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Current source density and functional connectivity extracted from resting-state electroencephalography as biomarkers for chronic low back pain

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Abstract

Introduction: Chronic low back pain (CLBP) is a global health issue, and its nonspecific causes make treatment challenging. Understanding the neural mechanisms of CLBP should contribute to developing effective therapies.

Objectives: To compare current source density (CSD) and functional connectivity (FC) extracted from resting electroencephalography (EEG) between patients with CLBP and healthy controls and to examine the correlations between EEG indices and symptoms.

Methods: Thirty-four patients with CLBP and 34 healthy controls in an open data set were analyzed. Five-minute resting-state closed-eye EEG was acquired using the international 10-20 system. Current source density across frequency bands was calculated using exact low-resolution electromagnetic tomography. Functional connectivity was assessed between 24 cortical regions using lagged linear connectivity. Correlations between pain symptoms and CSD distribution and FC were examined in patients with CLBP.

Results: Current source density analysis showed no significant differences between the groups. The CLBP group exhibited significantly reduced FC in the β3 band between the left middle temporal gyrus and the posterior cingulate cortex, and between the ventral medial prefrontal cortex and the left inferior parietal lobule. Prefrontal θ and δ activity positively correlated with pain symptoms. Increased β1 band FC between the right dorsolateral prefrontal cortex and right auditory cortex correlated with greater pain intensity.

Conclusions: We found altered neural activity and connectivity in patients with CLBP, particularly in prefrontal and temporal regions. These results suggest potential targets for pain modulation through brain pathways and highlight the value of EEG biomarkers in understanding pain mechanisms and assessing treatment efficacy.

Keywords: Biomarker, Chronic low back pain, Chronic pain, Electroencephalogram, Resting state

1. Introduction

Chronic low back pain (CLBP) has emerged as a significant global health problem,[18] with 85% of cases classified as "nonspecific," because of the lack of identifiable physiological cause.[27,44] Understanding neural mechanisms underlying CLBP is crucial for developing effective treatments. Electroencephalography (EEG) has become a widely used tool in chronic pain research, offering advantages, such as being noninvasive, relatively inexpensive, and having high temporal resolution.[51] Studies have found alterations in EEG frequency power in CLBP patients, particularly in α and θ bands.[5,61] Increased α power during resting state and active lumbar flexion has been observed in CLBP patients,

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possibly related to altered sensory information processing.[5] Other studies reported increased θ and β power in chronic pain patients compared with healthy controls (HCs).[61] Systematic reviews have noted increased θ and α power at rest and decreased evoked potential amplitude after sensory and cognitive stimulation in chronic pain patients.[49] EEG analyses of current source density (CSD) and functional connectivity (FC) revealed increased connectivity in θ and γ bands of frontal regions and network reorganization in the γ band.[56] These findings suggest that EEG could potentially serve as a diagnostic biomarker for chronic pain, including CLBP.[51,61] However, results of heterogeneity across studies indicate the need for further investigation to establish reliable EEG-based biomarkers.

Magnetic resonance imaging (MRI) has revealed structural and functional changes in CLBP individuals, including reduced gray and white matter volumes and altered FC, particularly in the default mode network.[42] Interventional studies have demonstrated recovery-related neural connectivity changes, such as increased middle temporal cortex activity following treatment.[3] However, MRI's high cost and poor temporal resolution limit its practicality for frequent, longitudinal studies.[26]

Previous studies have limitations, such as power analysis performed in electrode space,[56] which can be influenced by dominant occipital α rhythms.[54] Power analyses using spatial filters may better capture brain activity distribution and extract features not found in previous studies. Functional connectivity analyzed using linearly constrained minimum variance beamforming performs poorly with highly correlated activity.[40] Alternative spatial filters could improve result stability and reliability, providing a more comprehensive understanding of FC in chronic pain.

Another limitation is the variability in pain localization among participants, suggesting the need for more homogeneous patient groups. Few studies have investigated correlations between EEG markers and pain intensity or psychological factors in CLBP patients. Exploring these correlations may open new avenues for using EEG to assess chronic pain treatment efficacy. The aim of this study was to compare CSD distribution and FC in resting EEG between patients with CLBP and HCs and to examine the correlations between EEG indexes and symptoms in patients with CLBP, using open EEG data.

2. Methods

2.1. Study design

This study used an open EEG data set[2] containing data from CLBP patients and HCs.[36,56] This data set contains data from 3 different studies that were conducted at the Technical University of Munich since 2010 and focus on individuals with chronic pain. All participants provided written informed consent.

Inclusion criteria for the CLBP group were a clinical diagnosis of CLBP, persisting for at least 6 months and an average pain intensity of 4 or more out of 10 reported in the past 4 weeks (0 = no pain, 10 = worst pain imaginable). Exclusion criteria included acute changes in pain status within the past 3 months (eg, because of recent injury or surgery), major neurological illness (eg, epilepsy, stroke, dementia), major psychiatric illness other than depression, and severe general disease. In addition, patients taking benzodiazepines were excluded because these medications are reported to have a significant impact on EEG.[24] For HCs, exclusion criteria included a history of pain persisting for more than 6 months, any pain on the examination day, surgery or acute injury within the past 3 months, and neurological or psychiatric illness.

The study analyzed 34 CLBP patients (ie, CLBP group; age range: 24–82 years, mean ± SD: 56.56 ± 12.74) and 34 HCs (ie, HC group; age range: 37–79 years, mean ± SD: 58.53 ± 13.32).

2.2. Self-reported questionnaires to assess pain and mood status

The CLBP group completed self-reported questionnaires assessing pain symptoms and mood status immediately before EEG recording. Current pain intensity was measured using the numerical rating scale, pain quality with the Pain DETECT questionnaire,[16] and Short Form McGill Pain Questionnaire (SF-MPQ).[38] Depression symptoms were assessed using the Beck Depression Inventory-Second edition (BDI-II)[4] and anxiety with the State-Trait Anxiety Inventory (STAI).[35]

Participant information, including the self-reported questionnaire scores, is shown in **Table 1**.

2.3. EEG recording

EEG data were recorded using 64 electrodes and a BrainAmp MR plus amplifier (Brain Products, Munich, Germany). Electrodes were positioned according to the international 10-20 system with 19 channels, with the following additional electrodes: Fpz, CPz, POz, Oz, Iz, AF3/4, F5/6, FC1/2/3/4/5/6, FT7/8/9/10, C1/2/5/6, CP1/2/3/4. Two electrodes were placed below the outer canthus of each eye to monitor eye movements. All EEG electrodes were referenced to electrode FCz and grounded at electrode AFz. Data were recorded at 1000 Hz sampling frequency.

Recording was performed in a resting state with participants instructed to remain awake and relaxed. This study analyzed 5 minutes of continuous resting closed-eye condition data.

2.4. Preprocessing

EEG data preprocessing used the EEGLAB toolbox,[11] which is an open-source MATLAB (MathWorks, Natick, MA) toolbox for the analysis of single-trial EEG dynamics, including independent component (IC) analysis. Data were down sampled from 1000 to 500 Hz and filtered using a 1- to 50-Hz band-pass filter. Line noise of 50 Hz was removed using the CleanLine plugin for EEGLAB. This approach was advocated by Mitra and Bokil.[39]

Table 1

Participant characteristics.

	CLBP, n = 34	HC, n = 34
Gender (men/women)	16/18	14/20
	Mean (SD)	**Mean (SD)**
Age (y)	56.6 (12.7)	58.5 (13.3)
Current pain intensity (0–10)	5.2 (1.7)	—
Average pain intensity (0–10)	5.6 (1.6)	—
Pain duration (mo)	140.2 (118.1)	—
SF-MPQ-sensory	12.6 (4.8)	—
SF-MPQ-affect	3.8 (2.7)	—
SF-MPQ-total	24.8 (7.9)	—
PainDETECT	16.0 (6.3)	—
BDI-II	7.9 (12.7)	2.4 (3.2)
STAI	88.8 (15.8)	59.0 (10.1)

Pain intensity was measured by numerical rating scale rating from 0 to 10.
CLBP, chronic low back pain; HC, healthy control; SF-MPQ, short-form McGill Pain Questionnaire; BDI-II, Beck Depression Inventory-Second Edition; STAI, State-Trait Anxiety Inventory.

Table 2

Maximum exact low resolution electromagnetic tomography current source density and region for each frequency band in chronic low back pain group and healthy control group.

	δ (1.5–6.0 Hz)	θ (6.5–8.0 Hz)	α1 (8.5–10.0 Hz)	α2 (10.5–12.0 Hz)	β1 (12.5–18.0 Hz)	β2 (18.5–21.0 Hz)	β3 (21.5–30.0 Hz)	Ω (1.5–30.0 Hz)
CLBP								
Max CSD value	0.212	0.159	0.452	0.141	0.139	0.054	0.077	1.27
Region	Brodmann area 7	Brodmann area 18	Brodmann area 18	Brodmann area 19	Brodmann area 7	Brodmann area 5	Brodmann area 4	Brodmann area 18
	Postcentral gyrus	Middle occipital gyrus	Cuneus	Cuneus	Postcentral gyrus	Postcentral gyrus	Paracentral lobule	Cuneus
	Parietal lobe	Occipital lobe	Occipital lobe	Occipital lobe	Parietal lobe	Parietal lobe	Parietal lobe	Occipital lobe
HC								
Max CSD value	0.144	0.096	0.382	0.217	0.121	0.044	0.062	1.13
Region	Brodmann area 7	Brodmann area 39	Brodmann area 19	Brodmann area 18	Brodmann area 19	Brodmann area 18	Brodmann area 7	Brodmann area 18
	Postcentral gyrus	Angular gyrus	Cuneus	Cuneus	Cuneus	Cuneus	Postcentral gyrus	Cuneus
	Parietal lobe	Temporal lobe	Occipital lobe	Occipital lobe	Occipital lobe	Occipital lobe	Parietal lobe	Occipital lobe

Maximum CSD values and corresponding regions for each frequency band in the chronic low back pain group and the healthy control group. The maximum CSD values are the highest values in each frequency band among the 6239 voxels. There were no significant differences between the two groups about CSD. CLBP, chronic low back pain; CSD, current source density; HC, healthy control.

Artifact subspace reconstruction was used to correct bad burst in the EEGLAB tool.[8] The artifact subspace reconstruction algorithm identifies segments of data that exceed the specified standard deviation threshold and reconstructs these segments by projecting them onto a subspace that reflects the clean signal. A maximum acceptable standard deviation of 20 for a 0.5-second window was established. This method effectively reduces the influence of transient artifacts while preserving the underlying brain activity. Next, IC analysis (Runica) was executed, and the artifact discrimination value of each IC was calculated using ICLabel.[50] ICs with artifact discrimination values below 90% for Brain and above 90% for the other labels were excluded, and the EEG waveforms were then reconstructed.

2.5. Analysis of EEG data

2.5.1. Current source density

The cortical CSD distribution was analyzed using exact low-resolution electromagnetic tomography (eLORETA). The eLORETA can be used for functional localization, as in classical neuroimaging, and more importantly, it provides noninvasive intracranial recordings for the assessment of dynamic FC by evaluating connectivity between pairs of brain regions, minimally affected by volume conduction and low spatial resolution, thus revealing pure physiological connectivity.[46] The eLORETA method uses a linear-type weighted minimum norm inverse solution. The eLORETA head model and electrode coordinates are based on the Montreal Neurological Institute's mean MRI brain map (MNI152), with the intracerebral volume being partitioned into 6239 voxels of 5-mm spatial resolution and restricted to cortical gray matter. Previous studies have used functional MRI,[41,59] structural MRI,[60] positron emission tomography,[12] and intracranial EEG[62] to validate eLORETA tomography.

Preprocessed artifact-free EEG data were converted into 2-second epochs of text for use with eLORETA. In this study, we used the following frequency bands: δ (1.5–6.0 Hz), θ (6.5–8.0 Hz), α1 (8.5–10.0 Hz), α2 (10.5–12.0 Hz), β1 (12.5–18.0 Hz), β2 (18.5–21.0 Hz), β3 (21.5–30.0 Hz), and Ω (1.5–30.0 Hz)[28] and calculated eLORETA cortical CSD for each band.

Between-group differences in the CSD of each frequency band were evaluated using voxel-by-voxel unpaired *t*-tests based on eLORETA log-transformed CSD power. In addition, multiple comparisons were corrected using the eLORETA statistical nonparametric mapping method.[21] In the resulting statistical 3-dimensional images, cortical voxels displaying significant differences were identified using a nonparametric randomization approach (statistical nonparametric mapping method). To determine the critical probability threshold for the observed *t*-value, eLORETA used 5000 data permutations to determine the critical probability threshold values for the actually observed t-statistic values with correction for multiple comparisons across all voxels and all frequencies, without the need to rely on Gaussianity.[20,45,47] LORETA does not rely on "distributional assumptions" and instead provides an adjusted *t*-critical value effective for controlling type I error.[15]

Correlation analyses between the CSD values of all voxels and current pain intensity, average pain intensity, Pain DETECT, SF-MPQ, BDI-II, and STAI scores of the CLBP group were also performed using eLORETA. The critical probability threshold for the *P* value was set at $P = 0.05$. To address multiple comparisons, a bootstrapping method was applied. For self-reported questionnaires with significant correlations, the CSD value of the voxel with the maximum effect size and the questionnaire score were set as variables. 1,000 resamples were performed, and bias-corrected and accelerated (BCa) confidence intervals (CIs) were calculated. Correlation significance was evaluated using BCa 95% CIs. This approach aimed to reduce sampling errors and increase result robustness.

2.5.2. Functional connectivity

Functional connectivity analysis employed a voxel-by-voxel approach to determine 24 cortical regions of interest (ROIs) based on previous studies.[20,58] Preprocessed EEG data were split into epochs as in the CSD analysis. To measure the linear relationships of different regions over time, the lagged linear connectivity (LLC) was calculated for each of the 8 frequency bands; LLC is based on the concept that activity in one region at one time point affects activity in another region at a later time point.[48] This temporal relationship indicates that brain regions communicate through interactions that are time lagged, rather than occurring instantaneously. It is estimated by removing the zero-delay instantaneous phase interaction between EEG

sources that may be affected by the instantaneous physical propagation of neuroionic currents because of head volume conductor effects (This effect occurs because electrical currents from neural sources spread instantaneously through the conductive medium of the head, leading to misleading correlations.). By excluding instantaneous interactions, LLC isolates the time-delayed functional connections between brain regions, offering a more reliable measure of statistical interdependence that reflects genuine neural communication, rather than artifacts caused by volume conduction.

Unpaired *t*-tests in eLORETA generated *t*-statistics for FC. The t-statistic was permuted 5000 times, examining all couplings (276) between 24 ROIs across 8 frequency bands. A non-parametric randomization method based on "maximum statistics" corrected for multiple comparisons.[43] eLORETA examined FC of the 24 ROIs in 8 frequency bands ($276 \times 8 = 2208$) and overall connectivities between current pain intensity, average pain intensity, PainDETECT, SF-MPQ, BDI-II, and STAI score in the CLBP group. The critical probability threshold was set at $P = 0.05$. The bootstrap method was applied for multiple comparison correction in FC analysis, in the same way as in the CSD analysis. Specifically, for the self-reported questionnaires that showed significant correlation, the FC value and the questionnaire score were set as variables.

2.6. Ethical concerns

The original open data acquisition was approved by the Ethics Committee of the Medical Faculty of the Technical University of Munich and conducted in accordance with relevant guidelines and regulations. This study used anonymized open data, requiring no additional ethical approval.

3. Results

3.1. Current source density

Figure 1 shows the average CSD in each frequency band for the CLBP and HC groups according to the eLORETA analysis. Except for the Ω band, which combined all frequencies, the highest CSD value was found in the α1 band in the cuneus of the occipital lobe, for both the CLBP group (CSD value: 0.452) and the HC group (CSD value: 0.382). **Table 2** shows the maximum CSD values and corresponding regions for each frequency band, based on the highest values among the 6239 voxels. However, statistical analysis showed no significant differences between the 2 groups.

3.2. Functional connectivity

Compared with the HC group, the FC of the CLBP group was significantly lower in the β3 band (21.5–30 Hz) in the left middle temporal gyrus–posterior cingulate cortex (PCC) and ventral medial prefrontal cortex (PFC)–left inferior parietal lobule ($P > 0.05$, $t_{max} = 3.897$) connections (**Fig. 2**). No significant differences were found in other frequency bands.

3.3. Correlations between current source density and self-reported questionnaires

Exact low resolution electromagnetic tomography correlation analysis showed a significant positive correlation between left-sided dominant prefrontal θ activity and the SF-MPQ total score (maximum effect size in all voxels: $r > 0.56$) (**Fig. 3**). Higher SF-MPQ total scores indicate higher CSD in the θ band of the PFC. The 95% BCa CI was 0.281 to 0.758, confirming the correlation's significance. The bootstrap method showed bias of −0.009 (CSD value) and 0 (SF-MPQ total scores), with SEs of 0.129 (CSD value) and 0 (SF-MPQ total scores). However, there was no significant correlation between the affective ($P > 0.08$) or sensory ($P > 0.14$) score of the SF-MPQ and CSD in all frequency bands.

Left prefrontal δ activity showed a significant positive correlation with current pain intensity (maximum effect size in all voxels: $r > 0.56$) (**Fig. 4**). As current pain intensity increased, the CSD in the delta band of the left PFC also increased. The 95% BCa CI ranged from 0.282 to 0.759, confirming the correlation's significance. The bootstrapping showed bias of 0.006 (CSD value) and 0 (current pain intensity), with SEs of 0.084 (CSD value) and 0 (current pain intensity).

No significant correlations were found between CSD in all frequency bands and average pain intensity ($P > 0.13$), the Pain

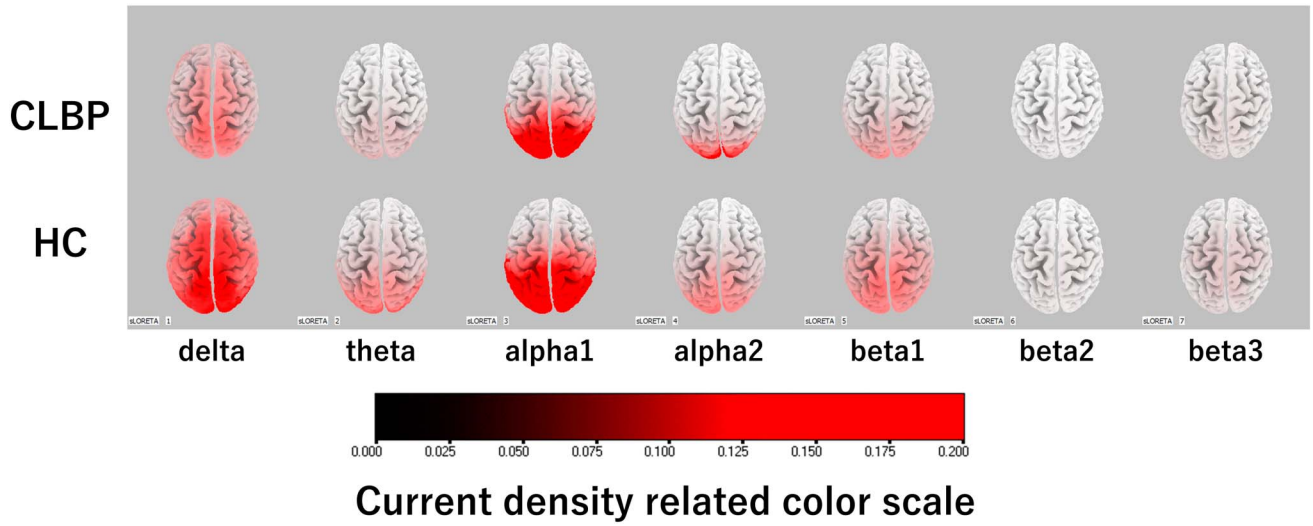

Figure 1. Averaged exact low resolution electromagnetic tomography CSD for each frequency band in the CLBP and HC groups. The color scale shows CSD from 0.000 (black) to 0.200 (red). Statistical analysis showed no significant differences between the 2 groups. CLBP, chronic low back pain; CSD, current source density; HC, healthy control.

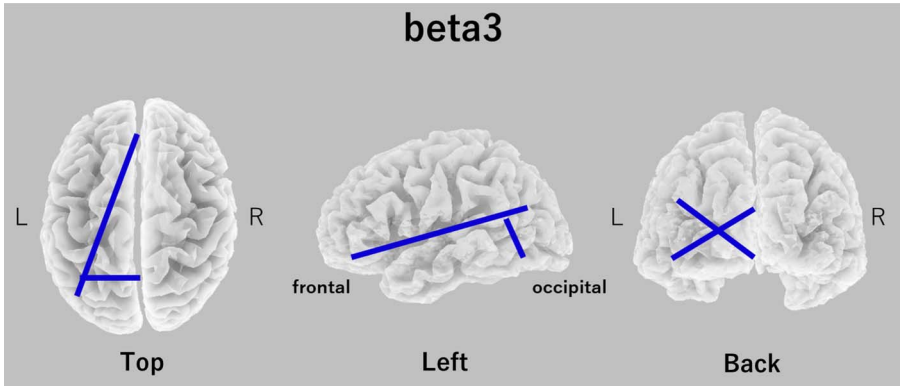

Figure 2. Exact low resolution electromagnetic tomography wire diagram indicating significantly reduced FC in the CLBP group compared with the HC group. The 2 blue lines indicate significant lower FCs in the β3 band (21.5–30 Hz) in the CLBP group compared with the HC group. One of the lines is between the left middle temporal gyrus–posterior cingulate cortex, and the other is between ventral medial prefrontal cortex–left inferior parietal lobule. CLBP, chronic low back pain; FC, functional connectivity; HC, healthy control.

DETECT questionnaire ($P > 0.49$), the BDI for evaluating depression symptoms ($P > 0.51$), or the STAI for evaluating anxiety (state anxiety: $P > 0.62$, trait anxiety: $P > 0.71$).

3.4. Correlations between functional connectivity values and self-reported questionnaires

Functional connectivity values in the right dorsolateral PFC (rDLPFC) and the right auditory cortex within the β1 band demonstrated significant positive correlations with the intensity of current pain ($P < 0.05$, $r > 0.62$) (**Fig. 5**). This means that the FC in the β1 band was higher when current pain was stronger. The 95% BCa CI based on the bootstrapping method is 0.370 to 0.798. The bias using the bootstrapping method were 0.006 (FC value) and 0 (current pain intensity), and the SEs were 0.088 (FC value) and 0 (current pain intensity).

However, there were no significant correlations observed between FC across all frequency bands and average pain intensity ($P > 0.96$), the Pain DETECT questionnaire ($P > 0.12$), SF-MPQ (total score: $P > 0.20$, affective score: $P > 0.64$, sensory score: $P > 0.28$), BDI ($P > 0.90$), and STAI (state anxiety: $P > 0.48$, trait anxiety: $P > 0.86$).

4. Discussion

This study compared patients with CLBP and HCs, revealing associations between certain brain activities and connectivity patterns with pain assessment. The highest CSD values in both groups occurred in the α1 band within the cuneus of the occipital lobe, with no significant differences between the groups. Notably, FC in the β3 frequency was significantly reduced in the CLBP group across specific brain regions, including the left middle temporal gyrus and PCC. Correlation analyses highlighted significant associations between pain intensity and brain activity, with increased prefrontal θ and δ activities correlating with higher MPQ scores and current pain intensity, respectively. In addition, FC in the β1 band between the rDLPFC and the right auditory cortex was significantly higher with greater pain intensity. These findings suggest that specific brain areas and frequencies are integrally linked to the perception and modulation of pain in CLBP.

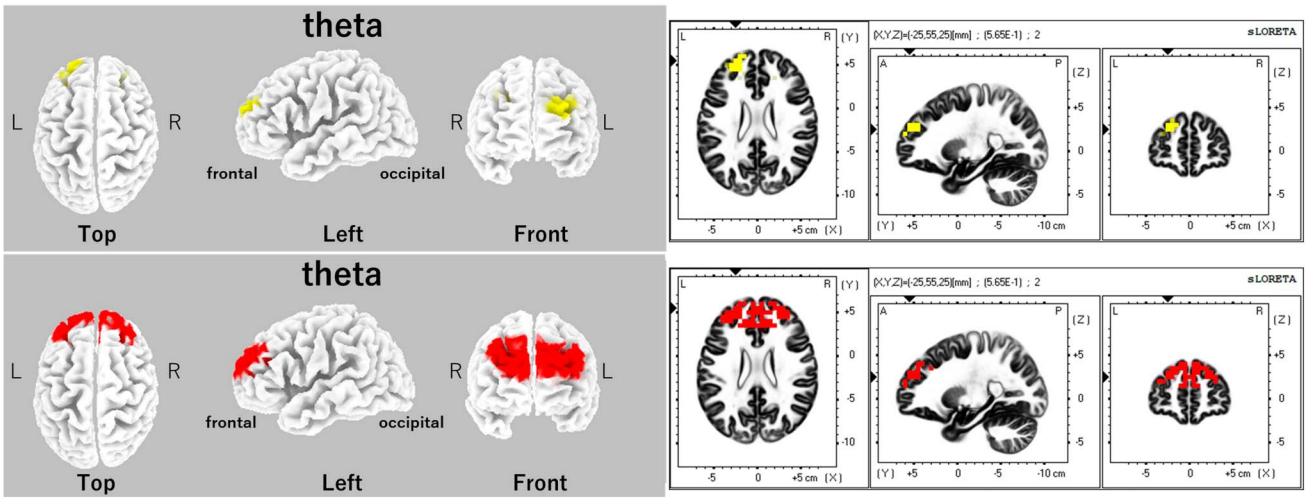

Figure 3. Exact low resolution electromagnetic tomography maps showing cortical regions that have a significant positive correlation with θ band CSD value and SF-MPQ total score. The voxels with θ band CSD value that showed a significant positive correlation with the SF-MPQ total score are colored. Significant positive correlation localizations are present in the left-side dominant prefrontal cortex. The image above shows the voxels indicated when the *P* value is set to 0.05 or less, colored yellow, and the image below shows the voxels indicated when the *P* value is set to 0.10 or less, colored red. CSD, current source density; SF-MPQ, Short Form McGill Pain Questionnaire.

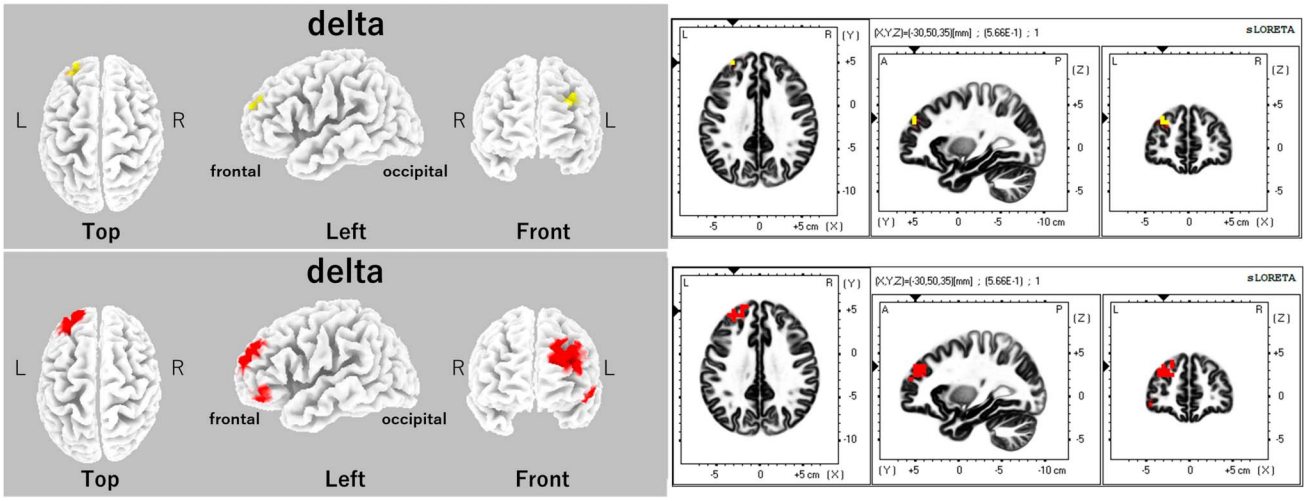

Figure 4. Exact low resolution electromagnetic tomography maps indicating cortical regions that have significant correlations with delta band CSD value and current pain intensity. The voxels that showed a significant positive correlation with the current pain intensity in the delta band CSD values are colored. Significant positive correlation localizations are present in the left prefrontal cortex. The image above shows the voxels indicated when the *P* value is set to 0.05 or less, colored yellow, and the image below shows the voxels indicated when the *P* value is set to 0.10 or less, colored red. CSD, current source density.

Functional connectivity between the left middle temporal gyrus and PCC has not previously been reported to have a direct effect on pain. However, the reduced FC of β3 frequencies in certain brain regions, such as the left middle temporal gyrus and PCC, can be interpreted in the context of pain processing and regulation. Research has shown that the PCC, undergoes changes in connectivity in response to pain. For instance, during pain conditions, the insular cortex exhibits altered connectivity with the medial prefrontal and lateral temporal cortices and decreased connectivity with the PCC, precuneus, and inferior parietal lobule, indicating that pain disrupts the connectivity between the insula and the default mode network.[44] This result suggests that the PCC's connectivity with other pain-related brain regions plays a role in the experience of chronic pain. The left middle temporal gyrus, along with other regions, has been implicated in brain activity during short-term memory of pain duration.[25]

The correlations between pain intensity and increased θ and δ activity in the PFC underscore its crucial role in pain perception and regulation. The medial PFC processes the emotional and cognitive components of pain,[29] whereas the dorsolateral PFC actively controls pain perception by modulating corticosubcortical and corticocortical pathways.[33] The anterior cingulate cortex (ACC), particularly the dorsal ACC, focuses on the experience and emotional evaluation of pain.[13] Previous studies have reported increased activity in the PFC, especially within the ACC, correlating with pain intensity and age.[14] Individual differences in perceived pain controllability also correlate with PFC activation.[52] Conversely, in conditions such as postherpetic neuralgia, functional MRI studies have shown a negative correlation between pain intensity and regional homogeneity in several prefrontal regions.[30] In terms of EEG, the frontal midline θ rhythm is thought to originate in the ACC,[23] reflects heightened vigilance, mental effort, or cognitive control.[7,22,37] Our results suggest that frontal midline θ may represent pain processing, pain attention, and coping with the unpleasantness associated with chronic pain.[1,34] Previous research on various chronic pain conditions—including the data used here for CLBP—has demonstrated increased connectivity in the θ and γ bands in frontal regions of patients, along with overall network reorganization in the γ band.[56] Sleep deprivation increases cortical θ and δ power,[6] and animal studies suggest that δ oscillations may indicate increased chronic neuropathic pain.[31] The responsiveness of GABAergic interneurons in the PFC to various cortical rhythms highlights the complexity of its role in pain regulation.[31]

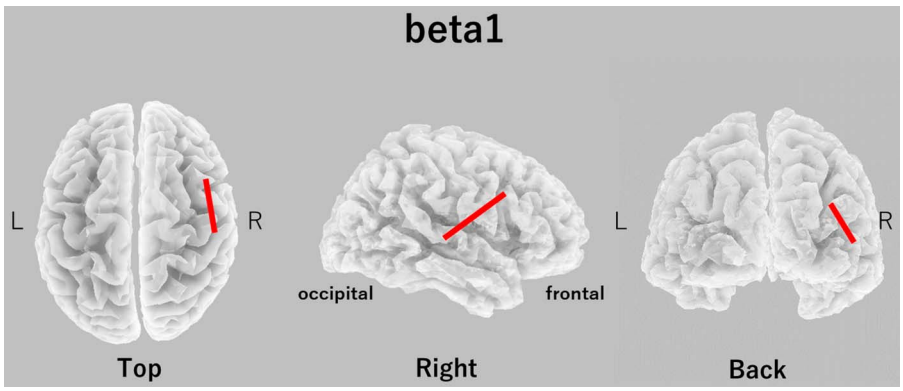

Figure 5. Exact low resolution electromagnetic tomography wire diagram indicating FC that showed significant correlations with current pain intensity. The red line indicates the β1 band (12.5–18.0 Hz) FC that was significantly positively correlated with current pain intensity. The line connects the right dorsolateral prefrontal cortex and the right auditory cortex. FC, functional connectivity.

These findings collectively reinforce the pivotal function of the PFC in pain management.

The significant increase in β1 band FC between the rDLPFC and right auditory cortex observed with higher pain intensity can be interpreted in the context of pain modulation. β1 band activity is associated with sensory information processing and cognitive function.[9] The rDLPFC is crucial for pain modulation, affecting pain perception and tolerance through interhemispheric connectivity.[55] Studies in patients with CLBP have demonstrated associations between the rDLPFC, depression, and pain levels.[19] Music-induced analgesia in fibromyalgia patients, involving increased FC between the left angular gyrus and rDLPFC, further highlights the role of rDLPFC in pain management.[17] Similarly, increased connectivity between the left motor cortex and PFC has been linked to dysfunction in the descending pain regulatory system in fibromyalgia.[10] These findings suggest that enhanced β1 band FC between the rDLPFC and the right auditory cortex may represent an adaptive mechanism to manage or alleviate increased pain intensity.

Our results showing no significant difference in CSD between CLBP patients and HCs are consistent with a previous study using the same open EEG data.[56] A systematic review reported increased α and θ power in patients with chronic pain,[49] associated with the thalamocortical dysrhythmia model of neuropsychiatric disorders.[32,57] In this model, abnormal nociceptive input triggers θ bursts in the thalamus, which are transmitted to the cortex, leading to disinhibition of nearby regions and abnormal γ oscillations, ultimately contributing to persistent pain. However, the thalamocortical dysrhythmia model is also observed in neurogenic pain, tinnitus, Parkinson disease, or depression, and the evidence supporting a causal relationship with chronic pain is still limited, and similar points have been made in previous study.[56] In addition, previous research has found no relationship between brain activity and FC measurements and clinical parameters, including drug therapy. However, in our study, we found a localization with CSD and FC value that significantly correlated with the pain index. The reasons for the different results on similar data include the following. First, the characteristics of the participants were controlled by including only patients with CLBP. Although a systematic review reported increased α and θ power in patients with chronic pain, brain activity may be specific to the region of pain.[49] In this study, our analysis was limited to CLBP patients, and brain activity related to CLBP pathophysiology may have been observed. Second, we used eLORETA to analyze power and FC, which accurately locates test point sources, even with low spatial resolution. Comparisons with other linear inverse solutions showed eLORETA's improved localization in the presence of noise and multiple sources.[46] Therefore, different results may stem from signal source estimation methods. In addition, the FC analysis was limited to 24 ROIs, allowing the extraction of characteristic FCs between relatively distant localizations. Other EEG features associated with chronic pain include higher spectral power in the 2 to 25 Hz frequency range and a shift of the dominant peak to lower frequencies in patients with chronic neuropathic pain.[53] In this study, we did not perform peak frequency analysis, and we analyzed CSDs in frequency bands, so we did not observe the slowed dominant frequency seen in previous studies. In addition, regarding spectral power, it is possible that the CSD analysis used in this study, which focuses on spatial distribution, did not show clear local changes in that distribution. As future analysis, it is necessary to compare the dominant frequencies between the CLBP and HC groups and to calculate channel-based spectral power and compare it between the 2 groups, to consider the differences from previous studies.

Although EEG can be used as a modality to assess treatment efficacy and determine prognosis in chronic pain, and it is expected to help predict treatment response,[51] few studies have analyzed functional coupling in chronic pain using EEG, with no control obtained. This study provides new insights into EEG-extracted FC in CLBP patients, leveraging EEG's superior temporal resolution compared with MRI to capture brain activity dynamics in more detail. These findings may support integrating EEG into clinical practice for improved treatment and care.

This study has certain limitations. First, as a cross-sectional study, it cannot establish causal relationships. Therefore, further longitudinal and interventional research is required to clarify causality. Second, the participants were recruited solely in Munich, leading to small sample sizes and potential representativeness issues. Because the open dataset used in this study did not include detailed demographic data on educational levels and comorbidities, caution is required when interpreting the results. Future studies should include a larger and more diverse sample of patients with CLBP from various cultural backgrounds and collect more diverse demographic data. Third, some CLBP participants exhibited depressive symptoms, potentially influencing EEG measurements. However, no correlations were found between depressive symptoms and CSD/FC, nor between anxiety and CSD/FC. Finally, although individuals on benzodiazepines were excluded, other medications were not considered and may have influenced EEG results. For practical reasons and because of the open data set, it was difficult to control for medications, such as antidepressants. Future studies should stratify participants based on antidepressant or analgesic use or control for medication effects, to reduce confounding and improve generalizability.

In conclusion, this study reveals key neurophysiological differences in pain perception and assessment between CLBP patients and HCs. Notably, we found altered FC in specific brain regions and frequencies, particularly a reduction in the β3 band, and changes in prefrontal θ and δ activities correlating with pain intensity. These findings highlight potential targets for modulating pain in CLBP through specific brain pathways, suggesting new directions for therapeutic interventions.

Disclosures

The authors have no conflicts of interest to declare.

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