



Hyperalgesia and Central Sensitization in Subjects With Chronic Orofacial Pain: Analysis of Pain Thresholds and EEG Biomarkers

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Introduction: The presence of a temporomandibular disorder is one of the most frequent causes of orofacial pain (OFP). When pain continues beyond tissue healing time, it becomes chronic and may be caused, among other factors, by the sensitization of higher-order neurons. The aim of this study is to describe psychological characteristics of patients with chronic OFP, their peripheral pain threshold, and electroencephalography (EEG) recording, looking for possible signs of central sensitization (CS).

Materials and methods: Twenty-four subjects with chronic OFP caused by temporomandibular disorder were evaluated using the Research Diagnostic Criteria for Temporomandibular Disorders Axis I and Axis II. Pain intensity, catastrophizing, and presence of CS were assessed through self-reported questionnaires. Pressure pain threshold (PPT) was recorded in facial and peripheral sites; EEG activity was recorded during open and closed eyes resting state and also during the pain threshold assessment. Pain thresholds and EEG recordings were compared with a cohort of pain-free age- and sex-matched healthy subjects.

Results: Patients with chronic OFP showed a significant reduction in their pain threshold compared to healthy subjects in all sites assessed. Greater reduction in pain threshold was recorded in patients with more severe psychological symptoms. Decreased alpha and increased gamma activity was recorded in central and frontal regions of all subjects, although no significant differences were observed between groups.

Discussion: A general reduction in PPT was recorded in people who suffer from chronic OFP. This result may be explained by sensitization of the central nervous system due to chronic pain conditions. Abnormal EEG activity was recorded during painful stimulation compared to the relaxed condition in both chronic OFP subjects and healthy controls.

Keywords: chronic pain, orofacial pain, central sensitization, pain threshold, EEG

INTRODUCTION

Chronic pain is defined as pain that lasts for more than 3 months beyond the normal healing time (Treede et al., 2015). Chronic pain impacts working life, somatic, emotional and social well-being, and quality of life of the affected individuals and is recognized as a major health care problem in Europe (Breivik et al., 2006). Involvement of cerebral circuits in chronic pain development has been broadly documented (Apkarian et al., 2004; Kim et al., 2013; Ferdek et al., 2019). Chronic pain seems to be associated with pain related to central networks, and neuroplastic changes in these circuits may change perception of pain independent of peripheral neural activation (Camfferman et al., 2017). The thalamus appears to play a key role in several chronic pain conditions, and its connection with cerebral cortex seems imputable to maintenance of pain (Llinás et al., 1999; Stern et al., 2006). Many studies have tried to identify an electroencephalography (EEG) pattern related to pain development and maintenance beyond physiological tissue healing time (Prichep et al., 2011; Jensen et al., 2013; Pinheiro et al., 2016). Despite the lack of certainty around cortical markers of chronic pain, a reduction in alpha activity in frontal lobes and increased theta activity in the posterior parietal cortex have been recorded in subjects who experience chronic pain in various conditions (Sarnthein et al., 2006; Sarnthein and Jeanmonod, 2008; Jensen et al., 2013; Camfferman et al., 2017). Recently, the International Association for the Study of Pain (IASP) distinguished between “chronic primary pain” and “chronic secondary pain.” In the first category, chronic pain is conceived as a disease in its own right; in the second, pain is a consequence of an underlying disease and may be initially conceived as a symptom (Treede et al., 2019). Orofacial pain (OFP) is usually classified as chronic secondary pain because, in most cases, it can be attributed to an underlying cause (Benoliel et al., 2019). Frequently, the pain starts from a problem with the temporomandibular joint (TMJ), outlasts the initiating event, and becomes the leading cause for ongoing treatment (Benoliel et al., 2019). Patients, following temporomandibular disease (TMD) resolution, no longer exhibit peripheral tissue damage but continue to feel pain, suggesting an abnormal functioning of the somatosensory system (Sarhani and Greenspan, 2005). This process may be due to an induced sensitization of higher-order neurons, a phenomenon well described by the central sensitization (CS) process (Campi et al., 2017). According to the IASP definition, CS is characterized by an increased responsiveness of nociceptive neurons in the central nervous system (CNS) to their normal or subthreshold afferent input (Loeser and Treede, 2008). With the introduction of the CS concept, pain starts to reflect a functional state of circuits in the CNS instead of being exclusively peripherally driven (Woolf, 2011). Injury or inflammation in peripheral tissue can alter the properties of somatic sensory pathways. This induced peripheral sensitization could trigger CS, leading to pathological pain states (Harte et al., 2018). Evidence for CS has been described in patients with TMD by Dworkin (1995), who found no correlation between physical signs of jaw dysfunction and levels of pain in a 3-year follow-up study. Quantitative sensory testing, such as pressure

pain threshold (PPT), can be used to document the patient’s somatosensory profile (Svensson et al., 2011). A generalized state of pain sensitivity can justify low PPT, linked to altered sensory processing, dysregulated endocrine function, hyperinflammatory states, or psychological processes (Lautenbacher et al., 1994). In a large prospective study, the OPPERA (Orofacial Pain: Prospective Evaluation and Risk Assessment) study, Slade et al. (2014) observed that PPT fluctuated in synchrony with the course of painful TMD. Further, a reduction of PPT in sites related to the TMJ has been identified as sign of peripheral sensitization (Campi et al., 2017). In case of sensitization due to supraspinal pathways, the local threshold is further reduced at the local site, but it is also reduced in more distant body sites not related to TMD. The comparison of a TMD cohort with a healthy and pain-free sample may be the only way to evaluate the degree of localized and spreading sensitization (Arendt-Nielsen et al., 2018). We can assume that changes in EEG activity and signs of sensitization can be recorded in people who suffer from long-lasting pain due to TMD. The objective of this study is therefore to describe features of chronic OFP through the analysis of patients’ psychological profile, peripheral pain threshold, and EEG recordings, looking for possible signs of CS.

MATERIALS AND METHODS

This cross-sectional observational study describes factors related to chronic OFP and characteristics of patients in a cohort of 24 subjects with OFP due to TMD. This study has been reviewed by the Ferrara University Hospital Ethics Committees. All the procedures described have been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Written informed consent was obtained before all procedures. The study meets the STROBE Guidelines for observational studies (von Elm et al., 2014).

Patients who underwent rehabilitation for TMD at Ferrara Rehabilitation Hospital between January 2018 and January 2019 were assessed for eligibility. Age, sex, occupation, side and duration of TMD, past treatment for the TMJ, comorbidities, and medications were recorded. All subjects with a Numeric Pain Rating Scale (NPRS) of less than 3 in the 2 weeks prior to assessment or who took pain relief medication were excluded from the study (Jensen et al., 2013). The other exclusion criteria were impaired cognitive functioning (score < 24 on the Mini-Mental Status Examination), neurological or psychiatric disorders, or pregnancy.

A medical doctor with an expertise in temporomandibular rehabilitation evaluated all subjects included in the study, following the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) Axis I (Schiffman et al., 2014).

The RDC/TMD Axis II was used to assess psychological distress and pain-related disability (Schiffman et al., 2014). For the purpose of this analysis, depression, anxiety, and non-specific physical symptoms (NSPS) were treated as dichotomous variables, and patients were classified as minimal/mild if their

total score was lower than 10; patients with a higher score were classified as moderate/severe (Campi et al., 2017). All subjects included were evaluated using a self-reported questionnaires for subjective description of pain and PPT for objective assessment of pain perception (Dworkin et al., 2005). Neural activity linked to pain sensation was recorded using EEG. PPT and EEG were also evaluated in a sample of age- and sex-matched healthy controls.

Self-Reported Questionnaire

Catastrophizing has been defined as “an exaggerated negative orientation toward actual or anticipated pain experiences” and reflects a tendency to misinterpret or exaggerate apparently threatening situations (Sullivan et al., 1995). The Pain Catastrophizing Scale (PCS) was used to assess the tendency to magnify the threat value of pain stimulus and to feel helpless in the context of pain (Quartana et al., 2009). A PCS score ≥ 30 was used to detect the presence of catastrophizing (Sullivan et al., 1995).

Central sensitization was assessed using the Italian version of the Central Sensitization Inventory (CSI-I) (Chiarotto et al., 2018). A CSI score ≥ 40 has been suggested as the cutoff score to determine if patients display CS (Neblett et al., 2013, 2015; Nijs et al., 2014).

Pressure Pain Threshold

Pressure pain threshold is defined as the minimum pressure applied to anatomical regions that can induce pain (Fischer, 1987). PPT measurement was performed with a handled digital dynamometer (Commander Algometer, JTECH Medical, United States), consisting of a device with a 1-cm² flat circular tip used to apply pressure on subjects' skin. A researcher was trained to apply increasing pressure of approximately 1 lb/cm²/s perpendicular to the skin using the dynamometer, following a protocol well described in literature (Campi et al., 2017). The stimulus intensity increased from zero, and the subject was instructed to stop the stimulation at the first perception of pain by pushing a button. At that moment, the pressure was removed, and the value of pressure applied was recorded. The sites of the stimulation were the muscle belly of the temporal and masseter muscles, the surface of the mandibular condyle, the middle part of the upper trapezius, and the center of the thenar eminence (Figure 1). During examinations subjects were in a comfortable sitting position with muscles relaxed. The researcher stabilized the subject's head gently applying manual resistance contralateral to the point of pressure application. This procedure was repeated three times for every site, on both sides, with an interstimulus interval of 30 s (Nie et al., 2009). The PPT value of the painful side was used for the analysis. When symptoms were present bilaterally, the value of the more affected side was used. This side was matched in measuring PPT in healthy subjects.

EEG Recording

Electroencephalography assessment was performed using an electrode montage of 32 Ag/AgCl pellet pin electrodes (Easy Cap GmbH, Herrsching, Germany) placed according to the 10–20 International System on a Fast'n Easy cap. A BrainAmp amplifier (Brain Products, Munich, Germany) was used to record

EEG activity. All scalp electrodes were referenced to nasion and grounded at AFz during recordings. Horizontal and vertical eye movements were detected, respectively, with electrodes placed at the left and right outer canthi at Fp1 and below the eye at the non-painful side. The impedance of all the electrodes was kept below 10 k Ω . The EEG signals were recorded with a 1,000-Hz sampling rate with a low cutoff frequency of 0.1 Hz and a high cut-off of 1,000 Hz.

Electroencephalography data were recorded during a 5-min resting state task with open eyes and a 5-min resting state task with closed eyes. Participants were instructed to stay relaxed and keep their eyes fixed on a cross in front of them during open-eyes recording. EEG was also recorded during the PPT assessment at the thenar eminence following the aforementioned protocol.

EEG Preprocessing

The EEG data were preprocessed in MATLAB, using the EEGLab toolbox (Delorme and Makeig, 2004). A notch filter centered around 50 Hz was applied in post-processing for eliminating the power noise. Then, data were re-referenced to the average reference. Eye movement artifacts were removed by means of an independent component analysis (ICA) procedure. ICA was used to determine the independent components. A visual analysis was used to discard components that were characterized by high-amplitude fluctuations and were mostly located at or close to the eye electrodes.

EEG Spectral Analysis

The spectral power in the different EEG bands (delta 1–4 Hz, theta 4–7 Hz, alpha 7–13 Hz, beta 13–30 Hz, gamma 30–60 Hz) was calculated, during both resting state tasks, in the middle minute of the 5 min of each recording. The power spectral density (PSD) was calculated using Welch's method, using 1-s windows and 80% of overlap over successive windows (Welch, 1967). The PSDs of all subjects during each trial were then transformed into *z*-scores to improve comparability of PSD values across subjects and conditions. For the pain stimulus trials, the PSD was calculated from the 3-s window before reaching the sensory threshold. The *z*-score of the PSD was calculated for each electrode of each subject during each condition by subtracting by each PSD spectrum its mean and dividing by its standard deviation. For the statistical analyses, in order to minimize the number of comparisons, we calculated the average PSD in the different bands for clusters of electrodes centered around locations F3, C3, P3, and their homologous on the right side of the scalp. For each location, the PSD in each band was calculated as the average PSD in the band among the central and directly adjacent electrodes. To visually assess for relative differences in EEG activity due to the pain, the *z*-score PSD calculated during the pain stimulus trials was expressed as a percentage of the average PSD calculated from the resting state trials with the eyes open of all subjects. This choice for normalization was dictated by the fact that subjects had their eyes open during the pain stimulus trials. These data were then plotted for both groups for visual comparison.

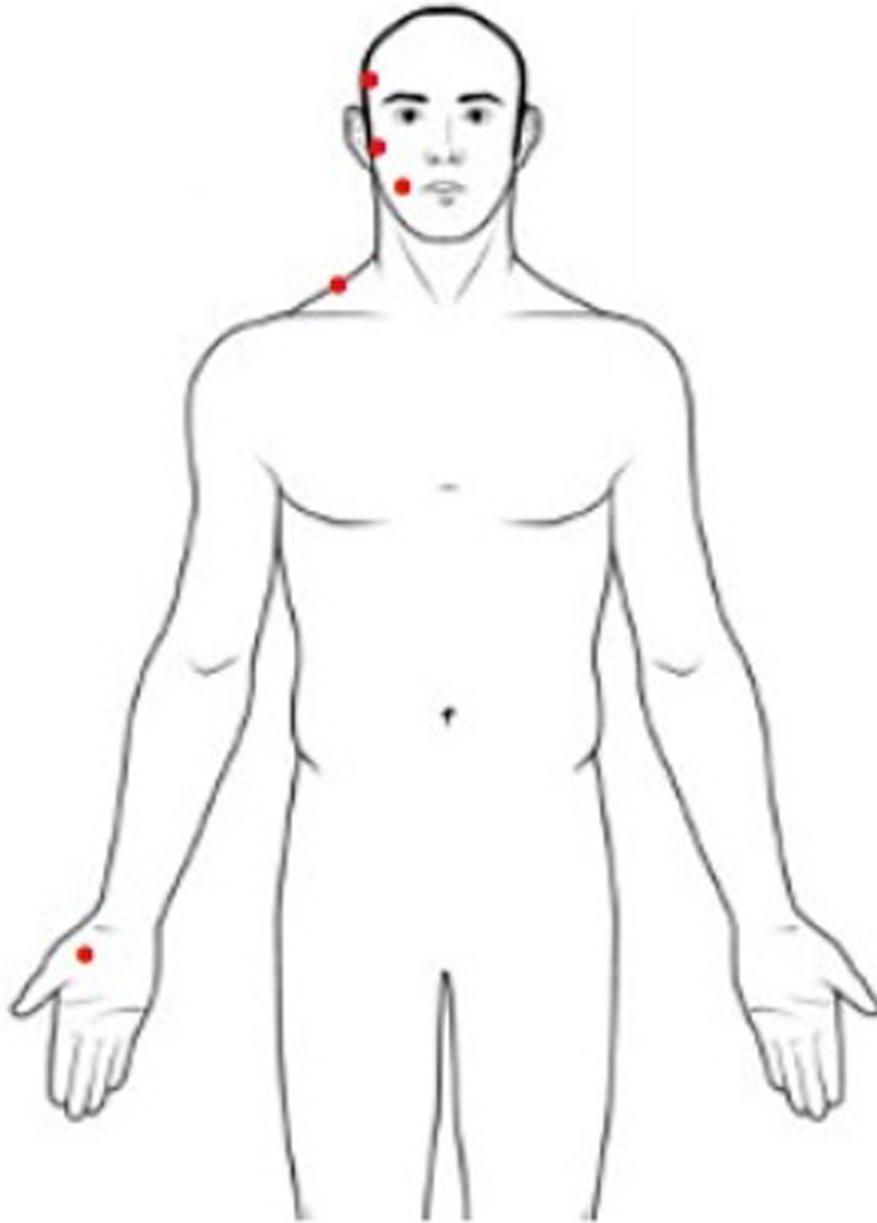


FIGURE 1 | Sites for pressure pain threshold assessment (right body sites for illustrative purposes only).

Statistical Analysis

Descriptive statistics were used for characterizing the sample. Continuous variables are reported as means and standard deviations, non-continuous variables as counts and percentages. Differences in PPT between patients with OFP and healthy subjects were assessed using the Wilcoxon rank-sum test due to non-normal data distribution. Patients with OFP were also divided according to intensity of pain, presence of psychological disorders, catastrophizing, and CS, and differences between groups were analyzed. Spearman rank correlation coefficient was used to measure strength and

direction of association between psychological scores and self-reported questionnaires.

This statistical analysis was performed using STATA 13.1 software with significance set at $p < 0.05$. Statistical analysis was also performed on the clustered EEG data. In this analysis, we compared the z-score PSD of the OFP and the healthy subjects in the eyes open and pain stimulus conditions for each band and electrode cluster. This analysis was based on a two-way analysis of variance (ANOVA) test. The significance level was set to 0.05. All the statistical analysis on the EEG data was performed in MATLAB using custom-made scripts.

RESULTS

The sample consisted of 19 women and 5 men. The mean age was 49.8 years, with a minimum of 23 and a maximum of 77 years. Detailed demographic and clinical features of the sample are summarized in **Table 1**. Most of the sample was classified as myofascial pain with spreading following the Axis I of DC/TMD. The mean pain intensity during the 24 h before at the NPRS was 6.42 (1.72 SD), with a minimum of 3 and a maximum of 9. Twenty-four age- and sex-matched healthy subjects were recruited. The assessment of PPT revealed a reduction in pain threshold in subjects with OFP in all the sites of assessment compared to healthy subjects. Differences between groups were statistically significant (**Figure 2**). Reduction in PPT in subjects with OFP compared to healthy subjects was observed even after removing people with fibromyalgia from the analysis ($p < 0.05$ for all the sites of assessment). Stratifying patients according to psychological assessment performed with RDC/TMD Axis II, we observed differences in PPT between groups of subjects with moderate or severe symptoms compared to those with low or mild; significant differences were recorded only for pain-related disability and depression ($p = 0.045$ and $p = 0.023$, respectively) (**Table 2**). No significant differences in pain threshold were identified in patients with CS signs. Positive correlations were found between CS and psychological disorders for every class of impairment $\rho = 0.331$ for depression, $\rho = 0.575$ for NSPS, $\rho = 0.365$ for catastrophizing, without reaching significant level.

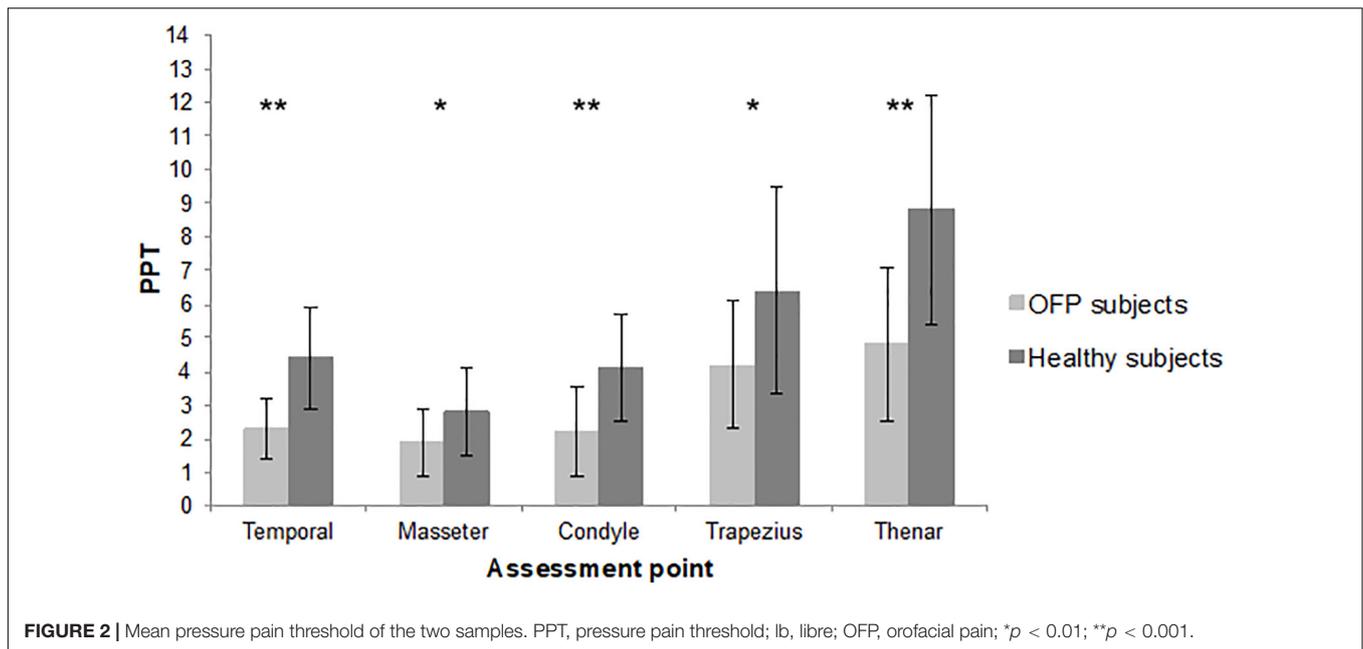
EEG Results

The average PSD z -score values for OFP and healthy individuals for both conditions are presented in **Table 3**. We did not notice specific qualitative trends in the PSD values between OFP and healthy controls, which translated in the absence of statistically significant differences in the ANOVA in the PSD calculated from all electrode clusters in all frequency bands among the two groups (**Table 4**). However, we observed a marked decrease in PSD values for both groups between the two conditions in the alpha and beta bands. This observed decrease in PSD translated in statistically significant differences in the ANOVA between the two conditions for all clusters in the alpha band and for clusters F3 and C3 in the beta band. In the gamma band, we observed a general qualitative trend of increased PSD values in both groups in most clusters. This trend translated in statistically significant differences in the ANOVA for all clusters (with the exception of P4) in the gamma band. The interaction analysis (**Table 4**) suggests that the differences observed in the gamma band are group-specific. We then analyzed the group-specific relative changes in PSD values due to the pain stimulus. This was done by expressing the z -score PSD values extracted during the PS trial and expressed as percentage changes with respect to the same values extracted during the EO trial. We observed a qualitative increase in the relative PSD values (with respect to the eyes open trial) in the gamma band in the controls that were localized mostly in the occipital region. In the patients, differently than the controls, increased values of PSD in the gamma band were instead observed in the central and frontal regions (C3/C4 F3/F4 electrodes) (**Figure 3**).

TABLE 1 | Descriptive data for the sample.

	Sample ($n = 24$) Mean (SD) or n (%)
Age (years)	49.8 (13.1)
Sex (n)	
Male/female	5 (21)/19 (79)
Occupation (n)	
Employed/unemployed	14 (58)/10 (42)
Principal comorbidities (n)	
Fibromyalgia	5 (21)
Hypertension	4 (17)
Enteric disease	3 (12)
Diabetes mellitus	1 (4)
Other rheumatic disease	1 (4)
None	10 (42)
Drug use (n)	
Non-steroidal anti-inflammatory drugs	5 (21)
Antidepressants	2 (8)
Muscle relaxants	2 (8)
Analgesics	3 (11)
None	12 (50)
Symptoms duration (months)	49.21 (68.59)
Symptoms frequencies (n)	
Continuous/episodic recurrent	7 (35)/17 (65)
Pain side (n)	
Right/left/bilateral	3 (10)/3 (15)/18 (75)
Previous treatment	
Physiotherapy	11 (45)
Arthrocentesis	10 (35)
Byte use	16 (65)
DC/TMD Axis I	
Myofascial pain	21 (90)
Myalgia	1 (5)
Arthralgia	2 (5)
DC/TMD Axis II	
Pain-related disability (n)	
Low	9 (37.5)
High	15 (62.5)
Depression (n)	
Minimal–mild	16 (66.7)
Moderate–severe	8 (33.3)
Anxiety (n)	
Minimal–mild	19 (79)
Moderate–severe	5 (21)
Non-specific physical symptoms (n)	
Minimal–mild	13 (54)
Moderate–high	11 (46)
NPRS	6.42 (1.72)
Catastrophizing (n)	
Not present	12 (50)
Present	12 (50)
Central sensitization (n)	
Subclinical–mild	12 (50)
Moderate–severe	12 (50)

n, number; SD, standard deviation; DC/TMD Axis I and Axis II, Diagnostic Criteria for Temporomandibular Disorders Axis I and Axis II; NPRS, Numeric Pain Rating Scale.



DISCUSSION

In this observational study, we tried to describe features and clinical signs of people with chronic OFP due to TMD by comparing them with healthy controls. Our main finding revealed that people who suffer from this debilitating condition present a generalized reduction in PPT. This reduction in pain threshold was observed not only in facial sites but also in areas not

involved by pathology, such as the upper trapezius and the thenar eminence. The phenomenon we observed may be due to CS, an increased responsiveness of nociceptive neurons to subthreshold input (Loeser and Treede, 2008). Fillingim et al. (2018) in their longitudinal study found that individuals who transitioned from being TMD-free to a TMD state tended to show reduction in PPT limited to the orofacial region and not to other body sites. The discrepancy between these and our results may be explained by the difference in time elapsed between OFP onset and PPT assessment in the two studies.

Fillingim et al.'s (2018) research did, in fact, involve a long-term follow-up, in which years separated original and follow-up assessments.

Again from the OPPERA study, Greenspan et al. (2011) found that people with chronic TMD were more pain-sensitive than controls to many mechanical and thermal stimuli, with particular sensitivity to pressure stimulation, applied to symptomatic and asymptomatic body sites.

In our study, PPT was assessed in patients with OFP from a median time of 33 months. Chronic pain, critical in development of CS, has to last for more than 3 months to be defined as such (Treede et al., 2015). Pain lasting for a shorter time may not contribute to hyperexcitability of the CNS, one of the main features of sensitization process (den Boer et al., 2019). In our study, we included patients with fibromyalgia, and this may represent a confounding factor in PPT assessment (Maquet et al., 2004). However, the analysis performed on the sample after exclusion of fibromyalgia patients showed no differences compared with the whole sample. Stratification of people with OFP based on psychological disorder severity revealed that subjects with moderate or severe depression and high level of pain-related disability showed generalized reduction in PPT. A large systematic review on pain sensitivity and depression found uncertain results about mechanisms underlying their

TABLE 2 | Pressure pain threshold for classes of impairment.

		Mean (SD)	p
DC/TMD Axis II			
Pain-related disability	Low ($n = 9$)	3.8 (1.3)	0.045*
	High ($n = 15$)	2.6 (1.1)	
Depression	Minimal–mild ($n = 16$)	3.5 (1.3)	0.023*
	Moderate–severe ($n = 8$)	2.3 (1.0)	
Anxiety	Minimal–mild ($n = 19$)	3.1 (1.3)	0.749
	Moderate–severe ($n = 5$)	2.9 (1.3)	
Non-specific physical symptoms	Minimal–mild ($n = 13$)	3.4 (1.4)	0.213
	Moderate–severe ($n = 11$)	2.7 (1.1)	
NPRS	Mild–moderate 3–6 ($n = 12$)	3.0 (1.3)	0.954
	Severe 7–10 ($n = 12$)	3.1 (1.3)	
Catastrophizing	Not present ($n = 12$)	3.2 (1.4)	0.427
	Present ($n = 12$)	2.8 (0.9)	
Central sensitization	Subclinical–mild ($n = 12$)	3.3 (1.5)	0.564
	Moderate–severe ($n = 12$)	2.9 (0.9)	

n, number; *SD*, standard deviation; *DC/TMD Axis II*, Diagnostic Criteria for Temporomandibular Disorders Axis II; *NPRS*, Numeric Pain Rating Scale. * $p < 0.05$.

relationship (Thompson et al., 2016). However depression and pain sensitivity frequently occur together (Von Knorring et al., 1983; Von Korff et al., 1988; Bair et al., 2003; Lépine and Briley, 2004; Agüera-Ortiz et al., 2011), probably due to dysfunction at the level of the serotonergic and noradrenergic neurons that affects not only psychological and somatic symptoms of depression but also physical painful symptoms (Stahl and Briley, 2004). Another possible explanation of the aforementioned results is that depressed people react negatively to painful

stimulation with stronger emotional involvement. A reduction in PPT as sign of CS may explain the link between sensitization of the CNS and emotional comorbidities. Smart et al. (2012) in their study on patients with low back pain reported significantly greater levels of pain-related disability, depression, and anxiety in people with signs of CS compared to those with nociceptive or neuropathic pain. Strong relationship between CS and psychological symptoms is confirmed by our analysis. What needs to be clarified is the causal link between them, establishing

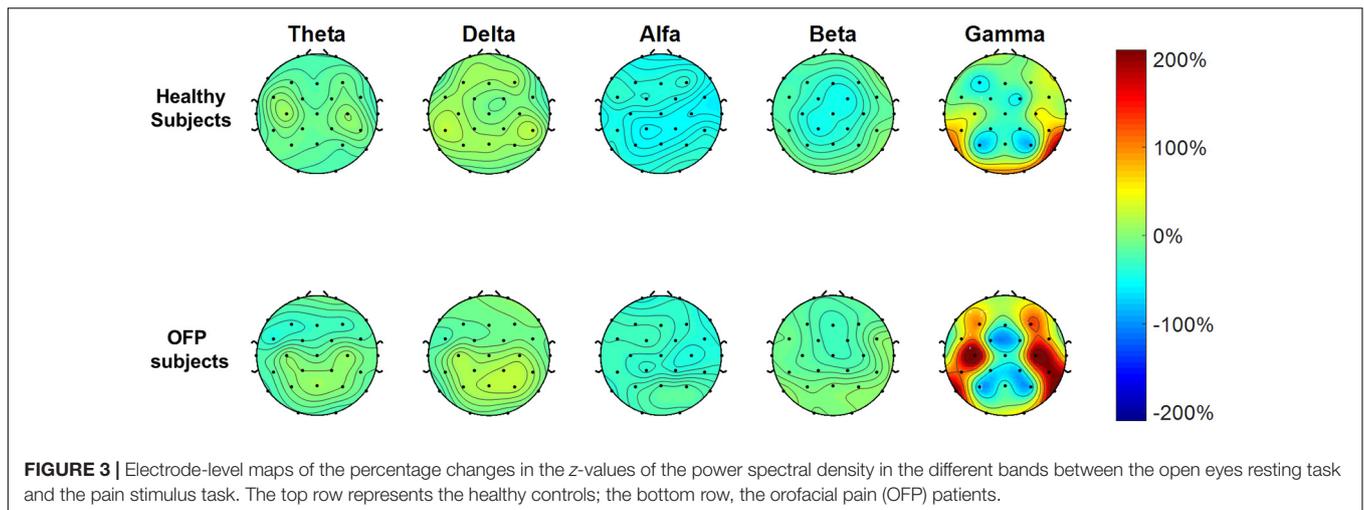
TABLE 3 | PSD values, expressed as mean (standard deviation) of the z-scores, for the different clusters, across all frequency bands, for the orofacial pain (OFF) patients and the healthy controls (HC) for the eyes open (top table) and pain stimulus (bottom table) conditions.

Eyes Open										
Cluster	Theta		Delta		Alfa		Beta		Gamma	
	OFF	HC	OFF	HC	OFF	HC	OFF	HC	OFF	HC
F3	0.67 (0.73)	0.75 (0.72)	1 (0.74)	1.2 (0.62)	0.78 (0.94)	0.78 (0.99)	0.15 (0.35)	0.21 (0.37)	-0.46 (0.11)	-0.5 (0.12)
F4	0.68 (0.66)	0.77 (0.58)	1.1 (0.64)	1.2 (0.63)	0.83 (0.91)	0.78 (0.89)	0.1 (0.35)	0.25 (0.38)	-0.42 (0.099)	-0.51 (0.13)
C3	0.52 (0.67)	0.66 (0.6)	1 (0.75)	1.2 (0.54)	1.1 (0.93)	1.1 (0.97)	0.18 (0.42)	0.22 (0.3)	-0.45 (0.095)	-0.47 (0.088)
C4	0.54 (0.65)	0.62 (0.5)	1.1 (0.7)	1.2 (0.6)	1.1 (0.93)	1.1 (0.95)	0.14 (0.45)	0.24 (0.32)	-0.41 (0.16)	-0.49 (0.098)
P3	0.67 (0.53)	0.8 (0.45)	1.1 (0.62)	1.3 (0.44)	1.5 (1)	1.3 (0.83)	0.16 (0.41)	0.16 (0.23)	-0.45 (0.077)	-0.47 (0.054)
P4	0.67 (0.55)	0.76 (0.42)	1.1 (0.69)	1.2 (0.48)	1.5 (1)	1.3 (0.85)	0.13 (0.42)	0.16 (0.21)	-0.43 (0.1)	-0.47 (0.072)
Pain stimulus										
F3	0.3 (0.52)	0.58 (0.51)	0.86 (0.68)	1.2 (0.55)	0.38 (0.69)	0.27 (0.5)	0.049 (0.3)	0.016 (0.24)	-0.4 (0.11)	-0.39 (0.11)
F4	0.43 (0.53)	0.55 (0.45)	1.1 (0.71)	1.1 (0.49)	0.31 (0.57)	0.19 (0.43)	0.067 (0.38)	0.03 (0.28)	-0.41 (0.13)	-0.39 (0.14)
C3	0.4 (0.37)	0.54 (0.5)	1.1 (0.57)	1.2 (0.62)	0.57 (0.8)	0.34 (0.5)	0.092 (0.33)	-0.0018 (0.17)	-0.41 (0.11)	-0.36 (0.12)
C4	0.44 (0.48)	0.47 (0.5)	1.2 (0.6)	1.1 (0.6)	0.45 (0.56)	0.25 (0.38)	0.086 (0.35)	0.036 (0.21)	-0.41 (0.12)	-0.36 (0.14)
P3	0.57 (0.36)	0.59 (0.5)	1.1 (0.43)	1.3 (0.52)	0.82 (0.77)	0.51 (0.47)	0.12 (0.33)	0.035 (0.19)	-0.44 (0.088)	-0.39 (0.085)
P4	0.57 (0.38)	0.52 (0.54)	1.3 (0.57)	1.2 (0.59)	0.86 (0.79)	0.55 (0.59)	0.084 (0.3)	0.062 (0.18)	-0.43 (0.074)	-0.4 (0.087)

TABLE 4 | Results of the ANOVA two-way analysis performed between groups [orofacial pain (OFF) and healthy controls (HC)], conditions [eyes open (EO) and pain stimulation (PS)], and the interaction between group and condition, expressed as *p*-value and the relative *F* statistic in parenthesis.

Group (OFF vs. HC)	Theta	Delta	Alpha	Beta	Gamma
F3	0.1977 (1.7)	0.1311 (2.3)	0.7615 (0.093)	0.8753 (0.025)	0.5755 (0.32)
F4	0.4174 (0.66)	0.6626 (0.19)	0.5988 (0.28)	0.4876 (0.49)	0.2082 (1.6)
C3	0.2479 (1.4)	0.1819 (1.8)	0.6626 (0.19)	0.7346 (0.12)	0.6789 (0.17)
C4	0.6331 (0.23)	0.8776 (0.024)	0.5007 (0.46)	0.7181 (0.13)	0.5621 (0.34)
P3	0.4754 (0.51)	0.1828 (1.8)	0.1597 (2)	0.5297 (0.4)	0.4509 (0.57)
P4	0.8361 (0.043)	0.8711 (0.026)	0.141 (2.2)	0.9361 (0.0065)	0.9474 (0.0044)
Condition (EO vs. PS)					
F3	0.0582 (3.7)	0.4898 (0.48)	0.0131 (6.5)	0.0441 (4.2)	0.0006 (13)
F4	0.0649 (3.5)	0.5521 (0.36)	0.0010 (12)	0.1152 (2.5)	0.0203 (5.6)
C3	0.3325 (0.95)	0.7877 (0.073)	0.0008 (12)	0.0337 (4.7)	0.0022 (10)
C4	0.3194 (1)	0.8800 (0.023)	<0.0001 (20)	0.1013 (2.8)	0.0369 (4.5)
P3	0.1313 (2.3)	0.7745 (0.083)	0.0001 (16)	0.2514 (1.3)	0.0141 (6.3)
P4	0.1263 (2.4)	0.6303 (0.23)	0.0005067 (13)	0.3014 (1.1)	0.0513 (3.9)
Interaction					
F3	0.4889 (0.48)	0.5522 (0.36)	0.7887 (0.072)	0.5419 (0.38)	0.3114 (1)
F4	0.8997 (0.016)	0.9310 (0.0076)	0.8260 (0.049)	0.2483 (1.4)	0.0498 (4)
C3	0.9984 (<0.0001)	0.9528 (0.0035)	0.4226 (0.65)	0.3287 (0.97)	0.1078 (2.6)
C4	0.8429 (0.04)	0.4403 (0.6)	0.6146 (0.26)	0.3170 (1)	0.0452 (4.1)
P3	0.6290 (0.24)	0.6967 (0.15)	0.7160 (0.13)	0.5159 (0.43)	0.0438 (4.2)
P4	0.5279 (0.4)	0.4067 (0.7)	0.8331 (0.045)	0.6767 (0.18)	0.1012 (2.8)

The three different shades of green represent three *p*-value threshold, specifically $p < 0.05$ (lightest shade), $p < 0.01$ and $p < 0.001$ (darkest shade).



if psychological disorders are involved in causing sensitization or whether they are a consequence of a sensitized system.

To our knowledge, the current study is the first investigating EEG PSD during PPT assessment in people with OFF vs. healthy control subjects. In this study, we found no differences between patients and control subjects during resting and pain stimulus trials. Our results about the reduction in the EEG alpha power during pain stimulation, which we observed in both cohorts, had already been observed in literature, without distinction between phasic or tonic pain (Chang et al., 2002; Peng et al., 2015). We observed also an increase in gamma band activity across all the electrodes between the two conditions. This translated, in the OFF patients, in a qualitative relative (with respect to the resting condition) increase in the central and prefrontal activity in the gamma band during peripheral stimulation just before stimulus was perceived as painful. Other studies investigating resting state EEG in people with chronic pain described significant overactivation of regions involved in the pain network. Prichep et al. (2018) recorded overactivity in insula areas, parietal lobule, thalamus, and the dorsolateral prefrontal cortex; significant differences between normal and pain patients were found in mid and posterior cingulate. Generalized overactivity was described in all areas belonging to the “pain matrix.” Our findings of an increase in gamma activity in the prefrontal areas may further support the model proposed by Baliki and Apkarian (2015) on dissociation in processing of longer lasting pain and nociceptive information. The authors described a dissociation of prefrontal component of the default mode network (DMN) in different types of chronic pain (Baliki and Apkarian, 2015). In fMRI studies, the DMN was described as one of the three brain systems that, with their dynamic interactions, are involved in spontaneous attentional fluctuations toward and away from pain (Kucyi and Davis, 2015). The DMN is activated when subject attention is not engaged by sensations from the external world (Andrews-Hanna et al., 2014). In opposition to the DMN, a system known as the salience network (SN) works to track how external stimuli capture attention (Downar et al., 2000, 2001, 2002, 2003; Mouraux et al., 2011; Uddin, 2015). Prefrontal areas,

in particular dorsolateral prefrontal cortex, are part of the SN (Seeley et al., 2007; Kucyi et al., 2012). Although in our study we did not observe statistically significant differences between patients and controls, an overactivity of the prefrontal cortex recorded in patients with OFF due to TMD may be representative of an exaggerated engagement of SN in people with long-lasting pain and a general tendency to focus attention on external stimuli that could generate pain. Similar results of increased prefrontal gamma activity were reported in chronic back pain patients (May et al., 2019) and patients with postherpetic neuralgia and fibromyalgia (Lim et al., 2016; Zhou et al., 2018). The association between gamma oscillations and involuntary attentional effects of pain has been well described in literature (Hauck et al., 2007; Tiemann et al., 2010; Schulz et al., 2015; Hansen et al., 2017) and has great relevance in cortical networks for behavioral and cognitive phenomena (Uhlhaas et al., 2009).

Increased activity of the primary motor cortex (M1) area in people with chronic pain has been previously described in literature in various musculoskeletal conditions (Di Pietro et al., 2013; Schabrun et al., 2015, 2017; Te et al., 2017). A recent systematic review found inconclusive results with regard to abnormal M1 activation in pain conditions due to the heterogeneity of studies and assessment tools (Chang et al., 2018). Our results seem to underlie abnormal brain activity recorded by C3/C4 electrodes just before the peripheral stimulus became painful. Increased gamma activity may indicate increased muscle activity during pain, which contaminates EEG signal during pain stimulation. However, we did not record muscular activity during pain threshold assessment (Whitham et al., 2007; Dowman et al., 2008). Furthermore, muscular activation would also be highlighted by altered EEG signal during the recording.

Movement dysfunction such as unnecessary protective behavior may justify our findings, when patients received a stimulus perceived as threatening. The primary motor cortex has already been target of brain stimulation treatment, with a positive impact on pain relief (Fregni et al., 2006; Straudi et al., 2018). Abnormal function of motor and prefrontal cortex during stimulus perception may be due to neuroplastic changes

that occur in the human brain subjected to long-lasting pain. Neurophysiological adaptations occur and seem to persist over peripheral tissue healing time in presence of emotional and behavioral aspects of pain that cause maladaptive changes in areas not normally involved in pain perception (Mansour et al., 2014). Structural as well as functional changes have been described in frontal and motor areas of patients with chronic pain due to coxarthrosis (Rodriguez-Raecke et al., 2013).

Interpretation of our findings is subject to several limitations. First, the small sample size does not allow us to confirm our results on PPT and EEG recordings. Even though CS may be hypothesized looking at our results, we cannot draw any definitive conclusion on the mechanism underlying sensitization of CNS. Second, interpretation of our results must consider the inclusion in our sample of fibromyalgia patients whose sensitivity to pain may influence their PPT.

CONCLUSION

In a convenience sample of patients with OFP due to TMD we observed generalized reduction in PPT compared to age- and sex-matched healthy controls, not limited to facial sites. Generalized decrease of pain threshold seems to be linked to the severity of psychological symptoms such as depression and perceived health-related disability. Abnormal EEG activity was recorded during painful stimulation of non-painful sites of patients with OFP due to TMD. This observational study tried to identify potential signs of CS through the analysis of patients' sensory and psychological profiles and brain activity. Our results can

open doors to new strategies for the assessment and treatment of patients with CS due to chronic pain conditions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ferrara University Hospital Ethics Committees. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AB, SS, SBu, and NB conceived the study and participated in its design. AB and SBo performed the instrumented and clinical data collections. AB and GS analyzed the data. AB, GS and SS interpreted the results, and drafted and revised the manuscript. All authors approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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