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Investigation of neural markers in chronic pain in spinal cord injury: a TMS and EEG preliminary study and a brief systematic review

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Abstract:

Objectives: *We aim to understand further neural mechanisms in spinal cord injury (SCI) pain as indexed by transcranial magnetic stimulation (TMS) and quantitative electroencephalography (qEEG).*

Design: *Observational study and a brief systematic review.*

Methods: *We assessed six SCI pain and 10 healthy subjects with TMS, qEEG and clinical measures involving Visual Analog Scale (VAS) for pain perception, Pressure-Pain Threshold (PPT), and Diffuse Noxious Inhibitory Control (DNIC). We also conducted a review of the literature to compare our TMS and EEG results with similar studies in chronic neuropathic pain associated with SCI, chronic neuropathic pain alone and SCI without pain.*

Results: *Our findings in SCI pain group were similar to the literature involving decreased intracortical inhibition (ICI), decreased peak frequency and decreased alpha power. Additionally, we showed that EEG power ratios (alpha/theta ratio and alpha/low-beta) positively correlated with changes in DNIC.*

Conclusion: *The similarities between our findings and the literature support the idea that SCI pain has a similar neural signature when compared to other deafferentation syndromes. Moreover, the correlation between EEG alpha ratios and response to DNIC can be used as a potential marker in future studies investigating neurophysiologic predictors of treatment response.*

Key-Words: *spinal cord injury, transcranial magnetic stimulation, pain, qEEG*

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INTRODUCTION

Spinal cord injury (SCI) affects approximately 270,000 individuals in the United States, with about 12,000 new cases every year (Center, 2013). More than half of SCI patients experience a significant level of pain (Siddall, 2003; Soler, 2007). This pain is associated with higher rate of depression (Ataoglu, 2013) and a decreased quality of life (Masri, 2012; Putzke, 2002). Amongst all the different types of pain associated with SCI, literature acknowledges neuropathic pain as the most incapacitating form (Masri, 2012). Although conventional pharmacological treatments are universally suboptimal for all types of pain, they are mostly ineffective to provide long-term analgesia in SCI patients with pain (Baastrup, 2008). A better understanding of the neurophysiologic mechanisms involved in neuropathic pain in SCI is crucial to develop useful and reliable pharmacologic treatments.

To further understand neural changes associated with chronic pain in SCI, we assessed cortical excitability in SCI pain and healthy subjects using TMS, qEEG and clinical measures. Also, to compare our results, we reviewed the literature investigating EEG and TMS outcomes in (1) SCI pain, (2) SCI without pain (SCI only) and (3) other types of neuropathic pain. We aimed, therefore, to assess simultaneously and preliminarily EEG and TMS markers in SCI pain.

METHODS

Participants

Participants were recruited at Spaulding Rehabilitation Hospital (Boston, MA) between June 2011 and December 2012. An independent physician diagnosed the patients with neuropathic pain. We included patients based on the following criteria: (1) age between 18 to 64 years-old; (2) presenting with a traumatic spinal cord injury (complete or incomplete); (3) experiencing stable chronic neuropathic pain for at least three preceding months; (4) presenting a score equal or higher than 4 (0='no pain' and 10 = 'worst possible pain') on the Visual Analogue Scale (VAS) for pain; and (5) presenting pain resistant to at least two traditional pharmacological treatments supplied in adequate dosages for at least six months.

The exclusion criteria included (1) pain attributable to other causes, such as peripheral inflammation or musculoskeletal pain; (2) clinically significant or unstable medical or neuropsychiatric condition; (3) a history of substance abuse; (4) documented traumatic brain injury, skull fracture, or objective neurological findings assessed at the time of recruitment suggestive of neurological conditions other than SCI; (5) pregnancy or (6) ventilatory support. We recruited six SCI pain subjects (2 women, mean age= 46; SD: ±14.8) meeting the inclusion criteria and ten healthy participants (5 women, mean age: 32.5; SD: ±13.02). All subjects gave their written informed consent, and the study was approved by Spaulding Rehabilitation Hospital Institutional Review Board (IRB).

Transcranial magnetic stimulation (TMS) Assessment

Electromyography (EMG) recordings were acquired using surface electrodes, with the positive electrode positioned over the right first dorsal interosseous (FDI) muscle or flexor carpi radialis muscle (FCR), the negative over the thenar eminence, and the reference to the anterior surface of the forearm close to the wrist. EMG signal was amplified (x1000) and band-pass filtered between 20 and 2000 Hz. The stimulation coil was held tangentially to the skull, with the handle pointing backward and laterally at 45◦ from the midline. EMG data was recorded and analyzed with LabChart 7 (AD Instruments Pty Ltd, Australia).

Resting motor threshold (MT) was established as the smallest intensity at which an MEP of at least 50μV could be elicited in at least 3 out of 5 consecutive trials. Paired-pulse stimulation protocols were used to measure intracortical inhibition (ICI at 2 and 3 ms interstimulus interval) and facilitation (ICF at 10 and 12 ms inter-stimulus interval). In the paired-pulse protocol, an initial sub-threshold pulse (conditioning stimulus) is set to 80% of MT, followed by a second pulse (test stimulus) with a set intensity to elicit an MEP of approximately 1mV. For each measure, we attempted ten trials over the left hemisphere. We evaluated the ICI and ICF as the ratio between the magnitude of the MEP during inhibition or facilitation and the first MEP measure. We calculated the MEP amplitude as the mean amplitude of single-pulsed MEPs elicited using a supra-threshold stimulus.

Quantitative Electroencephalography (qEEG)

QEEG data was acquired by using a vertex referenced 64-electrodes HydroCel Geodesic Sensor Net (Electrical Geodesics Inc, Oregon, USA), and the EGI Net Station software. During the EEG recording participants were asked to keep their eyes closed for ten minutes in a relaxed position but were not allowed to sleep. We used EEGLab (Delorme, 2004) and MATLAB (MATLAB R2012a, The MathWorks Inc. Natick, MA, 2000) to analyze the EEG data. Each data set was bandpass filtered (1-40 Hz), epoched and cleaned from artifacts by automatic epoch rejection followed by visual inspection of epochs. Following artifact removal, data was re-referenced to the average of all channels. We used a fast Fourier transformation to calculate the absolute power. We also calculated the mean power for each bandwidth spectrum (theta (4- 8Hz), alpha (8-12Hz), low-beta (12-21 Hz), and highbeta (21-30 Hz)), the dominant peak frequency and alpha/theta and alpha/beta ratios. For each frequency band, we chose the electrodes of interest using the common 10-20 EEG localization system (for the theta band, the electrodes corresponding to P3, P4, O1 and O2 (parietooccipital); for the alpha band, O1-Oz-O2 (occipital); for the beta band, F3 and F4 (frontal)). These electrode sites are considered as the most representative for each respective band (Kropotov, 2010).

Clinical Measures

Clinical measures included: (1) Visual Analog Scale (VAS) for pain; (2) Pressure-Pain Threshold (PPT); and (3) Diffuse Noxious Inhibitory Control (DNIC). For the VAS, subjects were asked to rate their pain on a visual scale, indicating the number that best described it at the moment of assessment, ranging from 0 ('no pain') to 10 ('worst possible pain'). VAS scores were obtained at both times: screening (to determine eligibility) and during the study visit. We included the VAS scores collected during the study visit in the data analysis to minimize the variability between measurements.

We assessed PPT by applying a blunt pressure delivered by a 1-cm 2 hard-rubber probe with an algometer (JTECH medical). During testing, a series of discrete weights were applied to the thenar area. Participants were to inform the investigator when the pressure became painful, and the pressure was recorded

as PPT. We repeated the procedure three times for each hand. In DNIC, we used a conditioning stimulus (cold water at 10-12ºC as the noxious stimulus that evokes DNIC activation) followed by a test stimulus (a second noxious stimulus used to evaluate the analgesic response to the conditioning stimulus – here, PPT). We chose cold water as our conditioning stimulus, as this is one of the most common paradigms used to induce DNIC (Pud, 2009). Subjects first immersed their contralateral hand into a water bath maintained at 10-12˚C for 1 min; then, while subject's hand is still in the water, we tested the PPT as described, and the value on the algometer was recorded as the outcome variable. DNIC represents the bottom-up activation of the descending endogenous analgesia system, which is known to be dysfunctional in patients with chronic pain (Lewis, 2012b; Pud, 2009). It is thought that the DNIC system leads to decreased pain input from other parts of the body when a new painful stimulus is introduced to a remote site of the body (Lewis, 2012a). We also assessed the patients with the Beck Depression Inventory (BDI).

Literature Review

We carried out a brief systematic review using PubMed as the primary search engine. We searched for original research articles in English published between January 1995 and December 2016. The search included studies investigating (1) TMS and/or (2) qEEG measures in human subjects with (3) SCI and pain, (4) SCI without pain (SCI only) and with other types of (5) neuropathic pain. We used the following search criteria: EEG OR electroencephalography OR qEEG OR quantitative electroencephalography OR neurophysiologic OR neurophysiological OR transcranial magnetic stimulation OR TMS OR motor evoked potentials OR motor thresholds OR MEP OR intracortical inhibition OR cortical inhibition OR cortical excitability OR cortex disinhibition) AND (SCI OR spinal cord injury OR neuropathic pain OR neural pain OR neurogenic pain OR central pain OR chronic pain OR CRPS OR phantom limb pain. The search resulted in a total of 1363 studies. One of the investigators initially inspected the titles and abstracts of the retrieved articles to eliminate irrelevant and nonhuman studies, s well as articles in other languages. We further excluded studies (1) testing repetitive TMS or any other interventions unless there was a baseline comparison of patients and healthy subjects, (2) using invasive EEG methods and (3) reporting cases. Investigators were not blinded to the authors and/or journals of the retrieved articles. Any disagreement among investigators was resolved by consensus. Finally, we included 79 studies fulfilling the above criteria in this study.

Statistical Analysis

We performed the statistical analyses using STATA 12 software (StataCorp. 2011, College Station, TX) and conducted separated analyses for each neurophysiologic measure (EEG: Peak frequency and power of theta, alpha, low-beta, high-beta bands; TMS: MT, paired-pulse measures, MEP) and clinical measures (VAS, PPT, DNIC). We used unpaired t-tests to assess differences between healthy and SCI pain subjects for the TMS measures, and Mann-Whitney for the EEG measures, as the EEG data did not follow a normal distribution. We conducted Spearman's rank correlation tests between clinical measures and neurophysiologic variables to assess whether neurophysiologic indicators were associated with modifications in clinical measures. The change in PPT induced by the noxious stimulus during DNIC was calculated using the following formula: (DNIC-PPT)/PPT. We used Spearman's correlation analysis between the change and different power bands ratio (alpha/theta, alpha/beta) to assess whether the difference in baseline EEG ratios would be associated with the response elicited by DNIC within groups. We also calculated exploratory correlation tests between TMS and EEG measures.

RESULTS

Individual characteristics of SCI pain subjects are summarized in Table 1.

Quantitative EEG

Data from one healthy and one SCI pain subject could not be analyzed because of excessive artifacts. Compared to the healthy subjects, SCI pain subjects had significantly lower alpha power (Mean ± SD; healthy: 1.74 ± 1.08 [CI: 0.96 - 2.52], SCI pain: 0.45± 0.26 [CI: 0.20 – 0.71], p = 0.02) (Figure 2) and lower alpha/theta ratio (p = 0.02). In addition, peak frequency was significantly lower (Figure 3) in SCI pain compared to healthy subjects (Mean ± SD; healthy: 9.99 ± 1.24 [CI: 9.09 - 10.89], SCI pain: 7.78 ± 1.52 [CI: 6.31 – 9.25], p = 0.009). There were no significant differences for other frequency domains such as theta (p = 0.94), alpha/lowbeta (p = 0.38) or alpha/high-beta (p = 0.16).

TMS measures

SCI pain subjects had decreased ICI (Figure 1) compared to healthy subjects (% of original MEP: 17 % healthy subjects [CI: 12.8 -21.88], 34% SCI pain subjects [CI: 18.93-49.72], p= 0.01). A trend for significance was found for the comparison of MT (p= 0.08) and MEP (p= 0.055). No significant differences were found regarding ICF (p>0.05).

A significant correlation was found between higher level of injury (cervical vs. below cervical) with decreased MEP amplitude (r= 0.82, p= 0.042), and with decreased ICI (r= -0.82, p= 0.042). Also ICI was found negatively correlated with EEG high-beta power (r= - 0.90, p = 0.03), but not with other frequency bands (p > 0.05).

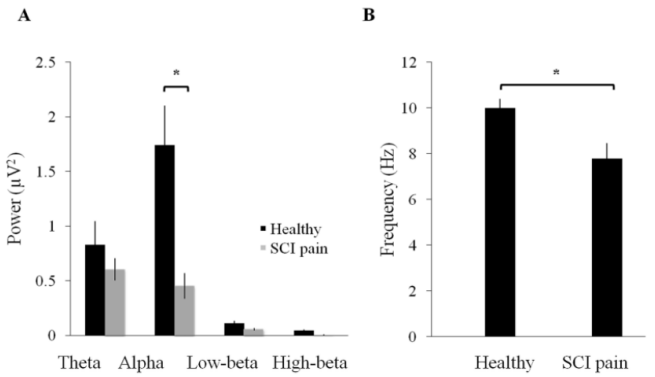

Fig.1. Comparison of intracortical inhibition (ICI) between healthy subjects and SCI pain. *Statistically significant

QEEG and clinical measures

In SCI pain subjects, alpha power positively correlated with VAS scores (p = 0.004; Spearman Rho: 0.97) and both alpha/theta ratios and alpha/low-beta ratios showed a significant correlation with a DNIC induced change in PPT on the right hand. SCI pain subjects who had lower ratios showed lesser changes with DNIC stimulation (alpha/theta: Spearman Rho: 0.9, p = 0.03; alpha/low-beta: Spearman Rho: 0.9, p = 0.03) (Figure 3A and Figure 3B). No such correlations were found for left hand DNIC stimulation and for healthy subjects (alpha/theta: Spearman Rho: 0.03, p = 0.93; alpha/low-beta: Spearman Rho: 0.18, p = 0. 63).

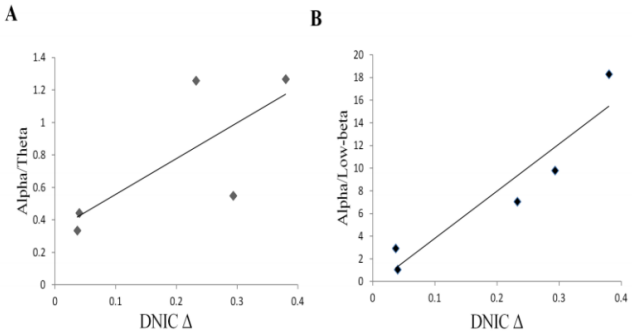

Fig.3. Comparison of EEG measurements between healthy subjects and SCI pain. (A) Power per frequency band; (B) Peak frequency. *Statistically significant Figure 3. Correlations between diffuse noxious inhibitory control (DNIC) induced pressure pain threshold changes (DNIC Δ) and EEG ratios in SCI pain. (A) DNIC Δ and alpha/theta (Spearman Rho: 0.9, p= 0.03); (B) DNIC Δ and alpha/beta (Spearman Rho: 0.9, p=0.03

Literature review

Most common findings are summarized in Table 2. QEEG studies in SCI with pain (SCI pain) and SCI without pain (SCI only) The most common finding reported in SCI pain subjects was a shift in peak frequency towards lower frequencies (Boord, 2008; Vuckovic, 2014; Wydenkeller, 2009) as compared to SCI only and healthy subjects. On the alpha band, SCI pain subjects were found to have lower power values (Jensen, 2013), and reduced reactivity to sensory input modulated by eyes open and closed states (Boord, 2008). However, conflicting results, such as increased alpha activity, were also reported (Vuckovic, 2014). Other findings in SCI pain included an increase in theta band power (non-significant trend) and a positive correlation between alpha power and pain levels (Jensen, 2013). Increased event-related desynchronization during movement imagination was also reported (Vuckovic, 2014).

Other studies compared SCI only subjects with healthy controls without separating SCI pain (Herbert, 2007; Tran, 2004). They also showed lower alpha powers, lower peak frequencies and higher beta powers in SCI subjects. Additional findings in SCI included abnormal or absence of somatosensory- evoked potentials (Cheliout-Heraut, 1998; Kuhn, 2012; Lewko, 1995; Spiess, 2008), altered event- related synchronization-desynchronization (Cremoux, 2013; Gourab, 2010; Muller-Putz, 2014; Muller-Putz, 2007) and cortical network changes (De Vico Fallani, 2007; De Vico Fallani, 2008; Mattia, 2009; Mattia, 2006).

QEEG Studies in Neuropathic Pain

EEG studies in neuropathic pain patients showed increased power in both lower and higher frequencies, including theta band (Drewes, 2008; Llinas, 1999; Michels, 2011; Olesen, 2011; J Sarnthein, 2003; Stern, 2006), delta band (Olesen, 2011), and beta band (Michels, 2011), or in broader bandwidths (J. Sarnthein, 2006). For the alpha band, both decrease and increase were reported (Michels, 2011; J. Sarnthein, 2006). Similar to SCI pain, a shift toward slower activities in dominant peak frequency (de Vries, 2013; J. Sarnthein, 2006) and a correlation between pain intensity and EEG activity (Michels, 2011) were also found. Other findings included disrupted patterns of post-movement beta synchronization (Reyns, 2008).

TMS measures in SCI

Most common findings in SCI patients were decreased MEP amplitudes and increased MEP latencies (Alexeeva,

No.	Age	Gender	Etiology	Level of injury	Nature of lesion	Pain Level	Duration of injury	VAS	BDI	QOLS	Medication
1	34	Male	Traumatic	C6	Incomplete	Below lesion	6	5	5	91	Gabapentin, Duloxetine, Oxycodone, Vicodin
2	39	Male	Traumatic	T12-L1	Incomplete	Below lesion	4	7	14	98	Gabapentin, Baclofen, Vicodin, Duloxetin
3	52	Male	Traumatic	C6	Incomplete	Below lesion	NA	6.5	9	78	Fentanyl Patch, Gabapentin, Duloxetine, Baclofen
4	27	Male	Traumatic	T2-T6	Incomplete	Below lesion	4	6	4	78	Gabapentin, Baclofen, Tizanidine, Oxycodon
5	62	Female	Traumatic	C6	Incomplete	Below lesion	5	3	0	70	Gabapentin, Baclofen, Fluoxetine
6	62	Female	Traumatic	C5-C7	Incomplete	Below lesion	7	6	0	110	Baclofen, Tizanidine, Gabapentin, Advil, Duloxetine

Table1.Baseline characteristics of SCI pain subjects. BDI-Beck Depression Inventory, QOL-Quality of Life, VAS-Visual Analog Scale for Pain

	SCI pain	SCI*	Neuropathic Pain
EEG	Shift in peak frequency toward lower frequencies, increased and decreased alpha power, increased theta power, positive correlation between alpha power and pain levels, increased ERD during movement	Shift in peak frequency toward lower frequencies, decreased alpha power, increased beta power, abnormal SSEP and ERS/ERD, cortical network changes	Shift in peak frequency toward lower frequencies, decreased alpha power, increased power in alpha, delta, theta and beta band, positive correlation between EEG activity and pain levels, disrupted patterns of post-movement beta synchronization
TMS	**	Decreased MEP amplitudes, increased MEP amplitudes above the level of injury, increased MEP latencies, altered MEPs with volunteer contractions, increased AMT and RMT below the level of injury, and decreased MT above the level of injury, associations between MEP/MT and degree of injury, severity of symptoms and functional outcomes; reduced SICI and LICI, decreased and increased SP, longer central conduction times	Reduced ICI, increased and decreased SP and MT, increased MEP

Table 2. Summary of the brief systemic review.* Includes studies that do not specify patients with pain separately. ** No TMS study was found differentiating between SCI and SCI pain. TMS: Transcranial Magnetic Stimulation; EEG: Electroencephalography; SCI: Spinal cord injury; ERD: Event-related desynchronization; ERS: Event-related synchronization; SSEP: Somatosensory evoked potentials; MEP: Motor evoked potentials; AMT: Active motor threshold; RMT: Resting motor threshold; SICI: Short interval cortical inhibition; LICI: Long interval cortical inhibition; SP: Silent Period; ICI: Intracortical inhibition

1998; Alexeeva, 1997; Barthelemy, 2010; Brouwer, 1997; Calancie, 1999; Cariga, 2002; Curt, 1998; Davey, 1999; Davey, 1998; Labruyere, 2013; Laubis-Herrmann, 2000; Lissens, 1996; Lotze, 2006; Puri, 1998; Roy, 2011; Smith, 2000a; Smith, 2000b; van Hedel, 2007; Wirth, 2008). Increased MEP amplitudes above the level of injury(Streletz, 1995), and altered MEPs with volunteer contractions (Bunday, 2013; Davey, 1999; Diehl, 2006) were also reported. In addition to MEP changes, increase in both active motor thresholds (AMT) (Davey, 1999; Freund, 2011) and resting motor thresholds (RMT) (Calancie, 1999; Davey, 1998; Shields, 2006; Smith, 2000a) below the level of injury and decrease in motor thresholds (MT) above the level of injury (Cariga, 2002)

were reported. Changes in MEPs and MTs were also found to be related to the degree of injury (Freund, 2011), severity of symptoms (Barthelemy, 2010; Bondurant, 1997; Lundell, 2011) and functional outcomes (Barthelemy, 2013; Cheliout-Heraut, 1998; Curt, 1998; Lewko, 1995; Petersen, 2012; Wirth, 2008). Another common finding in SCI was altered intracortical inhibition (ICI) (Barry, 2013; Bunday, 2013; Bunday, 2012; Bunday, 2014; Cheliout-Heraut, 1998; Davey, 1998; Kriz, 2012; McKay, 2005; Roy, 2011; Smith, 2000a; Smith, 2000b). These studies indicate that patients with SCI have reduced short and long interval inhibition and exhibit reduced changes to SICI when voluntary contractions are performed. The duration of silent period has been reported to be both increased (Barry, 2013; Freund, 2011; Lotze, 2006) and decreased (Shimizu, 2000). The absence of physiological lengthening of cortical silent period (Nardone, 2013) and longer central conduction times were also found in SCI patients (Han, 2008; Schmid, 2005). TMS measures in neuropathic pain

Studies investigating cortical excitability in chronic neuropathic pain syndromes, including Complex Regional Pain Syndromes (CRPS) (Eisenberg, 2005; Krause, 2004; Lenz, 2011; Schwenkreis, 2003), amputated limb pain (Schwenkreis, 2000), hand pain with neurogenic origins (Lefaucheur, 2006), central post-stroke pain (Hosomi, 2013) and incomplete peripheral nerve lesions (Schwenkreis, 2010) showed consistently reduced ICI. Findings regarding silent period (SP) and MT were conflicting. Two of the studies found shorter SP (Lefaucheur, 2006; Turgut, 2009), whereas the other study found increased SP (Strutton, 2003). Similarly, both increased (Hosomi, 2013; Strutton, 2003) and decreased MT (Turgut, 2009) were reported. MEPs were found increased (Karl, 2001).

DISCUSSION

The main goal of the present study was to explore the neurophysiologic characteristics of SCI patients with neuropathic pain (SCI pain) as compared to healthy subjects. Our results are in line with two of the most commonly reported neurophysiologic findings in neuropathic pain and SCI pain: decreased ICI measured by paired-pulse TMS and lower peak frequencies in EEG power spectrum. In fact, our results confirm the hypothesis that SCI pain presents similar findings as neuropathic pain. From our results and review, it seems that the neural signature of pain in SCI is more similar to patients with neuropathic pain than SCI only (without pain).

The aforementioned results are consistent with a common TMS finding in neuropathic pain: reduced intracortical inhibition. In neuropathic pain, a neural lesion in the corticospinal tract or the peripheral nerves can lead to deafferentation of sensory input in the cortex, resulting in loss of GABAergic inhibition and abnormal recruitment of glutamatergic receptors that would allow cortical re-organization (Canavero, 1998; Guilbaud, 1992; Koyama, 1993; Levy, 2002). These changes are reflected by an increase in cortical excitability and a decrease in inhibition which can be measured by TMS. However, it is not known if the decrease in ICI is the result of reorganization causing pain, or if the reduction in ICI itself may lead to secondary maladaptive plasticity resulting in pain. In addition to reduced ICI, we found a trend for increased MT and decreased MEPs, and a significant correlation between the level of injury and MEP and level of injury and ICI, which all reflect the global corticospinal hyperexcitability and decreased density of the number of corticospinal axons involved in SCI (Davey, 1998; Oudega, 2012).

Our EEG results are also similar to the literature in neuropathic pain as we demonstrated that alpha band is reduced when compared to healthy subjects and also a shift in peak frequency towards slower frequencies. One of the suggested mechanisms underlying these results is the thalamocortical dysrhytmia (TCD), which is known to play major role in variety of neuropsychiatric disorders. In TCD, deafferentation of excitatory input over thalamus leads to the generation of aberrant spontaneous oscillatory activity of the neurons and cause a shift in the dominant spectral power from the alpha band (8-13Hz) towards the lower theta band (4- 8Hz) frequencies with periods of high frequency oscillatory activity characterized by beta and gamma band rhythms (Llinas, 1999). The shift in the dominant spectral power to slower activities has consistently shown to be related to the presence of neuropathic pain, but not to other deafferentation conditions when there is no pain (Boord, 2008; Vuckovic, 2014; Wydenkeller, 2009). Furthermore, Wydenkeller et al.(2009) showed that EEG peak frequency could be discriminative in distinguishing SCI pain subjects from SCI subjects without pain (Wydenkeller, 2009).

Our results are also consistent with other EEG studies assessing SCI pain. Jensen et al.(2013) showed significantly lower alpha powers in subjects with SCI pain compared to SCI only (Jensen, 2013), and Boord et al.(2008) (Boord, 2008) showed reduction in peak theta-alpha frequencies and lesser changes in power spectrum densities in SCI pain subjects as compared with SCI only and healthy subjects. Another common finding in neurogenic pain conditions is the increase in theta band power (Llinas, 1999; Michels, 2011; J Sarnthein, 2003;

Stern, 2006). Although we did not observe higher theta band powers in SCI subjects, when we calculated the ratios between power bands, we found significantly lower alpha/theta ratios. Since TCD represents a shift from alpha spectrum to theta spectrum, comparing individual alpha/theta ratios could provide more robust information about the specific oscillatory activity related to "pain matrix".

An interesting result we found was that alpha/theta and alpha/beta ratios significantly correlated to DNIC induced PPT changes. Based on this, a decrease in the power of alpha accompanied by either theta or low-beta power increases can represent the effects of sensory deafferentation leading to reduced cortical modulation to pain response in SCI subjects. Therefore, the increments in the power of alpha and its ratio with the theta band might suggest a marker for treatment response in subjects with neuropathic pain, as those patients with "flexible" power ratios may have a better network synchronization within subcortico-cortical responses to the DNIC modulation. On the other hand, fixed oscillatory patterns that might resemble a hardwire circuitry cannot be disrupted by external intervention (DNIC). This may help to explain the variability observed in treatment response among patients.

Another interesting but expected finding was the negative correlation between ICI and high-beta power, suggesting the role of both cortical disinhibition (reduced ICI) and thalamocortical dysrhythmia (increased cortical reactivity) in pain.

Even though our literature search was limited to PubMed, based on our review, we found that there are a limited number of studies with EEG, and none with TMS, with the primary aim of investigating neurophysiologic markers in SCI pain. Multiple studies are looking at the general cortical excitability parameters in SCI and the therapeutic effects of rTMS in neuropathic pain. In addition to the lack of studies in SCI pain, the results from existing studies appear to have some inconsistencies that make it harder to draw conclusions. Identifying neural markers specific to SCI pain is as important as developing novel treatment approaches. Such neural markers could be used to monitor treatment response, as well identify SCI patients who are more prone to develop neuropathic pain, therefore providing an opportunity for early intervention. Our study supports the understanding that SCI pain has similar neurophysiologic signatures to other neuropathic pain conditions; however, larger systematic studies are needed to identify better the neurophysiologic changes associated with SCI pain.

There are several limitations in this study. First, we had a small sample size, which limits the power of the statistical analyses. Secondly, the level of injury of SCI pain subjects was heterogeneous, and the medications were not discontinued at the time of assessments. Another possible confounder that we did not address in this study is gender. It is suggested that pain is processed differently in males and females. This should be further explored in future studies (Granot, 2008; Greenspan, 2007). Nonetheless, we found significant and consistent changes in TMS and EEG measures when comparing healthy controls vs. SCI pain subjects. Finally, it should be noted that our systematic review was based on Pubmed. Therefore, papers indexed in other databases may not be included here. On the other hand, one of the main strengths of the present study is the use of both TMS and EEG in the same subjects to quantify the neurophysiology of SCI-related neuropathic pain.

CONCLUSION

In this preliminary study we demonstrated, in the same experiment, a neurophysiologic pattern in patients with SCI and pain characterized by (i) slower peak amplitudes and lower alpha power in the EEG; (ii) decreased intracortical inhibition as indexed by TMS; (iii) a correlation between alpha power and baseline pain level; (iv) an association between alpha power and response to DNIC; and (v) a correlation between ICI and high-beta power. These main findings not only confirm results from previous studies, but also demonstrate these findings from both techniques (TMS and EEG) in the same cohort of patients. Given the importance of establishing markers of pain in SCI, our data contribute to strengthening the notion that pain in SCI has a specific neural signature. Also, though preliminarily, we also showed a significant correlation between EEG assessments and conditional pain modulation (DNIC) which supports the hypothesis that maladaptive plasticity leads to a system that may be less responsive to neuromodulation approaches.

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Conflict of interest and financial disclosure

The authors followed the International Committee or Journal of Medical Journals Editors (ICMJE) form for disclosure of potential conflicts of interest. All listed authors concur with the submission of the manuscript, the final version has been approved by all authors. The authors have no financial or personal conflicts of interest.

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