Original research

Patients with temporomandibular disorders and chronic pain of myofascial origin display reduced alpha power density and altered small-world properties of brain networks

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ABSTRACT | BACKGROUND: Chronic pain is one of the most common symptoms of temporomandibular disorders (TMD). Although its pathophysiology is still a challenge, TMD has been associated with changes in central nervous system activity related to pain modulatory capacity. **OBJECTIVE:** To assess the cortical activity of patients with temporomandibular disorders and chronic pain of myofascial origin using quantitative electroencephalography (qEEG) in different mental states. **METHOD:** This study consists of a cross-sectional study. Individuals with TMD and chronic pain and healthy controls were evaluated using qEEG in four consecutive conditions, all with closed eyes: 1) initial resting condition; 2) non-painful motor imagery task of hand movement; 3) painful motor imagery task of clenching the teeth; 4) final resting condition. **RESULTS:** Participants with TMD and chronic pain overall presented decreased alpha power density during baseline at rest, non-painful and painful motor imagery tasks when compared to healthy controls. Furthermore, functional brain connectivity was distinct between groups, with TMD and chronic pain showing lower small-world values for the delta (all conditions), theta (painful and non-painful motor imagery task), and alpha bands (painful motor imagery task), and an increase in the beta band (all conditions). **CONCLUSION:** These results suggest that TMD and chronic pain could be associated with maladaptive plasticity in the brain, which may correspond to a reduced ability to modify brain activity during different mental tasks, including painful and non-painful motor imagery.

KEYWORDS: Temporomandibular Disorders. Chronic Pain. Electroencephalography. Imagery. Connectivity.

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1. Introduction

Temporomandibular disorders (TMD) include musculoskeletal and neuromuscular conditions affecting the temporomandibular joint, masticatory muscles, and associated structures.[1,2] TMD affects over 25% of the world population[3-5] with a prevalence four times higher among females than males.[6] Chronic pain is a common TMD comorbidity[7-9], and it has been associated with significant functional and structural changes in the thalamus and somatosensory cortex.[10] Thus, chronic TMD pain has also been associated with central sensitization, leading to abnormal nociceptive processing and increased pain perception.[11,12]

Quantitative electroencephalography (qEEG) has been used to evaluate pain-related brain functioning in healthy individuals[13] and subjects with different chronic pain conditions.[14] During rest state, subjects with neuropathic pain, fibromyalgia, cancer pain, and low back pain[14], as well as rheumatoid arthritis[15] displayed increased alpha and theta power densities as compared to healthy individuals. Patients with visceral pain[16] and neuropathic pain[17,18] showed a lower alpha peak frequency compared to controls. In addition, subjects with chronic pain present increased synchrony in the theta and gamma frequencies in the frontal brain areas.[17-19] However, data regarding chronic TMD pain are scarce and derived mainly from neuroimaging techniques.

A recent systematic review has shown that chronic TMD pain is associated with brain changes in the default mode network, trigeminal-thalamocortical pathway, antinociceptive network, and lateral and medial pain systems, as observed through functional magnetic resonance imaging (fMRI).[20] By contrast, EEG and magnetoencephalographic (MEG) studies offer higher temporal resolution, adding valuable insights into brain function. Data have shown that chronic TMD pain subjects present alterations in the perception and processing of non-painful facial stimuli, with persistent cortical activation after stimulation.[21] These alterations occurred in regions like the anterior cingulate, amygdala, and even the primary auditory cortex when vibrotactile stimuli were applied to the face or index finger.[22] Recent data showed an increased EEG power spectral density (PSD) in the 4Hz to 25Hz range in subjects with neuropathic orofacial pain, positively correlated to pain intensity.[23] However, this result was not observed in chronic TMD pain subjects compared with healthy individuals during a Pressure Pain Threshold (PPT) task.[24]

Considering that brain processing in chronic TMD pain subjects may be altered during daily-life events, such as skin touch, one might question whether similar conditions, like muscle contraction or jaw movement, also lead to abnormal brain activity. While cortical responses to movement-evoked pain appear altered in low back pain subjects, limited knowledge exists regarding the effects of motor tasks in other chronic pain conditions.[25] A recent study using a jaw force task showed that pain induced by this task can attenuate alpha and beta EEG bands responses.[26] Nevertheless, the use of overt pain-evoking motor tasks may provoke high discomfort in subjects. Hence alternative experimental tasks should be considered for the impact of motor activity on pain perception. Motor imagery (MI), is known to activate brain regions similar to those involved in movement execution[27], and may theoretically alter brain activity associated with pain regulation. Studies have indicated that subjective pain ratings and N200 amplitudes of event-related potentials elicited by painful stimuli can be increased by instructing subjects to imagine a forearm lesion.[28] While MI may worsen pain and edema in subjects[29], its discomfort is likely lower than actual movement experience, while still offering insights into brain dynamics during body actions. EEG analysis can discriminate between painful versus non-painful MI[30], making it a valuable strategy to understand brain dynamics during movement-provoked pain in chronic TMD pain, especially given the importance of jaw movements in daily life.

In addition to analyzing brain oscillations and event-related potentials, EEG provides insights into brain dynamics by evaluating functional connectivity and small-world properties in healthy and different painful conditions.[31,32] This small-world brain architecture of the brain features a dynamic and functional network characterized by many local connections and fewer long-range connections, analyzed through graph theory methods.[33] Previous fMRI studies have shown significant changes in small-world parameters in conditions such as low back pain[34], and post-herpetic neuralgia[35], indicating that chronic pain leads to an unstable and inefficient

brain networks topology, with reduced functional connectivity in cingulate, somatosensory and frontal cortices, as well as reduced nodal efficiency compared to healthy controls. However, despite some studies revealing altered connectivity in chronic TMD pain subjects[36-38], nothing is known about the small-world properties of brain networks assessed through EEG in these subjects.

In summary, the current knowledge on brain functioning assessed through EEG in chronic TMD subjects pain presents potential limitations that require further clarification. To address this, we propose to assess EEG PSD both at rest and during painful and non-painful motor imagery tasks, as well as analyze the small-world properties of brain networks. We predict that compared to healthy controls, subjects with chronic myofascial TMD pain will exhibit: (1) increased PSD in delta and theta frequencies and decreased PSD in alpha and beta frequencies at rest; (2) reduced alpha and theta power densities during painful motor imagery tasks; (3) altered small-world properties of brain networks.

2. Materials and methods

2.1 Study design and sample

In this cross-sectional study, 18 female subjects with chronic myofascial TMD pain with sex and age matched to healthy controls (HC) were recruited. A convenience sample was recruited to participate in this study. Individuals with TMD were referred from reference centers for the treatment of orofacial pain in the city of Salvador.

Two chronic TMD pain subjects and two HC were excluded after the EEG artifact rejection protocol. Thus, we had a final sample of 16 chronic TMD pain subjects (mean age = 40.19 ±10.68 years) and 16 healthy controls (mean age = 32.94 ±11.68 years). The study was approved by the Research Ethics Committee according 466/12 resolution of the Brazilian Health Ministry.

The Fonseca Anamnestic Questionnaire[39] was used during the screening of symptomatic subjects. To confirm the diagnosis, we used the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) questionnaire axis I. Only those with myofascial TMD were included in the study. Psychosocial aspects were assessed with RDC/TMD axis II, culturally adapted for the Brazilian population.[40] The HC was also assessed through the Fonseca Anamnestic Questionnaire to screen and confirm the absence of TMD symptoms. As inclusion criteria, subjects with TMD should also present daily or near-daily pain of myofascial origin for at least six months. Pain in the last six months should have an intensity equal to or greater than 3 in the Visual Numerical Scale (VNS), ranging from 0 to 10. Subjects with inflammatory connective tissue disease (e.g. ankylosing spondylitis, rheumatoid arthritis, and psoriatic arthritis), fibromyalgia, neurological disorders, dental pain, ongoing orthognathic surgery, or using dental splints were excluded. All subjects signed the informed consent form.

2.2 Evaluation Procedure

2.2.1 Clinical Assessment

For the initial evaluation, the Brazilian version of the RDC/TMD questionnaire (axes I and II) was used. Axis I is used for confirming the diagnosis and to classify the type of TMD, which may be myogenic, arthrogenic, or mixed. Axis II was used to collect the quality of life and sociodemographic data.[40]

Clinical assessment was performed immediately before the electroencephalographic evaluation. For both groups, we used an anxiety/depression assessment scale, The Hospital Anxiety and Depression Scale (HAD) composed of 14 items for the screening of anxiety and depression symptoms.[41] The pain quality was assessed through a culturally adapted McGill pain questionnaire for the Brazilian population[42,43], providing qualitative measures of clinical pain.

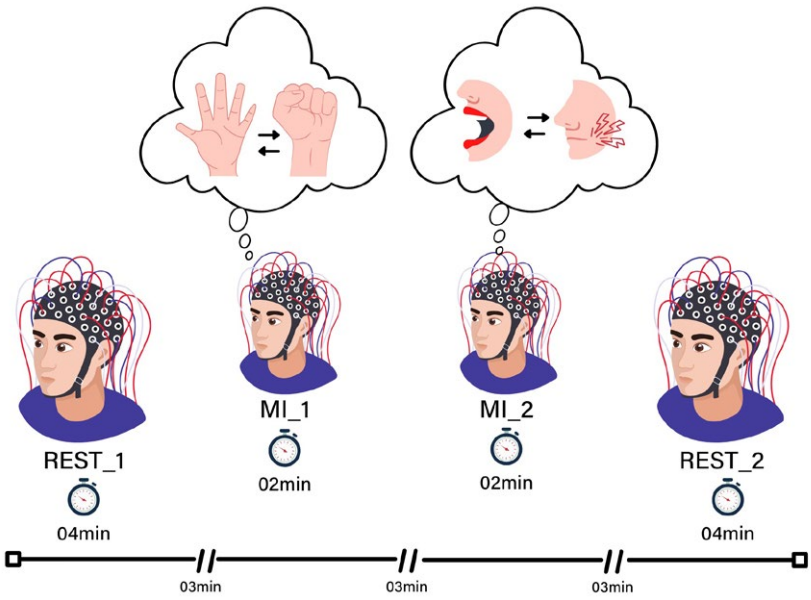
2.2.2 EEG data recording

The cortical activity was recorded by 20 gold-plated EEG electrodes, positioned on the scalp according to the 10/20 International System and using a BrainNet[36] device (EMSA, Brazil). The scalp was prepared using a Nuprep abrasive gel (Weaver and Company, Aurora, CO, USA).

Subjects were seated comfortably in a Faraday cage and were instructed to be relaxed, with eyes closed, while monitored to stay awake. The EEG sampling rate was 200 Hz, with an impedance lower than 5 kΩ, reference in Cz, and a notch filter of 60 Hz. The electrodes used were: Fp1-Fp2-F3-F4-F7-F8-Fz-T3-T4-T5-T6-C3-C4-P3-P4-Pz-O1-O2-Oz and a ground electrode, positioned on the left shoulder. Electromyography electrodes were placed on the flexor muscles of the dominant hand and at the masseter muscle of the dominant side to ensure participants were not making actual voluntary movements while attempting to perform imagery tasks.

At the beginning of the experimental session, the subjects were instructed on the two MI tasks to be used and received a brief training session. The trial period concluded after two or three attempts, when subjects confirmed their understanding of the task. Subsequently, subjects closed their eyes, and four conditions were sequentially applied: a) initial resting-state; b) non-painful MI task involving hand movement; c) painful MI of clenching teeth; d) final resting-state. The latter condition was included to ascertain if any changes during motor imagery would persist post-task. For the MI tasks, subjects were instructed to perform kinesthetic motor imagery, which involved imagining clenching their dominant hand for a non-painful motor imagery task and, in the subsequent condition, clenching their teeth for a painful motor imagery task. Each resting-state condition lasted four minutes, while each MI condition lasted two minutes. The time interval between conditions was three minutes. An audio recording of the words 'clenching' and 'relaxing' was played to prompt subjects to perform the two MI tasks. The 'relaxing' cue was played five seconds after 'clenching,' and the next 'relaxing' cue followed three seconds later. In total, subjects executed 16 'clenching' trials in each motor imagery condition (Figure 1).

Figure 1. EEG recordings were taken in four different conditions



Initial resting-state (REST_1), followed by imagery tasks of nonpainful (hand clenching and opening) (MI_1), and then painful (teeth clenching and opening) movements (MI_2), and finally by a final resting state condition (REST_2). EEG recordings at rest lasted four minutes, while EEG recordings during motor imagery tasks lasted two minutes. Source: the authors (2024).

2.3 EEG data processing and analysis

EEG data were analyzed using the EEGLab toolbox in the MATLAB environment. Data were filtered with a 0.5-45 Hz band-pass filter. The electrodes were re-referenced to the mean of all channels. Continuous recordings were segmented in epochs of 1,280 milliseconds, resulting in 186 epochs for the resting-state conditions and 93 epochs for the MI tasks. This epoch size allowed a consistent evaluation of power densities in the 1.5–30 Hz frequency range. All epochs were corrected by subtracting each data point from the mean amplitude of the first 100ms. In addition, a semi-automatic protocol was used to remove amplitude artifacts using an upper limit of +750 μV, a lower limit of -750 μV, and ±2 global standard deviations as rejection criteria. In addition, two authors visually assessed epochs to decide which epochs should be removed. The inter-rater reliability was approximately 95%. The individual's highest rejection rate was approximately 77 epochs during the resting-state conditions, whereas the highest was around 29 epochs during the imagery conditions. Based on this data, we opted for a uniform number of 29 epochs across all conditions.

The absolute PSD was calculated for each electrode separately by applying and averaging the Fast Fourier Transform of each epoch. Then, we computed the relative PSD for each frequency band by dividing the absolute PSD value of each electrode by their values in the total EEG power spectrum. In addition, we computed regions of interest by grouping electrodes and averaging their relative PSD as follows: frontal (Fp1-Fp2-F3-Fz-F4), temporal (T3-T5-T4-T6), central (C3-C4), parietal (P3-Pz-P4) and occipital (O1-Oz-O2), as described in a previous study.15 The power densities of the following frequency bands were analyzed: delta [1.5-3.5Hz], theta [4-7Hz], alpha [8-12Hz], and beta [13-30Hz].

2.4 Statistical analyses

We used the Shapiro-Wilk test to analyze the normality of the data distribution. Between-Groups differences in sociodemographic and clinical data were assessed by Student's t-test or Mann-Whitney U-test and Fisher's exact test according to variable type. We used the Bonferroni post-hoc correction of multiple comparisons when analyzing sociodemographic, clinical data, and ANOVA analysis as described below.

2.4.1 EEG relative PSD

Repeated-measures ANOVAs were used to evaluate differences between "group" (TMD patients with chronic pain vs. healthy controls), "brain region" (frontal vs. central vs. temporal vs. parietal vs. occipital), and "condition" (initial resting-state vs. nonpainful imagery vs. painful imagery vs. final resting-state). Three sets of ANOVAs were performed: A) To test our main hypothesis by comparing the two groups during the four experimental conditions. B) To test the effects of group and experimental conditions separately at the different brain regions. C) To test differences between the initial and the final resting-state conditions. All ANOVAs were controlled for symptoms of anxiety and/or depression, in case of significant effects due to the main factor "group'' or the interaction "group*condition". Violations of the sphericity assumption were corrected by the Greenhouse-Geisser. We tested statistical significance at the .05 level. The SPSS 20.0 software package was used for these analyses.

2.4.2 Brain connectivity

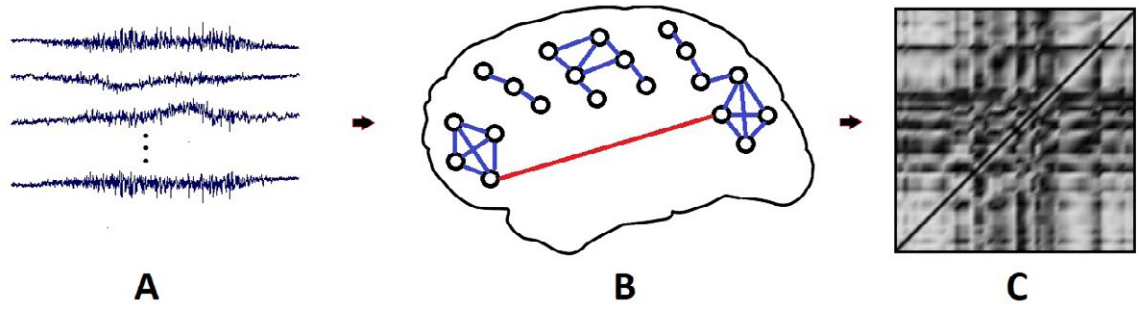
The effective or functional connectivity can be assessed using interconnection and clustering parameters over nodes and edges, distinguishing regular from randomized networks generating the global measures.[44,45] A global measure of the graph interconnectedness can be defined as the average path length L, which is the average number of steps from one node to another, taking the shortest path. A global measure of the graph density can be defined as the clustering coefficient C, which represents the proportion of neighbor nodes that are connected to each other, forming triangles. Ordered graphs exhibit long L and high C, while random ones have short L and low C. There are ordered graphs that show some efficiency in the sense of information diffusion when new long-distance connections arise causing the drop of the average path length while the average cluster coefficient remains practically unchanged. This phenomenon is called 'small-world', and here is referring to the idea of connecting any two different EEG channels with a few steps.[32] Small-world networks are identified by short L and high C and have been detected in neural contexts being considered an optimal architecture for synchronizing neural activity between brain regions.[46,47]

We inferred brain connectivity using a nonlinear causality measure called convergent cross-mapping (CCM)[48] which captures nonstationary coupling effects between brain areas. Given an EEG signal X={x1,..., xn}, CCM is based on embedding vectors Xev(i)=(xi,xi+τ, xi+2τ, xi+(m-1) τ), i=1,...,n-(m-1) τ, where m is the spatial dimension and τ is the time delay. For each Xev(i) we calculate wj , j=1,...,n-1, a normalized distance-related weight to the other embedding vectors.49 Considering a second EEG signal Y={y1,..., yn}, we can estimate predicted information from X, calculating ỹi= Σwjxj. Considering the prediction vector Ỹ={ỹ1,..., ỹn}, CCM is defined as the correlation between Y and Ỹ. If X and Y are coupled, in the sense of complex systems, CCM shows values close to -1 or 1.

After a narrowband decomposition and considering the connectivity strength between channels, for each subject, condition, and epoch, CCM was evaluated resulting in a 20x20 matrix, where the diagonal values were ignored and the absolute values were taken into account. For each subject and condition, the medians of the CCM values (from pairs of channels) were used as a threshold to turn matrices into a binary representation (adjacency matrices) and to define the graphs (Figure 2).

Graph analysis was performed for the adjacency matrices, calculating first the average path length (L) and the average clustering coefficient (C), and then the small-world parameter (S), defined as a ratio of standardized C and L values.[46-50] All these parameters were computed separately for each EEG dataset filtered within the four band frequencies (delta, theta, alpha, and beta). The connectivity data are not normally distributed and require a nonparametric approach. To attenuate inter- and intra-subject variability, we considered only the S-values in the interquartile interval for each condition, between the 25th and 75th percentiles. These statistical analyses were carried out by the nonparametric Mann-Whitney U-test for inter-groups comparisons, with a significance level of 0.05.

Figure 2. Illustration of the brain connectivity analysis for one epoch



(A) 20 Decomposed signals. (B) Graph representation based on 20 nodes (or channels) with local and global connections respectively depicted in blue and red lines. The number of edges or connections is determined by the absolute values of a nonlinear causality measure called convergent cross-mapping (CCM) thresholded by the median. (C) Adjacency matrix map (binary representation) of the graph used for C and L calculations.
Source: the authors (2024).

3. Results

All the subjects presented at least mild pain during data collection. Several subjects were taking only weak analgesics, and they were asked to interrupt their medication for at least 12 hours before data collection.

3.1 Clinical and Sociodemographic Data

There were no differences between groups for sociodemographic characteristics. Chronic TMD pain subjects presented higher scores of anxiety and/or depression [X2(1)=11.221, p=.002] (Table 1). Thus, we adjusted all ANOVA models for those symptoms, which were significant between-group differences in the clinical evaluation. Clinical pain characteristics of chronic TMD pain subjects are described in Table 2.

Table 1. Comparison of Demographic, Clinical Characteristics of Women with Temporomandibular Disorders and Healthy Controls

	Total sample(n=32) N(%) or mean (±SD)	TMD (n=16) N(%) or mean (±SD)	Controls (16) N(%) or mean (±SD)	P-value
Demographic Characteristics				
Age, in years	36.56(±11.61)	40.19(±10.68)	32.94(±11.68)	.07
Race/color				.70
White	10(31.3)	4(25.00)	6(37.50)	
Black, Mixed race, Others [a]	22(68.80)	12(75.00)	10(62.50)	
Marital Status				.47
Married	17(53.10)	10(62.50)	7(43.80)	
Separated/Divorced/ Widow	15(46.90)	6(37.50)	9(56.30)	
Clinical Characteristics				
Depression/Anxiety (HADS)				.002*
With anxiety and/or depression	11(34.40)	10(62.50)	1(6.30)	
Without anxiety and/or depression	21(65.60)	6(37.50)	15(93.80)	

Differences between groups were tested using Student's t-test for continuous variables, and Fisher's test or Mann Whitney for categorical variables.*P < .05, a Others = total of individuals self-declared ``Yellow/Oriental`` and ``Indian``; SD = Standard Deviation; TMD = Temporomandibular Disorders; HADS = Hospital Anxiety and Depression Scale.
Source: the authors (2024).

Table 2. Characteristics of the Pain in Women with Temporomandibular Disorders

Characteristics of pain	Mean (SD)
VNS[a], mean (SD)	3.69(3.15)
VNS in the past six months[b], mean (SD)	7.31(1.53)
Pain duration, in years[c], median (IQR)	1.58(0.5-4.25)
Number of pain descriptors[d], mean (SD)	14.13(3.64)
McGill pain index[e], mean (SD)	32.60(11.29)

SD=Standard Deviation, IQR=Interquartile Range, VNS = Visual Numerical Scale
a,b,c Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) – Axis I
d,e McGill Pain Questionnaire variables
Source: the authors (2024).

3.2 EEG relative PSD

3.2.1 Group differences across experimental conditions

Repeated measures ANOVA using the between-subjects factor "group", and the within-subjects factors "condition" and "brain region" were used to analyze overall differences in relative PSD at the four EEG band frequencies: delta, theta, alpha, and beta. These analyses revealed significant differences in relative PSD due to the factor "group" at the alpha [F(1,30) = 7.786, P = .009] and the beta frequency band [F(1,30) = 5.359, P = .028]. In addition, a significant interaction "condition x group" was found in relative PSD at the delta band [F(3,360) = 3.175, P = .043, GG epsilon = .634]. No significant differences were observed in relative PSD at the theta band.

To further analyze whether the above findings were due to group differences in mood, additional ANCOVAs were performed on relative PSD of delta, alpha, and beta frequency bands controlling for anxiety and depression. Significant effects due to “group” [F(1,29) = 6.613, P = .016] and "condition x group" [F(3,348) = 3.893, P =.022, GG epsilon = .736] were only observed in relative PSD in the alpha band, confirming that regardless of differences in anxiety/depression, chronic TMD pain subjects had a decreased alpha PSD at initial resting condition (mean difference=.166, P=.003), as well as during nonpainful (mean difference=.173, P=.006), and painful motor imagery tasks (mean difference=.125, P=.045) (Table 3). No significant effects were observed at the final resting condition. Regarding the beta band, only significant effects due to the factor “group” were observed [F(1,29) = 5.942, P = .021], however, in "condition x group" no effects were found, indicating only higher relative PSD in chronic TMD pain subjects than in healthy controls. Finally, no significant effects were yielded in PSD at the delta band when anxiety/depression was controlled for.

Table 3. Relative power density for the interaction between conditions and groups, controlling for symptoms of anxiety and/or depression, in women with TMD/CP and HC

Frequency band and Condition	TMD/CP Participants (n=16) Mean (±SD)	HC Participants (n=16) Mean (±SD)	*F* (3,348)	*P*-value
Delta			2,558	.080
REST_1	1.40(.16)	1.37(.16)		.55
MI_1	1.41(.16)	1.37(.16)		.48
MI_2	1.41(.17)	1.40(.17)		.88
REST_2	1.37(.18)	1.43(.18)		.39
Theta			1.221	.303
REST_1	1.20(.12)	1.23(.12)		.43
MI_1	1.20(.10)	1.22(.10)		.59
MI_2	1.21(.11)	1.25(.11)		.39
REST_2	1.19(.14)	1.27(.14)		.17
Alpha			3.893	**.022#**
REST_1	1.21(.13)	1.37(.13)		**.003***
MI_1	1.21(.15)	1.38(.15)		**.006***
MI_2	1.24(.15)	1.36(.15)		**.045***
REST_2	1.23(.15)	1.33(.15)		.115
Beta			0.218	.865
REST_1	.83(.05)	.78(.05)		.011
MI_1	.83(.05)	.78(.05)		.024
MI_2	.82(.06)	.77(.06)		.057
REST_2	.83(.06)	.78(.06)		.033

ANOVA of repeated measures. #P < .05 F-test statistics presented here for the interaction between conditions and groups. *P < .05 Between-group comparisons (Bonferroni correction) are in bold. TMD/CP = Temporomandibular disorder and chronic pain, HC = healthy controls, SD = standard deviation, REST_1 = initial resting state, MI_1 = non-painful motor imagery, MI_2 = painful motor imagery, REST_2 = final resting state.
Source: the authors (2024).

3.2.2 Effects of group and conditions on brain topography of alpha PSD

The second set of analyses aimed to examine the topographical distribution of the “group” and "condition x group" effects in the alpha frequency band. Thus, repeated-measures ANOVAs were performed for each brain region of interest (frontal, central, parietal, temporal, and occipital) with the between-subjects "group" factor (TMD patients with chronic pain versus healthy controls) and within-subjects. The analysis included subject factors of “condition” (initial resting-state vs. non-painful imagery vs. painful imagery vs. final resting-state) and was controlled for anxiety and/or depression. The analysis revealed that chronic TMD pain subjects showed reduced alpha PSD during the initial resting state, non-painful motor imagery, and painful motor imagery in the frontal region. However, there was no significant reduction in alpha PSD during the final resting state. This alpha PSD decrease was also observed in the temporal and parietal regions, but only during the initial resting state and non-painful motor imagery (Table 4).

Frontal. The ANOVA showed significant group differences in alpha power density [F(3,87) = 4.087, P = .019, GG epsilon = .725]. Post-hoc analysis revealed that TMD patients with chronic pain had decreased alpha power density during initial resting state (mean difference = .185, P = .004), painful (mean difference = .200, P = .005), and non-painful motor imagery (mean difference = .150, P = .039) conditions in comparison to healthy controls.

Central. The ANOVA showed no differences due to “group” or “condition x group” effects in alpha power density [F(3,87) = 2.599, P = .065].

Parietal. The ANOVA showed significant differences due to “condition x group” in alpha power density [F(3,87) = 3.326, P = .032]. Post-hoc analysis indicated decreased alpha power density in TMD patients with chronic pain during the initial resting state (mean difference = .173, P = .012) and the non-painful motor imagery (mean difference = .177, P = .015) conditions in comparison to healthy controls.

Temporal. The ANOVA showed significant group differences in alpha power density [F(3,87) = 3.456, P =.027]. Post-hoc analysis showed decreased alpha power density in TMD patients with chronic pain during the initial resting state (mean difference=.126, P=.011) and the non-painful motor imagery (mean difference =.121, P =.022) conditions in comparison to healthy controls.

Occipital. The ANOVA showed no differences due to “group” or “condition x group” effects in alpha power density [F(3,87) = 2.948, P = .059].

Table 4. Relative alpha power density for the interaction between regions of interest and groups, controlling for symptoms of anxiety and/or depression, in women with TMD/CP and HC

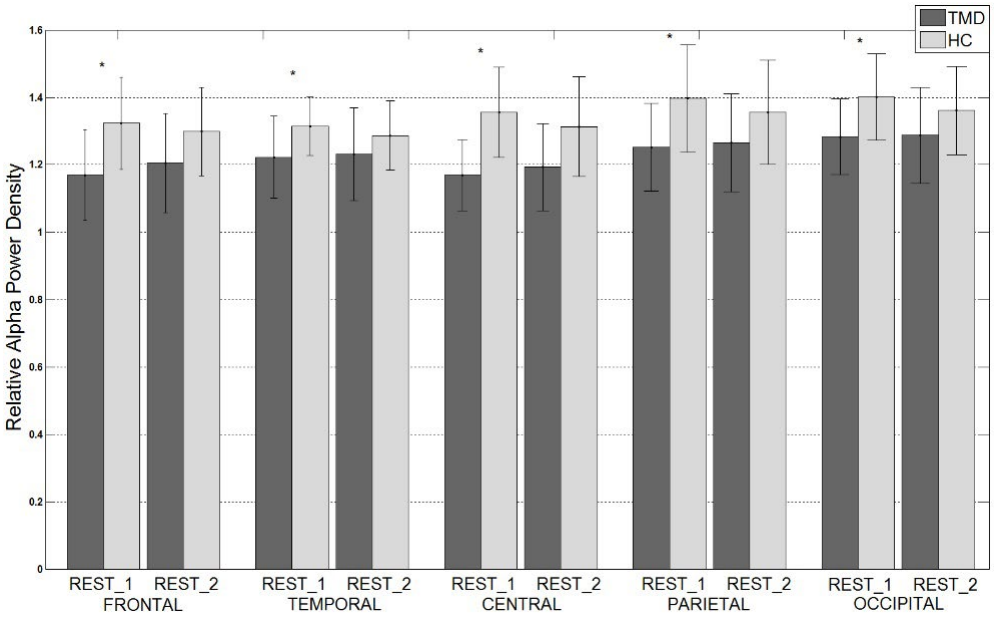
Regions of Interest (study condition)	TMD/CP Participants (n=16) Mean (±SD)	HC Participants (n=16) Mean (±SD)	*F* *(3,87)*	*P*-value
FRONTAL			*F* = 4.087	.019#
REST_1	1.17(.13)	1.32(.14)		**.004***
MI_1	1.19(.15)	1.34(.16)		**.005***
MI_2	1.21(.15)	1.34(.16)		**.039***
REST_2	1.20(.15)	1.30(.13)		.133
TEMPORAL			*F* = 3.456	.027#
REST_1	1.22(.12)	1.31(.09)		**.011***
MI_1	1.22(.13)	1.31(.10)		**.022***
MI_2	1.25(.11)	1.32(.11)		.187
REST_2	1.23(.14)	1.29(.10)		.274
CENTRAL			*F* = 2.599	.065
REST_1	1.17(.11)	1.36(.13)		.000
MI_1	1.18(.11)	1.36(.18)		.004
MI_2	1.19(.12)	1.37(.18)		.017
REST_2	1.19(.13)	1.31(.15)		.041
PARIETAL			F = 3.326	.032#
REST_1	1.25(.13)	1.40(.16)		**.012***
MI_1	1.25(.13)	1.39(.18)		**.015***
MI_2	1.26(.13)	1.38(.17)		.069
REST_2	1.26(.15)	1.36(.15)		.125
OCCIPITAL			*F* = 2.948	.059
REST_1	1.28(.11)	1.40(.13)		.025
MI_1	1.28(.14)	1.42(.15)		.014
MI_2	1.30(.12)	1.40(.14)		.075
REST_2	1.29(.14)	1.36(.13)		.247

ANOVA of repeated measures. #P < .05 F-test statistics presented here for the interaction "brain regions" study "conditions". *P < .05 Conditions that presented significant differences at the Post-hoc tests (with Bonferroni correction) are in bold. TMD/CP = Temporomandibular disorder and chronic pain, HC = healthy controls, SD = standard deviation, REST_1 = initial resting state, MI_1 = non-painful motor imagery, MI_2 = painful motor imagery, REST_2 = final resting state. Source: the authors (2024).

3.2.3. Post-effects of motor imagery (initial and final resting-state conditions compared)

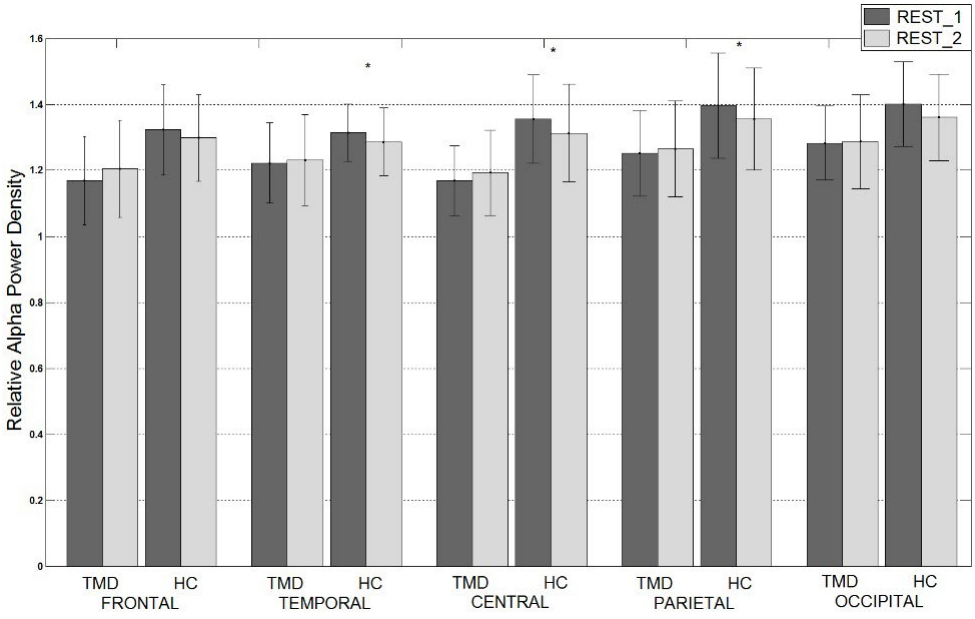
As PSD alpha allowed us to identify differences between groups and conditions, a third set of analyzes aimed to further examine group differences to verify the effect of motor imagery during the initial and final resting state conditions. For this purpose, separate repeated-measures ANOVAs were performed for each brain region of interest (frontal, central, parietal, temporal, and occipital) with "group" as a between-subjects factor (chronic TMD pain subjects versus healthy controls) and "condition" as a within-subjects factor (initial resting vs. final resting condition), and controlling for anxiety and/or depression. A significant "condition x group" effect [F(1,116) = 5.097, P = .037] was yielded. Post-hoc analyzes of this interaction effect showed that individuals with chronic TMD pain had reduced PSD compared to healthy controls during the initial resting state condition in all regions of interest: frontal (mean difference = .185, P = .004), temporal (mean difference = .126, P = .011), central (mean difference = .220, P < .0001), parietal (mean difference = .173, P = .012) and occipital (mean difference = .127, P = .025). However, no significant group differences were observed during the final resting condition (Figure 3).

Figure 3. Comparison of relative alpha power density between groups in initial resting state (REST_1) and final resting state (REST_2)



Source: the authors (2024).

Figure 4. Comparison of relative mean alpha power density within groups in initial resting state (REST_1) and final resting state (REST_2)



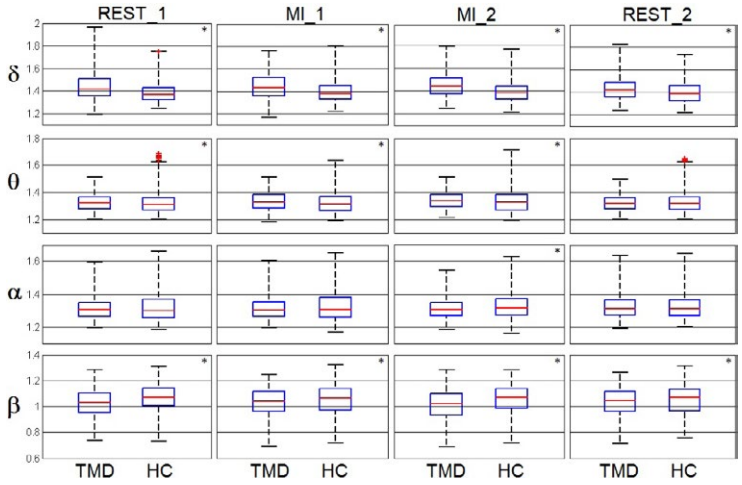
Source: the authors (2024).

Post-hoc analyzes of the interaction effect also revealed no significant differences between the initial and the final resting condition within chronic TMD pain subjects, whereas reduced alpha PSD was observed within healthy controls at temporal (mean difference = .042, P = .037), central (mean difference = .053, P = .036) and parietal regions (mean difference = .047, P = .024) during the final than during the initial resting condition (Figure 4).

3.3 Small-world properties of brain networks

The inter-group comparisons for the distributions of the S parameter are presented in Figure 5 for each group, condition, and EEG frequency band (delta, theta, alpha, and beta). The values of the S parameter were significantly different between groups for the delta, theta, and beta frequency bands across conditions (except for the theta band in the final resting condition). S medians were overall higher in healthy controls than in chronic TMD pain subjects for delta and theta frequency bands, whereas they were higher in chronic TMD pain subjects than in healthy controls for the beta frequency band. Furthermore, no significant group differences were observed in the S parameter for the alpha frequency band (except during the painful motor imagery condition).

Figure 5. Box plots of the 'small world parameter' σ distribution across groups, conditions and bands



REST_1 - initial resting state, MI_1 – non painful motor imagery, MI_2 – painful motor imagery, REST_2 – final resting state.
Mann-Whitney U-test. *significant difference between TMD/CP and HC groups (P<0.05)
Source: the authors (2024).

4. Discussion

Our objective was to assess brain activity and small-world properties of brain networks at rest and during painful and non-painful imagery tasks in chronic myofascial TMD pain subjects compared to healthy controls. Statistical analyzes were also controlled for symptoms of anxiety and depression, as they could be confusing variables in the interpretation of the results. Partially in accordance with our predictions[51,52], results indicated that chronic TMD pain subjects had lower relative PSD than healthy controls in the alpha frequency band at rest, especially in frontal, temporal, and parietal brain regions. Furthermore, chronic TMD pain subjects displayed greater attenuation of alpha power densities than controls during both painful and non-painful motor imagery tasks. Finally, we observed altered properties of small-world parameters of brain networks in chronic TMD pain subjects as compared to healthy controls for the delta, theta, alpha, and beta frequency bands of the EEG.

4.1 Relative EEG Power Spectral Density

4.1.1 Chronic TMD pain subjects displayed reduced alpha PSD at rest

We found that chronic TMD pain subjects displayed decreased alpha PSD in comparison to healthy controls at rest. Previous studies have found reduced alpha PSD at frontal, central, temporal, and parietal brain regions in pain patients with spinal cord injury[51], including tetraplegia[52], and mixed musculoskeletal and neuropathic pain subjects.[53] In this last study alpha PSD at the frontal and centro-parietal areas of the cortex were negatively correlated with both poor sleep quality and pain intensity.[53] However, other studies have found opposite findings in patients with central neuropathic pain associated with spinal cord injury[18,54], chronic pancreatitis[55,56], persistent

pain after breast cancer[57], and rheumatoid arthritis[15], demonstrated in increased alpha PSD. Also, decreased alpha power density is present in other conditions such as drowsiness[58], or even sleep deprivation[59-61], and depression[58], which are often comorbidities in chronic pain subjects. These discrepant results make it difficult to find a coherent behavior for alpha power density across different painful conditions. As we did not control the quality of sleep in our study, our results may be influenced by this variable, and future studies should consider assessing it.

In the present study, we specifically found group differences in alpha PSD in frontal, temporal, and parietal brain regions, even when anxiety and depression (which are closely related to sleep disturbance) were controlled for, but not in other EEG frequency bands (delta, theta, beta). Furthermore, these group differences were not limited to the resting condition but were maintained even during painful and non-painful motor imagery tasks. Thus, it appears that reduced power density of the alpha frequency band could be an intrinsic feature of brain activity in chronic TMD pain subjects, as it occurs in other functional pain syndromes.

Consistent with the view that reduced alpha PSD might be an intrinsic feature of brain oscillations in TMD, we found no difference between initial and final resting conditions or between imagery tasks in these patients, whereas a significant reduction of alpha PSD over temporal, parietal and central cortices was found from initial to final resting condition in healthy controls. On the one hand, these findings may suggest that the motor imagery tasks had a significant physiological post-effect in healthy controls, specifically reducing power density in the alpha frequency and not in other EEG frequency bands. This is partially in accordance with previous research showing that motor imagery alters brain synchronization patterns, resulting in specific changes in PSD of EEG in alpha and beta frequency bands.[62] Accordingly, some studies have shown reduced alpha (and beta) PSD over the sensorimotor cortex when imaging walking movements.[63] On the other hand, the lack of differences in PSD between initial and final resting conditions for all frequency bands in TMD may further suggest that altered brain oscillations could be considered a stable characteristic of neuroplasticity associated with the presence of pain over time in these subjects, as it occurs with other physiological markers of brain function.[20] In this sense, previous studies have found altered functional connectivity between the insula and several regions of the resting default-mode network (e.g., cingulate cortex and amygdala) which could be reflecting maladaptive neuroplasticity of pain-attention, endogenous pain inhibitory, affective, and motor systems in TMD subjects.[20] Thus, for instance, enhanced activation of some nodes of the default-mode network (e.g medial prefrontal and posterior cingulate cortices) has been positively linked to pain rumination in TMD subjects.[64,65]

4.1.2 Chronic TMD pain subjects displayed reduced alpha power spectral density during painful and non-painful motor imagery tasks

A further aim of the present research was to investigate how the brain of TMD subjects with chronic pain reacts to painful and non-painful motor imagery tasks. Our initial hypothesis was that imagining the contraction of the jaw muscles or the temporomandibular joint would be associated with pain perception and abnormal brain activity due to the recruitment of attention circuits in TMD. Physiologically, decreased alpha PSD in response to motor imagery has been mainly observed in the primary motor and somatosensory cortices.[66-68] Moreover, previous studies have also shown that this reduction in the PSD of the alpha band after imagery tasks seems to be greater in individuals with CP, specifically in paraplegic patients with CP56 reflecting an enhanced activation of the sensorimotor cortex area.[69,70] The findings of the present study are partially in line with previous studies, as individuals with chronic TMD pain showed reduced PSD alpha compared to healthy controls in response to painful and non-painful motor imagery tasks. Nevertheless, we failed to observe differential effects in brain responses to painful and non–painful imagery tasks in chronic TMD pain subjects. One possible explanation for this lack of effects in TMD is consistent with decreased brain responsiveness to sensory and cognitive stimulation, such as reduced amplitudes of brain responses to painful stimuli[71], as have been repeatedly seen in other chronic pain syndromes.[14,72,73] Further research should explore if amplitudes and oscillations of event-related brain potentials would be able to discriminate between TMD subjects with and without pain.

4.2 Brain connectivity

The range of S-values in chronic TMD pain subjects and healthy controls is consistent with those obtained previously.[46] We hypothesized that there would be a change in effective brain connectivity characterized by the "small world" network parameter between chronic TMD pain subjects and healthy controls. Considering S as the "small world" parameter, the hypothesis was confirmed with a significant decrease of S in chronic TMD pain subjects in the delta (all conditions), theta (baseline resting state, non-painful MI, and painful MI conditions), and alpha bands (painful MI condition). In the beta band, the results showed an increase of S in all conditions in chronic TMD pain subjects compared to healthy controls.

Studies of functional connectivity have raised new concepts of brain functionality. A significant number of studies on functional brain mechanisms with fMRI has grown in recent decades as in Alzheimer's disease, schizophrenia, and currently in chronic pain.[74] One approach is that the brain behaves as an interconnected network respecting a standard of effectiveness and stability characterizing "small world" networks. This network architecture may be optimal for synchronizing neural activity between brain regions.[46]

Networks that maintain normal brain function can be disrupted by the presence of diseases, including chronic pain. The (DMN) is one of the most studied networks in the resting state and reflects a coherent set of brain regions that are preferentially affected by the presence of chronic pain such as seen in fibromyalgia, chronic back pain, and diabetic neuropathy.[75-78] Studies of functional connectivity in TMD subjects also showed alterations of the DMN in the frontal, medial, and posterior cingulate cortex regions[64,65], as well as reduced functional connectivity of corticostriatal networks[38], suggesting relevant deficits in motor control, pain processing, and cognition in these patients. Studies of pain-evoked responses using EEG found decreased functional connectivity in theta band, suggesting top-down modulation in the pattern observed by the frontocentral node network.[79] In the present study, we found that chronic TMD pain subjects had reduced values of the "small world" parameters in three EEG frequencies (delta, theta, and alpha), indicating significant reductions of local nodes together with enhancements of long-distance node interactions, and suggesting a low-effective connectivity network. By contrast, "small world" parameters in beta frequency during all conditions in TMD were characteristics of an effective network. Future investigations should elucidate if these "small-world" parameters extracted from EEG and functional connectivity obtained from fMRI are complementary measures of the local and global connectivity networks that are disrupted in TMD subjects with chronic pain.

Like the DMN, the salience network is one of the networks that is active in the brain during rest and is involved in the processing of perceptible stimuli such as pain, for example. The salience network includes regions such as the insula, dorsolateral prefrontal cortex, and anterior cingulate cortex. In a previous study of functional connectivity, the beta band allowed the identification of differences in the activity of the salience network of individuals with sickle cell disease and pain and healthy controls. In this study, individuals with pain demonstrated increased salience network connectivity compared to healthy subjects.[80] Furthermore, the strength of the salience network increased with aging, suggesting that the longer the time of exposure to pain, the greater the activity of this network.[80] Thalamocortical dysrhythmia in individuals with chronic pain has already been described and may explain the changes perceived in both low-frequency waves and high-frequency oscillations, allowing the identification of brain activity patterns in these individuals.[81-84] However, we cannot establish a direct relationship between our findings and other data in the literature, as the analysis methods and parameters used are quite different. Therefore, more studies may be necessary to elucidate these findings.

4.3 Limitations

Our study has limitations that must be considered when interpreting the presented results. We evaluated only subjects with myofascial TMD, which limits the external validity of our findings. We chose myofascial because it is the most severe type of TMD in terms of pain intensity and duration.[85] Thus, the results cannot be extrapolated to all types of TMD, and future research should include other TMD classifications. Our sample size did not allow for studying subgroups of subjects with or without different natures of chronic

pain (e.g. neuropathic and non-neuropathic) or other factors that might have influenced the results, such as quality of sleep, and degree of pain. Future studies could try to subgroup these conditions in order to explore the possible existence of a common thread within these classifications.

5. Conclusion

Chronic myofascial TMD pain subjects show decreased alpha PSD during baseline at rest, but no changes during painful and non-painful motor imagery tasks, which may correspond to difficulty in changing brain states according to different tasks. Confirming these findings, chronic TMD pain subjects displayed a less effective `small world` connectivity as extracted from EEG. These results reinforce the idea that chronic pain in TMD subjects could be associated with maladaptive plasticity in the brain and that these changes can be detected by qEEG, a method that may be very important because of its characteristics of good temporal resolution and the possibility to be performed in naturalistic setups.

Ethics approval and consent to participate

We declare that this study was approved by the Research Ethics Committee of Maternity Climério de Oliveira, Federal University of Bahia (number: 1234340). Research participants signed a free and informed consent form for the study and all declared to be aware of the publication of research results. These and other procedures were based on CNS Resolution 466/12 and the Helsinki Declaration.

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Authors contributions

The authors declare that they have made sufficient contributions to the work in terms of the conception or design of the research; the acquisition, analysis or interpretation of data for the work; and the writing or critical review for relevant intellectual content. All authors approved the final version to be published and agreed to take public responsibility for all aspects of the work.

Conflicts of interest

No financial, legal, or political conflicts involving third parties (government, private companies, and foundations, etc.) were declared for any aspect of the submitted work (including but not limited to grants and funding, advisory board participation, study design, manuscript preparation, statistical analysis, etc.).

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