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Pain Sensitivity and Autonomic Factors Associated With Development of TMD: The OPPERA Prospective Cohort Study

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Abstract: Multiple studies report that individuals with chronic temporomandibular disorder (TMD) have enhanced sensitivity to experimental pain. Additionally, chronic TMD cases show altered autonomic function, including elevated heart rate and reduced heart rate variability. However, causal inferences regarding the association between TMD and pain sensitivity and autonomic function cannot be drawn from these cross-sectional observations. The prospective Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study examines whether measures of pain sensitivity or cardiac autonomic function provide predictive value in TMD incidence. A cohort of 2,737 initially TMD-free participants was followed for up to 5.2 years, during which time 260 developed first-onset TMD. Fourteen of 39 experimental pain measures produced significant hazard ratios, such that greater pain sensitivity was associated with greater TMD incidence. A single autonomic measure—heart rate at rest—was also associated significantly with greater TMD incidence. In contrast, using the same measures of pain sensitivity and cardiac autonomic function, we previously reported a larger group of variables that was significantly associated with chronic TMD in the OPPERA case-control study. Future studies should investigate whether premorbid pain sensitivity or autonomic function more specifically predicts risk of developing chronic TMD than first-onset TMD.

***Perspective:** Our previous case-control studies showed that associations with both pain sensitivity and cardiac autonomic function are profound in chronic TMD cases. Here we show that some measures of enhanced pain sensitivity contribute modestly to the risk of developing TMD whereas autonomic dysregulation appears to confer little or no risk for TMD incidence.*

***Key words:** Quantitative sensory testing, temporomandibular disorder, orofacial pain, heat pain, pressure pain, cardiovascular measures.*

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Considerable evidence has accumulated showing that physiological factors, including altered pain sensitivity and autonomic dysfunction, are associated with several chronic pain conditions, including temporomandibular disorder (TMD).[15] Specifically, in case-control studies, individuals with chronic TMD have been found to have greater pain sensitivity to experimental pain than TMD-free controls, even when experimental pain was evaluated at asymptomatic body sites.[7,16,17,23,26] This enhanced pain sensitivity has been documented for different pain domains (ie, both cutaneous and deep tissue evoked pain) and for different types of measures (ie, threshold and suprathreshold measures of pain). Additionally, individuals with chronic TMD have been found to have dysregulated autonomic system function, including higher cardiac output and lower total vascular resistance,[11] as well as higher cardiosympathetic tone both at rest and under stress.[18]

Although such case-control studies are informative about chronic pain associations, they cannot address the critical causal questions. Specifically, does the heightened pain sensitivity and autonomic dysregulation precede the development of chronic TMD, or do these characteristics develop as a consequence of having TMD for some period of time? Evidence to address these questions comes from prospective cohort studies that first measure pain sensitivity and autonomic function in people without TMD, and then monitor them prospectively to document those who develop TMD. To our knowledge, only 1 such study has been reported. The study found that heightened pain sensitivity was a predictive factor for TMD among a cohort of 171 women followed for 3 years.[25]

The current report describes results from the first large-scale prospective cohort study of TMD, evaluating the contribution of enhanced pain sensitivity and autonomic dysregulation to the incidence of TMD. The aim of the study described here was to identify which, if any, measures of experimental pain sensitivity and autonomic function would serve to predict the development of painful TMD, when assessed prior to TMD onset. The studies reported here are a part of the larger parent project Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA), which also included a previously reported case-control study[5] in which heightened pain sensitivity and autonomic dysregulation were found to be associated with chronic TMD.

Methods

This section summarizes the study methods that are explained in detail in the Supplementary Materials section and elsewhere in this issue.[2] Study participants were verbally informed of the study and provided signed consents. The OPPERA project was reviewed and approved by institutional review boards at each of 4 study sites and at the data coordinating center, Battelle Memorial Institute.

Study Design, Setting, and Participants

This paper reports findings from the OPPERA prospective cohort study of 2,737 participants who were enrolled in 2006 to 2008 and followed for up to 5.2 years, during which time 260 people developed painful TMD. When enrolled, the sample of community-based volunteers at 4 U.S. study sites was aged 18 to 44 years and did not have TMD when examined using OPPERA's adaptation of a restricted set of research diagnostic criteria for TMD (RDC/TMD).[19] At enrollment, study participants also completed questionnaires, autonomic function was measured, sensitivity to sensory stimuli was evaluated, and a blood sample was collected for genotyping.

This paper focuses on baseline measurements of pain sensitivity and autonomic function, which have been described previously.[7,18] Detailed specifications of measurement protocols can be found in the Supplementary Materials accompanying this article. Briefly, pain sensitivity tests encompassed 3 stimulus modalities: 1) pressure pain thresholds (PPTs) on 5 body sites—the center of the temporalis muscle, the center of the masseter muscle, overlying the temporomandibular joint, the center of the trapezius muscle, and overlying the lateral epicondyle; 2) cutaneous mechanical pain sensitivity, involving measures of threshold, ratings of suprathreshold stimuli, temporal summation, and aftersensations, assessed on the hand; and 3) heat pain sensitivity, involving threshold, tolerance, ratings of suprathreshold stimuli, temporal summation, and aftersensations, assessed on the forearm. Autonomic measures included arterial blood pressure, heart rate, and heart rate variability measures taken under rest and during 2 provocative conditions: an orthostatic challenge and a Stroop protocol.

At 3-month intervals after enrollment, study participants were asked to complete a screening questionnaire that asked about TMD pain symptoms. Those reporting symptoms were invited to study clinics for a follow-up examination that determined presence or absence of TMD using the same adaptation of RDC/TMD criteria. Specifically, 260 incident cases satisfied 2 criteria for TMD: 1) symptoms of orofacial pain reported for $\geq$5 days/month and 2) examiner findings of TMD myalgia, arthralgia, or both.

Statistical Analysis

For descriptive purposes, the average annual incidence of first-onset TMD was calculated as the number of people with first-onset TMD divided by the sum of follow-up intervals. To test hypotheses about associations between baseline characteristics and TMD incidence, univariate hazard ratios were first computed using Cox proportional hazard regression. For each baseline risk factor, scores were transformed to unit-normal deviates (mean = 0, standard deviation [SD] = 1). Unit-normal deviates were reversed (ie, the sign was changed) for measures of pain threshold, so that higher values represented greater sensitivity to the stimulus. Hazard ratios were computed both with adjustment for study site and with additional adjustment for demographics (age, gender, race/ethnicity, and lifetime U.S. residence). Hazard ratios were also computed using multiple imputation to account for 2 sources of potential bias associated with 1) nonexamination of 243 people with