ORIGINAL ARTICLE

Electroencephalographic slowing and reduced reactivity in neuropathic pain following spinal cord injury

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Study Design: Brain wave activity in people with paraplegia, with and without neuropathic pain, was compared to brain wave activity in matched able-bodied controls.

Objectives: To investigate whether spinal cord injury with neuropathic pain is associated with a slowing of brain wave activity.

Setting: Australia.

Methods: Electroencephalographic (EEG) data were collected in the eyes open (EO) and eyes closed (EC) states from 16 participants with paraplegia (eight with neuropathic pain and eight without pain) and matched able-bodied controls. Common EEG artefacts were removed using independent component analysis (ICA). Peak frequency in the θ – α band and EEG power in the δ , θ , α and β frequency bands were compared between groups.

Results: The results show significant slowing of the EEG in people with neuropathic pain, consistent with the presence of thalamocortical dysrhythmia (TCD). Furthermore, people with neuropathic spinal cord injury (SCI) pain had significantly reduced EEG spectral reactivity in response to increased or decreased sensory input flowing into the thalamocortical network, as modulated by the eyes open and eyes closed states.

Conclusion: The results provide further evidence for alterations in brain electric activity that may underlie the development of neuropathic pain following SCI.

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Keywords: neuropathic pain; spinal cord injury; EEG; slowing; reactivity; thalamocortical dysrhythmia

Introduction

Chronic neuropathic pain is a common sequela of spinal cord injury (SCI) occurring in around one-half of people with SCI and is a major contributor to decreased quality of life.¹ However, the mechanisms responsible for neuropathic SCI pain are poorly understood and there are currently no treatments that provide consistent and effective relief.² There is evidence that suggests that neuropathic pain may arise from changes in the dorsal horn of the spinal cord following injury and it has been demonstrated in animal SCI models that neuropathic pain-like behaviour is associated with an increased responsiveness of neurons within the dorsal horn.³

As well as these changes at a spinal level, increasing attention is turning to the brain to understand better the processes that may underlie neuropathic pain following SCI. Electrophysiological studies in animals⁴ and humans⁵ demonstrate an increased responsiveness and alterations in spontaneous activity of thalamic neurons associated with pain or pain-related behaviour following SCI.

One of the features of altered spontaneous neuronal activity following SCI is an increased proportion of thalamic cells firing in an oscillatory mode,^{4,6} a phenomenon that has been observed in other neuropathic pain conditions and termed thalamocortical dysrhythmia (TCD).⁷ In clinical studies using magnetoencephalography (MEG)⁷ and EEG⁸ to measure brain activity in cortical and subcortical regions, TCD has been characterized by a shift in the dominant spectral power peak towards lower frequencies with significant enhancement of activity in the θ frequency range (4–8 Hz).^{7,8} This enhancement of activity in θ frequency

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range occurs in regions associated with pain processing such as insular cortex, anterior cingulate cortex, and primary and secondary somatosensory cortices,⁹ and it has been suggested that TCD may form the basis for a range of neurological conditions, including neuropathic pain.^{6–9} This has been further supported by the finding that the relief of central neuropathic pain obtained with therapeutic surgical lesions of the thalamus is associated with a reduction in the enhanced activity in the θ frequency range.¹⁰

We recently published experimental evidence indicating a slowing of the human EEG in response to SCI.¹¹ In a comparison of 20 people with SCI and 20 controls matched for age and sex, the SCI group had consistently lower peak frequencies in the α frequency band (8–13 Hz) at 13 out of 14 sites recorded across the head, with six posterior sites showing a significant reduction ($P < 0.05$). Owing to the prevalence of neuropathic pain in SCI being as high as 50%,¹ we hypothesized that the observed slowing of EEG frequency in SCI may be associated with neuropathic pain.

In the present study, we compared groups of people with SCI with and without neuropathic pain to test the hypothesis that the observed slowing of EEG activity in SCI is associated with neuropathic pain and possibly indicative of TCD. In addition, we investigated differences in brain activity in the thalamocortical network in response to an increase in sensory stimulation by comparing the EEG in resting states with the eyes open (EO) and eyes closed (EC).

Methods

Participants

Twenty people with paraplegia (ASIA A, T4–T12 levels) were recruited, with four being later discarded after medical record checks revealed a history of traumatic brain injury. Eight of the remaining participants had neuropathic pain (seven male, one female, age 35.3 ± 11.3 years) and eight did not have neuropathic pain (eight male, age 33.5 ± 10.3 years) as determined by their medical records. Able-bodied controls were matched to the paraplegia group for sex and age (age 34.3 ± 10.7 years). Pain type and medication details are shown in Table 1. SCI participants were approached for their willingness to enter the study when they were in-patients in a rehabilitation ward or when they were attending an outpatient clinic for review. Exclusion criteria for the study included loss of consciousness or a period of post-traumatic amnesia following injury, as determined from the participant's medical records. Informed consent to participate was obtained from all volunteers, and ethics approval for the study was obtained from the hospital and university human ethics committees.

Data collection and processing

EEG data were recorded at 14 channels (Fp1, Fp2, F3, F4, Fz, C3, C4, P3, P4, T5, T6, Pz, O1 and O2),¹² referenced to Cz,^{11,13} filtered to a bandwidth of DC–500 Hz and sampled at 2048 Hz. Electroophthalmogram (EOG) data were recorded from electrodes placed above and below the right eye and at

Table 1 Clinical information for each participant, including type of neuropathic pain experienced and medication taken at the time of this study

Participant code	Time since injury (months)	Neuropathic pain	Medication
AB1–AB16	—	None	None
NP1	4	None	None
NP2	108	None	None
NP3	326	None	None
NP4	21	None	None
NP5	22	None	None
NP6	64	None	None
NP7	24	Musculoskeletal pain	T, O
NP8	7	Musculoskeletal pain	T, A
P1	129	At, below, above level	None
P2	119	At, below level	None
P3	3	At level	G, A, M
P4	5	Below level	G, S
P5	22	At, below level	P
P6	21	At, below level	A, Mo
P7	40	At, below level	P, A
P8	82	At, below level	G, P, A, M, D, Tz

Abbreviations: A, amitriptyline; AB, able-bodied; D, diazepam; G, gabapentin; M, mexiletine; Mo, morphine; NP, no pain; O, oxycodone; P, pain; P, pregabalin; S, sodium valproate; T, tramadol; Tz, temazepam.

the left and right outer canthi. Skin preparation reduced electrode impedance below 10 k Ω .

Participants were asked to open and close their eyes at 20 s intervals. Three intervals each of EC and EO data were collected and subdivided into 2 s epochs. Independent component analysis (ICA) was used to remove blink and saccade artefact present during EO states and saccades present during EC states.^{14,15} Epochs were multiplied by a Hanning window, transformed with an fast fourier transform (FFT), scaled to form the power spectral density (PSD) and averaged across channels. Peak θ – α band frequency (PTAF) was calculated as the frequency of peak power between 4 and 13 Hz. EC/EO reactivity computed EC power divided by EO power at each channel and averaged across the scalp. Power and reactivity measures were transformed with the natural logarithm (log_e) before statistical testing and before computing the group averages to reduce the effects of non-gaussian distributions.

Statistical analysis

Main effects of analysis of variances (ANOVAs) were used to test for differences in measures between groups, using the presence or absence of medication as a second factor in the analysis. Many people with SCI use medication for the treatment of neuropathic pain or other sequelae resulting from their injury. This presents an ethical dilemma for studies seeking to identify the mechanisms of neuropathic pain, as participants could potentially face severe pain or other complications if their medication is ceased. The inclusion of medication as a factor in the analysis was used to obtain an indication of any contribution of the medication to the effect being observed.

Differences between groups were tested using ANOVA. Sign tests were used to indicate the consistency of the direction of difference over all channels between groups rather than basing a decision only on the size of the difference.¹¹ In this test, the binomial distribution was used to calculate the probability that a given measure would produce the same direction of difference indicated by the results.

Results

Peak θ - α frequency

There was a significant shift towards lower EEG frequencies, with a reduction in PTAF in the EC state, at all EEG recording sites in the pain group compared to both able-bodied and no-pain groups (sign test, 14/14 sites, $P=0.00006$), with statistically significant reductions ($P<0.05$) at 12 sites compared with the able-bodied group, as shown in Figure 1. The no-pain group also had reduced PTAF at all sites compared with the able-bodied group, but with a significant difference at site O2 ($P=0.05$).

There was a significant reduction in PTAF as an effect of medication, only at three sites P3 (F-test, $F=5.4$, $P=0.03$), P7 (F-test, $F=4.9$, $P=0.04$) and Pz (F-test, $F=6.6$, $P=0.02$), for the combination of pain and able-bodied groups.

EC/EO reactivity

The mean EEG power spectral densities (PSD) over all channels for EC and EO states for the able-bodied, no-pain, and pain groups are shown in Figure 2. The able-bodied PSD is characterized by a change in spectral activity between EC and EO states, with an increase in power across a broad band of frequencies in the EC state, particularly at the α (8–13 Hz) and β (14–40 Hz) band spectral peaks, consistent with independent observations in the literature¹⁶ (Figure 2a). This change is, to a large extent, also reflected in the no-pain

group (Figure 2b). In contrast with the able-bodied and no-pain groups, the pain group is characterized by a limited change in spectral activity between EC and EO states across a broad band of frequencies, particularly at the α - and β -band spectral peaks (Figure 2c).

To quantify this change in reactivity, a measure of broadband (1–40 Hz) EC/EO reactivity was determined at each site, in each individual. The pain group had decreased broadband EC/EO reactivity across all recording sites in comparison to both the able-bodied and no-pain groups (sign test, 14/14 sites, $P=0.00006$), with ANOVAs indicating a significant decrease ($P<0.05$) at 11 sites compared with the able-bodied group, and at four central (C3, C4) and frontal (F3, Fp1) sites compared with the no-pain group, as indicated in Figure 3. Further analysis showed that EC/EO reactivity in the pain group was consistently reduced across all recording sites in all EEG frequency bands (δ 1–4 Hz, θ 4–8 Hz, α 8–13 Hz and β 14–40 Hz) (sign test, 14/14 sites, $P=0.00006$). The no-pain group had consistently reduced broadband (1–40 Hz) EC/EO reactivity across all sites in comparison to the able-bodied group, but this was not significant for any individual recording site.

There was no significant effect of medication on EC/EO reactivity at any site, for the combinations of pain and able-bodied, or pain and no-pain groups.

Discussion

The results of the present study show a generalized slowing of the EEG in people with neuropathic SCI pain. Although slowing of the EEG was present in both the pain and no-pain groups, it was clearly greater in the group with neuropathic pain, which had consistent slowing at all electrode sites in comparison to the no-pain group. Furthermore, in comparison to the able-bodied group, the pain group showed significant slowing at 12 electrode sites, whereas the no-pain group showed significant slowing at only one site.

Part of the EEG slowing observed in this study appears to be due to the medication taken to alleviate symptoms of neuropathic pain. However, when comparisons were made between the medication and no-medication groups, significant EEG slowing was observed at only a relatively small number of electrode sites (three). This compares with more generalized slowing over 12 sites when the pain group was compared with the able-bodied group. Therefore it appears that EEG slowing is not solely attributable to the use of medication. This is consistent with the study of Sarnthein *et al.*¹⁰ who also found that medication use had an additive effect on EEG activity in subjects with neuropathic pain but did not account for the extent of the changes.

Thus, the overall results suggest that neuropathic pain in SCI is associated with a slowing of the EEG towards the θ frequency range, consistent with the putative presence of TCD in this population. These results are consistent with other reports that demonstrate a shift in the dominant EEG frequency towards lower frequencies in people with neuropathic pain.^{9,10} However, previous studies have been performed in groups of people with neuropathic pain of mixed

Figure 1 Peak θ - α band (4–13 Hz) frequency (PTAF) in the eyes-closed state at each site for able-bodied (circles/solid), no-pain (squares/dashed) and pain (triangles/dotted) groups. The symbol * indicates sites, at which PTAF in the pain group was significantly less than PTAF in the able-bodied group.

Figure 2 Mean PSDs comparing eyes-closed (solid) and eyes-open (dashed) states for (a) able-bodied, (b) no-pain and (c) pain groups.

origins and this is the first study which has examined a group that only includes people with neuropathic pain following SCI.

TCD has been proposed to form the basis for a range of neurological disorders, including neuropathic pain.^{7–10} The relationship between changes in rhythmicity and pain, however, has been questioned and it has been suggested that they are not specifically related to pain.¹⁷ SCI itself may result in alterations in rhythmicity and recent experimental evidence from our own group also indicates a slowing of the human EEG in people with SCI.¹¹ The findings from the present study also indicate that changes in EEG activity occur in people with SCI but without pain, although not as

robust or as widespread. Thus, it appears that the presence of neuropathic pain may be due to either the severity of the changes or additional factors which may generate pain in the presence of an underlying alteration in rhythmicity.

TCD is thought to arise from a hyperpolarization of thalamic neurons, through either excess inhibition or disfacilitation of these cells.⁷ Hyperpolarization of these cells, leads to low-threshold calcium spike bursts⁶ producing widespread coherent slow-wave activity that drives thalamo-cortical modules at these rhythms and can be measured at the scalp.⁷ It is hypothesized that activation of cortico-cortical inhibitory interneurons at low frequencies reduces lateral inhibition and that this in turn disinhibits

Figure 3 Mean whole band EC/EO reactivity (1–40 Hz) at each site for able-bodied (circles/solid), no-pain (squares/dashed) and pain (triangles/dotted) groups. The symbol * indicates sites at which EC/EO reactivity in the pain group was significantly less than EC/EO reactivity in the able-bodied group.

neighbouring cortical modules, causing them to activate at high frequencies in a process called the ‘edge-effect’.^{7,8} A current view in neurophysiology is that modules or cortical networks activated at high frequencies (β - or γ -band frequencies, 20–40 Hz and above) are thought to provide a basis for perceptual binding,¹⁸ and that different configurations of activated networks are in some way mapped to conscious experience.¹⁹ The proposed role of TCD in the genesis of neuropathic pain, therefore, is through disinhibition and subsequent activation of those networks that map to conscious experiences of pain.

A second effect observed in this study is the reduced reactivity of the EEG frequency spectrum to an increase or decrease in sensory input, in the EO or EC state, respectively. This effect is evident from the EO and EC PSD graphs shown for each group in Figure 2, which show reduced reactivity across a broad frequency spectrum. This effect was consistently observed at all sites in the pain group in comparison to the able-bodied and no-pain groups with significantly reduced reactivity in the pain group at 11 sites in comparison to the able-bodied group, and at four sites in comparison to the no-pain group. In contrast, there was no significant effect on EO/EC reactivity associated with medication.

The difference in EEG activity between the EO and EC states is a useful indicator of the function of thalamocortical networks. Neurophysiological effects of EEG spectral changes during states of EC and EO have recently been explored using biophysical models of thalamocortical networks.²⁰ Through fitting the model’s theoretical EEG power spectrum to power spectra from 100 subjects in a normative database, neurophysiological changes could be inferred between states of EO and EC.²⁰ Significant changes occurred in various parameters between states, including excitatory gains within the cortex, excitatory cortico-thalamocortical feedback gains and intrathalamic inhibitory feedback gains.

Our results suggest that the neuronal networks in the able-bodied and no-pain groups adjust to the change in sensory

input between the EO and EC states, whereas the pain group fails to do so. This suggests that the dynamic mechanisms that adjust these parameters are significantly affected in people with neuropathic SCI pain.

In summary, the present study provides evidence that neuropathic pain following SCI is associated with alterations in brain electrical activity, observed as a shift in the EEG towards slower frequencies. This shift is consistent with the same phenomenon that has been observed in other neuropathic pain conditions and provides further insight into the changes occurring at a brain level that may contribute to the development of neuropathic SCI pain.

References

- Siddall PJ, McClelland JM, Rutkowski SB, Cousins MJ. A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. *Pain* 2003; 103: 249–257.
- Finnerup NB, Johannesen I, Sindrup S. Pharmacological treatment of spinal cord injury pain. In: Yezierski R, Burchiel K (eds). *Spinal Cord Injury Pain: Assessment, Mechanisms, Management*. IASP Press: Seattle, 2002, 341–351.
- Drew GM, Siddall PJ, Duggan AW. Responses of spinal neurones to cutaneous and dorsal root stimuli in rats with mechanical allodynia after contusive spinal cord injury. *Brain Res* 2001; 893: 59–69.
- Gerke MB, Duggan AW, Xu L, Siddall PJ. Thalamic neuronal activity in rats with mechanical allodynia following contusive spinal cord injury. *Neuroscience* 2003; 117: 715–722.
- Lenz FA, Kwan HC, Martin R, Tasker R, Richardson RT, Dostrovsky JO. Characteristics of somatotopic organization and spontaneous neuronal activity in the region of the thalamic principal sensory nucleus in patients with spinal cord transection. *J Neurophysiol* 1994; 72: 1570–1587.
- Jeanmonod D, Magnin M, Morel A. Low-threshold calcium spike bursts in the human thalamus. Common physiopathology for sensory, motor and limbic positive symptoms. *Brain* 1996; 119 (Part 2): 363–375.
- Llinás RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP. Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proc Natl Acad Sci USA* 1999; 96: 15222–15227.
- Sarnthein J, Morel A, von Stein A, Jeanmonod D. Thalamic theta field potentials and EEG: high thalamocortical coherence in patients with neurogenic pain, epilepsy and movement disorders. *Thalamus Relat Syst* 2003; 2: 231–238.
- Stern J, Jeanmonod D, Sarnthein J. Persistent EEG overactivation in the cortical pain matrix of neurogenic pain patients. *Neuroimage* 2006; 31: 721–731.
- Sarnthein J, Stern J, Aufenberg C, Rousson V, Jeanmonod D. Increased EEG power and slowed dominant frequency in patients with neurogenic pain. *Brain* 2006; 129: 55–64.
- Tran Y, Boord P, Middleton J, Craig A. Levels of brain wave activity (8–13 Hz) in persons with spinal cord injury. *Spinal Cord* 2003; 42: 73–79.
- Klem GH, Luders HO, Jasper HH, Elger C. The ten-twenty electrode system of the International Federation. The International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophysiol Suppl* 1999; 52: 3–6.
- Nuwer MR, Lehmann D, da Silva FL, Matsuoka S, Sutherling W, Vibert JF. IFCN guidelines for topographic and frequency analysis of EEGs and Eps. The International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophysiol Suppl* 1999; 52: 15–20.
- Jung TP, Makeig S, Humphries C, Lee TW, McKeown MJ, Iragui V et al. Removing electroencephalographic artifacts by blind source separation. *Psychophysiology* 2000; 37: 163–178.
- Tran Y, Craig A, Boord P, Craig D. Using independent component analysis to remove artifact from electroencephalographic mea-

- sured during stuttered speech. *Med Biol Eng Comput* 2004; **42**: 627–633.
- 16 Niedermeyer E. The normal EEG of the waking adult. In: Niedermeyer E, Lopes da Silva FH (eds). *Electroencephalography: Basic Principles, Clinical Applications, and Related Fields*. Williams & Wilkins: Baltimore, 1999, pp 149–173.
- 17 Radhakrishnan V, Tsoukatos J, Davis KD, Tasker RR, Lozano AM, Dostrovsky JO. A comparison of the burst activity of lateral thalamic neurons in chronic pain and non-pain patients. *Pain* 1999; **80**: 567–575.
- 18 Varela F, Lachaux JP, Rodriguez E, Martinerie J. The brainweb: phase synchronization and large-scale integration. *Nat Rev Neurosci* 2001; **2**: 229–239.
- 19 Llinas R, Ribary U, Contreras D, Pedroarena C. The neuronal basis for consciousness. *Philos Trans R Soc London B* 1998; **353**: 1841–1849.
- 20 Rowe DL, Robinson PA, Rennie CJ. Estimation of neurophysiological parameters from the waking EEG using a biophysical model of brain dynamics. *J Theor Biol* 2004; **231**: 413–433.