

Chronic temporomandibular disorders are associated with higher propensity to develop central sensitization: a case-control study

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Abstract

Temporomandibular disorders (TMD) include a group of musculoskeletal disorders that may involve increased responsiveness of nociceptive neurons in the central nervous system (ie, central sensitization). To test this hypothesis further, this study examined whether, as compared with healthy subjects, patients with chronic TMD have a greater propensity to develop secondary mechanical hyperalgesia—a phenomenon that can be confidently attributed to central sensitization. In this case-control study, we assessed the area of secondary mechanical hyperalgesia induced experimentally by delivering high-frequency electrical stimulation (HFS) to the volar forearm skin in 20 participants with chronic TMD and 20 matched healthy controls. High-frequency electrical stimulation consisted in 12 trains of constant-current electrical pulses (5 mA) delivered at 42 Hz. The area of secondary mechanical hyperalgesia was evaluated 30 minutes after applying HFS. The area of secondary mechanical hyperalgesia induced by HFS was on average 76% larger in the chronic TMD group ($M = 67.7 \text{ cm}^2$, $SD = 28.2$) than in the healthy control group ($M = 38.4 \text{ cm}^2$, $SD = 14.9$; $P = 0.0003$). Regarding secondary outcomes, there was no group difference in the intensity of secondary mechanical hyperalgesia, but allodynia to cotton after HFS was more frequent in the chronic TMD group. To the best of our knowledge, this is the first study to show that individuals with chronic TMD have an increased propensity to develop secondary hyperalgesia in a site innervated extratrigeminally. Our results contribute to a better understanding of the pathophysiology of chronic TMD.

Keywords: High-frequency electrical stimulation, Central sensitization, Secondary hyperalgesia, Temporomandibular disorders, Chronic pain

1. Introduction

Temporomandibular joint disorders (TMD) include a group of musculoskeletal disorders characterized by pain and dysfunction in the temporomandibular joint and/or surrounding muscles. Temporomandibular joint disorders affect 10% to 12% of the adult population and are about twice as common in females than in males.^{9,30} Nearly half of individuals diagnosed with TMD develop chronic or recurrent symptoms, often leading to a decline in quality of life, physical and emotional well-being, and functional status.^{22,26,30}

Gaining a better understanding of the neurobiological mechanisms leading to pain in chronic TMD is required to allow the

development of mechanism-based treatments and has been deemed a research priority.^{8,47} It is believed that increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input (ie, central sensitization²⁴) may contribute to the development, severity, and persistence of TMD, as well as to the high prevalence of comorbidities among individuals with TMD.^{2,5,21,25,32,41}

Through quantitative sensory testing, studies have shown that individuals with TMD tend to have lower pressure pain thresholds and experience more pain in response to repeated nociceptive stimuli (ie, temporal summation) at extratrigeminally innervated sites.^{12,21} Besides, a recent prospective study showed that pressure pain thresholds throughout the body decrease after the onset of TMD and return to normal after TMD remission.⁴² These findings suggest alterations in trigeminal and extratrigeminal nociceptive processing, but are hardly indicative of the pathophysiology of TMD.^{4,10} Moreover, the sensitivity to stimuli is not found to be globally altered in patients with TMD^{12,16,21}; therefore, studies on specific physiological mechanisms are needed.

Experimental pain models are complementary to quantitative sensory testing and can provide more precise insights into the pathophysiology of chronic pain conditions.^{13,34} High-frequency electrical stimulation of skin nociceptors (HFS) is a well-controlled, noninvasive experimental pain model, mimicking the initial high frequency at which nociceptive neurons discharge immediately after a cutaneous tissue injury.¹⁸ Shortly after HFS, a large area of skin surrounding the electrode reliably becomes more sensitive to

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mechanical pinprick stimuli. This phenomenon of secondary mechanical hyperalgesia^{11,18,31,45} can be confidently attributed to central sensitization.^{6,34,37,40,44} Indeed, seminal studies by the group of LaMotte et al. have shown, using intradermal capsaicin injection in primates, that mechanical pinprick stimuli delivered to the skin surrounding the injection site evoke increased responses of spinal nociceptive neurons.⁴⁰ Most importantly, they found no concurrent evidence for peripheral sensitization of primary nociceptive afferents,⁶ indicating that the increased responses to mechanical pinprick stimuli were mainly of central origin. There is a lack of studies examining chronic TMD with experimental pain models of central sensitization.

In this case-control study, we compared the propensity of patients with chronic TMD to develop central sensitization after HFS delivered to the volar forearm. We hypothesized that, as compared with matched healthy controls, HFS would produce a larger area of secondary mechanical hyperalgesia in participants with chronic TMD because of potential alterations in extratrigeminal nociceptive processing.

2. Materials and methods

2.1. Design

This was a case-control study with 2 groups: (1) 20 participants with chronic TMD and (2) 20 matched healthy controls. This study was preregistered (NCT04086732) and approved by the local ethical committee (B403201940693).

2.2. Participants

We recruited female adults younger than 50 years. Only females were recruited to avoid the confounding effect of sex on propensity to develop central sensitization.³⁸ Exclusion criteria for all participants comprised evidence of psychiatric/inflammatory/neurological/heart or metabolic disease on direct questioning; evidence of skin alteration on the ventral forearms, use of antidepressant or neuroleptic drugs, and use of any known substance that may interfere with HFS; and lack of dental check-up during the past 12 months and pregnancy.

Participants from the chronic TMD group presented with TMD (arthralgia and/or myalgia subtypes) as a main complaint for at least 3 months, diagnosed according to the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD).²³ Additional musculoskeletal disorders were allowed because of the high prevalence of comorbidities among individuals with TMD.^{3,14,25} Healthy controls were free from musculoskeletal disorder and closely matched with respect to age, sex, and weight. Eligibility was assessed by experienced healthcare professionals specialized in

musculoskeletal disorders, using the DC/TMD routinely, both clinically and for research purposes.

Participants were recruited by healthcare professionals from the Oral and Maxillofacial Surgery and the Physical and Rehabilitation Unit of the Cliniques Universitaires Saint-Luc (Brussels—Belgium). Control participants were recruited from social media groups, using posters on noticeboards on the university campus adjacent to the Cliniques Universitaires Saint-Luc and by word of mouth.

2.3. Experimental procedures

The study was conducted in a quiet room. Participants were asked to refrain from drinks containing caffeine or alcohol, nicotine, and intense physical activity the day of testing. They were also asked to avoid taking medication (except contraceptives) or otherwise to report their use. The instructions to the participants were standardized.

The timeline of experimental procedures is summarized in Figure 1.

2.3.1. High-frequency electrical stimulation

High-frequency electrical stimulation was applied to the ventral forearm. The arm onto which HFS was applied (dominant vs nondominant) was evenly distributed among participants and was the same for matching participants.

High-frequency electrical stimulation consisted of 12 trains of 42 square-wave electrical pulses (intensity: 5 mA; pulse width: 2 ms). The trains lasted 1 second each and were applied in a 9-second intertrain interval.⁴⁶ We used a custom electrode designed to preferentially activate nociceptive free nerve endings of the skin (Centre for Sensory-Motor Interaction, Aalborg University, Denmark). The cathode of this electrode consists of 16 blunt stainless-steel pins with a diameter of 0.2 mm, protruding 1 mm from the base and placed in a circle with a diameter of 10 mm.⁴⁶ The anode is a stainless-steel ring with an inner diameter of 22 mm and an outer diameter of 40 mm. The electrical pulses were triggered by a programmable pulse generator (Master-8; AMPI, Jerusalem, Israel) and applied by a constant current electrical stimulator (Digitimer DS7A; Digitimer, Welwyn Garden City, United Kingdom).

2.3.2. Psychophysical evaluation

2.3.2.1. Primary outcome: area of secondary mechanical hyperalgesia

The area of secondary mechanical hyperalgesia was evaluated with a 128-mN pinprick probe (The PinPrick; MRC Systems

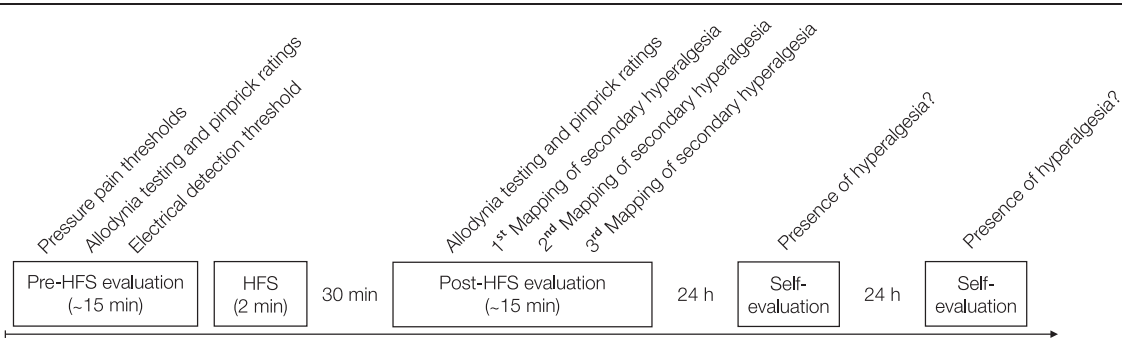


Figure 1. Timeline of the experimental procedures. HFS, high-frequency electrical stimulation.

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GmbH, Heidelberg, Germany), starting approximately 30 minutes after applying HFS. Pokes of 1-second duration were provided at a frequency of 0.5 Hz, starting well outside and approaching the stimulation site with steps of 0.5 cm from 4 different directions towards the application site (distal, proximal, lateral, and medial). Participants were instructed to report when they felt a “clear increase of pinprick sensitivity.” To improve reliability of this procedure, the area was assessed thrice with a 1-minute break between 2 evaluations and averaged.¹¹ The area of secondary mechanical hyperalgesia was estimated with a custom-written *Python* script, which determined the area based on a virtual polygon connecting the 4 borders of secondary mechanical hyperalgesia with best-fit parabolic segments.¹¹

2.3.2.2. Secondary outcomes

The intensity of pain elicited by the same pinprick probe was assessed in the region surrounding the electrode (HFS arm), as well as on the homologous site of the contralateral arm of the same participant (non-HFS arm), before HFS and 30 minutes after applying HFS. Participants were asked to rate the perceived pain intensity elicited by the mechanical stimuli on a 0 to 100 numerical rating scale (NRS) where 0 meant “no pain” and 100 “maximum pain imaginable.” For each measure, a total of 3 mechanical stimuli of 1-second duration were delivered to different sites within the tested area and averaged. We defined the intensity of secondary mechanical hyperalgesia as the NRS rating in the area of secondary mechanical hyperalgesia 30 minutes after applying HFS.

Dynamic mechanical allodynia was assessed in the test area before and 30 minutes after applying HFS using a cotton wisp exerting a force of 3 mN, a standardized brush (Somedic, Sweden) exerting a force of 200 to 400 mN, and a Q-tip fixed to an elastic strip exerting a force of 100 mN when slightly bent.³⁵ The tactile stimuli were applied with 3 strokes of approximately 2 cm in length over the skin. Participants were asked to report the quality of the stimuli as painful or nonpainful and to rate painful stimuli on the 0 to 100 NRS.

To assess the presence of secondary mechanical hyperalgesia in the region surrounding the electrode 24 hours and 48 hours after HFS, participants were taught how to assess their skin sensitivity by self-applying pinprick stimuli using a Neuropen (Owen-Mumford Ltd, Oxford, United Kingdom).⁴⁸

Baseline pressure pain thresholds were assessed with a pressure gauge device with a probe area of 1 cm² (FDX50; Wagner Instruments, Greenwich, CT) with a ramp rate of 50 kPa/s, bilaterally on the temporalis muscle,¹ the upper trapezius muscle,⁴⁹ and the tibialis anterior muscle.⁵⁰ Participants were instructed to say “stop” as soon as the pressure became painful. Pressure pain thresholds were assessed twice, with a 1-minute interstimulus interval. Pressure pain thresholds were averaged for each muscle. Participants were familiarized with the procedure before testing.^{7,19,20}

Electrical detection threshold to a single electrical pulse was determined using the methods of limits.¹¹

2.3.3. Questionnaires

Participants filled the Graded Chronic Pain Scale, the Jaw Functional Limitation scale, the Generalized Anxiety Disorder-7, the Patient Health Questionnaire-9 and -15, and the Oral Behaviors Checklist.²³ In addition, participants filled the Central Sensitization Inventory, and the Symptom Severity Scale.⁵² We calculated the fibromyalgia score based on the distribution of pain and the Widespread Pain Index.⁵²

2.4. Statistical analysis

Statistical analyses were conducted using SPSS 28 (SPSS, Chicago, IL), JMP Pro 16 (JMP Statistical Discovery LLC, Cary, NC) and PASS 15 (NCSS LLC, Kaysville, Utah). The alpha significance level was set to 5%.

2.4.1. Area of secondary mechanical hyperalgesia (primary outcome)

To look for differences between both groups in the area of secondary mechanical hyperalgesia, we checked the Gaussian distribution of the data using Q-Q plots and D'Agostino and Pearson normality tests and compared both groups with an independent unequal-variance *t* test. The variances were compared with an *F* test. As a post hoc analysis, we calculated the power to reject the null hypothesis of equal group means for the area of secondary mechanical hyperalgesia.

2.4.2. Secondary outcomes

General group characteristics (eg, demographics and responses to questionnaires), pressure pain thresholds, and electrical detection thresholds were compared with an independent *t* test or a Wilcoxon–Mann–Whitney rank-sum test, based on the normality of the data.

To compare the intensity of secondary mechanical hyperalgesia after HFS, we used a mixed design analysis of variance (ANOVA) to take repeated measures into account. The within-participant factors were the time (TIME: pre-HFS or post-HFS) and the arm (ARM: HFS or non-HFS arm). The between-participant factor was the group (GROUP: chronic TMD or healthy controls).

To assess whether dynamic mechanical allodynia and secondary mechanical hyperalgesia at the test site 24 hours and 48 hours after HFS were more frequent in participants with chronic TMD than in healthy controls, we used χ^2 tests or Fisher exact tests. If $\leq 20\%$ of expected cell counts were less than 5, we used the χ^2 test. If $> 20\%$ of expected cell counts were less than 5, we used the Fisher exact test.

To explore the associations between the area of secondary mechanical hyperalgesia and pressure pain thresholds, demographic characteristics, or the responses to questionnaires, we used the Pearson correlation coefficient for parametric variables and Spearman correlation coefficient for nonparametric variables. We did not adjust the secondary analyses for multiple comparisons because they are exploratory in nature.

3. Results

3.1. Sample characterization

On the day of the test, 1 participant in the healthy control group took paracetamol, and 2 participants in the TMD group took levothyroxine.

The mean age (SD) of participants with chronic TMD and healthy controls was, respectively, 25.6 (8.5) and 25.7 (7.5) years with no significant difference (Table 1). Likewise, there was no significant difference in height or weight. Participants with chronic TMD presented significantly higher scores to all questionnaires, except for the Oral Behaviors Checklist.

Of the 20 participants with chronic TMD, 18 had myalgia, of which 13 had myalgia only, 2 had both myalgia and headache attributed to TMD, and 3 had both myalgia and arthralgia. Two of the 20 participants had arthralgia with no myalgia. Of the 20

Table 1**Demographic characteristics, questionnaire scores, and pressure pain thresholds for participants with chronic temporomandibular disorders (TMD) and healthy controls.**

	TMD (n = 20) Mean (SD)	Healthy control (n = 20) Mean (SD)	P
Age, y	25.6 (8.5)	25.7 (7.5)	0.97
Height, cm	166.2 (6.9)	167.0 (6.5)	0.71
Weight, kg	63.9 (11.7)	65.0 (7.7)	0.73
Current pain, 0-100	14.5 (23.5)	0.4 (1.8)	0.0033
Graded Chronic Pain Scale, 0-4	1.3 (1.3)	0.3 (0.9)	0.0022
Jaw Functional Limitation Scale, 0-10	1.6 (0.8)	0.0 (0.1)	0.0001
Generalized Anxiety Disorder-7, 0-21	9.8 (4.7)	6.2 (3.7)	0.0044
Patient Health Questionnaire-9, 0-27	8.5 (4.0)	5.0 (4.2)	0.009
Patient Health Questionnaire-15, 0-30	8.7 (4.2)	5.5 (3.8)	0.017
Oral Behaviours Checklist, 0-84	28.2 (8.5)	22.2 (12.1)	0.078
Central Sensitization Inventory, 0-100	38.0 (11.1)	22.8 (8.9)	0.0001
Symptom Severity Scale, 0-12	5.5 (1.6)	3.0 (1.8)	0.0001
Widespread Pain Index, 0-19	5.0 (2.2)	1.0 (1.14)	0.0001
Fibromyalgia score, 0-31	10.4 (3.0)	4.0 (2.4)	0.0001
Temporalis pressure pain threshold, kPa	108.6 (48.9)	137.7 (48.7)	0.079
Trapezius pressure pain threshold, kPa	135.8 (53.0)	139.8 (49.6)	0.80
Tibialis pressure pain threshold, kPa	317.8 (274.4)	335.7 (140.4)	0.74
Electrical detection threshold, mA	0.14 (0.07)	0.12 (0.08)	0.26

A P-value less than 0.05 was considered statistically significant.

participants with chronic TMD, 12 had bilateral TMD. Participants with chronic TMD had an average of 5 painful comorbidities, and all but 1 participant with chronic TMD had at least 3 painful comorbidities. Low back pain was the most common painful comorbidity (n = 13), followed by neck pain (n = 12), shoulder pain (n = 10), thoracic pain (n = 9), and hip pain (n = 5). Four participants with chronic TMD met the American College of Rheumatology 2016 criteria for fibromyalgia.⁵² None of the control subjects met the DC/TMD criteria for TMD, and they were all free from musculoskeletal disorder.

3.2. Area of secondary mechanical hyperalgesia

The area of secondary mechanical hyperalgesia induced by HFS at the volar forearm was on average 76% larger in the chronic TMD group (M = 67.7 cm², SD = 28.2) compared with the healthy control group (M = 38.4 cm², SD = 14.9) (independent unequal-variance *t* test: *t* [28.87] = 4.11, *P* = 0.0003, *r*² = 0.37). Group sample sizes achieved a 98% power to reject the null hypothesis of equal means.

The variances in the area of secondary mechanical hyperalgesia differed between groups (*F* = 3.569, *P* = 0.0080). The area of secondary mechanical hyperalgesia of the chronic TMD group was more heterogeneous (Fig. 2).

3.3. Secondary outcomes

3.3.1. Intensity of secondary mechanical hyperalgesia

The ANOVA showed a significant main effect of TIME (*F* [1,38] = 57.09, *P* < 0.000, *η*² = 0.600), ARM (*F* [1,38] = 82.75, *P* < 0.000, *η*² = 0.685), and TIME × ARM (*F* [1,38] = 84.05, *P* < 0.000, *η*² =

0.689) on the perceived intensity of pain elicited by mechanical stimuli. This confirmed the successful induction of secondary mechanical hyperalgesia on the HFS arm (Fig. 3). However, there was no group difference in the intensity of secondary mechanical hyperalgesia after HFS, as shown by the TIME × ARM × GROUP interaction (*F* [1,38] = 3.21, *P* = 0.081, *η*² = 0.078, power = 41%).

3.3.2. Dynamic mechanical allodynia

Allodynia to cotton, brush, and Q-tip was more frequent in the chronic TMD group than in healthy controls (Table 2). There was a significant association between group status and cotton allodynia (Pearson χ^2 , *P* = 0.038, χ^2 = 4.29).

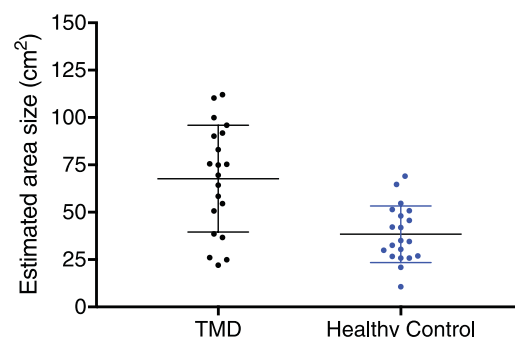


Figure 2. Estimated area of secondary mechanical hyperalgesia induced by HFS for participants with chronic TMD and matched healthy controls. Mean values and SDs are shown as horizontal bars. HFS, high-frequency electrical stimulation; TMD, temporomandibular disorders.

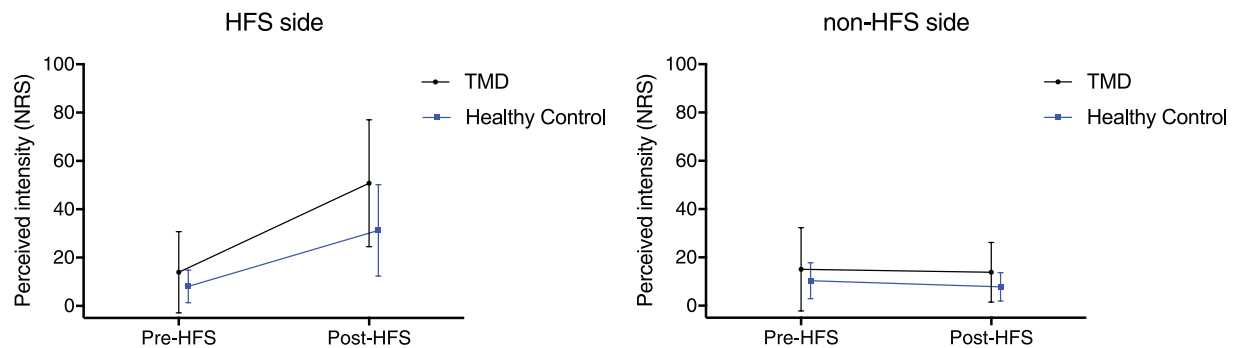


Figure 3. Perceived intensity of pain (mean + SD) elicited by mechanical stimuli on the HFS arm and the non-HFS arm for participants with chronic TMD and matched healthy controls. HFS, high-frequency electrical stimulation; NRS, numerical rating scale; TMD, temporomandibular disorders.

There was no statistically significant association between group status and brush (1-sided Fisher exact test, $P = 0.407$) or Q-tip allodynia (Pearson χ^2 , $P = 0.077$, $\chi^2 = 3.14$).

3.3.3. Presence of secondary mechanical hyperalgesia 24 and 48 hours after high-frequency electrical stimulation

We found no statistically significant association between group status and the presence of hyperalgesia 24 hours after HFS (Pearson χ^2 , $P = 0.063$, $\chi^2 = 3.46$) or 48 hours after HFS (1-sided Fisher exact test, $P = 0.584$, **Table 3**). Importantly, 3 participants in the chronic TMD group did not report the presence or absence of hyperalgesia at these time points.

3.3.4. Exploratory and post hoc analyses

We found that both anxiety scores (GAD-7) and fibromyalgia scores were positively correlated with the area of secondary mechanical hyperalgesia only in the chronic TMD group (respectively, $r = 0.53$, $P = 0.017$, and $r = 0.45$, $P = 0.045$). Responses to other questionnaires (eg, Widespread Pain Index), pressure pain thresholds, or demographic characteristics were not correlated with the area of secondary mechanical hyperalgesia.

To investigate whether our results were biased by the heterogeneity of the chronic TMD group regarding TMD subtypes or the concurrent presence of fibromyalgia, we ran post hoc analyses to focus on participants with TMD myalgia only and their healthy controls. Our results for the area of secondary mechanical hyperalgesia were largely unchanged when we (1) excluded the 2 participants with TMD arthralgia only ($N = 18$ TMD and $N = 18$ controls, $t [25.7] = 3.60$, $P = 0.001$, $r^2 = 0.33$, power = 93.4%), (2) excluded the 7 participants with TMD arthralgia only or mixed TMD ($N = 13$ TMD and $N = 13$ controls, $t [17.9] = 3.43$, $P = 0.003$, $r^2 = 0.39$, power = 94.4%), and (3) excluded the 9 participants with TMD arthralgia only or mixed TMD or fibromyalgia ($N = 11$ TMD and $N = 11$ controls, $t [15.11] = 2.58$, $P = 0.021$, $r^2 = 0.30$, power = 74.7%).

4. Discussion

Our case-control study showed larger areas of secondary mechanical hyperalgesia induced by HFS in participants with chronic TMD than in matched healthy participants. These results suggest that individuals with chronic TMD are more susceptible than healthy matched controls to develop central sensitization. Regarding secondary outcomes, there was no group difference

in the intensity of secondary mechanical hyperalgesia, but allodynia to cotton after HFS was more frequent in the chronic TMD group.

Several authors have hypothesized that central sensitization contributes to chronic TMD,^{2,5,21,25,41} but arguably experimentally induced secondary mechanical hyperalgesia is presently the only example that fulfills the definition of central sensitization as defined by the International Association for the Study of Pain.⁴⁴ We showed that chronic TMD is associated with larger areas of experimentally induced secondary mechanical hyperalgesia, suggesting that individuals with chronic TMD have an increased propensity to develop central sensitization. Importantly, secondary mechanical hyperalgesia was induced outside the trigeminal pathways. In a previous study using an experimental model of tonic muscle pain, infusion of hypertonic saline into the masseter muscle was found to be more painful and to extend to a larger area in participants with TMD compared with healthy controls.⁴³ However, no such difference could be detected at the tibialis anterior.⁴³ Experimental models that induce secondary mechanical hyperalgesia are perhaps more sensitive to changes in nociceptive processing associated with musculoskeletal pain. Indeed, larger areas of secondary mechanical hyperalgesia have also been found in patients with rheumatoid arthritis or fibromyalgia after topical capsaicin application on the forearm.^{27,28}

We found that the chronic TMD group was more heterogeneous regarding the area of secondary mechanical hyperalgesia as compared with matched healthy controls. Our sample size did not allow us to conduct valid subgroup analyses, but a case-control study of 1031 individuals with chronic TMD and 3247 TMD-free controls identified 3 clusters with respect to experimental pain sensitivity, psychological distress, and clinical features among individuals with TMD.⁵ The first cluster, called

Table 2

Frequency of cotton, brush, and Q-tip allodynia 30 minutes after applying high-frequency electrical stimulation.

	TMD (n = 20)		Healthy control (n = 20)		P
	n	%	n	%	
Cotton allodynia	9	45	3	15	0.038
Brush allodynia	5	25	2	10	0.407
Q-tip allodynia	8	40	3	15	0.077

%, percentage of individuals within a group; n, number of occurrences of allodynia; TMD, temporomandibular disorders.

Table 3
Frequency of secondary mechanical hyperalgesia 24 and 48 hours after high-frequency electrical stimulation.

	TMD (n = 17)		Healthy control (n = 20)		P
	n	%	n	%	
SH 24 hours after HFS	5	29	12	60	0.063
SH 48 hours after HFS	2	12	1	5	0.584

%, percentage of individuals within a group; HFS, high-frequency electrical stimulation; n, number of occurrences of SH; SH, secondary mechanical hyperalgesia; TMD, temporomandibular disorders.

"adaptive," represented 33% of their cohort and comprised individuals with few signs of increased pain sensitivity or psychological distress. The second and the third clusters, respectively, called "pain-sensitive" and "global symptoms," represented 66% of their cohort and comprised individuals with increased muscle pain sensitivity, more psychological disturbances, greater levels of clinical pain, a greater frequency of comorbid pain conditions, and more bodily pain. Future studies could help determine whether individuals from the "pain-sensitive" and the "global symptoms" clusters also have an increased propensity to develop central sensitization.

This study included only female participants, which have double the risk of developing TMD as compared with men,⁹ and an increased risk of TMD persistence after acute TMD.⁴¹ The cultural, sociological, biological, or psychological aspects that may predispose women to having more TMD than men are unclear. In addition to sex differences in hormonal factors, levels of stress, and health-seeking behaviors,⁹ there may be sex differences in the processing of nociceptive input. Indeed, increased temporal summation of pain could characterize women, but not men with TMD.³⁹ It could be the case that the propensity to develop central sensitization in human is also influenced by sex. Indeed, it has been shown with a rat model of temporomandibular joint pain involving monosodium iodoacetate injections that females have greater propensity to develop central sensitization and persistent pain.³⁸

In this case-control study, we focused on the area of secondary mechanical hyperalgesia because this feature was shown previously to be the most reliable.¹¹ This gave us sufficient power to look for group differences for this outcome. Some secondary findings, eg, the lack of correlation between the Central Sensitization Inventory scores and the area of secondary mechanical hyperalgesia, are supported by existing studies.³³ However, the statistical analysis of secondary outcomes such as the intensity of secondary mechanical hyperalgesia should be interpreted cautiously because of a risk of type II error.

One limitation of this study is that the assessor was not blinded to the group to which the participants belonged. Although the instructions given to the participants were standardized and the results of the DC/TMD were not known by the assessor, we cannot exclude the potential influence of the assessor's and participants' expectations on the results of the different assessments.^{29,36} A second limitation of this study is the heterogeneity of the TMD group in terms of TMD diagnosis and the number of musculoskeletal comorbidities that were present. Although this was not intended, we mainly recruited participants with TMD myalgia associated with an average of 5 painful comorbidities. Care should be taken when extrapolating our results to less prevalent patient populations (eg, patients with TMD but without comorbidities or with TMD arthralgia only) because we have included very few of these individuals and the

pain mechanisms underlying these different clinical TMD presentations may differ.^{15,25}

In healthy individuals, the area of secondary mechanical hyperalgesia varies from person to person exposed to similar nociceptive stimuli. However, the area of secondary mechanical hyperalgesia is stable when induced twice in an identical manner in the same healthy individual.^{11,17,51} Our study provides evidence that the propensity to develop central sensitization after HFS is associated with the presence of TMD, but the temporal link between the propensity to develop central sensitization and TMD cannot be determined because we examined both at the same time. Longitudinal studies could help determine (1) whether the risk of developing chronic TMD is associated with an increased propensity to develop central sensitization and (2) whether the propensity to develop central sensitization changes after the onset of TMD and its eventual remission.

5. Conclusion

To the best of our knowledge, this is the first study showing that chronic TMD is associated with a larger area of secondary mechanical hyperalgesia induced experimentally and outside the trigeminal pathways. This result suggests that individuals with chronic TMD have an increased propensity to develop central sensitization. The mechanism underlying this increased propensity is however yet unknown.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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