Autonomic and Psychologic Risk Factors for Development of Tinnitus in Patients with Chronic Temporomandibular Disorders

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Aims: To investigate the roles of autonomic regulation and psychologic condition in the development of tinnitus in patients with chronic temporomandibular disorders (TMD). **Methods:** In total, 55 participants (mean age 36.4 ± 12.6 years; 7 men, 48 women) were involved: 13 with no signs of painful TMD or tinnitus (CON), 15 with painful TMD without tinnitus (pTMD), and 27 with both painful TMD and tinnitus (TMDTIN). The Research Diagnostic Criteria for TMD and the Tinnitus Handicap Inventory (THI) were used to classify painful TMD and self-reported tinnitus, respectively. Measures of arterial heart rate (HR) and blood pressure (BP) were assessed at rest and in response to orthostatic challenges, cold-stress vasoconstriction, Valsalva maneuver, and psychologic stress. The sympathetic variables (BP responses to standing, cold stress, and psychologic stress) and parasympathetic variables (HR response to Valsalva maneuver [Valsalva ratio] and active standing [30:15 ratio]) were estimated. **Results:** Parasympathetic measures demonstrated significant differences between pTMD and TMDTIN. The period of pain duration showed significant positive correlations with BP variables during orthostatic challenges and/or cold stress in both pTMD and TMDTIN. THI scores showed significant positive correlations with results from the psychologic analysis. The range of motion of the mandible demonstrated a greater correlation with results from the psychologic analysis in TMDTIN compared to pTMD. **Conclusion:** Dysregulated psychophysiologic interactions may affect the development of tinnitus in patients with chronic TMD. *J Oral Facial Pain Headache 2019;33:362–370. doi: 10.11607/ofph.2237*

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Comorbidity is defined as a distinct and additional clinical entity occurring within the clinical course of the index disease.[1] Temporomandibular disorders (TMD) comprise a collection of conditions affecting the temporomandibular joint (TMJ) and masticatory muscles along with the surrounding structures, and the complexity of TMD could manifest through the presence of a diverse spectrum of comorbidities.

Tinnitus is an intrinsic and subjective perception of sound that cannot be attributed to an actual external sound source.[2] Many previous studies have demonstrated the coexistence of TMD and tinnitus.[3–5] Several reports have focused on the efficacy of TMD treatments in the improvement of tinnitus symptoms and suggested tinnitus as a comorbidity of TMD.[6,7] Other research has tried to reveal the relationships between tinnitus and TMD in terms of anatomical proximity, shared areas of nerve branching, and emotional stress[8–10]; however, clear pathophysiologic mechanisms explaining the coexistence of these two distinct conditions have not been completely clarified.

Several studies have investigated symptomatic characteristics of patients with both tinnitus and TMD. These studies demonstrated that TMD patients with tinnitus were more likely to have painful TMD and a longer pain duration compared to TMD patients without tinnitus, suggesting that chronicity and severity of the orofacial pain play a role in the development of tinnitus.[7,9,11–14] Multiple psychophysiologic regulatory

mechanisms may contribute to the pathophysiology of both painful TMD and tinnitus.[15,16] Dysregulated autonomic function seems to be associated with increased sensitivity and chronicity of pain in patients with TMD.[16–22] Moreover, TMD patients with a higher number of comorbidities also showed more severely compromised autonomic function.[17] Similar patterns have been observed in patients with other chronic pain syndromes, including chronic regional pain syndrome and fibromyalgia. These studies proposed relationships among sustained overactivation of the sympathetic nervous system, vasoconstriction, and pain augmentation mechanisms.[23,24] Dysregulated psychophysiologic mechanisms seem to affect not only the development of chronic pain disorders but also the occurrence of tinnitus, as a compromised autonomic regulatory system and psychologic stress were detected in individuals suffering from tinnitus.[15,25,26] Therefore, the hypothesis was derived that dysregulated autonomic function and psychologic stress arising from prolonged orofacial pain may be associated with the development of tinnitus in patients with chronic painful TMD.

To the best of the present authors' knowledge, sparse studies have been dedicated to investigating the role of the autonomic nervous system and psychologic factors in the occurrence of tinnitus in patients with painful TMD. The aim of the present study was to reveal the influences of autonomic dysfunction and psychologic stress in the development of tinnitus in patients with chronic painful TMD.

Materials and Methods

Participants

A total of 55 participants (mean age 36.4 ± 12.6 years; 7 men, 48 women) were involved. Participants with the following conditions were excluded: autoimmune diseases (including fibromyalgia, ankylosing spondylitis, and rheumatoid arthritis); craniofacial anomalies; uncontrolled hypertension; a history of head trauma in the last 6 months; regular use of medications such as antidepressants, muscle relaxants, and anticonvulsants; neuromuscular disorders; presence of other chronic pain conditions besides TMD, such as chronic fatigue syndrome and trigeminal neuralgia; and body mass index (BMI) over 25. Otolaryngologists confirmed that all participants were free from vascular/neurologic abnormalities related to otologic signs and hearing loss.

For the experimental group, 28 participants with both painful TMD and tinnitus (TMDTIN) and 17 participants with only painful TMD (pTMD) were consecutively recruited from patients who visited the TMJ orofacial pain clinic, Ajou University Dental Hospital, from June 22, 2017 to February 28, 2018. Two participants were excluded because of uncontrolled blood pressure during measurement. One participant withdrew without a specific reason, leaving a total of 42 participants (27 in the TMDTIN group and 15 in the pTMD group). The response rate was approximately 96.4% for TMDTIN and 88.2% for pTMD.

Participants in the TMDTIN and pTMD groups were diagnosed with painful TMD if they had myofascial pain and/or arthralgia according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD)[27] with pain duration of at least 6 months. The participants with tinnitus arising from the same side as the painful TMD comprised the TMDTIN group. Only participants whose tinnitus occurred later than painful TMD were included in the TMDTIN group to reduce the chances of including participants with tinnitus arising from factors other than TMD. A total of 13 volunteers without any signs of painful TMD or tinnitus for at least 6 months prior to study entry served as the control group (CON).

The research protocol was in compliance with the Helsinki Declaration and approved by the Institutional Review Board of the University Hospital (AJIRB-MED-SUR-17-131) on June 21, 2017. Informed consents were obtained from all participants.

Diagnosis of Painful TMD and Tinnitus

The RDC/TMD[27] and the Tinnitus Handicap Inventory (THI)[28] were used to classify painful TMD and self-reported tinnitus, respectively. Painful TMD was diagnosed using the RDC/TMD Axis I criteria, and participants diagnosed as Group I (myofascial pain) and/or Group IIIa (arthralgia) were included in the pTMD and TMDTIN groups. A single TMD and orofacial pain specialist (J.H.K.) was responsible for the assessment of painful TMD. Clinical parameters such as comfortable mouth opening (CMO), maximum mouth opening (MMO), number of sites of pain on palpation of masticatory muscles and TMJ capsule areas, and duration of symptoms were analyzed. A visual analog scale (VAS; 0 to 10 cm, with 10 cm indicating the worst pain imaginable) ,the Jaw Disability Checklist (JDC), and the Graded Chronic Pain Scale (GCPS) using RDC/TMD Axis II criteria were applied to assess the severity of chronic pain, disability, and functional impairment of the jaw. Myofascial trigger points were bilaterally explored in the temporalis, masseter, trapezius, sternocleidomastoid, suboccipitalis, and splenius capitis muscles by a single TMD and orofacial pain specialist (J.H.K.). Trigger point evaluation was based on the criteria suggested by Simons et al.[29]

Self-reported tinnitus was diagnosed using the THI questionnaire. The THI is a 25-item self-administered questionnaire that aims to quantify

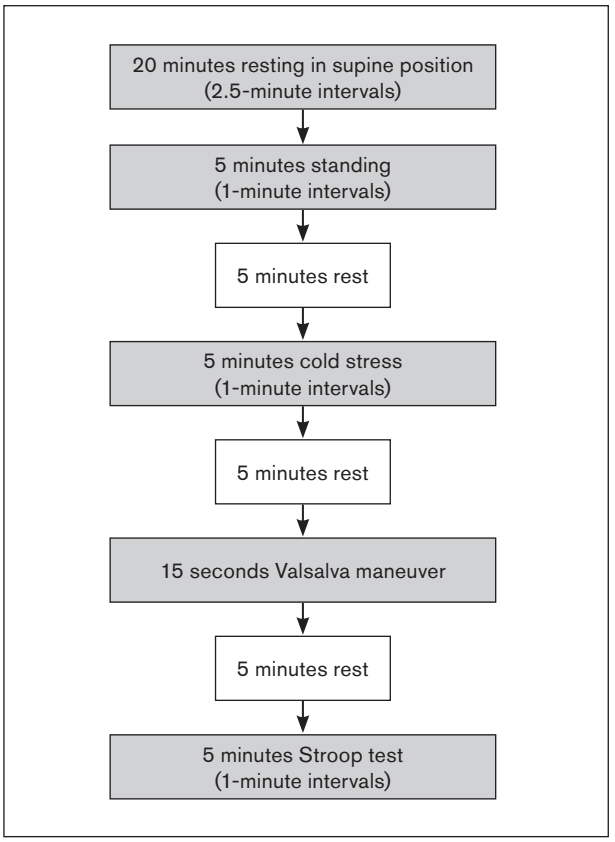

Fig 1 Protocols of autonomic function tests. Arterial blood pressure (BP) and heart rate (HR) were measured in 2.5-minute intervals with participants in the supine position and at 1-minute intervals during orthostatic stress, cold stimulation, and the Stroop test.

the impact of tinnitus on patients' daily life and its psychoacoustic characteristics. A THI score over 18 indicates unneglectable tinnitus[28]; therefore, participants with a THI score higher than 18 were included in the TMDTIN group.

Psychologic Evaluation

The Symptom Checklist-90-Revised (SCL-90-R)[30] was used to examine the psychologic status of the participants. The SCL-90-R is a tool for evaluating psychologic status consisting of 90 questions related to 9 symptomatic dimensions: somatization (SOM), obsessive-compulsive (O-C), interpersonal sensitivity (I-S), depression (DEP), anxiety (ANX), hostility (HOS), phobic anxiety (PHOB), paranoid ideation (PAR), and psychoticism (PSY). In addition, three global functioning indices—the global severity index (GSI), positive symptom distress index (PSDI), and positive symptom total (PST)—were utilized.

Autonomic Function Tests

Autonomic function tests were conducted between 7:00 am and 10:00 am to minimize variability due to circadian rhythm. The participants reported wake-up times from 5:30 am to 8:00 am, and the mean time interval between waking up and taking the autonomic function test was 1.92 ± 0.88 hours. Participants were instructed to refrain from eating and drinking for at least 8 hours prior to testing. Premenopausal women participated during their follicular phases.

All participants underwent combined testing of autonomous regulation of circulation based on evaluation of cardiovascular reflexes triggered by conducting specific provocative maneuvers. Sympathetic variables including arterial blood pressure (BP) responses to standing, cold stress, and psychologic stress (via the Stroop test) and parasympathetic variables including heart rate (HR) response to active standing (30:15 ratio) and Valsalva maneuver (Valsalva ratio) were estimated.[31,32]

Autonomic function tests were conducted using the following protocols (Fig 1). BP and HR were measured using automatic patient monitors (Dash 3000). All participants were placed in the supine position for 20 minutes, after which the participants were instructed to stand up as quickly as possible and maintain this position for 5 minutes. After a 5-minute rest, the cold pressure test was performed by immersing the participants' hand in ice water for 5 minutes. After another 5-minute rest, participants were instructed to conduct the Valsalva maneuver by performing moderately forceful exhalations against a closed airway for 40 seconds. After a 5-minute rest, participants underwent the Stroop test, in which they were instructed to choose the box not corresponding to the color of the word displayed on the screen. BP and HR were measured in 2.5-minute intervals with the participants in the supine position and at 1-minute intervals during orthostatic challenges, cold stimulation, and the Stroop protocol.

The sympathetic measures (ie, the responses of BP to orthostatic challenges) were determined by subtracting the first BP value measured right after active standing from the mean of the BP measures over the last three recordings during the 20 minutes in the supine position. Other sympathetic measures, such as the responses of BP to cold stimulation and the Stroop test, were obtained by subtracting the mean BP values measured in the five recordings in cold stimulation and in the Stroop period from the mean BP measures during the 20 minutes in the supine position, which were mentioned above. For parasympathetic measures, the 30:15 ratio was defined as HR around beat 30 after active standing divided by the HR peak near beat 15, which reflects the capacity of hemodynamic adaptations. The Valsalva ratio has been used as an index of baroreflex-mediated bradycardia and was calculated by dividing the HR nadir over the HR peak during the 40-second test period.

Table 1 Demographic Features and Clinical Parameters of the Three Study Groups

	CON (n = 13)	pTMD (n = 15)	TMDTIN (n = 27)	*P* value	Post hoc
Age (y)	30.5 ± 9.0	36.4 ± 12.9	35.7 ± 12.6	.147	–
Body mass index	20.4 ± 1.8	22.7 ± 2.2	20.8 ± 2.4	.051	–
Gender (male/female), n[a]	2/11	3/12	2/25	.476	–
Symptom duration (mo)	–	28.7 ± 25.8	29.2 ± 32.8	**.005**	CON–pTMD, CON–TMDTIN
CMO (mm)	51.2 ± 6.1	42.8 ± 6.0	43.4 ± 10.1	**.015**	CON–TMDTIN
MMO (mm)	51.2 ± 6.1	43.0 ± 5.8	46.0 ± 8.1	**.031**	–
Pain intensity (VAS)	–	4.27 ± 2.03	4.63 ± 2.58	**< .001**	CON–pTMD, CON–TMDTIN
No. of active trigger points	0	0 (0–1)	3 (2–4.5)	**< .001**	CON–TMDTIN, pTMD–TMDTIN
No. of latent trigger points	0	1 (0–3.5)	0 (0–2)	**.020**	CON–pTMD
No. of positive sites of TMJ capsule palpation	0	0 (0–0)	0 (0–1)	**.033**	–
Disability days in last 6 mo	0	32.9 ± 59.5	74.6 ± 73.8	**.006**	CON–TMDTIN
GCPS[a]	0	2 (1–3)	3 (1–4)	**< .001**	–
JDC	0	3 (2–3)	4 (2–5.5)	**.001**	CON–TMDTIN
THI	–	–	25.7 ± 15.5	–	–

Data reported as mean ± standard deviation or median (25th–75th percentile) unless otherwise indicated. Data were obtained using one-way analysis of variance with Bonferroni post hoc analysis or [a]chi-square test. Significant values are in bold.
CON = control group (participants showing no signs of painful TMD or tinnitus); pTMD = participants with painful TMD without tinnitus; TMDTIN = participants with both painful TMD and tinnitus; CMO = comfortable mouth opening; MMO = maximum mouth opening; VAS = visual analog scale (0 to 10 cm); TMJ = temporomandibular joint; GCPS = Graded Chronic Pain Scale; JDC = Jaw Disability Checklist; THI = Tinnitus Handicap Inventory.

Statistical Analyses

Based on the Kolmogorov-Smirnov normality test, the data were normally distributed; therefore, parametric tests were applied. To compare the differences among demographic features, clinical parameters, and results from autonomic function assessment, one-way analysis of variance (ANOVA) followed by post hoc analysis with Bonferroni test was applied. Pearson correlation was used to estimate interactions among variables. All tests were two-tailed, and *P* values less than .05 were considered statistically significant.

Results

Demographic Features and Clinical Evaluation

Differences in age and BMI and in gender distributions among the three groups were not significant. The duration of TMD symptoms was longer in TMDTIN than in pTMD, but this difference was not statistically significant ($P = .005$). The degree of the MMO did not show a statistically significant difference, but the degree of the CMO showed a significant difference between CON and TMDTIN ($P = .015$). Pain intensity was higher in TMDTIN (VAS = 4.63 ± 2.58) compared to that in pTMD (VAS = 4.27 ± 2.03), but the difference between these two groups was not statistically significant ($P < .001$ for both groups compared to control). TMDTIN showed a significantly higher number of active trigger points than pTMD ($P < .001$), but the number of latent trigger points was not significantly different between the two groups ($P = .020$). The number of disability days ($P = .006$) and of positive results on the JDC ($P = .001$) was higher in TMDTIN than in pTMD, but between-group statistical significance was not reached for either comparison. The GCPS score was significantly higher in TMDTIN than in pTMD ($P < .001$) (Table 1).

Autonomic Function Assessment

The sympathetic measures did not show statistically significant differences among the three groups. However, both parasympathetic measures, the 30:15 ratio ($P < .001$) and the Valsalva ratio ($P < .001$), showed statistical differences between TMDTIN and pTMD. Both ratios were highest in TMDTIN, followed in turn by pTMD and CON, with the Valsalva ratio being abnormally decreased in TMDTIN. Considering that orthostatic stress generally may lead to a decrease in BP, inverse response to orthostatic stress was observed in TMDTIN even though the sympathetic measures did not show statistically significant differences (Table 2).

Relationships Among Clinical Symptoms, Autonomic Function, and SCL-90-R Results

The SCL-90-R showed statistically significant differences in SOM ($P = .004$), GSI ($P = .023$), and PST ($P = .034$) between CON and TMDTIN, but no statistically significant differences were observed between pTMD and TMDTIN (Table 3). TMD symptom duration showed significant correlations with sympathetic measures in both pTMD and TMDTIN. The symptom duration in pTMD showed significantly positive correlations with systolic BP (SBP) responses ($r = 0.823$, $P < .001$) and diastolic BP

Table 2 Results of Autonomic Function Assessment

		CON	pTMD	TMDTIN	*P* value	Post hoc
Sympathetic measures (mmHg)						
Response to orthostatic stress	ΔSBP	−4.67 ± 10.2	−0.71 ± 10.9	1.33 ± 12.40	.366	–
	ΔDBP	−1.14 ± 6.93	−0.27 ± 4.90	1.25 ± 5.04	.657	–
Response to cold stimulation	ΔSBP	7.93 ± 7.79	7.06 ± 12.0	10.4 ± 14.1	.894	–
	ΔDBP	5.25 ± 7.77	4.61 ± 6.54	8.48 ± 8.46	.669	–
Response to psychologic stress	ΔSBP	−1.81 ± 11.77	−0.55 ± 10.72	2.25 ± 16.09	.426	–
	ΔDBP	−1.31 ± 4.71	−0.93 ± 5.42	−1.85 ± 7.80	.647	–
Parasympathetic measures						
30:15 ratio		1.23 ± 0.11	1.10 ± 0.04	1.04 ± 0.06	**< .001**	CON–pTMD, CON–TMDTIN, pTMD–TMDTIN
Valsalva ratio		1.22 ± 0.06	1.16 ± 0.10	1.06 ± 0.09	**< .001**	CON–TMDTIN, pTMD–TMDTIN

All data are reported as mean change ± standard deviation. Data were analyzed using one-way analysis of variance with Bonferroni post hoc analysis.
CON = control (participants showing no signs of painful TMD and tinnitus); pTMD = participants with painful TMD without tinnitus;
TMDTIN = participants with both painful TMD and tinnitus; SBP = systolic blood pressure; DBP = diastolic blood pressure.
Significant values are in bold.

Table 3 Results of Psychologic Evaluation with Dimensions of the Symptom-Checklist-90-Revised

	CON	pTMD	TMDTIN	*P* value	Post hoc
SOM	41.8 ± 3.4	49.5 ± 9.7	52.2 ± 8.8	.004*	CON–TMDTIN
O-C	40.5 ± 5.8	41.6 ± 5.1	44.9 ± 7.8	.520	–
I-S	41.0 ± 3.9	46.2 ± 4.4	43.1 ± 8.3	.328	–
DEP	39.0 ± 3.9	42.9 ± 5.7	44.7 ± 8.6	.058	–
ANX	42.1 ± 3.9	45.0 ± 5.1	47.5 ± 8.6	.074	–
HOS	42.5 ± 2.5	46.5 ± 8.2	44.6 ± 5.3	.333	–
PHOB	44.4 ± 2.3	44.7 ± 6.8	45.3 ± 4.3	.776	–
PAR	40.0 ± 1.8	42.7 ± 6.8	41.8 ± 5.5	.544	–
PSY	41.1 ± 2.4	42.9 ± 4.1	44.0 ± 6.6	.262	–
GSI	39.5 ± 3.1	43.6 ± 5.1	45.3 ± 7.2	**.023**	CON–TMDTIN
PSDI	46.0 ± 7.7	46.5 ± 5.9	49.7 ± 6.2	**.125**	–
PST	35.8 ± 3.5	43.6 ± 8.8	44.4 ± 10.4	**.034**	CON–TMDTIN

All data are reported as mean score ± standard deviation. Significant values are in bold. CON = control (participants showing no signs of painful TMD and tinnitus); pTMD = participants with painful TMD without tinnitus; TMDTIN = participants with both painful TMD and tinnitus; SOM = somatization; O-C = obsessive-compulsive; I-S = interpersonal sensitivity; DEP = depression; ANX = anxiety; HOS = hostility; PHOB = phobic anxiety; PAR = paranoid ideation; PSY = psychoticism; GSI = global severity index; PSDI = positive symptom distress index; PST = positive symptom total.

(DBP) (r = 0.730, P = .002) for orthostatic challenges, SBP (r = 0.739, P = .002) and DBP (r = 0.680, P = .005) for cold simulation, and SBP (r = 0.742, P = .002) for STROOP. In TMDTIN, symptom duration had significant positive correlations only with response of DBP to cold stimulation (r = 0.604, P = .001) (Table 4).

Duration of symptoms did not show significant correlations with results from the psychologic evaluation in pTMD, but did show significant positive correlations with O-C (r = 0.503, P = .008), I-S (r = 0.487, P = .010), DEP (r = 0.456, P = .017), ANX (r = 0.421, P = .029), PSY (r = 0.515, P = .006), and GSI (r = 0.476, P = .012) in TMDTIN. In addition, the degree of CMO and MMO did not show significant correlations with results from psychologic evaluation in pTMD. However, the amount of CMO showed significantly negative correlations with I-S (r = −0.559, P = .002), DEP (r = −0.464, P = .015), ANX (r = −0.464, P = .015), HOS (r = −0.456, P = .017), PHOB (r = −0.520, P = .005), PAR (r = −0.533, P = .004), PSY (r = −0.469, P = .014), GSI (r = −0.488, P = .010), and PST (r = −0.482, P = .011). Degree of MMO showed significantly negative correlations with I-S (r = −0.472, P = .013), HOS (r = −0.418, P = .030), PHOB (r = −0.393, P = .043), and PAR (r = −0.400, P = .039).

THI scores showed strong positive associations with results from the SCL-90-R. THI had statistically significant correlations with O-C (r = 0.462, P = .015), I-S (r = 0.590, P = .001), DEP (r = 0.704, P < .001), ANX (r = 0.644, P < .001), HOS (r = 0.389, P = .045), PHOB (r = 0.563, P = .002), PAR (r = 0.532, P = .004), PSY (r = 0.834, P < .001), GSI (r = 0.659, P < .001), and PST (r = 0.584, P = .001) in TMDTIN (Table 5).

Table 4 Correlation Coefficients Among Clinical Symptoms and Autonomic Function in pTMD and TMDTIN

		Symptom duration	CMO	MMO	VAS	No. of active trigger points	No. of latent trigger points	No. of positive pain on capsule palpation sites	THI
In pTMD group									
Sympathetic measures (mmHg)									
Response to orthostatic stress	ΔSBP	**0.823****	−0.348	−0.299	0.315	−0.184	−0.194	0.442	–
	ΔDBP	**0.730***	0.080	0.115	−0.004	−0.298	**−0.537***	**0.649***	–
Response to cold stimulation	ΔSBP	**0.739***	−0.074	0.054	−0.011	−0.104	−0.298	**0.586***	–
	ΔDBP	**0.680***	0.067	0.102	−0.069	0.022	−0.068	0.273	–
Response to psychologic stress	ΔSBP	**0.742***	−0.025	0.004	−0.135	0.037	−0.298	0.502	–
	ΔDBP	0.456	−0.170	−0.159	0.242	−0.202	−0.093	0.378	–
Parasympathetic measures									
30:15 ratio		0.246	0.250	0.162	−0.221	0.385	0.244	−0.052	–
Valsalva ratio		−0.260	0.067	0.019	0.083	0.053	0.162	−0.406	–
In TMDTIN group									
Sympathetic measures (mmHg)									
Response to orthostatic stress	ΔSBP	0.186	−0.264	−0.244	0.316	0.246	−0.035	0.025	−0.238
	ΔDBP	0.057	−0.250	−0.300	0.127	0.216	0.029	−0.132	−0.363
Response to cold stimulation	ΔSBP	0.365	−0.400*	−0.365	0.272	0.311	0.062	0.047	−0.103
	ΔDBP	**0.604***	−0.339	−0.210	0.069	0.348	0.222	−0.076	0.162
Response to psychologic stress	ΔSBP	−0.116	−0.346	**−0.435***	0.085	0.110	−0.187	−0.166	−0.306
	ΔDBP	−0.036	−0.287	−0.343	−0.097	0.114	−0.184	−0.251	−0.074
Parasympathetic measures									
30:15 ratio		0.246	0.250	0.162	−0.221	−0.309	0.256	**−0.397***	−0.241
Valsalva ratio		−0.260	0.067	0.019	0.083	0.026	−0.184	0.044	−0.094

pTMD = participants with painful TMD without tinnitus; TMDTIN = participants with both painful TMD and tinnitus; SBP = systolic blood pressure; DBP = diastolic blood pressure; CMO = comfortable mouth opening; MMO = maximum mouth opening; VAS = visual analog scale; THI = Tinnitus Handicap Inventory.
Bolded values indicate statistical significance according to Pearson correlation analysis. *$P < .05$. **$P < .001$.

Discussion

Tinnitus is regarded as one of the most well-known comorbidities of TMD.[3–5] Several studies have focused on the role of chronicity and severity of orofacial pain in the development of tinnitus in patients with TMD.[7,9,11–14] Complex physiologic and emotional regulatory systems could influence chronicity and pain augmentation processes, and dysregulated autonomic function has been observed in patients suffering from chronic pain disorders, including TMD.[16–24] Compromised autonomic functions and emotional stress were detected in patients with tinnitus as well.[26] However, sparse reports have investigated the influences of autonomic dysfunction and psychologic conditions in the development of tinnitus in painful TMD patients.

The aforementioned results are particularly meaningful to researchers and clinicians. Enhanced sympathetic activities seem to have interactions with the chronicity of orofacial pain. The positive correlations between pain duration and degree of sympathetic activities may imply that chronicity of orofacial pain may have relevance to enhanced sympathetic activity, with previous reports lending support to this idea. One study demonstrated that patients suffering from painful TMD showed diminished parasympathetic and increased sympathetic activity during sleep.[22] Another study showed that patients with fibromyalgia had lower heart rate increases to the posture challenge, but greater blood pressure increases to postural and speech task than control, and this implied that fibromyalgia patients showed enhanced sympathetic activity and decreased parasympathetic activity.[21] The concept of connections existing between the hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic nervous system has been widely accepted.[33] Patients with chronic TMD may exhibit a hyper-activated HPA axis due to sustained stress from prolonged orofacial pain that may lead to hyperactivation of the sympathetic nervous system and vasoconstriction. This may explain the inverse response of BP to orthostatic stress in patients with painful TMD and tinnitus. In addition, previous reports have suggested that an imbalanced autonomic nervous system might induce vasoconstriction of blood vessels in the inner ears, which could lead to abnormal sound perceptions.[34,35] Prolonged orofacial pain may cause

Table 5 Correlation Coefficients Among Clinical Symptoms and Results from Psychologic Evaluation in pTMD and TMDTIN

	Symptom duration	CMO	MMO	VAS	No. of active trigger points	No. of latent trigger points	No. of positive pain on capsule palpation sites	THI
pTMD								
SOM	0.217	0.206	0.235	−0.014	**0.587***	0.475	−0.236	–
O-C	−0.339	0.360	0.372	−0.249	0.278	0.146	−0.427	–
I-S	−0.062	−0.031	−0.031	0.355	−0.007	0.093	−0.496	–
DEP	−0.316	0.263	0.258	0.097	0.292	0.114	−0.314	–
ANX	−0.077	0.225	0.227	0.129	0.302	0.355	−0.282	–
HOS	−0.450	0.410	0.396	0.011	0.442	0.451	−0.190	–
PHOB	−0.033	0.057	0.060	0.504	−0.087	−0.120	−0.150	–
PAR	0.004	−0.180	−0.193	0.436	−0.181	0.074	−0.157	–
PSY	0.075	−0.009	−0.013	0.460	−0.064	−0.084	−0.169	–
GSI	−0.125	0.250	0.260	0.171	0.336	0.268	−0.364	–
PSDI	−0.536*	0.153	0.140	−0.278	0.365	0.540*	−0.293	–
PST	0.033	0.133	0.148	0.303	0.196	0.158	−0.382	–
TMDTIN								
SOM	0.334	−0.147	−0.026	0.139	0.222	0.378	0.087	0.249
O-C	**0.503***	−0.289	−0.173	0.156	0.153	0.242	0.128	**0.462***
I-S	**0.487***	**−0.559***	**−0.472***	0.084	0.098	0.241	0.188	**0.590***
DEP	**0.456***	**−0.464***	−0.351	0.139	0.113	0.077	0.065	**0.704****
ANX	**0.421***	**−0.464***	−0.300	0.072	0.145	0.058	0.369	**0.644****
HOS	0.169	**−0.456***	**−0.418***	0.153	−0.127	−0.003	0.287	**0.389***
PHOB	0.047	**−0.520***	**−0.393***	0.258	0.286	−0.081	**0.506***	**0.563***
PAR	0.275	**−0.533***	**−0.400***	−0.031	0.231	−0.096	0.064	**0.532***
PSY	**0.515***	**−0.469***	−0.297	0.122	0.178	0.244	0.333	**0.834****
GSI	**0.476***	**−0.488***	−0.349	0.171	0.195	0.165	0.205	**0.659****
PSDI	0.197	0.203	0.330	−0.007	0.051	0.247	0.185	0.173
PST	0.379	**−0.482***	−0.354	0.161	0.255	0.071	0.140	**0.584***

pTMD = participants with painful TMD without tinnitus; TMDTIN = participants with both painful TMD and tinnitus; CMO = comfortable mouth opening; MMO = maximum mouth opening, VAS = visual analog scale (0 to 10 cm); THI = Tinnitus Handicap Inventory; SOM = somatization; O-C = obsessive-compulsive; I-S = interpersonal sensitivity; DEP = depression; ANX = anxiety; HOS = hostility; PHOB = phobic anxiety; PAR = paranoid ideation; PSY = psychoticism; GSI = global severity index; PSDI = positive symptom distress index; PST = positive symptom total.
Bolded values indicate statistical significance according to Pearson correlation analysis. *$P < .05$. **$P < .001$.

altered autonomic functions, which could induce vasoconstrictions in the inner ear and development of tinnitus. These findings imply that dysregulated stress-related neuroendocrinologic interactions may have associations with sustained chronic orofacial pain and development of tinnitus.

The novel finding of the present study was that impairment of parasympathetic inhibitory action would be associated with the development of tinnitus. The statistically significant differences in the parasympathetic measures were observed between patients with only painful TMD and patients with both tinnitus and painful TMD. One animal study supported the idea that a relationship between parasympathetic function and Eustachian tube function exists, as rats injected with neostigmine, an acetylcholinesterase blocker, demonstrated a decrease in Eustachian tube activities.[36] A human study also demonstrated that improvement of tinnitus was positively correlated with pretreatment activity of the left insula and cortices, which control parasympathetic activity.[37] Decreased parasympathetic inhibitory activities in individuals with chronic pain disorders have been reported.[17,18,22–24] The complex interactions between the tympanic nerve (a branch of the glossopharyngeal nerve) and the tympanic plexus are widely known. The branches of the tympanic cavity in the tympanic plexus provide innervation to the mucosa of the middle ear. Decreased parasympathetic inhibition capacity due to sustained orofacial pain may affect the activity of the glossopharyngeal nerve, leading to dysregulated Eustachian tube activities and development of tinnitus.

Psychologic conditions appeared to have relevance to the annoyance from tinnitus. Relationships between depression and tinnitus in TMD patients have been reported.[7] Interestingly, compared to patients with TMD without tinnitus, patients with both TMD and tinnitus seem to have greater associations between psychologic status and range of jaw movement, as well as higher levels of functional disabilities. A previous study suggested a neurophysiologic

model that explained interrelations between psychologic and autonomic regulation and annoyance levels of tinnitus.[15] If the perception of tinnitus is associated with negative emotional feelings such as anxiety or fear, the limbic system facilitates enhancement of the tinnitus signal and induces activation of the autonomic nervous system, resulting in the feeling of annoyance. Thus, interactions of tinnitus perception, emotional reaction, and autonomic response can worsen the annoyance from tinnitus, creating a positive feedback loop. The exaggerated tinnitus and psychologic stress from this vicious cycle may have influence on the range of motion in chronic TMD patients. Relationships between levels of anxiety and depression and amount of mouth opening have been observed.[38] Other studies reported the relationship between anxiety levels and changes in jaw-closing muscle activity measured by electromyography.[39] Furthermore, a high degree of functional disability diagnosed by the RDC/TMD Axis II was detected in patients with increased levels of depression and somatization.[40] Similarly, the present results showed that patients with both painful TMD and tinnitus showed higher levels of GCPS and more disability days compared to patients with painful TMD alone. This may imply that enhanced associations with range of motion in patients with both painful TMD and tinnitus might be affected by the positive feedback loop from tinnitus and emotional stress.

Finally, the central sensitization process may play a role in the development of tinnitus. Compared to patients with only painful TMD, patients with both tinnitus and painful TMD showed a higher number of active trigger points in the cervical and masticatory muscles and widespread pain areas. Simons et al suggested that tinnitus may be related to pain referred from the sternocleidomastoid, deep masseter, and lateral pterygoid muscles.[29] Furthermore, activation of other masticatory and cervical muscles, including the splenius capitis, temporalis, and trapezius, could modulate tinnitus patterns.[41] Other studies reported that head and neck contractions might elicit tinnitus-like auditory perception and suggested that muscle spindles may initiate neural activation, modulating the central auditory pathway, including the dorsal cochlear nucleus.[42] The activation of the central nervous system due to sustained orofacial pain may have relevance to the development of active trigger points in the orofacial and cervical areas and finally may result in tinnitus.

The present study has several limitations. First of all, owing to a relatively small sample size, the power of statistical significance is inevitably compromised. Secondly, due to characteristics of the cross-sectional design, this study cannot provide information regarding longitudinal therapeutic effects of TMD on autonomic function in TMD patients. Future prospective studies with larger samples should be conducted to further elucidate the role of autonomic function in the development of tinnitus and chronic painful TMD.

Conclusions

With increased understanding of the orofacial pain modulation processes, it would not be surprising if greater attention is paid to revealing the pathophysiologic mechanisms of comorbities of TMD. The results from the present study demonstrate that tinnitus as a clinical comorbidity of painful TMD appears to be related to interactions among psychologic stress, autonomic dysfunction, and central sensitization processes from sustained orofacial pain. Therefore, dysregulated psychophysiologic interactions may affect the development of tinnitus in chronic TMD patients.

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