Entropy of Masseter Muscle Pain Sensitivity: A New Technique for Pain Assessment

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Aims: To test whether manipulation of mechanical pain sensitivity (MPS) of the masseter muscle is reflected in quantitative measures of entropy. **Methods:** In a randomized, single-blinded, placebo-controlled design, 20 healthy volunteers had glutamate, lidocaine, and isotonic saline injected into the masseter muscle. Self-assessed pain intensity on a numeric rating scale (NRS) was evaluated up to 10 minutes following the injection, and MPS was evaluated after application (at 5 minutes and 30 minutes) of three different forces (0.5 kg, 1 kg, and 2 kg) to 15 different sites of the masseter muscle. Finally, the entropy and center of gravity (COG) of the pain sensitivity scores were calculated. Analysis of variance was used to test differences in means of tested outcomes and Tukey post hoc tests were used to adjust for multiple comparisons. **Results:** The main findings were: *(1)* Compared with both lidocaine and isotonic saline, glutamate injections caused an increase in peak, duration, and area under the NRS pain curve ($P < .01$); *(2)* A pressure of 2 kg caused the highest NRS pain scores ($P < .03$) and entropy values ($P < .02$); *(3)* Glutamate injections caused increases in entropy values when assessed with 0.5 kg and 1.0 kg but not with 2.0 kg of pressure; and *(4)* COG coordinates revealed differences between the x coordinates for time ($P < .01$) and time and force for the y coordinates ($P < .01$). **Conclusion:** These results suggest that manipulation of MPS of the masseter muscle with painful glutamate injections can increase the diversity of MPS, which is reflected in entropy measures. Entropy allows quantification of the diversity of MPS, which may be important in clinical assessment of pain states such as myofascial temporomandibular disorders. *J Oral Facial Pain Headache 2017;31:87–94. doi: 10.11607/ofph.1756*

Keywords: *entropy, mechanical sensitization, musculoskeletal pain, pain assessment, palpation*

Pain is a complex, subjective feeling that involves different aspects such as intensity, location, distribution, expectation, and emotional and motivational states.[1–4] The complex nature of pain makes it challenging for pain sufferers to describe their pain and for health professionals to assess it. Several aspects of pain such as its perceived intensity,[5] location, and quality,[6] as well as the assessment of pain-related disability,[7] are essential in order to diagnose, explain, and manage pain. Manual palpation is a common clinical method used to evaluate mechanical pain sensitivity (MPS) and is an important part of the clinical examination of temporomandibular disorders (TMD)[8] and other musculoskeletal pain conditions including tension-type headache[9] and fibromyalgia.[10] The reliability of manual palpation applied to the masticatory muscles is normally considered adequate but not optimal.[11–13] Several devices have been developed to address this problem.[14,15] Nevertheless, the unreliability of assessment of mechanical sensitivity has not been completely resolved as factors that can influence outcomes of manual palpation persist, such as different palpation techniques, difficulty in localizing assessment sites, and changes caused by repeated palpation.[16]

Morphologic, histologic, and physiologic differences within the masseter muscle indicate a functional compartmentalization.[17–19] It would then be expected that pain perception in the masseter muscle

may vary depending on which part of the muscle is affected by noxious stimuli and examined. Therefore, a systematic assessment of the spatial distribution of MPS in the masseter muscle may contribute new and crucial information on characteristics of orofacial muscle pain.

Experimental pain studies have reported that an injection of glutamate into the masseter muscle of healthy human participants reliably evokes pain that shares many characteristics of persistent muscle pain in TMD patients.[20] Furthermore, a more uniform spatial distribution of electromyographic (EMG) activity of the masseter muscles has been observed following painful injections of glutamate.[21] Moreover, other investigations have demonstrated that the spatial distribution and entropy measures of EMG signals might be useful and valuable to clinically evaluate pain following an intervention.[22,23] Therefore, it may be that Shannon entropy,[24,25] which measures the complexity and the degree of diversity of information, could be used to assess localized muscle pain sensitivity in response to standardized palpation with a palpometer, which has been shown to cause less test-retest variability and provides a more accurate pressure stimulus than manual palpation.[14] Thus, the aim of this study was to test whether manipulation of MPS of the masseter muscle is reflected in quantitative measures of entropy.

Materials and Methods

Participants

A total of 20 healthy student volunteers (10 men, mean age: ± standard deviation [SD]: 26.5 ± 3.2 years; 10 women, mean age ± SD: 25.2 ± 4.0 years) were recruited from Aarhus University. All participants were without signs or symptoms of TMD according to the Research Diagnostic Criteria for TMD (RDC/TMD)[26] and had no complaints of orofacial pain. The study protocol followed the guidelines of the Declaration of Helsinki II and had the approval from the Regional Ethics Committee. The participants signed an informed consent document after receiving thorough written and oral information about the experiment. Exclusion criteria included pregnancy (participant-based report), fibromyalgia,[27] and the use of analgesics within 2 days of the planned experimental sessions.

Study Design

The study was performed as a randomized, single-blinded, placebo-controlled design. At each session, participants had either glutamate, isotonic saline (control), or lidocaine injected into the mid-portion of the masseter muscle (Fig 1a). The order in which solutions were injected was randomized before the first session, and the injection side was randomized for session 1. In session 2, the injection was done on the side opposite from that in session 1. In session 3, the injection was administered on the same side as the first session. Time between sessions was at least 5 days. Assessments of MPS were done at baseline and 5 and 30 minutes after injections. Furthermore, participants were asked to score their perceived intensity of pain on a 0–10-cm electronic visual analog scale (VAS) continuously for 10 minutes following each injection.

Injection Administration and Perceived Pain Intensity

Injections of either glutamate (0.5 mL, 1 mol/L; Ajinomoto Co),[20] lidocaine (0.5 mL, 0.9%), or isotonic saline (0.5 mL) were given as a bolus into the masseter muscle of the participants following previously described protocols.[28–32] A 27-G needle was used and the 0.5-mL volume was injected over 10 seconds. The participants were then instructed to continuously rate the perceived pain intensity evoked by each injection on a 0–10-cm VAS for 10 minutes. A computer sampled the VAS signals every 2 seconds. The lower endpoint of the VAS was labeled "no pain at all" and the upper endpoint was labeled "the most pain imaginable." Peak pain (VAS peak) intensity was measured as the peak VAS score; the area under the VAS curve (VAS AUC) was used to obtain a measure of the overall amount of pain, and the onset to offset of pain was determined from the VAS profiles and used as a measure of pain duration (VAS duration).

MPS

Numeric Rating Scale

The anterior-posterior and inferior-superior borders of the masseter muscle were identified by palpation during repetitive clenching by the participant, and the area was divided into 15 sites (3 × 5) (Fig 1a). The MPS was assessed on each of the 15 sites with 3 different forces (0.5 kg, 1.0 kg, 2.0 kg) applied using a palpometer (Palpeter, Sunstar Suisse SA).[14] The duration of a single palpation stimulus was approximately 2 seconds followed by an interstimulus interval of 2 seconds that allowed the participant to rate the perceived intensity on a numeric rating scale (NRS). The mean NRS scores were assessed for each of the 15 sites on the masseter muscle and for each of the injected substances as an overall assessment of MPS. The participants were carefully instructed in the use of the NRS, where 0 was defined as "no sensation at all," 50 was defined as "just barely painful," and 100 defined as "most pain imaginable."[28,33] Thus, scores < 50 characterized nonpainful sensations, and scores

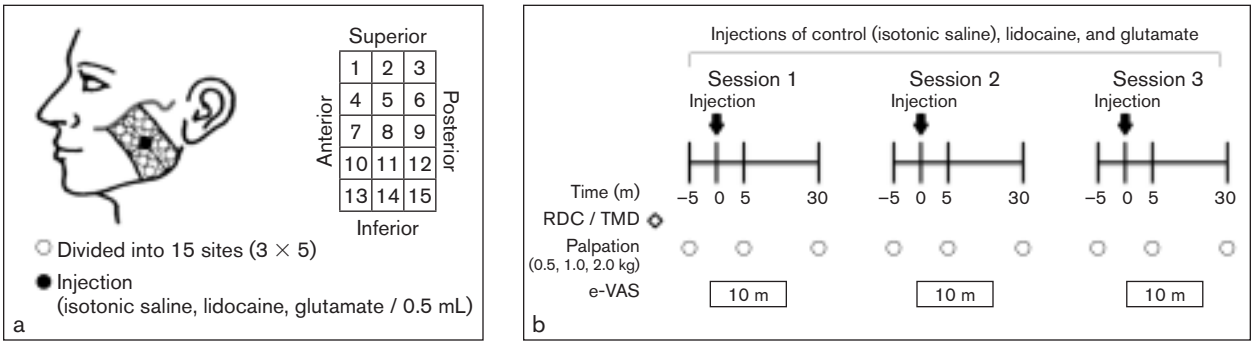

Fig 1 **(a)** The anterior-posterior and inferior-superior borders of the masseter muscle were identified and the area was divided into 15 sites (3 × 5). Injections of glutamate, lidocaine, or isotonic saline (0.5 mL) were given as a bolus into the mid-portion of the masseter muscle. **(b)** Both the injected side of the masseter muscle and the solution injected (glutamate, lidocaine, or isotonic saline) were randomized. Assessments of mechanical pain sensitivity (MPS) were done at baseline and at 5 and 30 minutes after injections. MPS was assessed with a numeric rating scale (NRS) at all 15 sites with 0.5, 1.0, and 2.0 kg of force applied by a palpometer. Furthermore, the participants were asked to continuously score their perceived intensity of pain on a 0–10-cm electronic visual analog scale (VAS) for 10 minutes following each injection.

> 50 denoted painful sensations. This NRS was chosen to encompass both nonpainful and painful sensations in one single scale.[28,33] The experimental protocol and sequence followed is illustrated in Fig 1b and was executed by one single researcher (TT).

Center of Gravity

The center of gravity (COG) calculation technique was based on principles related to spatial assessment of orofacial somatosensory sensitivity[34] and assessment of cortical mappings of motor-evoked potentials.[35] The COG coordinates (x = medial-lateral direction; y = superior-inferior direction) were defined as: Σxi*gridvaluei / Σgridvaluei; Σyi*gridvaluei / Σgridvaluei. The NRS scores from each of the 15 sites were used as the grid value. The weighting of the NRS scores in this way enabled the creation of a representational map of the "center" of NRS scores in quantitative terms; ie, each map in each participant generated an X and Y coordinate for assessment of MPS by the three different force levels. The two coordinates of the centroid of the NRS score (Gx and Gy) for the anterior-posterior and the inferior-superior directions were determined.

Entropy Measure

Entropy is a measure of diversity of values. The information, or Shannon, entropy for a particular experimental condition with a set of M possible outcomes is highest if all values have maximum diversity, whereas the minimum value of entropy is 0 if all outcomes are equal. In the context of diversity of MPS scores of the masseter muscle, entropy indicates the degree of diversity of the 0–100 NRS sensitivity scores, with higher entropy values corresponding to more diverse intensity registers of the NRS scores over the grid. Entropy was calculated in Excel from 15 NRS scores from each session and time point assessment.

Statistical Analyses

Analysis of variance (ANOVA) was used to test differences in means of VAS pain score outcomes (VAS peak, VAS duration, and VAS AUC) using sex (2 levels) and session (3 levels: glutamate, lidocaine, or isotonic saline) as factors. The NRS scores were tested by using sex, session, time (baseline, 5 minutes, and 30 minutes in reference to the injection time), and force (3 levels: 0.5 kg, 1.0 kg, and 2.0 kg) as factors (Fig 1a). The first ANOVA analysis was done for the averages of the NRS scores of the 15 sites of the grid by using sex, session, time, and force as factors. A second ANOVA analysis for the individual NRS scores was done separately for each different session by using sex, time, force, and site as factors. The scores of entropy and COG coordinates (x and y coordinates tested separately) of palpation were analyzed with multiple ANOVA with the following factors: sex, session, time, and force. Tukey post hoc test was used to adjust for multiple comparisons. For all tests the significance level was set at $P < .05$. Mean (± SD) values are reported in the text and figures.

Results

Perceived Pain Intensity

Peak pain intensity on the 0–10 VAS was 8.1 ± 2.3 following the injection of glutamate, 1.2 ± 1.6 following the injection of lidocaine, and 2.4 ± 2.9 following the injection of isotonic saline. ANOVA analyses showed a significant effect of session on the peak, duration, and AUC ($P < .01$). Moreover, post hoc analyses showed significantly higher values for the glutamate session compared with the other two sessions ($P < .01$), but no differences between control

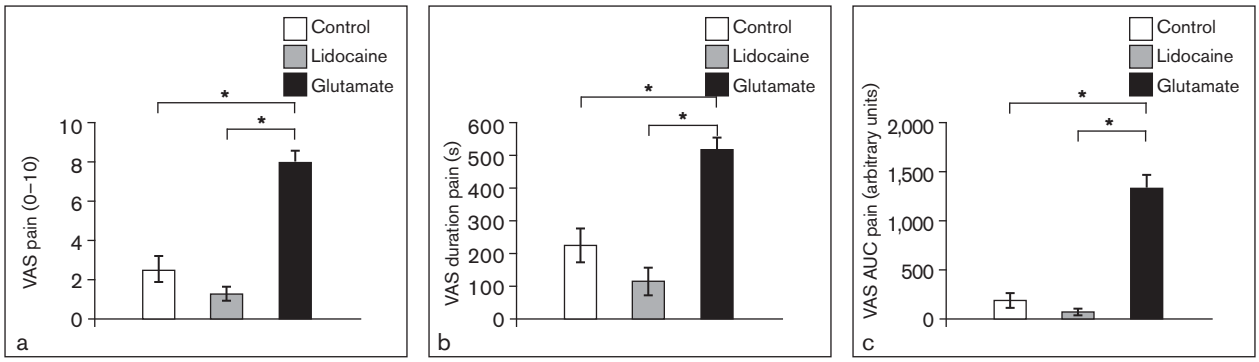

Fig 2 The bar graphs show the visual analog scale (VAS) outcome parameters. Significant differences were noted between the glutamate session and the lidocaine and isotonic saline session outcomes for **(a)** peak pain intensity, **(b)** pain duration, and **(c)** area under the curve (AUC). (*$P < .01$).

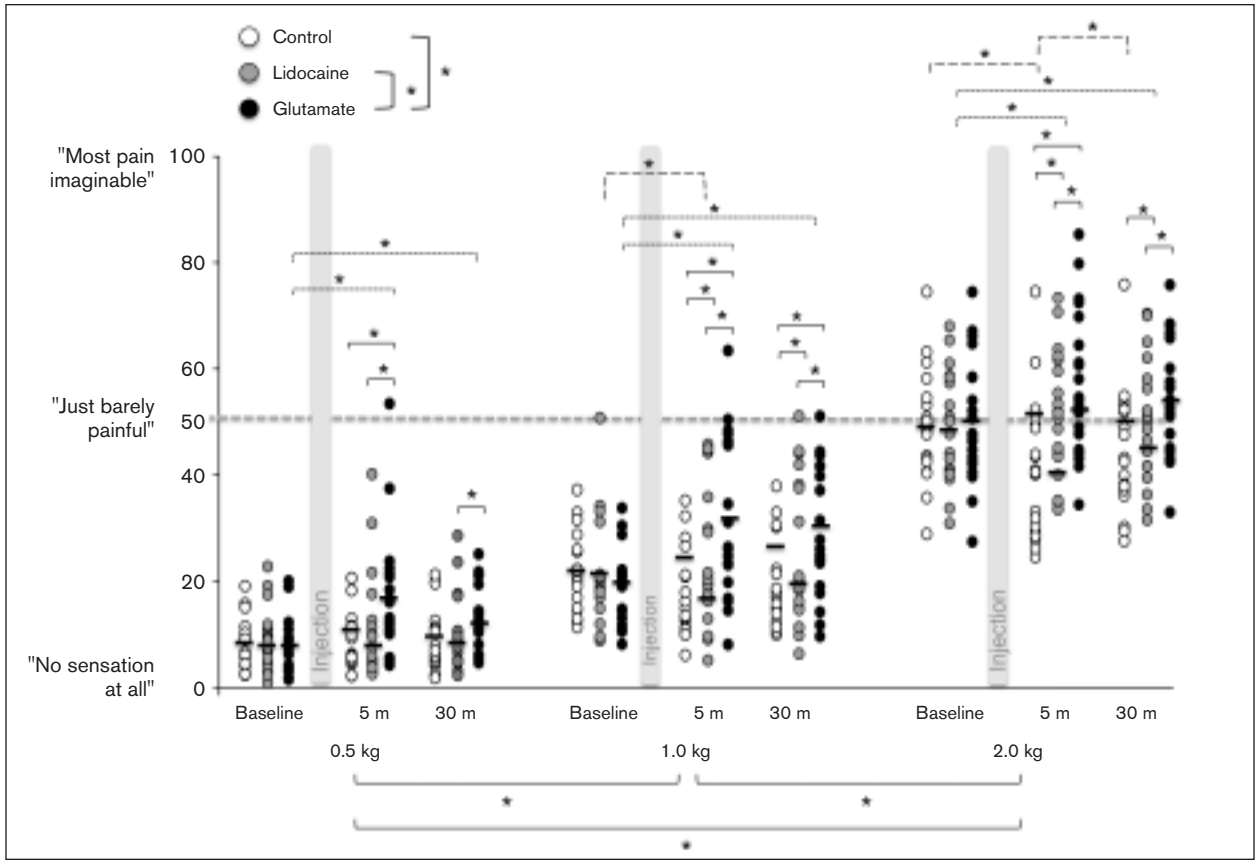

Fig 3 The graph shows the average of the 15 NRS scores of each participant as a circle, and group averages are shown as a horizontal line. Significant differences were noted between injected substance, time point, and force (*$P < .03$). Post hoc analyses showed that NRS scores were significantly increased following glutamate injection compared to lidocaine and isotonic saline injections (*$P < .03$). Analyses also showed that NRS scores when 2.0 kg of force was used were significantly different from those when 1.0 kg was used, and that using 1.0 kg of force produced significantly higher NRS scores than the 0.5-kg force (*$P < .03$).

and lidocaine ($P > .20$) on any of the VAS outcomes. Results are shown in Fig 2.

NRS Scores

ANOVA analysis of the averages of NRS scores for palpation of the 15 sites of the grid (Fig 1a) showed significant overall effect of session, time, and force levels ($P < .03$) (Fig 3). This analysis also showed significant interactions for session × time, sex × force levels, session × force levels, time × force levels, session × time × force levels, and sex × session × time × force levels ($P < .03$). ANOVA analyses for the individual NRS scores for each of the different sessions are shown in Fig 3.

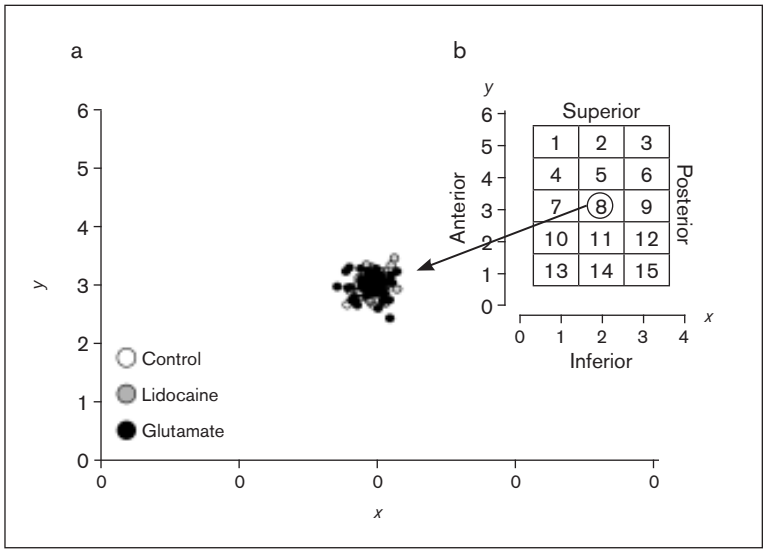

Fig 4 (a) The center of gravity (COG) of the MPS scores was plotted for each individual (session, time, and force) on a x/y coordinate system with 3.5y and 2.5y corresponding to the superior and inferior limits, respectively, and 1.5× and 2.5× corresponding to the anterior and posterior limits, respectively, of site 8. **(b)** The assessment grid of the masseter muscle is shown overlaying an x/y coordinate system.

COG

ANOVA analysis of COG coordinates revealed significant differences between the x coordinates for time ($P < .01$) and between time and force for the y coordinates *(P* < .01). There was a significant interaction for sex × time × force ($P < .01$) for the x coordinates and for session × time ($P < .01$) for the y coordinates. Post hoc analysis for the x coordinates showed a significant difference between baseline and 30 minutes after injection ($P < .01$). It also showed a significant difference for the y coordinates when comparing baseline to 5 and 30 minutes after injection ($P < .05$) and when comparing 0.5 kg to 1 and 2 kg ($P < .03$).

The COG of the MPS coordinates was plotted graphically to see if any of the factors affected its location. There were no relevant clinical changes in the location of the COG in any condition despite the significant but very small differences outlined above (Fig 4).

Assessment of MPS Entropy

ANOVA analysis of the entropy of the 15 NRS scores showed overall statistically significant differences between sessions, time points, and forces ($P < .01$). There were significant interactions for session × time, sex × session × force, and session × time × force ($P < .03$). Post hoc tests showed that the glutamate session had significantly higher entropy values than the other two sessions ($P < .02$). Post hoc analyses of the interaction between session, time, and force showed significant differences at 5 and 30 minutes after injection of glutamate when the MPS was assessed by using 0.5- and 1.0-kg forces ($P < .01$), but there were no significant differences when a force of 2.0 kg was used (Fig 5). Baseline assessments showed significantly lower entropy scores when compared with the two other time points ($P < .01$) (Fig 5). Finally, it was observed that increasing the force increased the entropy scores and that there were significant differences in the scores between the three forces ($P < .01$) (Fig 5).

Discussion

The main findings in this study were: *(1)* Based on the concept of entropy, glutamate injections (but not lidocaine or isotonic saline injections) increased the diversity of the masseter MPS scores; *(2)* Glutamate injections caused increases in entropy values when assessed with 0.5 and 1.0 (but not 2.0) kg of force applied to the injected masseter muscle; *(3)* The more force was applied to the masseter muscle the more entropy values increased; *(4)* The COG of MPS scores did not change its location on the grid before or after any type of injected solution; and *(5)* Applying 2.0 kg of force to the masseter muscle was likely to evoke pain in healthy subjects, which was not seen when applying 0.5 and 1.0 kg.

Perceived Pain Intensity Ratings

In this study, reported pain levels were similar to previous experiments with glutamate-evoked pain in the masseter muscle.[28,36,37] Moreover, this study showed that following lidocaine injection, small pain levels were reported that were not significantly different from the control (isotonic saline) injections. This may be due to mechanical trauma caused by the needle insertion or the bolus volume that was injected.[32,36,38]

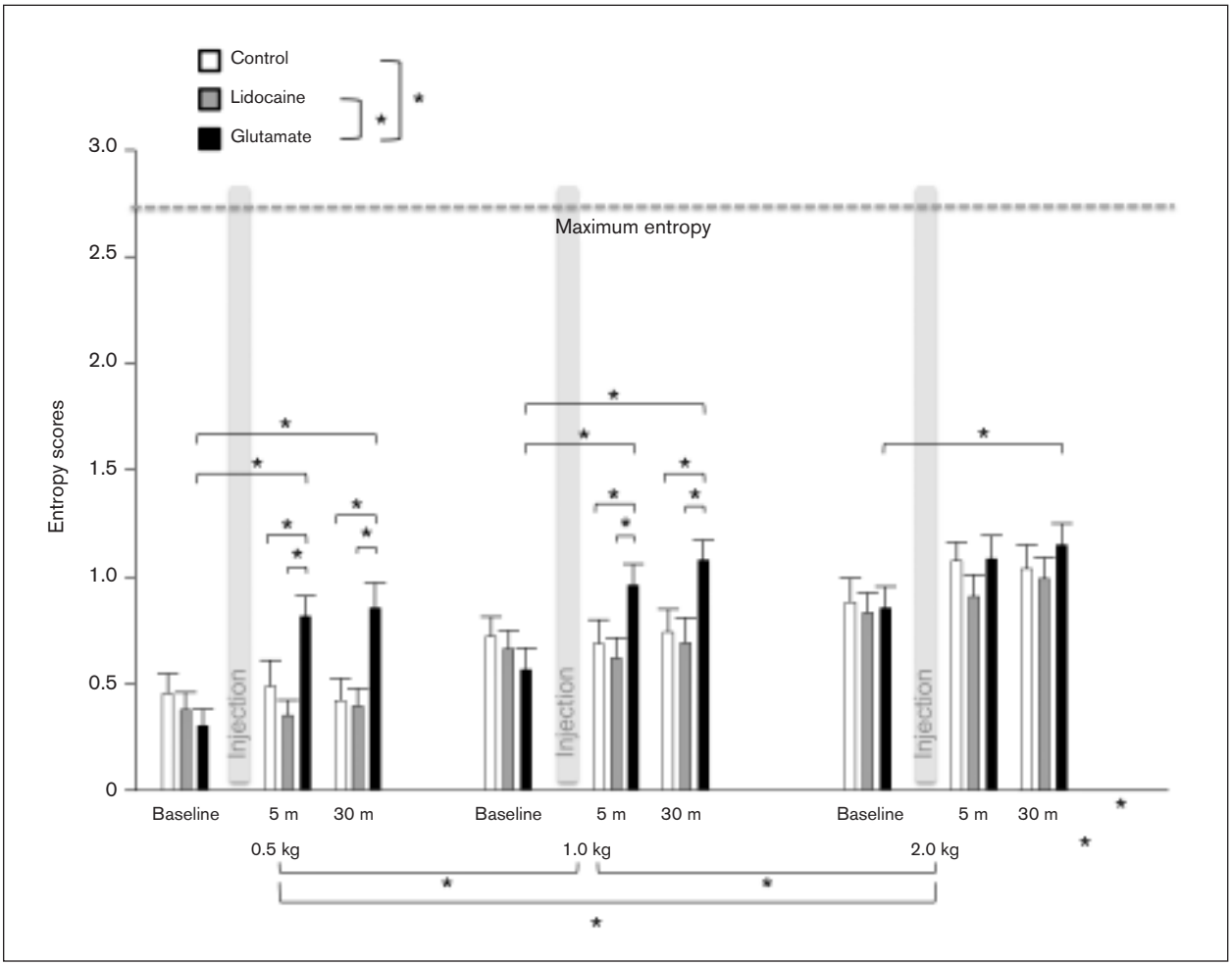

Fig 5 The bar graph shows the average (SE) entropy for each variable. There were significant differences between groups for injected substance, time point, and force (*P < .02). Post hoc analysis showed that entropy scores were significantly higher for the glutamate injection when compared to lidocaine and isotonic saline (*P < .02), and also that the highest entropy was achieved when applying the 2-kg force followed by 1.0 kg and 0.5 kg.

Assessment of MPS

Glutamate injection evoked a significant increase in MPS when compared with control and lidocaine for all forces, whereas the lidocaine injection induced a significant decrease in MPS when compared with control injections when assessed with 1 and 2 kg, but not 0.5 kg, of force. The present study replicated earlier findings of mechanical sensitization triggered by glutamate injections[20] as well as decreased sensitivity following lidocaine injections.[34] Furthermore, NRS scores increased as higher forces were applied to the masseter muscle in all sessions.

COG

Results showed that the COG MPS coordinates varied significantly in the x axis between baseline and 30 minutes after injection, and in the y axis when comparing baseline to 5 and 30 minutes after injection (P < .05) and when comparing 0.5 kg to 1.0 and 2.0 kg of force. Despite these significant but very small differences, the graphical representation of the COG for time, session, and force shows an almost nonexistent variation in the COG location. It can be concluded that although there were significant differences for the x and y coordinates, they are not clinically relevant, and that neither pain nor desensitization induces a clinically significant shift in the distribution of COG coordinates.

Entropy of MPS Scores

The main novelty of this study was the use of the concept of entropy[25] to assess the diversity of MPS scores within the spatial distribution of the masseter muscle. Recently, it has been proposed that the distribution of pain as a variable should be considered to enrich the characterization of different diagnoses

of myofascial pain.[8] However, there is little information available about the distribution and the diversity of pain scores for myofascial pain. Moreover, it is not clear if the diversity of MPS within the masseter muscle will have any significance for pain physiology.

The low entropy scores (< 1.00, with a highest score possible of 2.70) suggest that the MPS scores of the masseter muscle were quite uniform. This means that the scores registered in the 15 sites of the masseter muscle did not differ substantially from each other. Nevertheless, it was seen that the entropy of MPS scores was significantly increased following glutamate injection when compared to lidocaine and isotonic saline. Furthermore, an interesting finding was that significant increases in entropy of MPS scores occurred in the glutamate session when applying 0.5 kg and 1.0 kg of force but not when applying 2.0 kg. This may occur because the NRS scores of 2.0 kg were already more diverse than the 0.5 kg and 1.0 kg forces at baseline; and as such, following the injection of glutamate, the NRS scores after 2.0 kg of mechanical stimulation did not differ enough to cause further increases in entropy scores. This did not occur for the baseline control and lidocaine values for 0.5 kg and 1.0 kg, as the values following application of these forces were not so diverse. This would suggest that applying 2.0 kg of force during clinical examination of a painful masseter muscle is not adequate for discriminating between the more painful and less painful parts of the muscle.

Moreover, the present results suggest that the larger the force that is applied, the more diverse the pain scores, and that in healthy subjects the perception of mechanical pressure is very unlikely to be painful when applying forces ≤ 1.0 kg, and that it is more likely to be painful when applying 2.0 kg of force. This finding has clinical implications, as it could be difficult to determine abnormal mechanical sensitization responses when a nonstandardized or a high-pressure force (≥ 2.0 kg) is applied during the clinical examination. Therefore, these results support the importance of applying appropriate and standardized forces at the time of clinical examination as well as respecting the concept of familiar pain during the same examination.[8,26,39]

The entropy analyses of the effect of lidocaine injections on the distribution of the values of MPS did not significantly differ from the effect of isotonic saline. On the other hand, since injections of glutamate increased the entropy of MPS scores and the bolus volume was the same as the lidocaine and saline injections, it can be speculated that this increase in entropy is likely related to a selective activation of NMDA receptors throughout the masseter muscle by the glutamate.[32,36]

Limitations

It must be acknowledged that even though a glutamate-evoked pain model was used that mimics some characteristics of orofacial pain,[20] these results cannot be directly extrapolated to myofascial TMD because the unique characteristics of clinical chronic pain may affect its distribution and organization. Therefore, further research into the levels of entropy, including the entropy levels of patients with persistent orofacial pain, will have to be conducted.

Conclusions

These results suggest that manipulation of MPS of the masseter muscle with painful glutamate injections can increase the diversity of pain sensitivity scores in the masseter muscle, which is reflected in the entropy measure. Entropy may allow quantification of diversity of muscle pain sensitivity, which may be important in clinical assessment of pain states such as myofascial TMD.

Acknowledgments

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