Cortical Mapping of Nociception: An Electroencephalographic Approach

By
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Vita

Joshua Levitt was born in Brooklyn, New York on October 1st, 1991. He attended Stuyvesant High School in Manhattan, New York, and graduated in 2009. After high school, he began his Bachelor of Science degree at Bates College in Lewiston, Maine, which he finished in 2013 with a major in biology and concentrations in public health and the human body, and completed his senior project on the archeological importance of the soft-shell clam, *Mya arenaria*. After college, he began working at Montefiore Medical Center in the Bronx, New York, where he assisted with the conduct of clinical trials in the department of obstetrics, gynecology, and women's health. In 2015, he began work on his Master's of Science in Biomedical Engineering at Brown University in Providence, Rhode Island, where he has studied the electrophysiology of pain in the laboratory of Dr. Carl Saab. He plans to graduate in the Spring of 2017.

Acknowledgments

There are a number of friends, family members, colleagues and mentors without whom this thesis would not have been possible. My parents, Richard and Beverly, my sisters, Kate, Talia, and Ariana, have been bottomless sources of love and support when I needed it, and of distraction when I needed that as well.

The current and former members of the Saab laboratory, including Dr. Brian LeBlanc, Dr. Suguru Koyama, Kelsey Smith, Catherine Roach, and Jimmy Xia, have been essential to every step of my time at Brown, and contributed both labor and expertise to my thesis project with incredible generosity. I am also very grateful to June Choo, who helped get this project off the ground, and whose drive and effort helped make it a success.

Dr. Carl Saab has been an excellent mentor to me, and I have been a very lucky beneficiary of his time and knowledge, and of the effort he puts in to make his laboratory a community I'm proud to be a part of.

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1.0 Abstract

Chronic pain is a common medical condition across the globe, which impedes the daily lives of sufferers, and about which we have only a limited understanding of the neurologic basis of. We also lack truly objective ways to measure pain, and most interested studies rely on questionnaires, which may be inaccurate, confounded by other aspects of a patient's experience, and in some cases, may be difficult to use. In order to develop a biomarker for pain, and to test evidence from rodents that theta oscillations caused by thalamocortical dysrhythmia are associated with nociception, we asked 25 healthy volunteers to participate in a cold pressor test during an electroencephalographic recording. We found increased frontal theta synchrony (Z scores from 3.13-3.60) when comparing a lower pain condition to a higher pain condition, and decreased broad-spectrum power at posterior electrodes. We also analyzed coherence between several pairs of electrodes, and found a number of significant changes. These findings were partially supported by previous research, but the diversity of results from the existing literature makes it difficult to discern a single consensus trend. Based on the findings presented here, the Saab laboratory has begun a number of trials to expand upon and verify these findings in clinical chronic pain patients.

2.0 Background

Chronic pain is a very common medical condition, which impedes the daily lives of sufferers. Despite this, existing treatments for chronic pain, such as opioid prescription, remain unsatisfactory for a variety of reasons. They are not always effective, especially in the case of neuropathic pain, they have undesirable side effects, and they nurture dependence in some cases [1–3]. There are a number of other treatments for chronic pain that are currently in use, such as electrical stimulation of the spine and physical therapy, but these are not always effective, and bear some risks of their own, such as those associated with surgical implantation [4, 5]. In order to continue improving treatment, it is necessary that we continue to improve our understanding of nociception, and our methods for studying it.

The modern understanding of pain is often loosely described by the term "pain matrix," which refers to an interconnected group of structures within the brain that have been identified as involved in nociception. This term has been in use since at least the 1990s, and has been in a constant state of revision as our understanding of sensory perception and nociception have evolved [6]. The list of possibly related areas is diverse, and has included the primary and secondary somatosensory cortex, the anterior cingulate cortex, various parts of the thalamus, and the cerebellum, to name just a few [7–10]. In other words, this matrix hypothetically includes broad swaths of our central nervous tissue, including parts of the fore-, mid-, and hindbrain. Many of the implicated

structures are thought to be involved in other tasks as well, such as non-painful sensation.

One of the problems in trying to clearly outline which brain structures are involved in nociception and how is that everyone's experience with pain is different, and inherently subjective [11] . There are several types that are experientially and perhaps neurologically distinct, including tonic, chronic, acute, and neuropathic pain. In each case, the experience may be colored by the details of day-to-day life, which can cause mood changes such as frustration, exhaustion, or nausea in varying degrees. Furthermore, in studies of pain, especially in humans, there is no reliable objective measure of pain. Studies typically rely on some variation of the familiar Visual Analog Scale (VAS; Figure 1), or will use imperfect proxies, such as disability or impairment [12]. In addition to the fact that these methods do not perfectly measure pain, and may be altered by subjective factors such as pain tolerance, they may also not be useful in patients who have a limited capacity to respond to a questionnaire [13]. It is therefore desirable to find an alternative measure of pain. Ideally, this measure should be non-invasive, cheap and easy to use, objective, and reliable across patients.

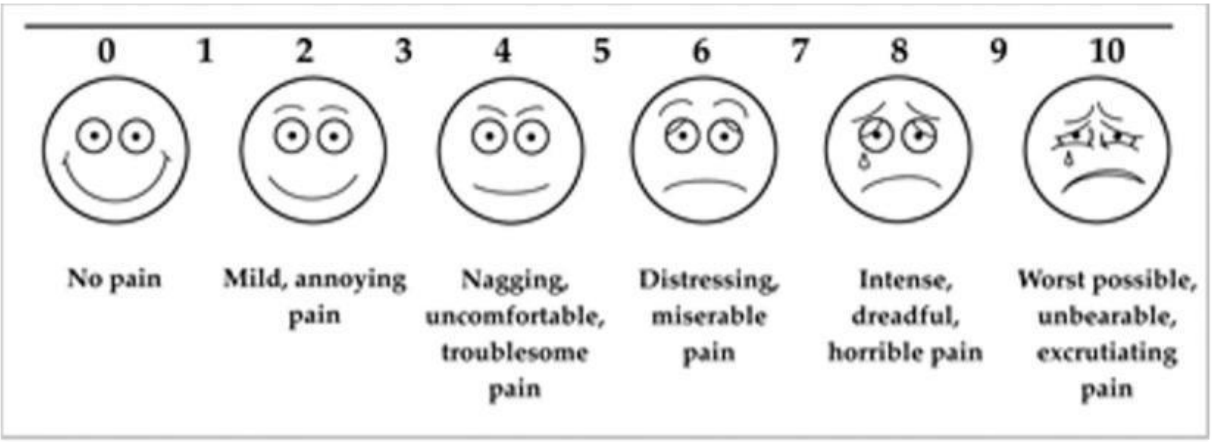

Figure 1. The Visual Analog Scale.

Electroencephalography (EEG) is one tool that may be used toward this end, but we first need to develop a better understanding of what the most reliable markers of pain in an EEG recording are. EEG transcranially measures electrical activity created by large ensembles of neurons behaving in rough synchrony. This creates rhythmic voltage oscillations colloquially called 'brain waves,' but can be more formally called 'cortical synchrony.' These oscillations are often described as falling into one of several 'bands,' often given the names delta, theta, alpha, beta and gamma, depending on their frequency. These bands have been associated with physiological states or processes [14][15]. The advent of computers has made it efficient to apply to EEG signals various mathematical techniques, collectively called quantitative EEG (qEEG)[16]. QEEG allows researchers to identify subtle changes in EEG patterns in way that can be statistically replicated.

There have been numerous efforts to describe the patterns of human EEG frequency domain changes associated with nociception, but the results are somewhat inconsistent, and a single unified picture has not presented itself [17-29]. I will discuss in more detail the findings of some these experiments below, but for now I will simply speculate as to the reasons behind this lack of concordance. It is perhaps because 'pain'

is such a broad category, and studies may use different models of pain in healthy volunteers, or may use chronic pain patients. There are amongst these studies also a number of differences in experimental design, such as how long a stimulus is applied for, what the control group is, which statistical and analytical methods are used, to name just a few parameters. I cannot say that this study solves, for once and always, all of these problems. However, I do hope that this thesis can establish its findings on a firm grounding as a direct extension to previous animal research, and that the choices made regarding experimental protocol were sound and well considered.

The Saab laboratory at Brown University has, for the past several years, explored the electrophysiology of pain in mice and rats. They have established a relationship between a rat chronic pain model, and elevation of the theta cortical rhythm using 3-channel electroencephalography (EEG), especially in frontal regions of the brain [30]. The Saab laboratory has primarily used two models of pain in rodents recently. One, called chronic constriction injury (CCI), is a chronic pain model, and involves tying a loose suture around the exposed sciatic nerve, causing abrasion and irritation in the affected limb over time. The other model, an acute pain model, involves injection of capsaicin into the hind limb, causing pain that dissipates over the course of hours. In a 2014 paper, LeBlanc et al. induced both pain models in rats, and observed an increase in theta power, as measured by both local field potential (LFP) and electrocorticography (ECoG), as compared with sham treatment and pretreatment recordings. Notably, this was observed with both models at an electrode placed above the primary somatosensory cortex (S1), but measurements taken via LFP from the ventral posterolateral thalamus (VPL), showed similar results only during capsaicin trials, not CCI, which suggest the importance of model choice on experimental outcomes. In addition to the spectral

analysis, LeBlanc et al. also analyzed coherence between the LFP and ECoG, and found that broad-spectrum (3-30Hz) coherence following administration of CCI/capsaicin was decreased relative to pre-intervention baseline. Both the coherence and amplitude findings of this study were reversed over time, as the animal's behavior returned to normal. In a subsequent study using these models LeBlanc et al. implanted 3 electrodes in the rodent's cranium [31]. They found increased coherence between electrodes only in the chronic/neuropathic CCI model, but with capsaicin. They also found broad-spectrum increases in power in each pain model. These results led to continuing research into the connection between theta power and pain in rats from the Saab laboratory, and more generally a search for objective biomarkers of pain.

The goal of the research presented below, then, is to serve as a beachhead for determining if the conclusions reached in rodents can be applied to humans as well. We predicted that frontal theta power would be increased with pain, as it was in rodents. We also expected that coherence will be decreased in this condition. These predictions, as will be discussed in detail below, were partially borne out by our findings, but the whole picture turned out somewhat more complex. We did identify a frontal increase in theta power, along with a number of other changes in power at various electrodes in several frequency bands. Coherence was also modulated by pain, but not exactly in the ways we anticipated. What follows is a description of this experiment, and the ensuing results.

3.0 Materials

3.1 Regulatory approval

This study was conducted under the supervision of, and with approval from, the Rhode Island Hospital Institutional Review Board (Committee# 2063-15).

3.2 Experimental Procedure

After having read and signed the informed consent form, participants were asked to complete a demographics questionnaire, and were then fitted with the StatNet EEG cap. Once the Statnet was adjusted such that the channel resistances were within acceptable limits, researchers explained the full protocol to the participant. After the recording began, the participant was to sit, facing a blank wall, with a covered bucket of ice or water adjacent on their right, their hands resting on their knees, and their eyes open, for 30 seconds. They were then prompted to close their eyes for 60 seconds, and open them again for 30 seconds. At this point, they were told to submerge their right hand, up to the wrist, in the bucket of either ice or room temperature water. Up to this point, the bucket had been covered with a cloth to conceal its contents (in order to blind the participant to randomization). After the participant's hand had been submerged for 5 and 15 seconds, the were asked to indicate their pain score on a scale of 0-5, using the fingers of their left hand. After 20 seconds of submersion, they were prompted to return to the starting position, and asked again to report their pain score as described above.

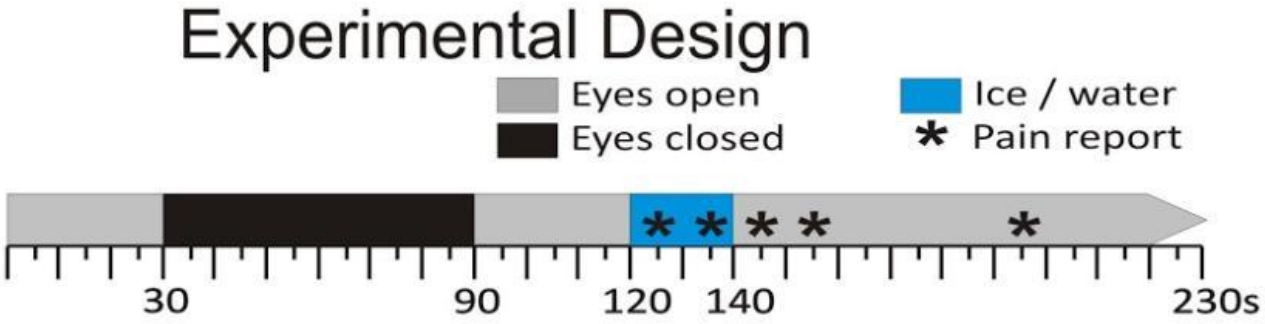

Figure 2. Time course of EEG recordings

They reported their pain score again 10 and 60 seconds later. 90 seconds after returning to the starting position, the recording was ended. The total recording length was 230 seconds (Figure 2). After removing the StatNet cap, the participant was asked to complete a qualitative posttest questionnaire. Ice water is here defined as a mixture of ice and water with a temperature no greater than 4°C.

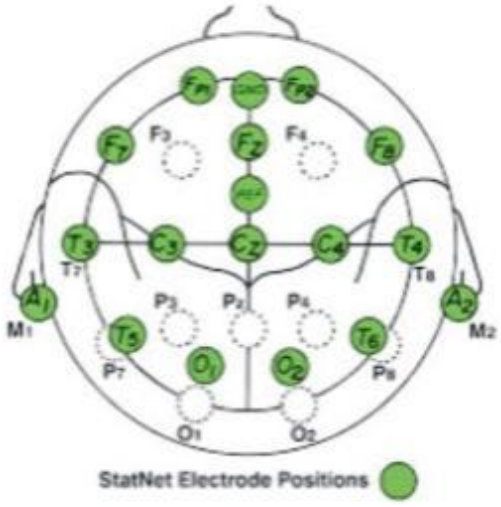

Figure 3. StatNet EEG Montage, Relative to Standard EEG

3.3 EEG Data Collection

We chose to use the MicroEEG and StatNet system, a portable FDA approved EEG system (BioSignal Group, Acton, MA)[32] for all of our recordings. We chose MicroEEG/StatNet because it can be applied without the assistance of a trained EEG technician, which would otherwise have been an obstacle to the conduct of the study, and because it is quicker to fit and remove, which we felt would minimize the inconvenience to participants. It is a 16-electrode system, which is fewer electrodes than many other clinical EEG montages, which often have 19-22 electrodes, although some have many more (figure 3). Given that our prior EEG research in rodents used 3 channels at most, we felt that a 16 channel EEG would be sufficient for the purposes of testing our hypotheses. MicroEEG samples at 250 Hz, which technically allows the

measurement of oscillations up to 125 Hz, which includes the delta, theta, alpha, beta and gamma frequency bands. However, studies of gamma often have more tightly controlled experimental conditions, including the use of a faraday cage or shielded room, and higher sample rates, which helps reduce in-band noise power. This is important, as gamma oscillations have relatively lower power, and therefore a worse signal-noise ratio. For these reason, and because many of the previous studies from the Saab Lab did not analyze gamma oscillations, we chose to limit our analysis to the range 3-30Hz, which includes the bands defined as follows: theta (4-8 Hz), alpha (8-12 Hz), low beta (13-21 Hz) and high beta (21-30 Hz).

3.4 EEG Preprocessing

EEG artifacts from blinking and movement were identified visually. 5-10 second segments of artifact-free recording were selected from each of the following time points: eyes closed (EC), eye open (EO), the first 10 seconds of hand submersion (HS1) and the second 10 seconds of hand submersion (HS2). When at least 5 contiguous artifact-free seconds were not available, 5 non-contiguous seconds were selected and concatenated together to form a single signal. Power spectral densities (PSDs) were calculated for each segment using Spike2 (Cambridge Electronic Design, UK).

PSD amplitude is affected by both neurological activity, and the quality of contact made by the EEG electrodes to the scalp, as well as the thickness of an individual's skull, amongst other factors which could vary both between individuals, and between electrodes in the same individual. In order to control for this variance, it is necessary to 'normalize' the PSDs to make it possible to make comparison across groups of individuals or electrodes. To this end, PSDs were normalized by dividing the power

values within each frequency bin by the total power from 3-30Hz. This results in values that sum to 1.00, and that can be interpreted as representing the percentage of total power contained in each bin. By normalizing in this way, we preserve the 'shape' of PSDs curves (the relative contribution of each bin/band to the spectrum), but we lose information about changes in total power, since the total normalized power spectra necessarily sum to the same thing for any normalized signal in this paradigm. This is an acceptable cost, as the non-neurological factors listed above make changes in total power unreliable to begin with.

Coherence, an indirect measure of functional connectivity, was calculated in Spike2 using the '*Coher*' script, between the following pairs of channels: Fz-C3, Fz-C4, Fz-O1, and C3-C4, within the previously described bands. Spectral coherence, *C,* is calculated for a given frequency f between two signals x and y by the following formula:

$$C_{xy}(f) = \frac{|G_{xy}(f)|^2}{G_{xx}(f)G_{yy}(f)}$$

where G_{xy} is the cross-spectral density between x and y, G_{xx} is the power spectral density of x and G_{yy} is the spectral density of y.

3.5 Statistical Analysis

Paired Student's *t*-tests were used to compare between time points within treatments. The significance

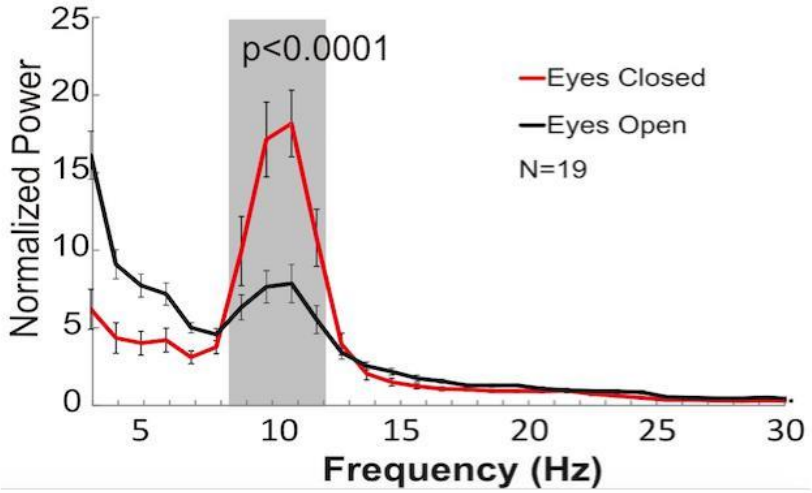

Figure 4. Alpha power at O1 is increased when subject close their eyes. Error bars indicate +/- SEM.

threshold for these tests was $P<0.05$. These were calculated using Microsoft Excel. Z-scores were also calculated to evaluate significance of changes in normalized power between HS1 and HS2, using the following formula:

$$Z_f = \frac{X_f - \mu}{\sigma_f / \sqrt{n}}$$

Where Z_f is the Z-score for a given frequency *f*, X_f is the mean difference in normalized power between HS2 and HS1 for frequency *f*, μ is the null hypothesis, which, in this case is 0, representing 0 change in normalized power, σ_f is the standard deviation in difference of normalized power for frequency *f*, and *n* is the number of subjects included in the sample. The significance threshold for Z-scores was chosen to be $|Z_f| > 2.93$, which corresponds to a $P<0.0017$, chosen by dividing 0.05 by the number of frequency bins, 29. This was also calculated using Microsoft Excel. Heat maps for figures were created in EEGLab, a toolbox for Matlab (Mathworks, MA, USA), using the '*Plot channel measures'* tool.

4.0 Results

We tested channel O1 for an increase in normalized alpha power from EC to EO. A paired *t*-test showed a significant increase (figure 4, n=19, $P<0.0001$).

We next compared the pain scores collected during HS1 and HS2 among subjects in the ice group. Pain score was significantly increased during HS2 (Figure 5, n=12,

P=0.0015, mean HS1 = 0.78, mean HS2 = 1.53). Qualitative surveys collected after the completion of the recordings similarly indicated that the ice stimulus was most painful toward the end of hand submersion. Subjects in the room temperature group reported pain scores of 0. Given this finding, we decided to investigate the differences in power and coherence between these time points.

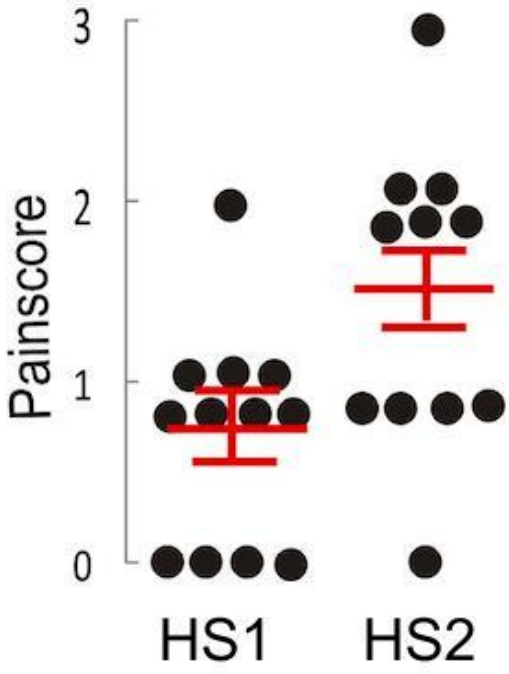

Figure 5. Pain score distribution during HS1 and HS2. Red lines indicate mean +/- SEM.

Using Z-scores and heat maps, we identified several changes in normalized power spectra. PSDs were significantly increased at the Fz electrode from HS1 to HS2, within the band 6-7 Hz (6 Hz: Z=3.13 *P*=0.0009; 7 Hz: Z = 3.60, *P*=0.0002 n=8). They were also significantly decreased at the O1 electrode across a broad frequency range (see fig 6 for details). These tests include only subjects in the ice group who reported an increase in pain from HS1 to HS2. One subject was excluded from Z-scoring for the Fz electrode, and one was excluded from the O1 electrode (power change > 2 SD beyond mean). These changes were not significant in the room temperature group (n=10) or in the subjects in the ice group who did not report an increase in pain (n=3).

Differences in coherence from HS1 to HS2 were also evaluated using *t*-tests, between the pairs of electrodes mentioned above, within the previously described

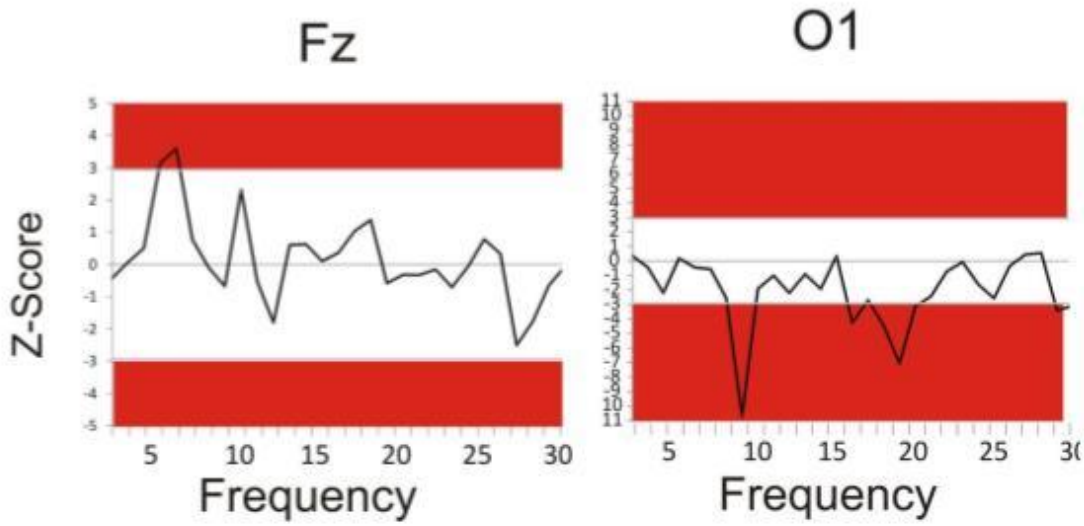

Figure 6. Z-scores of changes in PSD amplitude between HS1 and HS2 at electrodes Fz and O1 amongst ice subjects.

frequency bands. Significant changes in coherence ar e detailed in figure 7 and table 1. As above, these tests include only subjects in the ice group who reported an increase in pain from HS1 to HS2 (n=8).

5.0 Discussion

The significant increase in alpha power in the EC condition compared with EO is in accordance with our expectations, and suggests that the electrode montage and quality of the recordings were appropriate to continue with our analysis. The alpha rhythm associated with the closing of the eyes was the first EEG oscillation discovered by Hans Berger when he began experimenting with EEG, named on account of its prominence, and it has since become a staple of human EEG studies [33]. Had this

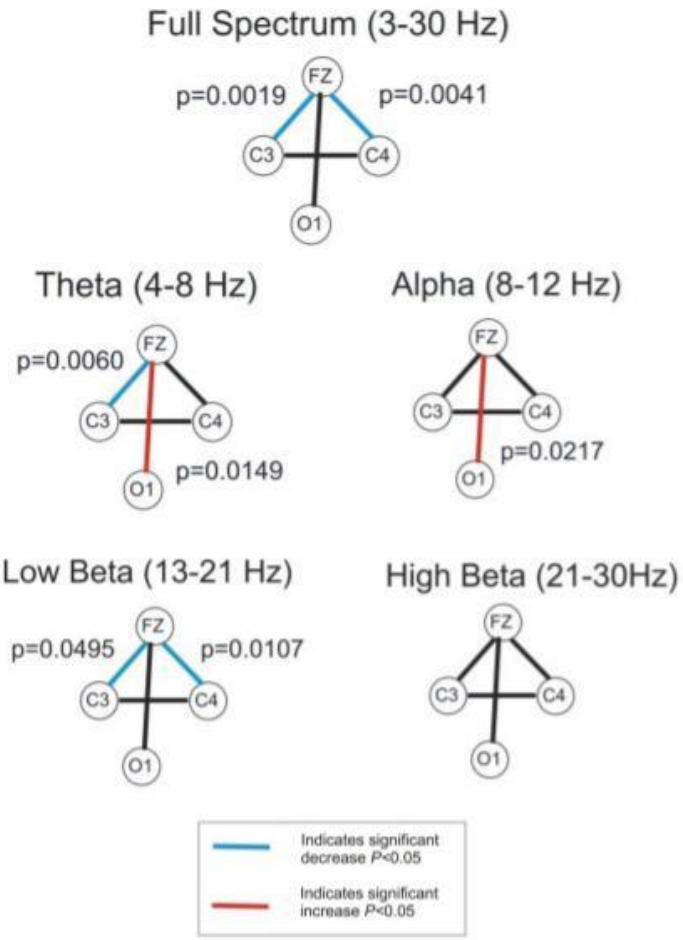

Figure 7. Coherence changes between HS1 and HS2, in electrodes Fz, C3, C4, and 01.

feature been absent, it would have called into question the reliability of our recordings. Its presence is therefore a form of data verification (figure 8).

We chose to make our primary comparison between the HS1 and HS2 conditions within the ice group (and within the majority of these subjects who reported an increase in pain score from HS1 to HS2), and to use the same comparison in the room temperature water group as a control, rather than compare directly between the ice and room temperature groups (figure 9). It is our assessment that by comparing a high pain condition and a low pain condition, rather than comparing two groups that received somewhat different stimuli, we are better able to isolate the variable we are most interested in: tonic pain. Pain level and time of submersion are the primary differences between the HS1 and HS2 conditions, and the room temperature group allows us to

Frequency range (Hz)	Electrodes	Early Time Interval	Late Time Interval	*P* value
3-30	Fz-C3	0.30 +/- 0.01	0.26 +/- 0.01	0.0019
	Fz-C4	0.31 +/- 0.01	0.27 +/- 0.01	0.0041
4-8 (Theta)	Fz-C3	0.33 +/- 0.02	0.24 +/- 0.02	0.0060
	Fz-01	0.23 +/- 0.02	0.30 +/- 0.03	0.0149
8-12 (Alpha)	Fz-01	0.20 +/- 0.02	0.28 +/- 0.03	0.0217
13-21 (Low Beta)	Fz-C3	0.29 +/- 0.02	0.25 +/- 0.02	0.0495
	Fz-C4	0.31 +/- 0.02	0.26 +/- 0.02	0.0107

Table 1. Coherence Changes between HS1 and HS2 amongst ice subjects.

control for time of submersion. It can therefore be concluded that the changes observed in EEG power and coherence, including the increase in theta power at the Fz electrode, are germane only to some element of tonic pain perception, and not to some other aspect of the participant's experience.

The increase in power from 6-7Hz at the Fz electrode was not surprising, as it is consistent with our hypothesis, and with animal data from capsaicin and CCI experiments, as mentioned previously. One possible explanation that has been suggested for why theta would be associated with nociception is thalamocortical dysrhythmia, a disruption in communication between the thalamus and the cortex. This has been measured to cause an increase in theta power using magnetoencephalography [34, 35]. This idea of thalamocortical dysrhythmia-induced theta has, in part, motivated the investigations into the relationship between this frequency band and nociception by the Saab laboratory recently.

However, the power decrease at O1 and other posterior electrodes across several bands (figure 9) was somewhat less predictable. The region of the cortex closest to O1 is the occipital lobe, which is mostly associated with vision, and is not generally mentioned as part of the pain matrix. I can only speculate as to the genesis of this result, but one possibility is that these electrodes were measuring synchrony form the cerebellum,

which is nearby and is potentially involved in nociception[36]. EEG does not provide excellent spatial resolution, and it is possible for an electrode to relay signals from parts of the cortex other than those which are closest.

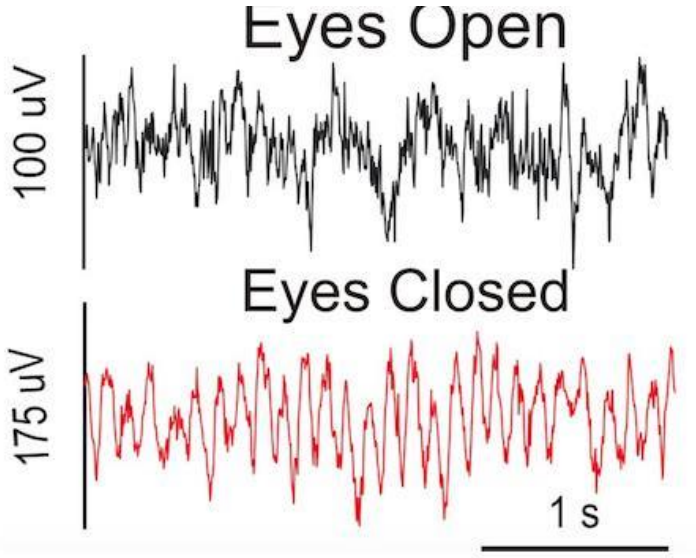

Figure 8. An example of alpha synchrony when subjects closed their eyes.

The changes in coherence are difficult to compare to previous findings in animals from the Saab lab. In a recent rodent, LeBlanc et al. observed increases in broad-spectrum coherence only 14 days after CCI, essentially a chronic/neuropathic pain model, but not during acute or inflammatory pain, or during early stage CCI [31]. This would suggest that we would not see many coherence changes in the human cold pressor model, but this turned out not to be the case. However, the results from the rodent study did not consider coherence by band, and only between 3 electrodes, only one pairing of which (PFC-S1; roughly analogous to Fz-C3 in this study) was discussed in depth. So it is difficult to say on this basis alone that these sets of results are incompatible with one another, but neither can it be said that they are in direct accord.

As discussed previously, there have been a number of related experiments published in the past, including several that have us ed cold water to stimulate tonic pain. As their results are fairly diverse and highly relevant to the results presented above, they are worthy of discussion here in some detail.

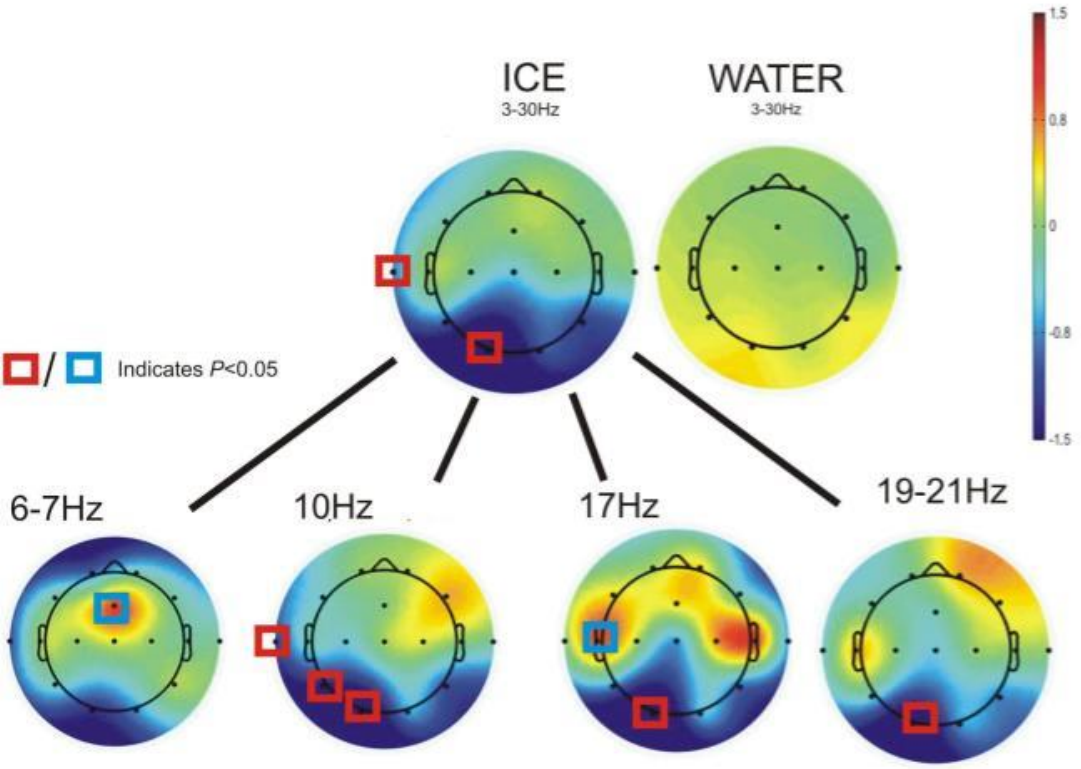

Figure 9. Select heat maps of changes in power from HS1 to HS2 in ice and water subjects.

Among the earliest similar experiment using EEG and the cold pressor test was that of Ferracuti et al. 1994 [24]. In this study, each subject submerged each hand in turn first in ice water for 2 minutes, and then, in a second recording, in warm water. VAS pain scores were collected after recordings. During submersion in ice water, they noted decreased frontal alpha during the first minute of submersion, and widespread increased delta synchrony. They also note, but do not discuss or describe, an increase in theta power. It must be noted that these comparisons are between the ice condition and a resting baseline condition, rather than between the first and second minute of submersion, or between the ice and warm water condition. Although they seem to have collected and organized their data in a manner that would have made these comparisons

possible, they are never presented as such. This is unfortunate, as a baseline condition isn't a true control for the ice condition. As the authors note, at least some of the increase in alpha synchrony may be attributed to "a generic arrest reaction or arousal," rather than to painful sensation per se. Another problem with this design is that pain scores were not collected contemporaneously with the experience of that pain, making them arguably even less dependable. A very similar abstract from Chen and Rappelsberger from the same year reports comparable findings, although also seems to have had similar problems [21].

In a subsequent study by Chen and Rappelsberger, they did actually make comparisons between two different water-submersion conditions [37]. They asked subjects to participate in three experimental conditions in succession: resting, 15°C water submersion, and ice water submersion. When they compared the PSDs from the ice condition to the 15°C condition, they found increased delta (frontal, central and parietal), and increased theta (T6 and O2). They also studied coherence, and found decreased beta coherence, and increased theta and delta coherence, between various electrodes. Although we did not examine the delta frequency band, the results of this study are not dissimilar from our own. We also observed increased theta in our more painful condition (albeit in a different area of the brain), and changes in coherence somewhat similar to our own. They did not, however, compare different timepoints within painful stimulation. In addition, their use of a 15°C water condition as a control was justified mainly by their conjecture that water of that temperature is cold but not painfully so, which is highly subjective.

In a study that did use multiple timepoints of painful stimulation (3 minutes of cold water submersion broken into 12 segments), Chang et al. did not identify dynamic

changes in global theta power [18]. This study did not however dynamically test PSD band power by electrode; they only examined global EEG power in this way. This approach could have the effect of diluting local changes in power past the point of detection, which the authors acknowledge. They did perform a by-electrode power comparison, but only between baseline, stimulus and post-stimulus conditions, not between the timepoints within the stimulus. In this comparison, they did find increased frontal theta power, much as we did.

Considering this sampling of the literature, along with additional similar studies, some of which used the cold pressor test, and others that used different models, the spatial and frequency domain regions associated with nociception are nearly as diverse as the regions that have been investigated for such an association. This includes increased gamma in the primary somatosensory cortex [26], increased delta [27], increased or decreased theta, at various parts of the EEG map, along with various theta coherence changes [37] [27], lower beta intensity and higher alpha [38], or decreased alpha power [39], to name just some of the effects previously identified. This is all to note that, despite the wealth of previous literature, there is no clear consensus regarding a cortical map of nociception.

With all of that in mind, we believe that this experiment offers certain advantages over those that preceded it. We included the following components together, where no other study to our knowledge did so: analysis of coherence, use of multiple time points to make by-electrode PSD comparisons, and the use of a more appropriate control condition (HS1) to draw our conclusions. It was guided by an extensive background of research in both animals and human, and its findings are consistent both with that background, and in a broad sense, with previous literature.

6.0 Ongoing and Future Research

Having conducted the experiment described above, the Saab laboratory has begun (or begun collaboration on) several projects to expand upon our findings, with the goal of recruiting subjects who have clinical pain, instead of healthy volunteers. The cold pressor test employed in this experiment is merely a model for studying pain; the experience of most pain patients is more complex, and involves qualitative experiences that cannot be completely replicated in the context of a controlled and blinded study. For this reason, efforts must be made to collect data from real-world pain cases.

One such project involves asking people who have chronic back pain to participate in EEG recordings over the course of their treatment at Rhode Island Hospital. The goal is to collect multiple recordings from each subject, spaced over weeks or months, so we can look for patterns in their EEG that co-vary with the fluctuation in their pain, and their responses to a panel of questionnaires. This would help us determine the clinical relevance of previous research, with our hypothesis being that theta power will be correlated with pain, and that we will see similar trends at other electrodes, notably O1, and similar patterns of coherence that we have observed here. Currently, this project has been approved by the RIH IRB, although recruitment has not yet begun.

There have, of course been a number of previous studies using EEG in the context of chronic pain. However, these studies are generally cross-sectional rather than

longitudinal. In meta-analysis of such studies by Pinheiro et al., the authors were able to identify only one longitudinal study, and it was specifically focused on photic driving in migraine patients, which would not be a focus of this study [40][41]. This meta-analysis indicated that chronic pain patients have elevated theta and alpha power at rest, and suggests that these bands could potentially serve as a biomarker for pain. This at least partially supports the results of our previous research, and the hypothesis for this upcoming project.

We have also recently begun a collaboration with Dr. Julie Roth, of the RIH department of neurology. In this study, we have begun collecting EEG recordings from patients who are admitted to RIH seeking treatment for a two-day ongoing migraine. We conduct regular recordings and questionnaires during their outpatient treatment at RIH, and ask them to return to the clinic for a follow up recording when they are not experiencing a migraine. This will allow us to learn about the electrophysiology of migraines at their peak and as they subside. By comparing baseline data to resting data we have already collected from non-migraine sufferers, we can also learn if there are characteristic differences even when not actively experiencing a migraine.

In addition to new projects, there is also a certain amount of data from this project that remains to be considered, and approaches to quantitative EEG not yet undertaken. Notably, there were three pain scores collected after hand submersion, as participants were recovering from the tonic pain. We have not considered data from these timepoints, except to note that pain scores decreased over time. We also have limited our analysis to four frequency bands from 3-30Hz, which excludes both gamma and delta oscillations. We chose to exclude these frequencies both due to concerns about the limited sampling frequency of our recordings, and to better match previously

published animal data. Nonetheless, the measurements of oscillations in these ranges are contained in our recordings and could potentially be the subject of further consideration. This may be an interesting line of inquiry, as both gamma and delta amplitude have been linked to nociception [42][27].

We also have not considered approaches to EEG analysis other than PSDs and coherence. One such approach is phase-amplitude coupling. There is some evidence in both animals and humans that this technique could be relevant to the study of nociception, more specifically between theta and gamma, and alpha and gamma [43][44]. It would be possible to conduct this sort of analysis on the data we have already collected, and the Saab lab has begun using this technique in some of our ongoing animal experiments. Another such technique that could be applied to our data is machine learning. This is a broad category of algorithms that can be used to complete classification tasks, and are therefore relevant to the search for reliable EEG pain biomarkers. Indeed, efforts to this effect have already begun, and the results indicate that theta power may be an important piece of an EEG pain classifier [45]. I have begun experimenting with these techniques on our dataset, although not with enough rigor to report any findings.

7.0 Conclusions

This thesis has sought to elucidate qEEG patterns of cortical synchrony and coherence, towards the goal of identifying a signature of tonic pain that could be used as a biomarker for nociception. It also attempted to convey both the importance and the

challenges inherent to this goal. The results from the EEG experiment partially supported the hypothesis that pain is associated with increased frontal theta synchrony. There were also some surprising results, for example the decrease in posterior power at various frequencies, and the changes in coherence. These results fit into a larger body of related experiments which do not tell a single consistent story.

Following this experiment, the Saab lab has begun a series of efforts to further define the hypothesis presented here, and to confirm or refute its applicability in humans, as it has in rodents for the past several years. This study is very much a starting point for a longer line of inquiry, and there remains a great deal of research and experimentation to be done.

8.0 References

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