Title: Differential cortical oscillatory patterns in amputees with and without phantom limb pain

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Abstract

Objective: 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's and relations to the psychological and cognitive dimension of chronic pain. We investigate differences in resting brain activities between amputees with and without pain. We hypothesis significant differences in activities of the motor cortex and parietal cortex that are related to pain perception. Also, we hypothesis 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.

Result: Results showed a significant decrease in the pain group for the Beta and Gamma waves, Also, for the Theta and Delta waves in the posterior temporal on both sides, during the eye-open condition. The eyes-closed condition showed Delta waves decrease on the right side of the cortex. Also, data showed significant differences in correlation of pain features with brain wavws between two groups.

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

Keywords: Phantom Limb Pain, Upper Limb Amputation, Electroencephalography, And Brain Wave Oscillation

Introduction

People who lose their limbs through 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) that has been approximately reported in 70% of them (IASP, 2014). The PLP is a neuropathic pain and usually shows its signs within the first week after amputation and presents for a month or even years after. Generally, the PLP is observed as shooting, pricking, and burning feelings in the missing limb. In most cases, the PLP is intermittent while the intensity and frequency of the attacks are decreased with time (IASP, 2014). It has been reported that females and upper limb amputees have a higher risk of PLP (IASP, 2014).

In fact, 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). Indeed, 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 bodily 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). The neural reorganization is generally viewed as a learning process for enabling the cortex to have a better function (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 amputation of an upper limb, shrinking of the amputee's upper-limb area, and expansion of the adjacent mouth/facial regions are observed 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 has been amputated, 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 law of use and disuse(Ewer, 1960; Palmer, 2012). The fMRI findings indicated that pain and non-pain somatosensory pathways by the amputated side were functionally deficient(Hu, 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 increase alpha 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).

Whereas most studies showed somatosensory cortex engaged in PLP, but 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 much 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, for offering beneficent treatment we should know more about the alteration of brain activities in all engaged areas by the PLP. Though ECoG-based BCI treatment is efficient(Gharabaghi et al., 2014) but 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 those 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 alpha frequency band would not be the main indicator of the PLP.

The human hand has a powerful role in all aspects of life; so, upper limb amputation could 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 along with chronic pain (in PLP condition), serious psychological and cognitive problems such as depression and catastrophizing of pain 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 change 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 could be comorbid with neural activity changes.

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

Method

Participants and Procedure

Participants of the 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 with unilateral upper limb amputees were amputated after age 16 identified; those with another type of amputation and history of brain injury were excluded. Eventually, nineteen unilateral upper limb amputees (2 females, mean age = 48 ± 11.71) took part in the experiment. Twelve (2 females, mean age = 47.92 ± 11.70) participants didn't have any pain at the time of study and the other seven subjects (all males) did have pain. The group of participants without PLP had a mean age of 27.00 ± 11.29 before amputation and the group with PLP had a mean age of 36.71 ± 16.17 before amputation (Table 1). All participants were assessed during a 60 to 90 minutes single session. The assessment included interviews about demographic information, the reason for amputation, PLP severity, psychological status, and electroencephalography acquisition. One participant from the no-pain group did not complete the questionnaire; so, just answers to the interviewer questions and EEG were 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:

1. Depression, Anxiety, and Stress scale (DASS-21): This scale included three self-report subscales for measuring depression, anxiety, and stress. Each subscale has seven-item that in which participants should grade the intensity of them through 0 to 4 (zero is never and 4 is almost ever) due to the past two weeks. At the Persian version of this scale, the internal consistency of subscales respectively is 0.92, 0.86, and 0.84(Mahmoodi-Aghdam et al., 2017).
2. Deiner's Satisfaction with Life Scale (SWLS): This five-item self-report scale 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 in 2003 prepared the Persian version of this scale with 0.8 alpha Cronbach. Also, other studies find proper validation for the Persian version of this scale (Tanhae et al., 2012).
3. The short form of the Mc-Gill pain questionnaire (SF-MPQ-2) has 22 items, that participants should score each through a 0 to 10 Likert spectrum. Tanhae et al investigate the statistical feature of the Persian version of this questionnaire. Through factorial analysis, she found three factors_ feeling pain, affective pain, and neuropathic pain_ for the Persian version of the questionnaire (Rahmati et al., 2016).
4. Pain Catastrophizing Scale (PCS): This scale was developed by Sullivans et.al (1995) and evaluate 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 speaking population reported good psychometric properties of this measure (alpha Cronbach=0.88)(Ranjbar et al., 2020).

EEG data recording and analysis

EEG data were obtained during the eyes-open and eyes-closed resting state, while the participant was situated in a quiet room and was asked to stay calm without any movement or talk during the experiment. Each part was acquired separately for at least 150 seconds. The Data were recorded with 21-channel Mitsar 201 amplifier (Mitsar Co, Petersburg Russia) and

WinEEG software (Informer Technologies, Inc. version 2.11) using 250 Hz sampling frequency. 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 kOhm.

Afterward, the EEG data was preprocessed offline using EEGLAB toolbox and in-house MATLAB scripts (The Math Works Inc., Natick, MA). Recordings were high-passed filtered 1 Hz and low-passed filter 40 HZ. Muscular movements and eye blinks were identified using independent components analysis (ICA) and bad components were marked using the adjust plug in the EEG lab, got 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 test of normality with Kolmogorov Smirnov, a two-sample t-test was hired to compare behavioral data of the PLP group with the No-PLP group. The procedure was performed using SPSS version 25 to identify significant differences with $p \text{ value} < 0.05$.

EEG data

We used the Matlab statistical toolbox (The Math Works Inc., Natick, MA) for the extraction power spectrum of each bandpass. After the test of normality 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 Benjamin and Hochberg (1995) algorithm and significant changes with $P \text{ value} < 0.05$ one-tailed, FDR corrected were reported.

Association between EEG band powers and behavioral data

Association between two behavioral and neural data was investigated using the Matlab statistical toolbox. Subscales of the Mc-Gill pain questionnaire, PCS, and DASS were investigated separately. The scatter plot was drawn for each dimension in both groups and significant associations with $p \text{ value} < 0.05$ one-tailed were identified.

Results

Demographic Results

At the interview session before the recording, subjects were asked about their age at the time of amputation, their current age, and estimate years of living with an amputated limb. The Result of the two-sample t-test comparison between the pain group and the no-pain group didn't 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 no-pain group (pain group: $M = 75.86 \pm 32.88$ no-pain group: $M = 2.08 \pm 7.21$). In the pain group, the pain catastrophizing scale was used for the evaluation of exaggeration and hopelessness. After grouping, a two-sample t-test comparison was used for identifying significant differences in DASS and SWLS scores. No significant differences were shown in the three subscales of DASS and SWLS (see Table 2).

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 anb beta: T value= -1.075, p^1 value= 0.074; T value= -1.180 ,P value=0.060), T6 (repectively gamma anb beta: T value=-1.465 ,p value= 0.050 ; T value=-2.599 ,P value=-1.299)), left posterior temporal (T5(repectively gamma anb beta: T value= ,p value= ; T value= -1.593 ,P value= 0.034)), parietal (P3(repectively gamma anb beta: T value= -0.914 , p value= 0.094 ; T value= -1.083 ,P value= 0.063), Pz(repectively gamma anb beta: T value= ,p value= ; T value= -1.412 ,P value= 0.041), P4(just in beta bandpass: T value= -0.975 ,P value= 0.065)), posterior frontal (C3(repectively gamma anb beta: T value= -0.901 ,p value= 0.094 ; T value= -1.051, P value= 0.063), CZ(repectively gamma anb beta: T value= -1.048, p value= 0.075; T value= -1.025 ,P value= 0.063), C4(repectively gamma anb beta: T value= -1.248 ,p value= 0.074 ; T value= -1.260 ,P value= 0.060)), and right midfrontal (F4(repectively gamma anb beta: T value= -1.098 ,p value= 0.074 ; T value= -1.010 ,P value= 0.063)) cortex. In addition, delta band activities also

¹ All P-values was after FDR correction and one-tailed P-value is considered.

showed significant differences in the posterior temporal of both sides (T5(T value= -1.441 ,P value= 0.062), T6(T value= -1.460 ,P value= 0.062)) and Theta band activities had noticeable significant differences in some parts of the parietal and temporal cortex (C4: T value= -2.303 ,P value= -1.151 , T4: T value= -2.297 ,P value= -1.148 , T5: T value= -3.239 ,P value= -1.620, P3: T value= -2.213 ,P value= -1.106 , PZ: T value= -2.537 ,P value= -1.268 , T6: T value= -2.599 ,P value= -1.299). Interestingly, Alpha band activities did not show any significant differences (figure 1).

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

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

Correlation between behavioral scores and significant EEG changes

A significant correlation between behavioral scores and significant changes of EEG waves powers in the eyes open condition was only observed in the pain group. These results include: positive correlation between affect subscale of McGill pain questionnaire and power of theta band activities at Pz ($r= 0.7$ $p= 0.079$ $p\leq 0.05$ one-tailed) (Plot 1), feeling subscale of McGill pain questionnaire on channel O2, beta bandpass ($r= 0.689$ $p= 0.09$ $p\leq 0.05$ one-tailed) (Plot2), exaggeration subscale of pain catastrophizing questionnaire on channel F4, beta bandpass ($r= 0.699$ $p= 0.080$ one-tailed) (Plot 3) and gamma bandpass ($r= 0.762$ $p= 0.046$ $p\leq 0.05$ one-tailed) (Plot 4), total score of pain catastrophizing questionnaire channel F4, beta bandpass ($r= 0.707$ $p= 0.075$ $p\leq 0.05$ one-tailed) (plot 5). In eye close position life satisfaction of the no-pain group had a significant relationship with delta bandpass at channel T5($r= 0.553$ $p= 0.077$ $p\leq 0.05$ one-tailed) (Plot 6) and the feeling subscale of McGill pain questionnaire of pain group had a significant relationship with delta bandpass at channel Pz ($r= 0.684$ $p= 0.090$ $p\leq 0.05$ one-tailed) (Plot 7).

Discussion

This study investigated EEG indicators of changes in cortical activity among patients suffering from phantom limb pain. People who had unilateral upper limb amputees were divided into two groups: those who have 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 didn't have significant differences between the two groups. EEG results showed a significant decrease in the pain group for the brain waves expect alpha during 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. Association 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 could be because of the low 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 alpha band frequency, despite significant differences that were mostly observed at the beta and the gamma bands and some differences at delta and theta bands. Significant differences mostly were observed in the regions related to pain perception including 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 could 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 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 al., 2005; Oshiro et al., 2008). Moreover, the results of this study were based on the resting state EEG data that could present stabilized changes in the cortical activities of the PLP.

A study by Tayeb et al. (2020) reported that severe pain causes an increase in activities at the motor cortex while slight to moderate pain causes an increase in activities of the parietal cortex and a decrease in activities at the central cortex (Tayeb et al., 2020). The Parietal cortex activities were reported to be linked to body imagery (Maakin & Flor, 2020), pain perception (Benuzzi et al., 2008), and recognizing somatosensory stimuli (Tayeb et al., 2020). In the same line, our results also showed a significant decrease in activities of the parietal cortex in the pain group as compared to the no-pain one. Although no study has investigated the delta band activities in PLP, a decrease in delta band activities has been reported by Shao et al. as a consequence of 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.

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 alpha 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 tend to avoid that by 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 there is a hypothesis that PLPs have a bias into painful stimuli and relate that to 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

region is related to somatosensory learning and consolidation rather than somatosensory perception (Medina & Rapp, 2014; Maakin & Flor, 2020). Almost all BCI-based treatments in PLP focused on the sensory-motor Cortex's alpha band. As our different results obtained through resting state on PLP _not at experimental pain_ it seems for more effective BCI treatment should consider pain perception regions and high bandpasses. Therefore, cognition-related deficits must be observed as well.

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 chronic pain and depression are accompanied by common neuroinflammation in PLP's (Walker et al., 2014) and such chronic pain could 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 because of a low 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 increasing activity in somatosensory (Gracely et al., 2004) and anterior cingulate cortex (Gracely et al., 2004; Semin & 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 frequent band-passes are related to high-level cognitive abilities such as memory process (Baars & Gage, 2013) while Vase et al, says pain catastrophizing may be related to memory process in rating pain retrospectively or prospectively (Vase et al., 2012). So, it seems studying the correlation between pain level and memory process may help understand the link between pain and pain catastrophizing (Vase et al., 2012). Although results showed the intensity of pain in PLP's is related to theta activity in Pz and beta activity in O2 at eyes open position and delta activity in O2 at eyes close position.

Limitations: Difficulties in finding and make contact with amputees cause a low number of participants.

Conclusion

It seems in chronic pain's such as PLP brain cortex areas related to pain perception rather than motor cortex had maladaptive neuroplasticity. In these patients, the motor cortex show more maladaptive activities during exposure 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 the correlation between pain intensity and catastrophizing relation with band-pass activity at the cortex level, it seems rather than neuroplasticity through amputation, some cognitive factors have a role in phantom limb pain. So, investigation of the cognitive aspect of PLP such as memory and the attentional process could help design a more effective treatment plan for PLP's.

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

Ethical Considerations

Compliance with ethical guidelines

Ethical approval was received from the Iran University of Medical science and the approval code is IR.IUMS.REC.1398.408.

Finding

This study was applied with the financial support of IRAN's Cognitive Science & Technologies council.

Authors' Contributions

Conceptualization: Javad Hatami, Reza Khosrowabadi, Ali Khatibi, Zahra Bagheri; Methodology: Reza Khosrowabadi, Javad Hatami, Zahra Bagheri; Investigation and Funding Acquisition: Zahra Bagheri; Writing – Original Draft, Author names: Zahra Bagheri, Reza Khosrowabadi; Writing – Review & Editing: all authors; Resources: Javad Hatami, Mohamad Javad Fatemi, Alireza Armani Kian; Supervision: Reza Khosrowabadi, Javad Hatami

Conflict of interest

The authors have declare no conflict of interest.

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Table 1. Group differences in terms of demographic data

Variables	Pain		No-pain		t score	p value	Effect size
	<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>			
Age	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

A significant difference is denoted by p-value <0.05. Pain and no-pain groups were identified based on the subject's answers to the Mc-Gill pain questionnaire

Table 2. Group comparisons for psychological data

Variables	Pain		No-pain		t score	p value	Effect size
	<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>			
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 Subscale	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 value <0.05. SWLS: Satisfaction With Life Scale W

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 no pain group at 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 no-pain group and the third column denoted the t values of changes between pain versus no-pain group.

Figure 2. Statistically significant changes in brain waves in the Pain versus no pain group at 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 no-pain group and the third column denoted the t values of changes between pain versus no-pain group

Plot 1. 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)

Plot 2. Correlation of Feeling subscale of McGill pain questionnaire in pain group with Beta bandpass at O2 in eyes open position ($r = 0.689$ $p < 0.05$ one-tailed)

Plot 3. 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)

Plot 4. 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)

Plot 5: 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)

Plot 6: Correlation of Feeling subscale of Life Satisfaction Scale in a no-pain group with Delta bandpass at T5 in eyes close position ($r=0.553$ $p<0.05$ one-tailed)

Plot 7: 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)