Short Communication

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Examining resting-state functional connectivity in key hubs of the default mode network in chronic low back pain

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Abstract

Objectives: Changes in brain connectivity have been observed within the default mode network (DMN) in chronic low back pain (CLBP), however the extent of these disruptions and how they may be related to CLBP requires further examination. While studies using seed-based analysis have found disrupted functional connectivity in the medial prefrontal cortex (mPFC), a major hub of the DMN, limited studies have investigated other equally important hubs, such as the posterior cingulate cortex (PCC) in CLBP.

Methods: This preliminary study comprised 12 individuals with CLBP and 12 healthy controls who completed a resting-state functional magnetic resonance imaging (fMRI) scan. The mPFC and PCC were used as seeds to assess functional connectivity.

Results: Both groups displayed similar patterns of DMN connectivity, however group comparisons showed that CLBP group had reduced connectivity between the PCC and angular gyrus compared to healthy controls. An exploratory analysis examined whether the alterations observed in mPFC and PCC connectivity were related to pain catastrophizing in CLBP, but no significant associations were observed.

Conclusions: These results may suggest alterations in the PCC are apparent in CLBP, however, the impact and functional role of these disruptions require further investigation.

Keywords: chronic low back pain; default mode network; fMRI; pain catastrophizing; resting-state.

Introduction

Chronic low back pain (CLBP) is a debilitating health condition [1] that is often associated with emotional and cognitive deficits [2, 3]. Recent neuroimaging studies have demonstrated structural and functional reorganisation of the brain that is associated with CLBP outcomes [4–6]. Identifying neural mechanisms may therefore further our understanding of how brain changes may be associated with CLBP.

In particular, the current literature suggests that brain activity during resting-state is often disrupted in the default mode network (DMN) in CLBP populations [4, 5]. The DMN consists of brain regions including the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), precuneus, middle temporal gyrus, middle frontal gyrus, and inferior parietal lobule [7–9], that are active at rest (i.e., when not engaged in an external task). It is therefore often associated with internal or self-referential processes such as mentalizing, autobiographic or episodic memory

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recall, and mind wandering, demonstrating it is involved in introspective processes [7, 9–11]. Previous studies have demonstrated that CLBP groups have increased high frequency oscillations in regions of the DMN including the mPFC, PCC, and precuneus compared to healthy controls [12, 13]. The reduced functional connectivity between the mPFC and other DMN areas such as the precuneus have also been observed in CLBP [13]. Stronger functional connectivity between mPFC and the nucleus accumbens (NAc) has also been found to be associated with persistent low back pain compared to those who had recovered from low back pain [14, 15].

Previous neuroimaging studies using a seed-based approach have reported altered functional connectivity within the DMN during resting-state in CLBP. These studies have identified reduced connectivity between the mPFC, a key region involved in the communication and integration (i.e., hub) of the DMN, with other DMN regions such as the precuneus, as well as increased connectivity to areas outside of the DMN, such as the insula and anterior cingulate cortex [12, 13]. Thus, they found disruptions both within the DMN as well as its projections to areas outside of the network in CLBP. However, these seed-based studies have predominantly focused on the mPFC in CLBP. Limited studies have explored how functional connectivity may be altered in other major hubs of the DMN in CLBP, such as the PCC.

Furthermore, the functional significance of DMN disruptions is not fully understood in CLBP. There is evidence to suggest it may be related to pain catastrophizing (i.e., exaggerated negative emotional and cognitive response to pain-related events [16, 17]) in other chronic pain conditions. For example, neuroimaging studies using the seed-based approach demonstrated that altered connectivity from the PCC to the dorsolateral prefrontal cortex (DLPFC) were related to pain catastrophizing in chronic migraine patients [18], while increased mPFC connectivity to other regions of the DMN in chronic temporomandibular disorder patients correlated with rumination (a subdomain of pain catastrophizing) [19]. In CLBP, only one study has investigated the relationship between the DMN with pain catastrophizing. This study investigated connectivity from the mPFC and PCC with specific subregions of the amygdala. While reduced connectivity was observed between these areas, it was not related to pain catastrophizing [20]. Thus, the relationship between changes in DMN connectivity and pain catastrophizing in CLBP remains unclear.

In this study, we examined functional connectivity of two key hubs of the DMN, namely the mPFC and PCC, in CLBP compared to healthy controls, using a seed-to-voxel approach. We also conducted an exploratory analysis to examine whether altered functional connectivity with the mPFC and PCC may be related to pain catastrophizing. Therefore, based on the findings of previous studies, we hypothesized that the CLBP group would exhibit altered functional connectivity with both mPFC and PCC seeds. Specifically, the CLBP group would exhibit stronger functional connectivity between the mPFC and the NAc compared to healthy controls. We also explored whether the DMN alterations observed in the CLBP would correlate with higher levels of pain catastrophizing.

Methods

This study recruited 12 individuals with CLBP and 12 healthy controls. All participants were right-handed (measured by the Edinburgh Handedness Inventory) [21] and female to control for any potential gender differences in the DMN [22, 23]. Participants were screened using the Mini international Neuropsychiatry Interview (MINI) [24] and were excluded if they had current or a history of any psychiatric conditions (with the exception of depression and anxiety following the onset of CLBP). Participants with CLBP were included if they reported having >3 months of moderate to severe non-specific LBP (>21% on the Oswestry Disability Index [25]). Participants in the healthy control group were pain-free and did not have a significant history of any chronic pain conditions.

Eligible participants provided informed consent before commencing the study. Participants completed a structural and functional MRI scan which were acquired on a Magnetom Skyra 3 Tesla MRI scanner with a 32 channel receive-only phased-array head coil (Siemens, Erlangen, Germany). First, high resolution magnetization prepared rapid acquisition gradient echo (MP2RAGE) T1-weighted structural data were acquired using the following parameters: 208 sagittal slices, repetition time (TR)=1,540 ms, echo time (TE)=2.55 ms, flip angle=9°, acquisition matrix=256×256, FoV=256 mm, 1 mm isotropic voxels. This was followed by the acquisition of whole-brain echo-planar images (EPIs) for resting-state data (approximately 6 min, TR=2570 ms, TE=30 ms, flip angle=90°, acquisition matrix=64 × 64, FoV=192 mm, slice thickness=3.0 mm). During this scan, participants were specifically instructed to keep their eyes open and allow their mind to wander. Participants also completed a series of self-report questionnaires, including the Pain Catastrophizing Scale (PCS) and the Beck Depression Inventory II (BDI-II). Both measures that have shown good validity and reliability in chronic pain and healthy populations.

All data were preprocessed and analyzed through the Conn toolbox in MATLAB 2017a (MathWorks, Sherborn, MA, USA). Resting-state data preprocessing steps included removal of the first 4 volumes, slice time correction, motion correction, co-registration of structural to functional image, segmentation of the structural image into white matter (WM), gray matter (GM) and cerebral spinal fluid (CSF), and normalization of the structural and functional images into MNI space. Functional images were smoothed at 5 mm FWHM Gaussian kernel. The preprocessed data were band-pass filtered at 0.008–0.09 Hz and denoised according to the CompCor method [26] to remove physiological noise. Additionally, head motion threshold was set at 3 mm translation and 3 degrees of rotation. None of the participants

exceeded this threshold, hence, were not excluded from analysis due to excessive head motion.

Seed-to-voxel analysis was conducted to assess resting-state functional connectivity of the DMN. This involves extracting the times series of a region of interest (ROI) as seeds and the correlation with the time course with the other voxels of the brain is calculated to determine functional connectivity with other regions. As the PCC (−8, −56, 39) and mPFC (*x*, *y*, *z*=4, 42, 3) are core hubs of the DMN, they were used as seeds in this study. The co-ordinates of the seed regions were obtained from meta-analysis [27]. A 10 mm sphere was created for each seed using the Marsbar toolbox [28].

First-level analysis involved extracting the time series from the seed regions and correlated with the rest of the voxels in the brain during resting-state for each individual and transformed into Fisher-transformed correlation coefficients. At the second-level analysis, one-sample *t*-tests were conducted to examine the CLBP and healthy controls separately and then independent *t*-tests were conducted to compare group differences for each seed. The six head motion parameters obtained in the realignment step during preprocessing were entered as covariates of no interest. Significance was set at $p < 0.05$ FWE-corrected at the cluster level. All brain regions were labeled using Automated Anatomical Labeling (AAL) atlases defined within MRIcro [29]. The connectivity values of the significant clusters observed in between group comparisons differences were extracted and the values were entered into a Spearman rho with the overall PCS and its subscale (rumination, magnification, helplessness) scores.

Results

The results showed that there were no significant group differences in age. As expected, the CLBP group had significantly lower overall PCS, magnification, and helplessness subscale scores, while no significant differences were observed in the rumination subscale. The CLBP group also reported significantly higher BDI-II scores compared to the healthy controls (Table 1).

With the PCC as the seed, the CLBP, and healthy control group showed similar patterns of functional connectivity with areas including superior frontal gyrus, middle temporal gyrus, angular gyri, parahippocampal gyrus, and regions of the cerebellum (see Figure 1 and Table 2). Similarly, both CLBP and healthy control groups showed functional connectivity between the mPFC seed with the anterior cingulate gyrus, angular gyri, middle temporal gyrus and regions of the cerebellum (Figure 2 and Table 3). Group comparisons showed the CLBP group had decreased functional connectivity between the PCC and angular gyrus compared to healthy controls (Figure 3). The CLBP group did not show significant clusters of increased functional connectivity to other regions of the brain compared to healthy controls. Further ROI-to-ROI analysis between the mPFC seed and NAc was also conducted to test our hypothesis. No significant results were observed in the left (t=0.61, p=0.94) or right NAc (t=−0.44, p=0.95) between the CLBP and healthy controls. The analysis using Spearman rho showed there were no significant correlations observed between the significant cluster of the group differences and the overall PCS scores (r=0.16, p=0.62), or the rumination (r=0.04, p=91), magnification (0.35, p=0.27), or the helplessness (r=0.10, p=0.75) subscale scores in the CLBP group.

Table 1: Demographic and behavioural measures in chronic low back pain and healthy control groups (M (SD)).

	Chronic low back pain	Healthy controls	p-Value	Cohen's *d*
Age, years	36.5 (10.6)	30.3 (5.22)	0.085	0.74
PCS	20.3 (8.99)	10.2 (10.9)	0.021	1.01
PCS rumination	7.08 (3.70)	4.75 (4.88)	0.20	0.54
PCS magnification	4.42 (2.81)	1.58 (1.88)	0.009	1.19
PCS helplessness	8.83 (3.83)	3.83 (4.78)	0.010	1.15
BDI-II	13.0 (9.05)	3.18 (2.60)	0.003	1.47

BDI-II, beck depression inventory II; PCS, pain catastrophizing scale.

As depression is highly comorbid with CLBP [30–32], and has also been shown to disrupt DMN connectivity [33–35], we ran a secondary exploratory analysis using Spearman rho to examine whether the observed differences in DMN connectivity between groups was related to scores on the BDI. We observed no significant correlations between the significant clusters in the PCC and the BDI-II scores (r=0.07, p=0.84).

Discussion

There are limitations to the current study that should be taken into account when interpreting the results. Our sample size was relatively small, and therefore, reduces the statistical power of this study. Due to the limited number of participants, groups were not matched for age and only consisted of females, which reduced the generalizability of our findings. While we used the standard functional resting-state scan time of 6 min, longer resting-state scans of up to approximately 13 min have found to significantly improved reliability [36]. Given the small sample size, the use of longer scan time could have improve reliability. Therefore, the results of this study should be interrogated in future work with current findings interpreted with caution.

In line with the existing literature that have observed disruptions within the DMN [12, 13, 37], our findings add further evidence to show altered connectivity in one of the core regions, the PCC is apparent in CLBP. Our results

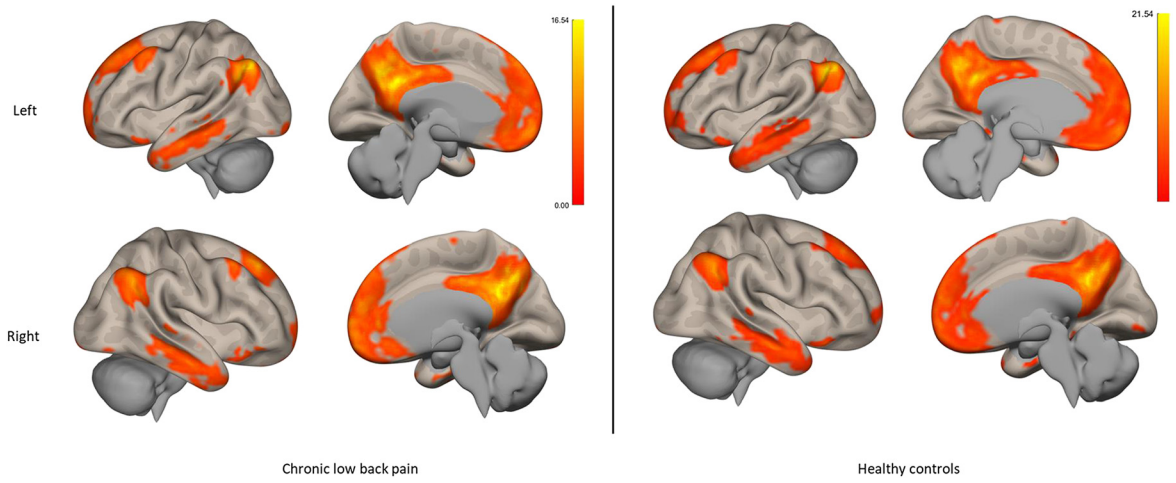

Figure 1: Significant clusters during resting-state with posterior cingulate cortex as the seed in the chronic low back pain and healthy control groups.

Table 2: Significant clusters during resting state with posterior cingulate cortex (PCC) as the seed.

Region	Cluster size	Peak, *t*	MNI Coordinates		
			x	y	z
Chronic low back pain					
R superior frontal gyrus	12,283	15.4	20	34	46
R precuneus	7,725	18.8	4	−54	26
R cerebellum (Crus II)	3,319	11.0	14	−88	−28
L angular gyrus	2,573	16.7	−42	−70	40
L middle temporal gyrus	2,064	10.2	−60	−12	−22
R middle temporal gyrus	2,049	10.1	68	−34	−4
R angular gyrus	1,991	11.7	44	−54	34
L cerebellum (lobule IX)	530	8.6	−4	−56	−48
R inferior frontal orbital gyrus	240	8.0	46	34	−16
R parahippocampal gyrus	112	7.0	26	−18	−20
Healthy controls					
L superior frontal gyrus	13,759	16.8	−4	48	42
L posterior cingulate gyrus	7,045	19.6	−6	−50	34
R cerebellum (Crus II)	4,952	12.9	30	−86	−34
L middle temporal gyrus	2,822	10.8	−62	0	−26
L angular gyrus	2,773	20.3	−48	−66	36
R middle temporal gyrus	2,647	10.2	66	−12	−22
R angular gyrus	2,064	13.7	44	−54	34
L parahippocampal gyrus	578	8.6	−20	−36	−10
R cerebellum (lobule IX)	523	7.8	4	−52	−50
L thalamus	453	7.6	0	−14	10

showed reduced connectivity between the PCC and the angular gyrus, which is also another core region of the DMN. Within the DMN, the angular gyrus is considered to be a cross-modal hub and is implicated in both the integration of information within the network, as well as processes related to attention, memory, and cognition [38]. Our findings may then reflect that information processed within the DMN may be compromised. Interestingly, our results did not yield any significant results from the mPFC seed, which does not support our proposed hypothesis. This is not in line with previous studies that observed stronger mPFC-NAc connectivity in subacute low back pain patients who developed persistent pain one year following initial onset compared to those who recovered [14, 15]. Discrepancies between study findings could be due to a number of factors. One of which could be that the current study used healthy pain-free controls with no history of pain conditions while the previous studies used patients who had recovered from subacute low back pain. While our results observed altered PCC connectivity and no differences in the mPFC in the CLBP group, considering the low number of participants in the study, future studies are required to investigate this further.

However, the functional significance of these disruptions remains unclear as the exploratory analyses correlating significant clusters and pain catastrophizing (PCS scores) did not yield significant results. This is consistent with previous studies that reported similar findings in CLBP [20] and other chronic pain conditions [39, 40]. However, this is in contrast to other studies finding significant correlations between altered DMN connectivity and pain catastrophizing in patients with chronic migraine and temporomandibular disorder [18, 19]. These inconsistencies may be due to the differences between chronic pain conditions as CLBP is a heterogeneous pain condition [41]. It is also possible that pain catastrophizing in CLBP are being underpinned by other neural networks. Indeed, one study found increased amygdala-central executive network (CEN) connectivity was related to pain catastrophizing in CLBP [20]. As the CEN has been associated with cognitive

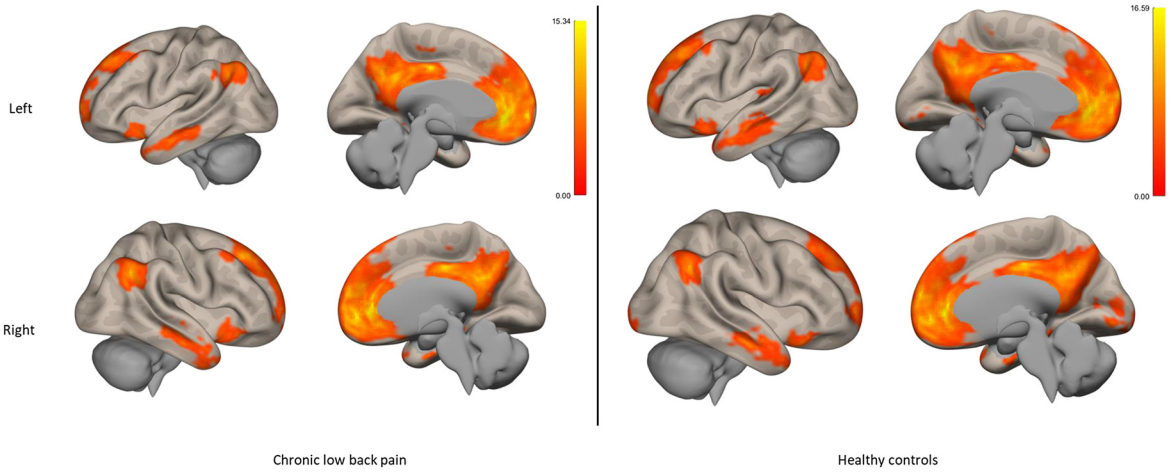

Figure 2: Significant clusters during resting-state with medial prefrontal cortex as the seed in the chronic low back pain and healthy control groups.

Table 3: Significant clusters during resting state with medial prefrontal cortex (mPFC) as the seed.

Region	Cluster size	Peak, *t*	MNI Coordinates		
			x	*y*	*z*
Chronic low back pain					
R anterior cingulate gyrus	23,779	19.6	4	38	8
L angular gyrus	1616	8.9	−50	−60	30
R angular gyrus	1475	9.2	56	−58	32
L middle temporal gyrus	812	8.2	−60	−10	−22
L cerebellum (Crus II)	673	6.9	−38	−82	−34
R cerebellum (Crus II)	436	7.2	48	−66	−40
L cerebellum (lobule IX)	384	8.6	−6	−56	−44
Healthy controls					
R anterior cingulate gyrus	24,338	19.0	4	38	8
L angular gyrus	1,451	9.3	−52	−62	32
L middle temporal gyrus	1,112	8.8	−54	−14	−18
R angular gyrus	1,080	8.0	48	−56	34
R inferior occipital gyrus	1,008	8.1	46	−72	−40
L Lingual gyrus	691	6.0	−20	−96	−18
L parahippocampal gyrus	626	9.6	−22	−16	−28
R Lingual gyrus	517	6.4	6	−86	−6
L cerebellum (lobule IX)	267	7.6	−6	−56	−44
Brainstem	210	10.2	0	−18	−24
R Calcarine gyrus	157	5.0	8	−86	8
L superior temporal gyrus	115	6.7	−38	−32	12
L cerebellum (Crus II)	101	7.2	−48	−62	−42

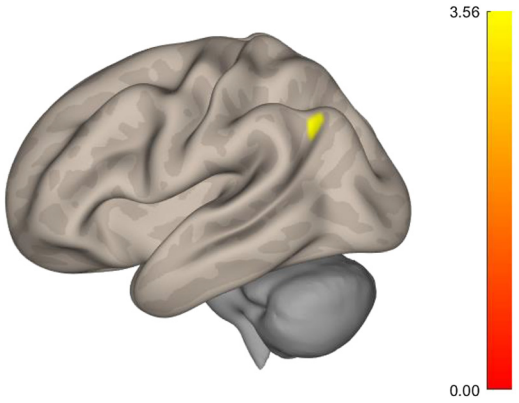

Figure 3: Significant cluster in the angular gyrus from group comparisons (HC>CLBP) in the PCC seed (t=6.83, cluster size (k) =102, MNI (x, y, z)=−52, −66, 36).

processes involved in attention and working memory [42, 43], increased activity is thought to reflect the negative cognitive bias from pain catastrophizing [20].

We also explored whether disrupted DMN connectivity was linked to depression scores, as shown in previous studies in patients with major depression [33–35]. Our results did not yield any significant associations with BDI-II scores, which was in line with previous CLBP studies [13, 20]. As the mean BDI-II score of the CLBP group in this study was not clinically significant (M=13, i.e., within minimal range), our findings may suggest that low levels of depressive symptoms do not affect the DMN in CLBP. Together, the absence of a relationship between BDI-II scores may suggest that the observed group differences are associated with CLBP specifically, rather than due to secondary emotional factors such as depression. However, it should be noted that we did not have the data to explore other processes that may influence the DMN, such as anxiety. Not only are high levels of anxiety often reported in CLBP populations [31, 32], it has also been associated with disrupted DMN activity [44, 45], and therefore, should be considered in future studies.

It is worth noting that there was high inter-individual variability in the clinical features of CLBP within our sample, which was likely to impact the underlying neural

networks. For instance, one study identified that a subgroup of CLBP patients reported showed low levels of emotional and cognitive deficits including low pain catastrophizing while another subgroup had prominent cognitive and emotional impairments [46]. This highlights heterogeneity in CLBP presentation, which is anticipated to have differential impact on neural mechanisms. Our behavioral data support this variability, with PCS scores ranging from 8 to 33 as well as BDI-II scores between 2 and 26 in the CLBP group. This suggests that those with CLBP may have different psychological profiles and, thus, there may be larger variability in brain connectivity within the population. However, we were unable to explore this further due to sample size.

A number of factors should be considered in future studies to improve on this research. Future studies should recruit a larger sample to not only increase generalizability of results but may also be used to explore whether there are different subgroups in CLBP population. Furthermore, the protocols used for fMRI data acquisition can also be improved, for example, with longer resting-state scan times to increase reliability. Secondary measures such as electro-oculography (EOG) to record eye movements to ensure the participants' eyes remained open during the scan were not used in this study. As a recent study have found that the state of the eyes (i.e., open vs. closed) may influence the activation of different networks [47], this may be an important consideration to factor in future studies. Additionally, as this was a cross-sectional study, the causality for the DMN disruptions observed in the CLBP group cannot be determined. Longitudinal studies following the progression from acute low back pain to the recovery and persistence of pain are essential to identifying factors that may predict low back pain outcomes. Furthermore, we only investigated how pain catastrophizing may be related to the DMN and did not account for other potential spontaneous thought processes that may occur during resting-state such as mind wandering, daydreaming or creative thinking [48]. Other processes associated with the angular gyrus such as attention, memory, and cognition could also be explored. While little is known about how these processes are affected in the context of pain, one study demonstrated that increased DMN activity during nociceptive pain may represent diversion of attention away from pain stimuli and reflect internal processes such as mind wandering [49]. However, as this study was conducted in healthy controls, future studies should explore this further in chronic pain conditions. Despite the limitations of the study, our pain group all reported the same chronic pain condition and consisted of females, eliminating any potential sex differences.

Overall, this study provides supporting evidence that demonstrate disrupted connectivity in the DMN, specifically in the PCC, in individuals with CLBP compared to healthy controls. However, our data does not support a relationship of altered DMN connectivity being related to pain catastrophizing in the CLBP. While there is a growing body of evidence demonstrating this network to consistently been implicated in CLBP, the functional significance of DMN changes in chronic pain requires further investigation.

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Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: PBF has received equipment for research from Medtronic, MagVenture A/S and Brainsway Ltd. He is on scientific advisory boards for Bionomics Ltd and LivaNova and is a founder of TMS Clinics Australia. There are no other potential conflicts of interest.

Informed consent: Informed consent has been obtained from all participants included in this study.

Ethical approval: This study was approved by the Monash University (CF12/2213–2012001190) and Alfred Health Human Research Ethics Committees (243/12).

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