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ABSTRACT

This study tested whether persons with TMJ arthralgia have a modality-specific and site-specific hypersensitivity to somatosensory stimuli assessed by quantitative sensory tests (QST). Forty-three healthy persons and 20 with TMJ arthralgia participated. The QST consisted of: sensory and pain detection thresholds and summation threshold to intra-articular electrical stimulation, tactile and pin-prick sensitivity in the TMJ area, pressure-pain threshold and tolerance on the lateral side of the TMJ and on the finger. Persons with TMJ arthralgia had lower pain detection and summation thresholds ($P < 0.001$), higher ratings of tactile and pin-prick stimuli ($P < 0.05$), and markedly lower pressure thresholds on the TMJ and finger ($P < 0.001$) than did healthy individuals. Correlation analysis revealed associations between several QST and clinical pain measures. This study provides new evidence of sensitization of the TMJs as well as central nociceptive pathways. QST may facilitate a mechanism-based classification of temporomandibular disorders.

KEY WORDS: orofacial pain, trigeminal physiology, quantitative sensory tests, temporomandibular disorders.

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A supplemental appendix to this article is published electronically only at http://www.dentalresearch.org.

INTRODUCTION

The pathophysiology and etiology of most craniofacial pain conditions are not completely understood, and there is still no mechanism-based classification (Woolf *et al.*, 1998; Woda and Pionchon, 1999, 2000; Svensson and Graven-Nielsen, 2001). Systematic investigations of somatosensory function in persons with painful temporomandibular disorders (TMD) may provide valuable information about the underlying pathophysiological mechanisms.

'TMD' is a collective term including several pathological conditions involving the temporomandibular joints (TMJ) and the masticatory musculature. The somatosensory function in persons with myofascial TMD pain has been described in several studies, and hyperexcitability in the central processing of nociceptive input has been implicated in the pathophysiology of TMD (Sarlani and Greenspan, 2003). Most studies in persons with TMD have shown hypersensitivity compared with healthy persons—for example, to ischemic stimuli, pressure stimuli, heat stimuli, or infusion of hypertonic saline (Malow *et al.*, 1980; Maixner *et al.*, 1995, 1997, 1998; Kashima *et al.*, 1999; Svensson *et al.*, 2001; Sarlani and Greenspan, 2005), but less clearly to electrical stimuli (Molin *et al.*, 1973; Eliav *et al.*, 2003). However, persons with TMJ arthralgia have lower thresholds to electrical cutaneous stimulation of the TMJ area compared with healthy individuals, suggesting large myelinated fiber hypersensitivity of the auriculotemporal nerve (Eliav *et al.*, 2003). Since relatively few studies have systematically examined the somatosensory function around the TMJ area, and no studies have assessed the sensitivity within the TMJ, we used a novel intra-articular stimulation technique (Ayesh *et al.*, 2007) and a battery of quantitative sensory tests (QST) to explore the hypothesis that persons with TMJ arthralgia have a modality-specific and site-specific hypersensitivity to somatosensory stimuli, and to test associations between QST and clinical pain measures.

MATERIALS & METHODS

Participants

Two groups were included: 43 healthy persons (24 men and 19 women; 19-32 yrs old) and 20 persons with TMJ arthralgia (three men and 17 women, 20-39 yrs old), in accordance with Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) (Dworkin and LeResche, 1992).

The inclusion criteria for persons with TMJ arthralgia were: (a) report of spontaneous pain or pain on movements in the TMJ (during lateral excursions, maximum unassisted opening, or assisted opening), and (b) pain on palpation of the lateral pole or posterior attachment of the TMJ on the same side. Persons with coarse crepitation (osteoarthritis) were excluded, but fine crepitation and clicks were allowed. Furthermore, pain on muscle palpation was accepted in addition to the specific criteria for TMJ arthralgia, since a

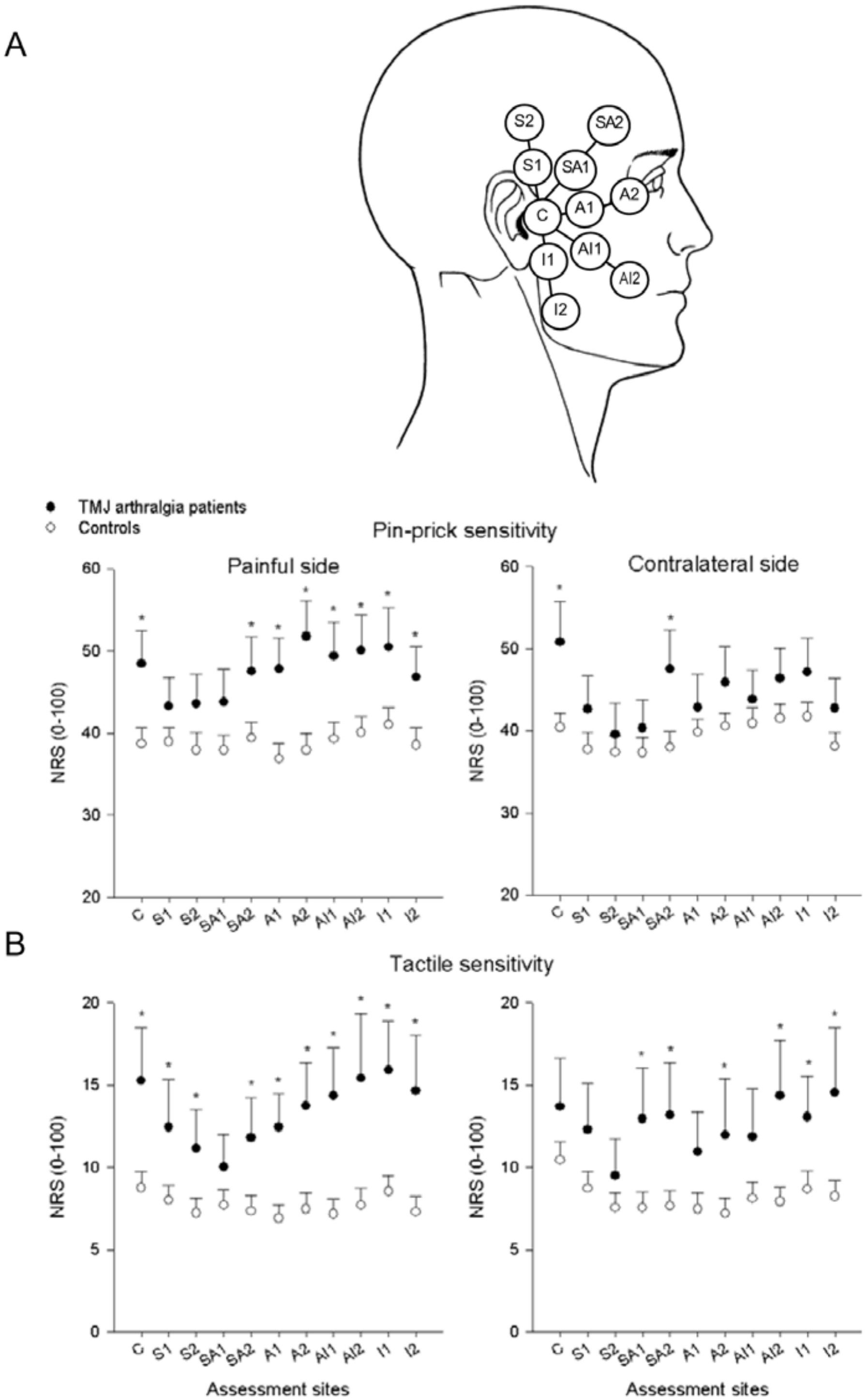

Figure 1. Outline of quantitative sensory tests. **(A)** Distribution of the 11 sites used for assessment of pin-prick and tactile sensitivity. The sites are identified according to their distribution in relation to the central point over the TMJ (C): A = anterior, I = inferior, S = superior. **(B)** Numerical rating scale (NRS) scores of pin-prick and tactile stimulation of 11 sites on the painful and contralateral sides in persons with TMJ arthralgia compared with 2 randomized sides in healthy persons. Mean scores (± SEM) from 43 healthy individuals and 20 persons with TMJ arthralgia. *Significant differences between healthy individuals and persons with TMD arthralgia (P < 0.05).

majority of persons with TMD have multiple diagnoses (Drangsholt and LeResche, 1999).

All persons with TMD were referred to the Department of Clinical Oral Physiology, University of Aarhus, while healthy individuals were recruited from different educational institutions in the city of Aarhus. Informed consent was obtained in accordance with the guidelines of the Helsinki Declaration and approved by a Local Ethics Committee.

Procedures

All participants were examined clinically according to the RDC/TMD. We used the following measures to characterize the groups: (1) spontaneous pain on a 0- to 10-cm visual analogue scale (VAS), with 0 labeled as 'no pain' and 10 as 'the most pain imaginable'; (2) the characteristic pain intensity as the mean of the present, the average, and the worst pain on a 0-10 VAS; (3) the duration of TMJ pain (yrs); (4) the unassisted jaw opening without pain (mm), and the maximal unassisted and assisted jaw openings (mm) with pain, assessed on a 0-10 VAS; (5) the number of muscle (0-20) and TMJ (0-4) sites with pain on palpation; and (6) the number of persons with TMJ clicking.

The QST battery consisted of: sensory detection threshold, pain detection threshold, summation threshold to intra-articular electrical stimulation, tactile and pin-prick assessment around the TMJ area, pressure-pain threshold, and pressure-pain tolerance on the lateral pole of the TMJ and on the finger (control site) (Ayesh *et al.*, 2007).

Assessment of Intra-articular Electrical Thresholds

Two unipolar needle electrodes were inserted into the posterior part of the upper joint compartment, and electrical stimuli were applied so that sensory and pain detection thresholds, and the summation threshold, could be determined (see APPENDIX; Ayesh *et al.*, 2007).

Electrical thresholds were measured only on the most painful side in persons with TMJ arthralgia, and randomly on either the right or left side in healthy persons.

Assessment of Tactile and Pin-prick Sensitivity

Two calibrated von Frey nylon filaments (5.16 g and 84.96 g) were used for assessment of tactile and pin-prick sensitivity at 11 sites around the TMJ (Ayesh *et al.*, 2007; Fig. 1a). A plastic template was designed for this purpose, so that the positions of the different sites could be determined and standardized.

Participants rated the intensity of von Frey filament stimuli on a 0-100 numerical rating scale (NRS), where 0 meant no sensation at all, 100 represented the most painful sensation imaginable, and 50 was just barely painful (Ayesh *et al.*, 2007). Assessment was done on both sides in participants with and those without TMJ.

Assessment of Pressure-Pain Threshold and Tolerance

We used a pressure algometer (Somedic, Hörby, Sweden) to test the sensitivity to deep stimuli applied to the lateral pole of the TMJ. The probe had a diameter of 1 cm, and the pressure was increased steadily at 30 kPa/sec (Ayesh *et al.*, 2007). The index finger on the non-dominant hand was tested as an extracranial control site. Pressure thresholds were assessed on both sides in persons without and those with TMJ.

Table. Clinical Characteristics of Persons With and Those Without TMJ Arthralgia (means ± SEM)

	TMJ arthralgia (*n* = 20)	Healthy Individuals (*n* = 43)	*P* value[b]
Age (yrs)	26.8 (1.4)	23.4 (0.6)	0.487
Spontaneous pain on the visit (VAS)	4.1 (0.6)	0	< 0.001
Duration of TMJ pain (yrs)	4.2 (0.6)	0	< 0.001
Characteristic pain intensity (0-100)	57.5 (5.9)	0	< 0.001
Maximum unassisted opening without pain (mm)	39.6 (2.1)	49.7 (1)	< 0.001
Maximum unassisted opening (mm)	48.5 (1.7)	54.9 (1.1)	0.018
Maximum assisted opening (mm)	50.6 (1.9)	56.3 (1.1)	0.027
Pain upon maximum opening (VAS)	4.8 (0.8)	1.1 (0.3)	< 0.001
No. of muscle sites with pain on palpation (0-20)	11.6 (1.4)	0.3 (0.1)	< 0.001
No. of TMJ sites with pain on palpation (0-4)	2.4 (0.3)	0.2 (0.1)	< 0.001
No. of persons with bilateral TMJ pain	10[a]	0	= 0.001
No. of persons with TMJ clicking	10	5	= 0.003

[a] All participants were able to define one side as "the most painful side".
[b] *P* values from comparisons with Mann-Whitney or Fisher Exact tests.

Statistics

The data were tested by analysis of variance (ANOVA) models. The factors in the ANOVA were: group (persons with and without TMJ), side (most painful and contralateral side in persons with TMJ, or right or left sides in healthy participants, except for electrical thresholds), sex (men, women), and sites for tactile and pin-prick sensitivity were also included (11 sites). When appropriate, the ANOVAs were followed by *post hoc* Tukey tests to compensate for multiple comparisons. A Mann-Whitney rank sum test or Fisher Exact test was used for comparison of age and clinical measures between groups, while Pearson product moment correlation tests were used to examine associations between QST and clinical pain measures (VAS spontaneous pain, characteristic pain intensity, pain duration, unassisted and assisted jaw opening). All data are presented as mean values and standard errors of the mean (SEM). The level of significance was set at $P < 0.05$.

RESULTS

Clinical Profile of Persons with TMJ Arthralgia

The clinical measures are summarized in the Table (also see the APPENDIX).

Intra-articular Electrical Thresholds

Pain detection and summation thresholds in persons with TMJ arthralgia (1.8 ± 0.2 mA; 1.2 ± 0.1 mA) were significantly lower than in healthy participants (3.9 ± 0.3 mA; 2.6 ± 0.2 mA) (P < 0.001). There were no differences between sensory thresholds in persons with TMJ arthralgia (0.6 ± 0.1 mA) and healthy participants (1.0 ± 0.1 mA) (P = 0.086), and there were no significant sex-related effects (P > 0.344).

Tactile and Pin-prick Sensitivity

The numerical rating scale scores for both tactile and pin-prick stimulation of the TMJ area were significantly higher in persons with TMJ arthralgia than in healthy participants (P < 0.013), and showed significant site-to-site differences (P < 0.001), but no side-to-side differences (P > 0.153) or significant sex-related effects (P > 0.480). *Post hoc* tests showed that the central, anterior, and inferior sites were generally the most sensitive to tactile and pin-prick stimulation (Fig. 1b). There were significant group x side interactions, indicating higher numerical rating scale scores on the most painful side and the contralateral side in persons with TMJ arthralgia, compared with both the left and right sides in healthy participants (P < 0.001), but no differences between the two sides in either persons with TMJ arthralgia (P > 0.128) or healthy participants (P > 0.672).

Pressure-Pain Threshold and Pressure-Pain Tolerance

Persons with TMJ arthralgia had significantly lower pressure thresholds than did healthy participants (P < 0.001), with a significant side-to-side effect (P < 0.001), but no sex-related differences (P > 0.132) (Fig. 2). There were significant group x side interactions, and *post hoc* analysis showed that pressure-pain and tolerance thresholds on the most painful side in persons with TMJ arthralgia were significantly lower than those on the contralateral side (P < 0.001 and P = 0.005, respectively). Both sides were significantly lower than in healthy participants (P < 0.001), in whom there were no significant side-to-side differences (P = 0.993 and P = 0.051, respectively).

Both pressure thresholds in fingers were significantly lower in persons with TMJ arthralgia compared with healthy participants (P < 0.001), without any sex-related effects (P > 0.073).

Post hoc Tests

The influence of TMJ clicking (disc displacement with reduction) on the QST data was examined in additional ANOVAs. Electrical thresholds in persons with TMJ arthralgia

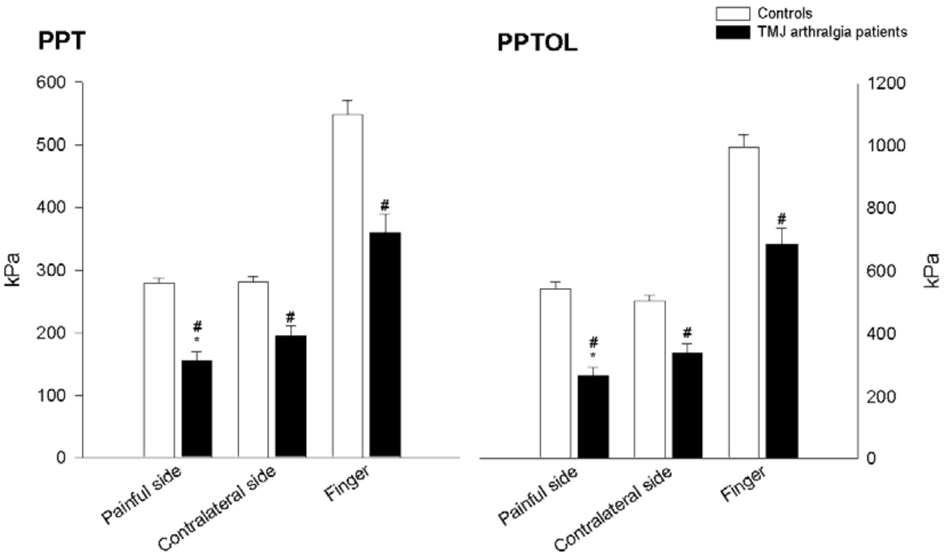

Figure 2. Pressure-Pain Threshold (PPT) and Tolerance (PPTOL) in healthy individuals (n = 43) and persons with TMD arthralgia (n = 20) on the painful and contralateral sides in persons with TMD arthralgia compared with 2 randomized sides in healthy individuals, and the index fingers of both groups. *Significant differences between painful and contralateral sides in persons with TMD arthralgia (P < 0.01). #Significant differences between persons without and those with TMD arthralgia (P < 0.001).

without clicking were lower than those in persons with clicking (P < 0.023) (see APPENDIX).

Correlation Analysis

There were associations among clinical pain measures, among clinical and experimental pain measures, and among various experimental pain measures of the same modality (Figs. 3A-3I) (see APPENDIX).

DISCUSSION

This appears to be the first study that directly assessed the sensitivity to standardized electrical stimuli applied within painful TMJs in addition to a QST battery. Significantly lower pain detection and summation thresholds were observed in persons with painful TMJs and increased sensitivity to both tactile and pin-prick stimuli in the TMJ area. Pressure thresholds were lowest on the most painful side in persons with TMJ arthralgia, but there were also lower pressure threshold values on the finger (control site). Correlation analysis revealed associations among several QST and clinical pain measures and among QST measures of the same stimulus modality. These findings suggest that not only do persons with persistent TMJ arthralgia have sensitization of large myelinated fibers in the auriculotemporal nerve, but also that sensitization of central nociceptive pathways may be involved.

Clinical Profile of Persons with TMJ Arthralgia

The clinical characteristics of participants in the present study are comparable with those reported from other TMD studies (Maixner *et al.*, 1995, 1998; Svensson *et al.*, 2001). We were careful to age-match the persons with TMJ arthralgia to the healthy participants; however, we recruited only a small number of males with TMJ arthralgia, reflecting the female predominance in this disorder. In terms of sex-related differences in TMJ sensitivity, our previous study (Ayesh *et al.*, 2007) was unable to show any significant differences. In the present study, we included sex as a factor in the ANOVA and found no significant difference, although more studies on gender difference should be executed, since the statistical power of the sample was low. However, it appears unlikely that the differences in QST data between persons with and those without TMJ arthralgia can be explained by sex-related differences in pain sensitivity. Finally, it should be noted that, for practical reasons, the QST technique was not done blinded; however, we used standardized and reliable psychophysical techniques. Furthermore, application of the QST technique by the clinical investigator may mimic the clinical situation, and there is good evidence in the literature that a standardized use of QST techniques is reliable, even when they are applied by unblinded investigators (Gracely, 2005).

Intra-articular Electrical Thresholds

This is the first study to report the sensitivity to painful electrical stimuli inside the TMJ in persons with arthralgia. This study has a unique and important feature, since all other current QST activate the cutaneous and overlying tissues, and therefore do not directly represent intra-articular sensitivity. However, this technique is still a research tool, and more studies will be needed before it can be recommended as a clinical test. Our recent methodological study (Ayesh *et al.*, 2007) showed a clear change in the 3 electrical thresholds after 20 min of painful electrical stimulation of the TMJ. In the present study, pain detection and summation thresholds were significantly lower in persons with TMJ arthralgia compared with healthy persons, and sensory detection thresholds showed the same tendency. Interestingly, the 3 electrical thresholds were different between persons with and without clicking, which indicates that a clicking TMJ is not strongly associated with intra-articular sensitization. Electrical stimulation is non-selective and probably bypasses the nociceptors (Curatolo *et al.*, 2005), and this suggests that central processing could play an important role in individual hypersensitivity. Furthermore, the high sensitivity to temporal summation stimuli is likely to be explained by central mechanisms (Svensson and Graven-Nielsen, 2001; Curatolo *et al.*, 2005; Sarlani and Greenspan, 2005).

Several studies have assessed psychophysical responses to electrical stimuli in the skin and muscles of persons with musculoskeletal pain, and have showed the same trend as observed in this study. Electrical thresholds with cutaneous and intramuscular stimuli are generally lower in persons with chronic tension-type headache or whiplash-associated pain

(Bendtsen *et al.*, 1996; Curatolo *et al.*, 2001; Ashina *et al.*, 2005). Persons with TMJ arthralgia have been shown to have hyperesthesia, while persons with myofascial TMD have hypoesthesia to cutaneous electrical stimulation (Eliav *et al.*, 2003). However, other studies have failed to show this difference in the skin over the masseter muscle (Davidson and Gale, 1983) or in the tooth pulp (Sharav *et al.*, 1982), while Hagberg *et al.* (1990) showed hyposensitivity in cutaneous electrical stimulation over the masseter area. However, persons with TMJ arthralgia according to RDC/TMD criteria are clearly more sensitive to painful electrical stimuli application within the TMJ, indicating a pronounced sensitization.

Mechanical Stimulation

The superficial mechanical stimuli (pin-prick and tactile) and the deep mechanical stimuli (pressure thresholds) used in this study showed hypersensitivity in persons with TMJ arthralgia compared with healthy persons. The present findings indicate a generalized hyperesthesia in persons with TMJ arthralgia that includes the skin over the TMJ and the extracranial site (the index finger). A central sensitization phenomenon is necessary to explain this general hypersensitivity, but does not exclude the involvement of peripheral sensitization. The findings are also in general agreement with those of most studies on other persons with TMD pain (Svensson *et al.*, 1995; Fredriksson *et al.*, 2003; Hansdottir and Bakke, 2004; Visscher *et al.*, 2004; Wang *et al.*, 2004; Silva *et al.*, 2005) and other musculoskeletal pain syndromes (Bendtsen *et al.*, 1996; Drobek *et al.*, 2001; Ashina *et al.*, 2005). Taken together, these QST findings may provide useful information, help to facilitate a mechanism-based diagnosis, and give an idea of the interplay among the distinct pain mechanisms that operate in any individual, ultimately leading to a polypragmatic therapeutic approach that addresses the specific combination of mechanisms occurring in each person (Baron, 2006).

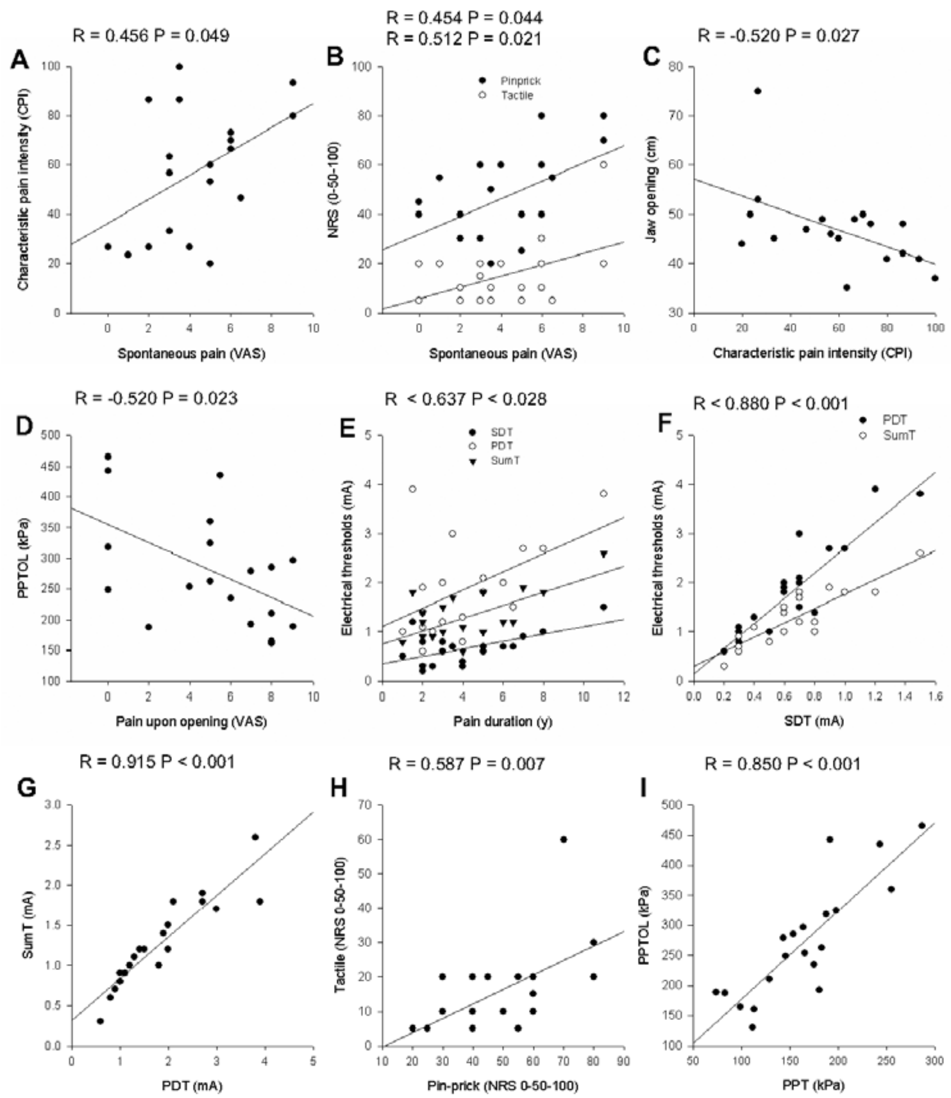

Figure 3. Correlation plots between various clinical and QST measures **(A-I)** in persons with TMJ arthralgia (n = 20). NRS, numerical rating scale; PPT and PPTOL, pressure-pain threshold and tolerance; SDT, sensory detection threshold; PDT, pain detection threshold; SumT, summation threshold.

Correlation Analysis

There were associations among clinical pain measures, among clinical and experimental pain measures, and among various experimental pain measures of the same modality. In a previous study on persons with myofascial TMD, there were no associations between the measures of somatosensory sensibility and clinical pain measures (Svensson *et al.*, 2001). More recently, a study showed associations between different sensory and pain assessment modalities in healthy individuals (Komiyama *et al.*, 2006), a finding that is in agreement with our results. The correlation between pain period and electrical thresholds indicates reduced responsiveness, which can be explained, in part, by the adaptation-level theory (Rollman, 1979) and appears to be in agreement with the current view that TMD improves with time (Goldstein, 1999).

In conclusion, this study provides new evidence of sensitization of the TMJs as well as central nociceptive pathways, and suggests that QST measures will help to facilitate a mechanism-based classification of temporomandibular disorders.

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