# Increased Pain Sensitivity to Intraoral Capsaicin in Patients with Atypical Odontalgia

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***Aims:*** *To use 2 well-characterized stimuli, the intraoral capsaicin model and the "nociceptive-specific" electrode, to compare superficial nociceptive function between patients with atypical odontalgia (AO) and matched healthy controls. Furthermore, the authors aimed to describe the sensitivity, specificity, and positive predictive values (PPV) of the techniques if group differences could be established.* ***Methods:*** *Thirty-eight patients with AO and 27 matched healthy controls participated in this study. Thirty microliters of 5% capsaicin was applied to the gingiva on the left and right sides of all participants as a pain-provocation test. The participants scored the capsaicin-evoked pain continuously on a 0-to-10 visual analog scale (VAS). Furthermore, individual electrical sensory and pain thresholds to stimulation with a "nociceptive-specific" electrode on the facial skin above the infraorbital or mental nerve were determined.* ***Results:*** *AO patients had higher VAS pain scores for capsaicin application than healthy controls (ANOVA: $F > 4.88$; $P < .029$). No differences between the painful sides and the nonpainful sides of the patients were found (ANOVA: $F < 1.26$; $P > .262$). No main effects of group or stimulation side on the electrical sensory and pain thresholds were detected (ANOVA: $F < 0.309$; $P > .579$). Sensitivity was 0.51; specificity, 0.81; and PPV, 0.77 when a VAS value of ≥ 8 for capsaicin-evoked pain was used.* ***Conclusion:*** *AO patients show increased sensitivity to intraoral capsaicin but normal sensitivity to "nociceptive-specific" electrical stimulation of the face in an area proximal to the painful site. The use of the intraoral pain-provocation test with capsaicin as a possible adjunct to the diagnostic workup is hampered by the only moderately good sensitivity and specificity.* J OROFAC PAIN 2006;20:107–114

**Key words:** atypical odontalgia, capsaicin, neuropathic pain, trigeminal pain

Capsaicin applied topically or intradermally is a widely used human experimental pain model to stimulate transient receptor potential vanilloid 1 (TRPV1) receptors on sensory nerve fibers.[1–6] Topical capsaicin applied for 15 minutes on the oral mucosa in healthy subjects causes moderate levels of pain and heat hyperalgesia[7] and has been proposed as a pain-provocation test for intraoral pain conditions similar to those that have been used for studies on pain mechanisms in postherpetic neuralgia[6] and rheumatoid arthritis.[8] Furthermore, this model has recently been used in the study of possible gender differences in the endogenous pain modulation system, termed *diffuse noxious inhibitory controls*

*(DNIC)*.[9] Because of the burning quality of the evoked pain, intradermal or topical application of capsaicin on skin is commonly used as a human surrogate model of neuropathic pain.[10] Additionally, evoked pain in the form of allodynia can be induced without injury with the use of intradermal capsaicin.[10]

Another method used to study trigeminal (V) nociception involves the use of a so-called "nociceptive-specific" (NS) electrode, which has been applied in electrophysiological studies of pain conditions such as migraine.[11–14] Instead of activating all types of primary afferent fibers of the skin, the NS electrode causes a depolarization limited to the superficial layer of the dermis containing nociceptive fibers when low stimulus intensities are used (0.6 to 1.6 mA).[11] When this electrode is used, stimulation of the skin of the face causes a distinct pinprick-like pain,[14] and it is possible to determine individual sensory and pain thresholds as well as onset latencies and response areas of blink reflexes (BR) elicited by this electrode in a reproducible manner.[11,14] For example, retest reliability has been evaluated and found high for BR onset latencies.[11] In patients with temporomandibular joint (TMJ) pain, but not in patients with muscle-related facial pain, large myelinated fiber hypersensitivity to electrical stimulation with an 8-mm diameter spherical gold-plated electrode has been found in the skin overlying the TMJ.[15]

No specific diagnostic test for the challenging orofacial pain condition of atypical odontalgia (AO) is available. AO is hypothesized to be a neuropathic pain condition,[16] but this has yet to be confirmed. AO often follows deafferentation of primary afferent trigeminal nerve fibers caused by, for example, tooth extraction or root canal therapy,[17] and it is reported to occur in 3% to 6% of endodontically treated teeth.[18,19] The search for relief of this pain condition often leads to numerous unnecessary invasive dental and surgical procedures without the desired result.

So far, few studies have directly compared sensory function between patients with chronic ongoing pain after deafferentation and patients who remain pain-free after a similar injury.[20,21] Therefore, the aim of this study was to use 2 well-established stimulus modalities, the intraoral capsaicin model and the NS electrode, to compare superficial nociceptive function between patients with AO and matched healthy controls. Furthermore, the authors aimed to describe the sensitivity, specificity, and positive predictive values (PPV) of the test if group differences could be established.

## Materials and Methods

### Subjects

Thirty-eight patients with AO, 30 women and 8 men (mean age 51.2 ± 15.9 years) were recruited from the Orofacial Pain Unit in Malmö, the Department of Neurology in Linköping, and the County Hospital in Kalmar, Sweden, and from the School of Dentistry in Aarhus, Denmark. Inclusion criteria included ongoing pain (> 6 months) in a tooth or in a place formerly occupied by a tooth (edentulous area). The pain had to be nonparoxysmal and present during most of the day, and there could be no signs of tissue pathology in clinical and radiological examinations.[22] The patients were thoroughly examined by a dentist and a neurologist. Exclusion criteria were presence of other known orofacial pain conditions such as trigeminal neuralgia, cluster headache, or odontogenic pain. Spontaneous AO pain on the day of the study ($VAS_{now}$), mean AO pain during the last month ($VAS_{mean}$), and worst AO pain during the last month ($VAS_{worst}$) were assessed by the patients using a 0-to-10 visual analog scale (VAS). The location of the pain was noted (mandible or maxilla, left or right side).

Twenty-seven healthy controls without orofacial pain, 18 women and 9 men (mean age 57.5 ± 16.5 years) who were patients from a general dental practice, enrolled in the study. The healthy controls were matched to the AO patients according to age, sex, and location of tooth extraction. Healing after tooth extractions had occurred for at least 6 months. Subject recruitment and the study protocol were approved by the local ethics committees (Aarhus County, Denmark and Lund University, Sweden), written informed consent was obtained from all participants, and the study was performed in accordance with the Declaration of Helsinki.

### Electrical Stimulation Test

The study was performed in a quiet room with a temperature of about 20°C. Two NS electrodes[14] were placed bilaterally on the skin over the entry zones of the infraorbital nerve (V2) or mental nerve (V3). For patients with pain in the maxilla, V2 was chosen for stimulation, and V3 was chosen for patients with pain in the mandible. Similarly, V2 was stimulated in controls with a history of tooth extraction in the maxilla, whereas V3 was stimulated if a tooth had been extracted from the mandible. Side of stimulation (left or right) was randomly selected.

The individual sensory ($I_0$) and pain thresholds ($I_p$) to the electrical stimuli on both sides of the face of all participants were determined with at least 2 series of ascending and descending stimuli. Each individual stimulus consisted of a train of 3 pulses with a duration of 0.3 ms at interpulse intervals of 3 ms. The sensory threshold was defined as the lowest stimulus intensity that evoked a sensation, and the pain threshold was the lowest stimulus intensity evoking a sensation that was just barely painful.

### Capsaicin Stimulation Test

Thirty microliters of 5% capsaicin (prepared by the pharmacy at Aarhus University Hospital) was applied for 15 minutes under a Urihesive (ConvaTec) bandage to the painful intraoral site of the patient and to the corresponding homologous contralateral area,[7] 1 side at a time, in randomized order. Likewise, in healthy controls, capsaicin was applied to the gingiva in the region of the extracted tooth and the corresponding homologous contralateral region. At least 30 minutes separated the 2 capsaicin applications. All subjects scored their perceived capsaicin-evoked pain intensity continuously for 15 minutes on a VAS in which 0 denoted "no pain" and 10 "the most intense pain imaginable." The VAS pain scores were sampled at 1 Hz by a computer. From the capsaicin-evoked VAS pain data, the following features were calculated: area under the curve (AUC), onset time of pain (VAS > 0), offset time of pain (VAS back to 0), duration of pain (offset time minus onset time), peak pain (the maximum VAS score), and peak time (time from beginning of VAS registration to the time when the maximum VAS pain score was registered).[7,23]

Raw VAS pain scores were then averaged every minute; this yielded 15 averaged VAS pain scores (T1 to T15) to test for time effects between groups.[9] The study session, including the capsaicin stimulation test on both sides, lasted approximately 90 minutes. One participant in the patient group dropped out of the study after testing of the painful side, because she felt the capsaicin-evoked pain was intolerable.

### Statistics

The results are presented as mean values with standard error of the mean (SEM). Two-way analyses of variance (ANOVAs) were used to analyze the sensory and pain thresholds ($I_0$ and $I_p$) and the features of the capsaicin-evoked pain, with group (patient versus control) and side (patients: painful versus nonpainful side, controls: extraction versus non-extraction side) as factors. Spearman's rank correlation analyses were performed between the AO pain parameters of the patients ($VAS_{now}$, $VAS_{mean}$, and $VAS_{worst}$) and the features of capsaicin-evoked pain (AUC, onset time, offset time, duration of pain, peak pain, and peak time). The $\chi^2$ test was used to compare between groups the proportion of participants who still experienced pain at the end of the continuous VAS capsaicin-evoked pain registration. A 3-way mixed-model ANOVA was used in the analysis of the averaged capsaicin-evoked pain scores (VAS) with groups and side as factors, and time (T1 to T15) as the repeated measurement factor. The Tukey honestly significant difference (HSD) test was used in post-hoc analyses and values of $P$ less than .05 were considered significant. Sensitivity, specificity, and PPV values were calculated for the capsaicin-evoked peak pain scores using different cutoff values.

## Results

### Subjects

The mean duration of AO pain was 7.3 years (range, 2 to 13 years). The mean spontaneous pain intensity on the day of testing was 4.5 ± 0.4 (SEM); the mean pain intensity during the last month was 5.3 ± 0.3; and the mean intensity of the worst pain in the last month was 7.3 ± 0.4 on the 0-to-10 VAS. Twenty-five patients experienced pain in the maxilla (11 on the left side, 14 on the right side) and 13 patients in the mandible (6 left and 7 right). Seventeen controls had a tooth extracted from the maxilla (9 left and 8 right) and 10 had 1 extracted from the mandible (4 left and 6 right).

### Electrical Sensory and Pain Thresholds

No main effects of group or side were found for $I_0$ or $I_p$ (ANOVA: $F < 0.309$; $P > .579$) (Fig 1).

### Capsaicin-Evoked Pain

Significant main effects of group on capsaicin-evoked pain features were detected. AO patients had greater AUC (ANOVA: $F = 4.88$; $P = .029$); later offset of pain (ANOVA: $F = 7.11$; $P = .009$); longer duration of pain (ANOVA: $F = 11.92$; $P = .001$); higher peak pain (ANOVA: $F = 8.49$; $P = .004$); and shorter peak time (ANOVA: $F = 6.31$; $P = .013$) compared with healthy controls. No main

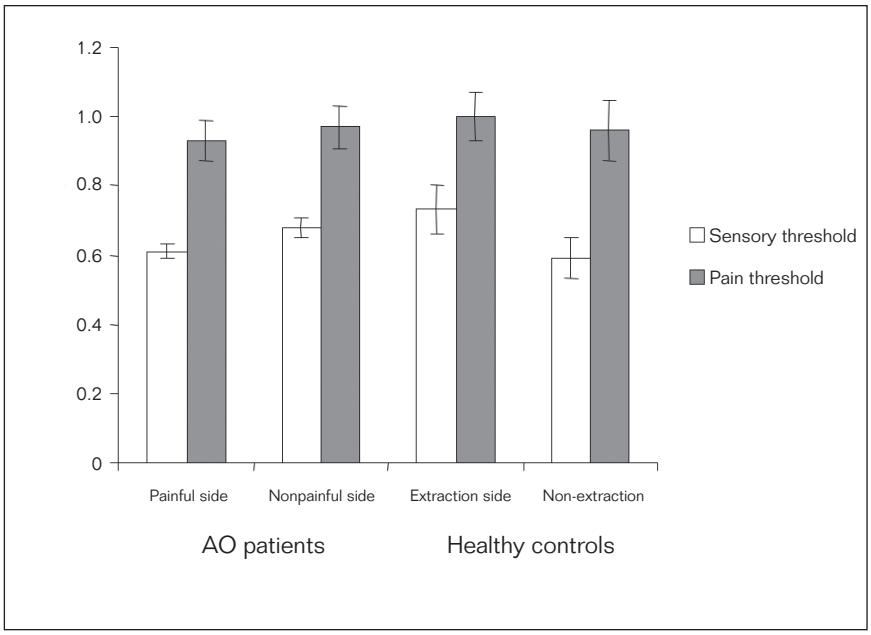


**Fig 1** Mean ± SEM of individual sensory and pain thresholds at baseline to NS electrical stimulation of the facial skin. Thresholds for both sides of the faces are shown.

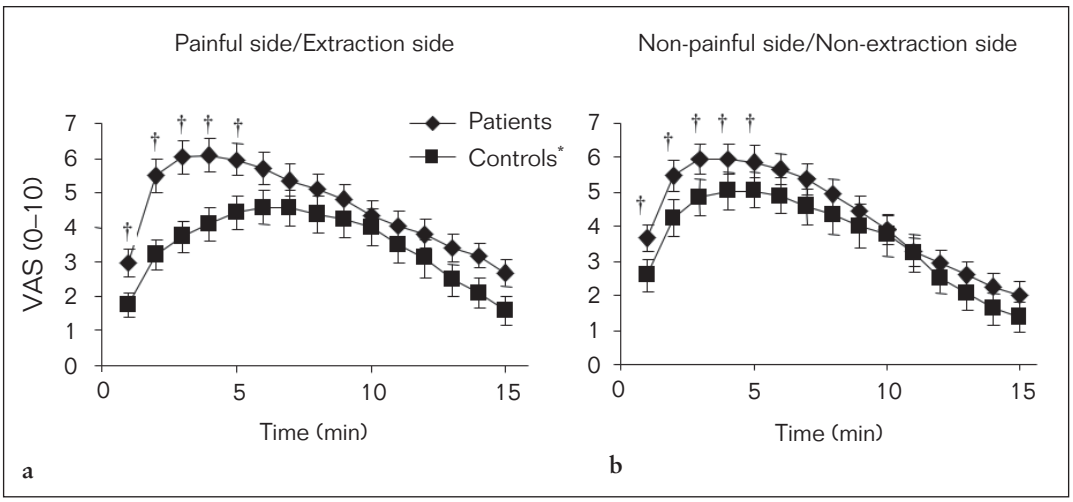


**Fig 2** The mean averaged capsaicin-evoked VAS pain at different timepoints (T1 to T15) during the 15-minute application period on *(a)* the painful side of the patient and the extraction side of the healthy controls and *(b)* the contralateral sides. Patients experienced higher levels of pain intensity than matched controls. * Main effect of group, ($P = .037$). † denotes a significant group × time interaction ($P < .025$).

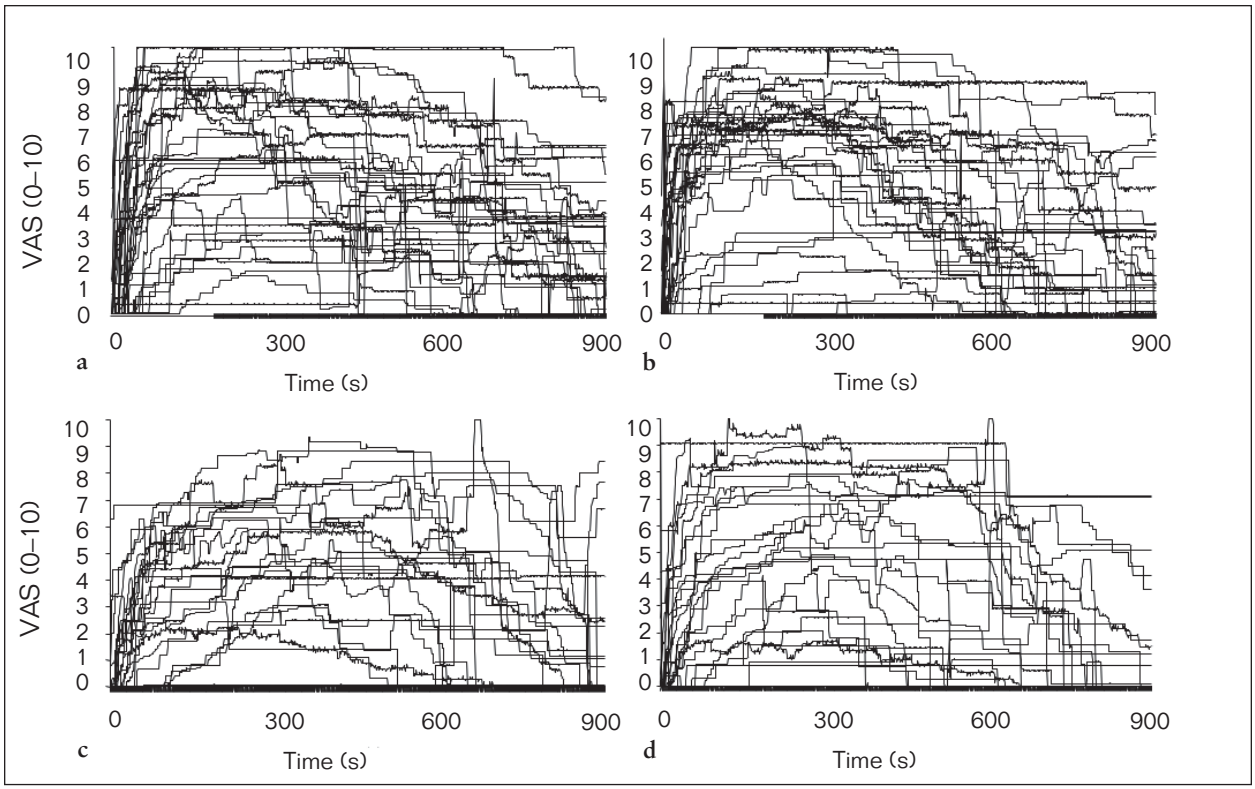


**Fig 3** The individual raw VAS pain curves of the capsaicin-evoked pain. *(a)* The painful side of the AO patients (n = 38). *(b)* The nonpainful side of the AO patients (n = 37). *(c)* The extraction side in healthy controls (n = 27). *(d)* The opposite side of the healthy controls (n = 27). The variation in the capsaicin-evoked pain responses is pronounced.

**Table 1 Means ± SEMs of the Features of the Capsaicin-Evoked Pain**

| | AO patients | | Controls | |
|---|---|---|---|---|
| | Painful side | Non-painful side | Extraction side | Non-extraction side |
| AUC* | 4014 ± 320 | 3747 ± 306 | 3092 ± 375 | 3138 ± 425 |
| Onset time (s) | 16 ± 3 | 20 ± 9 | 22 ± 7 | 24 ± 10 |
| Offset time (s)* | 874 ± 11 | 812 ± 23 | 809 ± 25 | 749 ± 32 |
| Duration (s)* | 858 ± 11 | 793 ± 24 | 700 ± 54 | 725 ± 34 |
| Peak pain (0-to-10 VAS)* | 7.1 ± 0.4 | 6.5 ± 0.4 | 5.3 ± 0.6 | 5.5 ± 0.6 |
| Time of peak pain (s)* | 250 ± 40 | 243 ± 33 | 386 ± 41 | 305 ± 33 |

*Difference between the patient and control groups was significant.

effect of group on onset time of pain was detected (ANOVA: F = 0.37; $P$ = .543). Capsaicin application side did not influence any of the VAS features (ANOVA: F < 1.26; $P$ > .262), and no significant interactions were found (ANOVA: F < 1.942; $P$ > .166) (Figs 2 and 3, Table 1). A significantly higher proportion of AO patients than controls continued to experience capsaicin-evoked pain at the end of VAS registration (28 of 37 patients versus 10 of 27 controls, or 74% versus 37%; $\chi^2$: $P$ = .003).

No significant correlations were found between the AO pain parameters of the patients and the features of their capsaicin-evoked pain (Spearman's $\rho$ < 0.33, $P$ > .061). The AUC was correlated to the offset-time, pain duration, and peak pain (Spearman's $\rho$ > 0.43, $P$ < .012), and the pain duration was correlated to the offset-time and peak pain (Spearman's $\rho$ > 0.37, $P$ < .034).

A main effect of group on the averaged capsaicin-evoked VAS pain scores (T1 to T15) was seen (ANOVA: F = 4.447; $P$ = .037); AO patients had

**Table 2 The Sensitivity, Specificity, and PPV of the Capsaicin Test at Different Cutoff Points for Peak Pain**

| Cutoff point (0-to-10 VAS) | Sensitivity | Specificity | PPV |
|---|---|---|---|
| 0 | 1.00 | 0.00 | 0.56 |
| 2 | 1.00 | 0.11 | 0.59 |
| 3 | 0.97 | 0.19 | 0.61 |
| 4 | 0.86 | 0.30 | 0.61 |
| 5 | 0.80 | 0.48 | 0.67 |
| 6 | 0.66 | 0.52 | 0.64 |
| 7 | 0.51 | 0.7 | 0.69 |
| 8 | 0.51 | 0.81 | 0.77 |
| 9 | 0.34 | 0.93 | 0.86 |
| 10 | 0.2 | 0.96 | 0.88 |

higher VAS pain scores than healthy controls. The side of capsaicin application did not influence the averaged VAS pain scores (ANOVA: F = .062; $P$ = .803), but a significant main effect of time was demonstrated (ANOVA: F = 68.677; $P < .001$), showing an overall significant peak in the capsaicin-evoked pain at T5 (the fifth minute of capsaicin application) compared with T1, T2, and T8 to T15 (Tukey: $P < .048$). A group × time interaction was shown (ANOVA: F = 2.915; $P < .001$), and the post-hoc test revealed that patients had higher VAS pain scores than controls at T1 to T5 (Tukey: $P < .025$), but not from T6 to T15 (Tukey: $P > .145$) (Fig 2).

Since capsaicin-evoked peak pain scores differed significantly between AO patients and controls, the sensitivity, specificity, and PPV values were calculated. These are presented with different cutoff values in Table 2.

## Discussion

The main finding in this study was the significant differences in sensitivity to intraoral capsaicin application between the patients and the controls. Patients with AO had significantly higher capsaicin-evoked VAS pain scores, shorter peak times, and longer duration of the capsaicin-evoked pain. Registration of capsaicin-evoked pain was terminated at the time of removal of the capsaicin (900 seconds), although many of the participants in both groups still experienced pain from the capsaicin application. Among the patients, 74% still experienced pain after registration stopped; so did 37% of the controls. This means that the researchers underestimated the duration of the capsaicin-evoked pain, and it will be necessary to perform additional studies to fully explore the differences in duration of the capsaicin-evoked pain between AO patients and healthy controls. The higher pain response to capsaicin application in AO patients may be related to an already-established sensitization in AO patients. Changes in somatosensory sensitivity and the presence of hyperexcitability are often found in neuropathic pain conditions,[24,25] and therefore the present data lend support to the notion of AO being a neuropathic pain condition. In a recent paper on taxonomy of orofacial pain conditions, it was suggested that AO and atypical facial pain (AFP) should be considered a single diagnostic entity because they share many clinical features and possibly may overlap.[26] Interestingly, post-traumatic neuralgia (PTN) was clearly separated from AO and AFP in this paper,[26] but the diagnostic criteria used to classify PTN may share several features with the diagnostic criteria used in the present study for AO, which were based on previous proposals,[22] including a predominantly constant (burning) pain following trauma with no objective signs of pathology.[26] It might be argued that AO can only be distinguished from PTN by the size of the trauma (tooth extraction or pulpectomy versus, for example, surgical procedures). Accordingly, the authors believe further studies on pain mechanisms in AO, AFP, and PTN are needed in order to improve classification and taxonomy of these intriguing orofacial pain conditions.

Because capsaicin application was performed on both sides on the same day, the risk of a possible sequence effect on the capsaicin-evoked pain was eliminated by randomizing the application side. No side differences in capsaicin-evoked pain or sensitivity to electrical stimulation within the patient group were detected, ie, the increased responsiveness to capsaicin was present on both the painful and the nonpainful side. These findings argue against peripheral sensitization as being responsible for the capsaicin hyperalgesia. Nerve damage and neuropathic pain are often associated with contralateral (mirrorlike) changes in sensitivity,[27] and in animal studies, contralateral hyperalgesia has been demonstrated in models of neuropathic pain, arthritis, and experimental myositis.[28–30] Likewise, no differences in pressure pain thresholds (PPTs) have been found between sides in patients with myogenous temporomandibular disorders (TMD),[31] and patients with TMD are generally more sensitive to noxious stimuli than healthy controls, indicating involvement of the central nervous system.[32] Similarly, it could be hypothesized that

AO patients in general may be more sensitive to painful stimuli than healthy controls, but the fact that the electrical sensory and pain thresholds at a site proximal to the painful site of the patients did not differ between groups argues against this. In contrast to the capsaicin application, which was applied directly to the painful intraoral site of the patients, the electrical stimulus was located on the skin overlying the V2 or V3 (depending on the location of the pain or extracted tooth). Hence, the affected V branch (and the corresponding contralateral V branch) was stimulated electrically but not at the specific peripheral site of injury (pain or tooth extraction). Patients with pain in the TMJ show reduced sensory thresholds to electrical stimulation of the skin overlying the joint, which may suggest activation of the nociceptive system and recruitment of normally non-nociceptive afferents of the auriculotemporal nerve into a nociceptive state.[15] The present data cannot demonstrate a similar phenomenon from stimulation of the facial skin adjacent to the painful site of AO patients.

Pain sensitivity varies considerably in humans. It is presently not known why some humans develop neuropathic pain after injury while others do not. Recently, genetic factors have come into focus with the discovery of high sensory and affective ratings of experimental pain and diminished regional μ-opioid system responses in healthy subjects homozygous for the met$^{158}$ allele of the catechol-O-methyltransferase (COMT) polymorphism (Val$^{158}$met).[33] Future studies are needed to determine the value of genetic analysis in identifying neuropathic pain patients or patients at risk of neuropathic pain.

In spite of the high interindividual variation in the capsaicin-evoked pain response (Fig 3), the possible diagnostic value of the pain provocation test with capsaicin was tested, and the clinical diagnosis AO (by a neurologist and a dentist) was used as a gold standard in the patient group. When a cutoff peak value of VAS ≥ 5 on the 0-to-10 VAS was used, the sensitivity (the proportion of AO patients who were correctly identified by the test) was 0.80 and the specificity (the proportion of healthy controls who were correctly identified by the test) was 0.48. The PPV (the proportion of participants with peak VAS pain ≥ 5 who were correctly identified by the test) was 0.67 in this study population. A cutoff value of VAS ≥ 8 could be used to attain a specificity level of 0.81, but unfortunately, this resulted in a reduction of sensitivity to 0.51 with a PPV of 0.77 (Table 2). These levels of sensitivity and specificity, although not ideal, are comparable to levels obtained in evaluation of quantitative sensory testing and neurophysiologic examination after iatrogenic injury to the inferior alveolar nerve[34] and to levels reported for pressure algometry as a diagnostic tool for myofascial pain.[35] With these levels of sensitivity and specificity, the pain provocation test with capsaicin cannot alone identify AO, but it may be of some value as an adjunct to a detailed diagnostic workup, including, for example, clinical and radiological examinations, electromyography, and quantitative sensory testing.[36–38] Whether the pain-provocation test with capsaicin can distinguish between AO and other chronic orofacial pain conditions needs to be tested in further research.

## Conclusions

It can be concluded from this study that, compared to matched healthy controls, patients with AO show greater sensitivity to intraoral capsaicin but normal sensitivity to NS electrical stimulation of the face. Furthermore, the sensitivity, specificity, and PPV of the capsaicin test were no more than moderately good.

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