Pain Medicine

Pain Medicine 2011; 12: 1241–1248
Wiley Periodicals, Inc.

# Case Report

# Evaluation of the Pain Matrix Using EEG Source Localization: A Feasibility Study

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The authors declare that they do not have a conflict of interest with any of the work presented in the manuscript.

## Abstract

**Objectives. An extensive neuroimaging literature on chronic pain demonstrates increased cerebral blood flow and metabolism consistent with increased neuronal activity in the structures comprising the "Pain Matrix"; furthermore, some of these regions have been shown to encode pain intensity. It is the objective of this study to demonstrate the feasibility of using quantitative electroencephalography (EEG) source localization to reflect and to quantify activity in the Pain Matrix.**

**Methods. Eyes closed resting EEG was recorded from 19 standardized scalp locations, in a pilot sample of five patients with chronic neuropathic pain, before and after pain reduction. Quantitative electro encephalography (QEEG) source localization was computed estimating the mathematically most probable source generators of EEG surface potentials in each state. Sources identified in this way have been demonstrated to coregister with those identified by neuroimaging methods.**

**Results. QEEG sources demonstrated frequency specific increased neuronal activity in the baseline high pain state in structures including the thalamus, somatosensory cortex, anterior and posterior insula, medial and lateral prefrontal cortex and cingulate. Significant reduction of activation in these regions was seen when pain was reduced (≥50% on subjective ratings).**

**Conclusion. The areas that were activated in the high pain state localized to the same regions reported by other neuroimaging methods and with frequency specificity. The frequency and regionally specific activation may indicate distinctive patterns of pathophysiology underlying the pain matrix. Although in a small number of patients, this work suggests that QEEG may be a useful tool in the exploration and quantification of the pain matrix in a clinical setting.**

**Key Words. Pain Matrix; QEEG Source Localization; Chronic Pain; Intensity Encoding**

## Introduction

There is an extensive literature on the use of neuroimaging in the study of pain, especially acute experimental pain, and demonstrating neuronal activation of the structures comprising the "pain matrix" [1] (activation) in chronic pain. Data obtained from a meta-analysis of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies provide evidence of multiple structures involved in the pain matrix [2]. PET studies in acute pain consistently showed increases in cerebral blood flow (CBF) in the secondary somatosensory (SII), insula, and anterior cingulate cortices (ACCs), with the insula/SII activated bilaterally in over 50% of studies. Less consistently, increases in CBF in the contralateral thalamus, somatosensory cortex (SI), cerebellum, and midbrain were shown in acute pain. In a number of studies, the thalamic response was bilateral, possibly related to the generalized arousal in reaction to pain. CBF in the anterior insula and retro-insular/SII cortices has been shown to correlate with intensity of thermal pain [3]. A number of imaging studies suggest the role of the ACC in intensity coding both in acute [4–7] and in chronic pains [8].

As multichannel electroencephalography (EEG) is limited by the fact that it is measured from the surface of the scalp and as such does not directly provide the location of the active neuronal generators, source localization methods

were used in this study to solve the "inverse" solution to describe the mathematically most probable underlying sources of the scalp recorded potentials. These methods assume that neighboring neurons are simultaneously and synchronously activated, resting on evidence from single-cell recordings in the brain that demonstrates strong synchronization of adjacent neurons. Using such source localization methods (low resolution electromagnetic tomographic analysis [LORETA]) in patients with intractable unilateral or bilateral neuropathic pain, similar sources as those noted above using conventional neuroimaging methods were found [9,10]. Enhanced activation of sources occurred mainly in 6–9 Hz and 12–16 Hz ranges in cortical structures including insula, ACC, prefrontal, inferior posterior parietal, primary (SI), secondary (SII), and supplementary somatosensory cortices. In a small subset of these patients evaluated 12 months following central lateral nucleus thalamotomy (CLT) with 95% pain relief reported, activation in the insula and cingulate cortices was significantly diminished.

While conventional neuroimaging studies clearly substantiate the existence of a pain matrix, the lack of portability and complexity of data acquisition with these imaging modalities precludes their use in detecting pain and monitoring analgesia in the clinical setting. As such, quantitative encephalography (QEEG) may provide a portable, relatively inexpensive, non-invasive, objectively verifiable, and quick method of detecting pain in a clinical setting, independent of the patients' ability to report pain level. This is a preliminary report on the application of QEEG source localization to detect pain in chronic pain patients.

## Methods

### *Subjects*

Five patients were included in this study, all five had neuropathic pain due to root and or nerve compression or trauma. One had, in addition, musculoskeletal pain primarily due to both inflammatory and degenerative arthritis, and one had presumable bone pain due to sacral metastasis from melonoma. All patients were at baseline and then re-evaluated at a later point following procedures that resulted in reduction of pain or spontaneous resolution of pain. Table 1 provides a clinical summary of each case including pain scores at the time of the initial and repeat evaluations, source of pain, procedure performed, length of time in pain when baseline was obtained, and demographics. Written informed consent was obtained in all cases.

### *EEG Data Acquisition*

Twenty minutes of eyes closed resting EEG were recorded from 19 electrodes, pasted on the scalp in accordance with the International 10/20 Electrode Placement System, referenced to linked earlobes. A differential eye channel (diagonally placed above and below the eye orbit) was used for the detection of eye movement. All electrode impedances were below 5,000 Ω. The EEG amplifiers had a bandpass from 0.5 to 70 Hz (3 dB points). Data were sampled at a rate of 200 Hz with 12-bit resolution. Patients were monitored throughout EEG recording.

### *QEEG Source Analysis*

The raw EEG data were visually reviewed by trained EEG technologists, to identify and eliminate artifacts from the EEG recordings. This was augmented by a computerized artifact detection algorithm to further aid in the identification of data contaminated by artifact. Two minutes of artifact-free EEG were then submitted for quantitative analysis, using a source localization method called variable resolution electrical tomography (VARETA) [11].

VARETA is a method that mathematically identifies the statistically most probable underlying sources of the scalp-recorded EEG data. With conventional EEG frequency analysis, wide bands of frequencies are used (e.g., delta [1.5–3.5 Hz], theta [3.5–7.5 Hz], etc.). Using VARETA, very narrow band (VNB) spectra are computed with bins 0.39 Hz wide from 1.5–20 Hz, for every electrode derivation. In both the conventional analysis and the VNB analysis, a fast Fourrier transform (FFT) is used to identify the frequency content of the EEG signal.

The scalp electrode positions were placed using the International 10/20 Standardized Electrode Placement System [12] and these are then placed in spatial registration with a Probabilistic MRI Brain Atlas [13]. Values in the voxel data were log transformed to obtain Gaussianity and then age regressed relative to age-appropriate normal values. Normative equations for the development of the EEG across the human life span have been published previously, replicated and shown to be culture free [14,15]. For each feature, *Z*-scores are computed as the difference between the predicted normative value and the value obtained from the individual patient for each voxel. In this way the probability that such a value might be obtained by chance from a healthy peer the exact age of the patient is estimated.

The probable sources of QEEG abnormalities recorded on the scalp are then superimposed upon magnetic resonance imaging (MRI) slices from the MRI Atlas, and the values computed for each frequency in every voxel were encoded using a color palette with hues proportional to the standard- or Z-scores of deviations from expected normative values. The anatomical accuracy of the functional QEEG source localization obtained by VARETA and other QEEG-based source localization methods has been repeatedly confirmed by coregistration with other brain imaging modalities, e.g., fMRI [16], PET [17,18], and computerized tomography (CT) [19].

### *Statistics*

Significant decreases in source activation in the regions of the pain matrix between the high and low pain states were the primary end points. It is also noted that since all voxels imaged are expressed as *z*-scores relative to

**Table 1** Demographics, pain scores, side of pain, source of pain at time of testing, length of time in pain, and medications taken at time of test

| Patient # | Age | Gender | Pain Score | Side Pain | Main Source of Pain at time of Testing | Length of Time in Pain at Baseline | Medications at Time of Testing |
|---|---|---|---|---|---|---|---|
| Patient 1 | | | | | | | |
| A | 61 | F | 8 | B | In the presence of advanced rheumatoid arthritis MRI documented bilateral pannus formation at $C_{1\text{-}2}$ with degeneration of the right $C_{1\text{-}2}$ joint, instability of the $C_{1\text{-}2}$ with bony destruction of the lateral masses of $C_1$ and of the attachment of the pedicle of $C_2$ to the body of $C_2$, had severe bilateral radiculopathy. She also had left buttock pain and bilateral leg parasthesias, due to bilateral $L_5$-$S_1$ foraminal stenoses. | 18 months | Nortriptyline, prednisone |
| B | | | 2 | R | One month after the first exam, she underwent cervical-occipital fusion resulting in resolution of her $C_2$ radiculopathy. The $L_5$-$S_1$ segment was later decompressed with good result. At the time of the second test, MRI documented right $L_{4\text{-}5}$ foraminal stenosis, with renewed right lumbar radiculopathy, painful degeneration of the right knee, and a painful right rotator cuff tear. | | Prednisone |
| Patient 2 | | | | | | | |
| A | 54 | F | 4 | L | Left lumbar radiculopathy due to an MRI documented $L_{4\text{-}5}$ disc herniation | 9 months | Hydrocodone |
| B | | | 0 | | Following surgical decompression | | None |
| Patient 3 | | | | | | | |
| A | 25 | M | 8 | R | MRI showed a large right more than left midline $L_{4\text{-}5}$ disc herniation compressing the right $L_5$ root and cauda equina and causing moderate to severe central stenosis. At $L_5$-$S_1$ there was a protrusion and annular tear without neural compression. | 24 months dull and intermittent, 2 months constant and severe | Hydrocodone |
| B | | | 2 | | Three months after an $L_{4\text{-}5}$ microdisectomy | | None |
| Patient 4 | | | | | | | |
| A | 54 | F | 6 | R | History of lumbar facet pain who then suffered trauma to her right $L_5$ nerve following a radiofrequency lesion of her $L_5$-$S_1$ facet, resulting in mild sensory loss and foot and toe extensor weakness and pain in the distal leg in $L_5$ distribution. | Five-month history of lumbar facet pain, combined with new trauma to L5 nerve | Pregabalin, nortripyline, venlafaxine, topiramate, acetaminophen/butalbital, dexamethasone |
| B | | | 3 | | Three months later with mild bilateral lower lumbar pain but no foot pain | | Pregabalin, dexamethasone |
| Patient 5 | | | | | | | |
| A | 34 | M | 6 | L | Painful left sacral melanoma metastasis | 12 months | Morphine, oxycodone, gabapentin, tizantidine, |
| B | | | 2 | | Seven weeks after resection of tumor | | Oxycodone, pregabalin |

MRI = magnetic resonance imaging; BL = baseline.

age-appropriate normative values, the probability of abnormality at the $P < 0.05$ confidence level is $\pm 1.96$ for the individual. The significance levels of the images also take into consideration the large number of measurements made, using the correction introduced by Worsley et al. [20].

Although the sample was very small and considered as a feasibility sample, the significance of the differences between group average VARETAs for the high pain state (A) and group average VARETAs for the low pain state (B) was evaluated using a *t*-test. This comparison was made using the source images at the frequency that showed the most significant differences across subjects (11.0 Hz) between states. Statistical significance was defined as $P < 0.05$.

## Results

Figures 1 and 2 show the source images for the baseline QEEGs (top row of each panel, A) and retest (bottom row of each panel, B). Significant decreases in activation ($P < 0.05$ based on the significance of the change in *Z* scale) occur between the two sessions in all patients shown in these figures. Patients #1–3 showed the most significant VNB activation in the alpha or low beta bands and Patients #4–5 had maxima in the theta band. These patients were best imaged in lower axial slices (see Figure 3), from the level of the subthalamic nuclei to the mid-posterior cingulate junction. The region that showed maximum activation for this group was the cingulate gyrus (Brodmann area 23, 24, and 30). Other areas of activation in the baseline painful condition of these patients included the superior and middle temporal gyri, insula, thalamus, cuneus, and somatosensory cortices (most often contralateral to side of pain).

For those in the theta band (Patients #4–5), the structures that show the greatest change between the two sessions where best imaged in the sagittal and parasagittal slices (see Figure 2), from the level of the mid-posterior cingulate junction to the medial frontal gyrus. The regions with maximum activation can be seen in the precuneus, mid to posterior cingulate (Brodmann areas 23, 24, and 30) and the postcentral gyrus. It is noted that Patient #4 showed deactivation of the anterior cingulate and the medial and lateral prefrontal gyri in the postoperative session B. It is suggested that there was an overall deactivation of the pain matrix in this patient that resulted in a downregulation of these regions that showed a tendency toward underactivation in the session A. It is also noted that the least change between sessions A and B is seen in Patient #5 who also showed the least change in her pain score and had the highest pain score of all patients' in session B.

Although reductions in pain scores appear within a patient to be related to reductions in significant activation, when considered across patients the relationship cannot clearly be seen in this small sample. However, a statistically significant difference was found between the A sessions and the B sessions, supporting decreases in activation with decreases in pain score. Figure 3 shows images of *t*-scores for the significance of the differences between group average VARETAs in the high and low pain states, at 11.0 Hz—the frequency of maximal difference between states. The regions that show the most significant change are color coded as blue, indicating decreased activation with reduction in pain. These regions include the insula, inferior and superior temporal gyri, hippocampal formation, frontal gyri, and lateral occipitotemporal gyrus.

## Discussion

The primary goal of this study was to determine if QEEG source localization could be used to identify activation of the pain matrix in chronic pain patients and to quantify and reflect change in reported pain intensity within an individual before and after amelioration of their pain. Results demonstrated that regions of the pain matrix activated in the painful state could be reflected in the sources of scalp-recorded EEG and that the activation decreased with decreases in pain scores. Regions of activation identified in this study were consistent with many of those identified in functional neuroimaging studies using fMRI and PET, supporting the role of the anterior, middle, and posterior cingulate, insula, prefrontal cortex, somatosensory cortex, the precuneus and the cuneus regions in the pain matrix. Most of the neuroimaging studies of pain done to date report on acute induced pain or induced pain in chronic patients but few look at the clinical painful state. Although there are many obstacles to the study of clinical pain, we sought to study a small sample of such subjects in the demonstration of the possible utility of the QEEG method proposed.

It is noted that in the studies by Stern et al. [9] and Sarnthein et al. [10], although patients were on many different medications, some including narcotics, all patients showed theta and beta abnormalities, as also seen in our study, suggesting that the shifts in the frequency spectrum were independent of medication. This is important both in the context of the interpretation of the results and in the consideration of the clinical utility of a potential objective tool for the quantification of pain, as clinical chronic pain patients will rarely be evaluated in the absence of any centrally acting medication.

Using QEEG source localization in patients with chronic pain before and after reduction of pain revealed significantly more activation in the high pain state. Although source localization of EEG has poor spatial resolution compared with that of other neuroimaging methods, the reduction of activity in pain-specific regions of the brain identified using this method was localized in the same regions reported by other neuroimaging methods and was frequency specific. The frequency and regionally specific patterns may relate to the pathophysiology underlying the activation of the pain matrix. It is interesting to note that in our chronic pain sample, regions of activation included those thought to be related to both the sensory (e.g., somatosensory cortices, thalamus, posterior insula cortex) and affective, motivational,

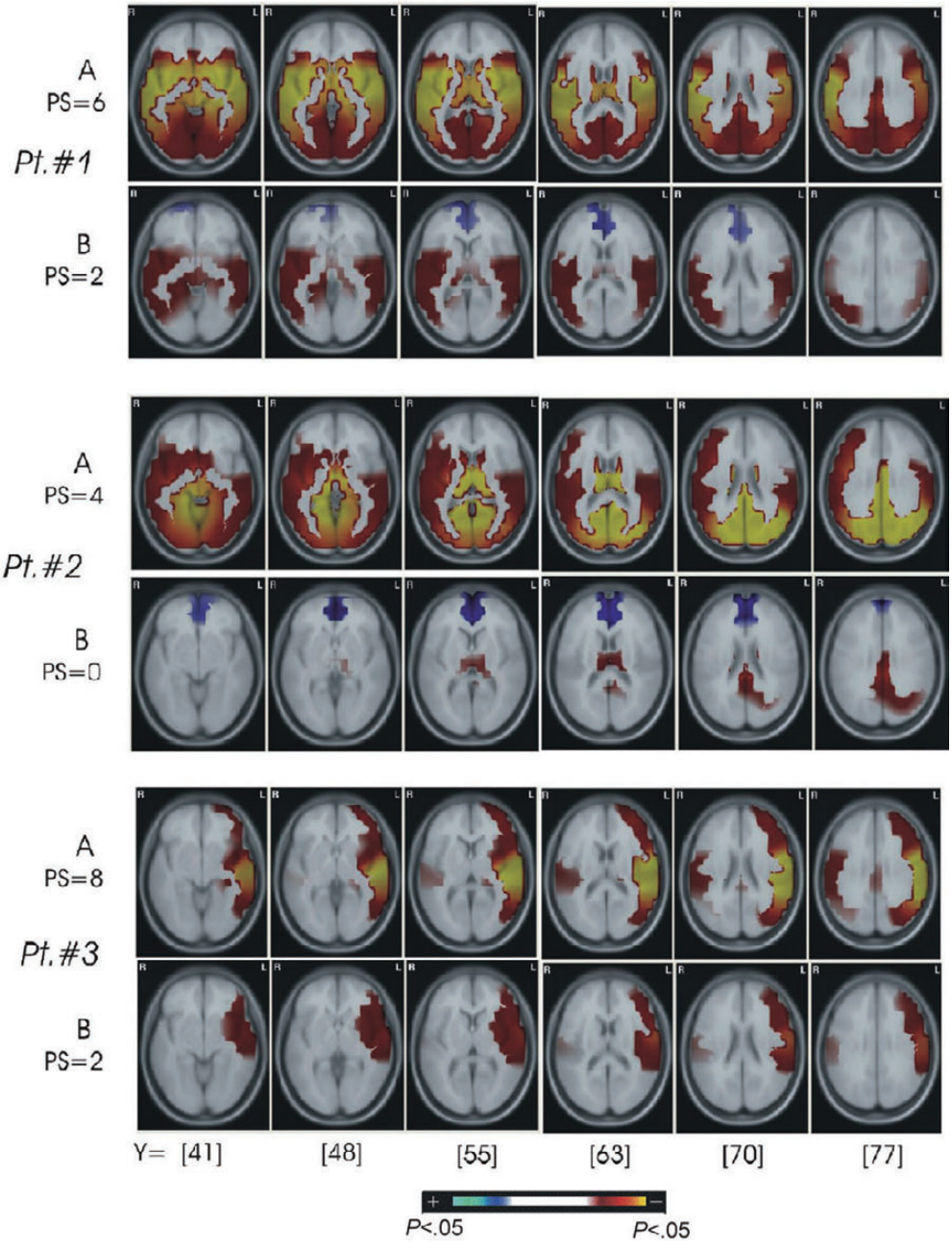


**Figure 1** VARETA QEEG source localization images superimposed upon axial slices from the Probabilistic MRI Atlas, for the baseline EEGs (top row of each panel) and retest (bottom row of each panel). Each patient's subjective pain score ratings (PS) are shown. Each row shows sagittal images of the regions activated at the VNB maxima in the beta band (most significant *z*-score). Statistical significance is given in *z*-scores relative to standard deviation units of the age-appropriate normative population, encoded by the color palette at the bottom of the figure, with increased activation represented in hues ranging from red to yellow, while decreased activation is depicted in hues ranging from dark blue to turquoise. The color scale in all images is individually scaled to maximize visibility of the activated structures within that condition and to minimize saturation of the color scale. The extremes of this scale represent findings at $P < 0.01$ in each case. 187 × 245 mm (350 × 350 DPI). VARETA = variable resolution electrical tomography; QEEG = quantitative electro encephalography; EEGs = electroencephalographies; VNB = very narrow band.

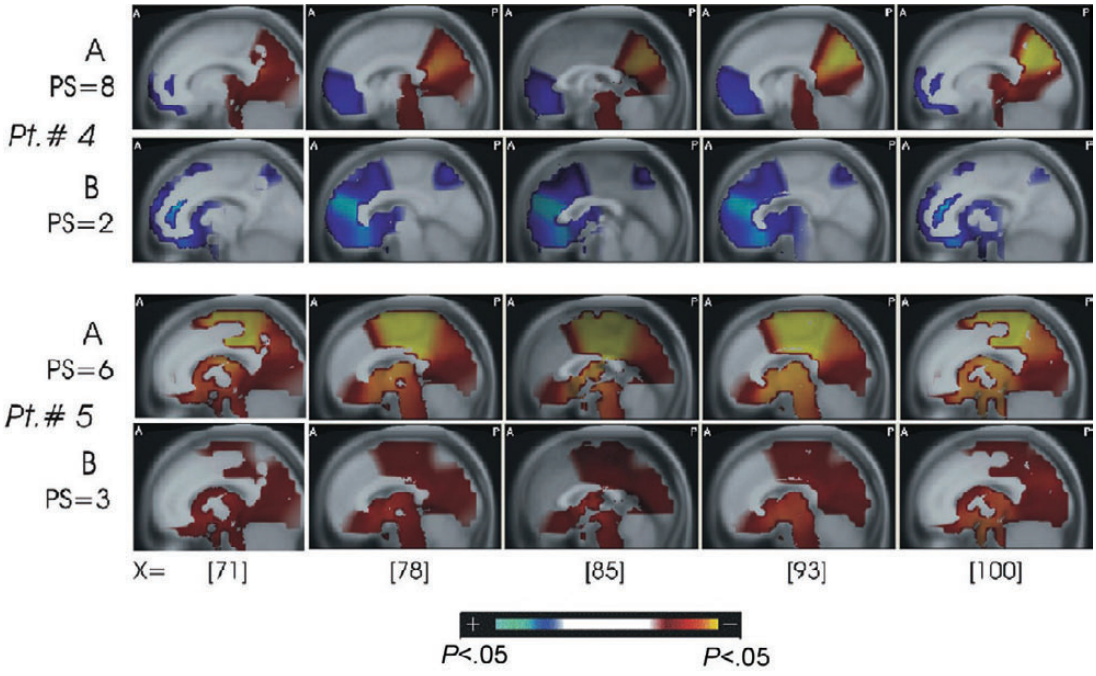


**Figure 2** VARETA QEEG source localization images superimposed upon sagittal slices from the Probabilistic MRI Atlas, for the baseline EEGs (top row of each panel) and retest (bottom row of each panel), each patient's subjective pain score (PS) ratings are shown. Each row shows sagittal images of the regions activated at the VNB maxima in the theta band (most significant *z*-score). Statistical significance is as described for Figure 1. 192 × 118 mm (350 × 350 DPI). VARETA = variable resolution electrical tomography; QEEG = quantitative electro encephalography; EEGs = electroencephalographies; VNB = very narrow band.

cognitive and memory (e.g., orbitofrontal cortex, anterior insula cortex and cingulate) components of pain [21].

Baliki et al. [22] demonstrated that the affective and sensory components of the pain processing matrix differentially encode intensity, dependent upon the type of pain. Using fMRI, the intensity of high-level sustained back pain was correlated with increased activity in the medial prefrontal cortex (MPFC), including the anterior cingulate cortex (ACC), which the authors suggest reflects processing of the affective component of pain. On the other hand, increasing back pain was associated with transient increased activity in areas such as the insula, which the authors suggest reflects sensory processing of acute pain. The intensity of thermal pain in both patients and normal subjects correlated best with insular activity. This study points to the fact that the patient's physical painful state is associated with an affective component. Thus, although the regions of the Pain Matrix show "sensitivity" to the painful state, they are not all "specific" to physical pain.

The authors note that there appears to be large intra-subject variability in the images of activation in this small sample presented. However, it is important to note that the statistical analysis (*t*-test for differences between high

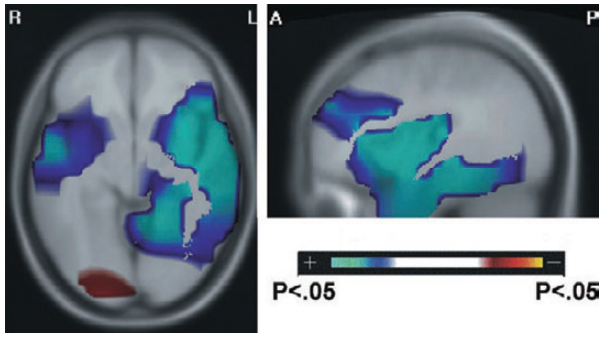


**Figure 3** *T*-scores for the significance of differences between the sources identified in the high (first test) and low (second test) pain states for the five patients, at the peak showing the most significant changes (11.0 Hz). The axial and sagittal slices in this figure were selected to show the maximal *t*-scores. Color coding is for significance of *t*-value, where the extremes of the scale are $P < 0.05$; thus, all light blue/green regions had significant decreased activation with reduction of pain. 105 × 74 mm (350 × 350 DPI).

pain and low pain states for the group) that takes the variance of the measures into account, reached significance for areas that support the activation of regions of the Pain Matrix. On the other hand, the intersubject variability reflected the expected decreased activation of the structures in the Pain Matrix with decreases in associated pain scores, as was hypothesized.

In conclusion, we recognize the limitations of this small pilot study of a heterogeneous population with different durations of pain, different periods of time between QEEG evaluations, different subjective pain ratings, and multifactorial etiologies of pain in some of the subjects. A much larger population including patients without pain as well as a clinical population stratified according to inclusion/exclusion criteria might allow demonstration of significant correlations between features of activation and subjective pain ratings. However, the results presented, showing statistically significant differences between the high and low pain states in this small group of subjects are suggestive of such a relationship and demonstrate the potential for using a cost-effective, readily available, non-invasive tool to reflect and potentially quantify activity in the Pain Matrix.

**Acknowledgments**

E. Roy John, PhD, passed away before the time of this submission; however, his contribution to the concepts explored in this research and his participation in the study are acknowledged by his authorship.

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