ORIGINAL ARTICLE

People with amputation and musculoskeletal pain show reduced electrical activity of Alpha brain waves: cross-sectional study

Pessoas com amputação e relato de dor musculoesquelética apresentam redução da atividade elétrica das ondas cerebrais Alpha: estudo transversal

Débora Pinheiro Aguiar[1], Paulo Cezar do Nascimento Filho[2], Amanda Guerra Moreira[1], Gabriella Coelho Vieira de Melo Alves[1], Gisele Harumi Hotta[1,3], Francisco Fleury Uchoa Santos-Júnior[1,2]

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ABSTRACT

BACKGROUND AND OBJECTIVES: Amputation causes associated clinical conditions, such as musculoskeletal pain (MSP), which causes suffering and interferes in the patient's life. Therefore, the development of diagnostic methods to measure these changes are encouraged, such as quantitative electroencephalography (qEEG). The aim of the study was to compare the electroencephalographic pattern of Alpha brain waves (8-12 Hz) in individuals with amputation with MSP unrelated to phantom limb pain and without MSP.

METHODS: Study conducted between January and February 2022, with 20 people with amputations divided equally into two groups (Control Group and with MSP report not related to the amputated segment). Pain intensity and interference were evaluated (Brief Pain Inventory), as well as the presence of central sensitization (CS) signs and symptoms (CS inventory) and qEEG (assessed with eyes open) with spectral analysis to measure the amplitude of the Alpha wave, standardized Low Resolution brain electromagnetic Tomography (sLORETA) to identify the differential generation site of said wave and Phase-Amplitude Coupling (PAC) to identify its interaction with fast waves.

RESULTS: People with amputation and MSP reported mild pain severity and interference. No difference was identified between individuals regarding the presence of signs and symptoms associated with CS. Regarding electrical activity, the Pain Group had lower Alpha wave amplitude compared to the Control Group (p=0.01), specifically in the parieto-occipital region.

CONCLUSION: People with amputation and reported MSP unrelated to the phantom limb had reduced electrical activity (activation) of the Alpha brain wave in the sensory cortex.

Keywords: Amputees, Electroencephalography, Musculoskeletal pain.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A amputação acarreta quadros clínicos associados, como a dor musculoesquelética (DME), que causa sofrimento e interfere na vida do paciente. Por isso, o desenvolvimento de métodos diagnósticos para mensurar essas alterações são incentivados, como a eletroencefalografia quantitativa (EEGq). O objetivo deste estudo foi comparar o padrão eletroencefalográfico das ondas cerebrais Alpha (8-12 Hz) em pessoas com amputação com DME não relacionada à dor no membro fantasma e sem DME.

MÉTODOS: Estudo realizado entre janeiro e fevereiro de 2022, com 20 pessoas com amputação divididas igualmente em dois grupos (Grupo Controle e grupo com relato de DME não relacionada ao segmento amputado). Avaliou-se intensidade e interferência da dor (Inventário Breve de Dor), presença de sinais e sintomas de sensibilização central (SC) (Inventário de SC) e a EEGq (avaliados com olhos abertos) com análise espectral para medir a amplitude da onda Alpha, *standardized Low Resolution brain electromagnetic Tomography* (sLORETA) para identificar o local de geração diferencial da referida onda e *Phase-Amplitude Coupling* (PAC) para identificar sua interação com ondas rápidas.

RESULTADOS: As pessoas com amputação e relato de DME apresentaram baixa gravidade e interferência de dor. Não se identificou diferença entre as pessoas em relação a presença de sinais e sintomas associados à SC. Quanto à atividade elétrica, o Grupo Dor apresentou menor amplitude da onda Alpha em relação ao Grupo Controle (p=0,01), especificamente na região parieto-occipital.

Débora Pinheiro Aguiar – https://orcid.org/0000-0002-9037-9231;
Paulo Cezar do Nascimento Filho – https://orcid.org/0000-0002-4963-7905
Amanda Guerra Moreira – https://orcid.org/0000-0001-6059-4830;
Gabriella Coelho Vieira de Melo Alves – https://orcid.org/0000-0002-6500-0453;
Gisele Harumi Hotta – https://orcid.org/0000-0001-5824-1737;
Francisco Fleury Uchoa Santos-Júnior – https://orcid.org/0000-0002-5685-4297.

1. Dell LEAD – Center of Research, Dell Development and Innovation, Fortaleza, CE, Brazil.
2. Le Santé Institute, Fortaleza, CE, Brazil.
3. University of São Paulo, Riberão Preto Medical School, Health Sciences Department, Riberão Preto, SP, Brazil.

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HIGHLIGHTS
- People with amputation and pain present reduced Alpha brain wave activity.
- Quantitative electroencephalography can be a tool for monitoring patients with musculoskeletal pain report.

Correspondence to:
Débora Pinheiro Aguiar
E-mail: deborapinheiroaguiar@gmail.com

CONCLUSÃO: Pessoas com amputação e relato de DME não relacionada ao membro fantasma apresentaram atividade elétrica (ativação) reduzida da onda cerebral Alpha no córtex sensorial.

Descritores: Amputados, Dor musculoesquelética, Eletroencefalografia.

INTRODUCTION

Amputation is conceptualized as the total or partial removal of a limb, and this is the treatment for several serious clinical conditions[1], such as car or work accidents, cancer, and diabetes mellitus[2]. In 2019, in Brazil, an incidence of 5.06 to 27.15 amputations per 100,000 inhabitants[3] was observed, it was predominant in males and, therefore, should be considered a national public health problem[4]. People with amputations may suffer functional, psychological and social changes[5], leading to clinical conditions of depression, stress, social isolation, sleep disorders and pain[6].

Pain is an experience that, even in low or moderate intensity, can evoke extreme suffering, interfering in daily life and relationships[7,8]. People with amputations can have phantom limb pain, pain in the remaining limb or musculoskeletal pain (MSP) in other body regions[9]. Additionally, it is relevant to consider in the clinical evaluation the patients' involved condition, such as the cause (example: diabetes, trauma, among others), the area of the amputation (disarticulation or transosseous) and the presence of pre-amputation MSP, as it contributes to the pain report[10]. In individuals with amputations, the risk of self-reported MSP increases and the use of prosthesis does not seem to prevent this episode. After amputation, the residual limb receives greater loads, presenting compensatory movements and transference of functions, which can result in musculoskeletal pain in other body regions[9,11].

Science and technology have advanced in recent years, developing diagnostic methods, such as electroencephalography (EEG), for the assessment and rehabilitation of individuals with amputations[12-15]. EEG records brain waves, such as the Alpha wave (8-12 Hz), which is related to pain control, sensory stimulus, and working memory; Beta (13-15 Hz), a working wave involved in sensorimotor rhythm, recognition memory, and tasks (motor and cognitive); Theta (4-7 Hz), related to memory consolidation and initial sleep states; Delta (1-4 Hz), related to sleep; and Gamma (33-44 Hz), which is involved in attentional information processing, conscious perception, and long-term memory[16,17].

The brain has the ability to reorganize itself after changes, as in amputation, which generates changes in brain functions through the phenomenon named post-amputation brain plasticity, which may be restricted to a local remapping[18] or a remapping in several cortical regions[19], presenting clinical manifestations, such as emotional and cognitive changes, in addition to pain[20]. Studies with the objective of investigating areas that present these alterations in brain activity in individuals with amputation have chosen the quantitative electroencephalography (qEEG) as the best assessment tool because it has a higher quality temporal image[21]. EEG, a technology that performs temporal and spatial investigation through images, helps in the comprehension of the electrical activity of brain structures that participate in the processing and perception of pain[22]. Moreover, EEG can be used for diagnosis and treatment of pain[23,24].

However, there is still a gap in the literature on how individuals with amputation present their brain function in MSP conditions that are not related to the amputated body segment, known as phantom limb pain. This can be an important aspect to support the development of new technologies for this population, especially when it is already known that individuals with amputation present alterations in brain connectivity, indicating plasticity[19]. Thus, the objective of the present study was to compare the electroencephalographic pattern of Alpha waves in individuals with amputation with and without MSP unrelated to phantom limb pain.

METHODS

Comparative cross-sectional observational study, based on a strategy of quantitative data secondary analysis, performed according to the guidelines outlined by the STrengthening the Reporting of Observational Studies in Epidemiology (STROBE), which can be viewed at: https://www.strobe-statement.org/[25].

The study was conducted at the Dell Research, Development, and Innovation Center (Ceará-Brazil) in the period from January to February 2022, upon approval by the Ethics Committee of the State University of Ceará with opinion no. 5.136.501, under protocol CAAE 51751021.4.0000.5534. The volunteers signed a Free and Informed Consent Term (FICT) to participate in the study.

The individuals who entered the sample were selected by convenience and contacted by telephone in clinics, social projects, and universities in the state of Ceará. The population was composed of individuals who had unilateral lower limb amputation due to trauma, accidents, gunshot wounds, and cancer.

The study included 20 adult individuals, aged between 18 and 50 years, height 1.55 to 1.75 m, maximum weight of ±100 kg for both genders, healthy, without associated vascular diseases (for example: coagulation disorders and decompensated diabetes) and with blood pressure classified as normotension (120/80 mmHg or up to ≤139/89 mmHg)[26].

Participants were divided into two groups, Control Group (n=10), composed of individuals with amputation but no report of MSP, and the Pain Group (n=10), composed of individuals with amputation and with a report of MSP, in a convenience sample. Phantom limb pain was not considered MSP for the present study and both groups had participants with a report of phantom limb pain. In addition, the period of amputation had to be at least one year. For those who were fully prosthetized, the process should have been completed at least six months prior to the study.

As exclusion criteria, the following were considered: amputees with blood pressure values ≥140/90 mmHg, classified with hypertension[26], vascular alterations (history of pulmonary or venous thromboembolism, aneurysm rupture less than 1 year ago) and/or cognitive disorders (Alzheimer's and/or Parkinson's in advanced stages) that would limit, in a decisive way, their answers to the applied questionnaires, such as panic syndrome, anxiety or depression crisis during the evaluation, or individuals with relevant speech impairments that would make it impossible for them to communicate/comprehend fully during the qEEG tests.

Sociodemographic aspects

To collect personal information, an anamnesis form was applied. The form contained questions regarding the respondents' profile, containing data such as name, gender, age, information about time, cause and side of amputation, weight, height and body mass index (BMI). To classify the anthropometric status of the volunteers, the following BMI cutoff points were adopted: BMI <18.5 kg/m^2 (underweight); BMI >18.5 to 24.9 kg/m^2 (eutrophy); BMI ≥25 to 29.9 kg/m^2 (overweight); and BMI >30.0 kg/m^2 (obesity). Participants were asked about report of MSP in the past week in body areas. It is worth noting that, for this study, the temporal factor of pain and, consequently, its classification (acute or chronic) was not addressed, ultimately considering pain broadly. In addition, the volunteers were asked if they felt pain in the phantom limb.

Brief Pain Inventory (BPI)

The BPI consists of nine items arranged in two dimensions: pain intensity (items 3 to 6) and pain interference (impact) on the patient's life (items 9a to 9g). The BPI asks patients to rate their intensity of pain and the interference of pain (in general activities, mood, ability to walk, normal work, relationships with other people, sleep, and enjoyment of life) on an 11-point scale ranging from 0 (no pain / no interference) to 10 (worst possible pain). A high score represents high pain intensity or interference. This instrument has two dimensions, pain intensity and pain interference, with Cronbach's α of 0.91 and 0.87, respectively[27].

Central Sensitization Inventory Brazilian Portuguese (CSI-BP)

The CSI-BP allows the identification and tracking of signs and symptoms associated with central sensitization (CS) and is divided into two parts: A and B. Part A contains 25 questions related to the current health symptoms. Each item is measured using five options of answers, with the following numerical classification scale: never (0), rarely (1), sometimes (2), frequently (3), and always (4). The score is cumulative and ranges from 0 to 100. Part B is used to identify other diagnosed disorders that may indicate a sign additional to the CS, but this part is not scored and can be used for qualitative analysis[28].

This inventory was validated and adapted for Brazilian Portuguese and shows an accuracy profile using a cutoff point of 35, sensitivity of 0.98 and specificity of 0.9 with an Area Under the Curve (AUC) of 0.8 (95% CI - 0.76-0.86). These findings have shown that, according to this cut-off point, the CSI-BP was correctly classified in more than 90% of those who presented signs and symptoms of CS[29]. It is important to highlight that only part A of this inventory was used for data analysis in this study.

Quantitative Electroencephalography (qEEG)

Data acquisition strategy

The test was performed with the participant sitting in a comfortable armchair, facing a white wall and instructed to remain in these conditions for 10 minutes and doing a minimal amount of movement as possible. A Neoprene cap was then put on, with 24 electrodes (950 silver) attached and arranged in specific areas according to the 10-20[30] international system. A carbopol gel (2%) was used to allow conduction of the brain electrical signals from the scalp to the electrodes. The electroencephalic data from each participant were collected for a total period of 10 minutes, and after collection the cap was removed and the experiment was finished for that participant.

The qEEG device used to perform the brain mapping recording was an iCelera® (São Paulo, São Paulo, Brazil) amplifier, model iBlue 52 (512 and 12bit sampling rate). The iCelera® software was used for data collection. The qEEG configurations selected for data collection were 20 channels of medium-mount, grounding and network in standard mode, with a passband filter from 0.5 Hz to 50 Hz. Subsequently, the data were processed and exported by the iCelera® software in European Data Format (EDF) template files. All qEEG analyses were performed with the participants with eyes open (EO), mimicking the condition of an awake individual, in the usual manner. Conditions with eyes closed (simulating sleep) or performing specific tasks (such as reading, for example) were not evaluated.

Analysis of the qEEG data:

After data collection in the iCelera® software, visual inspection was performed on all data using the Biolucida® software (BioNeuro & Lucida, Fortaleza, Ceará, Brazil) beta version. In this application, the Laplacian montage was used to improve the quality of the tracing and correct the polarity of the qEEG[31] in an automated manner within the Biolucida® (BioNeuro & Lucida) system. By using the Laplacian assembly, the electrodes have the same polarity at all points in relation to the determined reference electrode. This provides data with less interference. Moreover, the independent component analysis algorithm (MaxICA) was implemented and, with this, the removal of recorded artifacts, such as involuntary muscle contractions, eye movements, among others, was performed.

Subsequently, a new visual inspection was performed due to any possible need to manually cut out artifacts that persisted in the signal. The data was standardized for a time of 500 seconds and a bandpass filter of 1.5 Hz - 50 Hz was used. The software then extracted tables of qEEG data, dominant frequency, and mean frequency at each of the 20 electrodes recorded. The brain wave frequencies analyzed were: Alpha 1 (8-10 Hz), Apha 2 (10-12mHz) and total Alpha wave (8-12 Hz).

By selecting the EDF file with preprocessing, the data were inserted into the BRAINSTORM®[32] system (Los Angeles, California, United States) so the group calculations (generating one data from each group) could be performed. After this step, the generation of the Phase-Amplitude Coupling (PAC)[33] file of the groups and the sLORETA (standardized Low Resolution brain electromagnetic Tomography) file[34] of the groups were conducted, with an analysis of only the Pz channel (central parietal region of the brain), because it was the most active region in the topographic analysis. The PAC analysis was conducted by a coupling between the Gamma wave (above 30 Hz) and a band corresponding to the Theta (4-8 Hz)/Alpha (8-12 Hz) waves. Through these data, comparisons between the information from the amputee groups were performed in the Brainstorm®[32] system itself.

Statistical analysis

The data were described as mean and standard deviation or as absolute frequency and percentage, according to the type of data to be presented. Prior to the comparison between groups, a Shapiro-Wilk normality test was conducted, and the alpha waves did not present a normal distribution. All 20 channels in each group with 10 people were considered in order to obtain the Alpha response, which totaled 200 points measured in each group. These data were compared with the Mann-Whitney test using the Graphpad Prism 9.0 statistical software for MAC OS X and statistical significance was set at $p<0.05$.

RESULTS

A total of 20 individuals with lower limb amputation participated in the study, 10 in the Pain Group and 10 in the Control Group (without pain) The sociodemographic characteristics are shown in Table 1. The Control Group was composed of 9 (90%) male individuals, with a mean age of 37 years, with a BMI classified as overweight. The presence of pain in the phantom limb was reported by 6 (60%) individuals in this group. As for the Pain Group, 5 participants (50%) were males, with a mean age of 35 years old and eutrophic in their BMI. The phantom limb pain was identified in 9 (90%) participants of this group. Regarding the practice of physical activity and the weekly frequency of this activity, similar responses in both groups were observed.

In the measurement of CS by the CSI-BP, individuals with MSP presented a mean total score of 23.40 (7.32) (from 0 to 100 points) and the Control Group presented a mean score of 15.8 (10.26) as a total score, meaning that there was no difference between the groups regarding the presence of signs and symptoms of CS ($p=0.07$). None of the individuals had diagnoses of clinical conditions, suggested in the CSI-BP part B, that could potentiate CS.

The pain severity and intensity domains identified using the BPI questionnaire in the group of individuals with pain were characterized as mild. It should be emphasized that the MSP identified in the sample was not related to phantom limb pain, as both groups had reports of phantom limb pain (Table 1). In addition, when asked about affected body areas, individuals predominantly reported feeling MSP in areas such as hips/thighs, neck, and lower back.

The analysis of the Alpha brain waves (8-12 Hz) in the whole brain showed a mean electrical activity of 48.02 µV (12.87) in the Control Group, while the Pain Group showed an average electrical activity of 44.44 µV (12.03), with a difference of 7.5% of total Alpha wave activity between the groups ($p=0.01$). In the comparison between groups, the location of the reduction of the Alpha wave was identified in the posterior region of the brain (occipital lobe), to the right of the brain, in the group with pain. Also, descriptively, the areas of Alpha wave generation in the brain can be seen in Figure 1, while the topographic distribution of this wave in the brain can be seen in Figure 2.

In a coupling analysis of two different brain wave frequencies (PAC), a coupling of the Gamma frequency (34 Hz) with Theta frequency (4 Hz) was observed in the Control Group. In the Pain Group, higher values were observed for Gamma (38 Hz) with Theta (4 Hz). In addition, the Control Group presents higher coupling strength in Pz (34 Hz) compared to the Pain Group (37 Hz) (Figura3).

Table 1. Sociodemographic and assessment characterization of individuals with amputation (n=20).

Variables	Control (n=10)	With pain (n=10)
	(%)	
Gender (M)	9 (90%)	5 (50%)
	Mean (SD)	
Age (years)	37 (8.96)	35.1 (7.68)
Height (m)	1.72 (0.05)	1.66 (0.08)
Weight (kg)	86.4 (7.9)	68.4 (14)
BMI (kg/m²)	29.42 (3.28)	24.97 (5.23)
	(%)	
Physical activity (yes) (%)	8 (80%)	8 (80%)
	Mean (SD)	
Weekly frequency of physical activity (days)	2.6 (1.95)	3.4 (2.41)
BPI - Severity	-	3.90 (1.49)
BPI - Interference	-	2.27 (2.36)
CSI-BP	15.8 (10.26)	23.40 (7.32)
	(%)	
Report of phantom limb pain	6(60%)	9(90%)
	(n)	
Body areas with report of pain	Neck	5
	Shoulder	2
	Wrist/hand	2
	Lower back	4
	Hips/thighs	6
	Knees*	2
	Ankles/feet*	1

M = male; m = meters; kg = kilograms; kg/m² = kilograms per square meter; BMI = Body Mass Index; BPI = Brief Pain Inventory; CSI-BP = Central Sensitization Inventory Brazilian Portuguese. *Pain in the body segment in the non-amputated limb.
Source: Prepared by the authors.

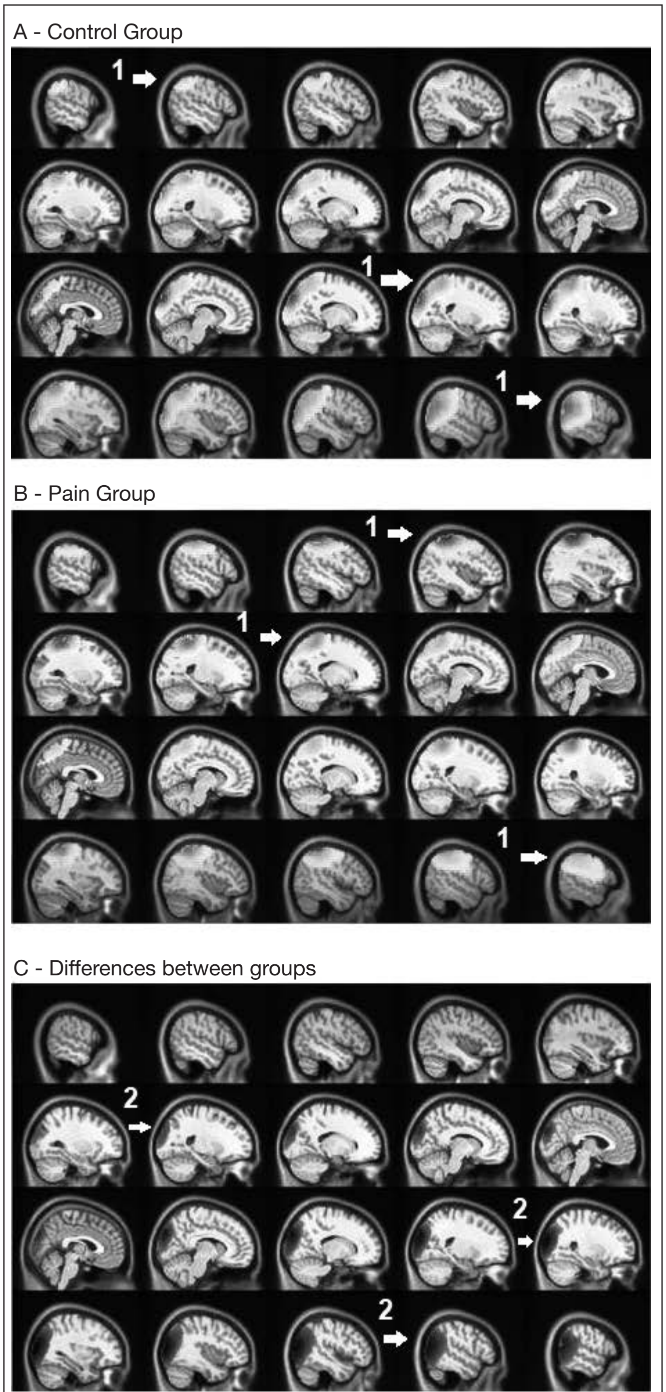

Figure 1. Quantitative electroencephalography of Alpha wave brain activities of the groups: (A) without pain, (B) with pain, (C) difference between groups: reduction of Alpha wave in the right posterior region of the brain of amputated individuals with musculoskeletal pain compared to the Control Group. Arrows with number 1 indicate higher Alpha generation, whereas arrows with number 2 suggest lower Alpha generation.

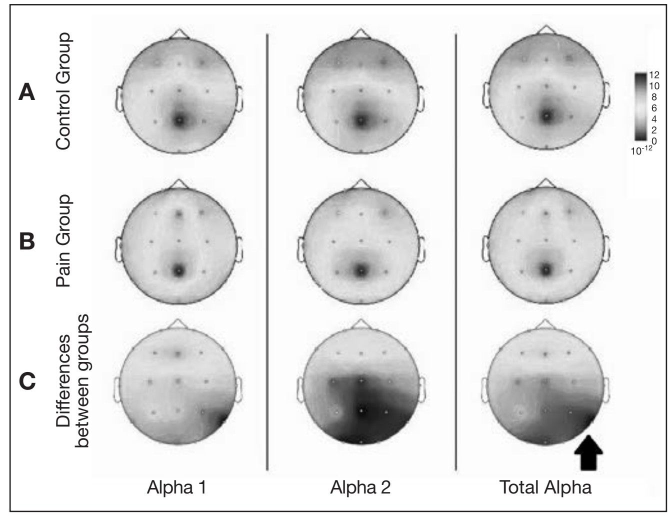

Figure 2. Brain topographic analysis by qEEG of the electrical activities of the Alpha wave of people with amputation: (A) without pain, (B) with pain, (C) difference between groups: reduction in the occipital region. Arrow indicates topographical distribution of Alpha brain wave reduction between groups.

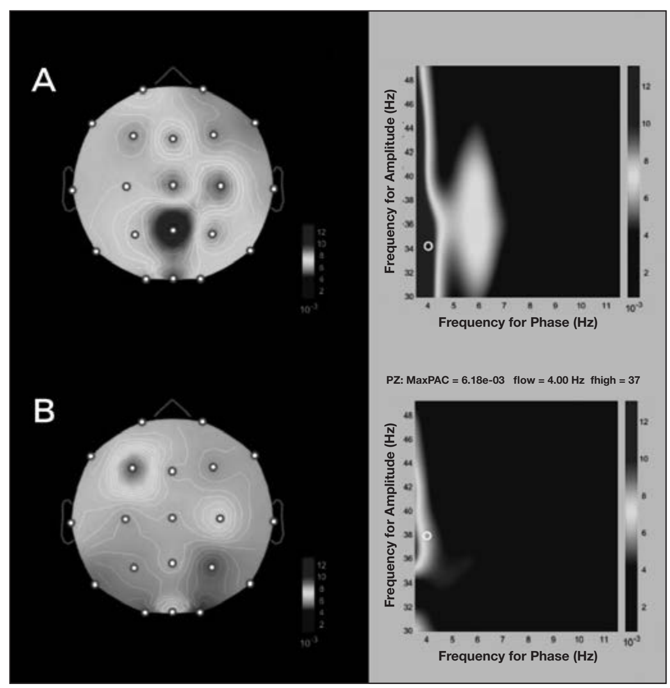

Figure 3. Phase-amplitude coupling (EG Phase-Amplitude Coupling - PAC) in Pz. (A) Control group. (B) Group of amputee individuals with musculoskeletal pain.

DISCUSSION

The study investigated the Alpha brain wave activity in individuals with amputation with and without symptoms of MSP. The results showed reduced Alpha brain wave amplitude in amputees who reported having MSP, which may infer a reduction in the number of recruited neurons performing action potentials, specifically at the frequency of 8-12 Hz, in the evaluated area. This outcome has broad clinical relevance because the Alpha wave is related to several brain functions, such as cognitive processing, emotional control and integrative functions[35], besides having a specific role in the regulation of sensory-motor processes[36].

The intensity of painful stimuli has been associated in the literature with changes in the Alpha wave in sensory-motor areas[37,38] in healthy individuals and individuals with fibromyalgia. In individuals with amputation, studies have found altered connectivity and increased clustering coefficient of the Alpha band, signaling synchronization and stronger functional connections, which may be related to sensory perception or to the phantom limb pain itself[21].

In the present study, a topographic analysis was also performed, i.e., a brain mapping, which showed the occipital area as the location where most of the decrease in the Alpha wave occurred in the group with MSP, a fact that may be related to a regulation of this oscillatory rhythm via neurotransmitters and neuromodulators, such as GABA (Gamma-AminoButyric Acid), glutamate blockers and serotonin potentiators[39]. In addition, the qEEG allows the mapping of brain waves, including in amputees[23] who experienced synesthetic pain (pain felt when they observe pain in another person), and showed a decrease in brain electrical activity in Tetha and Alpha waves, which may indicate an alteration in the processing of inhibitory control, which would facilitate the synesthetic experience of pain observed. It is important to note that in the present study the two groups with amputated patients brought reports of pain in the phantom limb, but in the analysis this pain did not present an association with the MSP, ruling out, a priori, the association of pain in the phantom limb with the outcomes.

This Alpha reduction observed in individuals with amputation and reports of pain is also in agreement with pre-existing data in the literature for a population with MSP in general[36]. Moreover, Alpha wave alterations have also been related to other clinical conditions, such as cognitive dysfunction[40] and chronic pain patients[41]. It is worth noting that it is already possible to relate chronic pain conditions with adaptations in the somatosensory brain function[42].

On the other hand, considering that chronic pain presents a high prevalence in the Brazilian population[43], using treatment strategies that are supported by the literature for chronic pain and that also seem to increase the activity of Alpha waves seems to be a safe path. Among these strategies, it's possible to mention neurofeedback training[44], exercises[45], meditation[46], and myofascial manual techniques[47]. The hypothesis of the relationship between the brain electrical pattern and pain becomes stronger when it was found that part of these interventions can be found in pain treatment guidelines[48,49].

Another point observed in the present study was the coupling of the Theta wave frequency with the Gamma wave. The Alpha wave did not present coupling with the Gamma wave in this analysis. When comparing the groups, the coupling, i.e., the junction of two brain wave frequencies working to perform a function, presented faster Gamma waves in the group with MSP. The increase in Gamma has been related to the signaling of nociceptive information perceived by the brain to cortical areas of pain processing and with behavioral responses arising from pain[50]; both aspects can be evidenced in the PZ, the area evaluated in the present study. This increase in Gamma oscillatory responses with higher frequencies has also been associated with painful stimuli[51], since this frequency, together with the Theta wave frequency, is involved in the processing of pain[52], which reinforces the prospect of repetition of this same pattern in individuals with amputation and pain report, despite the brain connectivity alterations already described in the literature[21].

Study strengths and limitations

The present study brings prospects for using qEEG as a method of tracking and mapping brainwave electrical activity in amputee patients with unrelated phantom limb MSP. To the authors' knowledge, this is the first study that analyzed the electrical brain activity of individuals with amputation targeting MSP that may be part of the daily life of this population and that impacts their activities and even social participation. In addition, the present study shows the feasibility of monitoring the pain of the studied population using qEEG, which may open space for longitudinal studies. As a limitation, the sample size is small for the representativeness of this population, even though it is similar to another study with qEEG[23], which may restrict extrapolations of the results.

CONCLUSION

In the present study, when brain electrical activity of the Alpha wave was compared between the groups, individuals with amputation and a report of MSP had an electrical pattern with lower amplitude (lower activation) of the Alpha wave compared to amputees without pain. It was also observed that this reduction of Alpha occurred specifically in the parieto-occipital area (related to sensory aspects). In addition, a coupling of Theta with higher Gamma frequencies was observed in the group with pain, suggesting higher connectivity of the Pain Group.

AUTHORS' CONTRIBUTIONS

Débora Pinheiro Aguiar
Data Collection, Resource Management, Research, Methodology, Writing - Preparation of the original, Visualization
Paulo Cezar do Nascimento Filho
Statistical analysis, Data collection, Conceptualization, Research, Methodology, Writing - Review and Editing, Validation, Visualization
Amanda Guerra Moreira
Data Collection, Resource Management, Research
Gabriella Coelho Vieira de Melo Alves
Data Collection, Resource Management, Research
Gisele Harumi Hotta
Conceptualization, Methodology, Writing - Review and Editing, Validation, Visualization
Francisco Fleury Uchoa Santos-Júnior
Statistical analysis, Data Collection, Conceptualization, Project Management,Writing - Review and Editing, Supervision, Validation, Visualization

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