Clinical Neurophysiology 148 (2023) 32–43

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

The predictive value of cortical activity during motor imagery for subacute spinal cord injury-induced neuropathic pain

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- Both subacute spinal cord injury (SCI) and central neuropathic pain (CNP) affect motor imagery (MI) activity and lateralization.
- MI activity is greater in SCI with upcoming CNP compared to SCI with no CNP.
- MI activity is more bilateral in SCI with upcoming CNP and more contralateral in SCI with existing CNP.

ARTICLE INFO

Article history:
Accepted 4 January 2023
Available online 25 January 2023

Keywords:
Spinal cord injury
Central neuropathic pain
Motor imagery
Source reconstruction
Event-related desynchronization
Laterality index

ABSTRACT

Objective: The aim of this study is to explore whether cortical activation and its lateralization during motor imagery (MI) in subacute spinal cord injury (SCI) are indicative of existing or upcoming central neuropathic pain (CNP).
Methods: Multichannel electroencephalogram was recorded during MI of both hands in four groups of participants: able-bodied (N = 10), SCI and CNP (N = 11), SCI who developed CNP within 6 months of EEG recording (N = 10), and SCI who remained CNP-free (N = 10). Source activations and its lateralization were derived in four frequency bands in 20 regions spanning sensorimotor cortex and pain matrix.
Results: Statistically significant differences in lateralization were found in the theta band in premotor cortex (upcoming vs existing CNP, p = 0.036), in the alpha band at the insula (healthy vs upcoming CNP, p = 0.012), and in the higher beta band at the somatosensory association cortex (no CNP vs upcoming CNP, p = 0.042). People with upcoming CNP had stronger activation compared to those with no CNP in the higher beta band for MI of both hands.
Conclusions: Activation intensity and lateralization during MI in pain-related areas might hold a predictive value for CNP.
Significance: The study increases understanding of the mechanisms underlying transition from asymptomatic to symptomatic early CNP in SCI.

1. Introduction

Spinal cord injury (SCI) is a devastating neurological condition with life-changing implications both physically and socioeconomically. The UK experiences around 16 new cases of traumatic SCI per million population per annum (McDaid et al., 2019). Apart from causing sensorimotor dysfunction below the level of injury, SCI can lead to chronic neuropathic pain (CNP). CNP is caused by an injury to the somatosensory system (Jensen et al., 2011) but typically appears months or years post-injury (Haanpää et al., 2011). It is a debilitating secondary consequence of SCI, present in approximately 65 % of people with SCI, in which the person experiences pain described as burning, tingling, stabbing, shooting, or an aching sensation at or below the level of injury. Both people with incomplete and complete injuries have CNP despite having no sensation or motor function preserved in the latter (Siddall and Loeser, 2001).

Motor imagery (MI) is a potential therapeutic tool for people with SCI for motor recovery as well as reduction of CNP (Aikat and Dua, 2016; Opsommer et al., 2020). MI triggers the same brain structures as motor execution (Lotze et al., 1999; Mulder, 2007). Measures of brain activity using electroencephalogram (EEG) have shown that both MI and motor execution induce changes in sensorimotor rhythms, in the alpha (8–12 Hz) and beta (12–30 Hz) band (Jeunet et al., 2019); this phenomenon is known as event-related

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https://doi.org/10.1016/j.clinph.2023.01.006
1388-2457/

desynchronization/synchronization (referred to as desynchronization and synchronization further in the text) implying decrease/increase in power of sensorimotor rhythms (Neuper et al., 2006; Pfurtscheller and Lopes da Silva, 1999).

EEG studies have shown that both SCI and SCI-induced CNP result in cortical neuroplasticity, affecting resting-state oscillatory brain activity (Jensen et al., 2013; Vuckovic et al., 2014). Our research group also demonstrated that dynamic EEG during motor actions, such as movement-related cortical potential and desynchronization/synchronization are affected by both chronic SCI and related CNP (Vuckovic et al., 2015; Xu et al., 2014). Studies measuring brain activity through functional magnetic resonance imaging (fMRI) have further revealed specific areas within the brain showing differences in movement-related activations between people with SCI and able-bodied controls (Kokotilo et al., 2009; Sharp et al., 2017). Additionally, fMRI studies on SCI-induced CNP have revealed an increase in pain when performing MI on account of the activation of pain matrix and primary motor cortex (Gustin et al., 2010, 2008). While previous studies explored the effect of SCI-induced CNP on the sensorimotor cortex in chronic SCI, little is known how the presence of CNP affects the oscillatory brain activity during motor action in subacute SCI. In our previous CNP study, we found evidence of changes in the resting state brain activity that precedes the onset of CNP in subacute SCI (Vuckovic et al., 2018a), thus it should be expected that it also affects active dynamic state such as motor imagery.

Cortical lateralization describes how functions are performed predominantly by either left or right hemispheres of the brain. With regards to motor control, lateralization is vital to carry out unilateral movements as well as a variety of more complex, coordinated activities (Welniarz et al., 2015). In healthy people, movement-related activity like desynchronization is lateralized towards the hemisphere contralateral to the hand performing real (Deiber et al., 2001; Formaggio et al., 2013) or imagined motor action (Nam et al., 2011; Vuckovic et al., 2018b). However, in high-level subacute SCI the movement-related activity may be bilateral and shift back towards the contralateral side in the chronic phase accompanied by functional recovery (Isa and Nishimura, 2014; Jurkiewicz et al., 2007; Kauhanen et al., 2006; Nishimura and Isa, 2009; Vuckovic et al., 2021). In a previous study, we demonstrated bilateral desynchronization in people with subacute tetraplegia; it was restored towards contralateral desynchronization in participants undergoing training using a brain-computer interface (Osuagwu et al., 2016). Bilateral activity can be attributed to a reduced intracortical inhibition early post-injury that facilitates the use of pre-existing neural systems. At a later stage of injury, however, the original systems are restored or other systems are recruited due to neuroplasticity (Nishimura and Isa, 2009).

There are published evidences that pain under the level of injury might have a detrimental effect on motor recovery in people with subacute SCI (Baumbauer et al., 2009; Ferguson et al., 2012; Mercier et al., 2017). It has been hypothesized that maladaptive plasticity due to central sensitization in nociceptive pathways and adaptive plasticity related to motor learning share common neural mechanisms and compete with each other (Mercier et al., 2017). Rehabilitation interventions of different types with chronic SCI participants have reported CNP alleviation in a few participants (Sato et al., 2017; Shokur et al., 2018; Yoshida et al., 2016). Considering a close link between the activity of the pain matrix and primary motor cortex during motor action, we hypothesize that CNP in subacute SCI might also affect sensorimotor activity during unimanual motor action, both in intensity and cortical lateralization.

The main objective of this work is to elucidate the differences in the activation and corresponding lateralization of the sensorimotor cortex and pain-related regions between able-bodied people and people with subacute SCI and existing CNP, no CNP, and upcoming CNP. Assuming that the lack of lateralization is inversely proportional to recovery, understanding the influence of CNP on laterality might potentially elucidate the effect of early CNP on motor recovery.

2. Materials and Methods

2.1. Participants

The study is a registered clinical trial NCT021789917 (Vuckovic et al., 2018a). All participants were between 18 and 75 years old and had no history of neurological disorders such as stroke, epilepsy, or brain injury. The Ethical approval was obtained from the West of Scotland Research Ethics Committee Clyde (reference 14/WS/1027) and all participants gave written consent for data sharing. The study was performed in line with the principles of the Declaration of Helsinki. Participants were recruited in three groups including 10 able-bodied people (ABP), 11 people with sub-acute SCI and CNP (PwP), and 20 people with SCI but no CNP at the time of recording, who were followed up to 6 months to check for the development of CNP. The group who went on to develop CNP is called PdP and the group that did not develop CNP is referred to as the PnP group.

2.1.1. Level of injury

The SCI groups included participants of both sexes with a mixture of paraplegics and tetraplegics with either a complete or an incomplete injury. The level and completeness of injury was assessed using American Spinal Injury Association (ASIA) impairment scale (Roberts et al., 2017). The different levels and completeness of injury were mixed as there is a lack of clear evidence showing a relation between the level of completeness of injury and the incidence of CNP (Siddall et al., 2003).

2.1.2. Sensory tests

To assess sensory profiles of participants with no pain at the time of EEG recording, mechanical wind-up test was performed (Zeilig et al., 2012). People with SCI at risk of developing CNP typically have allodynia and hyperalgesia and mechanical test can serve as an indication of the upcoming pain. The mechanical wind-up test was applied via a monofilament no. 6.65 four consecutive times on the participant with an inter-stimulus interval of 3 s (Zeilig et al., 2012), producing a stronger stimulus than a standard pinprick test.

2.1.3. CNP intensity

The participants who were diagnosed with CNP according to Mehta et al. were asked to rate their pain level on a visual numeric scale where 0 represents no pain and 10 represents worst pain imaginable (Mehta et al., 2016).

2.1.4. Handedness

The participants were asked about the hand they used for writing pre-injury to determine their handedness.

2.2. Experimental protocol

Based on studies showing differences in those with chronic SCI and CNP, and those with SCI and no CNP, a cue based motor imagery paradigm was adopted as the experimental protocol to reveal indices of upcoming pain (Gustin et al., 2010; Vuckovic et al., 2014). Although participants in this study had mixed level of injuries, we compared MI of left and right hand because our previous

study with chronic paraplegic patients (Vuckovic et al., 2015, 2014) showed that CNP affects MI of both paralyzed and painful, and non-paralyzed and non-painful limbs.

Participants were seated approximately 1.5 m in front of a computer screen. The sequence of events for a trial is shown in Fig. 1. The trial started at −2s and the participants were presented with a black screen. A warning cue in the form of a cross was displayed on a screen at t = -1s until t = 3 s. At t = 0 s, the initiation cue appeared on the screen. This cue was an arrow pointing either to the left, right, or down (corresponding to the imagination of the left-hand, right-hand, or leg respectively). The initiation cue remained until t = 1.25 s, however, participants were instructed to continue imagining for a total of 3 s i.e., until the cross disappeared. The resting period between trials pseudo-randomly varied between 3 to 5 s to avoid the expectation of a stimulus. In total there were 180 trials (60 for each type of MI) which were divided into six runs of 30 trials, each lasting five minutes. An experimenter observed participants to check adherence to the motor imagery protocol, so that real movements could be avoided. If real movement was found to be present in a session, the session was repeated.

2.3. Experimental setup

Forty-eight channel EEG data were recorded using a gUSBAmp amplifier (Guger Technologies, Austria) following the 10–10 standard EEG electrode recording system (Nuwer, 2018) as shown in Fig. 2. An ear-linked reference was used, and the ground was placed at the AFz location. The sampling rate was 256 Hz, and the EEG was filtered real-time between 0.5 and 60 Hz with a notch filter at 50 Hz using 5th order Infinite impulse response (IIR) Butterworth filters. The impedances were kept under 5 kΩ.

2.4. EEG Pre-processing

The EEG signals were processed in EEGLAB (Delorme and Makeig, 2004). Noisy trials with amplitudes above 100 μV were inspected visually and removed. The resulting EEG signals were re-referenced to a common average reference. Without any narrowband filtering, independent component analysis (Makeig et al., 1996), implemented using the Infomax algorithm, was applied on each participant data after concatenating the trials. A default residual variance of 0.8 was used to identify noisy components corresponding to eye blinks, muscle artifacts, and channel noise for reference. However, the spatial power distribution, power spectrum, and component time series of each independent component were nevertheless visually inspected alongside dipole locations, to finally remove a noisy component. On average, 3 out of 60 trials were removed per MI class.

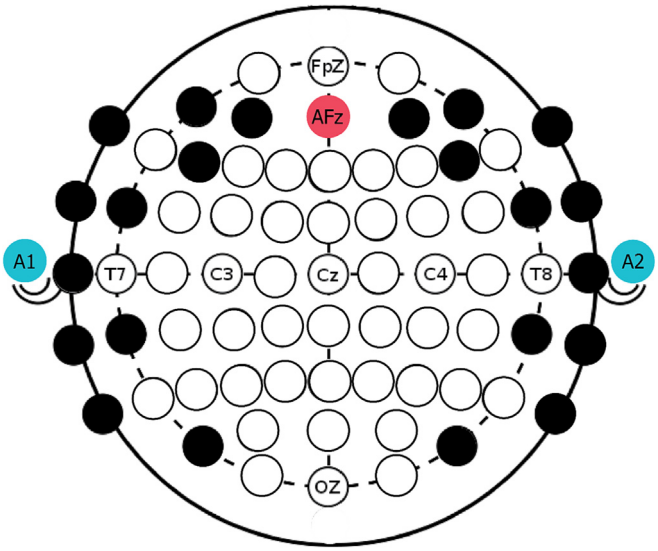

Fig. 2. The location of 48 electrode recording sites. The open circles indicate 48 electrodes used in the study while filled circles indicate the rest of the electrodes according to 10–10 systems (Nuwer, 2018). Red indicates the ground electrode AFz, and blue indicates the ear electrodes at A1 and A2.

2.5. EEG source localization

Frequency-domain source localization was performed using the Fieldtrip toolbox (Oostenveld et al., 2011) to obtain MI-related source activations for the left- and right-hand MI trials. The forward model was computed using a finite element volume conduction model (Vorwerk et al., 2018) based on a standard MRI template (Holmes et al., 1998). The template was segmented into grey matter, white matter, scalp, skull, and cerebrospinal fluid with conductivity values of 0.33, 0.14, 0.43, 0.01, and 1.79 S/m respectively (Piastra et al., 2021). The segmented brain volume was divided into a 3D mesh comprised of 4050 hexahedrons, called voxels, each belonging to one of the 5 tissues with a resolution of 1 cm.

The beamforming method was used in the frequency-domain to obtain the inverse model (Jaiswal et al., 2020). The method takes an adaptive spatial-filtering approach and scans each location within the source space independently. Among the various implementations of beamforming, dynamic imaging of coherent sources was used (Gross et al., 2001; Popov et al., 2018). This method can localize oscillatory brain activity and identify coherent brain areas using a frequency implementation of a spatial filter. The filter passes the activity in a specific frequency band of the sources at a particular position with unit gain, while suppressing contributions from all other sources. Thus, the spatial distribution of power and coherence can be obtained in chosen frequency bands, at all

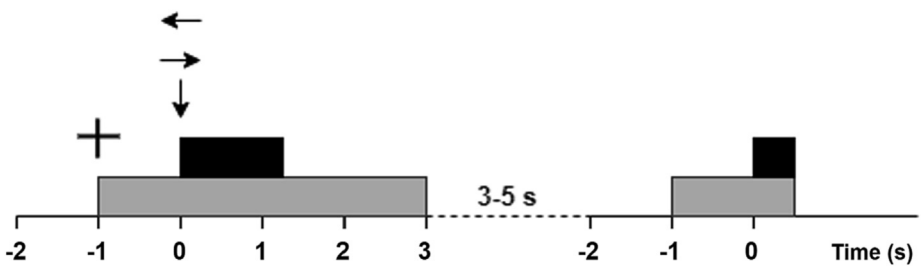

Fig. 1. The sequence of events for motor imagery (MI) trials. The cross represents the readiness cue at t = -1s. At t = 0 s the execution cue appears on top of the readiness cue in the form of an arrow. The grey rectangle represents the time for which the readiness cue is present on the screen while the black rectangle represents the time the execution cue is present on the screen.

grid points. It uses a cross-spectral density matrix as a starting point to obtain power and coherence values of recorded signals, which are ultimately used to derive spatial filters as solutions to a constrained optimization problem.

For the current study, a cross-spectral density matrix was calculated using the multitapers method for better control of time and frequency smoothing. This was done separately in four frequency bands of interest: theta (4–8 Hz), alpha (8–12 Hz), lower beta (12–20 Hz), and higher beta (20–30 Hz). For each subject and frequency band, a common spatial filter was obtained for both the baseline (t = -1.9 to −1.1 s) and MI (t = 0.5 to 2.5 s). This was done so that any differences found later between baseline and MI or between the two MI conditions could be attributed to actual differences between conditions, as opposed to a difference caused by different spatial filters for each condition separately. The assumption here is that the underlying sources are the same for different conditions, but active to a different extent. Another advantage of creating common filters is a better estimate of the inverse solution as more data is used for constructing the spatial filters. Finally, the common filter was applied to each task separately (left- and right-hand MI) to get the source activations, resulting in 8 estimates in total: theta, alpha, lower and higher beta band for the left and for the right-hand MI. The leg MI data was not used as it involved the use of both legs, which was assumed to generate non-lateralized activity. The normalized activation (NA in Eq. (1)) between the average power of the baseline and the MI was computed as per Eq. (1), where A_B and A_{MI} refer to source activations of baseline and MI, respectively. Negative normalized activation or decrease in activation with respect to baseline is desynchronization whereas positive normalized activation or increase in activation with respect to baseline is synchronization (Pfurtscheller and Lopes da Silva, 1999).

$$NA = \frac{A_{MI} - A_B}{A_B} \tag{1}$$

2.6. Desynchronization in regions of interest

Twenty regions of interest (ROI) were identified by combining areas available in the Brainnetome atlas (Fan et al., 2016). The first 14 represent sensorimotor regions: left and right premotor cortices (LPMC, RPMC), left and right supplementary motor area (LSMA, RSMA), left and right primary motor cortices (LM1, RM1), left and right somatosensory association cortices (LSAC, RSAC), left and right primary sensory cortices (LS1, RS1), left and right secondary somatosensory cortices (LSSC, RSSC), and left and right cingulate motor area (LCMA, RCMA) (Athanasiou et al., 2018; Mattia et al., 2009). The next 6 ROIs correspond to the cortical areas associated with the processing of pain: left and right prefrontal cortices (LPFC, RPFC), left and right insular cortex (LIC, RIC), and left and right anterior cingulate cortices (LACC, RACC) (Jensen, 2010). The left and right primary and secondary somatosensory cortices have also been associated with pain processing. The normalized activation was averaged over voxels of an ROI. Following a recommendation from the literature, the negative values were considered as desynchronization and all positive values, corresponding to synchronization, were set to zero.

2.7. Laterality index

Laterality index (LI) indicates the prevalence of activation in one hemisphere over the other (Brumer et al., 2020). Based on desynchronization, ten LI values were obtained from 20 ROIs comprised of left and right sensorimotor and pain regions following Eq. (2), where indexes C and I refer to desynchronization on the contralateral and ipsilateral sides, respectively. The LI ranges from −1 to 1, with a negative LI representing ipsilateral desynchronization dominance, positive LI representing contralateral desynchronization dominance, and a value of zero indicating bilateral symmetric activity (Nam et al., 2011). The magnitude of LI is useful in determining the extent of dominance.

$$LI = \frac{desynchronization_C - desynchronization_I}{desynchronization_C + desynchronization_I} \tag{2}$$

A review conducted by Seghier et al (Seghier, 2008) outlined the standard threshold value for concluding contralateral or ipsilateral dominance as 0.2 and −0.2, respectively. This is because when LI is equal to 0.2, the contralateral desynchronization would be 50 % greater than the ipsilateral desynchronization, therefore, is reasonable to attribute it to a significant difference in hemispheric activation. This criterion was used to evaluate LI type (ipsilateral, bilateral, or contralateral) such that LI values less than or equal to −0.2 were categorized as ipsilateral, LI values greater than or equal to 0.2 were categorized as contralateral, while LI values between −0.2 and 0.2 were categorized as bilateral. To visualize the distribution of LI type across the 3 categories (contralateral, ipsilateral, and bilateral), LI values were pooled across all areas and plotted in the form of a histogram showing the probability of LI value falling into the corresponding range mentioned before. The histograms were shown together in 4 pairs- ABP with PnP, PdP with PwP, PnP with PwP, and PnP with PdP. Another set of histograms were created after excluding people with tetraplegia in PdP and PwP groups so that all SCI groups contained paraplegic participants exclusively as level of injury could be a potential confounder. The reorganization post-SCI has been shown to be different for tetraplegia and paraplegia (Curt et al., 2002; Green et al., 1999; Kokotilo et al., 2009; Nardone et al., 2013).Tetraplegia-only groups could not be analyzed as the PnP group did not have any participant with tetraplegia.

2.8. Statistical analysis

2.8.1. Analysis of normalized activation at voxel level

A non-parametric cluster-based permutation test was carried out in Fieldtrip to compare the normalized activations in each condition in pairs as follows: ABP vs PnP, ABP vs PdP, ABP vs PwP, PnP vs PdP, PnP vs PwP, and PdP vs PwP. Only voxels corresponding to the 20 regions of interest were compared. A cluster-based permutation test increases the sensitivity of a standard permutation test by accounting for correlation in the activation of neighboring grid points (Maris et al., 2007). The test was two-sided, 10,000 permutations were used, and the significance level was set to $p < 0.05$.

2.8.2. Analysis of LI

A Kruskal Wallis test was conducted in SPSS (version 28.0.0) to compare LI between groups for each area (7), condition (2), and frequency band (4). The statistical significance level was set to $p < 0.05$. If a statistically significant difference was found, post-hoc tests were conducted and corrected for multiple comparisons using Holm-Bonferroni method.

2.8.3. Analysis of LI type distribution

To quantify the differences of LI type distribution between groups, chi-square tests were performed to determine if there is a relationship between the two categorical variables- group and laterality type. For each frequency band and condition, a 4×3 contingency table was created with group (ABP, PnP, PdP and PwP) as column and LI type (contralateral, ipsilateral, and bilateral) as row. The cells of the table were populated with the total counts of the particular LI type across all areas across all subjects for a given group such that the sum of cells in a column was 10 * Ng, where

Ng is the number of participants in the group and 10 is the number of brain areas for which LI type was evaluated. Note that the counts were neither averaged over subjects nor over areas and instead all counts were added to get a high enough expected frequency for each cell of the contingency table to facilitate a parametric version of the chi-square test. A chi-square test was used to see if there was a relation between the two categorical variables, group, and LI type. If a statistical significance was found ($p < 0.05$), pairwise post-hoc tests were performed using chi-square test and the resulting p-values were corrected for multiple comparison using Holm-Bonferroni correction. Following pairwise test were performed: ABP vs PnP, PdP vs PwP, PwP vs PnP, and PdP vs PnP. These tests provided systematic comparison between able-bodied and people with SCI and between SCI with different pain status. Another set of contingency tables were created by excluding people with tetraplegia in PdP and PwP groups, so that all SCI groups exclusively contained paraplegic participants, and the statistical tests were repeated.

3. Results and discussion

3.1. Participants

Among the 20 participants who were followed up, 10 developed CNP and 10 remained CNP-free. The demographics of study participants are shown in Table 1. In our previous study, we showed that there were no significant differences in age, time post-injury, or ASIA impairment between the SCI groups (PwP, PnP, PdP) (Vuckovic et al., 2018a). However, the injury levels differed among the groups with PnP showing 8 segments lower injury levels than the PdP group (for detailed statistical analysis see (Vuckovic et al., 2018a)). All participants in the PnP group were paraplegic. Within the PwP group, 4 participants were tetraplegic and the remaining 7 were paraplegics. Within the PdP group, 4 participants were tetraplegic while the other 6 participants were paraplegic. Hand laterality was not explicitly tested but all participants in the study used their right hand for writing.

The mean pain levels were 6.5 (SD = 1.3) in the PwP group and 4.3, (SD = 2.2) in the PdP group. When describing pain, the PwP group used descriptors typical of below-level neuropathic pains such as constant burning or stinging, intermittent shooting, etc. Only one person in PdP demonstrated sensory response to mechanical wind-up test. All participants were right-handed.

3.2. Comparison of normalized activations between groups

In the higher beta band, significant differences were found between PdP and PnP for both left-hand ($p = 4.99e\text{-}04$) and right-hand MI ($p = 0.0065$). Additionally, in the lower beta band for left-hand MI, ABP and PdP were significantly different ($p = 0.024$). The ROIs which show significant differences between groups are shown in Fig. 3, where areas with at least 30 % (arbitrary) of the voxels form part of the significant cluster are shown in red. The table with total number of voxels from each region, forming the significant cluster is provided in the Supplementary Material Table A1.

The normalized activations forming part of the cluster contributing to significant difference were pooled across all participants within a group and plotted for PdP and PnP, as shown in Fig. 4. On average, PdP had stronger desynchronization compared to PnP in the higher beta band for both left- and right-hand MI. PdP had stronger desynchronization compared to ABP as well for left-hand MI in the lower beta band.

3.3. Comparison of LI between groups in selected ROIs

Fig. 5 shows LI corresponding to left-hand MI in four groups in three areas, where a statistically significant difference was found between groups, with positive LI corresponding to contralateral and negative LI to ipsilateral activity. The statistical tests were conducted in 2 stages, first a Kruskal Wallis test to compare the four groups followed by pairwise comparisons when a significant p-value was obtained, which was the case in 3 area-frequency pairs for left hand MI. No differences were obtained for right hand MI.

Firstly, the LI was significantly different in theta band at PMC (Kruskal Wallis $p = 0.044$). Post-hoc tests revealed that PdP and PwP were significantly different (adj. $p = 0.036$), the former showing bilateral activity and the latter showing contralateral, as shown in Fig. 5. Secondly, the LI was significantly different in the alpha band at insular cortex (Kruskal Wallis $p = 0.014$). Post-hoc tests revealed that PdP and ABP were significantly different (adj. $p = 0.012$), the former showing ipsilateral and the latter showing contralateral activity (Fig. 5). Lastly, the LI was significantly different in the higher beta band at SAC (Kruskal Wallis $p = 0.017$). Post-hoc tests revealed that PdP and PnP were significantly different (adj. $p = 0.042$), the former showing ipsilateral (similar to PwP) and the latter showing contralateral activity (Fig. 5). It can be observed that PdP is the only group not showing contralateral activity in two out of three areas of interest. It can also be seen that all SCI groups show more ipsilateral activity at insular cortex.

3.4. Laterality index distribution between groups combining all ROIs

This section presents LI results when combining all ROIs over one hemisphere. The LI distribution is shown in Fig. 6 for right-hand MI and Fig. 7 for left-hand MI. The same distributions are shown in Supplementary Material Figures A1-A2 after excluding people with tetraplegia from PdP and PnP group. The chi-square test values are shown in Table 2 for the comparison of LI distributions. Overall, all groups show more bilateral activation (LI values between −0.2 and 0.2) than either contralateral or ipsilateral and ABP generally has larger contralateral activation than SCI groups. Out of all SCI groups, PdP has the strongest bilateral activation and PwP has stronger contralateral activity than PnP, for the right hand.

A detailed statistical analysis for different frequency bands shows that for the right-hand MI, ABP and PnP have similar LI in the theta and alpha bands. In the beta bands, ABP has more contralateral, while PnP has more ipsilateral activation. PdP and PwP show similar laterality in all bands except higher beta where PdP shows more bilateral while PwP shows more contralateral activation. PnP and PwP are similar in theta and alpha bands but differ in the beta bands where PnP has more ipsilateral activation in the lower beta band while PwP has more contralateral activation in the higher beta band. PdP and PnP are similar in all frequency bands except lower beta where PnP shows ipsilateral while PdP shows bilateral activation. Although not significant, similar trends can be seen after excluding people with tetraplegia in PdP and PwP groups (Supplementary Material Figure A1).

For the left-hand MI, both ABP and PnP groups show similarities in theta and beta bands. However, in the alpha band, ABP shows more contralateral while PnP shows more ipsilateral activation. Compared to PwP, PdP has more bi-lateral activation in the theta, alpha, and higher beta bands, whereas PwP shows more contralateral activity in those bands. This difference is significant in theta band. After removing people with tetraplegia from both groups, although not significant, this difference is retained (Supplementary Material Figure A2). Further, it is accentuated in alpha band, where PdP group shows bilateral activity while PwP shows either contralateral or ipsilateral activity. PdP and PnP groups show differ-

Table 1
Demographics of the study participants. For the spinal cord injury (SCI) groups, Lev and Com correspond to American Spinal Injury Association Impairment Scale (ASIA) level and completeness of injury respectively (Roberts et al., 2017). Com A represents complete loss of sensory and motor function; B represents compete loss of motor functions and some sensory function spared, C and D represent incomplete loss of both sensory and motor function, motor impairment being larger in group C. Medications PG, GP and TR refer to pregabalin, gabapentin and tramadol respectively. M and SD refer to mean and standard deviation.

No	1	2	3	4	5	6	7	8	9	10	11	M (SD)
Able bodied people (ABP)												
Age	37	32	36	34	32	27	45	34	49	27	-	35 (7)
SCI with no pain who remained pain-free (PnP)												
Age	51	22	47	41	59	43	24	38	62	34	-	42 (13)
Lev	T7/T10	L1	T11	T12	T6	T6/T7	L1	L1	T3/T5	T6	-	-
Com	D	B	D	A	A	B	A	A	A	A	-	-
Weeks with SCI	12	12	7	4	12	21	7	4	10	10	-	10 (5)
SCI with no pain who developed pain later (PdP)												
Age	52	51	70	49	19	69	32	46	49	32	-	47 (16)
Lev	C3/C4	C3/C4	T7/T8	T12	C5/C6	L2	T3	T5	T6	C3	-	-
Com	D	B	D	A	A	B	A	A	A	A	-	-
Weeks with SCI	12	8	9	6	12	6	24	6	4	6	-	9 (6)
Weeks before Pain	8	12	6	10	4	4	8	7	2	4	-	6 (3)
Location	Hands & upper back	At & below level	Feet	At & below level	Hands	Left leg	At & below level	At & below level	At & below level	Hands	-	-
SCI with existing pain (PwP)												
Age	33	59	64	27	32	30	59	29	37	49	75	45 (17)
Lev	T12	T7/T8	C3/C4	C5/C6	T3	T10	T8	C3	T6	C4	T6	-
Com	B	A	D	A	A	A	C	D	B	A	C	-
Weeks with SCI	20	12	16	17	24	12	26	6	28	6	6	16 (8)
Weeks pain	20	12	16	15	6	12	26	6	28	6	6	14 (8)
Location	At & below level	At & below level	Shoulders	Hands & Buttock	At & below level	Legs & feet	At level & feet	Right hand	Right leg	Hands	At & below level	-
Meds	PG	GP	TR	TR	PG	-	-	-	PG	GP	GP	

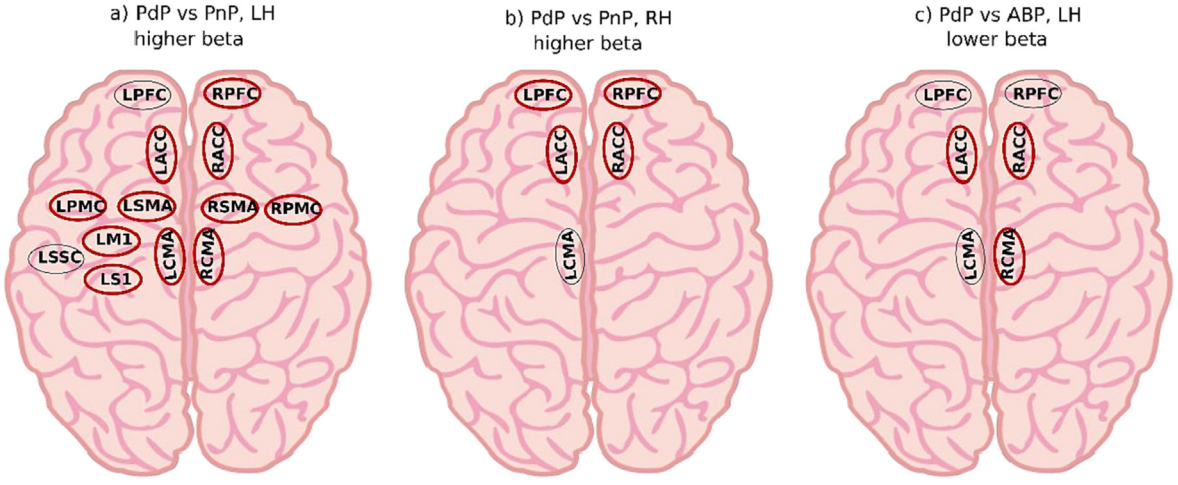

Fig. 3. Areas with voxels contributing to significant difference in normalized activations between groups. The areas with at least 30 % of the voxels forming the cluster are marked in red. No significant differences were found for other pairs and other frequency bands. ABP, PdP, and PnP respectively represent able-bodied people, people with SCI who developed CNP later, and people with SCI who did not develop CNP later. LH and RH refer to left-hand and right-hand motor imagery (MI) respectively. LPFC: left prefrontal cortex; RPFC: right prefrontal cortex; LACC: left anterior cingulate cortex; RACC: right anterior cingulate cortex; LPMC: left premotor cortex; RPMC: right premotor cortex; LSMA: left supplementary motor area; RSMA: right supplementary motor area; LCMA: left cingulate motor area; RCMA: right cingulate motor area; LM1: left primary motor cortex; LS1: left primary sensory cortex; LSSC: left secondary somatosensory cortex.

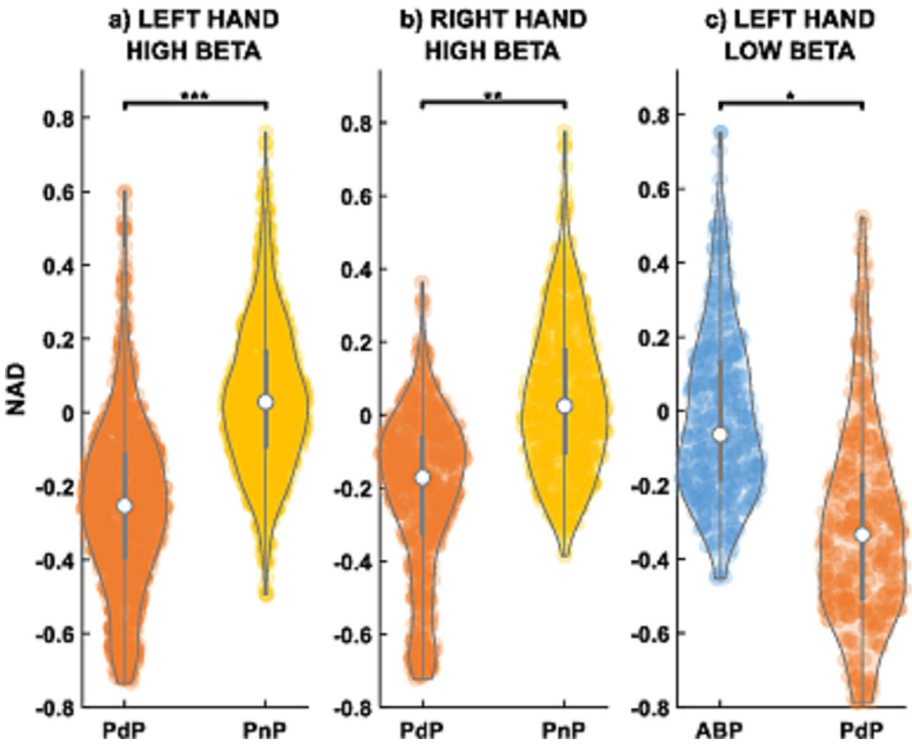

Fig. 4. Violin plot of normalized activation difference (NAD), pooled across voxels forming part of cluster contributing to a significant difference between a) PdP and PnP for left-hand motor imagery (MI) in the higher beta band, b) PdP and PnP for right-hand MI in the higher beta band, and c) ABP and PdP for left-hand MI in the lower beta band. Negative values represent desynchronization and positive values represent synchronization. Note that the spatial location of clusters differs for each plot. No significant differences were found for other pairs and other frequency bands. ABP, PdP, and PnP respectively represent able-bodied people, people with spinal cord injury (SCI) who developed central neuropathic pain (CNP) later, and people with SCI who did not develop CNP later. Statistical analysis was performed in the upper raw. * Represents $p < 0.05$, ** represents $p < 0.01$, and *** represents $p < 0.001$.

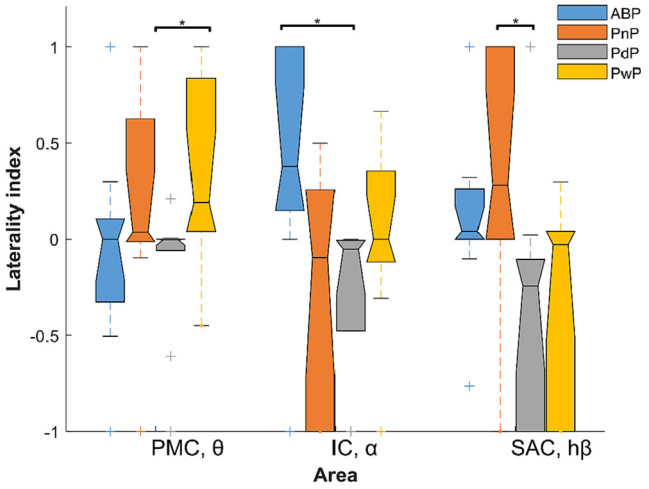

Fig. 5. Laterality index for left-hand motor imagery (MI) in theta (θ), higher beta (hβ) and alpha (α) frequency bands. ABP, PwP, PdP, and PnP refer to able-bodied people, people with spinal cord injury (SCI) and central neuropathic pain (CNP), people with SCI who developed CNP later, and people with SCI who did not develop CNP later. PMC and SAC stand for premotor cortex and Somatosensory association cortex respectively. No significant difference between groups was found in other brain regions and in other frequency bands. Positive LI values represent contralateral desynchronization dominance while negative desynchronization values represent ipsilateral desynchronization dominance. * Represents $p < 0.05$.

ences in the alpha band with PdP showing more bilateral activity while PnP showing more lateralized activity (either ipsilateral or contralateral). This difference is retained after removing people with tetraplegia from the PdP group. There are no differences between PnP and PwP for the left-hand MI.

4. Discussion

This study focused on two indices: the intensity of normalized activations (desynchronization/synchronization) in selected regions of interest and the corresponding lateralization of activity. We differentiated not only between people with SCI based on the presence of pain, but we also involved an SCI group with "upcoming pain". We also removed the confounding effect of level of injury by repeating analysis with only the paraplegic cohort when comparing overall LI between groups.

4.1. Differences in desynchronization between groups

The first objective of the study was to see if there were differences in movement-related oscillatory cortical activation between groups. People with SCI and upcoming CNP had stronger desynchronization compared to both able-bodied and CNP-free groups in the beta band in both sensorimotor (CMA, SMA, PMC, S1, M1) and pain areas (PFC and ACC), especially for the non-dominant left hand. Even though the theta band has been shown to have increased desynchronization in people with chronic SCI and CNP (Vuckovic et al., 2014) owing to thalamocortical dysrhythmia which affects theta directly and beta indirectly, increased event-related (de)synchronization (ERD) was not found in the theta band (Llinás et al., 1999; Sarnthein et al., 2006). Further, in our previous neurofeedback study with chronic SCI and CNP, we showed that reduction of both theta and higher beta in electrodes over sensorimotor areas was effective in reducing CNP (Hassan et al., 2015). This was also reflected in the reduction of beta powers in PFC and ACC. Since the group with existing CNP did not show the strongest desynchronization in pain areas in any frequency band as in

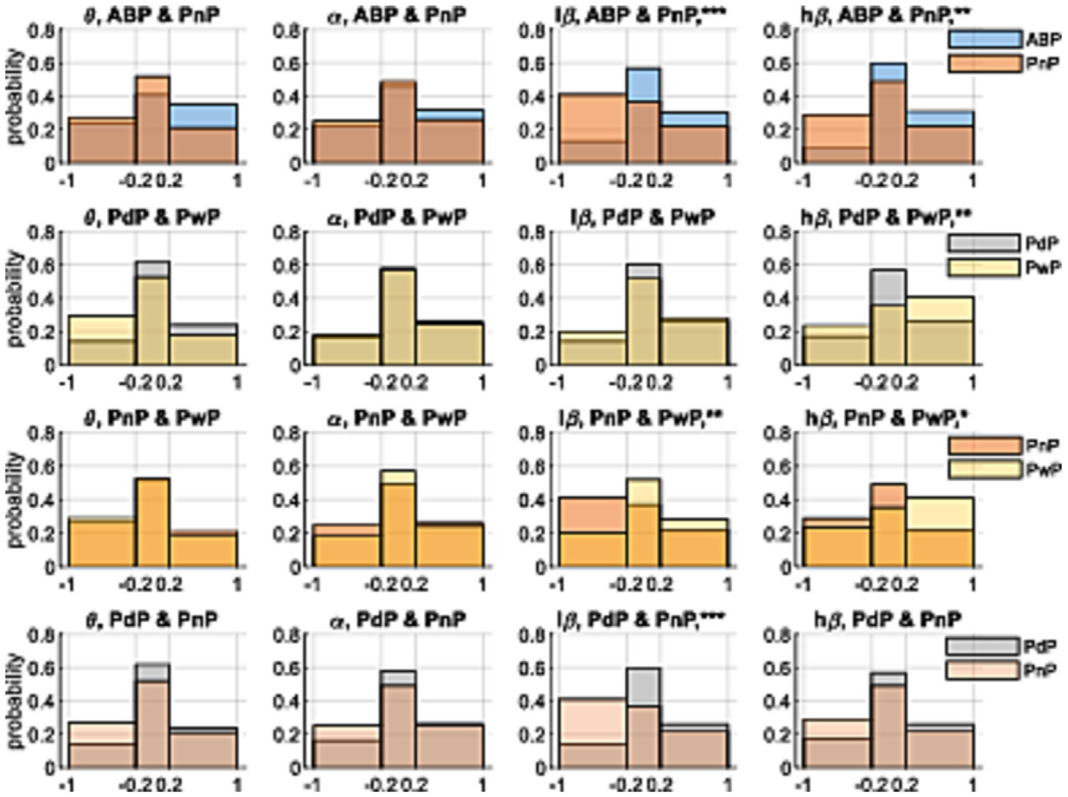

Fig. 6. Probabilities of laterality index (LI) falling into three ranges (LI<=-0.2 ipsilateral activation, −0.2 < LI < 0.2 bilateral activation, and LI >=0.2 contralateral activation) for right-hand motor imagery in theta (θ), alpha (α), lower beta (lβ), and higher beta (hβ) frequency bands. ABP, PwP, PdP, and PnP refer to able-bodied people, people with spinal cord injury (SCI) and central neuropathic pain (CNP), people with SCI who developed CNP later, and people with SCI who did not develop CNP later. * Represents $p < 0.05$, ** represents $p < 0.01$ and *** represents $p < 0.001$.

chronic CNP (Gustin et al., 2010; Stern et al., 2006), it is unlikely that overactivation in the pain areas may have contributed to the neuroplastic mechanisms leading up to the CNP in the upcoming-CNP group. All pain areas have also been shown to be active during motor imagery in the able-bodied MI such as insula (Hétu et al., 2013), prefrontal cortex (Kotegawa et al., 2021; Van der Lubbe et al., 2021), and anterior cingulate cortex (Koski and Paus, 2000; Picard and Strick, 2001). Nevertheless, the possibility that stronger activation in pain and sensorimotor areas might be related to upcoming CNP still cannot be excluded because once people have CNP, they can be more similar in activation to able-bodied controls than those that are CNP-free (Jutzeler et al., 2015). Interestingly, no differences were found in the alpha band which is also a sensorimotor rhythm alongside beta in able-bodied people (Neuper and Pfurtscheller, 2001).

4.2. The effect of SCI on lateralization during MI

The second objective of the study was to investigate how SCI and CNP affect cortical lateralization. While previous studies have used fMRI to evaluate the LI during movement in people with various neurological conditions such as Parkinson's (Wu et al., 2015) or stroke (Ito and Liew, 2016) as well as compared the LI between young and old able-bodied adults (Neyedli et al., 2018), literature investigating the LI concerning people with SCI is scarce. Specifically, there is little research investigating the effect of neuropathic pain, which is known to affect the sensorimotor cortex. In our previous study with chronic SCI participants with paraplegia, we found stronger desynchronization during MI of both the paralyzed legs and non-paralyzed arms. Therefore, although the level of injury might influence lateralization, the presence of pain or upcoming pain may affect the motor cortex of all limbs (Vuckovic et al., 2014). In the present study with subacute SCI participants, the LI was found to be different between SCI groups, implying a relationship between pain and lateralization.

Compared to able-bodied people, people with SCI and no pain show more ipsilateral activation, either in the alpha band for left-hand MI or in beta bands for right-hand MI. Lesser contralateral activity in subacute SCI could be attributed to the unmasking of pre-existing excitatory connections that are masked in able-bodied people. Laterality generally restores over time and is usually accompanied by functional restoration of movements (Jurkiewicz et al., 2007; Nardone et al., 2013; Nishimura and Isa, 2009). Area-wise analysis revealed a difference in alpha band laterality at the insular cortex where the able-bodied group showed contralateral while the group with SCI and upcoming CNP showed ipsilateral activation for left-hand MI. Given that other SCI groups also showed ipsilateral activation and the involvement of insula in MI (Hétu et al., 2013), this difference might be related to SCI and not CNP.

4.3. The effect of CNP on lateralization during MI

Significant differences were also observed between SCI groups with existing and those with no pain at the time of recording. The group with upcoming CNP showed more bilateral activation whereas the group with existing CNP showed more contralateral activation in theta for left-hand and higher beta band for the right-hand MI, more specifically at PMC in theta band for left-hand MI. Studies with chronic CNP have found a shift of the dominant frequency towards lower frequencies (Boord et al., 2008; Herbert et al., 2007; Jensen et al., 2013), thus part of the alpha

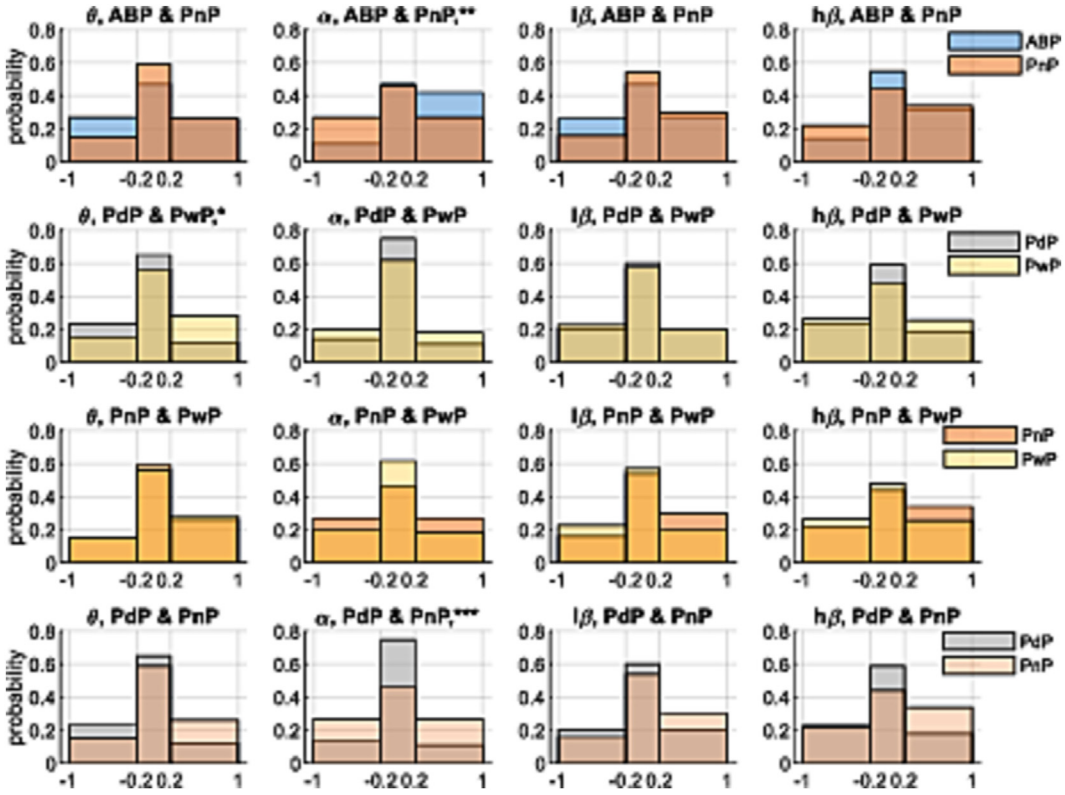

Fig. 7. Probabilities of laterality index (LI) falling into three ranges (LI<=-0.2 ipsilateral activation, −0.2 < LI < 0.2 bilateral activation, and LI >=0.2 contralateral activation) for left-hand motor imagery in theta (θ), alpha (α), lower beta (lβ), and higher beta (hβ) frequency bands. ABP, PwP, PdP, and PnP respectively refer to able-bodied people, people with spinal cord injury (SCI) and central neuropathic pain (CNP), people with SCI who developed CNP later, and people with SCI who did not develop CNP later. * Represents $p < 0.05$, ** represents $p < 0.01$ and *** represents $p < 0.001$.

Table 2
Results of statistical analysis using chi-square tests for comparison of laterality index (LI) type distribution between groups. The underlined values indicate significance after correction for multiple comparisons. LH and RH refer to left-hand and right-hand motor imagery (MI) respectively. θ, α, lβ and hβ refer to theta, alpha, lower beta, and higher beta bands. "Para only" represents statistical values after excluding people with tetraplegia from the spinal cord injury (SCI) groups.

Condition	Main p-value		post-hoc p values						
			ABP vs PnP	PdP vs PwP		PnP vs PwP		PnP vs PdP	
	All	Para only	All	All	Para only	All	Para only	All	Para only
LH θ	0.017	0.156	0.091	0.012	-	0.922	-	0.028	-
LH α	3.9e-07	2.1e-05	0.007	0.118	0.017	0.069	0.667	1.4e-04	0.004
LH lβ	0.274	0.052	-	-	-	-	-	-	-
LH hβ	0.060	0.498	-	-	-	-	-	-	-
RH θ	0.010	6e-04	0.083	0.029	0.019	0.861	0.987	0.074	0.008
RH α	0.456	0.284	-	-	-	-	-	-	-
RH lβ	2.9e-05	1.8e-04	4.5e-05	0.402	0.822	0.004	0.009	7.3e-05	0.012
RH hβ	2.2e-04	2.3e-04	0.001	0.007	0.103	0.013	0.006	0.131	0.337

desynchronization could be expressed as theta desynchronization (Llinás et al., 1999; Sarnthein et al., 2006; Vučković et al., 2019), resulting in a higher contralateral activation of existing CNP group compared to other SCI groups. The no-CNP group was also different from the existing CNP group, albeit only in higher beta band for right-hand MI with the existing CNP group showing more contralateral activation while the no CNP group showing more ipsilateral or bilateral activation. Therefore, overall, it appears that CNP might lead to contralateral activity in theta and higher beta band.

4.4. Transition from no CNP to upcoming CNP

While the upcoming CNP group shows larger desynchronization for MI of both left and right hand compared to no CNP group, the upcoming CNP group along with existing CNP group had ipsilateral activity whereas the no CNP group had contralateral activity at SAC specifically for left-hand MI in higher beta band. This could be interpreted as a marker of CNP. Considering that SAC is more posterior than central, this may also have been affected by level of injury as Kokotilo et al. observed that medial shifts in movement activation are observed for SCI with "at or below level thoracic injury" while posterior shifts are observed for "at or above level thoracic injury" (Kokotilo et al., 2009). Paraplegia-only analysis could not be performed for separate areas unfortunately to shed more light on this. Nevertheless, compound LI analysis, which was performed both with mixed and paraplegia-only cohort revealed that upcoming CNP group had more bilateral activation while the no CNP group had lateralized activity, either contralat-

eral or ipsilateral in alpha and lower beta bands. It could be that a lack of lateralization contributed to CNP later, however this needs to be confirmed in future studies.

4.5. Implications for CNP and motor recovery

We found differences between SCI groups, both with respect to intensity of activation and corresponding lateralization, especially in the higher beta band. However, whether these differences are indeed part of changes that contribute to CNP should be confirmed in future studies with increased sample size as well as EEG recording at a future time point, especially for SCI participants who developed CNP and who did not. Further, whether these changes affect motor recovery or merely represent different compensatory mechanisms need to be explored. A research study with a large cohort found that initial pain classification and intensity did not reveal any effect on motor recovery following acute SCI, but anticonvulsants conferred a significant beneficial effect on motor outcomes (Cragg et al., 2016). Most of the participants in the existing CNP group were on medication, implying that CNP might have affected motor recovery, but the medications may have helped.

5. Limitations

The first limitation is that source reconstruction is an ill-defined problem and can be influenced by the accuracy of the head model (Westner et al., 2022). We used a standard MRI, as opposed to subject-specific MRI assuming that the head properties such as head shape, skull thickness and conductivity are same for all, which is not the case. This, combined with the fact that the accuracy of derived sources depends on how well the assumption about the nature of sources by the source model holds for actual sources (Michel and Brunet, 2019) implies that the derived sources are an approximation at best. Another limitation is the small sample size as it limited detailed analysis accounting for the different completeness and levels of injury as well as times since injury. However, the sample size is comparable to that in similar studies (Cramer et al., 2005; Xu et al., 2014) and at least the paraplegia-only effects could be assessed. One final point to consider is that most participants in the existing CNP group were prescribed antiepileptic medication as pharmacological treatment at the time of EEG recording. These drugs have been known to reduce the dominant alpha frequency and increase the theta band power if taken in large doses; therefore, they may in theory influence the activations (Bauer and Bauer, 2012; Vienne et al., 1992). We minimized this effect by using a measure normalized with respect to the baseline of the participant itself.

6. Conclusions

This study characterizes differences in desynchronization and corresponding LI between able-bodied people and people with subacute SCI and varying status of CNP. Overall, the results indicate that CNP might affect laterality. The intensity of desynchronization in pain-related areas might hold a predictive value for CNP. Theta and higher beta bands appear to be more affected by CNP compared to alpha and lower beta, while the non-dominant left hand sensorimotor representations seem to be more affected by CNP than the dominant right-hand. Among all SCI groups, people with upcoming CNP had more bilateral activity as compared with people who had no CNP and people with existing CNP.

Funding statement

The study has been funded by a Commonwealth scholarship (INCS-2018–244), and by EPSRC scholarship (EP/T517896/1).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We are thankful to Euan McCaughey whose suggestions helped improve the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2023.01.006.

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