ORIGINAL REPORT: EPIDEMIOLOGIC RESEARCH

# The Adaptive, Pain Sensitive, and Global Symptoms Clusters: Evidence from a Patient-Based Study

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Abstract: ***Objectives:*** *The largest epidemiologic study conducted about painful temporomandibular disorders (pTMDs) to date identified 3 clusters of individuals with similar symptoms—adaptive, pain sensitive, and global symptoms—which hold promise as a means of personalizing pain care. Our goal was to compare the clinical and psychological characteristics that are consistent with a pTMD clinical examination among patients who are seeking care and assigned to the different clusters.*

***Methods:*** *This cross-sectional study used data from the medical records of patients attending Duke Innovative Pain Therapies between August 2017 and April 2021 who received a pTMD diagnosis (i.e., myalgia) and consented to have their data used for research. Data included orofacial and pain-related measures, dental features, and psychological measures. We used the Rapid OPPERA Algorithm to assign clusters to patients and multinomial regression to determine the likelihood (odds ratios [OR] and 95% confidence intervals [CI]) of being assigned to the pain sensitive or global symptoms cluster attributed to each measure.*

***Results:*** *In total, 131 patients were included in this study and assigned a cluster: adaptive (*n = *54, 41.2%), pain sensitive (*n = *49, 37.4%), and global symptoms (*n = *28, 21.4%). The PS cluster displayed greater numbers of temporomandibular joint sites (OR, 1.29; 95% CI, 1.01 to 1.65) and masticatory (1.48; 1.19 to 1.83) and cervical (1.23; 1.09 to 1.39) muscles with pain evoked by palpation. The GS cluster displayed greater scores of pain catastrophizing (1.04; 1.01 to 1.06) and perceived stress (1.23; 1.03 to 1.46) and was more likely to report persistent pain (16.23; 1.92 to 137.1) of higher impact (1.43; 1.14 to 1.80).*

***Conclusion:*** *Our findings support that care-seeking patients with pTMDs who are assigned to the GS cluster display a poorer psychological profile, even though those assigned to the PS cluster display more measures consistent with orofacial pain. Findings also establish the PS cluster as a group that does not display psychological comorbidities despite being hypersensitive.*

Knowledge Transfer Statement: *This study informs clinicians that patients seeking care for painful temporomandibular disorders, in specific cases of myalgia, can be classified into 1 of 3 groups that display unique profiles of symptoms. Most importantly, it emphasizes the importance of examining patients with painful temporomandibular disorders in a holistic manner that includes assessing symptoms of psychological distress. Patients with greater psychological distress will likely benefit from multidisciplinary treatment strategies that may include psychological treatments.*

Keywords: facial pain, tertiary care, cross-sectional studies, cluster analysis, odds ratio

## Introduction

Painful temporomandibular disorders (pTMDs) are conditions that affect 5% to 10% of the population worldwide—

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the hallmarks of which are pain and dysfunction in the masticatory muscles and/or temporomandibular joints (TMJs; Schiffman et al. 2014; Von Korff et al. 1988; National Academies of Sciences and Medicine 2020). The most frequent types of pTMDs associated with chronic pain (i.e., myalgia and arthralgia) are seemingly idiopathic and lack a clinically evident pathology that accounts for their symptoms (Murphy et al. 2013; Nicholas et al. 2019). This leads to problems linked to unspecific diagnosis and care that are reflected in the health care costs of pTMDs. In the United States, 17,800,000 workdays are lost yearly for every 100,000,000 working adults due to pTMDs (Fricton and Schiffman 1995). In the United Kingdom, having high-impact orofacial pain instead of low leads to an increase in out-of-pocket and indirect health care costs equal to nearly US $4,150 per person over 6 months (Breckons et al. 2018; this reference reported out-of-pocket and indirect costs of £311 and £2,312, respectively, which we combined and converted to 2022 US dollars using http://eppi.ioe.ac.uk/costconversion/).

The diagnostic criteria for TMDs (DC/TMD) have been extensively validated for the diagnosis of the most frequent types of pTMDs (i.e., masticatory muscle disorders and TMJ pain; Schiffman et al. 2014). However, the DC/TMD and other TMD diagnostic methods (Marciniak 2018) are anatomically based and do not incorporate the etiologic factors underlying pain (Gatchel et al. 2007). Other classification methods intended to distinguish etiologically distinct subpopulations within a chronic painful condition typically rely on extensive experimental pain-testing procedures (Freeman et al. 2014; Rabey et al. 2015; Vaegter and Graven-Nielsen 2016; Baron et al. 2017), psychological assessment (Rabey et al. 2016; Backryd et al. 2018), or both (Larsson et al. 2017), making them unpractical for clinical applications. One of the most promising clinically applicable findings of the Orofacial Pain Prospective Evaluation and Risk Assessment (OPPERA) Study—the largest population-based study designed to identify the biopsychosocial risk factors of the onset and persistence of pTMDs (Maixner et al. 2011; Slade et al. 2016)—was the identification of factors representing putative domains of pathophysiology (Bair et al. 2016). By drawing on hundreds of clinical measures, 3 phenotypic clusters of individuals were identified according to 4 clinically feasible measures: algometer-derived sensitivity to pressure pain in the trapezius muscle and survey-derived scores of anxiety, depression, and somatic symptoms. The adaptive (A) cluster is pain tolerant and has little psychological distress; the pain sensitive (PS) cluster is sensitive to experimental pain, with few psychological symptoms; and the global symptoms (GS) cluster is sensitive to experimental pain and has multiple symptoms of depression, anxiety, and general somatic complaints (Bair et al. 2016). Patients within clusters are expected to display greater homogeneity of the mechanisms underlying pain than patients with pTMD at large, and these mechanisms are expected to be of increasing complexity (i.e., A < PS < GS). The algorithm for cluster classification was later optimized, termed the Rapid OPPERA Algorithm (ROPA), and validated as a reliable tool to classify patients with pTMD and other chronic pain in clinical settings (Gaynor et al. 2021).

As dentists are the primary caregivers to patients with pTMD, here we sought to describe and compare the orofacial and psychosocial characteristics that would normally be assessed in the context of clinical care among patients seeking care for pTMD who are assigned to the A, PS, or GS cluster. We hypothesized that these characteristics would mirror the previously described phenotypic profile of individuals in the A, PS, and GS clusters; that is, patients with pTMD in the PS cluster would be more sensitive to orofacial pain than those in the A cluster, and those in the GS cluster would display a combination of pain sensitivity and comorbid psychological symptoms. Foreseeing a potential adaptation of the clustering algorithm to increase its clinical applicability, we also explored the correlation between algometer-derived sensitivity to pressure pain in the trapezius muscle and sensitivity to pain evoked by the palpation of cervical and orofacial sites.

## Methods

### Study Design

Data for this study were obtained from the data repository of patients with pTMD attending Duke Innovative Pain Therapies (DIPT) at Brier Creek, Duke University, between August 2017 and April 2021 who consented to contribute their clinical data to research. Patients <18 years (y) old, without English fluency, or without the cognitive ability to complete the surveys were not asked to participate in the registry; no other exclusion criteria were applied. The usage of clinical data for research purposes was explained prior to obtaining informed consent from each participant. All study procedures were approved and monitored by Duke University. The diagnosis of pTMD was rendered by 1 of 2 orofacial pain specialists at DIPT (A.A.A. or D.V.) and was based on the DC/TMD of myalgia (accompanied or not by arthralgia; Schiffman et al. 2014).

This study follows the STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology) for methodology and statistical analyses (von Elm et al. 2008).

### Study Data Set

Standard-of-care procedures at DIPT require patients to complete a trapezius muscle pressure pain threshold (PPT) test and a set of web-based surveys that assess demographic, pain-related, and psychosocial measures at each clinical visit, as previously described (Gaynor et al. 2021). At their clinic visit, patients undergo a clinical examination of their TMJs and orofacial and neck muscles, as well as a dental examination performed by 1 of 2 orofacial pain specialists trained in the DC/TMD clinical examination procedures (A.A.A. or D.V.).

### Demographic Variables

Demographic variables were self-reported and included gender, race, marital status, and smoking status. We categorized gender into male or female; race into White, Black, or other; marital status into single, married, or other (divorced, legally separated, widowed, unknown); and smoking status into smoker (former smoker, current smoker, light tobacco smoker) or nonsmoker.

### Clinical Variables

Orofacial characteristics and symptoms were assessed as follows:

- TMJ sounds (yes, no)
- Palpation pain in 14 masticatory muscle sites (right and left masseter, temporalis, submandibular, posterior mandibular, medial pterygoid, and lateral pterygoid, as well as right and left temporalis tendon)
- Palpation pain in 4 TMJ sites (right and left lateral and posterior poles)
- Palpation pain in 10 cervical muscle sites (right and left splenius capitis, upper lateral and medial trapezius, and upper and middle sternocleidomastoid)
- Familiarity with pain evoked by palpation of any of the 28 masticatory muscle, TMJ, or cervical muscle sites (i.e., whether pain evoked by palpation felt similar to the pain felt in that same part of the body in the previous 30 days)
- Mandibular range of motion (maximal pain-free opening, maximal assisted opening, right and left lateral movements, and protrusion)
- Limitation of cervical range of motion during neck flexion, extension, right and left lateral flexion, and right and left rotation (if any or none of the movements were limited)

As part of a routine dental evaluation, the following dental features were also annotated: angle class (class I or others), extension of overjet and overbite (in millimeters), crossbite (yes or no), posterior contacts (bilateral or nonbilateral), anterior and posterior attrition (presence or absence), and number of missing teeth.

### Pain-Related Variables

We used a numerical rating scale of 0 to 100 to assess the patients' average, highest, and lowest pain intensities for the past 4 weeks (wk), as well as their current pain intensity (i.e., at the moment of clinical examination). Patients were also asked to estimate the amount of their waking day spent in pain during the last 4 wk using a scale of 0 to 100, where 0 represents *none of the time* and 100 represents *100% of the time*. The Pain, Enjoyment, and General Activity (PEG) survey was used to generate a measure that combines pain intensity and disability (Krebs et al. 2009). This 3-item validated survey tracks the past week's average pain and the interference of pain with the enjoyment of life and with general activities based on a numeric rating scale of 0 to 10. A score is then derived by averaging the 3 items' responses, with greater scores suggesting higher-impact clinical pain (Von Korff et al. 2016). In addition, we used an item from painDETECT (Freynhagen et al. 2006) to assess the course of pain: 1) patients were classified as having persistent pain if they reported persistent pain with slight fluctuations, persistent pain with pain attacks, or pain attacks with pain in between; 2) patients were classified as having intermittent pain if they reported pain attacks without pain in between.

### Psychosocial Variables

Patients' stress levels were assessed with the 10-item Perceived Stress Scale (Cohen et al. 1983). The Perceived Stress Scale tracks the frequency with which individuals considered situations stressful that occurred in the last month using a 5-point Likert scale: never (0), almost never, sometimes, fairly often, and very often (4). The rank values of each answer were then summed to generate a score, with greater scores being indicative of greater stress.

The Brief Symptom Inventory–18 (BSI-18) includes 3 subscales (6 items each) that track somatic, anxiety, and depression symptoms. The BSI-18 asks individuals to rate how much a given problem has distressed or bothered them in the past week using a 5-point scale: not at all (0), a little bit, moderately, quite a bit, or extremely (4). A score for each subscale (range, 0 to 24) was calculated by summing the rank values of the answers to the 6 items in each subscale (Rath and Fox 2018).

Two single-item questions derived from validated surveys were used to assess the patients' perceived self-efficacy to decrease their pain (Anderson et al. 1995; "As of now, how certain are you that you can decrease your pain quite a bit?") and their pain-catastrophizing levels (Sullivan et al. 1995; "When I feel pain it is terrible, and I feel it is never going to get any better") on numerical rating scales of 0 to 100.

### Pressure Pain Threshold

PPT was assessed by a trained examiner using a commercially available algometer (Pain Test Force Dial FPK/N; Wagner Instruments) applied to the trapezius muscle bilaterally. Briefly (Greenspan et al. 2011), after a trial test to familiarize patients with the procedure, the examiner applied gradually increasing pressure at a point in the muscle until the patient first indicated pain by pressing a button. The amount of pressure (in kilopascals, kPa) that triggered pain was recorded, and this procedure was repeated at the same test site until either 2 values were recorded within 20 kPa of each other or 5 trials were administered. In either case, the mean of the 2 closest values was recorded as the PPT estimate (lower PPTs are indicative of greater pain sensitivity). If the patient did not indicate pain at the point when the stimulus reached 600 kPa, a value of 600 was recorded as the threshold value.

### Clustering

We used ROPA to assign individuals to the A, PS, or GS cluster, as previously described (Gaynor et al. 2021). Briefly, ROPA uses nearest-centroid models to define each cluster by a centroid,

or the clustering measures' mean among individuals within a cluster (i.e., survey-derived mean scores of anxiety, depression, and somatic symptoms and mean PPT). Study participants were then assigned by ROPA to a cluster by minimizing the distance between the centroid and each participant. The data set used to generate ROPA derives from the OPPERA study, which used the Symptoms Checklist–90 Revised (Schmitz et al. 2000) to assess anxiety, depression, and somatic symptoms. As there is a strong correlation between the Symptoms Checklist–90 Revised (Schmitz et al. 2000) and the BSI-18 (Spitzer et al. 2011) subscales (range, 0.92 to 0.98; Gaynor et al. 2021), here we used the BSI-18 to assess these symptoms because the shorter length of this survey makes it more suitable for clinical use.

### Data Analysis

We performed a multinomial regression analysis to calculate the odds ratios (ORs) and the corresponding 95% CIs. Goodness of fit was evaluated with the Pearson and deviance tests. In the multinomial regression model, the A cluster was considered the reference group. Statistical analyses were carried out via SPSS version 27.0 (IBM Corp). A simple linear regression analysis was used to study the association between PPT scores and the total number of masticatory, TMJ, and cervical muscle sites with palpation pain (i.e., up to 28 sites).

## Results

Data were collected for 214 patients with pTMD, of which 83 were excluded from the data set due to missing data that did not allow clustering. Of the 131 patients with pTMD in this study (mean ± SD age, 44.7 ± 13.5 y), 108 (82.4%) were female and 23 (17.6%) were male. In addition, 54 (41.2%) were assigned to the A cluster (mean age, 45.41 ± 14.12 y), 49 (37.4%) to the PS cluster (44.22 ± 13.78 y), and 28 (21.4%) to the GS cluster (44.00 ± 12.11 y).

The demographic characteristics of study patients assigned to the A, PS, and GS clusters are shown in Table 1. Females were more likely to be assigned to the PS cluster (OR, 3.56; 95% CI, 1.01 to 1.65), and individuals who were current or past tobacco smokers were more likely to be assigned to the PS (2.88; 1.00 to 8.33) and GS (3.78; 1.18 to 12.10) clusters. These findings should be interpreted with caution as regression models were not well fitted to the data ($P < 0.05$). Age, self-reported race, and marital status did not affect the likelihood of being assigned to the PS or GS cluster. Males were more likely to be among the set of 83 patients excluded from the analysis (Appendix Table).

Regarding orofacial characteristics and symptoms (Table 2), patients assigned to the PS cluster were more likely to report a greater number of TMJ sites (OR, 1.29; 95% CI, 1.01 to 1.65), masticatory muscles (1.48; 1.19 to 1.83), and cervical muscles (1.23; 1.09 to 1.39) with pain evoked by palpation. They were also more likely to display reduced protrusive range of motion (0.71; 0.51 to 0.99). Patients assigned to the GS cluster were more likely to report a greater number of masticatory muscles with pain evoked by palpation (1.28; 1.01 to 1.62). The number of TMJ sites, masticatory muscles, or cervical muscles for which palpation evoked the report of familiar pain was not associated with differences in the likelihood of being assigned to the PS or GS cluster. The presence of TMJ sounds and the report of limited cervical range of motion due to pain, as well as the mandibular range of motion during pain-free opening, maximal assisted opening, and right or left lateral movements, did not affect the likelihood of being assigned to the PS or GS cluster.

Patients assigned to the GS cluster were consistently more likely to report worse pain-related outcomes, including greater amount of waking day spent in pain (OR, 1.03; 95% CI, 1.012 to 1.05), higher-impact clinical pain (1.43; 1.14 to 1.80), and persistent pain (16.23; 1.92 to 137.1; Table 3). They also displayed poorer psychological profiles, as they were more likely to report greater pain catastrophizing (1.04; 1.01 to 1.06) and perceived stress (1.23; 1.03 to 1.46). Patients assigned to the PS cluster were more likely to report only a greater amount of waking day spent in pain (1.01; 1.001 to 1.03).

The dental features of patients assigned to the PS or GS cluster are presented in the Appendix Table. Patients assigned to the GS cluster were more likely to display reduced overbite (OR, 0.62; 95% CI, 0.4 to 0.98), to not have bilateral posterior contacts (17.14; 1.95 to 150.6), and to have a greater number of missing teeth (1.35; 1.05 to 1.74).

Last, we explored whether the trapezius PPT (one of the measures used by ROPA to assign clusters) correlated with the number of sites sensitive to pain evoked by palpation (i.e., cervical muscles, masticatory muscles, and TMJs). We found a statistically significant negative correlation ($P < 0.001$; $r = -0.40$) between these measures (i.e., the lower the PPT, the greater the number of painful sites).

## Discussion

In this study, we leveraged data from care-seeking patients with pTMD to contrast clinical and psychological characteristics that are consistent with an orofacial pain clinical examination among individuals assigned to 1 of 3 previously identified and validated phenotypic clusters (Bair et al. 2016; Gaynor et al. 2021). Here we provide additional evidence of the poorer psychological profile of individuals assigned to the GS cluster, as they reported more severe psychological symptoms, as previously shown (Bair et al. 2016; Gaynor et al. 2021), and were more likely to report that pain was always present and had greater intensity and impact, even though those assigned to the PS cluster reported more clinical measures consistent with pain. This aligns with the concept that patients assigned to the GS cluster display greater complexity of the biopsychosocial underpinnings of pain, which likely translates into poorer prognosis. Research currently underway will

**Table 1.**
Demographic Characteristics of Patients with pTMD Assigned to the Adaptive, Pain Sensitive, and Global Symptoms Clusters ($N = 131$).

| Variable | Patients, *n* (%) | | | | Odds Ratio (95% CI) | *P* Value |
|---|---|---|---|---|---|---|
| | Total | Adaptive | Pain Sensitive | Global Symptoms | | |
| **Gender** | | | | | | |
| **Male (reference)** | 23 | 13 (24.1) | 4 (8.2) | 6 (21.4) | | |
| **Female** | 108 | 41 (75.9) | 45 (91.8) | 22 (78.6) | PS: 3.56 (1.07 to 11.81)<br>GS: 1.16 (0.38 to 3.48) | 0.037<br>0.788 |
| **Age, y** | | | | | | |
| **18 to 31 (reference)** | 27 | 11 (20.4) | 11 (22.5) | 5 (17.9) | | |
| **32 to 45** | 43 | 17 (31.5) | 16 (32.6) | 10 (35.7) | PS: 0.94 (0.32 to 2.77)<br>GS: 1.29 (0.35 to 4.82) | >0.999<br>0.752 |
| **46 to 59** | 42 | 18 (33.3) | 15 (30.6) | 9 (32.1) | PS: 0.83 (0.28 to 2.46)<br>GS: 1.10 (0.29 to 4.14) | 0.788<br>>0.999 |
| **≥60** | 19 | 8 (14.8) | 7 (14.3) | 4 (14.3) | PS: 0.88 (0.24 to 3.26)<br>GS: 1.10 (0.22 to 5.45) | >0.999<br>>0.999 |
| **Race** | | | | | | |
| **White (reference)** | 113 | 44 (81.5) | 44 (89.8) | 25 (89.3) | | |
| **Black** | 10 | 5 (9.3) | 3 (6.1) | 2 (7.1) | PS: 0.6 (0.13 to 2.66)<br>GS: 0.7 (0.12 to 3.89) | 0.502<br>0.688 |
| **Others** | 8 | 5 (9.3) | 2 (4.1) | 1 (3.6) | PS: 0.4 (0.07 to 2.17)<br>GS:0.35 (0.03 to 3.18) | 0.289<br>0.353 |
| **Marital status** | | | | | | |
| **Single (reference)** | 33 | 14 (25.9) | 13 (26.5) | 6 (21.4) | | |
| **Married** | 81 | 35 (64.8) | 30 (61.2) | 16 (57.1) | PS: 0.92 (0.37 to 2.26)<br>GS: 1.06 (0.34 to 3.28) | 0.861<br>0.910 |
| **Other** | 17 | 5 (9.3) | 6 (12.2) | 6 (21.4) | PS: 1.29 (0.13 to 5.27)<br>GS: 2.8 (0.61 to 12.85) | 0.721<br>0.186 |
| **Smoking status** | | | | | | |
| **Nonsmoker (reference)** | 103 | 48 (88.9) | 36 (73.5) | 19 (67.9) | | |
| **Smoker** | 28 | 6 (11.1) | 13 (26.5) | 9 (32.1) | PS: 2.88 (1.001 to 8.33)<br>GS: 3.78 (1.18 to 12.10) | 0.050<br>0.025 |

shed light on the prognosis of patients assigned to different clusters.

Most important, our findings solidify the PS cluster as its own group. In a previous study, the pain-related and psychosocial measures of patients with chronic pain who were assigned to the PS cluster were mostly similar to those of patients assigned to the A cluster (Gaynor et al. 2021), casting doubt on its clinical relevance. Here, we demonstrate that patients assigned to the PS cluster display greater orofacial and cervical hypersensitivity, suggesting the existence of a large degree of local sensitization or segmental sensitization (Arendt-Nielsen et al. 2018).

Reporting familiar pain during clinical examination in at least 1 masticatory muscle or TMJ site is a requirement for a DC/TMD diagnosis of myalgia

**Table 2.**
Orofacial Characteristics and Symptoms of Patients with pTMD Assigned to the Adaptive, Pain Sensitive, and Global Symptoms Clusters ($N = 131$).

| Variable | Patients, *n* (%) or Mean ± SD | | | | Odds Ratio (95% CI) | *P* Value |
|---|---|---|---|---|---|---|
| | Total | Adaptive | Pain Sensitive | Global Symptoms | | |
| TMJ sounds | 53 | | | | | |
| No (reference) | 40 | 11 (73.3) | 16 (69.6) | 13 (86.7) | | |
| Yes | 13 | 4 (26.7) | 7 (30.4) | 2 (13.3) | PS: 1.20 (0.28 to 5.12)<br>GS: 0.42 (0.06 to 2.76) | 0.802<br>0.369 |
| Pain evoked by palpation | | | | | | |
| TMJ sites | 131 | 2.0 ± 1.6 | 2.7 ± 1.6 | 2.5 ± 1.4 | PS: 1.29 (1.005 to 1.65)<br>GS: 1.21 (0.90 to 1.62) | 0.047<br>0.200 |
| Masticatory muscles | 131 | 3.2 ± 1.6 | 5.1 ± 2.9 | 4.2 ± 2.0 | PS: 1.48 (1.19 to 1.83)<br>GS: 1.28 (1.01 to 1.62) | <0.001<br>0.037 |
| Cervical muscles | 131 | 4.4 ± 3.9 | 7.1 ± 3.3 | 5.9 ± 3.3 | PS: 1.23 (1.09 to 1.39)<br>GS: 1.11 (0.98 to 1.26) | <0.001<br>0.083 |
| Familiarity with pain evoked by palpation | | | | | | |
| TMJ sites | 131 | 1.3 ± 1.5 | 1.4 ± 1.7 | 1.2 ± 1.4 | PS: 1.05 (0.82 to 1.35)<br>GS: 0.97 (0.71 to 1.31) | 0.685<br>0.847 |
| Masticatory muscles | 131 | 1.7 ± 1.5 | 2.2 ± 1.6 | 2.0 ± 1.2 | PS: 1.26 (0.95 to 1.65)<br>GS: 1.13 (0.82 to 1.56) | 0.098<br>0.430 |
| Cervical muscles | 131 | 1.1 ± 2.6 | 2.2 ± 2.8 | 2.2 ± 3.2 | PS: 1.16 (0.99 to 1.35)<br>GS: 1.16 (0.97 to 1.38) | 0.058<br>0.089 |
| Cervical ROM limitation | 69 | | | | | |
| No (reference) | 39 | 15 (65.2) | 16 (53.3) | 8 (50.0) | | |
| Yes | 30 | 8 (34.8) | 14 (46.7) | 8 (50.0) | PS: 1.64 (0.53 to 5.02)<br>GS: 1.87 (0.51 to 6.89) | 0.386<br>0.344 |
| Mandibular ROM | | | | | | |
| Pain free opening | 62 | 37.4 ± 9.6 | 35.2 ± 10.3 | 37.1 ± 9.4 | PS: 0.97 (0.92 to 1.03)<br>GS: 0.99 (0.92 to 1.07) | 0.447<br>0.922 |
| Maximal assisted opening | 60 | 47.3 ± 6.9 | 45.1 ± 6.2 | 47.8 ± 7.6 | PS: 0.95 (0.87 to 1.04)<br>GS: 1.01 (0.91 to 1.12) | 0.288<br>0.820 |
| Right lateral movement | 59 | 8.8 ± 1.9 | 7.4 ± 3.4 | 9.2 ± 0.9 | PS: 0.79 (0.61 to 1.04)<br>GS: 1.09 (0.78 to 1.52) | 0.094<br>0.607 |
| Left lateral movement | 59 | 8.8 ± 2.1 | 8.0 ± 3.2 | 8.4 ± 2.1 | PS: 0.89 (0.70 to 1.13)<br>GS: 0.94 (0.71 to 1.24) | 0.352<br>0.674 |
| Protrusion | 58 | 7.3 ± 2.5 | 5.9 ± 2.0 | 6.6 ± 1.6 | PS: 0.71 (0.51 to 0.99)<br>GS: 0.83 (0.59 to 1.17) | 0.044<br>0.304 |

ROM, range of motion; TMJ, temporomandibular joint.

**Table 3.**
Pain-Related and Psychological Characteristics of Patients with pTMD Assigned to the Adaptive, Pain Sensitive, and Global Symptoms Clusters ($N = 131$).

| Variable [a] | Patients, *n* (%) or Mean ± SD | | | | Odds Ratio (95% CI) | *P* Value |
|---|---|---|---|---|---|---|
| | Total | Adaptive | Pain Sensitive | Global Symptoms | | |
| Pain intensity | 93 | | | | | |
| Average | | 47.5 ± 25.9 | 52.0 ± 22.9 | 63.3 ± 20.1 | PS: 1.0 (0.98 to 1.02)<br>GS: 1.03 (10.005 to 1.05) | 0.442<br>0.020 |
| Highest | | 63.2 ± 24.7 | 69.5 ± 20.2 | 83.2 ± 11.3 | PS: 1.01 (0.99 to 1.03)<br>GS:1.06 (1.02 to 1.10) | 0.230<br>0.001 |
| Lowest | | 20.5 ± 21.7 | 25.5 ± 22.5 | 38.9 ± 24.0 | PS: 1.01 (0.98 to 1.03)<br>GS: 1.03 (1.009 to 1.06) | 0.355<br>0.009 |
| Current | | 38.8 ± 29.7 | 45.8 ± 26.6 | 58.9 ± 20.5 | PS: 1.01 (0.99 to 1.02)<br>GS: 1.03 (1.007 to 1.05) | 0.286<br>0.010 |
| Waking day in pain | | 50.3 ± 32.2 | 66.7 ± 33.6 | 80.1 ± 19.4 | PS: 1.01 (1.001 to 1.03)<br>GS: 1.03 (1.012 to 1.05) | 0.042<br>0.002 |
| PEG survey | 104 | 4.7 ± 2.5 | 5.3 ± 2.7 | 6.9 ± 2.0 | PS: 1.10 (0.92 to 1.21)<br>GS: 1.43 (1.14 to 1.80) | 0.276<br>0.002 |
| Pain course | 100 | | | | | |
| Intermittent (reference) | 24 | 12 (41.4) | 11 (23.4) | 1 (4.2) | | |
| Persistent | 76 | 17 (58.6) | 36 (76.6) | 23 (95.8) | PS: 2.31(0.84 to 6.28)<br>GS: 16.23 (1.92 to 137.1) | 0.101<br>0.010 |
| Self-efficacy | 101 | 49.9 ± 31.2 | 56.3 ± 26.4 | 41.9 ± 30.0 | PS: 1.0 (0.99 to 1.02)<br>GS: 0.99 (0.97 to 1.009) | 0.341<br>0.306 |
| Catastrophizing | 101 | 22.2 ± 23.3 | 28.1 ± 26.9 | 52.2 ± 30.0 | PS: 1.01 (0.99 to 1.02)<br>GS: 1.04 (1.01 to 1.06) | 0.320<br>0.001 |
| Stress | 102 | 18.0 ± 4.3 | 18.5 ± 2.7 | 20.2 ± 3.7 | PS: 1.02 (0.91 to 1.17)<br>GS: 1.23 (1.03 to 1.46) | 0.565<br>0.020 |

or arthralgia, respectively. This means that a patient reporting, for instance, familiar pain only in the right masseter muscle and a patient reporting familiar pain in the right and left masseter and temporalis muscles will receive the same diagnosis of myalgia. Hence, we also investigated whether the number of masticatory muscle, TMJ, or cervical muscle sites for which palpation evoked a familiar pain sensation was linked to the likelihood of belonging to the PS or GS cluster, but such associations were not found. Pain familiarity has been incorporated to the DC/TMD framework, as it improved sensitivity and specificity for the diagnoses of the most frequent types of pTMD (i.e., myalgia and arthralgia; Schiffman et al. 2014). However, here it did not contribute to the likelihood of being assigned to a specific phenotypic cluster, nor has it been linked to pTMD prognosis (Meloto et al. 2019). In other words, while pain familiarity undoubtedly contributes to the anatomic location of pain, hypersensitivity (i.e., pain that is evoked by palpation but does not necessarily mimic the patient's chief complaint) seems to be more informative about pain's pathophysiology.

Lifetime history of tobacco smoking was linked to increased likelihood of being assigned to the GS cluster in the OPPERA study, which was based on a sample of community-derived individuals with pTMD (Bair et al. 2016), and we now have replicated this finding in a sample of patients with pTMD seeking care. We also found it to be marginally linked to an increase in the chances of being assigned to the PS cluster. Smoking

is overwhelmingly known for its various harmful effects, including those that may contribute to pain (Sanders et al. 2012), and it has been linked to increased pain intensity, depression, and anxiety symptoms among those with chronic pain (Khan et al. 2019). Our findings add to the overwhelming evidence that smoking contributes to poor oral and general health outcomes (Khan et al. 2019), including risk of having different chronic pain conditions, such as pTMD (Sanders et al. 2012), and they reinforce the role of dentists in raising awareness among their patients about the harmful effects of smoking.

We have reported the dental features of patients assigned to different clusters, because dental examination is a standard-of-care procedure in dental practice. However, we advise caution when interpreting our findings. While there is consistent and extensive data from well-designed studies to support the role of biopsychosocial and environmental factors in the pathophysiology of chronic pain conditions (Gatchel et al. 2007; Maixner et al. 2016; Gaynor et al. 2021), including pTMDs (Bair et al. 2016), there is little and inconsistent evidence to support a role for occlusal factors in pTMDs (Manfredini et al. 2017). Put into scientific context, our findings that reduced overbite, nonbilateral posterior contacts, and greater number of missing teeth are linked to an increased likelihood of being assigned to the GS cluster are more likely to be incidental. Nonbilateral posterior contact and number of missing teeth are intrinsically related measures that could be accounted for by age, a known risk factor for tooth loss (Hassel et al. 2018), and socioeconomic status. In this study, there was no age difference among clusters, and socioeconomic status, despite not being formally assessed, is likely to be similar, as the study sample is largely composed of individuals who can afford treatment in a tertiary clinic. It is possible that the increased number of missing teeth in the GS cluster may be a result of inappropriate pain diagnosis leading to unnecessary tooth extractions.

Using PPT as the pain sensitivity measure to assign clusters, instead of pain in specific anatomic locations, has benefits that include the generalizability of clustering to other pain conditions (Gaynor et al. 2021) and the potential to identify individuals at risk of developing pain (Bair et al. 2016). Nonetheless, replacing PPT by a measure of palpation pain could increase the clinical feasibility of cluster assignment, since 1) the former requires the use of a device not routinely used in health care and 2) palpation of cervical muscles, masticatory muscles, and TMJs is an integral part of an orofacial pain clinical examination (Schiffman et al. 2014). Our findings that pain sensitivity correlates with the number of sites painful to palpation are encouraging and support future explorations of the reliability of cluster assignment based on pain evoked by palpation.

Data for this study were originally collected as part of real-life clinical examinations and not as part of a research study. As answering all questionnaire items was not mandatory, a large set of patients ($n$ = 83) did not provide data that allowed cluster assignment, precluding the analysis of the whole patient data set and possibly affecting the distribution of clusters in this study (A > PS > GS) that was different from that of previous studies (A < PS < GS; Bair et al. 2016; Gaynor et al. 2021). We also had to contend with missing data in other study variables, leading to ORs linked to wide confidence intervals. Future clinical studies collecting a standardized data set from study patients are warranted to support our findings. In addition, our sample is limited to mostly females who can afford treatment at a tertiary clinic. Hence, future investigations of larger and more diverse groups are also required to support our findings.

In summary, this patient-based study supports the concept that when compared with individuals assigned to the A cluster, those assigned to the GS cluster display a more complex profile encompassing poorer clinical and psychological aspects. Most important, our findings establish the PS cluster as a group that does not display psychological comorbidities despite being hypersensitive. These differences in clinical and psychological presentation may signify that distinct mechanisms sustain pain in patients belonging to different clusters and, ultimately, that distinct treatment strategies may be needed to better care for these patients.

## Author Contributions

F.S. Al-Hamed, C.B. Meloto, contributed to conception and design, data acquisition, analysis, and interpretation, drafted and critically revised manuscript; A.A. Alonso, contributed to design, data acquisition, critically revised the manuscript; D. Vivaldi, contributed to design, acquisition and interpretation, critically revised manuscript; S.B. Smith, contributed to conception and design, data acquisition, analysis, and interpretation, critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work.

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