Restoration of Altered Somatosensory Cortical Representation With Spinal Cord Stimulation Therapy in a Patient With Complex Regional Pain Syndrome: A Magnetoencephalography Case Study

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Objectives: Development of effective chronic pain treatment strategies has been hampered by the lack of an objective pain biomarker. Magnetoencephalography (MEG) has demonstrated cortical disorganization corresponding to the affected limb of complex regional pain syndrome (CRPS) patients and spinal cord stimulation (SCS) can acutely treat CRPS in a reversible and adjustable fashion. In order to better define a potential MEG-sensitive biomarker for chronic pain, our goal was to study the effects of therapeutic SCS on cortical disorganization in patients with unilateral limb CRPS.

Methods: Two patients treated with either thoracic or cervical SCS with leg or arm CRPS were studied with MEG. Baseline and tactile-evoked responses were recorded with and without effective SCS therapy.

Results: All MEG recordings were obtained with minimal interference. In the patient with arm CRPS, with the stimulator off, first and fifth digit primary somatosensory (SI) cortical representations (D1/D5) were significantly disorganized and spatially inverted as compared with the opposite unaffected limb. Effective SCS therapy was then able to acutely normalize or restore hand cortical organization in the affected CRPS limb. This restoration of cortical organization was partially maintained with lingering pain relief when the stimulator was subsequently turned off.

Conclusions: This is the first report of a MEG study showing D1/D5 cortical disorganization and its apparent reversal or restoration with cervical SCS therapy. Ours also is the first report of an apparent acute reversible interchange in the cortical representations of D1 and D5. Our limited data demonstrate that disorganization of SI cortex might be a neurophysiologic marker of chronic pain as shown with instantaneous normalization of SI disorganization or restoration of SI organization with therapeutic SCS. As a clinically proven tool for functional mapping, MEG might be shown to provide an objective measure of chronic pain. More data are required to further investigate this possibility.

Keywords: Biomarker, complex regional pain syndrome, magnetoencephalography, spinal cord stimulation

Conflict of Interest: The authors report no conflict of interest.

INTRODUCTION

The societal costs of chronic pain are overwhelming and the success rate for its treatment is poor (1). Commitment to pain research and drug discovery remains high but progress has been hampered due to the lack of an objective diagnostic test or biomarker that can complement the subjective assessment of chronic pain conditions. Biomarkers help with diagnosis, prognosis, and the evaluation of treatment responses and can be used to inform rational drug/treatment development (2,3). Any potential biomarker must be shown to be sensitive, specific, and reproducible through a rigorous process of scientific validation and clinical qualification.

The development of biomarkers for central nervous system (CNS) diseases (such as chronic pain) is perhaps more challenging due to the inaccessibility of the brain so that a noninvasive measure would be most attractive. Because pain behavior results from activity in brain circuits through the participation of many brain regions, specific measures for the disease state and potential therapeutic effects can be defined using functional brain imaging. Tremendous advances have been made in functional imaging in the field of pain and analgesics (4,5), but there has been less emphasis on the potential of using imaging to discover and define biomarkers of pain.

Structures that can exhibit reproducible and specific changes during chronic pain that can be detected by neuroimaging include...
the primary somatosensory cortex (SI). SI activation has been correlated with subjective pain ratings of experimental noxious stimuli with functional magnetic resonance imaging (fMRI); however, data have been inconsistent and not always reproducible (6). Some studies reported brain activation in an abnormal location within the SI cortex that shifts to the expected location when pain symptomatically abolishes (cortical reorganization [7]). There are limitations in temporal/spatial resolution, invasiveness, exposure to magnetic fields, and the need for pooled data with fMRI, positron emission tomography, or single photon emission computed tomography.

Magnetoencephalography (MEG) is a completely noninvasive technique for localizing spontaneous and evoked cortical activity with superior spatial resolution high enough to demonstrate the somatotopic organization of the SI homunculus with less need for pooled data. Previous MEG studies have shown similar cortical disorganization with altered localization of responses to mechanical stimuli in chronic pain patients that revert back to normal patterns with clinical improvement (8–10). There have been limitations with these studies. Chronic pain conditions typically are not easily amenable to most traditional clinical drug-evaluation studies, which further complicates clinical and basic research efforts.

Ideally, one would like to work with a chronic pain model in which a subject could serve as their own control. Complex regional pain syndrome (CRPS) or reflex sympathetic dystrophy is a chronic pain syndrome that develops in about 5% of traumas, typically affects a unilateral limb and is characterized by constant pain, motor symptoms, swelling, and autonomic changes in the skin (11). Such a pain model could potentially allow for the unaffected contralateral limb to serve as an internal control. Its pathophysiology is not completely understood and may include changes in the CNS as well as peripheral changes (12). Functional imaging of the CNS in CRPS has been summarized (13). Using MEG, others (8,9) observed an increased strength of magnetic fields and a reduced distance between the first and fifth digit representation (D1 and D5) after tactile stimulation in the SI contralateral to the affected hand in CRPS patients. Furthermore, Mailhofner et al. found a normalization of this cortical disorganization with clinical improvement that was seen after one year of treatment (10). Reduction in pain seemed to predict this restoration or normalization of cortical disorganization, further supporting somatotopic-activation mapping in SI as a potential marker for clinical recovery. The sensitivity of the method remains to be defined and, given a time frame of at least one year of treatment, it is not known whether this functional correction or restoration predate clinical improvement following standard therapeutic regimens (10).

Therefore, in order to better define this potential marker for pain and clinical recovery, one would like to work within this chronic pain treatment model in which one can instantaneously and reversibly adjust, document, and calibrate pain relief in a unilateral CRPS limb, with the unaffected opposite limb potentially serving as an internal control. In this way, prolonged longitudinal studies and comparisons with control populations could be obviated. Spinal cord stimulation (SCS) therapy can be used to treat CRPS (14) and its uniqueness of adjustability and reversibility with the potential for calibration may have tremendous advantages in further defining this MEG-sensitive, SI cortical disorganization as a possible biomarker for pain. Our goal was to begin to work with this system, utilizing this unilateral CRPS model with the ability to uniquely modulate the pain with SCS techniques. This unilateral CRPS model may be limited to some extent as CRPS frequently progresses to the contralateral limb, which could have some undetected level of subclinical involvement when studied.

### METHODS

#### MEG

After informed consent was obtained, somatosensory mapping was acquired on a whole head MEG system with 148 MEG channels (4Dneuroimaging Inc., San Diego, CA, USA) using clinical routine parameters. Tactile stimulation was 20–25 or 15–17 lb/in²; low pass was 0.1 Hz; sampling rate was 508.63 Hz with a band pass of 100 Hz; epoch duration was 330 msec; pretrigger was 107 msec; and there were 350 epochs repetition for each finger. Thin-slice three-dimensional MRI images were acquired using transmit/receive radio frequency coil on a GE 1.5-T MR scanner from a patient with an MRI-compatible Medtronic SCS system following standard Food and Drug Administration-approved labeling requirements. The data were filtered with a band pass between 2 and 40 Hz. They also were visually inspected and the noisy epochs (eye movement) were removed from averaging. There are at least 300 artifact-free epochs. The peak of averaged evoked magnetic fields between 30 and 70 msec is defined as primary somatosensory cortical response. The correlation coefficient is set at least 0.97. The equivalent current dipole model was applied. The MRI was coregistered with the MEG data using fiducials at the left and right preauricular points and nasion and with assistance from the head digitization points.

#### Interference With MEG

In order to determine the extent of interference from a device and/or electrical stimulation, a MSI recording was initially performed on a patient with a thoracic spinal cord stimulator system.

Patient #1: 24-year-old woman with bilateral lower extremity CRPS type 1 (CRPS-1) for eight years from trauma with constant pain disproportionate to any known inciting event, touch allodynia, edema, and documented skin temperature changes. After a successful trial of SCS, she had a surgical tripolar paddle electrode (Medtronic 565; Medtronic Inc., Minneapolis, MN, USA) implanted. With the patient prone, she was allowed to go to sleep with conscious sedation. With further local anesthetic, the electrode was placed after midline T12 L1 laminotomies and centered at the T10-11 level. She was awakened briefly to confirm stimulation paresthesias covering her areas of pain. Subsequently, her implantable pulse generator (IPG; RestoreAdvanced, Medtronic Inc.) was placed in the right flank region. MEG recordings were performed with the stimulator off and then repeated with the stimulator turned on.

Patient #2: 41-year-old woman with CRPS-1 involving her entire right upper extremity from shoulder to finger tips for eight years after a traumatic injury without evidence of major nerve damage. She describes a constant deep, burning, aching, dysesthesia with a sensation of crawling, which would be a constant 4/10 with best medical management at the direction of the pain clinic. The pain would be consistently increased to 9–10/10 with stress, changes in weather, and increased activity of the right upper extremity such as driving. The pain was disproportionate to any known inciting event. She would experience color changes, swelling, and documented temperature changes in the right upper extremity with some touch allosthenia. She would experience temporary improvements in pain with ketamine injections and sympathetic blocks. As part of our multimodality SCS program, she was offered a trial of cervical SCS with a percutaneous trial lead placed slightly to the right of midline from the C2/3 junction down to the bottom of C5. This was completed by the interventional pain physicians, which reduced her constant pain down to a 1/10 with no increases in pain brought on with increased activities with improved arm and
hand function, reduced swelling, and reduced allodynia. The temporary trial lead was removed after five days of testing and a permanent surgical paddle lead (Specify; Medtronic Inc.) was placed about seven weeks later. With the patient prone and her head resting in a neutral position in a horseshoe headrest, she was allowed to go to sleep with conscious sedation. With further local anesthetic, the electrode was placed after midline C5/6 laminotomies with the electrode spanning the C2/3 junction down to the C4/5 junction. She was awakened briefly to confirm stimulation paresthesias covering her areas of pain. Subsequently, her IPG (RestoreUltra; Medtronic Inc.) was placed in her right flank region. MEG recordings were done under the following three conditions within a 60-min period: 1) stimulation off for several hours with pain on visual analog scale (VAS) of 7/10 and moderate touch allodynia; 2) stimulation on for 30 min (1.3 V, 360 μsec, and 85 Hz) and VAS of 2/10 and no touch allodynia; and 3) stimulation turned back off for 30 min with lingering, sustained pain relief at 2/10 but with mild touch allodynia.

**RESULTS**

Data in our two patients showed that a cervical or thoracic spinal cord stimulator did not interfere with MEG recordings with the stimulation on or off. The frequency and timing of the SCS were recorded with the high temporal resolution. In patient #2, with the stimulator turned off for several hours and the patient in pain, localization of SI cortex is disorganized as compared with the contralateral SI (Fig. 1). The area of the hand region is smaller and the location of D1 and D5 representing cortical region is flipped (D1 region is superior to the D5 region). When the pain is significantly reduced with the SCS turned on for 30 min, the corresponding SI region is similar as compared with the contralateral SI. The flipping of D1 and D5 region is restored to the more normal state when the SCS was turned off for 30 min after the second recording and the patient experiencing persistent and lingering reduction in pain, the D1 and D5 region remains in the same order as the contralateral SI.
For the three recording conditions as described above, there were no significant differences in the peak latencies of the somatosensory-evoked magnetic fields following tactile stimulation of D1 and D5 on the CRPS side and the normal side (data not shown). Differences in the mean strengths of the magnetic fields could not be determined.

**DISCUSSION**

This is the first report of a MEG study showing hand D1/D5 SI cortical disorganization and its apparent reversal or restoration with cervical SCS therapy. In an abstract with MEG, Mogilner et al. reported that the sensory cortical source for an affected painful lower limb (personal communication) shifted with therapeutic thoracic SCS (15). No further report has been published in this or other institutions to the best of our knowledge. We also have now shown in our two patients that MEG recordings can be obtained in patients with cervical or thoracic spinal cord stimulator systems, with minimal interference and no adverse effects, and that a sensory cortical shift can occur with electrical stimulation of the spinal cord, again demonstrating reproducibility. Therefore, this now begins to form the groundwork for the criteria for a potential chronic pain biomarker. We have further demonstrated, for the first time, that not only could this cortical disorganization be acutely restored to a more normal configuration with effective SCS but that the extent of restoration could be graded depending upon the extent of pain relief with SCS.

This MEG-sensitive cortical D1/D5 disorganization has been shown in CRPS patients by several groups (8–10,16). Reversal of this disorganization or restoration has been shown to occur with diminished pain after treatment for at least one year with physical therapy and medications (10) or with six months of treatment with the central-acting N-methyl-D-aspartate receptor antagonist drug memantine (16). In our study, in one patient, we showed similar restoration of this disorganization with diminished pain from SCS therapy. This normalization of disorganization or restoration seems to be a robust observation. Thus, it is unlikely that our observation was a result of some kind of stimulation artifact or epiphenomenon because similar results occurred with pain relief as a result of very different therapies. In addition, our subject had maintained normalization of disorganization (restoration) with lingering pain relief after the stimulation had been turned off. If this cortical disorganization and its restoration prove to be sufficiently reproducible, the shift from an abnormal to a normal location of activation with pain therapies could be used as a marker of treatment efficacy. Furthermore, our results were instantaneous and immediately adjustable, which has never been reported before. This could then support a mechanism of plastic changes that could be explained by a SCS-induced unmasking of preexisting but previously latent afferent connections to SI (10). Given the acute time frame of changes in cortical restoration with SCS, structural reorganization like axonal sprouting is likely excluded as has been previously speculated (10). Acute changes within SI with pain have been shown before. With MEG, Sosor et al. showed that acute pain, evoked by intradermal injection of capsaicin in normal subjects, caused rapid functional disorganization of the somatosensory cortex (17). Kriakopoulos et al. performed fMRI on patients with leg pain treated with thoracic SCS, demonstrating SI activation with stimulation, but these fMRI studies required externalized lead systems and no evoked responses were elicited (18).

Both Juottonen et al. and Maihofner et al. found that somatosensory-evoked magnetic fields were significantly increased on the CRPS side compared with the unaffected side (8,9). We were not able to quantify this with our limited data set. Juottonen et al. could not establish an individual correlation between pain intensity and the amount of cortical alteration (8). In contrast, Maihofner et al. established a correlation between the amount of cortical disorganization and the intensity of CRPS pain and the extent of mechanical hyperalgesia as assessed with the McGill Pain Questionnaire, whereas the rating of acute pain was not correlated (9). We could not establish such a correlation with our very limited data set. However, the extent of restoration of cortical disorganization seemed to be correlated with our patient’s perception of pain load and not the acute level of pain. Ours is the first report of a graded restoration of cortical representation with partial pain relief as a result of SCS when the stimulator was turned off. This does emphasize the potential to correlate and calibrate the extent of pain and pain relief and cortical disorganization and subsequent restoration in an instantaneous fashion in an individual patient with the ability to modulate the patient’s pain perception in a graded and reversible fashion with SCS. This further raises the potential use of developing an objective measuring tool or biomarker for pain in which we can now begin a calibration process.

Using MEG, Walton et al. found peaks of low-frequency activity in the delta and theta bands concentrated over the somatosensory representation of the region in which pain was localized in CRPS patients (19). However, the effects of successful pain treatment on these bands of activity have not been fully investigated. Although Zonenshayn et al. found that these bands of activity did not exhibit significant differences between the stimulator on vs. off states in five subjects with spinal cord stimulators, their preliminary results support the potential use of MEG as a noninvasive screening tool in the selection of possible candidates for SCS therapy (20). It may be possible that the extent of restoration of evoked cortical disorganization during a trial phase of SCS might help predict success of SCS therapy.

Ours also is the first report of an apparent acute reversible interconnection in the cortical representation of D1 and D5. It may be that with further chronicity of CRPS, the disorganization or contraction of D1 and D5 representations may eventually lead to inversion. Previous reports (8,9,16) have been in patients with relatively shorter duration of CRPS disease (several months to less than two years), whereas our patient suffered from CRPS for more than eight years. Some patients with CRPS can develop limb dystonia and SCS can be helpful in the treatment of dystonia, although this has been controversial (21–23). Our patient did not have any clear hand dystonia.

Patients with focal hand dystonia (FHD) are known to have spatial inversion of digit somatotopy within the SI cortex (24–26), with the extent of inversion correlating with the severity of dystonia (27). However, abnormal finger digit somatotopies appear to be present in both hemispheres of FHD patients despite the fact that only one hand has FHD. Reversal of this spatial inversion has not been shown in FHD. Using a different methodologic approach, Pleger et al. used electroencephalograms (EEG) to localize dipole sources of somatosensory-evoked potentials (SEPs) after electrical stimulation of the median and ulnar nerve in patients with CRPS (28). They found that the cortical representation of the CRPS-affected hand was significantly smaller than that of the contralateral healthy hand. Mean pain intensity over several weeks appeared to be a valid predictor for the amount of cortical disorganization. Although there is a paucity of work utilizing EEG with SCS, Polacek et al. demonstrated in failed back surgery patients that SCS attenuated the cortical responses to tibial and sural nerve stimuli in the SI cortex (29). It was thought that the suppression of somatosensory processing during SCS might contribute to the reduction of allodynia that accompanies successful...
treatment of neuropathic pain with SCS. There have been no reports utilizing EEG or somatosensory evoked potentials attempting to define a biomarker for chronic pain or their use in combination with SCS for this purpose.

Others have reported that the extent of cortical disorganization could not be correlated with immediate pain levels but with average pain levels over longer periods of time (8–10, 28). This was more likely as a result of the limitations of those previous studies because they could not instantaneously modulate pain levels with the SCS tool. Our case study and the study of Polacek et al. have suggested that the extent of cortical disorganization can be instantaneously modulated with SCS (29).

CONCLUSION

Our limited data demonstrate that disorganization of SI cortex might be a neurophysiologic marker of chronic pain as shown with instantaneous normalization of SI disorganization or restoration of SI organization with therapeutic SCS. As a clinically proven tool for functional mapping, MEG might be shown to provide an objective measure of chronic pain. More data are required to further investigate this possibility.

Acknowledgement

The report was supported by the United Hospital Research and Education Fund.

Authorship Statements

Both authors were involved in the research design, data acquisition, analysis, and interpretation and in drafting the paper and reviewing it critically.

How to Cite this Article:


REFERENCES


COMMENTS

Although only two subjects were involved in this study, I believe this is an important preliminary piece of work. In the current era of evidence based medicine, one of the greatest challenges facing neuro-modulation and pain medicine is a lack of objective patient measures. These objective measures are needed for continued design of prospective randomized trials which justify the use of expensive and invasive therapies related to neuromodulation.

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The ability to have an objective marker such as MEG to not only diagnose a painful condition like CRPS but to also use it as a confirmatory modality to determine that indeed cortical processing of pain signals has changed is a significant step forward towards independent markers for pain diagnosis. While in case report form, this manuscript asks the important question of what cerebral processing is being
altered with spinal cord stimulation and paves the way for future investigation, using yet another measure of functional change with regard to an interventional technique.

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Comments not included in the Early View version of this paper.