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Research Paper

Differential Cortical Oscillatory Patterns in Amputees With and Without Phantom Limb Pain

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ABSTRACT

Introduction: Phantom limb pain (PLP) as neuropathic pain affects the life of amputees. It is believed an efficient PLP treatment should consider the underlying neurological mechanisms. Hereby, we investigated brain activity in PLP and its relationships to the psychological and cognitive dimensions of chronic pain. We investigate differences in resting brain activities between amputees with and without pain. We hypothesize significant differences in the motor cortex and parietal cortex activity that are related to pain perception. Also, we hypothesize two groups have significant differences in cognitive and psychological components.

Methods: Behavioral assessment (psychological status, life satisfaction, and pain level) and EEG signals of 19 amputees (12 without pain and 7 with pain) were recorded. Data were statistically compared between the two groups. Also, the association between behavioral and neurophysiological data was computed.

Results: The results showed a significant decrease in the pain group for the beta and gamma waves, as well as, for the theta and delta waves in the posterior temporal on both sides, during the eye-open condition. The eyes-closed condition showed that the delta waves were decreased on the right side of the cortex. Also, data showed a significant difference in the correlation of pain features with brain waves between the two groups.

Conclusion: Significant differences were mostly observed in regions related to pain perception rather than the motor cortex. This can be due to the learned strategies to deal with pain and the degree of pain. Results showed maladaptive cognitive processes had a relationship with brain wave activities. According to the result of brain wave activities, it seems that cognitive factors have a role in the experience of PLP rather than neuroplasticity through amputation.

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Highlights

- Differences found in the parietal and temporal regions of phantom limb pain's (PLP's) suggests cognition's role in the persistence of PLP.

- Decreased delta power at the posterior temporal cortex in PLP's could be the focus of treatments.

- Increased activity of the parietal cortex could be helpful in the treatment of PLP's.

Plain Language Summary

PLP is an annoying neurologic pain. A wide range of treatments have focused on this type of pain but couldn't be effective. Recently, researchers suggest BCI-based treatments for better treatment. For this type of treatment, we should know the neurological aspect of PLP. In most studies to investigate or treatment of neurological aspects of PLP, researchers induced pain experimentally or studied acute phantom limb pain. We believed for a better understanding of PLP, should investigate it in a natural and stabilized position. Therefore we studied brain activities in amputees with and without PLP in a resting state to find out differences. Trends in this field express the alpha band differences in the motor cortex. On the contrary, our results showed the most significant difference in high-frequency bandpasses such as beta and gamma. Also, in our study, it seems the parietal and temporal cortex that are related to pain perception is the more relevant to PLP. This study showed a psycho-cognitive aspect of pain such as pain exaggeration has a relation with PLP's brain wave activities. So, we can suggest rather than neuroplasticity through amputation, cognitive factors have a role in the experience of PLP.

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1. Introduction

People who lose their limbs to cancer, traffic accident, trauma, wars, etc., may experience a vivid sensation of a missing limb which is observed in about 80% of the amputees (Basha et al., 2017) and or feel pain in the missing limb called phantom limb pain (PLP) which is reported in approximately 70% of them (IASP, 2014). PLP is a neuropathic pain and usually shows its signs within the first week after amputation and presents for a month or even years afterward. PLP is observed as shooting, pricking, and burning feelings in the missing limb. In most cases, PLP is intermittent while the intensity and frequency of the attacks decrease with time (IASP, 2014). Women and upper limb amputees have been reported to be at higher risk of PLP (IASP, 2014).

Various internal and external factors may contribute to the modulation of PLP, including attention, distress, urination, manipulation of a stump, and prosthesis use. Nevertheless, it isn't clear what causes the phantom limb presentation and perception. Considering the complexity of PLP causation, the PLP does not respond to the formal treatment of the pain, such as medication, surgery, or psychological intervention (Basha et al., 2017). The mechanism of PLP is complex and involves the contribution of activities at peripheral, spinal, and supraspinal sites (IASP, 2014). Among these mechanisms, a possible explanation for the PLP refers to changes in the neural pathways and synapses caused by physical injury (Cohen et al., 1991; Elbert et al., 1997; Ramachandran & Rogers-Ramachandran, 2000; Ramachandran et al., 1992).

Another accepted view is that PLP is a result of a maladaptive neural reorganization of the cortex (Flor et al., 2006). Neural reorganization is generally viewed as a learning process for enabling the cortex to function better (Andoh et al., 2018); however maladaptive reorganization in several cortical regions resulting from injury (Latremoliere & Woolf, 2009; Lozano, 2011) and chronic pain (Andoh et al., 2018). In PLP as chronic pain, during the reorganization, cortical areas representing the amputated extremity are taken over by the neighbor zones in both primary somatosensory and motor cortex (Costigan et al., 2009; Flor et al., 2006; Ramachandran et al., 2010). For instance, after upper limb amputation, the amputee's upper limb area shrinks, and the adjacent mouth/facial regions expand mainly in the primary somatosensory and motor (M1) cortex (Bolognini et al., 2013). Along with the sensorimotor cortex, amputation-related plastic changes may also involve the posterior parietal cortex (PPC), a key area for corporeal awareness and pain perception (Bolognini et al., 2013).

Typically, after the limb amputation, the cortical maps of the removed limb in the postcentral gyrus (primary somatosensory cortex, S1) are engaged with the area around them (Birbaumer et al., 1997; Lotze et al., 2001; Montoya et al., 1998). In response to the long-lasting pain experience, the function of the S1 area of the amputated limb could be enhanced in terms of sensitivity to pain-related context according to the use and disuse rule (Ewer, 1960; Palmer, 2012). The functional magnetic resonance imaging (fMRI) findings indicated that pain and non-pain somatosensory pathways by the amputated side were functionally deficient (Hu et al., 2016) and studies have reported increased cortical gamma oscillations in neuropathic pain (Gross et al., 2007; Kim et al., 2015; Schulz et al., 2015) and also increased α activity in chronic pain patients during the resting state (Pinheiro et al., 2016). Some studies also showed the conscious experience of a phantom limb depends on a complex interplay between the somatosensory thalamus and cortical representations of the missing limb (Basha et al., 2017).

While most studies showed the somatosensory cortex engaged in PLP, a full understanding of PLP's neural basis has not yet been obtained (Aternali & Katz, 2019). The PLP as neuropathic pain is related to many changes in various brain regions, such as the parietal cortex (Benuzzi et al., 2008; Makin & Flor, 2020) and prefrontal (Bunk et al., 2018) that we still don't know enough about the alteration of brain-wave activities due to the PLP. On the other side, this is accepted that efficient treatment for PLP should spot the neural feature. Therefore, to provide beneficent treatment, we should know more about the alteration of brain activities in all areas involved by the PLP. Though electrocorticogram (ECoG)-based brain–computer interface (BCI) treatment is efficient (Gharabaghi et al., 2014), this is invasive and not easily accessible. Hence, accessible and non-invasive BCI treatment based on electroencephalography (EEG) is preferred. Therefore, the current study was designed to investigate the alteration pattern of brain waves at various regions in amputees with PLP as compared to people without PLP. We hypothesized that the main difference between the groups should be in an intentional process and a cognition-related deficit. Therefore, the main changes must be observed in the delta band as the indicator of the intentional process (Harmony et al., 1996), and beta and gamma bands as the main frequency indicators of binding information for the cognitive process (Rodriguez et al., 1999). Hence, changes in the activity of the somatosensory cortex at the α frequency band will not be the main indicator of the PLP.

The human hand has a powerful role in all aspects of life; therefore, upper limb amputation can affect a human's ability in social and occupational activity (Cordella et al., 2016; Shahsavari et al., 2020). These kinds of impairments cause psycho-cognitive deficiency and challenges (Shahsavari et al., 2020). If this condition is accompanied by chronic pain (in PLP condition), serious psychological and cognitive problems, such as depression and pain catastrophizing may appear (Andoh et al., 2018; Gracely et al., 2004; Seminowicz & Davis, 2006; Walker et al., 2014) and significantly affect the quality of life (Lewis & Kriukelyte, 2016). Some studies showed psychological and cognitive changes in PLP related to changes in brain circuits and activity (Elman et al., 2013; Rodriguez et al., 1999). Thereupon, this study expects to see differences in the psychological and cognitive dimensions of participants with and without PLP. Also assumed these differences can be associated with neural activity changes.

In this regard, the study was designed to identify a pattern of changes in brain waves associated with the psycho-cognitive aspect in amputation groups with and without PLP.

2. Materials and Methods

Participants and procedure

The participants in this experiment were selected from clients of the Iranian Red Crescent Society, referral Hazrat-E-Fatemeh hospital in Tehran, and veterans of the Iran-Iraq war. All clients were amputated with unilateral upper limb amputees after the age of 16 years; those with another type of amputation and a history of brain injury were excluded from the study. Eventually, 19 unilateral upper limb amputees (2 women, Mean±SD age=48±11.71) took part in the experiment. Twelve participants (2 women, Mean±SD age=47.92±11.70) did not have any pain at the time of study and the other seven subjects (all males) had pain. The group of participants without PLP before amputation had a mean age of 27.00±11.29 and the group with PLP before amputation had a mean age of 36.71±16.17 (Table 1). All participants were assessed during a 60- to 90-minute single session. The assessment included interviews about demographic information, the reason for amputation, PLP severity, psychological status, and electroencephalography acquisition. One participant from the pain-free group did not complete the questionnaire; therefore, only the answer to the interviewer's questions and EEG was acquired from her. The experiment was conducted following the Helsinki Declaration and Institute approval board code of IR.IUMS.REC.1368.4.

Behavioral assessment

The subject's psychological status (depression, anxiety, and stress), life satisfaction, and pain level were measured using the following questionnaires:

Depression, anxiety, and stress scale (DASS-21): DASS-21 included three self-report subscales to measure depression, anxiety, and stress. Each subscale has seven items for which participants should grade the intensity from 0 to 4 (0 never and 4 almost always) due to the past two weeks. In the Persian version of this scale, the internal consistency of the subscales is 0.92, 0.86, and 0.84, respectively (Mahmoodi-Aghdam et al., 2017).

Deiner's satisfaction with life scale (SWLS): Deiner's satisfaction with life scale (SWLS) was developed by Deiner et al in 1985. Participants should range each item from 1 (not satisfied) to 5 (very satisfied). The higher score represents more satisfaction with life. Khayer and Samani prepared the Persian version of this scale with Cronbach α 0.8. Also, other studies find proper validation for the Persian version of this scale (Tanhae et al., 2012).

The short form of the McGill pain questionnaire (SF-MPQ-2) has 22 items, and the participants should score each of them on a Likert scale of 0 to 10. Tanhae et al investigate the statistical feature of the Persian version of this questionnaire. Through factorial analysis, she found three factors of feeling pain, affective pain, and neuropathic pain for the Persian version of the questionnaire (Rahmati et al., 2016).

Pain catastrophizing scale (PCS): The pain catastrophizing scale (PCS) was developed by Sullivans et.al (1995) and evaluates the tendency to a catastrophic perception of painful situations. This scale includes 13 questions and the investigation of factorial structure in the Persian version showed two subscales. The subscales of PCS are exaggeration and rumination/hopelessness (Ranjbar et al., 2020). Previous studies in Farsi peaking population reported good psychometric properties of this measure (Cronbach α=0.88) (Ranjbar et al., 2020).

Electroencephalography (EEG) data recording and analysis

EEG data were obtained during the eyes-open and eyes-closed resting state, while the participant was in a quiet room and asked to stay calm without any movement or talk during the experiment. Each part was acquired separately for at least 150 s. Data were recorded with a 21-channel Mitsar 201 amplifier (Mitsar Co, Petersburg Russia) and WinEEG software, version 2.11 (Informer Technologies, Inc.) using a sampling frequency of 250 Hz. Electrodes were placed on the scalp using the 10-20 standard montage and referenced to the right ear while electrode impedances were kept below 5 kΩ.

EEG data were then preprocessed offline using the EEGLAB toolbox and in-house MATLAB scripts (The Math Works Inc., Natick, MA). Recordings were a high-pass filter 1 Hz and a low-pass filter of 40 Hz. Muscular movements and eye blinks were identified using independent components analysis (ICA) and bad components were marked using the adjusting plug in the EEG lab, checked, and removed by visual inspection. Lastly, bad channels were identified and get interpolated with the average activity of their neighboring electrodes. Subsequently, the EEG data were referenced to the average channel.

Statistical data analysis

Behavioral data

For demographic and psychological data, after the normality test with Kolmogorov Smirnov, a two-sample t-test was used to compare the behavioral data of the PLP group with the non-PLP group. The procedure was performed using SPSS software, version 25 to identify significant differences with P<0.05.

Electroencephalography (EEG) data

We used the Matlab statistical toolbox (The Math Works Inc., Natick, MA) to extract the power spectrum of each bandpass. After the normality test using Kolmogorov Smirnov, two-sample t-test comparisons were applied to determine significant differences (P<0.05 one-tailed) between the two groups. To reduce the risk of type I errors, the results were corrected for multiple comparison effects using the false discovery rate (FDR) by Benjamini and Hochberg (1995) algorithm and significant changes were reported with P<0.05 one-tailed, false discovery rate (FDR) corrected.

Association between EEG band powers and behavioral data

The relationship between two behavioral and neural data was investigated using the Matlab statistical toolbox. Subscales of the McGill pain questionnaire, PCS, and DASS were investigated separately. The scatter plot was drawn for each dimension in both groups and a significant relationship was observed with a P<0.05 one-tailed.

3. Results

Demographic results

At the pre-recording interview session, subjects were asked about their age at the time of amputation, their current age, and estimated years of living with an amputated limb. The comparison results of the two-sample t-test between the pain group and the pain-free group did not show any significant differences in these three variables (see Table 1).

Behavioral results

Mc-Gill pain questionnaire was used for grouping participants in the pain and pain-free groups (pain group: Mean±SD=75.86±32.88 pain-free group: Mean±SD=2.08±7.21). In the pain group, the pain catastrophizing scale was used to evaluate exaggeration and hopelessness. After grouping, a two-sample t-test comparison was used to identify significant differences in DASS and SWLS scores. No significant differences were observed in the three subscales of DASS and SWLS (Table 2).

Electroencephalography (EEG) results

In this study, EEG data were acquired during resting state in eyes open and eyes closed conditions. Significant differences were observed at both condition, nevertheless, the eyes open condition showed more significant differences than the eyes close condition. Results of eyes open condition showed absolute power of Gamma and Beta had significant differences in the right temporal (T4 (repectively gamma and beta: T=-1.075, P=0.074; T=-1.180, P=0.060), T6 (repectively gamma and beta: T=-1.465, P=0.050; T=-2.599, P=-1.299)), left posterior temporal (T5 (repectively gamma and beta: T=-1.504 P=0.05; T=-1.593 ,P=0.034)), parietal (P3 (repectively gamma and beta: T=-0.914, P=0.094; T=-1.083, P=0.063), Pz (repectively gamma and beta: T=-1.160, P=0.016; T=-1.412, P=0.041), P4 (just in beta bandpass: T=-0.975, P=0.065)), posterior frontal (C3 (repectively gamma and beta: T=-0.901, P=0.094; T=-1.051, P=0.063), CZ (repectively gamma andbeta: T=-1.048, P=0.075; T=-1.025, P=0.063), C4 (repectively gamma and beta: T=-1.248, P=0.074; T=-1.260, P=0.060)), and right midfrontal (F4 (repectively gamma and beta: T=-1.098, P=0.074; T=-1.010, P=0.063)) cortex. In addition, delta band activities also showed significant differences in the posterior temporal of both sides (T5 (T=-1.441, P=0.062), T6 (T=-1.460, P=0.062)) and Theta band activities had noticeable significant differences in some parts of the parietal and temporal cortex (C4: T=-2.303, P=-1.151, T4: T=-2.297, P=-1.148, T5: T=-3.239, P=-1.620, P3: T=-2.213, P=-1.106, PZ: T=-2.537, P=-1.268, T6: T=-2.599, P=-1.299). Intrestingly, α band activities did not show any significant differences (Figure 1).

Eyes closed condition had different results than eyes open. We did not see any significant differences in any bandpasses except delta and just in F4 (T=0.016, P=0.082), F8 (T=0.025, P=0.085), C4 (T=0.012, P=0.082), T5 (T=0.017, P=0.082), Pz (T=0.030, P=0.085), T6 (T=0.012, P=0.082), and O2 (T=0.031, P=0.085) channels (Figure 2).

For more details about significant channels and bandpasses could see supplementary documents.

Correlation between behavioral scores and significant electroencephalography (EEG) changes

A significant correlation between behavioral scores and significant changes in EEG wave powers in the eyes open condition was only observed in the pain group. These

Table 1. Group differences in terms of demographic data

Variables	Mean±SD		t Score	P	Effect Size
	Pain	Pain-free			
Age (y)	48.14±12.69	47.92±11.70	0.39	0.23	0.01
Age of amputation	36.71±16.17	27.00±11.29	1.46	0.16	0.33
Age vs Age of Amputation	11.43±10.29	19.17±12.07	-1.42	0.17	-0.33

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A significant difference is denoted by P<0.05. Pain and pain-free groups were identified based on the subject's answers to the Mc-Gill pain questionnaire.

Table 2. Group comparisons for psychological data

Variables	Mean±SD		t Score	P	Effect Size
	Pain	Pain-free			
McGill pain total score	75.9±32.9	2.1±7.2	7.6	0.000	0.84
McGill feeling subscale	30±13.8	1.4±4.9	6.6	0.000	0.81
McGill affect subscale	27.1±17.1	0.1±0.6	5.6	0.000	0.74
McGill neurotic subscaale	18.7±13.8	0.5±1.7	4.6	0.000	0.68
Depression	1.26±1.83	0.32±1.25	1.31	0.21	0.29
Anxiety	0.98±2.16	-0.08±1.09	1.20	0.26	0.30
Stress	1.37±1.23	0.71±1.58	0.93	0.34	0.23
SWLS	18.57±6.78	21.90±10.09	-0.77	0.45	-0.18

A significant difference is denoted by a P<0.05.

SWLS: Satisfaction with life scale.

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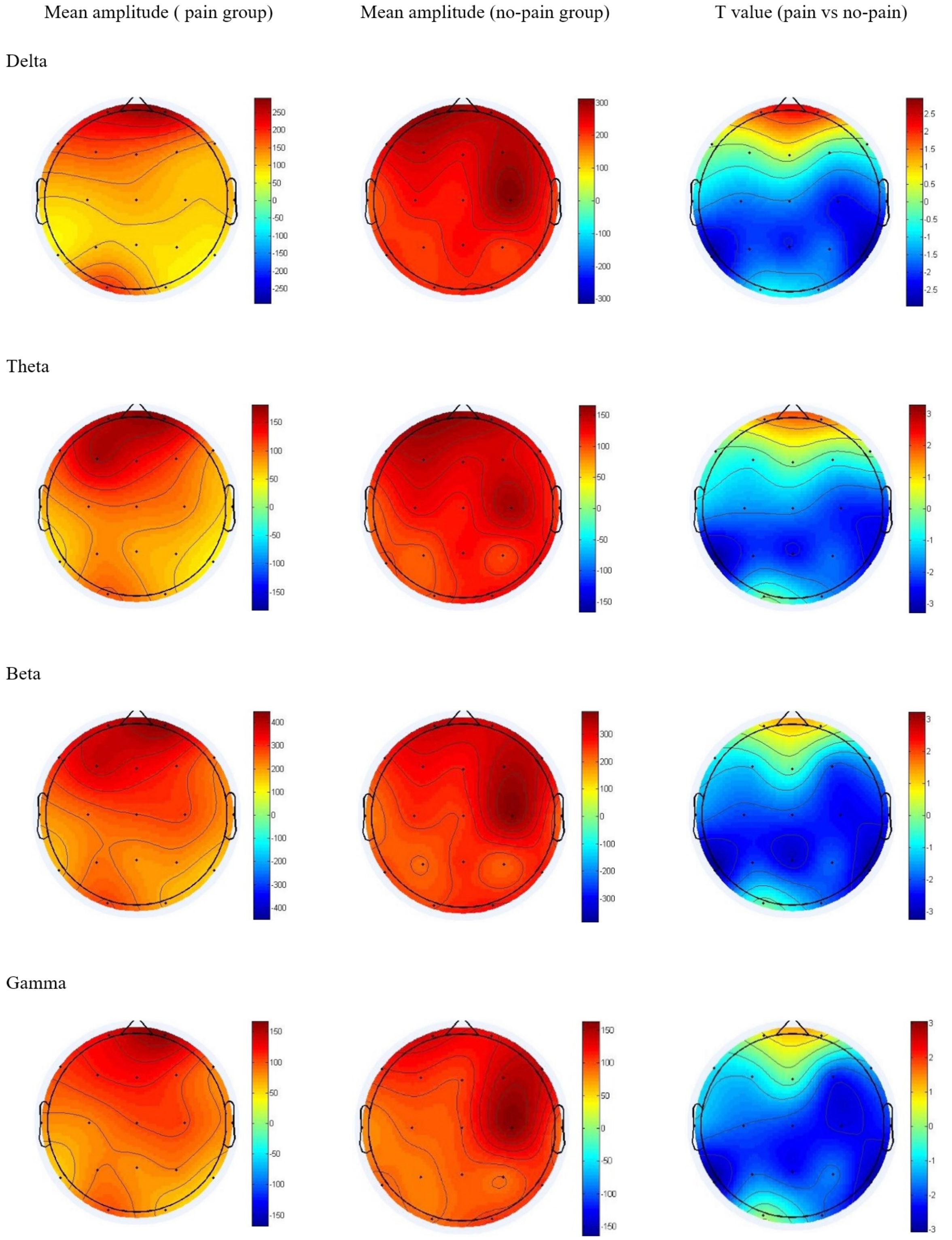
results include a positive correlation between the affect subscale of the McGill pain questionnaire and the power of theta band activities at Pz (r=0.7, P=0.079, P≤0.05 one-tailed) (Figure 3), feeling subscale of the McGill pain questionnaire on channel O2, beta bandpass (r=0.689, P=0.09, P≤0.05 one-tailed) (Figure 4), exaggeration subscale of pain catastrophizing questionnaire on channel F4, beta bandpass (r=0.699, P=0.080 one-tailed) (Figure 5) and gamma bandpass (r=0.762, P=0.046, P≤0.05 one-tailed) (Figure 6), the total score of pain catastrophizing questionnaire channel F4, beta bandpass (r=0.707, P=0.075, P≤0.05 one-tailed) (Figure 7). In the eye close position life satisfaction of the pain-free group had a significant relationship with delta bandpass at channel T5 (r=0.553, P=0.077, P≤0.05 one-tailed) (Figure 8) and the feeling subscale of the McGill pain questionnaire of the pain group had a significant relationship with delta bandpass at channel Pz (r=0.684, P=0.090, P≤0.05 one-tailed) (Figure 9).

4. Discussion

This study investigated EEG indicators of changes in cortical activity in patients with phantom limb pain. People with unilateral upper limb amputees were divided into two groups, those with pain and those without pain. Both groups answered demographic questions, psychological questionnaires, and the examiner recorded their EEG during resting state in eyes open and eyes closed conditions. Psychological factors did not have significant differences between the two groups. EEG results showed a significant decrease in the pain group for the α brain waves in the eye-open condition. Also, the results of EEG data during the eyes-closed condition showed delta waves decrease on the right side of the cortex. The relationship between behavioral data and EEGs showed significant differences in pain features with brain waves in both conditions.

Psychological factors affected the course and the severity of pain in amputees (Hill, 1999; Sherman et al., 1987). Stress, anxiety, depression, and other emotional triggers also contribute to the persistence or exacerbation of PLP (Davidson et al., 2010; Hirsh et al., 2010). Despite expectations, the psychological, and demographic results of this study did not show any significant differences between the two groups. However, these results can be due to the small number of participants.

According to our hypothesis, we expect to see significant differences in delta, beta, and gamma bands between the two groups. As hypothesized, the results of our study did not show any significant differences at the α band frequency, despite significant differences observed in the beta and the gamma bands and some differences in the delta and theta bands. Significant differences mostly were observed in the regions related to pain perception, including the parietal (Benuzzi et al., 2008) and sensory regions, but the motor cortex did not show specific differences. The reason for not observing any difference in the sensorimotor cortex can be a strategy that participants learned during past years to deal with chronic pain. As mentioned in other studies, the motor cortex is active through severe pain and causes some movements to help



Mean amplitude (pain group)
Mean amplitude (no-pain group)
T value (pain vs no-pain)

Delta

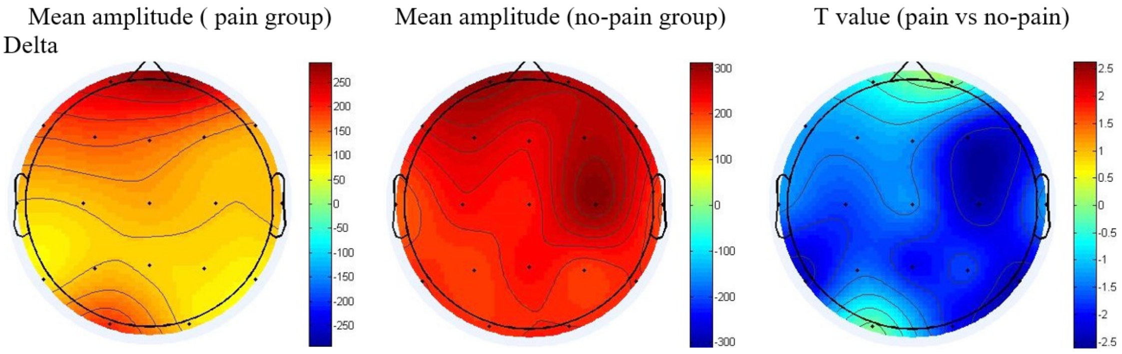
Theta

Beta

Gamma

Figure 1. Statistically significant changes in brain waves in the pain versus pain-free group at the eyes open condition

The first column indicates the average of EEG band powers in the pain group. The second column indicates the average of EEG band powers in the pain-free group and the third column denoted the t values of changes between pain versus pain-free group.



Mean amplitude (pain group) Mean amplitude (no-pain group) T value (pain vs no-pain)

Delta

Figure 2. Statistically significant changes in brain waves in the pain versus pain-free group at the eyes close condition

The first column indicates the average of EEG band powers in the pain group. The second column indicates the average of EEG band powers in the pain-free group and the third column denoted the t values of changes between pain versus pain-free group.

a person avoid the pain (Benuzzi et al., 2008). Indeed, in less severe painful situations, intensity of perceived pain causes parietal activation but cannot activate the premotor regions (Benuzzi et al., 2008; Tayeb et al., 2020). On the other hand, other related studies such as Benuzzi's research (Benuzzi et al., 2008) have been performed to monitor participant's brain activities during the presentation of painful stimuli or representation of amputated limb movement; While we know mental activities during the experimental pain is different from real subjective feeling of the pain (Ong et al., 2019; Apkarian et a., 2005; Oshiro et al., 2008). Moreover, the results of this study were based on the resting state EEG data, which can present stabilized changes in the cortical activities of the PLP.

Tayeb et al. reported in a study that severe pain causes increased activities in the motor cortex while mild to moderate pain causes increased activities of the parietal cortex and decreased activities in the central cortex (Tayeb et al., 2020). The parietal cortex activities were reported to be linked to body imagery (Makin & Flor, 2020), pain perception (Benuzzi et al., 2008), and recognion of somatosensory stimuli (Tayeb et al., 2020). In this regard, our results also showed a significant decrease in activities of the parietal cortex in the pain group compared to the pain-free group. Although no study has investigated the delta band activities in PLP, a decrease in delta band activities has been reported by Shao et al. resulting in objective pain (Shao et al., 2012). In this regard, our findings showed subjective pain is accompanied by a delta decrease at the posterior temporal cortex.

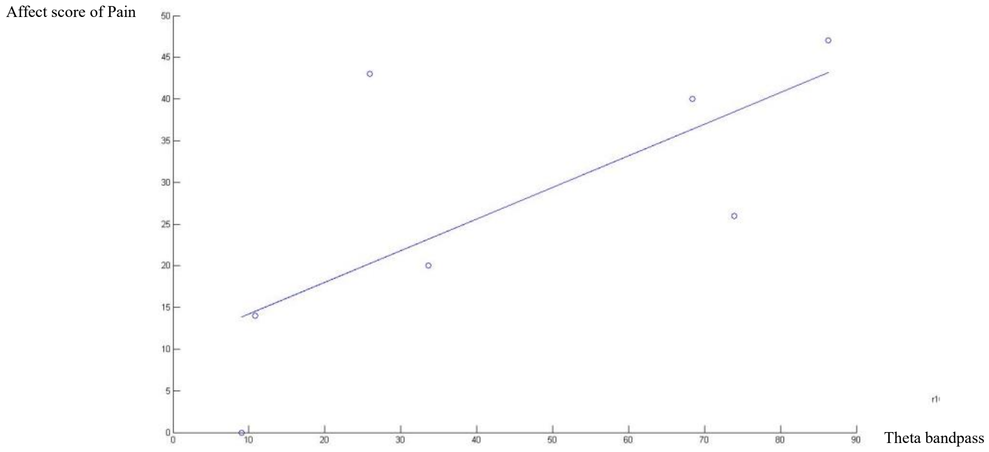


Figure 3. Correlation of affect subscale of mcgill pain questionnaire in pain group with theta bandpass at Pz in eyes open position (r=0.7, P<0.05 one-tailed)

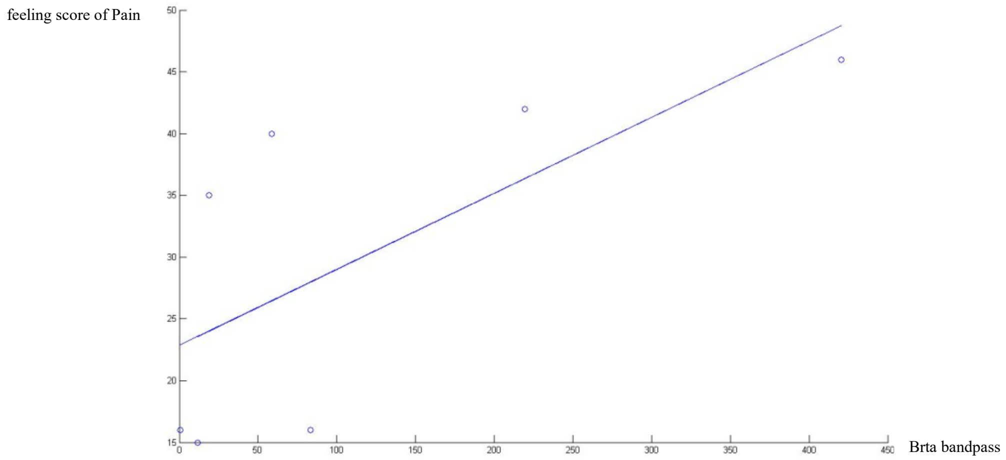


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Figure 4. Correlation of feeling subscale of McGill pain questionnaire in pain group with beta bandpass at O_2 in eyes open position (r=0.689, P<0.05 one-tailed)

Overall, the findings of this study express differences in central, parietal, and temporal regions between the PLP and the non-PLP groups. The important point results did not present any significant differences at the α rhythm power and the motor cortex. We think of two main reasons. First, this study was based on the resting-state data while previous studies were based on the investigation of brain activities during the presentation of a sort of painful stimuli or representation of the phantom limb movement in such situations, the subject confronts painful stimuli and tends to avoid them with some physical movements (Benuzzi et al., 2008). Second, previous studies mostly reported an increase in the rhythm of gamma-band activities in pain conditions. Nonetheless, our results presented a decrease in the power of gamma-band activities may be due to differences in the experimental condition, or a hypothesis exists that PLPs have a bias toward painful stimuli and associate it with their phantom limb (Vase et al., 2012). Therefore, when they confront the painful stimuli, gamma activities at the related cortex regions are increased but not at the resting-state condition.

Moreover, the results of this study showed a significant difference between the theta frequency bands in the two groups. These findings have not been mentioned in previous studies and require more attention. Also, differences at the right occipital and the left posterior temporal regions have not been found previously. According to these findings, the trend to focus only on the primary sensory cortex in PLPs may not be completely true. This

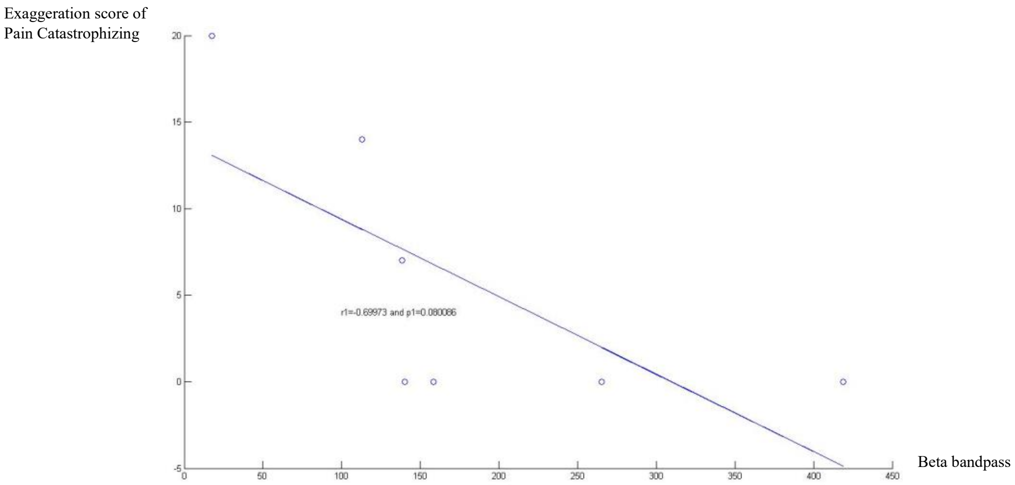

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Figure 5. Correlation of exaggeration subscale of pain catastrophizing scale in pain group with beta bandpass at F4 in eyes open position (r=0.699, P<0.05 one-tailed)

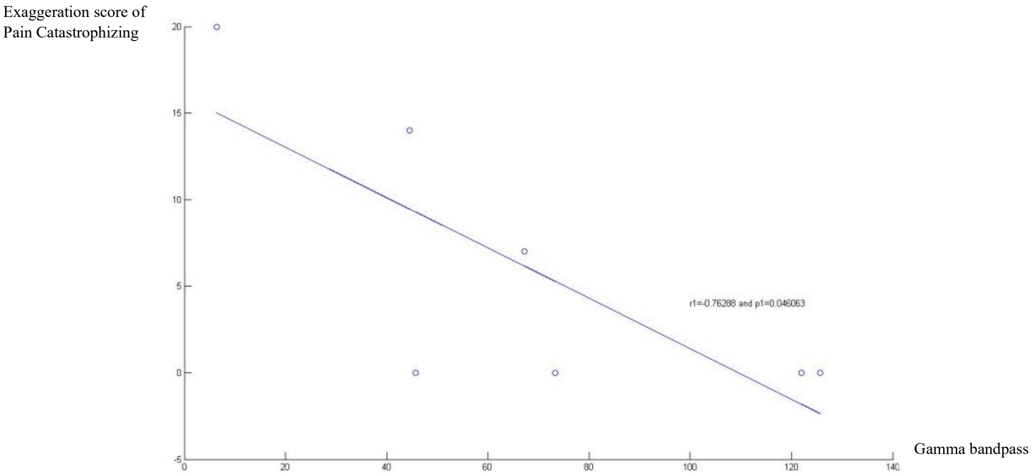

Figure 6. Correlation of exaggeration subscale of pain catastrophizing scale in pain group with gamma bandpass at F4 in Eyes open position (r=0.762, P<0.05 one-tailed)

region is related to somatosensory learning and consolidation rather than somatosensory perception (Medina & Rapp, 2014; Makin & Flor, 2020). Almost all BCI-based treatments in PLP focused on the sensory-motor cortex's α band. As our different results were obtained through resting state on PLP_not at experimental pain_ it seems that for more effective BCI treatment, pain perception regions, and high bandpasses should be considered. Therefore, cognitive deficits should also be observed.

On the other hand, studies have shown psychological factors related to chronic pain can change the circuit and functional connectivity in the brain (Kucyi et al., 2014; Loggia et al., 2015). For instance, Walker believes that chronic pain and depression are accompanied by common neuroinflammation in PLP (Walker et al., 2014) and such chronic pain can significantly affect the quality of life (Lewis & Kriukelyte, 2016). Although, we did not find any significant correlation between pain level and depression or life satisfaction in our subjects may be due to the small number of participants in the pain group. Also, studies showed catastrophizing as maladaptive cognitive processes enhanced during chronic pain (Andoh et al., 2018). Pain catastrophizing is defined as "the exaggerated orientation toward nociceptive stimuli" that cause magnify the value of pain stimuli, feel helpless in pain contexts, and inability to inhibit pain-related thoughts during or after painful events (vase et al., 2012). Studies showed this phenomenon related to

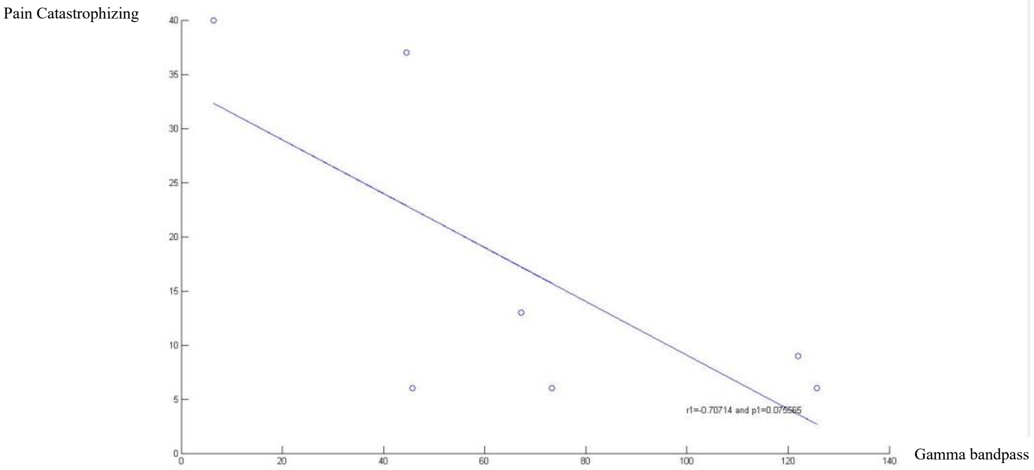

Figure 7. Correlation of total score of pain catastrophizing scale in pain group with gamma bandpass at F4 in eyes open position (r=0.707, P<0.05 one-tailed)

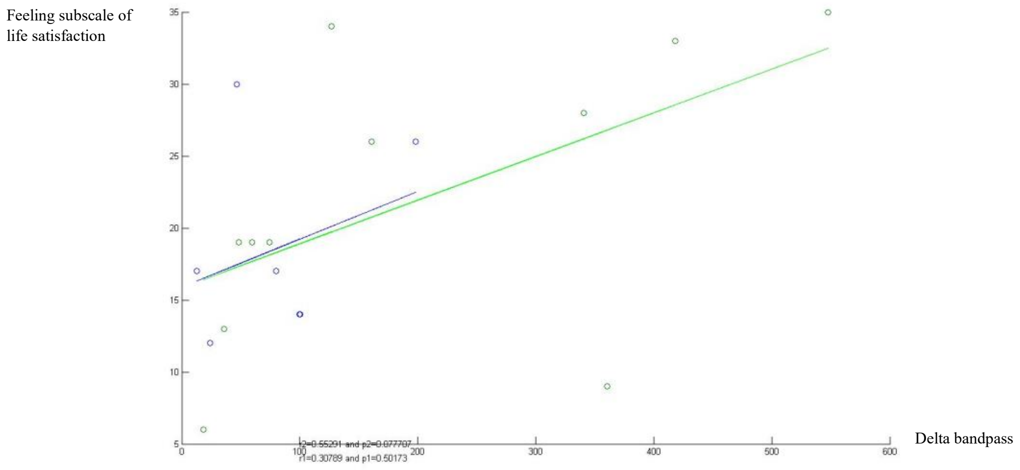

Figure 8. Correlation of feeling subscale of life satisfaction scale in a pain-free group with delta bandpass at T5 in the eyes close position (r=0.553, P<0.05 one-tailed)

increasing activity in somatosensory (Gracely et al., 2004) and anterior cingulate cortex (Gracely et al., 2004; Seminowicz & Davis, 2006). The findings of the current study are consistent with previous studies that showed a significant correlation between pain catastrophizing and F4 channel activity in gamma and beta bandpasses. These high-frequency bands are related to high-level cognitive abilities, such as memory processes (Baars & Gage, 2013) while Vase et al suggest that pain catastrophizing may be related to memory process in retrospective or prospective rating pain (Vase et al., 2012). So, it seems studying the correlation between pain level and memory processes may help understand the link between pain and pain catastrophizing (Vase et al., 2012). Although results showed the intensity of pain in PLP is related to theta activity in Pz and beta activity in O2 at the eyes open position and delta activity in O2 at the eyes closed position.

5. Conclusion

It seems in chronic pain, such as PLP, brain cortex areas related to pain perception rather than the motor cortex have maladaptive neuroplasticity. In these patients, the motor cortex shows more maladaptive activity when exposed to painful stimuli or pain-related emotional situations, but for effective treatment, we should consider stabilizing changes in the cortex that exist even in a resting state. Considering

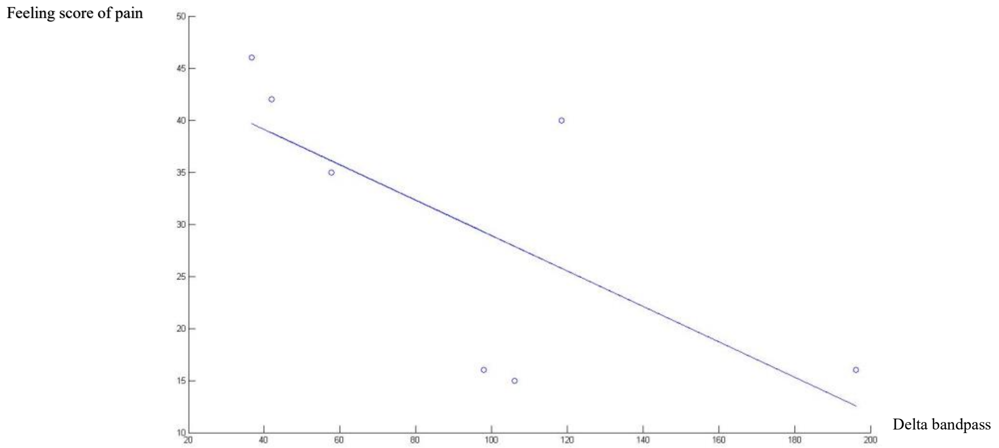

Figure 9. Correlation of feeling subscale of McGill pain questionnaire in pain group with delta bandpass at Pz in eyes close position (r=0.684, P<0.05 one-tailed)

the correlation between pain intensity and catastrophizing relation with band-pass activity at the cortex level, it seemsthat some cognitive factors have a role in phantom limb pain rather than neuroplasticity through amputation. Therefore, investigation of the cognitive aspect of PLP, such as memory and the attentional process can help design a more effective treatment plan for PLP.

Repeating the study with more participants and in analogous patients, such as brachial plexus conditions, can be beneficial. Investigating connectivity between the parietal, temporal, and posterior frontal of the cortex can be the aim of future work. For future work, investigating the cognitive aspect of PLP and comparing it with other chronic pain conditions could help design a comprehensive treatment plan.

Limitations

Difficulties in finding and communicating with amputees reduce the number of participants.

Ethical Considerations

Compliance with ethical guidelines

Ethical approval was received from the Iran University of Medical Science (Code: IR.IUMS.REC.1398.408).

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Authors' contributions

Conceptualization: Javad Hatami, Reza Khosrowabadi, Ali Khatibi and Zahra Bagheri; Methodology: Reza Khosrowabadi, Javad Hatami, Zahra Bagheri; Supervision: Reza Khosrowabadi and Javad Hatami; Resources: Javad Hatami, Mohamad Javad Fatemi and Alireza Armani Kian; Investigation and funding acquisition: Zahra Bagheri; Writing–original draft: Zahra Bagheri and Reza Khosrowabadi; Writing–review, and editing: All authors.

Conflict of interest

The authors declared no conflict of interest.

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