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Dynamic Oscillatory Signatures of Central Neuropathic Pain in Spinal Cord Injury

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Abstract: **Central neuropathic pain (CNP) is believed to be accompanied by increased activation of the sensorimotor cortex. Our knowledge of this interaction is based mainly on functional magnetic resonance imaging studies, but there is little direct evidence on how these changes manifest in terms of dynamic neuronal activity. This study reports on the presence of transient electroencephalography (EEG)-based measures of brain activity during motor imagery in spinal cord–injured patients with CNP. We analyzed dynamic EEG responses during imaginary movements of arms and legs in 3 groups of 10 volunteers each, comprising able-bodied people, paraplegic patients with CNP (lower abdomen and legs), and paraplegic patients without CNP. Paraplegic patients with CNP had increased event-related desynchronization in the theta, alpha, and beta bands (16–24 Hz) during imagination of movement of both nonpainful (arms) and painful limbs (legs). Compared to patients with CNP, paraplegics with no pain showed a much reduced power in relaxed state and reduced event-related desynchronization during imagination of movement. Understanding these complex dynamic, frequency-specific activations in CNP in the absence of nociceptive stimuli could inform the design of interventional therapies for patients with CNP and possibly further understanding of the mechanisms involved.**

Perspective: ***This study compares the EEG activity of spinal cord–injured patients with CNP to that of spinal cord–injured patients with no pain and also to that of able-bodied people. The study shows that the presence of CNP itself leads to frequency-specific EEG signatures that could be used to monitor CNP and inform neuromodulatory treatments of this type of pain.***

Key words: *Central neuropathic pain, spinal cord injury, event-related synchronization/desynchronization, motor imagery, electroencephalography.*

Central neuropathic pain (CNP) is caused by an injury to the somatosensory system[3,19] and has a high prevalence in patients suffering from amputation (80%),[15] spinal cord injury (SCI; 40%),[47] multiple sclerosis (27%),[43] Parkinson disease (10%),[6] and stroke (8%).[2] Its symptoms do not respond well to medication, and the drugs used are often associated with significant adverse effects.[4,37,57] This has generated interest in non–drug-based treatment methods such as cognitive-behavioral therapies[21,23] and interventions such as repetitive transcranial magnetic stimulation (rTMS),[20,21,29,30,38,45,52] transcranial direct current stimulation (tDCS),[10,12,21,29,38,45] and neurofeedback (NF).[22,25,27,48,56] Although multiple studies have confirmed efficiency of these stimulation interventions for various types of acute or chronic pain, including CNP,[10,20,25,26,30,45,56] the stimulation parameters and spatial targets are often determined heuristically.[25,29,30]

Many studies have shown a correlation between CNP and reorganization of the sensorimotor cortex[15,17,59]

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where, because of sensory loss caused by the injury, the affected cortical somatotopy undergoes remapping or reorganization.[59] Comparative functional magnetic resonance imaging (fMRI) studies involving SCI patients demonstrate that during the performance of imagined movements, those patients with CNP show activation of brain areas related to both motor imagery (MI) and pain processing.[18] It has now been proposed that the intensity of the perceived pain is proportional to the extent of reorganization influencing cortical sensorimotor processing.[59] However, the observation that phantom pain in amputees correlates more strongly with maintained phantom representation than with a remapped representation of intact body parts contradicts this hypothesis.[32] Nevertheless, the above results indicate that relationships exist between the pathology underlying CNP and long-term adaptive changes in cortical activation associated with sensorimotor behavior even in the absence of a painful peripheral stimulation.

Although fMRI studies of patients with CNP can provide an anatomic spatial focus for further investigations, the method cannot provide the temporal resolution needed to understand the dynamics of the activation patterns that may exist in CNP. In this regard, electroencephalography (EEG) can provide a useful noninvasive basis for experimental investigation. On the other hand, EEG has a very limited spatial resolution as it records the electrical activity from the surface of the skull, thus measuring the combined activity of near and distant cortical sources. Furthermore, EEG measures only surface cortical activity, and as a result the activity of deeper cortical structures involved in processing of chronic pain, such as anterior cingulate cortex and insular cortex, cannot be measured.

At present, EEG recordings of patients with CNP have been limited to studies of resting EEG in eyes open (EO) and eyes closed (EC) states,[11,24,36,46] suggesting that the increased power in the theta range and decreased frequency of the dominant alpha rhythm are major signatures of CNP. These observed changes in EEG power were widespread and not restricted to any specific area of the cortex.[11,24,36,46]

Although these studies demonstrate altered EEG activity in resting states, they do not attempt to explore how CNP influences brain activation patterns during performance of tasks that require sensorimotor processing analogous to those used in fMRI studies.[18,59] Accordingly, we undertook this EEG-based study to quantitatively examine the brain activation patterns associated with the presence and absence of CNP in patients with SCI while they performed imagined motor tasks.

MI induces dynamic activation of sensorimotor cortical areas that can be recorded by EEG in healthy subjects and in patients with paralysis due to SCI. The use of MI as an activation probe and EEG as the recording modality therefore presents a simple noninvasive way to explore the comparative cortical activation patterns that accompany MI in patients with and without CNP. This study's principal aim was to examine the evidence for altered cortical activations in patients with and without CNP in the absence of peripheral nociceptive stimulation. Our final goal was to determine if EEG-based electrophysiological markers of the condition can be identified and whether this knowledge can assist in designing more effective rTMS, tDCS, or NF treatment interventions for CNP.

Methods

Participants

A total of 30 age-matched adult (between 18 and 55 years old) volunteers were recruited in 3 groups of 10. The groups were as follows:

1. Paraplegic patients with diagnosed CNP below the level of their spinal cord injury (3 female [F], 7 male [M], age 45.2 ± 9.1 [mean ± standard deviation])
2. Paraplegic patients with no chronic pain (2 F, 8 M, age 44.4 ± 8.1)
3. Able-bodied volunteers with no chronic pain (3 F, 7 M, age 39.1 ± 10.1)

The neurologic level of SCI was determined using the American Spinal Injury Association (ASIA) Impairment Classification.[33] All SCI patients were at least 1 year post-injury and had a spinal lesion at or below T1. Inclusion criteria for patients with CNP were a positive diagnosis of CNP; a reported pain level ≥5 on the visual numerical scale; and a treatment history of CNP for at least 6 months. The general exclusion criteria for all 3 groups were a presence of any chronic (non-CNP) or acute pain at the time of the experiment; brain injury; or other known neurology that would affect EEG interpretation or would prevent patients from understanding the experimental task. Information on both patient groups is shown in Tables 1 and 2.

Informed consent was obtained from all participants, and ethical approval was obtained from the university ethical committee for the able-bodied group and from

Table 1. Information About Patients With CNP (PWP Group)

No.	Level of Injury	ASIA Classification	Years After Injury	Pain VNS	Years With Pain	Medications
1	T5	A	7	7	7	Baclofen, carbamazepine, gabapentin
2	T5/6	A	11	6	11	None
3	T5	A	7	8	7	Pregabalin, gabapentin
4	L1	B	15	7	15	Gabapentin
5	T6/T7	D	4	7	3	Pregabalin
6	T7	B	6	8	5	None
7	T6/7	B	25	10	24	Gabapentin
8	T1	A	25	5	10	Pregabalin
9	T5	A	14	5	13	Amitriptyline, baclofen, diazepam
10	L1	B	5	5	4	None

Abbreviation: VNS, visual numerical scale.