Research Paper

PAIN®

Neuropathic pain and pain interference are linked to alpha-band slowing and reduced beta-band magnetoencephalography activity within the dynamic pain connectome in patients with multiple sclerosis

Junseok A. Kim[a,b], Rachael L. Bosma[a], Kasey S. Hemington[a,b], Anton Rogachov[a,b], Natalie R. Osborne[a,b], Joshua C. Cheng[a,b], Jiwon Oh[c], Adrian P. Crawley[d], Ben T. Dunkley[e], Karen D. Davis[a,b,f,*]

Abstract

Chronic pain is a common occurrence in multiple sclerosis (MS) that severely affects quality of life, but the underlying brain mechanisms related to these symptoms are unknown. Previous electroencephalography studies have demonstrated a role of alpha-band and beta-band power in pain processing. However, how and where these brain signals change in MS-related chronic pain is unknown. Here, we used resting state magnetoencephalography to examine regional spectral power in the dynamic pain connectome—including areas of the ascending nociceptive pathway, default mode network (DMN), and the salience network (SN)—in patients with chronic MS pain and in healthy controls. Each patient was assessed for pain, neuropathic pain (NP), and pain interference with activities of daily living. We found that patients with MS exhibited an increase of alpha-band power and a decrease of beta-band power, most prominently in the thalamus and the posterior insula of the ascending nociceptive pathway and in the right temporoparietal junction of the SN. In addition, patients with mixed-NP exhibited slowing of alpha peak power within the thalamus and the posterior insula, and in the posterior cingulate cortex of the DMN. Finally, pain interference scores in patients with mixed-NP were strongly correlated with alpha and beta peak power in the thalamus and posterior insula. These novel findings reveal brain mechanisms of MS-related pain in the ascending nociceptive pathway, SN, and DMN, and that these spectral abnormalities reflect the impact of pain on quality of life measures.

Keywords: Multiple sclerosis, Neuropathic pain, MEG, Spectral power, Default mode network, Salience network

1. Introduction

Multiple sclerosis (MS) is an autoimmune disease of the nervous system, which manifests as sensorimotor, cognitive, and psychological abnormalities.[30] Chronic pain occurs in approximately 50% of patients with MS[2,56] and severely affects the patient's quality of life, yet little is known of the underlying brain mechanisms.[70] The few studies, which have examined brain correlates of chronic pain in MS, were limited to case studies or only focused on the relationship between lesions, plaques, and white-matter integrity.[70] These studies failed to find any association between structural abnormalities and chronic pain.[17,41,75,79] As such, the brain mechanisms underlying pain in MS remain unknown.

We have proposed that pain is believed to arise from activity in the dynamic pain connectome—a system of brain regions involved with nociceptive processing and pain modulation, including ascending nociceptive pathways, the salience network (SN), the default mode network (DMN), and the descending antinociceptive pathways.[43,44] Several functional magnetic resonance imaging studies of chronic pain have identified abnormalities[5,15,34,53,61,67,72] in the DMN, SN, ascending nociceptive, and descending antinociceptive pathways.

The brain is a flexible system, which dynamically engages various neural networks in response to the external environment. This concept of neural dynamics is a major component of the dynamic pain connectome concept based on functional magnetic resonance imaging findings, but these findings are limited by poor temporal resolution and being based on haemodynamics, which is an indirect measure of neural activity. Techniques such as electroencephalography (EEG) and magnetoencephalography (MEG) have great utility in capturing neurophysiological data on a millisecond scale. Previous studies using EEG have demonstrated a link between pain perception and alpha-band/beta-band activity and showed that peak alpha frequency was related

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

[a] *Division of Brain, Imaging, and Behaviour-Systems Neuroscience, Krembil Brain Institute, Krembil Research Institute, Toronto Western Hospital, University Health Network, Toronto, ON, Canada,* [b] *Institute of Medical Science, University of Toronto, Toronto, ON, Canada,* [c] *Division of Neurology, Department of Medicine, St. Michael's Hospital, Toronto, ON, Canada,* [d] *Department of Medical Imaging, University of Toronto, Toronto, ON, Canada,* [e] *Neurosciences & Mental Health Program, The Hospital for Sick Children Research Institute, Toronto, ON, Canada,* [f] *Department of Surgery, University of Toronto, Toronto, ON, Canada*

**Corresponding author. Address: Division of Brain, Imaging, and Behaviour -Systems Neuroscience, Krembil Brain Institute, Krembil Research Institute, University Health Network, 399 Bathurst St, Room MP12-306, Toronto, ON M5T 2S8, Canada. Tel.: (416) 603-5662. E-mail address: karen.davis@uhnresearch.ca (K.D. Davis).*

PAIN 160 (2019) 187–197

http://dx.doi.org/10.1097/j.pain.0000000000001391

to prolonged heat pain sensitivity in healthy participants.[26] In addition, alpha-band and beta-band activity is suppressed in response to phasic[36,59] and tonic[37,54,69] pain. In patients with chronic neurogenic pain, resting state EEG indicated that low-frequency spectral power is increased in anterior cingulate, dorsolateral prefrontal cortex, and the insula.[74] Importantly, leftward shift of the alpha power peak frequency within the frontocentral region has been reported in a small group of chronic neuropathic pain (NP) patients.[67] These studies demonstrated that patients with chronic pain exhibit abnormalities in spectral power within regions of the dynamic pain connectome. However, it is unknown whether these abnormalities extend to MS-related pain. Here, we use magnetic source imaging through a beamforming technique to spatially resolve activity using MEG, allowing us to localize regional spectral abnormalities in patients with MS.

In addition to the role of spectral abnormalities in MS-related pain, it is not known whether there are specific brain abnormalities associated with different types of MS-related pain, which can include both neuropathic and non-neuropathic characteristics. Furthermore, little is known of the brain mechanisms underlying pain interference. Thus, the aims of the current study were to identify the spectral power abnormalities in different aspects of MS pain to determine (1) locations of regional abnormalities, (2) abnormalities specific to patients with NP vs non-neuropathic pain (NNP), and (3) the relationship between identified brain abnormalities with interference of pain on patient's daily activities.

2. Materials and methods

2.1. Participants

Study participants consisted of 27 patients diagnosed with MS (17 women; 10 men; mean ± SD age 39 ± 10 years) and 26 age- and sex-matched healthy controls (HCs) (16 women; 10 men; mean ± SD age 35 ± 9 years). All participants provided informed written consent approved by the local research ethic boards of the University Heath Network and St. Michael's Hospital. Patients with MS were recruited from a MS clinic at St. Michael's Hospital. The inclusion criteria were (1) diagnosis of MS according to the 2010 McDonald criteria, confirmed by neurologists at St. Michael's Hospital, (2) able to ambulate without assistance, (3) free of any pain conditions other than MS-related pain conditions, and (4) no contraindications for the MRI. The inclusion criteria for the HC group were (1) no previous history of chronic pain or current experience of pain on a regular basis, (2) free of metabolic, psychiatric, or neurologic conditions, (3) no history of major surgery, and (4) no contraindications for the MRI.

2.2. Clinical assessment and questionnaires

Clinical information collected include year of MS symptom onset, duration of MS, specific MS subtype, and the Expanded Disability Status Scale (EDSS) score,[46] which is a commonly used global neurological disability score in MS. The EDSS ranges from 0 to 10 with increasing scores reflecting an increase in neurological disability. Patients also completed the painDETECT[25] for classification into mixed-neuropathic, which contains patients with mixed-NP and definitive NP and NNP subgroups. PainDETECT scores range from 0 to 38 with scores 19 to 38 considered to be definitively neuropathic, scores 13 to 18 considered to be mixed-neuropathic, and scores 0 to 12 considered to be non-neuropathic. The Brief Pain Inventory (BPI)[21,58,80] was used to measure general levels of pain and pain interference. The specific items measured in the BPI include pain levels rated 0 to 10 (worst pain previous day, least pain previous day, average pain, and pain right now), pain relief from medication and pain interference (ranges from 0 to 10, 0 = no interference and 10 = complete interference) with items such as general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. The Hospital Anxiety and Depression Scale[85] was self-administered by the participants to assess nonphysical symptoms of anxiety and depression with scores of 8 and over being considered clinically significant.

2.3. Magnetoencephalography acquisition

All participants underwent a 5-minute MEG session to acquire resting state brain activity detected with a 306 channel Elekta Neuromag TRIUX system with a sampling rate of 1000 Hz and recording DC bandpass of 330 Hz. Participants were seated in the upright position in a magnetically shielded room and were free of any metallic objects or traces of metal from makeup or hair products. Fiducial reference points were obtained at the nasion, right and left preauricular points for registration, and motion correction purposes. Resting state signals were recorded during the continuous acquisition while participants looked at a fixation cross ("eyes-open" resting state) inside a dark room. Throughout the resting state scan, head position was recorded using head position coils placed on 5 positions around the participant. Artifact correction was performed using the tSSS algorithm implemented in the MaxFilter program.

After the MEG session, each participant underwent a 3T MRI (GE) of the brain to acquire high-resolution T1 anatomical images ($1 \times 1 \times 1$ mm^3 voxels, matrix = 256×256, 180 axial slices, repetition time = 7.8 seconds, echo time = 3 ms, inversion time = 450 ms). Magnetoencephalography data for each participant were coregistered to their anatomical MRI scan using the fiducial points obtained before the MEG session for source reconstruction/inverse solution.

2.4. Magnetoencephalography data preprocessing and beamforming

Resting state data were analyzed using MATLAB-based program FieldTrip (http://www.fieldtriptoolbox.org/). Resting state data were bandpass-filtered at 1 to 150 Hz, and a notch filter was applied at 60 and 120 Hz. Independent component analysis (ICA) was used to remove components from the time series data that were likely to reflect breathing and eye-blink artifacts, identified by visual inspection. Fiducial points identified on the MRI were used to register each individual's high-resolution anatomical image to the resting state MEG data. A single-shell model of the head was used for the forward model.

Specific regions of interest (ROI) based on previously defined coordinates[34,45,64] were used to construct "virtual sensors" and extract a continuous resting state time series for each of the seeds/ROIs. Reconstruction of the time series corresponding to a voxel at the center of mass of each ROI was performed using a linearly constrained minimum variance beamformer[81] based on the anatomical location of each participant. Beamforming is a spatial filtering technique used to obtain the signal of interest only within the designated region of interest while optimally suppressing the signals from other sources.[71] To do this, a weighting vector is calculated for each source location in the brain and is applied to the physical sensor's time course; the resultant time series are summated and give a reconstructed signal for the specified source location over time.[81] These magnetic source imaging methods based on atlas-guided

beamforming to characterize regional power spectrum in health and disease have been used for a number of years and are in widespread use.[22,23,35,51]

2.5. Regions of interest

The ROIs for nodes of the dynamic pain connectome were selected for the atlas-guided beamforming. The coordinates were determined based on our previous work[34,45,64] on the dynamic pain connectome and were visually confirmed on a standard MNI152 anatomical template. The coordinates of the ROIs (x, y, z) were ascending nociceptive pathway: left primary somatosensory cortex (S1) (−34, −30, 54), right S1 (34, −28, 54), left secondary somatosensory cortex (S2) (−60, −30, 20), right S2 (60, −22, 18), left posterior insula (−34, −20, 18), right posterior insula (34, −20, 18), left thalamus (−12, −18, 8), right thalamus (12, −18, 8); SN: right temporoparietal junction (TPJ) (50, −32, 28), right anterior insula (34, 18, 4), mid cingulate cortex (2, 12, 34), right dorsolateral prefrontal cortex (34, 46, 22); and DMN: posterior cingulate cortex (PCC) (−2, −46, 28) and medial prefrontal cortex (−2, 50, 2).

2.6. Power spectra analysis

Power spectra for each ROI seed location were calculated using the Welch power density estimate (MATLAB 2015b) over the resting state time series (300 seconds, no epochs or overlapping windows). The Welch power density estimate uses a short fast Fourier transform with a Hanning window to obtain a power value per frequency point determined by the sampling rate (1-Hz sampling rate). Each subject's resting state time series was normalized by *z*-scoring the beamformed time series data to account for individual differences in broadband spectra. The Welch power density estimate applied on the normalized data resulted in power values per frequency point for each ROI in every subject. For group comparisons, the mean and SD for power were calculated at each frequency point. Peak alpha frequency was measured by identifying individual power maxima restricted to the alpha band (8-13 Hz) on a subject by subject basis in all of the MS and HC subgroups and calculating the mean and SD for each group in each ROI. We considered the following ranges to belong to frequency bands: theta 4 to 8 Hz, alpha 8 to 13 Hz, beta 13 to 30 Hz, and gamma 30 to 150 Hz.

2.7. Statistical analysis

Student *t* tests were conducted (false discovery rate [FDR] corrected with Benjamin Hochberg method at FDR < 0.05 across ROI) between the main groups (HC and MS) and between patient subgroups (mixed-NP and NNP) and their respective matched HCs to compare group averages of spectral power at each frequency point in alpha and beta across each ROI. Effect size for each *t* test was measured using Cohen's *d*. For the frequencies and ROIs at which there were group differences, we used a Spearman correlation to assess the rank-ordered relationship between power spectra values and pain interference as well as power spectra values and average pain levels.

3. Results

3.1. Clinical data

Demographic data for the MS and HC groups and for the NP/NNP subgroups are summarized in **Table 1**. The HC and MS groups did not differ in age ($t = 1.5$, $P = 0.15$) or sex. However, the patients with MS had significantly higher scores for depression ($t = 4.3$, $P < 0.0001$) and anxiety ($t = 3.8$, $P = 0.0004$). Between the MS subgroups (NP vs NNP) there was no significant difference in sex or age of onset ($t = 1.9$, $P = 0.06$), although the NP group was older than the NNP group ($t = 3.1$, $P = 0.004$). In the pain-related measures, the NP group had significantly higher average pain levels ($t = 3.5$, $P = 0.002$) and significantly higher average pain interference ($t = 4.6$, $P < 0.0001$) compared with the NNP group. The NP group also had significantly higher EDSS ($t = 3.5$, $P = 0.001$), depression ($t = 3.2$, $P = 0.003$), and anxiety scores ($t = 2.3$, $P = 0.02$) compared with the NNP group.

3.2. Increased alpha power and decreased beta power in multiple sclerosis

Patients with MS exhibited abnormalities in spectral power of the alpha and beta bands within several regions of the dynamic pain connectome (**Figs. 1 and 2**).

Table 1

Demographics and characteristics of HC and MS groups.

	Groups		MS subgroups	
	HC	MS	MS (NP)	MS (NNP)
N	26	27	13	14
Age (y)	35 ± 9	39 ± 10	44 ± 9	34 ± 8*
Sex	10 M, 16 W	10 M, 17 W	5 M, 8 W	5 M, 9 W
Years since MS onset	N/A	10 ± 7	12 ± 9	8 ± 5
Average EDSS (/10)	N/A	2 ± 2	3 ± 2	1 ± 1*
Type of MS	N/A	26 RR, 1 RIS	13 RR	13 RR, 1 RIS
Avg. pain (/10)	N/A	3.4 ± 2.7	5 ± 2.5	2 ± 2*
Avg. pain interference (/10)	N/A	3.5 ± 2.9	5.4 ± 2.5	1.6 ± 1.8*
HADS depression (/21)	3 ± 2†	8 ± 5†	11 ± 5	5 ± 4*
HADS anxiety (/21)	3 ± 3†	7 ± 5†	9 ± 4	5 ± 4*

All mean values are provided with SD. EDSS scores for the NP group (n = 11, scores missing for 2 patients).

* Significant subgroup differences at $P < 0.05$ between the MS (NP) and MS (NNP) subgroups.

† Significant differences at $P < 0.05$ between the HC and MS groups.

HC, healthy control; MS, multiple sclerosis; NP, mixed neuropathic pain; NNP, non-neuropathic pain; EDSS, Expanded Disability and Severity Scale; HADS, Hospital Anxiety and Depression Scale; RR, relapsing remitting; RIS, radiologically isolated syndrome.

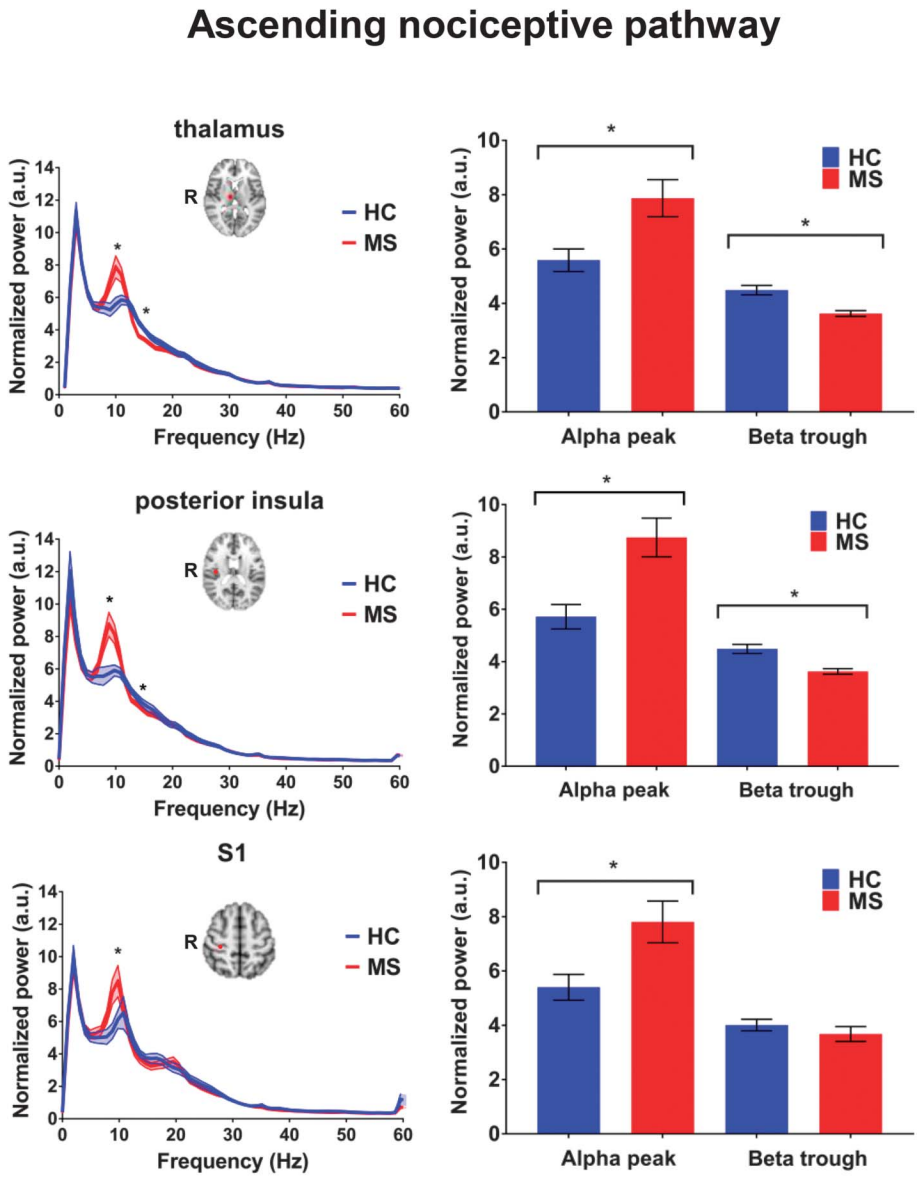

Figure 1. Power spectra comparisons showing mean (±SEM) between HC (blue) and MS (red) in the ascending nociceptive pathway. Bar graphs represent mean (±SEM) of peak alpha power and beta trough in the HC (blue) group compared with the MS (red) group. *FDR-corrected group differences at $P < 0.05$. FDR, false discovery rate; HC, healthy control; MS, multiple sclerosis.

Within the alpha band, specifically at 9 to 10 Hz, spectral power was significantly increased in the MS group compared with the HC group within the nodes of the ascending nociceptive pathway, specifically in the left ($P = 0.0001$, FDR < 0.05, $d = 1.2$) and right posterior insula ($P = 0.007$, FDR < 0.05, $d = 0.94$) (**Fig. 1**), the right S1 ($P = 0.01$, FDR < 0.05, $d = 0.73$) (**Fig. 1**), the left ($P = 0.0001$, FDR < 0.05, $d = 1.14$) and right thalamus ($P = 0.007$, FDR < 0.05, $d = 0.78$) (**Fig. 1**), as well as the left ($P = 0.004$, FDR < 0.05, $d = 0.92$) and the right S2 ($P = 0.006$, FDR < 0.05, $d = 1$). Furthermore, patients with MS had significantly higher power in the right TPJ ($P = 0.006$, FDR < 0.05, $d = 0.8$) (**Fig. 2**), a node of the SN.

Compared with HCs, beta spectral power at 13 to 14 Hz in the MS group was significantly decreased in several nodes of the ascending nociceptive pathway, including the left ($P = 0.002$, FDR < 0.05, $d = 0.89$) and right thalamus ($P = 0.00007$, FDR < 0.05, $d = 1.2$) (**Fig. 1**), left ($P = 0.016$, FDR < 0.05, $d = 0.68$) and right S2 ($P = 0.025$, FDR < 0.05, $d = 0.63$), and the left ($P = 0.007$, FDR < 0.05, $d = 0.76$) and right posterior insula ($P = 0.016$, FDR < 0.05, $d = 0.68$). Furthermore, a significant decrease in the beta-band power in the MS group compared with the HC group was observed within the nodes of the SN (right anterior insula [$P = 0.024$, FDR < 0.05, $d = 0.62$] (**Fig. 2**) and the mid cingulate cortex [$P = 0.008$, FDR < 0.05, $d = 0.78$]) (**Fig. 2**). None of the other ROIs examined showed significant group differences.

3.3. Beta power reduction and "slowing" of alpha-band power in patients with mixed-neuropathic pain

We next examined whether the alpha-band and beta-band abnormalities were specific to a particular subgroup of patients with MS who have either mixed-NP or NNP (**Fig. 3**). Because of the slight age differences between the NP and NNP groups, we

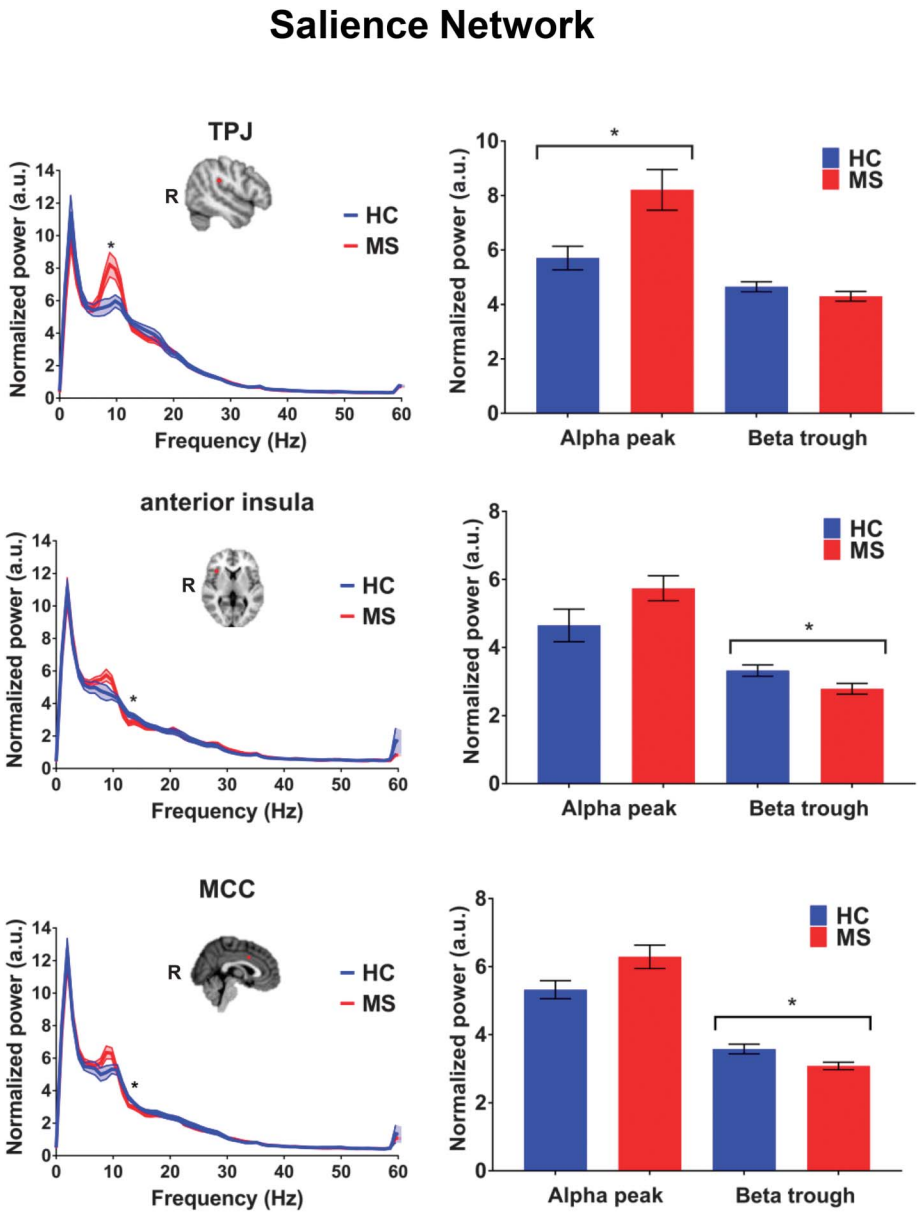

Figure 2. Power spectra comparisons showing mean (±SEM) between HC (blue) and MS (red) in the salience network. Bar graphs represent mean (±SEM) of peak alpha power and beta trough in the HC (blue) group compared with the MS (red) group. Uncorrected significant group differences are marked with the * indicating FDR-corrected group differences at $P < 0.05$. FDR, false discovery rate; HC, healthy controls; MCC, mid cingulate cortex; MS, multiple sclerosis; TPJ, temporoparietal junction.

carefully used separate groups of age-matched HCs for each subset of patients.

We found that the beta power at 13 Hz was significantly decreased in the NP group compared with their control group within the regions of the ascending nociceptive pathway including the left ($P = 0.0017$, FDR < 0.05, $d = 1.38$), right thalamus ($P = 0.0019$, FDR < 0.05, $d = 1.37$) (**Fig. 3A**), and the left posterior insula ($P = 0.009$, FDR < 0.05, $d = 1.12$). Furthermore, alpha power at 9 to 10 Hz was prominently increased in NNP within the regions of the ascending nociceptive pathway left thalamus ($P = 0.014$, FDR < 0.1, $d = 1.04$), left posterior insula ($P = 0.015$, FDR < 0.1, $d = 1.04$), and right posterior insula ($P = 0.015$, FDR < 0.1, $d = 1.04$) (**Fig. 3A**). None of the other ROIs tested exhibited a significant difference.

Despite the findings of abnormal spectral power noted above, there were no significant differences in spectral power peaks between the NP and NNP pain subgroups within any ROIs of the dynamic pain connectome. However, a trend of "slowing" or leftward shift of the peak alpha frequency was observed in the NP in the PCC (a region of the DMN) {mean ± SD peak alpha frequency (Hz), 8.7 ± 1.8 (MS [NP]), 9.5 ± 1.4 (MS [NNP]), 10 ± 1.4 (HC [NP]), 10.5 ± 0.6 (HC [NNP])} (**Fig. 4A**), and regions of the ascending nociceptive pathway: the left posterior insula {mean ± SD peak alpha frequency (Hz) 9.6 ± 1.1 (MS [NP]), 9.6 ± 1.1 (MS [NNP]), 10 ± 1.1 (HC [NP]), 10.5 ± 0.9 (HC [NNP])} and right posterior insula {mean ± SD peak alpha frequency (Hz), 8.9 ± 1.5 (MS [NP]), 9.9 ± 1.1 (MS [NNP]), 9.6 ± 1.2 (HC [NP]), 10.3 ± 1.1 (HC [NNP])} (**Fig. 4B**), and the left {mean ± SD peak alpha frequency (Hz), 8.6 ± 1.9 (MS [NP]),

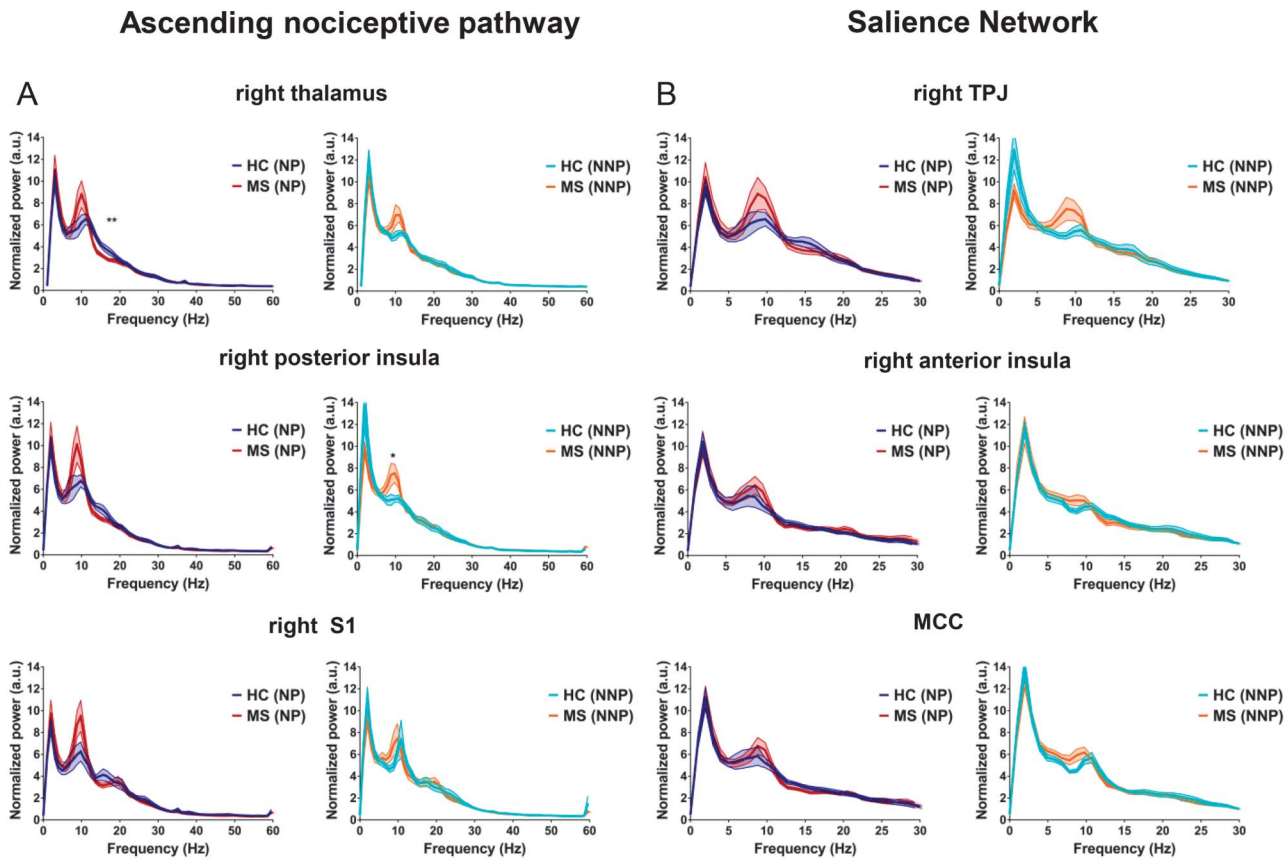

Figure 3. Power spectra comparison between MS NP and NNP subgroups against matched HC in the dynamic pain connectome. Uncorrected significant group differences are marked with the * and corrected significant group differences are marked with ** indicating group differences at $P < 0.05$. (A) Group differences in the ascending nociceptive pathway. (B) Group differences in the salience network. HC, healthy controls; MS, multiple sclerosis; NP, mixed neuropathic pain; NNP, non-neuropathic pain.

9.2 ± 1.1 (MS [NNP]), 9.4 ± 1.6 (HC [NP]), 10.5 ± 0.8 (HC [NNP])} and right thalamus {mean ± SD peak alpha frequency (Hz), 8.9 ± 1.5 (MS [NP]), 9.6 ± 0.8 (MS [NNP]), 9.9 ± 1.2 (HC [NP]), 10.5 ± 1.2 (HC [NNP])} (**Fig. 4C**).

3.4. Pain interference is related to alpha and beta power within the ascending nociceptive pathway and default mode network

We examined the relationship between pain interference and resting state spectral power within the dynamic pain connectome in all patients with MS and in each MS subgroup. First, we extracted spectral power from the ROIs in the earlier analyses, which exhibited a significant difference in power between MS and HC groups. Second, we also extracted spectral power from ROIs that demonstrated alpha peak slowing in the MS group. The most robust finding was a negative correlation between pain interference scores and beta power (13 Hz) within the whole MS group in the left posterior insula (rho = −0.49, $P = 0.008$) (**Fig. 5A**). This relationship was present in patients with NP (rho = −0.71, $P = 0.006$) (**Fig. 5A**) but not in the NNP group (rho = −0.23, $P = 0.43$) (**Fig. 5A**). Pain interference scores were also positively correlated with alpha power (9 Hz) within the whole MS group in the left thalamus (rho = 0.39, $P = 0.045$) (**Fig. 5B**) and in the NP group (rho = 0.53, $P = 0.06$) (**Fig. 5B**) but not in the NNP group (rho = 0.16, $P = 0.59$) (**Fig. 5B**). Finally, there was a trend of alpha power (9 Hz) being positively correlated with pain interference within the whole MS group in the PCC (rho = 0.35, $P = 0.07$) (**Fig. 5C**) and significantly correlated in the NP group (rho = 0.73, $P = 0.004$) (**Fig. 5C**) but not in the NNP group (rho = −0.23, $P = 0.43$) (**Fig. 5C**). Pain interference scores were trending towards negative correlation with beta power at 13 Hz within the whole MS group in the left thalamus (rho = −0.36, $P = 0.06$), but there was a significant negative correlation in the NP group (rho = −0.65, $P = 0.02$) and no significant correlation in the NNP group (rho = −0.09, $P = 0.77$). Pain interference scores were not correlated with beta power at 13 Hz within the whole MS group in the right thalamus (rho = −0.21, $P = 0.30$); however, it was significantly negatively correlated in the NP group (rho = −0.66, $P = 0.01$) but not in the NNP group (rho = 0.16, $P = 0.59$).

No other ROIs that showed power difference between HC and MS showed significant relationships with pain interference scores.

3.5. Average pain level is related to alpha and beta power within the ascending nociceptive pathway and default mode network

We also examined the relationship between average pain within the last week and power spectra within the dynamic pain connectome. Pain interference and average pain scores were strongly correlated (rho = 0.89, $P < 0.01$), and so, the relationships between spectral power and average pain level were to the correlations noted above to pain interference.

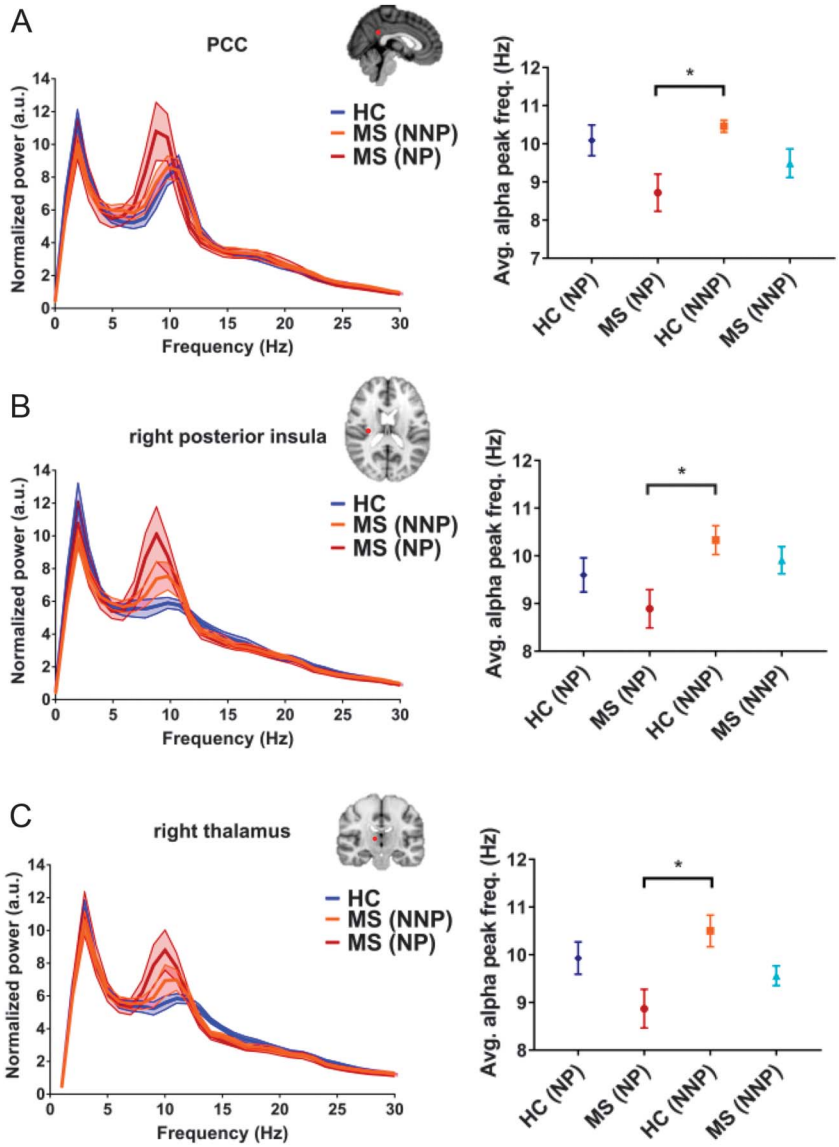

Figure 4. Slowing of the alpha peak power in the MS (NP) group compared with the MS (NNP) and HC groups. All the regions demonstrated slowing of the alpha peak in the NP group compared with the NNP and HC. Mean (±SD) frequency for each group is displayed on the right of the power spectra. The regions are posterior cingulate cortex (PCC) (A), right posterior insula (B), and right thalamus (C). *Group differences between MS (NP) and HC (NNP) groups. The NP and NNP for the HC group refer to the age-matched groups. HC, healthy controls; MS, multiple sclerosis; NP, mixed neuropathic pain; NNP, non-neuropathic pain.

Specifically, in the whole MS group, average pain was correlated with spectral power in the left posterior insula (rho = −0.55, $P = 0.003$) at 13 Hz, and in the left thalamus at 9 Hz (rho = 0.39, $P = 0.04$) and at 13 Hz (rho = −0.46, $P = 0.02$). However, average pain was not significantly correlated with spectral power in the PCC (rho = 0.29, $P = 13$) at 9 Hz, or in the right thalamus (rho = −0.32, $P = 0.1$) at 13 Hz. Within the NP subgroup, average pain and spectral power were correlated in the PCC (rho = 0.57, $P = 0.04$) at 9 Hz, and in the left (rho = −0.67, $P = 0.01$) and right (rho = −0.71, $P = 0.006$) thalamus and left posterior insula (rho = −0.65, $P = 0.02$) at 13 Hz, but not in the left thalamus (rho = 0.46, $P = 0.11$) at 9 Hz. Within the NNP group power, there were no statistically significant correlations between average pain and spectral power in the PCC (rho = −0.08, $P = 0.77$) or left thalamus (rho = 0.38, $P = 0.18$) at 9 Hz, or in the left thalamus (rho = −0.36, $P = 0.21$), right thalamus (rho = −0.11, $P = 0.71$), or left posterior insula (rho = −0.47, $P = 0.1$) at 13 Hz.

4. Discussion

This study demonstrates novel findings that patients with chronic MS pain exhibit spectral power abnormalities in the alpha and beta bands within nodes of the ascending nociceptive pathway and the SN. We also found that (1) these spectral power abnormalities were particularly prominent in a subset of patients with MS with mixed-NP, (2) the abnormalities in alpha and beta spectral power were related to pain interference in regions of the ascending nociceptive pathway and were most pronounced in patients with mixed-NP, and (3) patients with mixed-NP exhibited "slowing" of the peak alpha frequency in regions of the ascending nociceptive pathway and in regions of the DMN.

Our finding that patients with MS mixed-NP have decreased beta power within nodes of the ascending nociceptive pathway, and the SN is novel as previous studies of chronic pain focused on increases in alpha/theta power.[18,47,67,74] Beta oscillations

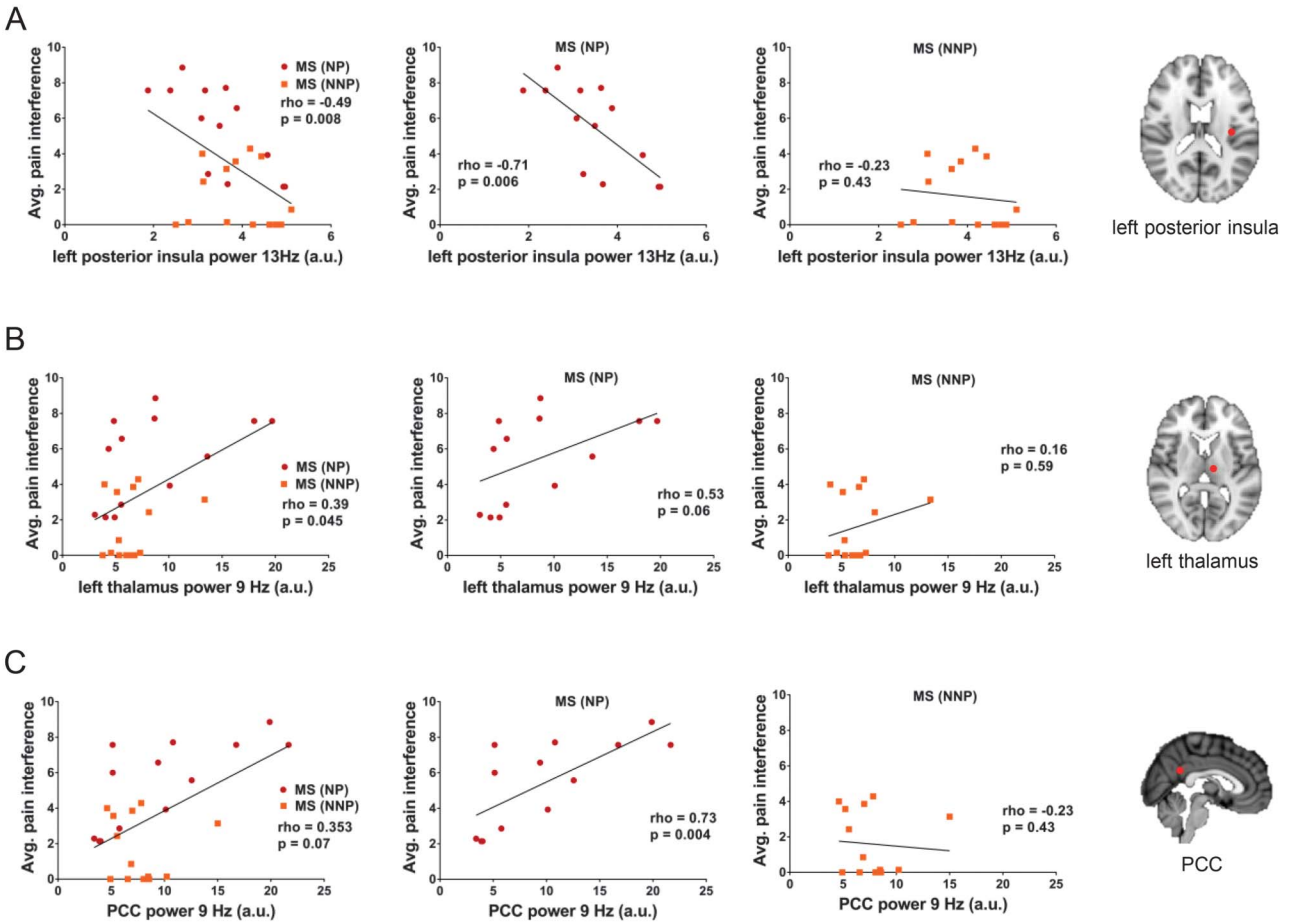

Figure 5. (A) Significant negative correlation between beta power and pain interference scores in the left posterior insula but not in the MS pain subgroups. (B) Significant positive-correlation between alpha power and pain interference scores in the left thalamus but not in the MS pain subgroups. (C) Significant positive correlation between alpha power and pain interference scores in the PCC only in the MS NP group. MS, multiple sclerosis; PCC, posterior cingulate cortex; NP, mixed neuropathic pain; NNP, non-neuropathic pain.

have previously been associated with motor functions such as maintenance of posture[82] and prevention of voluntary movement in favour of tonic activity.[1,28,60] In studies of attention and cognition, increase in beta-band activity was associated with maintaining current cognitive status, but beta power was decreased in response to a change in the cognitive system because of an external stimuli.[39,57] Given the results of these studies, one possible role of beta oscillations may be a top-down mechanism to prevent future actions and maintain the current status. If so, beta-band activity may be greatest if there is no top-down adjustment needed within a neural system, and a decrease in beta-band activity may indicate that there is top-down involvement required to respond to an impending situation. Thus, reduced beta power in nodes of the ascending nociceptive pathway and SN may reflect a state of flux of these networks because of the intermittent pain qualities associated with NP.

The observed increase in alpha power in several nodes of the SN and ascending nociceptive pathway in MS chronic pain is in line with previous chronic pain studies.[48,74] Many studies have described the possible role of the alpha rhythm in local inhibition, and gating of perception[19,32,55,65] as alpha activity is related to reduced local inhibition and reduced gating. Therefore, an increase in alpha-band power in patients with MS-related pain may reflect a reduction of sensory gating in regions of the ascending nociceptive pathway and/or SN. This may be why alpha power is especially increased in patients with mixed-NP because these patients can exhibit allodynia, hyperalgesia, sensory loss, as well as tingling burning and shooting sensations, which may be related to reduced gating within nodes the ascending nociceptive pathway.[29] Furthermore, increased alpha power in the right TPJ may reflect an increased likelihood of the SN being active in patients with mixed-NP. Thus, the increased alpha power in the TPJ could indicate that the SN is overactive in these patients as a result of overflowing sensory information due to reduced sensory gating. As such, the alpha power abnormalities observed within regions of the ascending nociceptive pathway and the SN may be tightly linked. Of note, our findings are at odds with previous MEG studies that did not find alpha power abnormalities in MS within the ascending nociceptive pathway and the SN.[14,68,77] However, these previous studies did not specifically investigate pain, and these patients may not have had chronic pain.

Our finding of a "slowing" of the peak alpha frequency in patients with MS mixed-NP is consistent with previous studies in small groups of NP patients.[16,48,67,83] Thus, alpha slowing may be a general marker of NP. Thalamocortical dysrhythmia is the most prominent theory proposed to explain slowing of the peak alpha frequency in NP.[49] The main tenet of this concept is that there is a continuous overproduction of slow rhythms, which are then propagated through thalamocortical loops. However, our results suggest an additional or alternative explanation for this phenomenon based on age effects. We found that patients with

mixed-NP and those with NNP showed "slowing" of the peak alpha frequency compared with their age-matched controls. Interestingly, when we investigated alpha peak frequencies of each subgroup, we observed that younger patients with non-neuropathic MS pain had similar alpha peak frequencies as the older HC group. As such, the older HC group showed a trend of peak alpha frequency slowing compared with the younger HC group. Peak alpha frequency slowing with aging has already been observed in multiple studies.[10,27,33,84] Therefore, peak alpha frequency slowing could be an indicator of the aging brain, which could be accelerated by chronic pain. Accelerated gray-matter loss in aging has been demonstrated in chronic pain patients with fibromyalgia.[42] The authors postulated that the accelerated loss of gray matter could have resulted from increased exposure to inflammatory agents, and prolonged exposure to pain had negative effects in brain regions involved with pain processing. Therefore, in an inflammatory disease such as MS, inflammation from chronic pain may further exacerbate the accelerated aging process of the brain. As such, patients with MS mixed-NP may have thalamocortical dysrhythmia as well as accelerated aging of the brain, mechanisms which may work in isolation or in conjunction that may have led to the slowing of the alpha power peak in many regions of the dynamic pain connectome especially in the regions involved with sensory processing. Interestingly, we have previously shown that gray-matter abnormalities in chronic pain patients with temporomandibular disorder are due to a complex interaction between age and pain,[52] which may show that there are changes in brain morphology and brain function related to chronic pain, which could be the result of a complex relationship between aging and chronic pain.

We found a link between pain interference scores and the abnormalities in alpha and beta oscillations in regions of the ascending nociceptive pathway and the DMN. Interestingly, this relationship was driven mainly by the patients with mixed-NP. Pain interference is an item within the BPI, which measures the degree to which pain interferes with daily activities. We found that patients with mixed-NP had significantly greater pain interference compared to those with NNP, and this could explain why the patients with mixed-NP were the only ones to exhibit a relationship between abnormal power and pain interference. Most of the significant correlations between alpha and beta power and pain interference were observed within regions of the ascending nociceptive pathway. We also found that pain interference correlated with alpha power in the PCC, a region of the DMN, which is commonly abnormal in chronic pain patients[5,34,53,76] including those with NP.[9] The DMN is also implicated in mind wandering away from pain.[45] Therefore, the significant relationship between alpha power and pain interference may represent a mechanism by which patients may have difficulty ignoring their pain, and thus their day to day activities are impacted the most by their pain experience.

Chronic pain in MS does not occur in isolation, and so, interpretation of these spectral band abnormalities should consider the complex milieu of attentional and sensorimotor conditions experienced by these patients. Chronic pain is also highly comorbid with psychiatric disorders including depression and anxiety and shares similar neural underpinnings.[8] As such, these factors must be taken into consideration when interpreting our findings. In addition, caution must be used to interpret our results that arose from measuring signals from deeper sources such as the thalamus. Although we made careful methodological considerations to extract only signals of interest, technical limitations in MEG source reconstruction could still restrict the ability to perfectly resolve deeper sources, resulting in mixed signals (ie, signal leakage) from surrounding regions. This could arise from the beamformer not being able to perfectly suppress those adjacent sources because of reduced SNR. There is no direct electrophysiological evidence to confirm the location of oscillatory activity that we attributed to deep sources. However, there is an increasing body of empirical evidence that demonstrates the capability of MEG to detect weak signals originating from deep brain structures such as the hippocampus,[13,31,40,50,62,63,73] amygdala,[11–13,20,38] and thalamus.[6,7,66,78] In addition, realistic simulations[3,4,24,63] that examined beamformer or minimum current estimate solutions to localize deep generators have demonstrated that MEG is able to reliably detect deep sources.

In conclusion, our study revealed that patients with MS-related chronic pain, and especially those with mixed-NP, have abnormalities in spectral power within the regions of the dynamic pain connectome. Abnormal increases in alpha-band power, decreases in beta-band power, and slowing of the alpha power peak observed in patients with mixed-NP was mainly observed in the nodes of the ascending nociceptive pathway. As the increase in alpha power and slowing of the alpha peak frequency was in line with previous research with NP patients, this particular alteration in spectral profile may be a hallmark of mixed-NP. Finally, correlations with pain interference scores suggested that altered resting state spectral power may be a robust neural correlate for pain interference in patients with MS mixed-NP.

Conflict of interest statement

The authors have no conflict of interest to declare.

Acknowledgements

The authors thank Eugen Hlasny and Keith Ta for expert technical assistance in MRI acquisition, Drs Luis Garcia Dominguez and Richard Wennberg for technical assistance in MEG acquisition, and Geoff Pope for technical assistance.
This work was funded by the Multiple Sclerosis Society of Canada. R.L. Bosma was a recipient of a CIHR Post-doctoral Research Award, K.S. Hemington and J.C. Cheng were supported by CIHR Doctoral Research Awards, and J.A. Kim was supported by an MS Society of Canada endMS Doctoral Studentship Award.

Article history:
Received 18 May 2018
Accepted 29 August 2018
Available online 3 September 2018

References

[1] Androulidakis AG, Doyle LM, Yarrow K, Litvak V, Gilbertson TP, Brown P. Anticipatory changes in beta synchrony in the human corticospinal system and associated improvements in task performance. Eur J Neurosci 2007;25:3758–65.
[2] Archibald CJ, McGrath PJ, Ritvo PG, Fisk JD, Bhan V, Maxner CE, Murray TJ. Pain prevalence, severity and impact in a clinic sample of multiple sclerosis patients. PAIN 1994;58:89–93.
[3] Attal Y, Schwartz D. Assessment of subcortical source localization using deep brain activity imaging model with minimum norm operators: a MEG study. PLoS One 2013;8:e59856.
[4] Balderston NL, Schultz DH, Baillet S, Helmstetter FJ. How to detect amygdala activity with magnetoencephalography using source imaging. J Vis Exp 2013;76.
[5] Baliki MN, Geha PY, Apkarian AV, Chialvo DR. Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. J Neurosci 2008;28:1398–403.

[6] Bardouille T, Ross B. MEG imaging of sensorimotor areas using inter-trial coherence in vibrotactile steady-state responses. Neuroimage 2008;42:323–31.
[7] Bish JP, Martin T, Houck J, Ilmoniemi RJ, Tesche C. Phase shift detection in thalamocortical oscillations using magnetoencephalography in humans. Neurosci Lett 2004;362:48–52.
[8] Boakye PA, Olechowski C, Rashiq S, Verrier MJ, Kerr B, Witmans M, Baker G, Joyce A, Dick BD. A critical review of neurobiological factors involved in the interactions between chronic pain, depression, and sleep disruption. Clin J Pain 2016;32:327–36.
[9] Cauda F, Sacco K, Duca S, Cocito D, D'Agata F, Geminiani GC, Canavero S. Altered resting state in diabetic neuropathic pain. PLoS One 2009;4:e4542.
[10] Clark RC, Veltmeyer MD, Hamilton RJ, Simms E, Paul R, Hermens D, Gordon E. Spontaneous alpha peak frequency predicts working memory performance across the age span. Int J Psychophysiol 2004;53:1–9.
[11] Cornwell BR, Baas JM, Johnson L, Holroyd T, Carver FW, Lissek S, Grillon C. Neural responses to auditory stimulus deviance under threat of electric shock revealed by spatially-filtered magnetoencephalography. Neuroimage 2007;37:282–9.
[12] Cornwell BR, Carver FW, Coppola R, Johnson L, Alvarez R, Grillon C. Evoked amygdala responses to negative faces revealed by adaptive MEG beamformers. Brain Res 2008;1244:103–12.
[13] Cornwell BR, Johnson LL, Holroyd T, Carver FW, Grillon C. Human hippocampal and parahippocampal theta during goal-directed spatial navigation predicts performance on a virtual Morris water maze. J Neurosci 2008;28:5983–90.
[14] Cover KS, Vrenken H, Geurts JJ, van Oosten BW, Jelles B, Polman CH, Stam CJ, van Dijk BW. Multiple sclerosis patients show a highly significant decrease in alpha band interhemispheric synchronization measured using MEG. Neuroimage 2006;29:783–8.
[15] Davis KD, Moayedi M. Central mechanisms of pain revealed through functional and structural MRI. J Neuroimmune Pharmacol 2013;8:518–34.
[16] de Vries M, Wilder-Smith OH, Jongsma ML, van den Broeke EN, Arns M, van Goor H, van Rijn CM. Altered resting state EEG in chronic pancreatitis patients: toward a marker for chronic pain. J Pain Res 2013;6:815–24.
[17] Deppe M, Muller D, Kugel H, Ruck T, Wiendl H, Meuth SG. DTI detects water diffusion abnormalities in the thalamus that correlate with an extremity pain episode in a patient with multiple sclerosis. Neuroimage Clin 2013;2:258–62.
[18] Di Pietro F, Macey PM, Rae CD, Alshelh Z, Macefield VG, Vickers ER, Henderson LA. The relationship between thalamic GABA content and resting cortical rhythm in neuropathic pain. Hum Brain Mapp 2018;39:1945–1956.
[19] Doesburg SM, Roggeveen AB, Kitajo K, Ward LM. Large-scale gamma-band phase synchronization and selective attention. Cereb Cortex 2008;18:386–96.
[20] Dumas T, Dubal S, Attal Y, Chupin M, Jouvent R, Morel S, George N. MEG evidence for dynamic amygdala modulations by gaze and facial emotions. PLoS One 2013;8:e74145.
[21] Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J; IMMPACT. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. PAIN 2005;113:9–19.
[22] Dymond S, Lawrence NS, Dunkley BT, Yuen KS, Hinton EC, Dixon MR, Cox WM, Hoon AE, Munnelly A, Muthukumaraswamy SD, Singh KD. Almost winning: induced MEG theta power in insula and orbitofrontal cortex increases during gambling near-misses and is associated with BOLD signal and gambling severity. Neuroimage 2014;91:210–19.
[23] Engels MM, Hillebrand A, van der Flier WM, Stam CJ, Scheltens P, van Straaten EC. Slowing of hippocampal activity correlates with cognitive decline in early onset Alzheimer's disease. An MEG study with virtual electrodes. Front Hum Neurosci 2016;10:238.
[24] Fasoula A, Attal Y, Schwartz D. Comparative performance evaluation of data-driven causality measures applied to brain networks. J Neurosci Methods 2013;215:170–89.
[25] Freynhagen R, Baron R, Gockel U, Tolle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006;22:1911–20.
[26] Furman AJ, Meeker TJ, Rietschel JC, Yoo S, Muthulingam J, Prokhorenko M, Keaser ML, Goodman RN, Mazaheri A, Seminowicz DA. Cerebral peak alpha frequency predicts individual differences in pain sensitivity. Neuroimage 2017;167:203–10.
[27] Giaquinto S, Nolfe G. The EEG in the normal elderly: a contribution to the interpretation of aging and dementia. Electroencephalogr Clin Neurophysiol 1986;63:540–6.
[28] Gilbertson T, Lalo E, Doyle L, Di Lazzaro V, Cioni B, Brown P. Existing motor state is favored at the expense of new movement during 13–35 Hz oscillatory synchrony in the human corticospinal system. J Neurosci 2005;25:7771–9.
[29] Gilron I, Baron R, Jensen T. Neuropathic pain: principles of diagnosis and treatment. Mayo Clin Proc 2015;90:532–45.
[30] Goldenberg MM. Multiple sclerosis review. Pharm Ther 2012;37:175–84.
[31] Hamada Y, Sugino K, Kado H, Suzuki R. Magnetic fields in the human hippocampal area evoked by a somatosensory oddball task. Hippocampus 2004;14:426–33.
[32] Hanslmayr S, Gross J, Klimesch W, Shapiro KL. The role of alpha oscillations in temporal attention. Brain Res Rev 2011;67:331–43.
[33] Hashemi A, Pino LJ, Moffat G, Mathewson KJ, Aimone C, Bennett PJ, Schmidt LA, Sekuler AB. Characterizing population EEG dynamics throughout adulthood. eNeuro 2016;3:e0275–16.
[34] Hemington KS, Wu Q, Kucyi A, Inman RD, Davis KD. Abnormal cross-network functional connectivity in chronic pain and its association with clinical symptoms. Brain Struct Funct 2016;221:4203–19.
[35] Hillebrand A, Barnes GR, Bosboom JL, Berendse HW, Stam CJ. Frequency-dependent functional connectivity within resting-state networks: an atlas-based MEG beamformer solution. Neuroimage 2012;59:3909–21.
[36] Hu L, Peng W, Valentini E, Zhang Z, Hu Y. Functional features of nociceptive-induced suppression of alpha band electroencephalographic oscillations. J Pain 2013;14:89–99.
[37] Huishi Zhang C, Sohrabpour A, Lu Y, He B. Spectral and spatial changes of brain rhythmic activity in response to the sustained thermal pain stimulation. Hum Brain Mapp 2016;37:2976–91.
[38] Hung Y, Smith ML, Bayle DJ, Mills T, Cheyne D, Taylor MJ. Unattended emotional faces elicit early lateralized amygdala-frontal and fusiform activations. Neuroimage 2010;50:727–33.
[39] Iversen JR, Repp BH, Patel AD. Top-down control of rhythm perception modulates early auditory responses. Ann N Y Acad Sci 2009;1169:58–73.
[40] Kirsch P, Achenbach C, Kirsch M, Heinzmann M, Schienle A, Vaitl D. Cerebellar and hippocampal activation during eyeblink conditioning depends on the experimental paradigm: a MEG study. Neural Plast 2003;10:291–301.
[41] Kister I, Caminero AB, Monteith TS, Soliman A, Bacon TE, Bacon JH, Kalina JT, Inglese M, Herbert J, Lipton RB. Migraine is comorbid with multiple sclerosis and associated with a more symptomatic MS course. J Headache Pain 2010;11:417–25.
[42] Kuchinad A, Schweinhardt P, Seminowicz DA, Wood PB, Chizh BA, Bushnell MC. Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain? J Neurosci 2007;27:4004–7.
[43] Kucyi A, Davis KD. The dynamic pain connectome. Trends Neurosci 2015;38:86–95.
[44] Kucyi A, Davis KD. The neural code for pain: from single-cell electrophysiology to the dynamic pain connectome. Neuroscientist 2017;23:397–414.
[45] Kucyi A, Salomons TV, Davis KD. Mind wandering away from pain dynamically engages antinociceptive and default mode brain networks. Proc Natl Acad Sci U S A 2013;110:18692–7.
[46] Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444–52.
[47] Leblanc BW, Lii TR, Silverman AE, Alleyne RT, Saab CY. Cortical theta is increased while thalamocortical coherence is decreased in rat models of acute and chronic pain. PAIN 2014;155:773–82.
[48] Lim M, Kim JS, Kim DJ, Chung CK. Increased low- and high-frequency oscillatory activity in the prefrontal cortex of fibromyalgia patients. Front Hum Neurosci 2016;10:111.
[49] Llinas RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP. Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc Natl Acad Sci U S A 1999;96:15222–7.
[50] Mills T, Lalancette M, Moses SN, Taylor MJ, Quraan MA. Techniques for detection and localization of weak hippocampal and medial frontal sources using beamformers in MEG. Brain Topogr 2012;25:248–63.
[51] Misic B, Dunkley BT, Sedge PA, Da Costa L, Fatima Z, Berman MG, Doesburg SM, McIntosh AR, Grodecki R, Jetly R, Pang EW, Taylor MJ. Post-traumatic stress constrains the dynamic repertoire of neural activity. J Neurosci 2016;36:419–31.
[52] Moayedi M, Weissman-Fogel I, Salomons TV, Crawley AP, Goldberg MB, Freeman BV, Tenenbaum HC, Davis KD. Abnormal gray matter aging in chronic pain patients. Brain Res 2012;1456:82–93.

[53] Napadow V, LaCount L, Park K, As-Sanie S, Clauw DJ, Harris RE. Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. Arthritis Rheum 2010;62:2545–55.
[54] Nir RR, Sinai A, Moont R, Harari E, Yarnitsky D. Tonic pain and continuous EEG: prediction of subjective pain perception by alpha-1 power during stimulation and at rest. Clin Neurophysiol 2012;123:605–12.
[55] O'Connell RG, Dockree PM, Robertson IH, Bellgrove MA, Foxe JJ, Kelly SP. Uncovering the neural signature of lapsing attention: electrophysiological signals predict errors up to 20 s before they occur. J Neurosci 2009;29:8604–11.
[56] O'Connor AB, Schwid SR, Herrmann DN, Markman JD, Dworkin RH. Pain associated with multiple sclerosis: systematic review and proposed classification. PAIN 2008;137:96–111.
[57] Okazaki M, Kaneko Y, Yumoto M, Arima K. Perceptual change in response to a bistable picture increases neuromagnetic beta-band activities. Neurosci Res 2008;61:319–28.
[58] Osborne TL, Raichle KA, Jensen MP, Ehde DM, Kraft G. The reliability and validity of pain interference measures in persons with multiple sclerosis. J Pain Symptom Manage 2006;32:217–29.
[59] Ploner M, Gross J, Timmermann L, Pollok B, Schnitzler A. Pain suppresses spontaneous brain rhythms. Cereb Cortex 2006;16:537–40.
[60] Pogosyan A, Gaynor LD, Eusebio A, Brown P. Boosting cortical activity at beta-band frequencies slows movement in humans. Curr Biol 2009;19: 1637–41.
[61] Porreca F, Ossipov MH, Gebhart GF. Chronic pain and medullary descending facilitation. Trends Neurosci 2002;25:319–25.
[62] Pu Y, Cheyne DO, Cornwell BR, Johnson BW. Non-invasive investigation of human hippocampal rhythms using magnetoencephalography: a review. Front Neurosci 2018;12:273.
[63] Quraan MA, Moses SN, Hung Y, Mills T, Taylor MJ. Detection and localization of hippocampal activity using beamformers with MEG: a detailed investigation using simulations and empirical data. Hum Brain Mapp 2011;32:812–27.
[64] Rogachov A, Cheng JC, Erpelding N, Hemington KS, Crawley AP, Davis KD. Regional brain signal variability: a novel indicator of pain sensitivity and coping. PAIN 2016;157:2483–92.
[65] Romei V, Gross J, Thut G. On the role of prestimulus alpha rhythms over occipito-parietal areas in visual input regulation: correlation or causation? J Neurosci 2010;30:8692–7.
[66] Roux F, Wibral M, Singer W, Aru J, Uhlhaas PJ. The phase of thalamic alpha activity modulates cortical gamma-band activity: evidence from resting-state MEG recordings. J Neurosci 2013;33:17827–35.
[67] Sarnthein J, Stern J, Aufenberg C, Rousson V, Jeanmonod D. Increased EEG power and slowed dominant frequency in patients with neurogenic pain. Brain J Neurol 2006;129:55–64.
[68] Schoonheim MM, Geurts JJ, Landi D, Douw L, van der Meer ML, Vrenken H, Polman CH, Barkhof F, Stam CJ. Functional connectivity changes in multiple sclerosis patients: a graph analytical study of MEG resting state data. Hum Brain Mapp 2013;34:52–61.
[69] Schulz E, May ES, Postorino M, Tiemann L, Nickel MM, Witkovsky V, Schmidt P, Gross J, Ploner M. Prefrontal gamma oscillations encode tonic pain in humans. Cereb Cortex 2015;25:4407–14.
[70] Seixas D, Foley P, Palace J, Lima D, Ramos I, Tracey I. Pain in multiple sclerosis: a systematic review of neuroimaging studies. Neuroimage Clin 2014;5:322–31.
[71] Sekihara K, Nagarajan SS, Poeppel D, Marantz A, Miyashita Y. Reconstructing spatio-temporal activities of neural sources using an MEG vector beamformer technique. IEEE Trans Biomed Eng 2001;48: 760–71.
[72] Staud R. Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions. Expert Rev Neurother 2012;12:577–85.
[73] Stephen JM, Ranken DM, Aine CJ, Weisend MP, Shih JJ. Differentiability of simulated MEG hippocampal, medial temporal and neocortical temporal epileptic spike activity. J Clin Neurophysiol 2005; 22:388–401.
[74] Stern J, Jeanmonod D, Sarnthein J. Persistent EEG overactivation in the cortical pain matrix of neurogenic pain patients. Neuroimage 2006;31: 721–31.
[75] Svendsen KB, Sorensen L, Jensen TS, Hansen HJ, Bach FW. MRI of the central nervous system in MS patients with and without pain. Eur J Pain 2011;15:395–401.
[76] Tagliazucchi E, Balenzuela P, Fraiman D, Chialvo DR. Brain resting state is disrupted in chronic back pain patients. Neurosci Lett 2010;485:26–31.
[77] Tewarie P, Balk LJ, Hillebrand A, Steenwijk MD, Uitdehaag BMJ, Stam CJ, Petzold A. Structure-function relationships in the visual system in multiple sclerosis: an MEG and OCT study. Ann Clin Transl Neurol 2017; 4:614–21.
[78] Tewarie P, Schoonheim MM, Stam CJ, van der Meer ML, van Dijk BW, Barkhof F, Polman CH, Hillebrand A. Cognitive and clinical dysfunction, altered MEG resting-state networks and thalamic atrophy in multiple sclerosis. PLoS One 2013;8:e69318.
[79] Tortorella P, Rocca MA, Colombo B, Annovazzi P, Comi G, Filippi M. Assessment of MRI abnormalities of the brainstem from patients with migraine and multiple sclerosis. J Neurol Sci 2006;244:137–41.
[80] Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, Cleeland C, Dionne R, Farrar JT, Galer BS, Hewitt DJ, Jadad AR, Katz NP, Kramer LD, Manning DC, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robinson JP, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Witter J. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. PAIN 2003;106:337–45.
[81] Van Veen BD, van Drongelen W, Yuchtman M, Suzuki A. Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. IEEE Trans Biomed Eng 1997;44:867–80.
[82] van Wijk BC, Daffertshofer A, Roach N, Praamstra P. A role of beta oscillatory synchrony in biasing response competition? Cereb Cortex 2009;19:1294–302.
[83] Walton KD, Dubois M, Llinas RR. Abnormal thalamocortical activity in patients with complex regional pain syndrome (CRPS) type I. PAIN 2010; 150:41–51.
[84] Woodruff DS, Kramer DA. EEG alpha slowing, refractory period, and reaction time in aging. Exp Aging Res 1979;5:279–92.
[85] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.