Assessment of Somatosensory Function, Pain, and Unpleasantness in Two Surrogate Models of Trigeminal Nerve Damage: A Randomized, Double-Blind, Controlled Crossover Study

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Aims: To assess the pain and/or unpleasantness and the somatosensory changes caused by two experimental models of trigeminal nerve damage (topical application of capsaicin and local anesthetics) in healthy participants using extensive evaluation tools. **Methods:** This double-blinded, randomized, placebo-controlled, crossover study included 20 healthy adult participants who underwent three separate sessions of testing. In each session, the psychophysical quantitative sensory testing (QST) and the electrophysiologic electrically evoked trigeminal "nociceptive-specific" blink reflex (nBR) investigations were performed at baseline. Following a 15-minute topical application of 0.1% capsaicin, 5% EMLA, or Vaseline (placebo) agents, the maximum numeric rating scale pain and unpleasantness scores were recorded. Additionally, qualitative sensory testing and somatosensory mapping were performed. The QST and nBR investigations were repeated immediately after each application. Data were analyzed using repeated-measures analysis of variance. **Results:** Capsaicin application was associated with significantly higher pain and unpleasantness scores when compared to EMLA and Vaseline ($P < .001$), with varied bidirectional somatosensory changes among the participants and significant loss of thermosensory function ($P < .030$). EMLA application induced loss of thermal and mechanical somatosensory function ($P < .030$) and a significant reduction in electrically evoked pain scores on nBR investigation ($P < .001$). No significant changes were seen in the electrophysiologic component of the nBR after any of the applications ($P = .922$). **Conclusion:** Topical capsaicin and EMLA application mimicked certain aspects of somatosensory changes seen in trigeminal nerve damage patients and may be used as surrogate models of such changes. *J Oral Facial Pain Headache 2020;34:92–107. doi: 10.11607/ofph.2423*

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The sensory branches of the trigeminal nerve play a crucial role in daily activities such as trituration, enjoyment of food, communication, grooming, and intimacy.[1] Damage to the trigeminal nerve may be from different etiologies[2] and may lead to somatosensory disturbances such as loss or gain of somatosensory function, either alone or in combination with neuropathic pain.[3–5] These disturbances may have a considerable impact on the psychosocial status of the affected patients.[6,7]

Pain has been described as having a unique component called algosity[8] that separates it from stimulus-related unpleasantness (primary unpleasantness) and memory- and context-based unpleasantness (secondary unpleasantness; the affective dimension of pain).[8] For the trigeminal region, experimental models have generally focused on mimicking pain associated with trigeminal nerve damage, whereas unpleasantness related to pain and/or somatosensory disturbances has not been systematically studied.[3,9,10] Both pain and unpleasantness may have a significant effect on a person's quality of life,[1,7] and understanding the mechanisms behind the manifestations of pain and unpleasantness may improve the evaluation, management, and rehabilitation of trigeminal nerve injury patients.

The currently recommended evaluation of somatosensory function involves the highly standardized and validated quantitative sensory testing (QST) protocol proposed by the German Research Network on Neuropathic Pain (DFNS).[11–13] However, performance of the complete protocol requires specialized equipment, examiner training, and time.[14] The use of the full QST is therefore mostly limited to specialized clinical and/or research institutes. However, in primary dental care settings, chairside qualitative sensory testing (QualST) can be used.[14] QualST is a simple, quick, and inexpensive way to assess hyper- and hyposensitivity to tactile, cold, and pinprick stimuli in the orofacial region.[14] Although not as comprehensive as QST, it has been found useful for initial orofacial screening of somatosensory function.[14] Additionally, electrophysiologic tests, such as the electrically evoked trigeminal "nociceptive-specific" blink reflex (nBR),[15] may also be used to assess trigeminal nociceptive function.[16,17]

Human experimental pain models have been extensively used to examine aspects of pain-related somatosensory function and nociceptive processing[18,19] and could be useful for establishing additional surrogate models of aspects of trigeminal nerve damage. The currently available human experimental models for acute pain have inherent limitations for mimicking chronic neuropathic pain, and further development of models is therefore needed for the study of the complex somatosensory changes seen in trigeminal nerve damage.[19] Therefore, application of multiple models, such as the topical capsaicin and local anesthetic models, is likely needed to address different aspects of somatosensory disturbances caused by trigeminal nerve damage.[9,20–23] Systematic use of a comprehensive set of evaluation tools for assessment of somatosensory changes in experimental models of trigeminal nerve damage may help optimize such models to better mimic the somatosensory disturbances seen in patients with trigeminal nerve damage.[13]

The aim of the present study was to assess the pain and/or unpleasantness and the somatosensory changes caused by two experimental models of trigeminal nerve damage—topical application of capsaicin and local anesthetics—in healthy participants using extensive evaluation tools.

Materials and Methods

This study was conducted at the Section for Orofacial Pain and Jaw Function, Department of Dentistry and Oral Health, Aarhus University, Denmark. The participants were invited to participate in the study via advertisements posted on web pages and flyers at and around the university. The participants were provided monetary compensation of 100 Danish kroner per hour for their time and effort devoted to the study.

Participants

For this double-blinded, randomized, placebo-controlled crossover study, the sample size was calculated based on the risk of types I and II errors, determined as 5% and 20%, respectively, with the estimated intra-individual variation in the tests at around 20%.[11,24] A total of 22 healthy adult participants (aged 18 years and above) were recruited. Two participants dropped out due to reasons unrelated to the study, and therefore 20 participants (mean age ± standard deviation [SD] 25.5 ± 4.7 years; 9 men/11 women) completed the study. The exclusion criteria were: inability to communicate in English or Danish; systemic, neurologic, or psychologic illness; current use of any medication; and chronic pain in the last 6 months. The participants were provided with written information about the study and their rights as a research participant at least 24 hours before commencement of the study, and verbal information was given prior to obtaining informed consent. The study was conducted in accordance with the Declaration of Helsinki II and was approved by the Central Denmark Region ethical committee (approval no. 1-10-72-105-16).

Study Protocol

Each participant underwent three separate sessions in a randomized fashion. The randomization list was generated using randomization.com. Each session involved an initial baseline assessment of somatosensory function using QST, QualST, and nBR in the right infraorbital (V2) region (see description below). All tests were performed by a single examiner (R.S.P.).

Temporary somatosensory disturbances were experimentally induced in the V2 region using topical application of 1 mL of: 5% local anesthetic agent containing 2.5% lidocaine and prilocaine each (EMLA, AstraZeneca A/S) for experimental somatosensory impairment; 0.1% capsaicin agent (CVS pharmacy) for experimental pain and/or somatosensory disturbance; and Vaseline (Apotekets Vaseline, Apoteket) as a placebo agent.[23,25,26] A 3- × 4-cm dressing pad (Mepore Pro, Mölnlycke Health Care) was used as the mode of delivery. The preparation of the dressing pad and the randomization were performed by a staff member who was not involved in the study. Both the examiner and participants were blinded to the agents used in the sessions. The dressing pad with the agent was applied for a period of 15 minutes, during which the participants were asked to rate the perceived intensity of pain and unpleasantness separately every 3 minutes on separate numeric rating scales (NRS) from 0 to 100, where 0 indicated no pain/unpleasantness at all and

100 indicated the worst pain/unpleasantness imaginable.[27] The participants were also asked to score the maximum pain and/or unpleasantness they felt during the 15 minutes. Immediately after removal of the dressing pad, the participants filled out the standard McGill Pain Questionnaire (MPQ) to represent the words that best described their ongoing pain (if present).[28] Directly following the application period, the participants underwent QualST and somatosensory mapping (see description below). QST and nBR were again performed within the mapped area of somatosensory disturbance.

Tests

Quantitative Sensory Testing. The standardized battery of QST, performed according to the DFNS protocol, consists of 7 tests measuring 13 parameters that cover relevant nerve function.[12] A detailed description of the protocol was provided by Rolke et al.[12] The protocol investigated the following somatosensory parameters:

- Thermal parameters: Cold detection threshold (CDT), warmth detection threshold (WDT), cold pain threshold (CPT), heat pain threshold (HPT), thermal sensory limen (TSL), and paradoxical heat sensations (PHS) during the TSL procedure
- Mechanical parameters: Mechanical detection threshold (MDT), vibration detection threshold (VDT), mechanical pain threshold (MPT), and pressure pain threshold (PPT)
- Stimulus-response function: Mechanical pain sensitivity (MPS) and dynamic mechanical allodynia (DMA); wind-up ratio (WUR).[12]

Qualitative sensory testing. The tools used for QualST were: a cotton bud for tactile stimulation, a dental spatula kept in a 5°C temperature-controlled refrigerator for thermal stimulation, and a toothpick for pinprick stimulation.[14] All the stimuli were applied on the left ("control") side first, followed by the right ("test") side. The QualST was performed at baseline to confirm lack of somatosensory disturbances and in a standardized fashion after application of each agent. The tactile stimulus with the cotton bud was applied as three strokes with constant light force over a distance of 3 to 4 cm. The cold stimulus using the dental spatula was applied once for a period of approximately 2 seconds.[14] Similar to the tactile stimulus, the pinprick stimulus was applied as three quick (~1-second) pricking motions with enough force to be painful but not penetrate the skin.[14] For each stimulus applied on either side of the face, the participant was asked to report hypersensitivity ("more intense"), hyposensitivity ("less intense"), or normal sensitivity ("same") on the test side compared to the control side.[13,14]

Somatosensory Mapping. To assess the area of somatosensory changes, mapping was performed for tactile and pinprick sensation using the cotton bud and toothpick, respectively.[13,29] For the mapping of changes in tactile sensitivity, the cotton bud was moved from well outside the application area slowly toward the center of the application area. The participant was asked to indicate the exact point where they felt a change in sensation, and the spot was marked using colored pencils. This was repeated from all directions to create a map of the area with somatosensory changes.[29] This method was repeated with the pinprick stimulus using a similar pattern. The somatosensory maps were traced on a transparent sheet, scanned, and quantified using ImageJ software (National Institute of Health).[29,30]

Trigeminal "Nociceptive-Specific" Blink Reflex. The nBR was performed with the participant in a comfortable sitting position in a quiet environment. After skin preparation using alcohol wipes, two self-adhesive EMG electrodes (Neuroline 70, Ambu A/S) were placed over the orbicularis oculi muscles on both sides.[5,15,31] A common reference electrode was attached to the wrist of the left arm.[5] The recorded EMG signals were amplified and bandpass filtered between 20 and 1,000 Hz with a sampling rate of 2,000 Hz (Nicolet Viking, Natus Medical).[5,31,32] A custom-built planar concentric electrode[15] consisting of a central metal cathode of 0.5-mm diameter and an external anode ring of 5-mm diameter was used to elicit the blink reflex. The electrode was configured to deliver an electrical stimulus, which consisted of a train of three pulses (duration: 0.3 milliseconds each, rate: 333 Hz). The stimulus was applied to the skin directly above the entry zone of the right infraorbital branch of the trigeminal nerve.[5,31] The sensory threshold (I_0) and pain threshold (I_P) were determined prior to the nBR recordings using an ascending-descending staircase method with stimulus intensities starting from 0.1 mA with 0.2-mA increments.[5,15,33] The I_0 was the lowest stimulus intensity that evoked the slightest sensation, and the I_P was the lowest intensity that evoked a sharp pinprick sensation.[31]

A total of five different stimulus intensities were delivered to the participants based on their IP (100%, 150%, 200%, 300%, and 400% of IP).[5,32] The intensities of 300% and 400% were tested after the lower intensities to avoid the likelihood of a sudden, relatively high intensity of pain, leading to the potential risk of participant withdrawal. Except for the 300% and 400%, the order of intensities was randomized. For each stimulus intensity, sets of six stimuli were applied with inter-stimulus intervals of approximately 15 seconds to minimize habituation.[5,34] The R2 component of the nBR was assessed as the root mean square (RMS) of the averaged EMG signals in the time window from 27 to

87 milliseconds.[15,31,32,35] The participants were familiarized with each stimulus intensity prior to the averaging and recording of signals to avoid overlapping with the startle reaction and the related R3 response.[32] The participants were asked to score the stimulus-evoked pain at the end of each level on a numeric rating scale from 0 to 100, where 0 indicated "no pain at all" and 100 indicated the "worst pain imaginable."[27]

Oral Health–Related Quality of Life and Psychosocial Status

All participants filled out questionnaires, including the Oral Health Impact Profile (OHIP)[36] and the extended package of the psychosocial evaluation (Axis II) questionnaires from the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD)[37] to evaluate their oral health–related quality of life and psychosocial status. Axis II of the DC/TMD contains the following questionnaires: the Graded Chronic Pain Scale version 2 (GCPS), the Jaw Function Limitation Scale (JFLS), the Patient Health Questionnaire (PHQ-9 and -15), the Generalized Anxiety Disorder (GAD-7), and the Oral Behavior Checklist (OBC).[37]

Statistical Analyses

All data are presented as mean ± SD. Data distribution was assessed using Q-Q plots. Parametric tests were used for normally distributed data, and nonparametric tests were used when the data were not normally distributed. For all tests, statistical significance was set at $P \leq .050$. Data analysis was performed using Statistica version 13 (StatSoft) and Statistical Package for the Social Sciences (SPSS) version 24 (IBM).

Pain and Unpleasantness Scores. Independent samples *t* tests and Mann-Whitney tests were used for comparisons of maximum NRS pain and unpleasantness scores within the capsaicin and EMLA sessions between men and women. The maximum NRS pain and unpleasantness scores were compared between sessions (capsaicin, EMLA, Vaseline) using Friedman test with Wilcoxon signed ranks test for pairwise comparisons and Bonferroni correction for multiple comparisons. Correlation between maximum NRS pain scores and the maximum NRS unpleasantness scores was evaluated using Pearson and Spearman correlation coefficients.

McGill Pain Questionnaire. For the McGill Pain Questionnaire, words used by more than 30% of the participants ($n \geq 6$) to describe the sensation evoked by the topical application were recorded.[31] Each word was ranked based on its position and the ranks were summed to obtain the total pain rating index (PRI).[28] Calculation of PRI was also made for the four categories within the MPQ: sensory, affective, evaluative, and miscellaneous.[28]

QST Data. All QST values except for CPT, HPT, VDT, and PHS were logarithmically transformed before analysis.[12] A small constant of 0.01 was added to the pain ratings before log transformation to avoid loss of values rated as 0.[38] Two-way repeated measures analysis of variance (ANOVA) and Tukey honest significant difference (HSD) post hoc test were used to assess all the QST parameters except for PHS and DMA. The two factors in the ANOVA were Session (capsaicin, EMLA, Vaseline) and Time (baseline and after application).

Assessment of individual QST test data (after application) relative to the group mean QST baseline data (before application) was performed by calculating *z* scores using the expression:

$$z\ \text{score}^{20,39-41} = \frac{(\text{mean}_{\text{individual test}} - \text{mean}_{\text{group baseline}})}{\text{SD}_{\text{group baseline}}}$$

The signs of the *z* scores were adjusted in such a way that positive *z* scores would indicate gain of somatosensory function (hyperesthesia, hyperalgesia, allodynia) and negative *z* scores would indicate loss of somatosensory function (hypoesthesia, hypoalgesia).[41] *z* scores above +1.96 and below –1.96 indicated values outside the 95% confidence interval (CI) of the baseline group scores.[42,43]

To further evaluate the somatosensory changes caused by the topically applied agents and to compare the QST data to the QualST data, the LossGain coding system was applied.[43] The LossGain codes combine the abnormalities in the QST parameters into easily readable scores for individual participants. The scores are presented as a combined score of loss of somatosensory function (L0, L1, L2, L3) and gain of function (G0, G1, G2, G3).[43] The number suffix 0 indicates no somatosensory abnormalities of QST, 1 indicates abnormalities in the thermal modalities, 2 indicates abnormalities in the mechanical modalities, and 3 indicates a combination of thermal and mechanical abnormalities.[39,43] For a more detailed description of the LossGain coding system, please refer to Maier et al.[43]

QualST Data. Proportions of participants reporting hypersensitivity, hyposensitivity, or normal sensitivity to tactile, cold, and pinprick stimuli after application were calculated for each session. Percent agreement between LossGain codes determined from QST and QualST data was assessed as the proportion of the group for which: the LossGain codes of L2 and L3 were in agreement with QualST tactile hyposensitivity; G2 or G3 were in agreement with QualST tactile hypersensitivity; L1 or L3 were in agreement with QualST cold hyposensitivity; G1 and G3 were in agreement with QualST cold hypersensitivity; G2 or G3 were in agreement

with QualST pinprick hypersensitivity; and *z* scores of less than –1.96 for MPT, MPS, or PPT were in agreement with QualST pinprick hyposensitivity.[39] The agreement was considered as absolute when both QualST and the LossGain code showed the same pattern of somatosensory disturbance (hypersensitivity, hyposensitivity, or normal sensitivity). When one test showed a somatosensory disturbance but the other showed normal sensitivity, it was considered to be partial disagreement. When both tests showed opposite directions of somatosensory disturbance, it was considered to be absolute disagreement.[20] Additionally, the deviation of classification in QualST from QST was evaluated with QST as the benchmark.[20]

Somatosensory Mapping. A 1-cm line placed on each participant's traced sheet was used to calibrate their mapping records. Using ImageJ software,[30] the area contained within the somatosensory map of each stimulus modality was calculated after manually selecting the boundaries of the maps. One-sample *t* test was used to assess the difference from the total area of the applied 3- × 4-cm patch (test value: 12 cm^2). Two-way repeated measures ANOVA and Tukey HSD post hoc test were used for comparisons of the mapped areas of somatosensory alterations with Session (EMLA and capsaicin) and stimulus modality (pinprick and tactile) as factors.

nBR Data. One participant was unwilling to be tested for the nBR responses for the 400% of I_P during all sessions because of the anticipated pain level. Since the dataset was otherwise complete, it was decided to perform a missing value analysis for the particular variable, as sufficient data were available for the imputation. The Expectation-Maximization Algorithm was used to compute and impute the missing data prior to further data analysis.[44]

Two-way repeated measures ANOVA with Tukey HSD post hoc test was used to analyze the nBR sensory and pinprick thresholds, with session and time as the two factors. A three-way repeated measures ANOVA with Tukey HSD post hoc test was applied to assess the effects of *Session*, *Stimulus Intensity* (100%, 150%, 200%, 300%, and 400% of I_P), and *Time* on the electrically evoked nBR responses (R2 values and NRS pain scores). The area-under-the-curve (AUC) of the nBR stimulus-response function was also computed.

Spearman rank correlation coefficient was used to assess the correlations of QST parameters with AUC for baseline and test nBR data. Mean differences (Δ) between baseline and test data were computed for the capsaicin, EMLA, and Vaseline sessions, and Spearman correlation coefficient was used to assess possible correlations between ΔQST parameters and ΔAUC of nBR responses.

Questionnaire Data. The scoring criteria for the OHIP-49 and the DC/TMD questionnaires are described elsewhere.[36,45] The assessment of correlations of separate domains of the OHIP-49 and JFLS and the total scores of the PHQ-9 and -15, GAD-7, and OBC with the maximum NRS pain and unpleasantness scores were performed using Spearman correlation analyses.

Results

Pain and Unpleasantness Scores

After capsaicin application, the maximum NRS pain scores were significantly higher in women than in men (women: 57.6 ± 30.2, men: 31.1 ± 15.1, $P = .022$), but maximum unpleasantness scores were not (women: 53.7 ± 32.5, men: 32.6 ± 12.4, $P = .067$). No significant differences were seen in maximum NRS pain and unpleasantness scores between genders after EMLA application ($P > .766$). The maximum NRS pain and unpleasantness scores for all three sessions, in addition to the progression of pain and unpleasantness every 3 minutes over the 15-minute application, are shown in Fig 1. A statistically significant difference was seen in the maximum NRS pain scores between the *Sessions* ($\chi^2 = 36.85$, $P < .001$). Post hoc tests revealed that NRS pain scores, as expected, were significantly higher during capsaicin application when compared to both the EMLA (45.7 ± 27.6 vs 1.5 ± 3.2, $P < .001$) and Vaseline applications (0.0 ± 0.0, $P < .001$). No statistically significant difference was seen in the maximum NRS pain scores between EMLA and Vaseline applications ($P = .135$). For the maximum NRS unpleasantness scores, again, a significant difference was seen between sessions ($\chi^2 = 32.96$, $P < .001$). Maximum NRS unpleasantness scores were significantly higher in capsaicin vs EMLA (44.2 ± 27.2 vs 4.0 ± 5.7, $P < .001$), capsaicin vs Vaseline (44.2 ± 27.2 vs 0.1 ± 0.2, $P < .001$), and EMLA vs Vaseline ($P = .015$). For assessment of the correlations between maximum NRS pain scores and maximum NRS unpleasantness scores, statistically significant correlations were seen in the EMLA ($r = 0.705$, $P < .001$) and capsaicin ($r = 0.492$, $P = .028$) sessions. Since Vaseline application produced no pain, correlation analysis was not performed within this session.

MPQ

During capsaicin application, the most frequently used (> 30% of participants) descriptive words for the perceived pain were burning, hot, pricking, stinging, hurting, intense, annoying, and sharp (Table 1). As expected, none of the descriptors were used by more than 30% of the participants to describe pain evoked

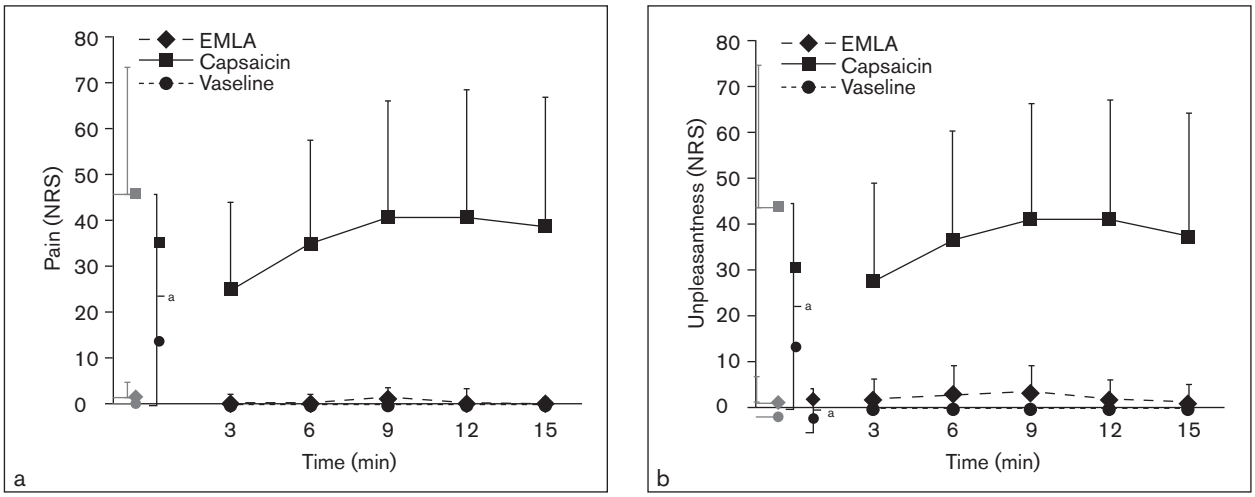

Fig 1 Participant-reported 0–100 numeric scale ratings (NRS) for **(a)** pain and **(b)** unpleasantness every 3 minutes for 15 minutes during capsaicin, EMLA, and Vaseline applications. Maximum NRS pain and unpleasantness scores are presented in gray. [a]$P < .05$ for capsaicin and EMLA compared to Vaseline.

during EMLA or Vaseline application (Table 1). The average MPQ PRI scores and the category scores are presented in Table 1.

Quantitative Sensory Testing

Statistically significant main effects of Session were seen for CDT ($F_{2,38} = 3.15$, $P = .043$), WDT ($F_{2,38} = 32.50$, $P < .001$), TSL ($F_{2,38} = 21.55$, $P < .001$), MDT ($F_{2,38} = 9.84$, $P < .001$), MPT ($F_{2,38} = 25.29$, $P < .001$), and MPS ($F_{2,38} = 18.72$, $P < .001$). For time, main effects were seen for WDT ($F_{1,19} = 86.70$, $P < .001$), TSL ($F_{1,19} = 145.49$, $P < .001$), CPT ($F_{1,19} = 12.99$, $P = .002$), HPT ($F_{1,19} = 4.71$, $P = .004$), MDT ($F_{1,19} = 14.44$, $P = .001$), MPT ($F_{1,19} = 8.79$, $P = .008$), MPS ($F_{1,19} = 15.95$, $P < .001$), VDT ($F_{1,19} = 7.77$, $P = .012$), and PPT ($F_{1,19} = 9.50$, $P = .006$). Statistically significant interactions between *Session* and *Time* were seen for CDT ($F_{2,38} = 3.11$, $P = .044$), WDT ($F_{2,38} = 40.77$, $P < .001$), TSL ($F_{2,38} = 71.12$, $P < .001$), CPT ($F_{2,38} = 11.89$, $P < .001$), MDT ($F_{2,38} = 10.77$, $P < .001$), MPT ($F_{2,38} = 33.47$, $P < .001$), MPS ($F_{2,38} = 29.53$, $P < .001$), and VDT ($F_{2,38} = 10.12$, $P < .001$). Post hoc analyses of the main effects of *Session* revealed a statistically significant somatosensory loss of function in the EMLA session compared to the capsaicin and Vaseline sessions for WDT, TSL, MDT, MPT, and MPS ($P < .003$). Post hoc analysis of the main effects of *Time* demonstrated a statistically significant somatosensory loss of function in WDT, TSL, CPT, MDT, MPT, MPS, and VDT ($P < .012$) and a significant gain of somatosensory function in HPT ($P = .040$) after application. Post hoc analysis of the interactions showed significant mean somatosensory loss of function after the capsaicin application for the thermal parameters WDT, TSL, and CPT when compared to baseline ($P < .030$). EMLA application caused significant somatosensory loss in thermal and mechanical parameters CDT, WDT, TSL, CPT, MDT, MPT, MPS, and VDT when compared to baseline ($P < .030$) (Fig 2). Also, regarding between-session effects, a significant postapplication somatosensory loss of function was seen regarding WDT and CPT in the capsaicin session compared to Vaseline ($P < .030$). Significant postapplication somatosensory loss of function was seen in CDT, WDT, TSL, CPT, MDT, MPT, MPS, and VDT for EMLA compared to Vaseline ($P < .028$) (Fig 2). No significant differences were seen between the sessions at baseline for any of the QST parameters ($P > .255$).

Table 1 Distribution of Words (McGill Pain Questionnaire) Used for Pain Description after Application of Capsaicin, EMLA, and Vaseline

	Capsaicin	EMLA	Vaseline
Word frequency,[a] no. of patients			
Burning	**18**	1	0
Hot	**14**	0	0
Pricking	**10**	1	0
Stinging	**10**	0	0
Hurting	**10**	0	0
Intense	**9**	0	0
Annoying	**8**	2	0
Sharp	**7**	2	0
Pain rating index, mean ± SD score			
Average	15.1 ± 9.2	0.9 ± 2.1	0.0 ± 0.0
Sensory	9.4 ± 4.9	0.8 ± 1.8	0.0 ± 0.0
Affective	0.8 ± 1.8	0.1 ± 0.2	0.0 ± 0.0
Evaluative	2.0 ± 2.1	0.1 ± 0.3	0.0 ± 0.0
Miscellaneous	3.0 ± 3.6	0.0 ± 0.0	0.0 ± 0.0

[a]Descriptor words used by more than 30% (n ≥ 6) of the participants (n = 20) in bold.
SD = standard deviation.

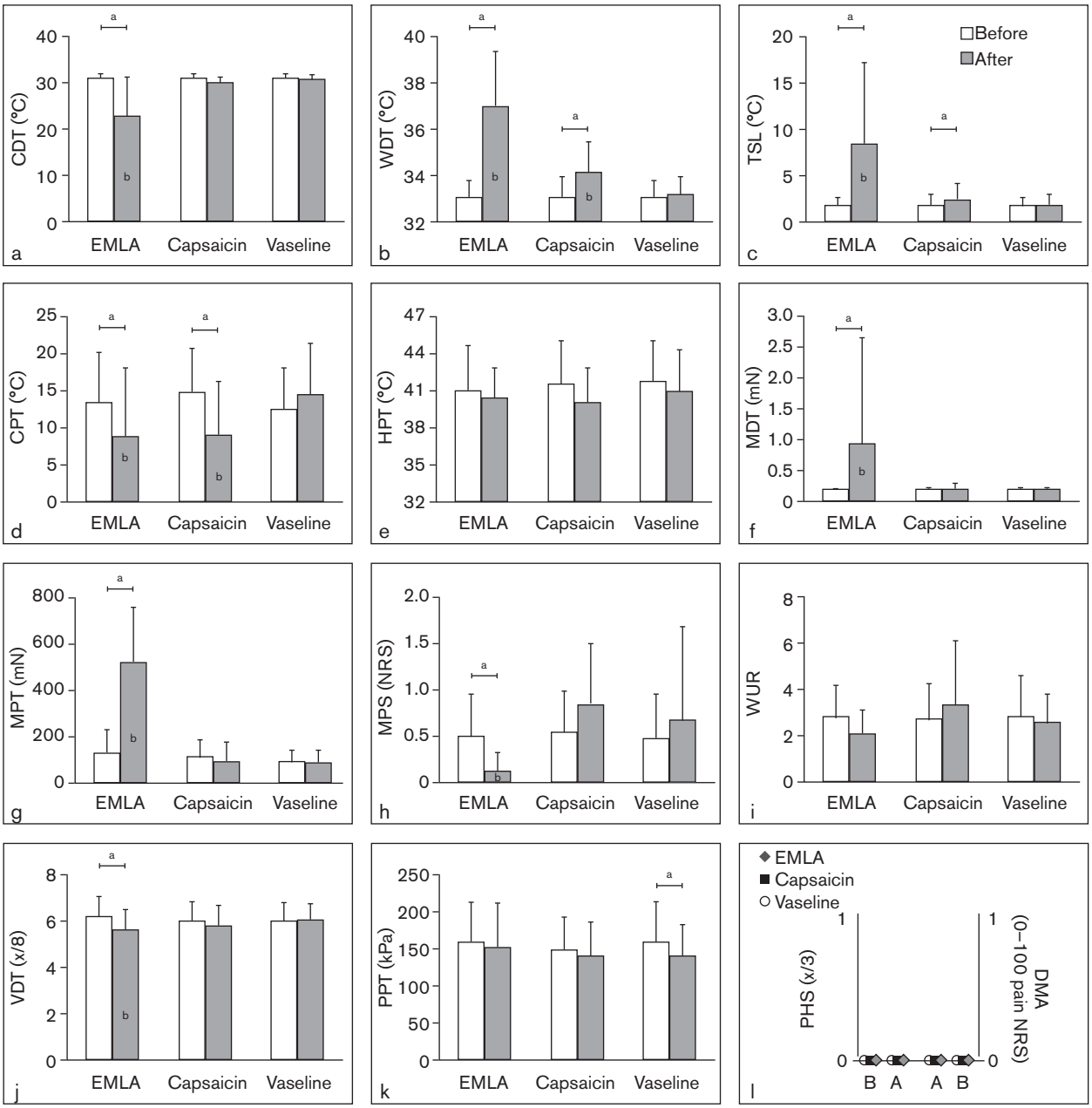

Fig 2 Results from all tested parameters of the quantitative sensory testing performed before and after the application of capsaicin, EMLA, and Vaseline (mean ± standard deviation). [a]*P* < .05 before and after application within each agent. [b]*P* < .05 after application compared to Vaseline. CDT = cold detection threshold; WDT = warmth detection threshold; TSL = thermal sensory limen; CPT = cold pain threshold; HPT = heat pain threshold; MDT = mechanical detection threshold; MPT = mechanical pain threshold; MPS = mechanical pain sensitivity; WUR = wind-up ratio; VDT = vibration detection threshold; PPT = pressure pain threshold; PHS = paradoxical heat sensation; DMA = dynamic mechanical allodynia.

Somatosensory Profiles

The individual *z* score profiles for the QST parameters after capsaicin, EMLA, and Vaseline application are shown in Fig 3. Using this assessment approach, somatosensory loss of function was seen after EMLA application in CDT (80% of participants), WDT (85% of participants), TSL (75% of participants), MDT (55% of participants), MPT (70% of participants), MPS (60% of participants), and WUR (75% of participants) (Fig 3b). Although the group average (Fig 3d) did not indicate significant somatosensory changes after capsaicin or Vaseline application, wide variations were seen for capsaicin in the individual *z* scores (Fig 3a), with 11 (55%) participants showing either loss or gain of function in at least one sensory modality after application (Fig 4).

Qualitative Sensory Testing

The QualST at baseline showed no side-to-side differences in any participants in any of the sessions. After

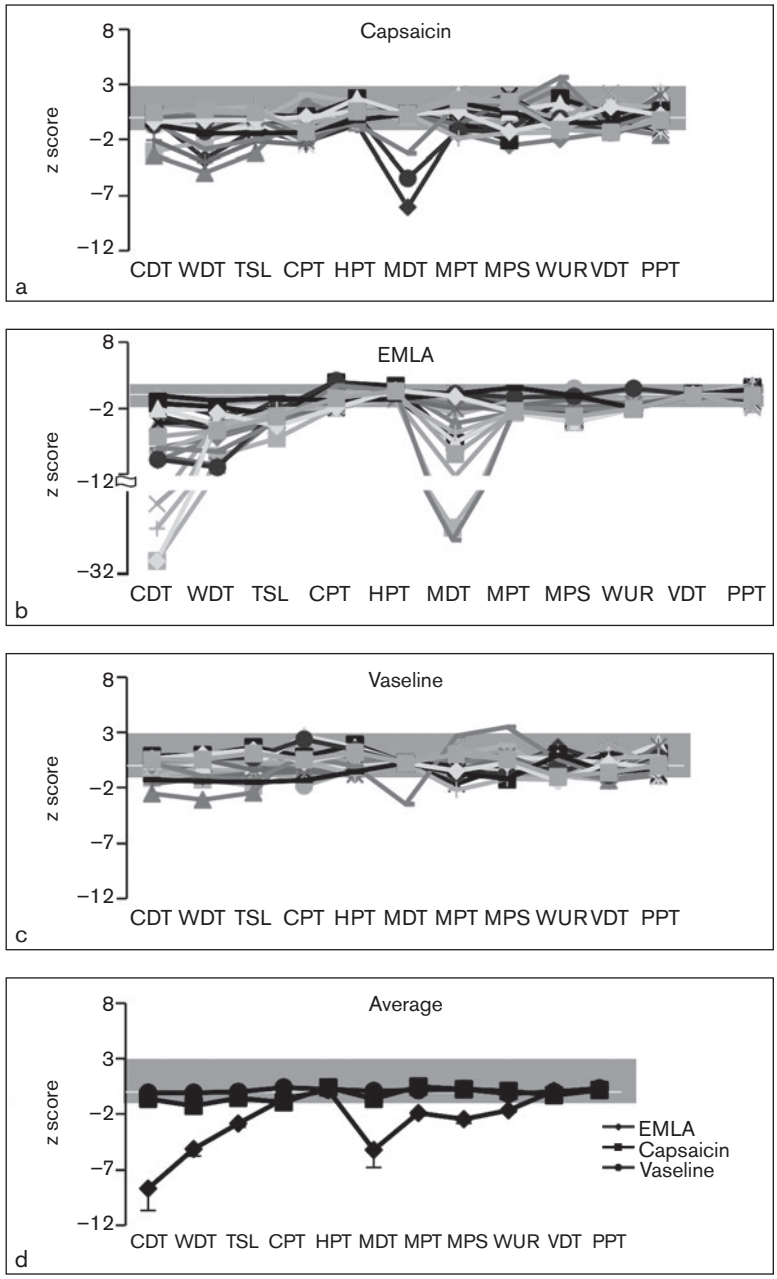

Fig 3 (a–c) Individual somatosensory *z* score profiles and **(d)** group mean *z* score profiles for the quantitative sensory testing parameters after capsaicin, EMLA, and Vaseline applications. The gray area indicates the *z* scores between 1.96 and −1.96, representing the normal range calculated from the baseline data. Values above 1.96 indicate somatosensory gain of function, and values below −1.96 indicate somatosensory loss of function. CDT = cold detection threshold; WDT = warmth detection threshold; TSL = thermal sensory limen; CPT = cold pain threshold; HPT = heat pain threshold; MDT = mechanical detection threshold; MPT = mechanical pain threshold; MPS = mechanical pain sensitivity; WUR = wind-up ratio; VDT = vibration detection threshold; PPT = pressure pain threshold.

capsaicin application, 40% of the participants reported hyposensitivity to tactile stimulation, 45% reported hypersensitivity, and 15% reported normal sensitivity. For cold sensitivity after capsaicin application, 25% reported hyposensitivity, 35% reported hypersensitivity, and 40% reported normal sensitivity. Half of the participants reported hypersensitivity to pinprick stimuli after capsaicin application, 30% reported hyposensitivity, and 20% reported normal sensitivity. After EMLA application, 85% of the participants reported hyposensitivity to tactile stimulation, and 100% reported hyposensitivity to cold and pinprick. None of the participants reported sensory abnormalities to any stimulus modality after Vaseline application.

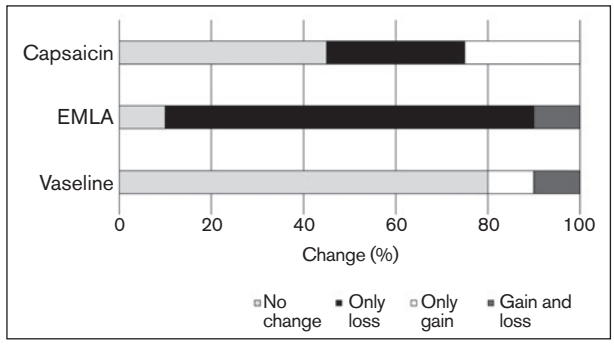

Fig 4 The proportion of participants presenting with gain and/or loss of somatosensory function based on the LossGain coding system[43] after application of capsaicin, EMLA, and Vaseline.

Table 2 Agreement (No. of Patients [%]) Between LossGain Codes and Qualitative Sensory Testing (QualST) After Capsaicin, EMLA, and Vaseline Applications

	Capsaicin			EMLA			Vaseline		
	Tactile	Cold	Pinprick	Tactile	Cold	Pinprick	Tactile	Cold	Pinprick
Absolute agreement	6 (30)	8 (40)	12 (60)	12 (60)	18 (90)	20 (100)	18 (90)	17 (85)	18 (90)
Partial disagreement	12 (60)	9 (45)	7 (35)	8 (40)	1 (5)	0 (0)	2 (10)	3 (15)	2 (10)
Absolute disagreement	2 (10)	3 (15)	1 (5)	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)

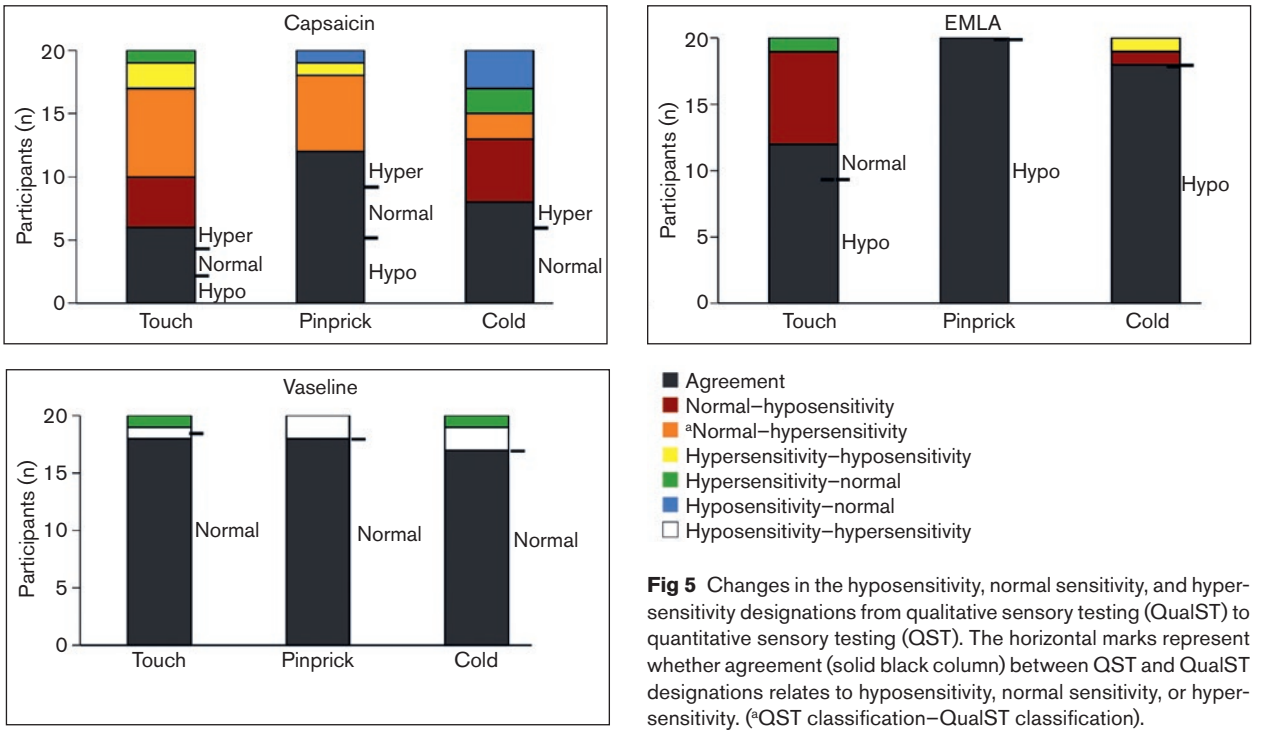

Fig 5 Changes in the hyposensitivity, normal sensitivity, and hypersensitivity designations from qualitative sensory testing (QualST) to quantitative sensory testing (QST). The horizontal marks represent whether agreement (solid black column) between QST and QualST designations relates to hyposensitivity, normal sensitivity, or hypersensitivity. ([a]QST classification–QualST classification).

Agreement Between LossGain Codes and Qualitative Sensory Testing

The distribution of loss and/or gain of somatosensory function after application, determined from the LossGain coding, is presented in Fig 4. The agreement between the QualST and LossGain coding is presented in Table 2. The highest percentage of agreement was observed for assessment of sensitivity to pinprick stimuli in all sessions after application. Capsaicin application led to the highest partial and absolute disagreements for tactile, cold, and pinprick stimuli.

When using QST as a benchmark, Fig 5 shows the deviation of classification in QualST. Among the disagreements between the QualST and QST modalities, capsaicin application showed the most changes in classification. In the capsaicin session, the agreement between QST and QualST was lower for all three test modalities than in the EMLA and Vaseline sessions (Fig 5). Vaseline application led to the lowest disagreement among the three sessions between QST and QualST, with disagreement caused by somatosensory changes seen only in QST scores.

Somatosensory Mapping

Two participants were unable to precisely note the point of demarcation between normal sensation and altered sensation. Hence, no somatosensory mapping could be recorded for these two participants. Additionally, for the same reason, one participant could provide a somatosensory map for the pinprick stimulus only after EMLA application, and another participant could not provide somatosensory maps for pinprick or tactile stimuli for the capsaicin session. Since no sensory disturbance was found on QualST in the Vaseline session, none of the participants provided somatosensory maps.

When comparing the area of the somatosensory alterations for tactile and pinprick stimuli with the test value of 12 cm^2 (area of the patch), no significant differences were found after capsaicin (tactile: 14.13 ± 7.03 cm^2, pinprick: 13.99 ± 4.66 cm^2) or EMLA (tactile: 11.25 ± 4.70 cm^2, pinprick: 11.79 ± 3.25 cm^2) application ($P > .109$). No significant differences were seen in the somatosensory map areas when comparing between EMLA

and capsaicin applications for tactile or pinprick stimuli ($P > .097$). The somatosensory maps of the capsaicin and EMLA sessions for a single participant are shown in Fig 6.

"Nociceptive-Specific" Blink Reflex

Statistically significant main effects of *Session* (I_0: $F_{2,38} = 6.68$, $P = .003$, I_P: $F_{2,38} = 25.49$, $P < .001$) and *Time* (I_0: $F_{1,19} = 44.54$, $P < .001$, I_P: $F_{1,19} = 79.28$, $P < .001$) were seen on both electrically evoked sensory and pinprick thresholds (ie, I_0 and I_P) (Fig 7). There were statistically significant interactions between *Session* and *Time* on I_0 ($F_{2,38} = 20.55$, $P < .001$) and I_P ($F_{2,38} = 42.32$, $P < .001$). Post hoc analyses of the main effects showed that both I_0 and I_P were higher in the EMLA session compared to the capsaicin (I_0: $P = .011$, I_P: $P < .001$) and Vaseline (I_0: $P = .007$, I_P: $P < .001$) sessions. Also, post hoc analysis of the main effects of *Time* showed that I_0 and I_P significantly increased after application compared to baseline ($P < .001$). Post hoc analyses of the interactions showed that the I_0 and I_P after application were increased in the EMLA session ($P < .001$), but not in the capsaicin or Vaseline sessions ($P > .086$), when compared to baseline (Fig 7). When comparing between sessions, I_0 and I_P were significantly higher after EMLA application compared to thresholds after Vaseline applications ($P < .001$). No significant difference was seen in either threshold after capsaicin application compared to thresholds after Vaseline application ($P > .738$). No differences in I_0 or I_P were seen at baseline between sessions ($P > .600$).

For electrically evoked NRS pain scores, significant main effects were seen for *Session* ($F_{2,38} = 4.98$, $P = .012$), *Time* ($F_{1,19} = 14.37$, $P = .001$), and *Stimulus Intensity* ($F_{4,76} = 46.86$, $P < .001$) (Fig 8). Significant interactions were seen between *Session* and *Time* ($F_{2,38} = 4.17$, $P = .023$), *Time* and *Stimulus Intensity* ($F_{4,76} = 9.85$, $P < .001$), *Session*, *Time*, and *Stimulus Intensity* ($F_{8,152} = 2.31$, $P = .023$). Post hoc analysis of the main effects of *Session* showed significantly reduced NRS pain scores during the EMLA session when compared to Vaseline session ($P = .011$). For *Time*, NRS pain scores were significantly reduced after the applications when compared to baseline ($P = .001$). The post hoc analysis of the main effect of *Stimulus Intensity* showed a significant increase of NRS pain scores at 200%, 300%, and 400% of I_P when compared to 100% of I_P ($P < .001$). The post hoc analysis of the interactions between *Session* and *Time* showed significantly reduced pain scores after EMLA application when compared to baseline ($P < .001$). When comparing between the sessions, significantly lower NRS pain scores were seen after the application of both capsaicin and EMLA when compared to NRS pain scores after Vaseline application ($P < .027$). No significant

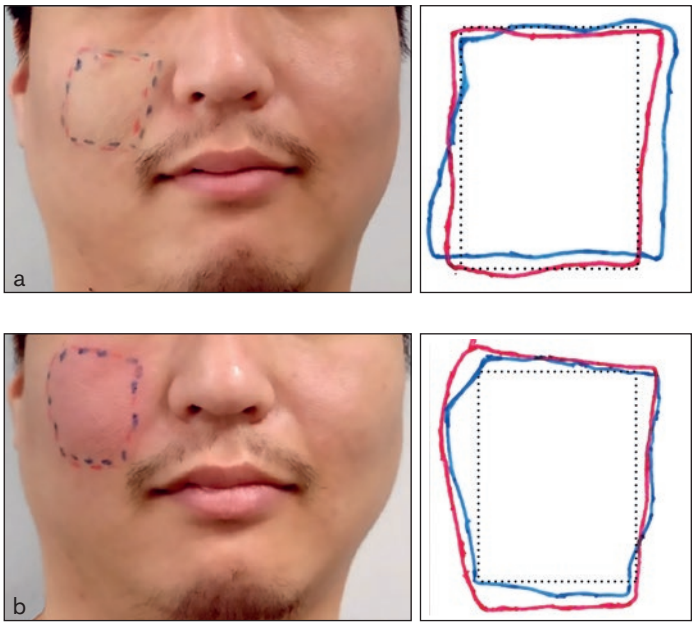

Fig 6 Representative somatosensory maps obtained after application of **(a)** EMLA and **(b)** capsaicin on a model's face and the corresponding traced maps showing the boundaries of altered sensitivity to tactile *(red)* and pinprick *(blue)* stimuli. The black dotted rectangle on the traced maps represents the boundaries of the 3- × 4-cm dressing pad used for the agent delivery.

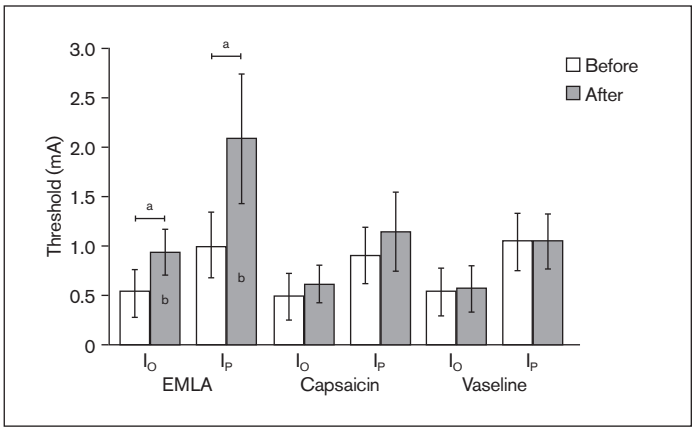

Fig 7 Electrically evoked sensory (I_0) and pinprick thresholds (I_P) before and after application of capsaicin, EMLA, and Vaseline, expressed as means and standard deviations. [a]$P < .05$ between baseline and after application. [b]$P < .05$ after EMLA or capsaicin application compared to after Vaseline application.

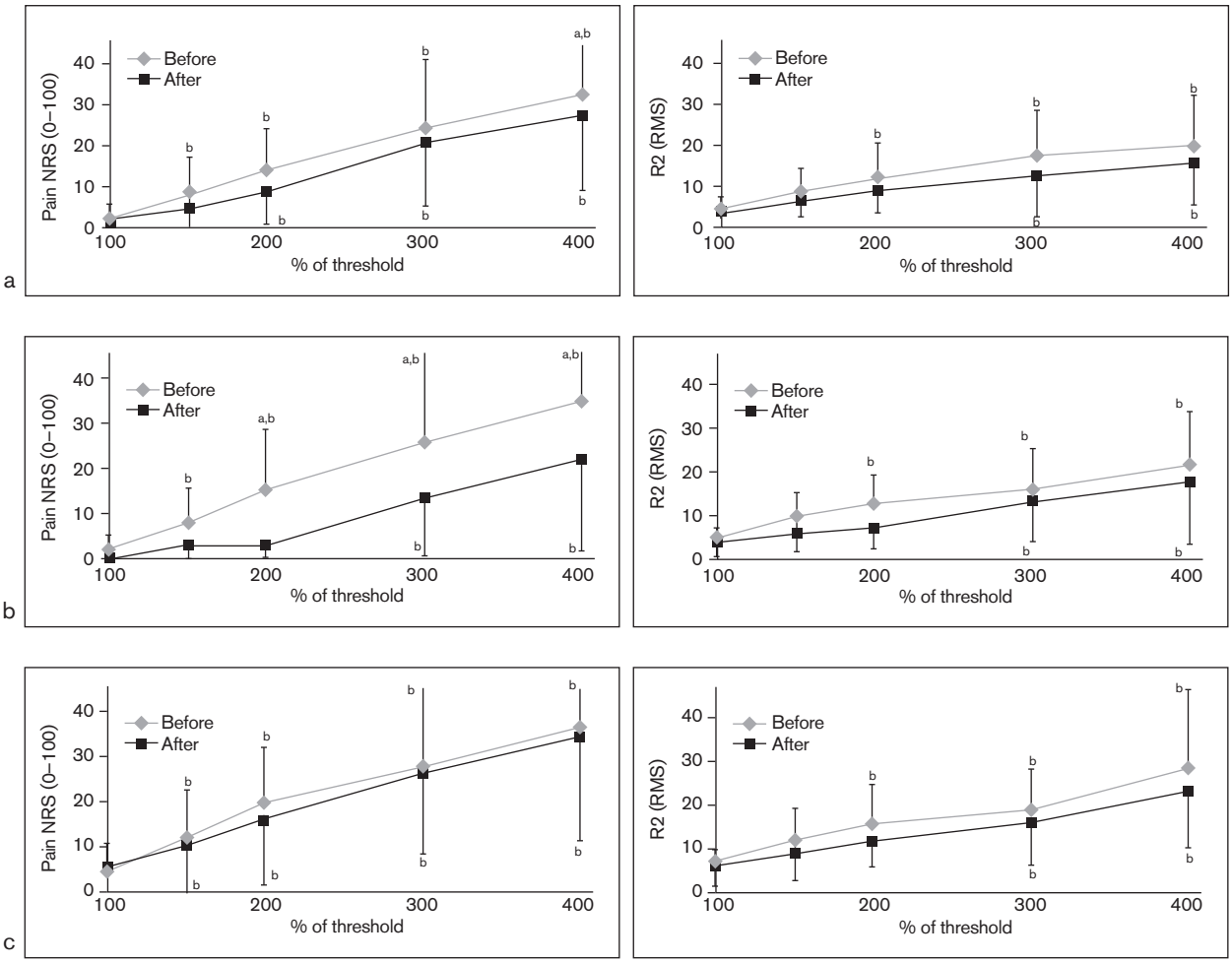

Fig 8 Electrically evoked numeric rating scale (NRS) pain scores and nBR responses presented as root mean square (RMS) values of R2 responses assessed at 100%, 150%, 200%, 300%, and 400% of the pinprick threshold before and after the application of **(a)** capsaicin, **(b)** EMLA, and **(c)** Vaseline. [a]$P < .05$ from baseline. [b]$P < .05$ from stimulation with 100% of I_P.

differences in NRS pain scores were seen between sessions at baseline. Post hoc analysis of the interaction between *Time* and *Stimulus Intensity* showed a significant increase in the NRS pain scores both at baseline and after application at all applied suprathreshold intensities when compared to the respective 100% of I_P ($P < .003$). There was a significant reduction in NRS pain scores after application when compared to baseline at all suprathreshold intensities ($P < .013$). Post hoc analysis of the interactions between *Session*, *Time*, and *Stimulus Intensity* (Fig 8a) showed significantly decreased NRS pain scores at suprathreshold stimulation intensities of 200%, 300% and 400% of I_P after EMLA application, and at 400% of I_P for the capsaicin application when compared to baseline ($P < .004$). After application, NRS pain scores were significantly lower in the EMLA session when compared to the capsaicin session at stimulation with 200% and 300% of I_P ($P < .006$). The NRS pain scores were significantly reduced at all applied suprathreshold stimulus intensities in the capsaicin and EMLA sessions when compared to the Vaseline session ($P < .013$).

For the R2 values of the nBR, statistically significant main effects were seen for *Time* ($F_{1,19} = 14.55$, $P = .001$) and *Stimulus Intensity* ($F_{4,76} = 69.36$, $P < .001$), and a trend toward significance was seen for *Session* ($F_{2,38} = 3.17$, $P = .054$) (Fig 8). A significant interaction was seen between *Time* and *Stimulus Intensity* ($F_{4,76} = 3.61$, $P = .010$) (Fig 8b). Post hoc analysis of the main effect of *Time* showed a significant decrease in the R2 values after application when compared to baseline ($P = .001$). The post hoc analysis of the main effect of *Stimulus Intensity* showed a significant increase in the R2 values at all the applied stimulus intensities when compared to 100% of I_P ($P < .008$). Post hoc analysis of the interaction between *Time* and *Stimulus Intensity* showed no significant differences in any relevant pairwise comparisons.

Table 3 Psychosocial Status of the Study Participants

Instrument		Scores or no. of participants
OHIP-49, mean ± SD scores	Functional limitation	6.5 ± 0.7
	Physical pain	10.3 ± 0.6
	Psychological discomfort	6.1 ± 0.5
	Physical disability	2.9 ± 0.3
	Psychological disability	2.6 ± 0.1
	Social disability	0.7 ± 0.1
	Handicap	0.7 ± 0.1
GCPS	No pain/disability	20
	Low intensity pain, without disability	0
	High intensity pain, without disability	0
	Moderately limiting	0
	Severely limiting	0
JFLS, mean ± SD	Mastication limitation	0.1 ± 0.2
	Mobility limitation	0.1 ± 0.2
	Verbal and emotional expression limitation	0
	Global	0.01 ± 0.1
PHQ-9	No depression	19
	Mild depression	1
	Moderate depression	0
	Moderately severe depression	0
	Severe depression	0
GAD-7	No anxiety	19
	Mild anxiety	1
	Moderate anxiety	0
	Severe anxiety	0
PHQ-15	No physical symptoms	17
	Mild physical symptoms	3
	Moderate physical symptoms	0
	Severe physical symptoms	0
OBC	Normal	11
	Low risk for TMD onset	8
	Higher risk for TMD onset	1

Data are presented as no. of participants unless otherwise indicated. SD = standard deviation; OHIP-49 = Oral Health Impact Profile; GCPS = Graded Chronic Pain Scale; JFLS = Jaw Function Limitation Scale; PHQ-9 and -15 = Patient Health Questionnaire; GAD-7 = Generalized Anxiety Disorder; OBC = Oral Behavior Checklist.

Correlations Between QST and nBR Parameters

Correlation analyses between the QST parameters and nBR responses did not yield any statistically significant correlations after application of Bonferroni correction. This was true for correlations assessed between QST parameters and AUC of nBR responses at baseline and after applications, as well as between the ΔAUC nBR responses and ΔQST parameters.

Questionnaires

The OHIP-49 and DC/TMD questionnaires presenting the participants' psychosocial statuses are shown in Table 3. After Bonferroni correction, no significant correlation was seen between the questionnaire data and NRS pain and unpleasantness scores.

Discussion

The present study was the first to examine somatosensory disturbances induced by topical cutaneous application of capsaicin and EMLA to the trigeminal region using both qualitative and quantitative psychophysical tests, somatosensory mapping, and the electrophysiologic nBR.[13] Overall, the present study showed that a 15-minute topical application of 0.1% capsaicin to the trigeminal region evoked pain and unpleasantness and led to varied somatosensory responses in healthy participants. In contrast, EMLA application, as expected, led to a more uniform loss of somatosensory function.

The baseline QST values in the present study were similar to the reference values provided by DFNS for the face.[12]

0.1% Capsaicin Model

On average, application of capsaicin produced moderate pain and unpleasantness, which is similar to previous studies.[3,5,20,40,46] The maximum NRS pain and unpleasantness scores were not significantly correlated with the psychosocial questionnaires. One possible explanation for this could be that the present study included only healthy volunteers with low scores and low variation in the applied questionnaires (Table 3).

Topical cutaneous capsaicin application induces two areas of reduced thresholds for pain: a primary zone at the site of application exhibiting heat hyperalgesia, and a secondary surrounding zone exhibiting mechanical hyperalgesia.[47–52] The present study was performed in the primary zone and did not demonstrate significant changes in mechanical sensitivity after capsaicin application on a group mean level, in accordance with previous studies.[47,53,54] Interestingly, capsaicin application caused a significant mean loss of nonnociceptive thermal function (WDT, TSL) and cold, but not heat, hypoalgesia. Since the primary effect of capsaicin is on the heat-activated TRPV1,[55] it is expected to predominantly affect WDT and HPT. However, a few studies have shown the presence of cold hypoalgesia after topical capsaicin application.[9,56] Although the underlying mechanism is unclear, rat models have shown that an inversely acting co-expression might exist between TRPV1 and cold-sensing TRPM8.[56–58] It has been theorized that the release of inflammatory mediators after capsaicin application shifts the thresholds of TRPM8-expressing neurons, thereby possibly explaining the presence of cold hypoalgesia.[56,59]

Application of capsaicin induced a varied individual response among the test population, with participants showing somatosensory hyper- and/or hypofunction among different sensory modalities, similar to the phenotypical heterogeneity seen across neuropathic pain conditions[43,60] (Figs 3a and 4). The variations were apparent in the somatosensory QST *z* score profiles and the QualST findings (Figs 3a and 4). However, the mean somatosensory profile indicated that all the mean QST parameters after capsaicin application were within the normal range (Fig 3d). The presence of both somatosensory hyper- and hypofunction after capsaicin application suggests that the group mean is not representative of the effect.[43,60] The inter-individual variation in somatosensory changes seen with the capsaicin model may also apply to certain somatosensory aspects of other chronic pain conditions such as burning mouth syndrome, postherpetic neuralgia, complex regional pain syndrome, and temporomandibular disorders pain.[43,60–63] In corroboration with the QST parameters, the QualST also showed a varied response among the participants after capsaicin application. The QualST pattern of hyper-, hypo-, and normal sensitivity was similar to what has previously been reported in patients with atypical odontalgia.[14] In agreement with the study by Agbaje et al,[20] capsaicin application led to the least agreement between QST and QualST for all test modalities (30% to 60% agreement), with responses to pinprick stimulation showing the highest agreement (Table 2, Fig 5). In the absence of a gold standard, QualST may still be useful as a quick screening test.[14,20,39] Although a previous study has shown good to excellent agreement between intraorally performed QST and QualST in AO patients for all three stimulus modalities, future studies performed extraorally in different orofacial pain conditions may prove beneficial.[39]

For the nBR assessment, the present study used a custom-built "nociceptive-specific" electrode designed to stimulate the nociceptive afferents as selectively as possible.[15,34] Two previous studies have assessed the effect of capsaicin on the blink reflex.[5,64] Of these two studies, de Tommaso et al used a non–"nociceptive-specific" stimulus electrode to elicit the blink reflex by stimulation of the supraorbital nerve (V1) region, while capsaicin was applied to the skin of the hand.[64] In the study by Baad-Hansen et al, the stimulation site was on the skin overlying the infraorbital (V2) or mental nerve (V3), and the capsaicin was applied intraorally.[5] This difference in the site of stimulation to elicit nBR and the site of capsaicin application constitutes a major difference between these two studies and the present study, where the site of electrical stimulation was the same as the site of capsaicin application. However, the present study stands in agreement with de Tommaso et al regarding the lack of changes in the electrical I_0 and I_P.[64] Also, unlike the present study, both de Tommaso et al and Baad-Hansen et al showed a significant reduction in pain scores and R2 values after capsaicin application.[5,64] These reductions in the nBR responses were attributed to activation of the endogenous pain inhibitory systems instead of being a direct effect because of differences between the application site and test site in the two studies.[5,64] It is important to note, however, that the 0.1% concentration of capsaicin used in this study may not have been sufficient to induce significant changes in the nBR responses, and further studies may assess the effect of different concentrations of capsaicin on the nBR responses.

5% EMLA Model

As expected, the topical application of EMLA did not lead to pain, but a few participants reported low levels of unpleasantness. The QST demonstrated a significant loss of somatosensory function regarding both thermal and mechanical parameters in accordance with other studies.[65,66] This effect may be considered similar in character to the loss of somatosensory function seen in some trigeminal nerve damage patients.[43] In the QualST, all participants reported hyposensitivity to cold and pinprick stimuli after EMLA application, in agreement with the QST findings. However, the response to the tactile stimulus showed the lowest agreement between QualST and QST (60%). Also, 10% of participants reported normal sensitivity to tactile stimuli in QualST after

EMLA application. The duration of application and differential permeation of the EMLA agent to deeper layers could explain the lack of change in sensitivity to tactile stimulation in some participants.[67]

After EMLA application, the nBR revealed a significant increase in the electrically evoked sensory and pinprick thresholds without a significant change in the R2 responses. This is in agreement with a previous study using non–"nociceptive-specific" stimulus electrodes in V1, where topical EMLA was applied to the stimulus area for longer periods than in the present study (60 to 120 minutes).[68] Also, the present results are in agreement with Kaube et al, who showed lack of change in R2 values after a 45-minute application of 2.5% EMLA to the stimulation site using stimulus intensities above 1.2 mA with a "nociceptive-specific" electrode.[15] Additionally, in the present study, electrically evoked pain scores obtained during the nBR examination were significantly reduced after EMLA application for all suprathreshold stimulation intensities, in agreement with another study.[68]

Correlations Between QST and nBR Parameters

No significant correlations were seen between the QST measures of sensory and pinprick thresholds (MDT, MPT) and the electrically evoked thresholds (I_0, I_P) for either model, before or after application. However, Komiyama et al, using a non–"nociceptive-specific" electrode, assessed the correlation between the electrically and mechanically evoked I_0 and I_P and found a significant correlation for I_P, but not for I_0.[69] It is important to note that the I_0 determination was performed in a similar way to the present study. However, I_P was assessed based on 13 fixed intensities ranging from 5 to 35 mA, unlike the present study, where I_P was determined similarly to I_0.[69] Moreover, in Komiyama et al,[69] the electrical and mechanical stimuli were not applied to the same skin site, with the electrical stimulus applied to the skin above the mental nerve and the mechanical stimulus applied to the skin overlying the masseter muscles. The present study did not show any significant correlations between any of the QST parameters and the nBR NRS pain scores and R2 values, concordant with other studies showing a lack of significant correlations for the psychophysical and electrophysiologic responses between different stimulus modalities.[70,71]

Conclusions

In conclusion, 0.1% capsaicin applied topically for 15 minutes produced somatosensory changes with large inter-individual variations in degree and direction, whereas 5% topical EMLA application led to a more uniform loss of somatosensory function regarding thermal and mechanical QST parameters. However, neither capsaicin nor EMLA, in the current concentration and application times, were sufficient to cause significant changes in the R2 values of the nBR. The perceived somatosensory changes and the QST and QualST findings after capsaicin and EMLA application mimicked certain somatosensory disturbances seen in patients with trigeminal nerve damage when assessed using such techniques. Therefore, topical application of capsaicin and local anesthetics may be considered useful for modeling of some of the somatosensory aspects of trigeminal nerve injury.

Acknowledgments

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