ORIGINAL RESEARCH

Disrupted interhemispheric functional coordination in patients with chronic low back-related leg pain: a multiscale frequency-related homotopic connectivity study

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Objective: Chronic low back pain has been observed to decrease movement coordination. However, it is unclear whether the existing alteration of inter-hemispheric synchrony of intrinsic activity in patients with chronic low back-related leg pain (cLBLP). The present study aims to investigate the alteration of homotopic connectivity and its clinical association with the cLBLP patients.

Participants and methods: A cohort of cLBLP patients (n=25) and well-matched healthy controls (HCs) (n=27) were recruited and underwent MRI scanning and a battery of clinical tests. The voxel-mirrored homotopic connectivity (VMHC) was used to analyze the inter-hemispheric coordination in the typical (0.01–0.1 Hz) as well as five specific (slow-6 to slow-2) frequency bands and associated with clinical index in cLBLP patients.

Results: We observed that cLBLP patients with lower homotopic connectivity than HCs in the inferior temporal gyrus, the superior temporal gyrus, the basal ganglia, the middle frontal gyrus, and the medial prefrontal cortex in the typical and five specific frequency bands, respectively. In the typical and five specific frequency bands, significant positive correlations were observed between the VMHC values of medial prefrontal cortex and the visual analogue scale scores, while the VMHC values of basal ganglia negative correlated with the values of two-point tactile discrimination (2PD) test for the right hand in cLBLP patients, etc. Further receiver operating characteristic curve analysis revealed that VMHC in the above regions with decreased could be used to differentiate the cerebral functional plasticity of cLBLP from healthy individuals with high sensitivity and specificity.

Conclusion: Our results imply that multiscale frequency-related interhemispheric disconnectivity may underlie the central pathogenesis of functional coordination in patients with cLBLP.

Keywords: interhemispheric integration, voxel-mirrored homotopic connectivity, chronic low back-related leg pain, chronic pain, resting-state fMRI

Introduction

Low back pain is an extremely common acute episode and/or chronic disorder, it affects millions of individuals each year on a world scale.[1] In fact, approximately two-thirds of patients with low back pain also report leg pain (involving the nerve root), so-called, low back-related leg pain (LBLP). Previous studies observed a relationship between the increased disability and pain, poorer quality of life, poor

outcomes, as well as lower functional status in patients with chronic LBLP (cLBLP), when compared to the patient with simplicity low back pain.[2–4] In fact, including in chronic low back pain and cLBLP patients, sensation and/or movement coordination impairment was been observed and discussed as one of the possible mechanisms.[3,5,6] Although it is unclear, it is reasonable to believe that neural plasticity or rewiring of the brain might play a role in sensation and/or movement coordination of LBLP patients.

It is not altogether without reason to say so. Because in recently, functional MRI studies showed that widespread abnormalities of intrinsic oscillation amplitude[7] and local connectivity[8] in the pain matrix (including somatosensory and motor cortices) and information-processing regions and the default mode network in cLBLP patients. Moreover, in chronic pain or chronic low back pain, morphometry and structural studies also demonstrated that significant altered neuronal-glial interactions in the somatosensory cortex,[9] inconsistent cortical atrophy[10,11] or thinning[12] in the sensorimotor, medial and lateral frontal white matter structural damage,[13–15] which provide an anatomy foundation in understanding the functional alterations.

Right now, the challenge is how to comprehensive understand functional coordination related coding of interhemispheric activity in patients with cLBLP, despite the apparent lack of ongoing straight evidence of structural damage in the corpus callosum. Voxel-mirrored homotopic connectivity (VMHC) is a data-driven method of resting-state functional magnetic resonance imaging (rs-fMRI), by computing the connectivity between each voxel in one hemisphere and its mirrored counterpart, designed to quantify an important feature of the brain intrinsic functional architecture.[16,17] Homotopic connectivity was conducted to reflecting the importance of interhemispheric communication with the integration of brain functions, as a reliable and reproducible rs-fMRI metric.[16,18] Recently studies have observed that the status of interhemispheric connectivity is associated with pain sensitivity,[19] somatosensory neuroplasticity in chronic pain,[20] and rehabilitation treatment of post-stroke pain.[21]

On the other hand, recent studies have shown that connectivity within specific low-frequency ranges was linked with a variety of neural processes, including input selection, binding, and the cyclic modulation.[22–25] Experimental animal investigations confirmed that increased rhythmic oscillatory astrocyte activity in

neuronal firing is associated with neuropathic pain.[26,27] Thus, it is conceivable that, in individuals with cLBLP, to explore the homotopic connectivity and it's an association in pain conditions, frequency bands should be considered.

In this study, we hypothesize that the disconnection of interhemispheric in patients with cLBLP, hinting a decrease of the coordination or integration ability of left and right cerebral hemisphere. Herein, we employee VMHC in different frequency subbands (for frequency property) to examined extract the neurophysiological basis of interhemispheric connectivity in cLBLP patients at resting state, and associated with disease severity or others index. Also, we used a seed-based functional connectivity analysis to reveal the heterotopic connectivity patterns of the regions with altered VMHC in patients, because homotopic connectivity might influence its specific networks.

Materials and methods
Participants

At first, two groups of participants were recruited for this study, including 33 right-handed cLBLP patients and age-, gender- and education-matched healthy controls (HCs). All the subjects were recruited from our hospital and the local community from Oct. 2016 to Jan. 2018. The LBLP patients were including criterion as follows: (1) clinical and radiology diagnosed with clear evidence of discogenic compression on a lumbar CT and/or MRI, when available (For example, Figure 1); (2) chronic (more than 12 weeks) radiating pain the buttock(s) and lower limb(s); (3) Visual analogue scale (VAS) scores of all patients were above 4 (moderate to severe pain); (4) failed to respond to conservative treatment of medications, e.g., anti-inflammatory drugs (Motrin, Advil and Naproxen) and acetaminophen (e.g., Tylenol) without opioids, exercise and physical therapy.[28] The cLBLP and HCs were also excluded (1) if they reported a major systemic disease or history of head and spinal cord injury; (2) spinal stenosis due to calcifications on the spinal protrusion, lateral recess stenosis, spinal stenosis, pyriformis syndrome, or sciatica.

This study was approved and performed following the guidelines of the Medical Research Ethics Committee and the Institutional Review Board of the First Affiliated Hospital, Nanchang University, China, and following the Declaration of Helsinki (2000). All patients and HCs give
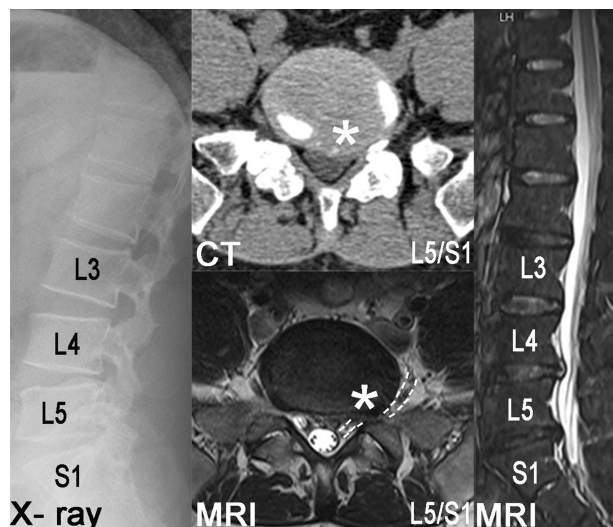
Figure 1 A case of male patients with chronic low back and leg pain (40 years), axial CT and T2W images (middle), and sagittal T2W images (right) provide clear evidence of discogenic compression (asterisk).

their written informed consent to participate in this study before beginning any of the procedures.

Clinical assessment

Before rs-fMRI scanning, each participant underwent a battery of tests that including the VAS (0–10) for pain, the Japanese Orthopaedic Association (JOA) Back Pain Evaluation questionnaire (−6 to 29) to examine the impact on neuropathic or nociceptive pain on quality of life,[29] Fugl-Meyer assessment for sensorimotor impairment measurement and the two-point tactile discrimination (2PD) test to assess tactile spatial resolution ability.[30]

Data acquisition

All the subjects were scanned using a 3.0 Tesla Trio scanner (Siemens, Munich, Germany) at the First Affiliated Hospital, Nanchang University. During the resting-state fMRI scan, the participants were asked to keep their eyes closed and lie quietly without system thinking in the scanner. The BOLD fMRI scan acquisition included 30 interleaved axial slices with a slice thickness of 4 mm, repetition time (TR) =2000 ms, echo time (TE) =30 ms, raw voxel size =3.44×3.44, matrix =64×64, each functional scan lasted for 8 min. High-resolution T1-weighted images were also acquired using a magnetization-prepared rapid gradient-echo sequence, including 176 sagittal slices with a slice thickness of 1.0 mm, no slice gap, TR =1900 ms, TE =2.26 ms, FOV =215 mm ×230 mm, matrix =240×256. Additional conventional T2-weighted

and T2-fluid-attenuated inversion recovery (FLAIR) sequences were acquired in the lumbar spine and discs from L1 to S3 for a diagnosis of LBLP, another conventional T2-weighted and T2-fluid-attenuated inversion recovery (FLAIR) sequences were acquired in the brain for rule out apparent pathological changes. At the end of the scanning sessions, regarding their waking state in BOLD fMRI, all subjects were required to report that they had not fallen asleep during the scan via the Epworth sleepiness scale questionnaire.

Data preprocessing

BOLD fMRI preprocessing was performed using the Data Processing and Analysis of Brain Imaging (DPABI) v3.0 (http://www.rfmri.org/dpabi) toolbox,[31] which is based on the Statistical Parametric Mapping software (SPM12, http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and running in the MATLAB platform (The MathWorks Inc., Natick, MA, USA). Mainly preprocessing steps included: (1) discarding of the first 10 images to allow for signal equilibration effects; (2) remaining 230 consecutive volumes were corrected for slice-timing and motion corrections (realign); (3) registration of the individual high-resolution T1 images to the mean functional data; (4) transformation and normalization of the resulting realigned functional data to the Montreal Neurological Institute (MNI) standard space with the segmented information from high-resolution T1 template by the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) toolkit; (5) resampling the functional imaging to 3-mm cubic voxels and spatial smoothing of 6-mm FWHM Gaussian kernel; (6) nuisance linear regression with the cerebrospinal fluid, white matter, and Friston-24 head motion parameters (including 6 head motion parameters and their historical effects as well as the 12 corresponding squared items);[18] and (8) detrend linear drift and temporal band-pass filtered (0.01–0.1 Hz) to reduce low-frequency drift and high-frequency noise.

Additional, we evaluated the mean absolute displacement of each brain volume to reducing the head motion effects in functional connectivity analysis. The largest mean displacement of all subjects was less than 0.2 mm according to the criteria of Van Dijk et al,[32] and there was no significant difference in mean displacement between cLBLP patients and HCs (0.044±0.025 for LBLP and 0.046±0.039 for HCs; P=0.787) using a two-sample two-tailed t-test.

Temporal filtering and voxel-mirrored homotopic connectivity calculation

To obtain the interhemispheric homotopic connectivity at the single-voxel level, (1) the normalized mean T1 structural images was used to create a group-specific symmetric T1 template (left-right mirror); (2) individual normalized T1 images were re-normalized to the symmetric T1 template by nonlinear registration; (3) above information of transformation was applied to individual preprocessed functional data, and (4) calculated each pair of symmetrical interhemispheric voxel's time series (Pearson's correlation) as interhemispheric resting-state homotopic connectivity (VMHC). Moreover, this symmetric T1 template did not include the brain midline (X =0) area.

In consideration of the frequency property, predefined settings were used to calculate the VMHC, including divided the rs-fMRI data into a typical frequency band (0.01–0.1 Hz) and five specific frequency bands: slow-6 (0–0.01 Hz), slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz) and slow-2 (0.198–0.25 Hz), according to the Buzsáki framework.[33]

When the VMHC was calculation in each predefined frequency band, then a Fisher's r-to-z transformation were implementing for subsequent group two-sample t-tests analyses to determine regional group differences of VMHC data between LBLP and HCs groups (with age and gender treated as covariates; voxel-wise $P<0.01$, Gaussian random field (GRF) theory connected cluster level, $P<0.05$). In this study, after defined the region with significant group differences in VMHC, we further evaluated the specific networks influenced by homotopic connectivity (show in Supplementary materials). Then, extract the connectivity coefficient of the regions with significant altered VMHC, we further evaluated the relationships between the altered VMHC and the clinical metrics (disease duration, VAS, JOA, Fugl-Meyer and 2PD test scores), using partial correlation analyses in SPSS for the LBLP group, with age and gender treated as covariates ($P<0.05$ with Bonferroni corrections).

Discriminant analyses of altered VMHC values

We plotted a receiver-operating characteristic (ROC) curve analysis to estimated the optimal cut-off values in the regions with decreased VMHC of cLBLP patients with

or without distinguishing ability form HCs. We adopted a leave-one-out cross-validation (LOOCV) test to validate the reproducibility of our results.

Statistical analyses of clinical characteristics

We compared the demographic and clinical metrics between the two groups using SPSS software (version 18.0; IBM, Armonk, NY, USA). An independent two-sample Student's t-test was used to compare the differences in mean head motion, disease duration, VAS, JOA, Fugl-Meyer and 2PD test scores, and the Chi-square test used to compare the differences in gender (categorical data). P-values <0.05 were considered statistically significant.

Results

Demographics and clinical characteristics

In total, 25 cLBLP patients and 27 well-matched HCs were enrolled for the homotopic and heterotopic connectivity analysis in this study, and their clinical characteristics and indices are shown in Table 1. Significantly JOA ($t=14.764$, $P<0.001$) and VAS scores ($t=29.569$, $P<0.001$) were detected in the cLBLP group than the HCs group. All the cLBLP patients presented with lumbar disk herniation and obvious low-back pain; 15 (60%) and 8 (32%) patients presented with left and right leg pain and numbness, respective; and 2 (8%) patients presented with bilateral leg symptoms. In those cLBLP patients, 2PD test scores decreased to different degrees in the

Table 1 Comparison of the demographic data and index of the cLBLP and HC groups

Characteristic	cLBLP Patients	Healthy controls	P-values
	Mean (SD)	Mean (SD)	
Gender (M/F)	10/15	15/12	0.283[#]
Age (y)	55.56(8.67)	53.37(8.18)	0.354
Duration of symptoms (months)	38.96 (50.26)	n/a (n/a)	n/a
VAS scores	5.84(1.01)	28.92(0.27)	<0.0001
JOA scores	14.16(5.13)	28.92(0.27)	<0.0001
Fugl-Meyer scores	20.12 (1.98)	n/a (n/a)	n/a
ICV (mm^3)	0.775(0.028)	0.782(0.018)	<0.351
Mean head motion*	0.044(0.025)	0.046(0.039)	0.787

Note: cLBLP, chronic low-back and leg pain; F, female; ICV, intracranial volume; JOA, Japanese Orthopaedic Association; M, male; n/a, not available; SD, standard deviation; VAS, visual analog scale; y, years. [#]Chi-square tests; *Head motions were evaluated according to the framewise displacement (FD) criteria described by Van Dijk et al (2012).[32]

right (30.12±1.37 mm) and left (30.04±1.23 mm) feet and the right (24.9±1.18 mm) and left (25.0±1.22 mm) hands. The cLBLP and HCs group exhibited no significant differences in age (*P*=0.354), or sex (*P*=0.283), mean framewise displacement (*P*=0.787) or intracranial volume (*P*=0.351).

Homotopic connectivity pattern and group comparisons within the frequency subbands

In the typical frequency band (0.01–0.1 Hz), homotopic connectivity spatial distributions shown in Figure 2A; while the cLBLP patients showed only reduce VMHC in the right and left inferior temporal gyrus (ITG), the right and left basal ganglia (BG), the right and left middle frontal gyrus (MFG), the right and left superior temporal gyrus (STG), the right and left medial prefrontal cortex (mPFC) (*P*<0.01, GRF-correction with cluster level of *P*<0.05; Figure 2B and Table 2).

In five specific frequency bands, similar spatial distributions of VMHC was detected in the cLBLP and HCs group, but relatively strongly connected with lower frequency bands (shown in Figure S1). Figure 3 and Table 3 showed the alterations of VMHC in the five specific frequency bands using voxel-based analyses in the LBLP patients and HCs (*P*<0.01, GRF-correction with cluster level of *P*<0.05).
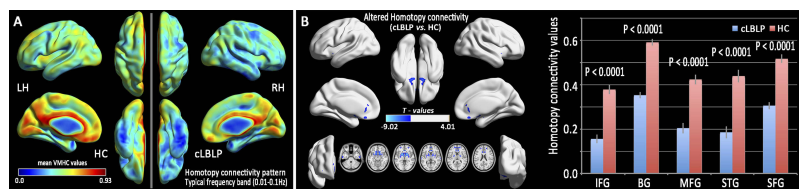

Figure 2 Group means (**A**) and group comparison (**B**) of homotopy connectivity in the cLBLP and HC groups in the typical (0.01–0.1 Hz) frequency bands.
Note: Column B shows the group comparison at voxels level (left, *P*<0.01, GRF-corrected at a cluster level of *P*<0.05) and cluster level (right), while details information can be found in Table 2.

Table 2 Group comparison of homotopic connectivity between the cLBLP patient and HC subject in the typical (0.01–0.1 Hz) frequency bands (*P*<0.01, GRF-corrected for multiple comparisons at a cluster level of *P*<0.05)

Brain region	BA	Voxels size	Peak t-value	Peak coordinates in MNI space			Effect size (Cohen's d)
				X	Y	Z	
Inferior temporal gyrus (ITG)	20	29	−5.432	±54	−15	−36	2.136
Basal ganglia (BG)		537	−9.019	±9	12	−9	3.180
Middle frontal gyrus (MFG)	10	26	−4.999	±30	54	−3	1.870
Superior temporal gyrus (STG)	22	20	−5.434	±55	−24	0	0.657
Medial prefrontal cortex (mPFC)	10	129	−6.256	±18	57	9	0.736

Note: BA: Brodmann's area. t: statistical value of peak voxels showing significant differences between the two groups (negative values: Clblp < HC; positive values: cLBLP > HC). MNI: Montreal Neurological Institute Coordinate System; X, Y, Z: coordinates of primary peak locations in the MNI space (same as all figure and table).
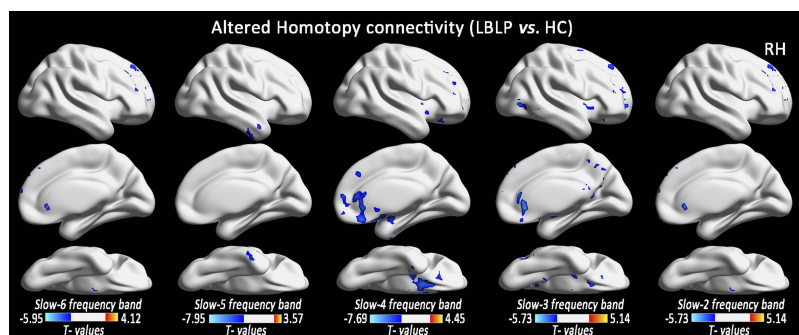

Figure 3 Alterations of VMHC between the cLBLP patients and HCs in the five specific (slow-6 to slow-2) frequency bands (two-tailed, voxel-level *P*<0.01, GRF correction, cluster-level *P*<0.05).

Table 3 Alterations of VMHC of five specific frequency bands between the cLBLP and HC group (two-tailed, voxel-level $P<0.01$, GRF correction, cluster-level $P<0.05$)

Brain regions	BA	Peak T-scores	MNI coordinates			Cluster size (voxels)	Effect size (Cohen's d)
			x	y	z		
Altered VMHC at slow-6 (0–0.01 Hz) band (cLBLP *vs* HC)							
Medial frontal gyrus/anterior cingulate cortex	25,47	−5.590	±15	21	−18	803	
Inferior frontal gyrus	38,44	−5.147	±48	36	−6	126	
Superior temporal gyrus	22,42	−3.952	±60	−33	−6	94	
Precuneus	7,31	−4.864	±3	−57	27	101	
Altered VMHC at slow-5 (0.01–0.027 Hz) band (cLBLP vs HC)							
Middle temporal gyrus	20,21	−4.426	±60	−6	−33	174	
Superior temporal gyrus/putamen	47,22	−7.954	±15	6	−6	2137	
Altered VMHC at slow-4 (0.027–0.073 Hz) band (cLBLP vs HC)							
Medial and superior frontal gyrus/basal ganglia	10,47	−7.688	±9	12	−9	1802	
Altered VMHC at slow-3 (0.073–0.167 Hz) band (cLBLP vs HC)							
Middle temporal gyrus	21,37	−4.660	±42	−75	0	168	
Putamen		−5.714	±12	15	−6	875	
Superior frontal gyrus	9,10	−4.970	±18	51	10	437	
Precuneus	7	−5.525	±3	−48	51	269	
Precentral and postcentral cortex	6,3	−3.991	±33	−12	51	261	
Altered VMHC at slow-2 (0.167–0.25 Hz) band (cLBLP vs HC)							
Thalamus/basal ganglia		−5.621	±18	18	0	238	
Superior frontal gyrus	10	−4.590	±42	45	18	163	
Middle Frontal Gyrus	10☐46	−5.246	±15	42	51	169	

Interactions between disease status and the five specific frequency bands

The *full-factorial* analysis showed significant interactions between disease status and the five specific frequency bands of the cerebellum anterior lobe (CAL), the middle temporal gyrus (MTG) and the anterior cingulate cortex (ACC) (Figure 4 and Table 4).

Discriminatory analysis of the homotopic connectivity coefficient

To verify the ability to distinguish the cLBLP patients from the HCs, the mean connectivity coefficients of reducing VMHC in the typical frequency band (0.01–0.1 Hz) were extracted from the cLBLP and HCs group. The ROC analysis revealed that the areas under the curves (AUCs) were 0.936 for right and left ITG, 0.996 for the right and left BG, 0.916 for the right and left MFG, 0.889 for the right and left STG, and 0.944 for the right and left mPFC (Figure 5 and Table 5). The LOOCV showed cross-validated AUCs to be

0.936±0.004(0.934–0.949) for the right or left ITG, 0.995 ±0.008 (0.995–0.997) for the right or left BG, 0.915±0.006 (0.912–0.948) for the right or left MFG, 0.889±0.006 (0.884–0.908) for the right or left STG, and 0.944±0.005 (0.941–0.977) for the right or left mPFC. In the five specific frequency bands, the disrupted VMHC regions also showed a greater ability to distinguish the disease from HCs (Figure 5 and Table 6).

Clinical metrics associated with homotopic connectivity coefficient in cLBLP patients

In typical frequency band (0.01–0.1 Hz), significant correlations were observed between the VMHC values of BG and the values of 2PD of right hand ($\rho=-0.446$, $P=0.033$), between the VMHC values of mPFC and the VAS score ($\rho=0.476$, $P=0.022$) (Figure 6) in the cLBLP group; while no significant relationship was observed between the altered VMHC and the clinical metrics, such as the disease
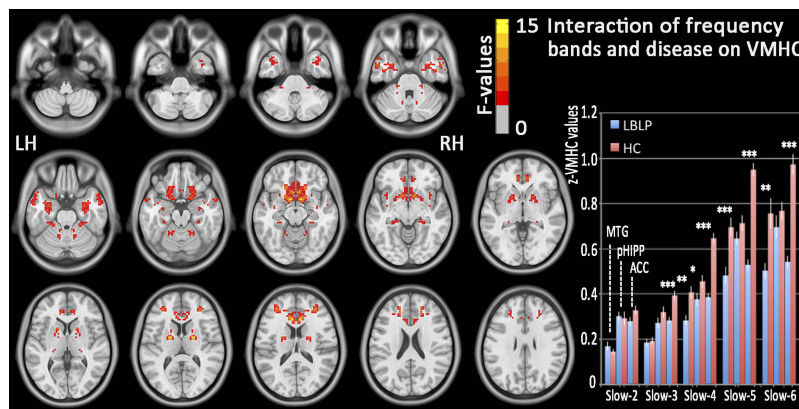
Figure 4 Interactions between the five specific frequency bands (slow-2 to slow-6) and group (cLBLP patients and HCs) on VMHC at voxels level (left) and cluster level (right).

Table 4 Significant interaction between disease status and the five specific frequency bands on VMHC (full-factorial design, 2×5)

Brain regions	BA	Peak F-scores	MNI coordinates			Cluster size (voxels)
			x	y	z	
Middle temporal gyrus	21,38	9.646	±51	15	−30	211
Cerebellum anterior lobe		7.882	±21	−33	−6	105
Anterior cingulate cortex	25,47	15.681	±6	30	12	525

Note: All clusters were analyzed using a two-tailed test with a voxel-level threshold of $P<0.01$, GRF correction and cluster-level of $P<0.05$.

duration, and JOA Back Pain Evaluation scores ($P=0.061$–0.991).

Similarly, significant correlations were observed between the VMHC values of slow-4 band of medial and superior frontal gyrus/basal ganglia and the values of 2PD of right hand ($\rho=-0.624$, $P=0.0015$), between the VMHC values of slow-2 band of thalamus/basal ganglia and the values of 2PD of right hand ($\rho=-0.470$, $P=0.024$), between the VMHC values of slow-2 band of superior frontal gyrus and the values of 2PD of right hand ($\rho=-0.456$, $P=0.029$).

Discussion

We investigated the interhemispheric functional coordination in patients with cLBLP. We showed disease related to disrupting interhemispheric connectivity of cLBLP patients, which was summarized as (1) a significantly decreased VMHC in the typical and then five specific frequency bands; (2) further demonstrated significant interactions between disease status and the five specific frequency bands of several regions; (3) significant correlation was observed between the decreased VMHC values and VAS score, 2PD test score in the cLBLP patients.

Disrupted interhemispheric connectivity in cLBLP patients in typical frequency bands

The correlation between the fMRI signals and the mirrored brain regions at rest has been developed to estimate the strength of resting-state functional connectivity, VMHC, as one of the reliable and reproducible metrics of the brain intrinsic architecture.[16,18] In this study, we observed only significantly reduced homotopic connectivity in cLBLP patients in the ITG, the BG, the MFG, the STG, and the mPFC.

ITG mainly connected with left and right MFG, contralateral ITG, while evidence of functional neuroimaging studies has revealed that ITG has a role in identifying objects and/or processes the visual information processing, memory, and spatial awareness.[34] Some studies have linked the ITG to represents stored limbs-postures for planning and predicting object-directed actions and activities.[35] In this study, the mainly influenced specific (heterotopic connectivity) network of decreased ITG is contralateral ITG, right and left MFG. The strategic location and the effect of connections suggest that ITG is a major association area that subserves readiness or contingency awareness of limb in patients with cLBLP.
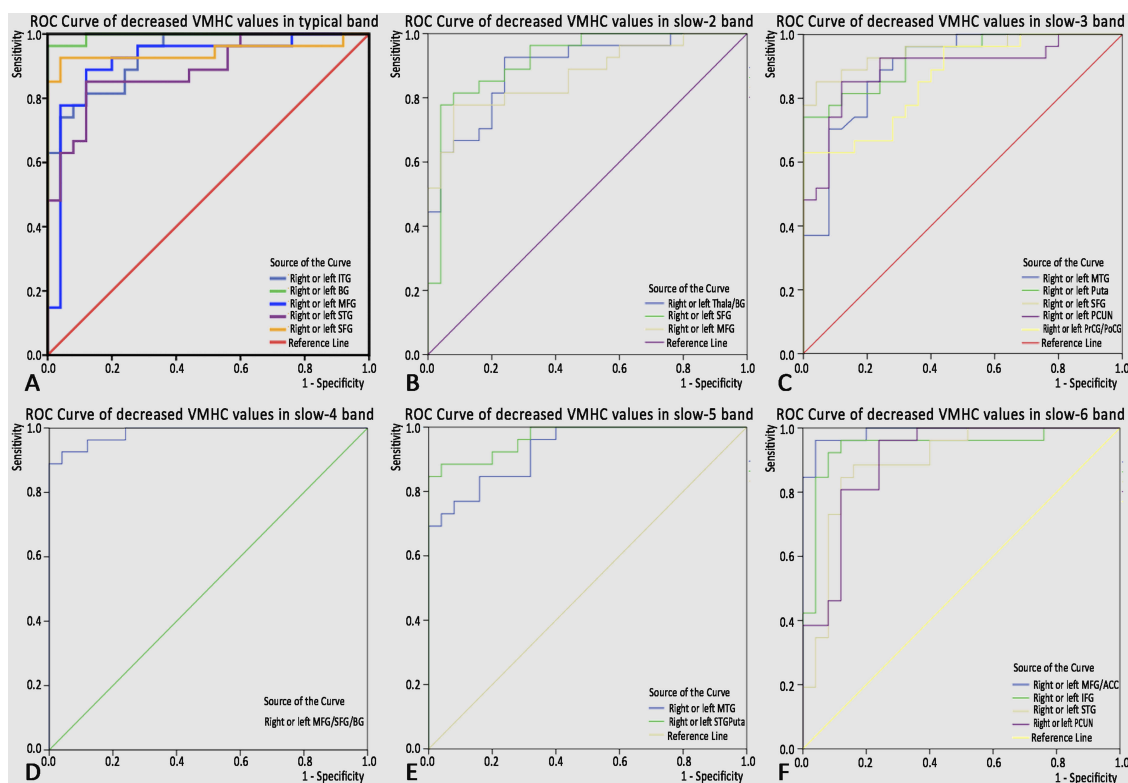
Figure 5 Significantly decreased VMHC values in the ROC analysis showing a moderate differentiating ability for cLBLP.

Table 5 ROC discriminatory analysis of the homotopic connectivity coefficient in the typical (0.01–0.1 Hz) frequency bands

Brain regions	Area Under the Curve	Cut-off point	Sensitivity	Specificity
Inferior temporal gyrus	0.936	0.298[a]	81.5%(22/27)	92.0%(23/25)
Basal ganglia	0.996	0.475	96.3%(26/27)	100%(25/25)
Middle frontal gyrus	0.916	0.302	88.9%(24/27)	88.0%(22/25)
Superior temporal gyrus	0.889	0.288	85.2%(23/27)	88.0%(22/25)
Superior frontal gyrus	0.944	0.426	92.6%(25/27)	96.0%(22/25)

Notes: [a]By this cut-off point, the VMHC value of the inferior temporal gyrus could correctly classify 23 of 25 cLBLP patients and 22 of 27 healthy subjects and resulted in a specificity of 92.0% and a sensitivity of 81.5%. The means of other cut-off points were similar.

Another region with decreased homotopic connectivity, BG mainly influenced bilateral anterior cingulate cortex/MFG in this study. As same as, this study observed that decreased VMHC values of BG negative with the values of 2PD of the right hand in patients with cLBLP. 2PD is commonly used for assessing tactile spatial discrimination ability with highly intra-observer reliability.[36] Decreased VMHC values of BG meaning interhemispheric incoordination is influenced to tactile discrimination ability. But corresponding to the function of BG, we know, it are not simply involved in the control of movement, but more related to aspects of cognitive function.[36] Decreased heterotopic connectivity between the BG and anterior cingulate cortex/MFG

hinting an impairment in certain higher-level functions, such as attention allocation, contingency awareness, and optimal decision making. It might originate from long-term, chronic pain, and numbness in cLBLP patients.

When decreased VMHC of MFG and mPFC were observed, evidence from disrupting those regions connected with the default-mode and attention network by heterotopic connectivity analyses. In other words, the MFG and mPFC are an important part of the default-mode and attention network. Studying with fMRI has shown an abnormal response to the brain default mode network of an attention task, even disrupts normal activity during the brain resting state in chronic back pain patients.[7,37] It is known that an intrinsic activity

Table 6 ROC discriminatory analysis of the homotopic connectivity coefficient in five specific frequency bands

Brain regions	Area Under the Curve	Cut-off point	Sensitivity	Specificity
The regions with altered VMHC at slow-6 (0–0.01 Hz) band (cLBLP *vs* HC)				
Medial frontal gyrus/anterior cingulate cortex	0.988	0.430	96.2%(26/27)	96.0%(24/25)
Inferior frontal gyrus	0.943	0.344	92.6%(25/27)	92.0%(23/25)
Superior temporal gyrus	0.892	0.453	84.6%(23/27)	88.0%(22/25)
Precuneus	0.902	0.617	96.2%(26/27)	76.0%(19/25)
The regions with altered VMHC at slow-5 (0.01–0.027 Hz) band (cLBLP *vs* HC)				
Middle temporal gyrus	0.931	0.471	77.8%(20/27)	96.0%(24/25)
Superior temporal gyrus/putamen	0.968	0.479	88.9%(24/27)	100%(25/25)
The regions with altered VMHC at slow-4 (0.027–0.073 Hz) band (cLBLP *vs* HC)				
Medial and superior frontal gyrus/basal ganglia	0.985	0.419	92.6%(25/27)	96.0%(24/25)
The regions with altered VMHC at slow-3 (0.073–0.167 Hz) band (cLBLP *vs* HC)				
Middle temporal gyrus	0.897	0.232	85.2%(23/27)	80.0%(20/25)
Putamen	0.927	0.354	74.1%(20/27)	100%(25/25)
Superior frontal gyrus	0.950	0.273	85.2%(23/27)	92.0%(23/25)
Precuneus	0.892	0.477	85.2%(23/27)	88.0%(22/25)
Precentral and postcentral cortex	0.862	0.279	63%(17/27)	100%(25/25)
The regions with altered VMHC at slow-2 (0.167–0.25 Hz) band (cLBLP *vs* HC)				
Thalamus/basal ganglia	0.890	0.346	92.6%(25/27)	76.0%(19/25)
Superior frontal gyrus	0.919	0.198	85.2%(23/27)	84.0%(21/25)
Middle Frontal gyrus	0.870	0.396	77.8%(21/27)	92.0%(23/25)
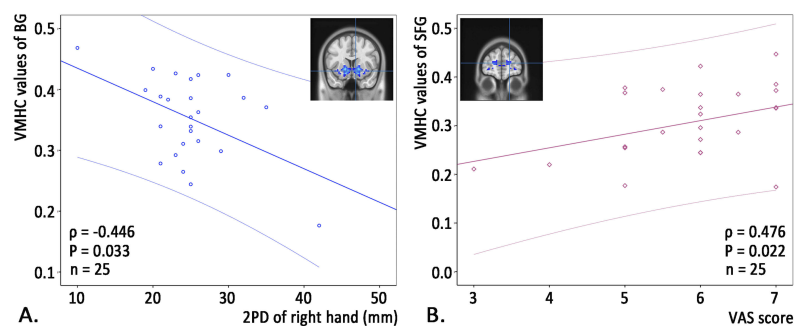
Figure 6 Correlations between the VMHC coefficients and the clinical index in the cLBLP patients in the typical (0.01–0.1 Hz) frequency bands.

in the default mode network when the absence of explicit brain input or output or the brain is at wakeful rest. But for cLBLP patients, the pain and numbness become a spontaneous percept, this status might result in a different "intrinsic" organization. In this study, we found a VAS score positively related alterations in the homotopic connectivity of the mPFC, together with others in this study about disrupted homotopic and heterotopic connectivity (show in Figure S2) indicated that chronic stimulation of extrinsic participated in the central functional reorganization of the default mode network. In short, this new observation in VMHC is consistent with previous intrinsic functional connectivity showing that due to a mismatch of the temporal patterns of neuronal intrinsic activity or of the functional statuses, which might play a critical role in attention, memory, prospection, and self-processing in cLBLP patients.

Interactions between frequency-based VMHC and disease status in cLBLP patients

Significant interactions were observed in several regions, involving unconscious information processing (CAL), contemplating distance processing (MTG), and certain higher-level functions (ACC), between frequency-based VMHC and disease status in cLBLP patients. Inputs into the CAL are mainly from the spinal cord and responsible for mediating unconscious proprioception. A recent study has shown speed-specific neuro-functional and -structural correlates with the CAL,[38] and it can deteriorate in the alcoholics associated with sensorimotor integration.[39] The exact function of MTG is unknown, but it has been connected with processes as different as contemplating distance, and multimodal semantic processing.[40] While the ACC is involved monitoring the experience of pain and emotional reaction. Regarding the intrinsic activity, distinct frequency-specific functional properties may arise from the various cytoarchitectural or synaptic types in this area.[17,41] In the above regions, more frequency-dependent properties or increased richness in scales of VMHC measures, suggesting that different frequency bands may have specific pathological relevance to this region, might explain the clinical symptom.

In this study, different altered pattern of VMHC in the five specific frequency bands, and it influenced heterotopic connectivity (shown in Figures S3 and S4), implied an interhemispheric interaction of pain and paresthesia (numbness) in the frequency-related alterations in specific brain regions in the patients with LBLP. Baliki et al[25] found that a closed relationship exists anatomical structures and the intrinsic activity in a specific frequency bands. Our findings may underlie the neurophysiological basis of the interhemispheric functional coordination. These findings suggest that specific frequency ranges, even high-frequency bands, should be selected to detect pain-related homotopic connectivity in future studies of cLBLP patients.

Discriminant validity of altered VMHC values in cLBLP patients

Currently, the clinical diagnosis of cLBLP is base on physical examination and the evidence of discogenic compression on a lumbar CT and/or MRI. Therefore, an accurate and objective diagnosis of central sensitization or central plasticity in cLBLP has high clinical value to explore the new treatment or prognostic evaluation. With

this aim, we showed that disrupted VMHC differentiated the plasticity brain of cLBLP from healthy individuals with high sensitivity and specificity, using a ROC analysis. To the best of our knowledge, few studies have attempted to use intrinsic functional metrics as a classification tool for judge central sensitization in chronic pain patients. Hence, this discriminant analyses presented here, as a preferential candidate, are preliminary because they have not been verified in a separate group. It needs further studies are warranted in the future.

Limitations

This exploratory finding is promising, but several issues need to be noted. First, to expose the intrinsic functional architecture stabile and precisely is challenging in a relatively small sample size. Thus, the interesting findings will require replication to increase the statistical power in a larger sample size study. Second, the human brain is unsymmetrical. We tried to use symmetrical standard template to improve the functional coherence in interhemispheric homotopic regions. Hence, morphometric asymmetry could not account for the altered VMHC. Third, these current results were obtained under pain and numbness of limb condition. What is also unclear is the mechanism for leg pain with low back pain afferent input on central neurons. Future studies should combine both pain and pain-free condition, or other task-based fMRI to observe interhemispheric connectivity in cLBLP patients. Additionally, the altered connection strength of this study without characterizing the anatomical basis of the interhemispheric connection (e.g. diffusion tensor tractography), the underlying mechanisms of disrupted VMHC in cLBLP, and the difference in intrinsic functional connectivity with other chronic low back pain. It needs further studies to expose to future research.

Conclusion

In conclusion, the present study found that cLBLP patients showed disrupted interhemispheric coordination, with different heterotopic connectivity patterns in these regions with decreased VMHC. Moreover, VAS scores correlated alteration of VMHC may provide a useful and sensitive screening approach for observed interhemispheric "intrinsic" organization in patients with chronic pain.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work. None of the authors have any personal or financial involvement with organizations that have a financial interest in its content.

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