel electroencephalography-based tool for objective assessment of network dynamics activated by nociceptive stimuli.* Eur J Pain, 2016. **20**(2): p. 250-62.

12. Wang, L., et al., *Neural correlates of heat-evoked pain memory in humans.* J Neurophysiol, 2016. **115**(3): p. 1596-604.

13. Kisler, L.B., et al., *Bi-phasic activation of the primary motor cortex by pain and its relation to pain-evoked potentials - an exploratory study.* Behav Brain Res, 2017. **328**: p. 209-217.

14. Chen, A.C.N., D.M. Niddam, and L. Arendt-Nielsen, *Contact heat evoked potentials as a valid means to study nociceptive pathways in human subjects.* Neuroscience Letters, 2001. **316**(2): p. 79-82.

15. Misra, G., et al., *Automated classification of pain perception using high-density electroencephalography data.* J Neurophysiol, 2017. **117**(2): p. 786-795.

16. Read, G.L. and I.J. Innis, *Electroencephalography (Eeg)*, in *The International Encyclopedia of Communication Research Methods*. 2017. p. 1-18.

17. Nir, R.R., et al., *Pain assessment by continuous EEG: association between subjective perception of tonic pain and peak frequency of alpha oscillations during stimulation and at rest.* Brain Res, 2010. **1344**: p. 77-86.

18. Nir, R.R., et al., *Tonic pain and continuous EEG: prediction of subjective pain perception by alpha-1 power during stimulation and at rest.* Clin Neurophysiol, 2012. **123**(3): p. 605-12.

19. Giehl, J., et al., *Responses to tonic heat pain in the ongoing EEG under conditions of controlled attention.* Somatosens Mot Res, 2014. **31**(1): p. 40-8.

20. Hjorth, B., *EEG analysis based on time domain properties.* Electroencephalography and Clinical Neurophysiology, 1970. **29**(3): p. 306-310.

21. Furman, A.J., et al., *Cerebral peak alpha frequency predicts individual differences in pain sensitivity.* Neuroimage, 2018. **167**: p. 203-210.

22. Bunk, S.F., et al., *Does EEG activity during painful stimulation mirror more closely the noxious stimulus intensity or the subjective pain sensation?* Somatosens Mot Res, 2018: p. 1-7.

23. Nickel, M.M., et al., *Brain oscillations differentially encode noxious stimulus intensity and pain intensity.* Neuroimage, 2017. **148**: p. 141-147.

24. Huishi Zhang, C., et al., *Spectral and spatial changes of brain rhythmic activity in response to the sustained thermal pain stimulation.* Hum Brain Mapp, 2016. **37**(8): p. 2976-91.

25. Peng, W., et al., *Changes of spontaneous oscillatory activity to tonic heat pain.* PLoS One, 2014. **9**(3): p. e91052.

26. Mancini, F., et al., *Changes in cortical oscillations linked to multisensory modulation of nociception.* Eur J Neurosci, 2013. **37**(5): p. 768-76.

27. Schulz, E., et al., *Prefrontal Gamma Oscillations Encode Tonic Pain in Humans.* Cereb Cortex, 2015. **25**(11): p. 4407-14.

28. Vijayakumar, V., et al., *Quantifying and Characterizing Tonic Thermal Pain Across Subjects From EEG Data Using Random Forest Models.* IEEE Trans Biomed Eng, 2017. **64**(12): p. 2988-2996.

29. Levitt, J., et al., *Electroencephalographic frontal synchrony and caudal asynchrony during painful hand immersion in cold water.* Brain Res Bull, 2017. **130**: p. 75-80.

30. Shao, S., et al., *Frequency-domain EEG source analysis for acute tonic cold pain perception.* Clin Neurophysiol, 2012. **123**(10): p. 2042-9.

31. Gram, M., et al., *Dynamic spectral indices of the electroencephalogram provide new insights into tonic pain.* Clin Neurophysiol, 2015. **126**(4): p. 763-71.

32. Peng, W., et al., *Subjective pain perception mediated by alpha rhythms.* Biol Psychol, 2015. **109**: p. 141-50.

33. Ploner, M., C. Sorg, and J. Gross, *Brain Rhythms of Pain.* Trends Cogn Sci, 2017. **21**(2): p. 100-110.

34. Peng, W., et al., *Subjective pain perception mediated by alpha rhythms.* Biological Psychology, 2015. **109**: p. 141-150.

35. Mouraux, A., et al., *A multisensory investigation of the functional significance of the “pain matrix”.* NeuroImage, 2011. **54**(3): p. 2237-2249.

36. Iannetti, G.D., et al., *Beyond metaphor: contrasting mechanisms of social and physical pain.* Trends in Cognitive Sciences, 2013. **17**(8): p. 371-378.

37. Salomons, T.V., et al., *The “Pain Matrix” in Pain-Free IndividualsThe “Pain Matrix” in Pain-Free IndividualsLetters.* JAMA Neurology, 2016. **73**(6): p. 755-756.

38. Geha, P. and S.G. Waxman, *Pain Perception: Multiple Matrices or One?Pain PerceptionEditorial.* JAMA Neurology, 2016. **73**(6): p. 628-630.

39. Sowell, E.R., et al., *In vivo evidence for post-adolescent brain maturation in frontal and striatal regions.* Nature Neuroscience, 1999. **2**(10): p. 859-861.