

The Analysis of Spontaneous Electroencephalogram (EEG) in Chronic Low Back Pain Patients Compared with Healthy Subjects

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Abstract

Background: Quantitative electroencephalography (EEG) power spectra analysis was applied to assess brain activation during chronic pain. Although many studies have shown that there are some common characteristics among individuals suffering from various pain syndromes, the data remains inconclusive. The present study aimed to assess chronic low back pain (CLBP) based on functional brain changes with EEG in CLBP patients compared with healthy controls.

Methods: Multichannel electroencephalogram data were recorded from 30 subjects with CLBP and 30 healthy controls under eye-open resting state conditions and active lumbar forward flexion, and their cortical oscillations were compared using electrode-level analysis. Data were analyzed using a pair t-test.

Results: A total of 30 patients (19 men and 11 women in the case group (mean [SD] age, 35.23 [5.93] years) with 30 age and sex-match healthy controls participated in the study. A paired t-test was applied to identify whether there was any difference in the absolute and relative power of frequency spectra between CLBP patients and healthy controls. The results showed a significant increase in alpha relative power in CLBP patients compared with healthy controls in an open-eye resting state ($P < 0.050$) and active lumbar forward flexion ($P < 0.050$).

Conclusion: The enhanced alpha relative power in CLBP patients could be relevant to attenuating sensory information gating and excessive integration of pain-related information. Increased power at the EEG seems to be one of the clinical characteristics of individuals with CLBP. EEG can be a simple and objective tool for studying the mechanisms involved in chronic pain and identifying specific characteristics of CLBP patients.

Keywords: Chronic Low Back Pain, Electroencephalography, EEG, Pain, Alpha Oscillation

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Introduction

Traditionally, scientists believed pain is a peripheral phenomenon and a reflexive response to tissue injury, with the central nervous system having no role in pain processing (1). In 1965, Melzack and Wall proposed the

gate theory of pain perception. This model described nociceptive or painful input as being modulated by gating mechanisms in the spinal cord on its way to the brain (2). Later research points toward an increasingly important

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↑What is “already known” in this topic:

Objectively and accurately assessing pain in clinical settings is challenging. Previous studies showed altered electroencephalogram (EEG) frequency power in chronic low back pain (CLBP) patients. Most studies assess brain function in resting state conditions. This study aimed at assessing CLBP in resting state eye open condition and active lumbar forward flexion.

→What this article adds:

Based on our study results, alpha relative power in eye open resting state and active lumbar flexion was increased in CLBP patients compared with healthy controls. Analysis of EEG frequency power is a simple and objective tool for identifying specific characteristics of CLBP patients.

role for supraspinal mechanisms in pain perception. The neuromatrix of pain theory shifted pain processing from the peripheral to the central nervous system (2-4). The current understanding of pain processing involves multiple neurophysiological mechanisms of integration and modulation involving the complex interplay among peripheral tissues, the spinal cord, and the brain (4, 5). This interplay appears to be of particular importance in chronic low back pain (CLBP) (6). CLBP is the most common and important clinical, social, economic, and public health problem of all chronic pain disorders. Despite the high incidence and prevalence of CLBP, little is known about the precise causes (7). Peripheral factors like trauma or structural deficits should not be neglected for their role in LBP. However, those peripheral factors alone are insufficient to explain the recurrence or chronification of LBP, as the pain often persists long after peripheral causes or noxious input have resolved (4). Hence, it is clear that CLBP is a complex interaction between peripheral input and central changes. MRI and fMRI studies have shown widespread structural and functional brain changes in CLBP groups compared with healthy, pain-free controls (4, 7). An interesting mechanism in the human central nervous system is its capacity for plasticity. Although neuroplasticity has various positive (adaptive) characteristics, it can be maladaptive in chronic pain syndromes such as CLBP. Due to these maladaptive neuroplastic changes, analyzing brain properties may be of great value (8, 9). While there is growing knowledge on the peripheral and spinal neuronal mechanism of pain chronification processes, there is only a limited understanding of central nervous changes in CLBP (10). Although numerous methods are available for investigating the central mechanisms underlying chronic pain, Electroencephalography (EEG) is particularly useful due to its non-invasive nature and ability to provide reliable and pertinent information about brain function. EEG is a safe, cost-effective, and easy methodology, which makes it an appropriate tool for use in clinical practice (11, 12). The most frequently analyzed EEG parameter is the power spectra of continuous EEG recordings by transforming them from the time domain to the frequency domain for analysis. Different EEG frequency bands such as delta (1–3.8 Hz), theta (4.0–7.8 Hz), alpha (8.0–13.8 Hz), beta (14.0–34.8 Hz), and gamma (35–50 Hz) have been linked to pain perception even though there has not been a clear consensus determining which rhythmic band has the most reliable correlation with CLBP (5, 13-17).

Compared to other frequency domains, alpha-band oscillations have been extensively studied in the context of chronic pain (18). Gamma waves generated deep in the brain, are challenging to record with scalp EEG, and data on pain-related beta EEG activity are limited (13, 19). Regarding spontaneous brain activity, studies that collected ongoing EEG data and analyzed power spectra (or power density) have reported altered resting-state cortical oscillations in chronic pain patients (10, 16, 20). The increased resting-state alpha oscillation in patients with multiple sclerosis, the enhanced alpha oscillation in patients with neuropathic pain, and the positive correlation be-

tween pain duration and alpha oscillation power among patients with CLBP pain were reported in related studies (13). However, some studies also reported a decrease in alpha oscillation power among patients with CLBP and patients with chronic pain after spinal cord injury (21, 22). The alterations of cortical oscillations in other frequency bands were also reported for chronic pain patients. Fibromyalgia patients showed general increases in theta oscillation power at the left dorsolateral prefrontal (23, 24). Among CLBP patients, a positive association between ongoing pain intensity and prefrontal beta and gamma oscillations has been reported (13, 23, 24).

Prior studies have examined the EEG data obtained in the eye-open condition in the resting state to determine appropriate baseline readings for protocol development (5, 10, 25, 26). To the best of our knowledge, we did not find any study that examined the EEG spectrum of CLBP patients during a functional movement. The forward flexion movement is commonly used in clinical evaluations of spinal function, and it can induce changes in the activity of the cortical regions involved in processing pain and sensory information from the back. These changes in cortical activity can be captured by EEG recordings and analyzed to provide insights into the neural mechanisms underlying LBP.

Our study hypothesized that the forward flexion movement could change the power of the EEG signals in the alpha frequency band, which is associated with attention and cognitive processing, and in the gamma band activity, which is thought to be involved in sensory processing and pain perception (27-29). Therefore, this study aimed to identify abnormalities in EEG oscillations during the eyes-open resting state condition as a baseline and active lumbar forward flexion movement as a functional movement in CLBP patients compared to healthy controls. Additionally, the study aimed to assess differences in EEG power alternation based on the duration of chronic pain and pain severity.

Methods

Study design

We conducted a case-control, observational study at the Iran University of Medical Sciences, Tehran, Iran. The study was performed between July 2021 and February 2022. All participants were informed about the aim and scope of the study, and all signed a reviewed and approved consent form. The procedures were conducted following the ethical standards of the Declaration of Helsinki, and participation was voluntary. The ethical committee of the Iran University of Medical Sciences approved this study (IR.IUMS.REC.1398.1041). All personal information was kept strictly confidential and anonymous. None of the participants received any rewards for participation.

The sample size was calculated using G*Power software 3.1.9.4 (Düsseldorf, Germany) based on a pilot study (effect size = 0.37, α = 0.05, power = 0.80) and accounted for t-tests, resulting in a total sample size of 60 individuals.

Study population

Sixty individuals participated in our study, which included 30 (11 women and 19 men) CLBP patients (case group) from Iran University of Medical Sciences hospitals and clinics, and the same number of healthy subjects, age and sex-matched (control group) via colorful posters and flyers were placed in the university community and surrounding neighborhood area. Participants were eligible for the CLBP group if they had: 1) age between 18-50; 2) permanent or intermittent low back pain (LBP) for three months or more. Inclusion criteria for the control group were: 1) age between 18-50; 2) have not experienced LBP in the last three years. The most important exclusion criteria were: non-musculoskeletal origins low back pain; spine surgery in the past three years; prior spine or limb fractures; apparent postural deformities (i.e., kyphosis and scoliosis); history of having a rheumatoid disease, fibromyalgia, neuropathy, progressive neurological disease, malignancy, systemic infection, headache, dizziness, nausea, epilepsy, migraines, and mental disorders. On the day of the experiment, before recording EEG signals, pain intensity was measured using a Numeric Rating Scale (NRS). The participant in the case group should have pain during rest or lumbar active range of motion between 3-10/10 based on the NRS on the day of the experiment. Table 1 provides the demographic and baseline characteristics data of participants.

EEG recording

We used a 64-channel amplifier (EB Neuro, Italy) to record continuous EEG. The system was set up with a bandwidth of 0.00-0.70 Hz, band-pass filtered between 0.05 and 60 Hz, and a sampling rate of 512 Hz. The cap with Ag-AgCl electrodes was positioned according to the international 10-20 system. The impedance of all electrodes was kept below 15 kOhm by cleaning the skin with alcohol and injecting a gel between the electrode and the skin. Reference and ground electrodes were placed on the mastoid processes (A1 and A2) and Fpz region. The 19 electrodes were placed at Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, Oz, O2. A pair of electrodes were placed above and below the right eye and another pair on the outer canthi of both eyes to record vertical and horizontal electrooculogram (30). Blinking and eye movement artifacts were controlled with the electrooculogram and the O1 and O2 electrodes. Measurements were conducted between 9 a.m. and 12 p.m. to mitigate the influence of sleepiness. All participants had to abstain from caffeine on the day of the test. EEG assessment took place in a sound and electromagnetically attenuated chamber. Within an experimental session, spontaneous EEG was recorded under two conditions: three minutes of eyes-open resting state and 20 seconds of lumbar forward flexion movement. For the eyes open condition, participants sat comfortably in a chair and were instructed to avoid excessive body and eye movements, gaze at a fixed point on the wall, and relax their minds (Figure 1). The EEG recording lasted three minutes.

For the active lumbar forward flexion movement, participants were standing in a relaxed position with their feet



Figure 1. Participants resting state position with eyes open

shoulder-width apart and their hands crossed on their shoulders. In response to a counting synchronized auditory device, participants were forward flexed. At first, participants stood in the starting position for 5 seconds (counting from 1 to 5). Then they forward flexed in 5 seconds (counting from 1 to 5). After that, they remained in the forward flexion position for 5 seconds (counting from 1 to 5). Then they returned to the starting position in 5 seconds (counting from 1 to 5). The whole test lasted 20 seconds. All the cables were fixed on the patient's back to control movement artifacts (Figure 2).

EEG data processing

Raw EEG data, including reference channels and artifacts, were processed offline using EEGLAB, an open-source toolbox running under the MATLAB environment (The MathWorks Inc., Natick, Massachusetts, United States). All EEG signals were visually examined for the identification of corrupted channels and artifacts. Independent component analysis (ICA) was performed to remove eye blinking, eye movement, muscle activity, heartbeats, and channel noise. All ICA components were visually inspected and components were manually selected for rejection. These initial pre-processing steps were carried out on the full EEG dataset before unblinding of the study. Then, EEG data were epoched into 1-second windows. Each epoch was visually inspected in the temporal domain and bad epochs contaminated with muscle artifacts, eye blinks and movements were corrected using ICA. After preprocessing and selection, the remaining artifact-free, 1 s epochs from all 60 subjects were selected for further analyses. After the reconstruction of the data, a common average reference (CAR) filter was applied to remove common activity across channels. For power spectral density estimates, the segmented EEG epochs were trans-



Figure 2. Test position for active lumbar forward flexion. (a) starting position. (b) active lumbar forward flexion

formed from the time domain to the frequency domain, using fast Fourier transformation (FFT), yielding power spectra. A fast Fourier transform (FFT) was computed with a 1-second Hamming window and the window was shifted with 50% overlap (Welch method). Then, the absolute EEG power spectra estimate was obtained by taking the average magnitude of Fourier coefficients of each trial and five frequency domains were extracted in delta (1–3.9 Hz), theta (4.0–7.9 Hz), alpha (8.0–13.9 Hz), beta (14.0–34.9 Hz), and gamma (35–50). The relative power of each frequency domain was computed by dividing the absolute power at each frequency by the total power across all frequencies. The absolute and relative (percentage of total EEG power) EEG power spectra density was measured at the following frequency domains delta, theta, alpha, beta, and gamma at prefrontal, frontal, parietal, temporal, and occipital electrode locations (the electrode locations for each brain region are summarized in Table 2). The same processing was used for resting-state and forward flexion EEG signals. Further, values for each electrode location were also statistically analyzed to yield spatial information on brain activity.

Statistical Analysis

All data were analyzed using Stata, version 14.2 (StataCorp LLC; College Station, TX, USA), and SPSS (version 22). Continuous and categorical baseline variables were summarized using mean (SD) and frequency (percentages) to determine descriptive statistics. The demographic characteristics of subjects were compared between groups with an independent t-test (Table 2). Normality was evaluated using the Kolmogorov-Smirnov test and by examining histograms. After the normality of the data distribution was confirmed for all variables, we used parametric statistical tests to analyze the data. A paired t-

test was applied to identify whether there was any difference in the absolute and relative power of frequency spectra between CLBP patients and healthy controls. To explore the relationship between the absolute and relative power of frequency spectra and the duration of chronic pain in patients with CLBP, Pearson correlation coefficients (r) were calculated. The Pearson correlation coefficients were

classified according to Hopkins' extension of Cohen's guidelines (0.00–0.09 nonexistent, 0.10–0.29 small, 0.30–0.49 medium, 0.50–0.69 large, 0.70–0.89 very large, 0.90–0.99 nearly perfect, and 1.00 perfect) (31). Statistical significance was indicated at $P \leq 0.05$ (2-sided), and the confidence interval was set at 95%. The statistician was blind to group allocation.

Results

A total of 30 people with CLBP (mean [SD] age, 35.23 [5.93] years; 11 [37%] women and 19 [63%] men) and 30 healthy controls (mean [SD] age, 35.23 [5.93] years; 11 [37%] women and 19 [63%] men) were included in this present study. The demographic and baseline characteristics of these participants are presented in Table 1. As shown in Table 1, the two groups had similar demographic characteristics at baseline.

The absolute power of the eye-open resting-state condition

The results of the paired t-test showed significant differences in alpha absolute power in temporal electrodes; beta absolute power in prefrontal, frontal, central, parietal, and temporal electrodes; and gamma absolute power in parietal, temporal, and occipital electrodes under eye-open resting state conditions between CLBP patients and healthy controls. The spectral absolute power was significantly decreased in CLBP patients compared with healthy

Table 1. Demographic and baseline characteristics of the CLBP and control subjects

Characteristic	Case group (n=30)	Control group (n=30)
Sex, No. (%)	11 (37%)	11 (37%)
Female		
Age, year, mean (SD)	5.93 (35.23)	5.93 (35.23)
Body height, cm, mean (SD)	(9.30) 173.02	(10.50) 174.03
Body weight, kg, mean (SD)	(8.90) 84.00	(11.13) 85.50
Education, year, mean (SD)	15.60 (1.87)	15.26 (2.12)
Pain duration, No. (%)	3 (9)	4 (11)
3-12 month		
12-60 month	19 (69)	19 (69)
>60 month	8 (22)	7 (20)

Table 2. Definitions of electrode-level

Brain region	Electrode-level (electrodes)
Prefrontal	Fp1, Fp2
Frontal	F7, F3, Fz, F4, F8
Central	C3, Cz, C4
Parietal	P3, Pz, P4
Temporal	T3, T4, T5, T6
Occipital	O1, Oz, O2

controls in these regions.

The relative power of the eye-open resting-state condition

The results of the paired t-test showed significant differences in theta relative power in prefrontal, frontal, parietal, and occipital electrodes; alpha relative power in prefrontal, frontal, central, parietal, and occipital electrodes; beta relative power in prefrontal electrodes; and gamma relative power in prefrontal, parietal, and occipital electrodes under eye-open resting state conditions between LBP patients and healthy controls. The spectral relative power was significantly increased in theta and alpha frequencies and decreased in beta and gamma frequencies in CLBP patients compared with healthy controls in these regions.

The absolute power of active lumbar forward flexion

The results of the paired t-test showed significant differences in alpha absolute power in parietal electrodes; beta absolute power in parietal, temporal, and occipital electrodes; and gamma absolute power in parietal, temporal, and occipital electrodes under active lumbar forward flex-

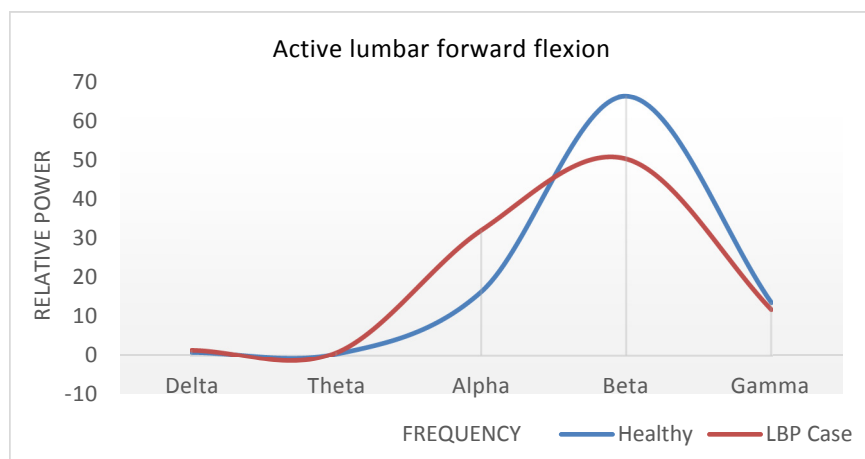
ion between CLBP patients and healthy controls. The spectral absolute power was significantly decreased in CLBP patients compared with healthy controls in these regions.

The relative power of active lumbar forward flexion

Figure 3 shows the mean EEG power spectral densities in active lumbar forward flexion. The results of the paired t-test showed significant differences in alpha relative power in all electrode regions, beta relative power in all electrode regions, and gamma relative power in prefrontal, frontal, central, and parietal electrodes under active lumbar forward flexion between CLBP patients and healthy controls. The spectral relative power was significantly increased in alpha frequency and decreased in beta and gamma frequency in CLBP patients compared with healthy controls in these regions.

The sLORETA cortical alpha density for resting state and active lumbar forward flexion for CLBP patients and healthy controls are shown in Figure 4.

Table 3 shows the descriptive and the results of the paired t-test for the relative power of alpha frequency in

**Figure 3.** Group-average EEG power densities in active lumbar forward flexion

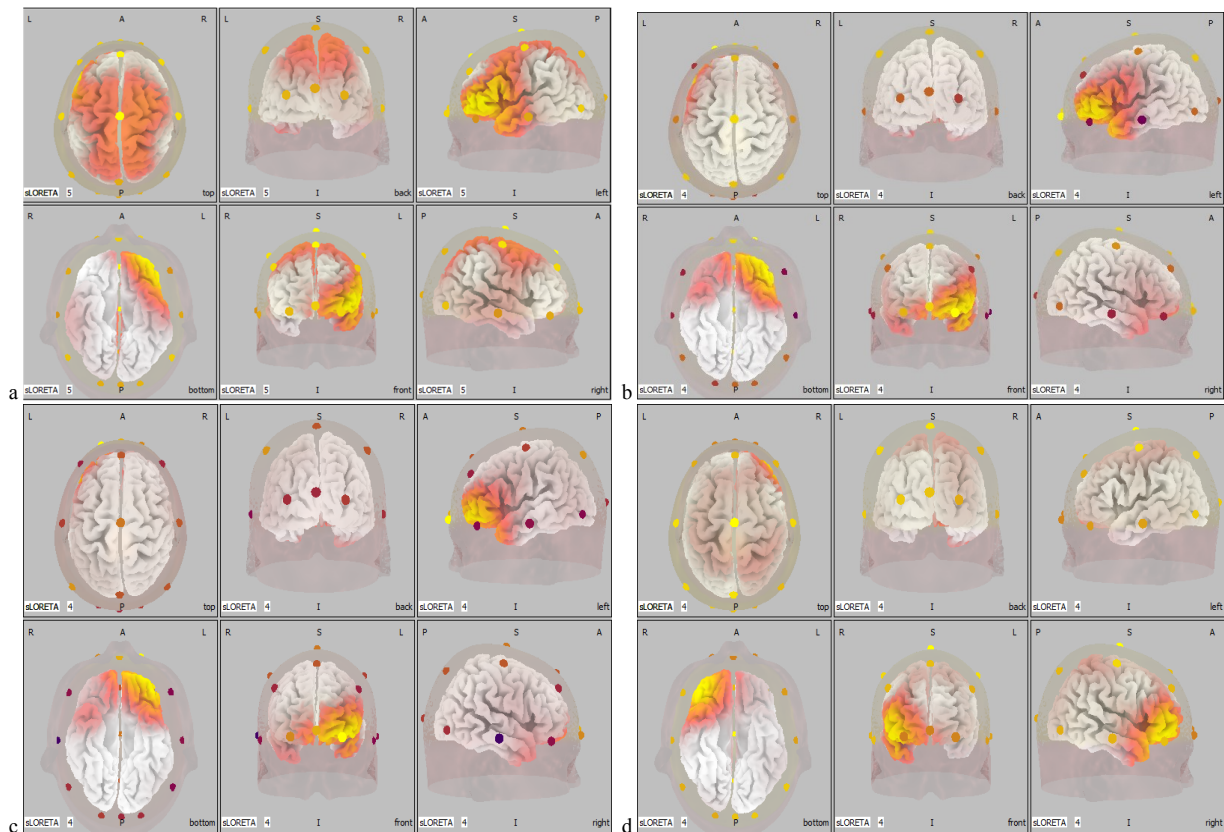


Figure 4. Resting state and active lumbar forward flexion movement EEG alpha relative power, sLORETA cortical current density. (a) alpha relative power in resting state in healthy controls (b) alpha relative power in resting state in CLBP patients (c) alpha relative power in forward flexion in healthy controls (d) alpha relative power in forward flexion in CLBP patients.

Table 3. The pair t-test comparing the relative alpha power (%) between CLBP patients and healthy controls

	Case group (n=30) mean (SD)	Control group (n=30) mean (SD)	t statistics	P value
Relative power of open-eye resting state				
Prefrontal	19.77 (11.87)	10.17 (5.76)	3.79	0.<001*
Frontal	12.79 (12.12)	7.01 (3.86)	2.65	0.013*
Central	14.99 (14.18)	10.48 (7.46)	1.60	0.121
Parietal	212.19 (291.25)	9.38 (8.42)	3.71	0.008*
Temporal	160.55 (241.48)	5.98 (2.46)	3.50	0.004*
Occipital	13.14 (12.50)	7.36 (6.45)	2.66	0.013*
Relative power of active lumbar forward flexion				
Prefrontal	34.70 (18.80)	21.68 (9.28)	3.35	0.002*
Frontal	34.40 (25.74)	14.64 (7.59)	4.07	<0.001*
Central	35.41 (26.31)	18.06 (8.98)	3.52	0.001*
Parietal	35.38 (24.25)	18.42 (10.30)	4.02	<0.001*
Temporal	33.84 (25.93)	12.57 (5.10)	4.67	<0.001*
Occipital	33.99 (26.57)	15.66 (9.08)	4.12	<0.001*

Statistical significance was $P \leq 0.05$

*Significant differences

an open-eye restingstate and active lumbar forward flexion.

Correlation between spectral power and subjective pain rating

The correlations between the spectral absolute and relative powers in the eye open resting state condition and active lumbar forward flexion and the subjective pain intensity (NRS) showed no linear relationship in any region in alpha and gamma frequency ($P > 0.05$). There was no linear relationship between spectral powers in alpha and

gamma frequency in all regions and the duration of chronic low back pain ($P > 0.05$).

Discussion

In this study, we recorded EEG data from CLBP patients and healthy controls during a resting state with eyes open and active lumbar forward flexion, and their spectral power of EEG frequency, as an objective neurophysiological parameter, was compared based on electrode level. Our findings showed increased alpha relative power in CLBP patients compared with healthy controls in an open-

eye resting state and active lumbar forward flexion. The study results showed no correlations between these frequency alternations and the duration of chronic LBP or the severity of pain. These alterations demonstrated the frequency-dependent hyperactivation of EEG oscillations among the CLBP patients, which could implicate hypersensitive attention and somatosensory amplification in these patients.

We mainly focused on the relative power of the alpha frequency for feature extraction within the frequency band. Compared with other frequency domains, alpha-band oscillations are related to the amount of experimentally induced pain in the somatosensory cortex (32-35). It is noted that gamma oscillation features have also been reported to be related to pain perception. However, the signal-to-noise ratio of gamma oscillation is poor since higher frequency data are typically readily contaminated by plenty of nonneural artifacts. Additionally, due to the deep generation of gamma waves in the brain, EEG recording is challenging (36, 37).

As described by Berger in the 1920s, alpha rhythmic activity is the strongest electrophysiological signal measured from the surface of the awake human brain. Several studies have found the power of frequency, a primary measure of alpha activity, to be a reliable indicator, showing high intra-individual stability. Alpha oscillations reflect inhibitory and excitatory mechanisms in the thalamocortical networks involved in attention, perception, and consciousness. Alpha power has been shown to increase in response to sensory stimuli and cognitive demands, is modulated by various factors such as attention and mental effort, and can be dysfunctional in chronic pain. In chronic pain, increased alpha power has been associated with reduced sensory processing and attentional resources, as well as, enhanced pain perception. Considering the functional role of alpha oscillations in local inhibition and sensory gating, the increased alpha oscillations in CLBP patients could be reflecting attenuated sensory information gating and excessive integration of pain-related information, thus appearing as somatosensory amplification in these patients. Additionally, the general role of alpha rhythms in inhibiting different processes within the brain can be used as a framework to interpret the results (4, 5, 15, 26-30). Increased alpha power may be potentially reflecting alterations in neural processing and connectivity associated with chronic pain (38). However, the exact mechanisms underlying this phenomenon are not fully understood. One possibility is that increased alpha power reflects a compensatory mechanism in response to ongoing pain and associated cognitive demands. Alternatively, it may reflect a maladaptive response that contributes to the maintenance of chronic pain by reducing the ability of the brain to attend to other stimuli or engage in other cognitive tasks (12).

It should be noted that some studies have reported mixed or conflicting results regarding alpha power in CLBP patients. For example, a study by Grooms et al. (2017) found no significant differences in alpha power between CLBP patients and healthy controls during a cognitive task, although there was a trend towards in-

creased alpha power in the resting state (39). Similarly, a study by Tu et al. (2018) reported reduced alpha power in the left parietal cortex of CLBP patients during a motor task, suggesting that alpha power changes may be specific to certain brain regions or cognitive processes (33).

The observed increased alpha oscillation among CLBP patients was consistent with findings from many chronic pain studies. For example, among patients with multiple sclerosis, Kim et al. observed an increase in alpha oscillation power within several nodes of the salience network and ascending nociceptive pathway, which was interpreted as a result of overflowing sensory information due to reduced sensory gating (34). The increased alpha oscillation has also been identified among migraine patients, suggesting an over-integration of sensory information in these patients (40). Also, the increase in alpha oscillation in chronic pain patients is in line with the findings from animal models of neuropathic pain, which exhibited increased cortical oscillation within a broad frequency band (3–30 Hz) (41, 42).

In this study, we evaluate the relationship between the alpha and gamma absolute and relative power and subjective reports of experienced pain in people with CLBP. The results of the correlation analysis showed a very weak and negligible linear correlation between subjective pain and EEG frequency power.

Several limitations should be noted in the present study. First, the study used a cross-sectional design, which means that it was conducted at a single point in time. Therefore, it is difficult to establish a causal relationship between the neural activity differences observed and the experience of CLBP. Second, the study used a limited number of electrodes, which may have resulted in an incomplete picture of neural activity in the brain. Third, the study sample was relatively homogeneous in terms of age and gender, which may limit the generalizability of the findings to other populations. Fourth, we had a greater percentage of male participants. In the present study, we did not take gender balance as an influencing factor, considering that the previous study did not observe any significant fixed effect from gender differences in EEG features of pain. Pearson correlation analysis assessed the linear relationship between continuous variables. It may not effectively capture the non-linear or complex relationship that exists between pain and EEG variables. Consequently, we might have overlooked important associations that do not adhere to a linear pattern. Future studies might be considered to gain a more comprehensive understanding of the intricate dynamic among the variables.

Conclusion

In this study, the differences in the absolute and relative power of EEG frequency spectra between CLBP patients and healthy controls were investigated. This study provided evidence for enhancing alpha relative power in CLBP patients compared with healthy controls, which could be functionally relevant to the sustained attention to bodily sensations and hypervigilance of these patients. These results suggest that individuals with CLBP may have altered neural activity compared to healthy individuals,

which may contribute to their experience of pain.

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Ethics approval and consent to participate

This study was approved by the ethical committee of the Iran University of Medical Sciences (IUMS) approved this study (IR.IUMS.REC.1398.1041), and all participants gave their informed consent before participation.

Author contributions

Access to data and data analysis: Ms Bemani and Dr Sarrafzadeh had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; Concept and design: Bemani, Sarrafzadeh, Talebian; Acquisition, analysis, or interpretation of data: Bemani, Salehi; Drafting of the manuscript: Bemani, Noorizadeh, Zarei; Critical revision of the manuscript for important intellectual content: Sarrafzadeh, Salehi; Statistical analysis: Bemani, Salehi, Talebian; Administrative, technical, or material support: All authors; Supervision: Sarrafzadeh, Noorizadeh.

Conflict of Interests

The authors declare that they have no competing interests.

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