Exploration of the Pathophysiology of Chronic Pain Using Quantitative EEG Source Localization

Leslie S. Prichep¹,², Jaini Shah³, Henry Merkin⁴, and Emile M. Hiesiger⁵

Abstract
Chronic pain affects more than 35% of the US adult population representing a major public health imperative. Currently, there are no objective means for identifying the presence of pain, nor for quantifying pain severity. Through a better understanding of the pathophysiology of pain, objective indicators of pain might be forthcoming. Brain mechanisms mediating the painful state were imaged in this study, using source localization of the EEG. In a population of 77 chronic pain patients, significant overactivation of the “Pain Matrix” or pain network, was found in brain regions including, the anterior cingulate, anterior and posterior insula, parietal lobe, thalamus, SI, and dorsolateral prefrontal cortex (DLPFC), consistent with those reported with conventional functional imaging, and extended to include the mid and posterior cingulate, suggesting that the increased temporal resolution of electrophysiological measures may allow a more precise identification of the pain network. Significant differences between those who self-report high and low pain were reported for some of the regions of interest (ROIs), maximally on left hemisphere in the DLPFC, suggesting encoding of pain intensity occurs in a subset of pain network ROIs. Furthermore, a preliminary multivariate logistic regression analysis was used to select quantitative-EEG features which demonstrated a highly significant predictive relationship of self-reported pain scores. Findings support the potential to derive a quantitative measure of the severity of pain using information extracted from a multivariate descriptor of the abnormal overactivation. Furthermore, the frequency specific (theta/low alpha band) overactivation in the regions reported, while not providing direct evidence, are consistent with a model of thalamocortical dysrhythmia as the potential mechanism of the neuropathic painful condition.

Keywords
EEG, chronic neuropathic pain, low-resolution electromagnetic tomographic analysis (LORETA), brain imaging, thalamocortical dysrhythmia (TCD), Pain Matrix, pain network

Received September 17, 2015; revised August 31, 2017; accepted September 4, 2017.

Introduction
Chronic pain affects more than 35% of the US adult population and as such represents a major public health imperative. Currently, there is no objectively verifiable, clinically useful means of identifying the presence of pain or quantifying the severity of pain. The standard of care relies on subjective ratings, using a visual analog scale (VAS), frequently resulting in suboptimal or excessive treatment and inappropriate distribution of resources. The ability to quantify pain objectively also has therapeutic implications for patients who are obtunded, unconscious, or very young, in whom current subjective methods cannot be used.

Following the seminal publication by Melzack and Wall,¹ functional neuroimaging methods have been used to study the neuronal basis of pain and pain perception, and have demonstrated that painful stimulation activates extensive areas of cortical and subcortical brain regions²-⁵ which they referred to as the “Pain Matrix.” Neuroimaging studies further suggest the specific role of the anterior cingulate (ACC) and/or the insula in intensity encoding of pain.⁶-⁸ Vogt⁹ describes a dynamic role played by the cingulate cortex in pain perception with different functions of the anterior, mid, and posterior regions. Using the significantly increased temporal resolution of electromagnetic method, Bromm¹⁰ compared findings with that of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), and demonstrated that the more posterior parts of the cingulate play an important role in the painful state, occurring prior to projection to the ACC, suggesting that the increased temporal resolution of electromagnetic measures may allow a more precise identification of the pain network. Significant differences between those who self-report high and low pain were reported for some of the regions of interest (ROIs), maximally on left hemisphere in the DLPFC, suggesting encoding of pain intensity occurs in a subset of pain network ROIs. Furthermore, a preliminary multivariate logistic regression analysis was used to select quantitative-EEG features which demonstrated a highly significant predictive relationship of self-reported pain scores. Findings support the potential to derive a quantitative measure of the severity of pain using information extracted from a multivariate descriptor of the abnormal overactivation. Furthermore, the frequency specific (theta/low alpha band) overactivation in the regions reported, while not providing direct evidence, are consistent with a model of thalamocortical dysrhythmia as the potential mechanism of the neuropathic painful condition.

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time resolution allows a more precise identification of the pain pathway.

A number of pain studies using electromagnetic recordings, report oscillatory shifts in the frequency spectrum in the presence of pain, especially in theta and beta frequency bands. Using source localization of scalp recorded EEG data (low-resolution electromagnetic tomographic analysis [LORETA]) in patients with chronic neuropathic pain, sources consistent with those sources identified using conventional neuroimaging methods were reported, including the insula, ACC, prefrontal, inferior posterior parietal, cortices. No differences in the frequency specific overactivation were found in those taking analgesic medications. Furthermore, patients reevaluated following successful central lateral nucleus thalamotomy (CLT), showed significant diminution in overactivation in the insular and cingulate cortices. Such results support a model suggesting the neuropathology in chronic pain is based on a thalamocortical dysrhythmia (TCD). In addition, recent studies have suggested the potential of EEG as a biomarker in the prediction of treatment response to opioids.

Using similar technology Prichep et al published a feasibility study demonstrating significant frequency specific (theta and beta EEG bands) overactivation of the "Pain Matrix" or pain network in chronic neuropathic pain patients. All patients were evaluated in a high pain state and then reevaluated following pain relieving procedure/treatment that resulted in a 50% or more decrease in their pain rating. Significant reduction in overactivation of brain regions of the pain network was found in the lower pain state with maximal change across patients occurring in the insula, thalamus, and cingulate.

This study was conducted in a large population of chronic pain patients, using quantitative EEG (QEEG) source localization to investigate the overactivation of the pain network, the relationship between the level of activation and the severity of self-rated pain, the evidence of TCD underlying the abnormalities observed, and the potential to use QEEG biomarkers as a predictor of the level of pain reported by the patient.

Methods

Subjects

Male and female chronic pain patients, aged 19 to 85 years, were candidates for study. This population was referred from pain clinics and pain practitioners in the New York City area. Written informed consent was obtained in all cases.

All patients had a history of symptoms for at least 3 months’ duration (chronic pain as defined by the International Association for the Study of Pain [IASP] criteria), and a diagnosis from the referring physician, which supported the symptoms. The etiology of the pain included most commonly radicular (neuropathic) pain, involving lumbar or cervical root compression from benign degenerative causes (as determined by MRI and/or computed tomography [CT] scans), and/or myofacial/musculoskeletal pain, as the predominant source of their pain. Patients were permitted to continue their analgesic medication during the study.

Patients were excluded who had prior histories of neurological or psychiatric illness, head injuries with loss of consciousness, or skull abnormalities. Patients on permanent disability and those with a spinal cord stimulator or other implantable devices which precluded MRIs, were also excluded.

Seventy-seven age- and gender-matched controls were selected from the Brain Research Laboratories NYU School of Medicine database and used as controls for this study. Subjects in this normative database did not have any evidence of clinically significant pain, depression, or anxiety.

EEG Data Acquisition

Twenty minutes of eyes closed resting EEG was recorded from 19 electrodes, placed using the international 10/20 electrode placement system, referenced to linked earlobes, using a Deymed Tru-Scan EEG system. A differential eye channel (diagonally above and below the eye orbit) was used for the detection of eye movement. All electrode impedances were less than 5000 ohm. Amplifiers had a bandpass from 0.5 to 70 Hz (3 dB points), with a 60 Hz notch filter. Data were sampled at a rate of 200 Hz with 12-bit resolution. Patients were monitored during EEG recording.

Pain Scales and Clinical Data

The following self-rating scales were used to provide data on severity of pain, pain related disability, presence of depression and anxiety, presence of neuropathic pain, and relevant medical history:

Brief Pain Inventory (BPI) and Follow-up Pain Ratings. The BPI was used to rate overall pain, current pain and maximal pain over varied time periods, to indicate regions of pain, and to rate the influence of pain on activities of daily life and quality of life.

Oswestry Disability Questionnaire. Oswestry Disability Questionnaire was used to quantify information about how the patient’s pain affects the ability to manage everyday life.

Neuropathic Pain Questionnaire. The validated Neuropathic Pain Questionnaire rates the presence or absence of neuropathic pain.

Beck Depression Inventory (BDI). Because of the high incidence of comorbid depression in pain patients we measured depression using the BDI. This is the standard scale for self-rating depression which is correlated with the presence of clinical depression.

Beck Anxiety Inventory (BAI). The BAI is the standard scale for self-rating anxiety which is correlated with the presence of clinical anxiety.

Clinical History and Treatment History. The referring physician filled out a form containing clinical history, pertinent radiological
and electro-diagnostic data and relevant clinical findings. Special attention was paid to details of the treatment history, the time since onset of painful symptoms and medication history, including the present.

**EEG Data Analysis and Source Localization**

The raw EEG data were visually edited off-line by trained EEG technologists, to identify and eliminate artifacts (eg, signals due to eye [electro-oculography, EOG] or muscle movement [electromyography, EMG]), augmented by a computerized artifact algorithm. The EEG recordings were not reviewed by a neurologist as the analyses to be performed were statistical in nature (taking advantage of advances in signal processing of the EEG signal) and performed only on the first 2 minutes of artifact-free EEG data. The use of 2 minutes as an adequate sample for the estimation of the stationary ground state of the brain electrical activity is the standard in the field of quantitative electrophysiology.26-28 Quantitative analyses included fast Fourier transform (FFT) to convert the data from the time to the frequency spectrum. Inter- and intrahemispheric relationships, frequency bands between 1.5 and 35 Hz (delta, 1.5-3.5 Hz; theta, 3.5-7.5 Hz; alpha, 7.5-12.5 Hz; beta, 12.5-25 Hz; and beta2/gamma1, 25-35Hz bands), and total power for the entire frequency spectrum. Inter- and intrahemispheric relationships, including power gradients and synchrony (coherence) were also computed for each electrode pairs. Following neurometric QEEG methodology,26,29,30 all quantitative features were log transformed to obtain an approximately Gaussian distribution and z-transformed relative to age expected normal values. The age-regression equations used in the z-transform of the data in this study were those published and validated by John and colleagues38 on an independent normal population. The z-score (standard score) was computed taking the difference between the individual patient value for the feature and the mean value for the feature in the normal population for that age and dividing by the standard deviation of the norm population for that age. Computation of source localization was conducted using sLORETA,31,32 a standardized, discrete, distributed, linear, minimum norm inverse solution for estimating the source generators of the scalp recorded EEG.

Similar to the wide band frequency spectra described above, this algorithm computes the very narrow band (VNB) frequency spectra or current density from each of the VNB from 0.5 to 50 Hz in 0.39-Hz steps, as well as conventional broad bands, delta (1.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz), beta (12.5-25 Hz), and beta2/gamma1 (25-35 Hz). sLORETA (LORETA freeware programs: http://www.uzh.ch/keyinst/NewLORETA/Software/Software.htm) requires no a priori assumptions of the number of active dipoles for each component and implements a three concentric shells spherical head model. Current density is computed as the linear, weighted sum of the scalp electrical potentials, squared for each voxel, yielding power of current density. Computations are made in a realistic head model,33 using the Montreal Neurological Institute (MNI) 152 template34 with the 3-dimensional solution space restricted to cortical gray matter, as determined by the probabilistic Talairach atlas.35 The scalp electrode positions are placed in spatial registration with the Montreal Probabilistic MRI Brain Atlas (PBA).36 Z-scores of deviations from expected normative values are computed for each voxel relative to age-expected normative values. The significance levels of the images take into consideration the large number of measurements made, using the correction introduced by Worsley and colleagues.37 The voxel norms are based on replicated, validated normative equations which describe the features of the broad band EEG resting state (“ground state” or default network) as a set of mathematical equations as a function of age30,38 and extended to the very narrow band spectra (done in collaboration with Pasqual-Marquis). Significant maxima in bands of interest were selected for source imaging and the inverse solution applied.

In this work, a modification of the sLORETA algorithm was used which extended the model to include regions to the level of the thalamus. The neocortical volume in the sLORETA mask is divided into 6896 voxels of dimension 5 mm3. In addition to individual voxels, a generalized solution is computed for the specific ROIs of interest, to include, ACC, mid-CC, as well as all ROIs for regions thought to be part of the pain network (eg, left and right insula, parietal lobule, DLPFC, SI, etc). Three-dimensional color-coded tomographic images were generated, with source generator distributions superimposed upon transaxial, coronal, and sagittal slices (4 mm3) of the PBA which correspond to the loci of the inverse solutions. These images are not used for analysis, but rather for purposes of visualizing the data for descriptive purposes only. Tables of z-values for each ROI are constructed to aid in interpretation of the images.

Within each patient the largest z-score peak in the VNB spectra was identified. A VNB maxima was found within the range 5.46 to 9.36 Hz (theta/low alpha) in the vast majority of the patients. Source images were derived for each patient at their maxima within this band. The averages shown in the figures represent the group average of the sLORETA for each individual. This approach takes individual differences into account by requiring that sources were derived at a peak frequency for each individual patient. In addition, this band covered the frequency specific range reported in the scientific literature for patients in the pain population.16-18 Group average images were computed using sources derived from the individual maxima. There are many approaches used in the literature to characterize each ROI, in this case we used the mean of the 10% largest voxel z-scores in each ROI. Using this method takes advantage of the strength of using the most significant value, while eliminating a single outlier value and is not subject to the regression to the mean which can cause blurring and underestimates of the effects.

Only the VNB source data are presented in this article as the focus of this study was to demonstrate the use of EEG source localization to reflect activation in the pain network of the brain described from conventional neuroimaging.
Statistical Analyses

Images were constructed for z-scores for all voxels and computed z-scores for ROIs in the pain population, and for ROIs in the high and low pain populations. The following statistical analyses were conducted to test for the significance of the differences in ROIs between groups, including:

1. T-tests for differences between pain patients and normal matched controls for ROIs of the pain network; corrected for multiple comparisons using permutation tests
2. T-tests for differences between groups for ROIs of the pain network comparing high and low pain populations; corrected for multiple comparisons using permutation tests
3. An exploratory stepwise logistic regression was conducted to identify those features of the QEEG which optimized the relationship between the prediction based on QEEG and self-rated pain score.

Results

Subjects

Seventy-seven chronic pain male and female patients, with a mean age of 49.3 years (SD = 15.8, range 19.5-81.7 years), 53% females, were included for study. The mean pain score reported on the 10-point VAS reported was 4.97 (SD = 2.32, range 1-10); which was consistent with the mean pain score obtained on the BPI of 5.07 (SD = 2.04, range 0.28-9.14). Seventy-nine percent of the patients were right handed, 16% left handed, and 5% ambidextrous. The mean number of years in pain was 8.4 years (SD = 8.3). The mean BDI score was 13.27 (SD = 7.25 [1-30]) and the mean BAI score was 12.29 (SD = 8.30 [0-35]). Using the Oswestry scale 33% of the patients reported moderate and 49% reported severe impairment in functions of daily life. There were 40 patients who reported moderate to severe pain (VAS ≥5) and 37 reported low pain scores (VAS <5). The high pain group had a mean age of 50.9 years (SD = 16.2), with a VAS score of 6.8 (SD = 1.48) and average years of pain of 7.63 years (SD = 8.09). The low pain group had a mean age of 47.5 years (SD = 15.4), with a VAS score of 2.97 (SD = 1.01) and average years of pain of 9.32 years (SD = 8.65). Normal controls were matched for age and gender, with a mean age of the normal controls was 50.25 (SD = 16.6, range 19.4-81.8).

The vast majority of the subjects suffered from neuropathic pain and or myofascial pain. The most common location of pain was back and or leg. The most common predominant sources of pain were root compression, herniations, osteophytes of foraminal stenosis. Forty-five percent of patients’ pain was reported to be bilateral, 26% left side, and 29% right side. All patients were on medication for their chronic pain, including oral and transcutaneous narcotics, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), nonsteroidals, and corticosteroids.

QEEG Source Localization

Figure 1 shows source localization images (sLORETA) for the group average z-scores for ROIs in the frequency band of interest, 5.46 to 9.36 Hz, for the pain population. As can be seen in this image, significant overactivation (orange/yellow) was present for many ROIs, with the most significant abnormalities seen in the parietal lobule (L > R, regardless of the side of pain), the insula, the mid cingulate, the dorsolateral prefrontal cortex, S1. Overactivation is also observed in the ACC, although less than that seen in the mid cingulate.

Figure 2 shows t-scores for the significance of the differences in the ROIs between the patients with pain and controls. Highly significant differences can be seen between these groups in the regions of the pain network, with the most significant differences being in the mid and posterior cingulate, the insula (L > R), the DLPFC (L > R), the parietal lobule (L > R), and S1.

Table 1 shows the significance of the differences between mean z-scores for each ROIs of the pain network, shown in Figure 1. Highly significant differences were found in the mid and anterior cingulate, anterior and posterior insula, S1, DLPFC, supplementary motor area, hippocampus, and thalamus.

When patients were divided into those who reported high pain scores (5-10) and compared with those reporting low pain scores (1-4), similar patterns of overactivation in the pain network were found, as can be seen in Figure 3, top and middle panels, although more significant overactivation was seen in the high pain group (top panel). The bottom panel of Figure 3 shows the significance of the differences in ROIs between the high and low pain populations. Highly significant differences were obtained between groups, with the most significant differences found on the left hemisphere in the parietal lobule, the insula (posterior > anterior), S1, and the DLPFC.

Table 2 shows the means and standard deviations for the high and low pain populations for each ROI, and the significance of the difference between the two subpopulations. The regions where significance was obtained included the DLPFC, parietal lobule, S1, anterior and posterior insula, (posterior > anterior) and the medial frontal gyrus; all on the left hemisphere. It is noted that using a measure of functional impairment in the presence of pain (Oswestry), divided by mild, moderate, or severe levels, significant correlations were found with z-scores in medial frontal, ACC, DLPFC, and left anterior insula ROIs. The correlation between Oswestry and VAS was significant (r = 0.43, P < .01).

A preliminary analysis was performed using a stepwise logistic regression to test the feasibility of predicting the pain scores reported by the patient based on a small number of QEEG features from a limited montage selected by the logistic regression analysis (n = 67, a subset of the full population due to missing information). These features included most importantly frontal and central scalp locations and features in the theta and beta frequency bands. Figure 4 shows the regression curve. Highly significant prediction accuracy was obtained,
It can be seen that the tightest fit is on the extremes of the scale and that the largest variance is in the middle of the scale, suggesting that it is the middle of the scale where the patients have the most difficulty in assigning a score. With anchors at both ends of the scale, the estimates from the equation are potentially more reliable objective estimates.

**Clinical Features and ROI z-Scores**

None of the ROIs were found to correlate significantly with depression scores on the BDI. There was only 1 ROI that showed a significant correlation with anxiety on the BAI and that was the medial frontal region ($R = 0.33, P < .04$).
However, although reaching significance, this low correlation was not considered to be clinically meaningful. There were no significant correlations with ROIs for chronicity (the number of years the patient reported to have been in pain).

When considering if there was a relationship between side of reported pain and the z-score for the ROIs. Patients were divided into those who reported bilateral pain, including bilateral in combination with either side, left side only and right side only. There were no significant relationships with z-scores for ROIs.

**Discussion**

This study represents one of the largest chronic pain populations studied with electrophysiological imaging reported in the literature. Using EEG source localization, the data demonstrate the significant overactivation of regions described as part of the
pain network using conventional functional neuroimaging methods. These regions include most significantly the mid and posterior cingulate, the anterior and posterior insula, the parietal lobule, the thalamus, and the DLPFC. Since this study was conducted in pain patients in the absence of nociceptive stimuli, results support continuous overactivation of regions of the pain network in the chronic pain state. It is noted that the mid and posterior cingulate show highly significant differences between normal and pain patients, while significance was not seen in the ACC ROI often associated with the painful state in conventional neuroimaging studies. The ROI for the anterior cingulate in this study was not limited to the rostral ACC, where others have indicated the maximal differences in the ACC region, but included posterior and mid cingulate regions as well. The differences obtained may reflect the advantage of the temporal resolution of electrophysiological data which although averaged across FFT epochs, is based on high-resolution frequency encoded information captured by the EEG signal and support the importance of these areas of the cingulate cortex in chronic pain.9,10

Support for the relationship between the magnitude of overactivation in the significant ROIs and encoding of the level of pain was also demonstrated in this study. Highly significant differences were obtained in comparisons between patients reporting high versus low pain scores. It was observed that most significances were on the left hemisphere (independent of the side of reported pain) and the largest significance was found in the DLPFC. In a PET study of the relationship between DLPFC and pain intensity, Lorenz and colleagues39 reported that DLPFC activity correlated negatively with perceived intensity and unpleasantness of pain. More specifically, during high left DLPFC activity inter-regional correlation of midbrain and thalamic activity was reduced, which they interpreted as reflecting modulation of effective connectivity between midbrain-thalamic pathways. Further evidence of the left hemisphere in the encoding of pain was reported by Favilla and colleagues40 who rank-ordered fMRI ROIs based on the relationship with perceived pain level and found the most significant relationship to be in the left mid cingulate cortex. Further exploration of the functional significance of such asymmetric representation in the encoding of pain is needed. The fact that the differences between high and low pain states occur in a subset of ROIs of the pain network suggests that these regions are more involved in the encoding of the subjective intensity of pain, while the others represent the presence of pain regardless of severity. It is also important to note that the evidence of several ROIs showing significant differences in the difference between high and low pain states supports distributed processing of pain intensity, also suggested by others.41

Table 1. Mean and Standard Deviation Voxel Values for Pain and Control Groups for Each Region of Interest.7 It is important to note that the probability associated with group mean z-scores would be computed times the square root of the n of the group, thus 8.77 times the group z-score shown.

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Pain, Mean (SD)</th>
<th>Control, Mean (SD)</th>
<th>t</th>
<th>Permutation Test P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cingulate</td>
<td>0.63 (1.26)</td>
<td>0.55 (0.90)</td>
<td>1.58</td>
<td>.11</td>
</tr>
<tr>
<td>Mid cingulate</td>
<td>0.95 (1.39)</td>
<td>0.65 (0.92)</td>
<td>5.34</td>
<td>&lt;.0001**</td>
</tr>
<tr>
<td>Posterior cingulate</td>
<td>0.79 (1.53)</td>
<td>0.37 (1.02)</td>
<td>6.22</td>
<td>&lt;.0001**</td>
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<td>Anterior L insula</td>
<td>0.57 (1.39)</td>
<td>0.29 (0.88)</td>
<td>5.07</td>
<td>&lt;.0001**</td>
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<tr>
<td>Posterior L insula</td>
<td>0.91 (1.61)</td>
<td>0.40 (0.92)</td>
<td>7.90</td>
<td>&lt;.0001**</td>
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<tr>
<td>Anterior R Insula</td>
<td>0.50 (1.43)</td>
<td>0.29 (0.88)</td>
<td>3.62</td>
<td>.0008**</td>
</tr>
<tr>
<td>Posterior R Insula</td>
<td>0.65 (1.54)</td>
<td>0.37 (0.96)</td>
<td>4.37</td>
<td>&lt;.0001**</td>
</tr>
<tr>
<td>L SI</td>
<td>1.20 (1.53)</td>
<td>0.51 (0.98)</td>
<td>11.17</td>
<td>&lt;.0001**</td>
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<tr>
<td>R SI</td>
<td>0.89 (1.48)</td>
<td>0.45 (1.00)</td>
<td>7.14</td>
<td>&lt;.0001**</td>
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<td>L inferior parietal lobule</td>
<td>1.26 (1.59)</td>
<td>0.48 (0.98)</td>
<td>12.13</td>
<td>&lt;.0001**</td>
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<tr>
<td>R inferior parietal lobule</td>
<td>0.81 (1.50)</td>
<td>0.42 (0.99)</td>
<td>6.28</td>
<td>&lt;.0001**</td>
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<tr>
<td>L DLPFC</td>
<td>0.95 (1.41)</td>
<td>0.52 (0.88)</td>
<td>7.60</td>
<td>&lt;.0001**</td>
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<tr>
<td>R DLPFC</td>
<td>0.81 (1.31)</td>
<td>0.47 (0.85)</td>
<td>6.24</td>
<td>&lt;.0001**</td>
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<td>SMA</td>
<td>0.73 (1.36)</td>
<td>0.46 (0.95)</td>
<td>4.66</td>
<td>&lt;.0001**</td>
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<td>Medial frontal cortex</td>
<td>0.35 (1.25)</td>
<td>0.30 (0.94)</td>
<td>1.02</td>
<td>.30</td>
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<tr>
<td>L parahippocampal gyrus</td>
<td>0.63 (1.54)</td>
<td>0.28 (0.93)</td>
<td>5.74</td>
<td>&lt;.0001**</td>
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<td>(hippocampus/amygdala)</td>
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<td></td>
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<tr>
<td>R parahippocampal gyrus</td>
<td>0.54 (1.50)</td>
<td>0.30 (0.95)</td>
<td>3.85</td>
<td>.0002**</td>
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<td>(hippocampus/amygdala)</td>
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<td>Thalamus</td>
<td>0.63 (1.54)</td>
<td>0.40 (0.97)</td>
<td>3.76</td>
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<td>L caudate</td>
<td>0.72 (1.46)</td>
<td>0.50 (0.92)</td>
<td>3.70</td>
<td>&lt;.0001**</td>
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<td>R caudate</td>
<td>0.63 (1.43)</td>
<td>0.51 (0.93)</td>
<td>2.09</td>
<td>.03*</td>
</tr>
</tbody>
</table>

Abbreviations: L, left; R, right; DLPFC, dorsolateral prefrontal cortex; SMA, supplementary motor area.

* t value and corrected P values (using permutation tests) are shown for each region of interest.

** P < .001. * 0.001 < P < .05.
between functional severity and ROI activation was also seen using the Oswestry disability scale, further supporting the potential scaling of impairment using these methods. The regression between subjective report of pain and the predicted level of pain using a small subset of QEEG features was found to be closest at the extremes of the scale, while self-report in the middle range (3-6 on VAS, for example) shows larger differences between self-rated and predicted values. Since the mid region of the scale is where patients report the most difficulty in assigning a number, coupled with the reported lack of test-retest reliability of the VAS, suggests that it is in this range that an objective measure derived from overactivation of the pain network might have the greatest clinical utility. Further studies might incorporate the referring physicians’ independent estimates of level of pain as related to their review of the history, clinical presentation, and imaging in the patient. This would allow a comparison between the self-ratings and the predicted ratings from the QEEG, especially when divergent. While this regression supports the potential for a predictive relationship between QEEG features and subjective report of pain level, it must be interpreted with caution until replicated and systematically optimized.

Since chronic pain is reportedly accompanied by depression in the vast majority of cases, it was important to investigate the relationship between the magnitude of activation in pain related ROIs and the self-report of depression. Depression ratings (BDI) showed no significant correlation with mean z-scores in any ROIs, supporting the fact that pain state could be reliably measured in the presence of depression. Similarly, only one ROI, the medial frontal cortex, was found to have a significant correlation with anxiety self-ratings (BAI). This is consistent with reports that cerebral blood flow in this region was found to be inversely correlated with anxiety self-rating in a study delivering painful stimuli.42

Based on electrophysiological studies, a model has been proposed to explain the underlying pathophysiology of pain,18,19,43 which shares common electrophysiological characteristics, based on activity in the thalamocortical system. In such a model, persistent thalamic slow wave activity serves as a trigger for TCD, in which a region of the cortex oscillates at low frequency (theta), surrounded by beta or gamma activity (edge effect) and that this
activity disrupts (disconnects) normal circuit function. In the context of this and other studies in neuropathic pain patients when the EEG sources of the frequency specific abnormalities (theta and beta) occur in regions of the pain network, including the thalamus, TCD has been hypothesized to be the pacing/oscillatory mechanism that perpetuates the painful condition.16,17,44,45 The peak of maximal abnormalities reported in this study were found to be frequency specific in the theta/low alpha band in regions of the pain network and were found to show more overactivation in high pain compared with low pain states, consistent with such a model. Limitations of this study include the use of 19-lead EEG as input to the source localization. While there is literature that demonstrates concordance between source findings based on 19 leads and other neuroimaging tools46,47 studies of source localization when used to localize epileptic sources report that LORETA can lead to oversmoothed solutions.48 Another limitation of this study is the focus on neuropathic chronic pain patients and suggests the need for further studies which include more types of pain (eg, musculoskeletal, visceral, migraine) to explore the robustness of the findings. However, it is noted that these findings are consistent with reports in the literature where other types of pain patients were studied. Also, the heterogeneity within this study population related to chronicity and side of pain would be expected to add variance to the population statistics, resulting in the reported findings being conservative. Likewise, potential medication effects, although previously reported not be a factor in the frequency specific overactivation reported, present concern as it would be considered medically unethical to prohibit these patients from taking analgesics.

Table 2. Mean and Standard Deviation Voxel Values for High and Low Pain Groups for Each Region of Interest. It is important to note that the probability associated with group mean z-scores would be computed times the square root of the n of the group.

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Mean (sd) High</th>
<th>Mean (sd) Low</th>
<th>t-Value</th>
<th>Perm p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cingulate</td>
<td>0.67 (1.29)</td>
<td>0.60 (1.23)</td>
<td>0.82</td>
<td>0.41</td>
</tr>
<tr>
<td>Mid cingulate</td>
<td>1.00 (1.37)</td>
<td>0.90 (1.41)</td>
<td>1.09</td>
<td>0.29</td>
</tr>
<tr>
<td>Posterior Cingulate</td>
<td>0.86 (1.50)</td>
<td>0.72 (1.56)</td>
<td>1.38</td>
<td>0.17</td>
</tr>
<tr>
<td>L anterior insula</td>
<td>0.66 (1.36)</td>
<td>0.48 (1.42)</td>
<td>1.84</td>
<td>0.06*</td>
</tr>
<tr>
<td>L posterior insula</td>
<td>1.03 (1.61)</td>
<td>0.77 (1.60)</td>
<td>2.33</td>
<td>0.02*</td>
</tr>
<tr>
<td>R anterior insula</td>
<td>0.43 (1.51)</td>
<td>0.57 (1.34)</td>
<td>−1.34</td>
<td>0.17</td>
</tr>
<tr>
<td>R posterior insula</td>
<td>0.62 (1.65)</td>
<td>0.67 (1.42)</td>
<td>−0.47</td>
<td>0.64</td>
</tr>
<tr>
<td>L SI</td>
<td>1.38 (1.44)</td>
<td>1.01 (1.59)</td>
<td>3.55</td>
<td>0.0002**</td>
</tr>
<tr>
<td>R SI</td>
<td>0.88 (1.50)</td>
<td>0.89 (1.47)</td>
<td>−0.10</td>
<td>0.93</td>
</tr>
<tr>
<td>L inferior parietal lobule</td>
<td>1.44 (1.55)</td>
<td>1.06 (1.62)</td>
<td>3.46</td>
<td>0.0002**</td>
</tr>
<tr>
<td>R inferior parietal lobule</td>
<td>0.80 (1.59)</td>
<td>0.82 (1.40)</td>
<td>−0.21</td>
<td>0.83</td>
</tr>
<tr>
<td>L DLPFC</td>
<td>1.14 (1.42)</td>
<td>0.75 (1.37)</td>
<td>4.05</td>
<td>&lt;0.0001**</td>
</tr>
<tr>
<td>R DLPFC</td>
<td>0.82 (1.36)</td>
<td>0.80 (1.25)</td>
<td>0.20</td>
<td>0.83</td>
</tr>
<tr>
<td>SMA</td>
<td>0.78 (1.30)</td>
<td>0.68 (1.42)</td>
<td>1.04</td>
<td>0.31</td>
</tr>
<tr>
<td>Medial frontal gyrus</td>
<td>0.44 (1.28)</td>
<td>0.26 (1.21)</td>
<td>2.17</td>
<td>0.03*</td>
</tr>
<tr>
<td>L parahippocampal gyrus (hippocampus/amygdala)</td>
<td>0.68 (1.56)</td>
<td>0.57 (1.52)</td>
<td>1.04</td>
<td>0.29</td>
</tr>
<tr>
<td>R parahippocampal gyrus (hippocampus/amygdala)</td>
<td>0.51 (1.57)</td>
<td>0.53 (1.43)</td>
<td>−0.42</td>
<td>0.67</td>
</tr>
<tr>
<td>Thalamus (all regions)</td>
<td>0.63 (1.56)</td>
<td>0.64 (1.53)</td>
<td>−0.09</td>
<td>0.93</td>
</tr>
<tr>
<td>L caudate</td>
<td>0.75 (1.46)</td>
<td>0.69 (1.46)</td>
<td>0.59</td>
<td>0.55</td>
</tr>
<tr>
<td>R caudate</td>
<td>0.61 (1.44)</td>
<td>0.660 (1.42)</td>
<td>−0.50</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Abbreviations: L, left; R, right; DLPFC, dorsolateral prefrontal cortex; SMA, supplementary motor area.

* t-value and corrected P values are shown for each region of interest.
** 0.001 < P < .05. ***P < .001.

Figure 4. Preliminary prediction equation based multivariate stepwise logistic regression using regression selected quantitative EEG features from a limited montage. The x-axis is the reported pain score on the visual analog scale and the y-axis is the predicted value from the regression equation based on EEG features. Open circles are individual patients (n = 67).
Caution should be used in interpreting the results of the preliminary data presented here on the relationship between self-report and predicted pain values. These data remain to be expanded and replicated in future studies.

In summary, this study demonstrates significant overactivation of the pain network using quantitative EEG in a large population of chronic neuropathic pain patients lending support to a TCD model for the pathophysiology of chronic pain. The concordance with conventional functional neuroimaging findings suggests the possible clinical utility of such a methodology, which is readily available, cost-effective, and noninvasive for the objective evaluation of pain at the point of care. These data also support the potential to derive an objective quantitative measure of the severity of pain using information extracted from a multivariate descriptor of the abnormal brain activity activation in the regions of the pain network. Such an index (or biomarker) of pain could assist the clinician in better assessment of subjective, self-report of pain and its intensity, helping minimize over- and under-use of medications and help to optimize the care and evaluation of care in chronic pain patients.

Acknowledgments

The authors acknowledge the patients who despite being in pain volunteered to participate in this important research. They also acknowledge Robert Isenhart for his thoughtful input and E.R. John whose legacy has inspired this work.

Author Contributions

LSP contributed to conception and design; contributed to analysis and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. JS contributed to data analysis. HM contributed to data acquisition. EMH contributed to conception and design; contributed to interpretation; critically revised manuscript; gave final approval.

Declaration of Conflicting Interests

The author(s) declared the following conflicts of interest with respect to the research, authorship, and/or publication of this article: Drs Prichep and Hiesiger are inventors of a patent assigned to NYU that was licensed to the company (Advanced Neural Metrics) at the time they funded this study (in part), this intellectual property was not used in this work. The funding company had no input to the study design, conduct of the study, analysis of the data, or writing of the manuscript.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Funded in part by Advanced Neural Metrics.

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