Title page

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Painful stimulation and transient blocking of nerve transduction due to local anesthesia evoke perceptual distortions of the face in healthy volunteers

Keywords

Dissociation; Local anesthesia; Orofacial pain; Painful stimulation; Perceptual distortions of the face.

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Abstract

Anecdotally, orofacial pain patients sometimes report that the painful face area feels ‘swollen’. Because there are no clinical signs of swelling, such illusions may represent perceptual distortions. In this study, we examine whether nociceptive stimulation can lead to perceptual distortion of the face in a way similar to that of local anesthesia. Sixteen healthy participants received injections of 0.4 mL hypertonic saline to induce short-term nociceptive stimulation, 0.4 mL Mepivacain (local anesthetics) to transiently block nerve transduction and 0.4 mL isotonic saline as a control condition. Injections were performed in both the infraorbital and the mental nerve region. Perceptual distortions were conceptualized as perceived changes in magnitude of the injected areas and the lips, and it was measured using 1) a verbal subjective rating scale and 2) a warping procedure. Prior to the study, participants filled in several psychological questionnaires. This study shows that both nociceptive stimulation ($p<0.05$) and transient blocking of nerve transduction ($p<0.05$) can lead to perceptual distortion of the face. A test-retest experiment including nine new healthy subjects supported the results. Perceptual distortions were positively correlated with the psychological variable dissociation in several conditions ($p<0.05$). Perceptual distortions may therefore be influenced by somatosensory changes and psychological mechanisms.

Perspective

Knowledge of the factors that influence the perception of the face is important to understand the possible implications of perceptual distortions in orofacial pain disorders (and possibly other chronic pain states). Such information may ultimately open up for new treatment strategies for persistent orofacial pain.

Keywords:

Dissociation; Local anesthesia; Orofacial pain; Painful stimulation; Perceptual distortions of the face.

Introduction

Around 17-26% of the population reports to suffer from orofacial pain, of which 7-11% is persistent and accordingly substantially impacts these persons' quality of life[4]. While most acute facial pain conditions can be managed efficiently, treatment of persistent orofacial pain remains insufficient[7].

Anecdotally, patients suffering from persistent orofacial pain due to damage of nerve fibers sometimes report that the painful face area feels 'swollen' or 'different'. As there are no clinical signs to support this, these reports may represent a kind of disrupted body image or a 'perceptual distortion of the face'[14,22,25,37], and it can be speculated whether such phenomena may contribute to the maintenance of orofacial pain. Phrases like 'perceptual distortions' and 'body image disruptions' have been used interchangeably and cover somewhat different phenomena. However, common to such phenomena is a kind of disturbance in the way an individual *perceives* his/her body[14,25,37].

Perceptual distortions have been described following local anesthesia, e.g. the feeling of a 'swollen lip' after dental treatment[14,25,37]. Such phenomena have been related to cortical reorganization. This theory is justified by studies showing that transient blocking of nerve transduction due to local anesthesia can cause functional reorganization of the primary somatosensory cortex (S1)[6,28]. At present, no studies have systematically investigated perceptual distortions in orofacial pain patients. Nevertheless, perceptual distortions or body image disruptions have been observed in chronic pain states such as chronic back pain[20] and complex regional pain syndrome (CRPS)[18,21], where patients perceive the painful area differently from what it really looks like. It is unknown; however, which factors mediate such perceptual distortions. We speculate that these pain-related perceptual distortions involve nociceptive stimulation. Therefore, this study tests whether nociceptive stimulation can cause perceptual distortions.

As psychological processes are also known to influence chronic pain[16,35], it is relevant to test whether psychological phenomena like ‘dissociation’[5], ‘pain catastrophizing’[31], ‘somatosensory amplification’[2], ‘depression’[3], and ‘anxiety’[30] also contribute to perceptual distortion of the face in a top-down manner.

This is the first controlled study to test whether nociceptive stimulation can entail perceptual distortions of the face in a way similar to that of local anaesthetics. Sixteen healthy subjects were exposed to experimental pain to stimulate nociceptive receptors, local anesthesia to transiently block nerve transduction, and isotonic saline as a control condition. Injections were performed in the infraorbital and mental nerve regions of the face. Nine additional healthy subjects participated in a test-retest experiment. The study was explorative, and perceptual distortions were measured via verbal subjective reports and a warping procedure. Moreover, participants filled in a set of standardized psychological questionnaires in order to investigate if psychological variables interfered with the findings. Knowledge of factors that influence the perception of the face is important in order to understand the possible relation between orofacial pain and perceptual distortions. The following hypotheses were tested:

1) Nociceptive stimulation can lead to perceptual distortions of the face in a way similar to that of transient blocking of nerve transduction.

2) Psychological processes contribute to perceptual distortions of the face.

Materials and Methods

Participants

Sixteen healthy and pain-free participants were recruited to the main study (eight men and eight women) (mean age: 22.9, standard deviation (SD): 1.8) after they had given written informed consent. In a test-retest experiment, nine additional healthy subjects were included (one male and eight women) (mean age: 23.4, SD: 2.8). All participants were compensated with 750, - DKK for their participation. The study was approved by the Local Ethical Committee of the Central Denmark Region (ESDH 1-10-72-139-12) and conformed to the Declaration of Helsinki.

Injections

In each session, participants were given an injection of either 0.4 mL hypertonic saline (HS, pH value 7.4) to evoke medium-to-high-intensity pain for approximately 5 minutes, 0.4 mL local anesthesia (LA) (Mepivacain 10 mg/ml without vasoconstrictor (short duration)) in order to transiently block nerve transduction, or 0.4 mL isotonic saline (ISO) as a control condition. Although hypertonic saline has frequently been injected into the jaw muscles to induce experimental pain[32], this is, to our knowledge, the first study to use this procedure close to the trigeminal nerves.

Injection and rating sites

Injections were always performed on the right side of the face in the infraorbital nerve region (close to the infraorbital foramen) and the mental nerve region (close to the mental foramen). Injections followed the clinical guidelines for an infraorbital and mental nerve block[23]. The injection sites were selected because pilot testing had demonstrated that perceptual distortions could occur in these regions.

For injections in the infraorbital nerve region, participants were asked to evaluate perceptual distortions in both the infraorbital nerve region and the upper lip (see below). Likewise, when injections took place in the mental nerve region, participants were asked to estimate perceptual distortions in the mental nerve region and the lower lip. This division was based on pilot testing and nerve anatomy as the infraorbital nerve innervates the upper lip and the mental nerve innervates the lower lip. In practice, this meant that participants were instructed to focus on two different regions of the face when evaluating perceptual distortions following all injections.

Pain measures

In all conditions, participants rated their pain intensity on a 0 (no pain) to 10 (worst imaginably pain) numerical rating scale (NRS)[15]. Pain intensity measures relate to the painful sensations experienced in the test side of the face (the side that received the injections); thus, only one pain measure was obtained for each injection.

Perceptual distortion measures

The examination of perceptual distortions of the face performed in this study was explorative. Its primary aim was to clarify whether nociceptive stimulation of the face and transient blocking of facial nerve transduction due to LA can entail perceptual distortions at all. No brain imaging intended to clarify the underlying mechanisms of perceptual distortions was performed. The study was designed as a repeated measures study. Perceptual distortions of the face were defined as ‘changes in perceived magnitude of the concerned face areas’ (feelings of swelling or reductions) not related to clinical or physical signs. This definition is based on a pilot study which found that nociceptive stimulation of the face may often cause experiences of swelling of the affected face region. As this definition of a perceptual distortion is very subjective, we included two different measurement tools to strengthen the validity of the measures. The findings of the two measurement tools were compared in order to establish the consistency of the measures.

Measurement 1: Verbal subjective rating scale. Participants were asked to give a subjective estimate of the perceived magnitude of the face areas following injections: did the concerned regions feel larger (swollen), smaller, or the exact same size as the unaffected left side of the face. The comparison with the unaffected left side of the face was intended to give participants a frame of reference (with no perceived changes in magnitude) against which the perceived magnitude of the affected regions could be compared. If any changes in perceived magnitude of the face areas were reported, the participants were asked to give a subjective estimate of the perceived change on a scale ranging from -100% (indicating that the magnitude of the concerned face region was perceived half as large as the unaffected left side of the face), through 0% (meaning that no changes in magnitude of the face area was perceived), to +100% (indicating that the magnitude of the concerned face area was perceived twice as large as the unaffected left side of the face (swollen)). The verbal subjective rating scale has proven useful in pilot testing and was therefore used in this study. Measurement 2: Warping procedure (see Fig. 1). To strengthen the evaluation of the patients' perceptual distortions of their face, we developed and added a second procedure. Using the computer programme Abrosoft FantaMorph, we performed region-specific manipulations in which the four concerned face areas were gradually enlarged from normal to maximal distortion in a short, region-specific movie-clip (warp). These region-specific enlargements looked like swelling.

Fig. 1 close to here

Participants were instructed to assess any experiences of perceived swelling by interrupting the movie when the region on the manipulated face looked as they perceived their own face. An estimate of the perceived swelling was calculated as the mean of three runs. To increase the likelihood that participants could identify with the warped movie-clips, the warping procedure was based on a picture of each participant (on a white background and with a neutral expression). The warping procedure followed standardized algorithms so that results from all participants could be compared. On the basis of a coordinate system, the area for swelling of each region was calculated with reference to standardized points in relation to the size and the shape of each individual's face. The stepwise swelling (warps) of each region was made in separate movie-clips. For all participants, the area of the infraorbital nerve region was gradually enlarged by 30% with the location of the infraorbital foramen as the reference (origo). The area of the mental nerve region was also enlarged by 30%. In this case, the location of the mental foramen was used as reference (origo). In movie-clips where the lips were enlarged, three points of reference were chosen (outermost side of lips and the middle of the upper and lower boundary of the upper and lower lip, respectively). From these reference points, the area of the 'normal' lip was calculated, and the area was enlarged with either 150% (upper lip) or 70% (lower lip) (see Figure 2). This study was the first to use Abrosoft FantaMorph to illustrate perceptual distortions of the face. Hence, the warping procedure was developed specifically for this study. The reference points and the percentage-wise enlargement used to illustrate swelling were based on the author's assessment of the most realistic manipulation. Because of 2D restrictions, the manipulations could easily look artificial, which we tried to avoid. When the reference points and percentage-wise enlargement were set, these standardized manipulations were used on the pictures of all participants.

Fig. 2 close to here

The movie-clips were always run with the same speed (150 frames/min). In each session, participants could see one or two different warps because we wanted to focus on the infraorbital nerve region/upper lip and the mental nerve region/lower lip for injections in the infraorbital and mental nerve region. The computer manipulations were only used when participants had already reported perceived swelling of the particular region. Thus, the warping procedure was not used if participants reported ‘no changes in magnitude of the concerned face areas’ or ‘a reduction in magnitude of the concerned face areas’. The warping procedure was only used when participants reported perceived swelling of the affected region primarily due to technical limitations regarding the warps. However, pilot testing indicated that injections of experimental pain and LA consistently led to feelings of swelling and we therefore considered the warping procedure valid in combination with the subjective verbal reports. Moreover, no participants reported any reductions in magnitude of the concerned face areas in this study (for either injections of HS, LA or ISO). The warping procedure may therefore be valid despite the mentioned limitations.

Procedure

Before the first session, participants filled in psychological questionnaires. The experiment took place in a quiet room; and during the first session, participants underwent a standardized clinical examination to confirm normo-sensitivity on both sides of the face[1]. All participants went through six randomized, double-blinded, placebo-controlled sessions separated by at least 24 hours (3 injections x 2 regions). The participants and the experimenter were blinded with respect to the type of injection (HS, LA or ISO), as an independent researcher had beforehand prepared the needle. Most participants quickly realized the type of injection; however, a few participants were unfamiliar with LA and therefore a bit unsure about this procedure. Moreover, a few participants were unsure about the injections of HS versus ISO. After injections, participants regularly (30 sec, 5 min, 10 min, 30 min) rated pain intensity and perceptual distortions of the face (two regions) using both types of measuring techniques (see Fig. 3).

Fig. 3 close to here

Psychological questionnaires

The Danish version of the Dissociative Experiences Scale (DES-II)[5] was used to measure dissociative symptoms, which cover a wide array of experiences from mild detachment from immediate surroundings to more severe detachment from physical and emotional experiences. The DES-II consists of 28 questionnaires about dissociative experiences. One of these questions (item 19) refers to an individual's ability to ignore pain. We found it interesting to test whether this tendency alone was crucial for the experience of perceptual distortions. For this reason, scores of the DES-II questionnaire were calculated twice, first as a total of the 28 items and, secondly, as a total of 27 items (without item 19). Pain catastrophizing was assessed by means of the Danish version of the Pain Catastrophizing scale (PCS), which measures thoughts and feelings when experiencing pain[31]. The Danish version of the Somatosensory Amplification Scale (SSAS)[2] was used to measure somatosensory amplification, defined as a tendency to perceive normal somatic and visceral sensations as being relatively intense, disturbing, and noxious. Depressive symptoms were measured with the Danish version of Beck's Depression Inventory (second edition) (BDI-II), which measures psychological and physiological aspects of depression[3]. Anxiety was measured with the Danish version of Spielberger's State-Trait Anxiety Inventory (STAI) for adults, which assesses anxiety about an event and anxiety level as a personal characteristic, respectively[30]. For all psychological questionnaires, higher scores indicate a higher degree of the psychological factor under investigation.

Test-retest

To examine the reliability of the perceptual distortions of the face, we performed a test-retest experiment in which nine additional healthy participants underwent HS, LA, and ISO injections in the infraorbital nerve region. Injections were performed twice separated by approximately one month. The test-retest followed the exact same procedure as the main study except that injections were limited to the infraorbital nerve region and no psychological measures were included.

Statistics

Data were analysed using SPSS version 21. Data about perceptual distortions in both the main test and the test-retest experiment were analyzed using two-way repeated measures ANOVA. The dependent variable in these statistics is the magnitude of the perceived changes in size (perceptual distortions) (measured via the verbal subjective rating scale (-100% to +100%) or via the warping procedure (only perceived swelling)). The independent factors were 1) the time for measurements (30 sec, 5 min, 10 min, and 30 min after the injection were performed) compared with baseline (before injection took place) and 2) the type of injection (HS and LA) compared with the control condition (ISO). The F-statistics, degrees of freedom, as well as significance level is given for all main effects of the two-way repeated measures ANOVA. Higher F-statistics indicate a higher reported magnitude of the perceptual distortion. In statistics where Mauchly's test of sphericity is violated, the Greenhouse-Geisser test is reported. Post hoc tests were performed on data from the verbal subjective rating scale to obtain specific information about which means were significantly differently from each other (regarding time, injection, and time*injection). The consistency between the two types of measuring techniques (measurement 1: verbal subjective rating scale, and 2: warping procedure) was evaluated using correlation analysis. As the study was explorative, the examination of any involvement of psychological factors was made using correlation analysis between participants' scores on the psychological questionnaires. The magnitude of the perceptual distortions was calculated as the area under curve ranging from baseline to 10 min after injection (later time intervals were not included since perceptual distortions had entirely or nearly entirely disappeared 10 min after the injection). Finally, correlation analysis (Pearson's r) was conducted to compare the progression of reported pain intensity with the degree of perceptual distortion at the different measuring times (based on means). $P < 0.05$ was considered statistical significant.

Results

Perceptual distortions

Overall, the findings of this study indicate that nociceptive stimulation (injections of HS) as well as transient blocking of nerve transduction due to LA can lead to perceptual distortions of the face. All reports of perceptual distortions were expressed as perceived 'swelling'. Hence, no participants reported perceived reductions in magnitude of the affected face areas following injections of HS, LA, or ISO. Injections of HS almost exclusively entailed perceptual distortions in the injected areas (the infraorbital and the mental nerve region). No participants reported perceptual distortions of the lower lip following injections of HS in the mental nerve region. One participant out of sixteen reported perceptual distortions of the upper lip following injections of HS in the infraorbital nerve region. In opposite, injections of LA caused perceptual distortions in both the injected areas (the infraorbital and mental nerve region) and in the related lip. The results concerning perceptual distortions due to nocieptive stimulations and transient blocking of nerve transduction are shown in Tables 1 and 2 (main tests of the two-way repeated measures ANOVA) and Fig. 4 (post hoc tests). Fig. 4 also gives an overview of the temporal progression, magnitude, and distribution or spreading of the perceptual distortions (based on the verbal subjective rating scale).

Table 1 close to here

Table 2 close to here

Fig. 4 close to here

The reports of perceptual distortions of the face based on the different types of measurement were strongly correlated (see Table 3).

Table 3 close to here

Test-retest reliability of perceptual distortions

The test-retest performed in the infraorbital nerve region supported the robustness of perceptual distortions of the face caused by both nociceptive stimulation and transient blocking of nerve transduction due to LA (see Table 4). Data are only shown for the first test in the test-retest as the two tests performed were almost similarly (see Table 5 for inter-class correlations (ICCs) between the test-retest sessions).

Table 4 close to here

Table 5 close to here

Pain correlations

Correlation analyses revealed that the magnitude of the perceptual distortions (the perceived swelling) evoked by injections of HS ($p \leq 0.041$, $r \geq 0.89$) and ISO ($p \leq 0.005$, $r \geq 0.97$) were positively correlated with the participants' reported pain intensity. This was true for the magnitude of the perceptual distortions measured with both measurement tools. Contrary to this, the magnitude of the perceptual distortions evoked by transient blocking of nerve transduction due to LA was not positively correlated with the reported pain intensity in any regions ($p = 0.261$, $r \leq 0.62$) (see Table 6 for mean pain intensity).

Table 6 close to here

Psychological variables

When psychological factors were correlated with conditions where perceptual distortions were pronounced, we found that the perceptual distortions were positively correlated with the psychological factor 'dissociation'[5] in several conditions. These results did not differ if we removed the question regarding the participant's ability to ignore pain (item 19) (Table 7). No significant correlations were found between perceptual distortion of the face and the psychological variables: pain catastrophizing[31], somatosensory amplification[2], anxiety[30], or depression[3].

Table 7 close to here

Discussion

Perceptual distortion of the face

To our knowledge this is the first controlled study showing that nociceptive stimulation can cause perceptual distortion of the face in a way similar to that of transient blocking of nerve transduction due to LA. This finding confirms our first hypothesis which suggests that nociceptive stimulation of the face can, indeed, lead to perceptual distortions. The present study combined verbal subjective reports with a more sophisticated warping technique, and both methods supported the existence of perceptual distortions. Moreover, the test-retest experiment supported the perceptual distortions measures, thereby indicating that perceptual distortion of the face is a robust phenomenon.

Several participants reported perceptual distortions of the face. These distortions were consistently described in terms of perceived swelling of either one or both measured face areas. Nevertheless, the temporal progression and the spreading of the perceptual distortions differed across injection types (see also Fig. 4). Regarding temporal progression, nociceptive stimulation caused perceptual distortions shortly after the injections were performed and while the pain intensity was high. In contrast, perceptual distortions due to LA arose more slowly and stayed for a longer time. With regard to spreading, perceptual distortions following nociceptive stimulation were reported only in the injected areas (the infraorbital and mental nerve region) and thereby stayed local. Transient blocking of nerve transduction also caused perceptual distortions in the injected areas. However, these perceptual distortions also spread to the lips. Taken together, these findings indicate that perceptual distortions of the face may not be a unified phenomenon. Instead, nociceptive stimulation of trigeminal nerve fibers may cause perceptual distortions in another way than transient blocking of trigeminal nerve fibers do.

How changes in somatosensory inputs may relate to perceptual distortions

Several studies have examined the effect of LA on different body parts, including the face[14,25,37]. The results of these studies indicate that somatosensory changes in the form of transient blocking of nerve transduction can cause perceptual distortions that are felt as swelling. The findings of the present study provide further support for this hypothesis by showing that transient blocking of the infraorbital and the mental nerve region can cause feelings of perceived swelling. Based on this study, it is not possible to establish whether neuronal mechanisms are involved. Nevertheless, it has been proposed elsewhere that perceptual distortions due to LA may be related to cortical reorganization[14,25,37]. The reason for this is that the body surface is somatotopically represented in the S1 , and blocking of nerve transduction may change the structure of the S1 and thereby disturb the representation of the body in the brain[6,24,26,28]. This theory is based on scientific evidence which reveals that the adult brain is capable of neuroplastic changes in areas as the S1, i.e. 'cortical reorganization'[8,9,12,26,27].

Only limited research has investigated whether nociceptive stimulation *per se* can cause perceptual distortions. In the present study, we used experimental pain to demonstrate that somatosensory changes consisting of nociceptive stimulation of the facial nerves can cause perceptual distortions expressed as perceived swelling. This was further corroborated by the fact that higher pain intensity increased the magnitude of the perceptual distortions (swelling). The findings of the present study are in accordance with the results from Gandevia and colleagues who showed that painful cooling of the thumb can cause perceived swelling of the stimulated digit; however, to a lesser extent than following anesthesia[14]. Interestingly, in that study, painful cooling of the thumb also caused perceived swelling of the lips. In order to explain this, the authors refer to cortical reorganization[14]. Hence, afferent inputs from the thumb and lips are somatotopically represented next to each other within the S1, and it was hypothesized that changes in somatosensory inputs from the thumb might also disturb the cortical representation of the lips. This explanation is, however, not confirmed by direct neuronal evidence. Nor did our study allow for an investigation of the possible involvement of cortical reorganization. Yet, one study has shown that acute pain can induce S1 reorganization, and it is possible that the perceptual distortions following nociceptive stimulation of the face are also related to such rapid reorganization[29]. This should be tested in future studies. Furthermore, it would be important to examine whether the mechanisms underlying perceptual distortions following nociceptive stimulation and LA are alike. This may probably not be the case as blocking of nerve transduction and nociceptive stimulation of nerves most likely affects the S1 in different ways.

The above-mentioned studies may help explain the perceptual distortions observed in chronic pain disorders that might, at least partially, be a result of nociceptive stimulation[18,20,21]. This knowledge may also be essential to our understanding of the possible association between orofacial pain and perceptual distortions. Importantly, researchers have speculated that perceptual distortions observed in chronic pain disorders are also related to structural S1 reorganization as cortical reorganization has been demonstrated in chronic pain states[13,19,20,21].

Psychological processes

In addition to the involvement of somatosensory changes, this study showed that perceptual distortions were positively correlated with the psychological variable dissociation. This supports our second hypothesis, which proposes that psychological processes contribute to perceptual distortions. Dissociation is characterized by detachment from physical and emotional experiences, and participants who experienced a high level of dissociation prior to the study also experienced a larger degree of perceptual distortion during the study[5]. Because participants filled in the psychological questionnaires before any injections were performed, the dissociation scores are probably not a result of somatosensory alteration, which has been suggested elsewhere[17]. Instead, it is likely that dissociation contributes to the perceptual distortions following nociceptive stimulation and transient blocking of nerve transduction.

Interestingly, no statistically significant association between perceptual distortion and the psychological variables pain catastrophizing, depression, anxiety and somatosenory amplification as measured by questionnaires was found. These findings suggest that it is not enhanced psychological problems in general but rather a specific tendency to detach from physical experience that is related to perception distortion. Still, it cannot be precluded that the lack of significant findings are due to healthy volunteers having low ratings on the items measured in the psychological questionnaires.

The proposal that top-down psychological processes and bottom-up somatosensory alterations in the form of transient blocking of facial nerve transduction and nociceptive stimulation of the face can cause perceptual distortions may also be corroborated by studies which indicate that the mental representation of the face is malleable and can easily be manipulated by somatosensory changes[10,11,33,34,36]. Therefore, we suggest that perceptual distortion of the face is an actual experience rather than simple response bias.

Limitations

This explorative study contained some methodological limitations that should be controlled for in future studies. First, ISO was used as a control condition, but these injections produced small and short-termed perceptual distortions which may have influenced the results. Specifically, this may explain why we observed no significant differences in the magnitude of perceptual distortions for injections of ISO and HS 30 sec after the injections. Injections of ISO were significantly correlated with reported pain intensity and possibly reflect the pain conditions to a lesser extent. Perceptual distortions following injections of ISO may therefore be a result of the needle penetration as well as the small volume injected into the tissue, which can cause low levels of pain in some people. We therefore believe that perceptual distortions following injections of ISO were due to the painful sensations related to this injection rather than to other confounding variables. Second, statistical analyses of perceptual distortions and contribution of psychological variables were run as separate analyses. Hence, no control for multiple comparisons was performed. Third, no correlations were found between perceptual distortions and the psychological measures of pain catastrophizing, somatosensory amplification, depression, and anxiety. We have suggested that these variables do not contribute to the perceptual distortions. However, it is possible that no correlations were seen because the study included pain-free young adults who reported very few abnormal values for these measures. Finally, no brain imaging was performed and we therefore cannot confirm the possible involvement of structural S1 reorganization in the perceptual distortions observed in this study.

Conclusion and future directions

Despite the above-mentioned limitations, we presume that this study provides a fundamental understanding of perceptual distortions of the face in healthy volunteers. It has been shown that both nociceptive stimulation and transient blocking of nerve transduction due to LA can cause perceptual distortions of the face felt as perceived swelling. In addition to bottom-up somatosensory inputs, perceptual distortions may also be influenced by top-down psychological modulation. Because the progression and spreading of the perceptual distortions differed, we propose that perceptual distortions due to nociceptive stimulation and LA are not identical phenomena. This may also relate to the neuronal mechanisms underlying perceptual distortions, which may be important to clarify in future studies using brain imaging, for example. Based on the results that nociceptive stimulation can lead to perceptual distortions, we speculate whether orofacial pain patients also experience perceptual distortions of the face. Such experiences may be related to the painful sensations experienced by these patients. Moreover, psychological processes like dissociation may also be involved in such phenomena. This will be important to investigate in future studies as it can be speculated that perceptual distortions may contribute to the maintenance of orofacial pain.

Disclosures

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Figure legends

Fig. 1. A: Normal face. **B:** Distorted upper lip. **C:** Distorted infraorbital nerve region. **D:** Distorted lower lip. **E:** Distorted mental nerve region.

Fig. 2: Illustrations of the warping procedure using FantaMorph. **A:** Enlargement of the infraorbital nerve region. **B:** Standardized warping algorithm of the infraorbital nerve region. **C:** Standardized warping algorithm of the upper lip. Black line represents the normal area (inner matrices). Grey line represents enlarged area, cheek: 30 %; upper lip 150 % (outer matrices).

Fig. 3: Study design.

Fig. 4: Post hoc data from the two-way repeated measures ANOVA on perceptual distortion of the face measures via the verbal subjective rating scale. ***** Indicates a significant effect on time. *a indicates a significant difference between injections of HS (pain) and ISO (control) at the specific time point. *b indicates a significant difference between injections of LA and ISO (control) at the specific time point.

Tables

Table 1. Two-way repeated measures ANOVA for perceptual distortions (verbal subjective rating scale)

Region	Main effect	df	F	p
Infraorbital nerve region	Injection	2, 30	4.13	0.026*
	Time	1.98, 29.76	14.48	<0.001***
	Injection*time	3.15, 47.26	5.27	0.003**
Mental nerve region	Injection	1.26, 18.96	10.13	0.003**
	Time	1.73, 25.98	15.96	<0.001***
	Injection*time	2.77, 41.49	6.89	0.001**
Infraorbital nerve region	Injection	2, 30	21.58	<0.001***
	Time	2.21, 33.15	12.61	<0.001***
	Injection*time	8, 120	12.61	<0.001***
Mental nerve region	Injection	2, 30	6.98	0.003**
	Time	1.65, 24.78	5.10	0.018*
	Injection*time	8, 120	5.10	0.001**

*significant at the 0.05 level
**Significant at the 0.01 level
***Significant at the 0.001 level

Tabel 2. Two-way repeated measures ANOVA for perceptual distortions (warping procedure)

Region	**Main effect**	**df**	**F**	**p**
Infraorbital nerve region	Injection	2, 30	4.53	0.019*
	Time	2.40, 35.96	22.04	<0.001***
	Injection*time	3.91, 58.61	5.64	<0.001***
Mental nerve region	Injection	2, 30	13.04	<0.001***
	Time	2.09, 31.34	14.61	<0.001***
	Injection*time	3.71, 55.62	5.08	0.002**
Infraorbital nerve region	Injection	2, 30	27.26	<0.001***
	Time	2.36, 35.41	15.48	<0.001***
	Injection*time	8, 120	15.48	<0.001***
Mental nerve region	Injection	2, 30	10.44	0.001**
	Time	2.69, 40.36	5.48	0.004**
	Injection*time	8, 120	5.48	<0.001***

*significant at the 0.05 level
**Significant at the 0.01 level
***Significant at the 0.001 level

Table 3. Correlation coefficients (Pearson's r) for perceptual distortion measures based on 1) the verbal subjective rating scale, and 2) the warping procedure

Injection	**Region**	**Time** **30 sec**	**5 min**	**10 min**	**30 min**
HS	Infraorbital nerve region	0.86	0.91	0.93	1.00
	Upper lip	1.00	-*	-*	-*
	Mental nerve region	0.83	0.80	0.95	1.00
	Lower lip	-*	-*	-*	-*
LA	Infraorbital nerve region	0.86	0.90	0.85	0.76
	Upper lip	0.84	0.91	0.92	0.84
	Mental nerve region	0.63	0.76	0.57	0.55
	Lower lip	.087	0.71	0.78	0.65
ISO	Infraorbital nerve region	0.70	0.92	0.81	1.00
	Upper lip	-*	-*	-*	-*
	Mental nerve region	0.73	0.92	0.99	1.00
	Lower lip	-*	-*	-*	-*

r = 0.1 (small correlation), r = 0.3 (medium correlation), r = 0.5 (high correlation)
-* No calculation because data has zero variance

Table 4. Two-way repeated measures ANOVA for perceptual distortions in the retest (part one) measured via 1) verbal subjective reports (sub) and 2) warping procedure (warp)

Region	Main effect	df	F	p
Infraorbital nerve region (sub)	Injection	1.05, 9.41	5.81	0.037*
	Time	1.88, 16.88	3.80	0.046*
	Injection*time	2.27, 20.40	4.10	0.028*
Infraorbital nerve region (warp)	Injection	2, 18	5.44	0.014*
	Time	1.77, 15.91	4.07	0.041*
	Injection*time	2.64, 23.72	3.30	0.043*
Upper lip (sub)	Injection	2, 18	12.98	<0.001***
	Time	1.99, 17.87	9.89	0.001**
	Injection*time	8, 72	9.89	<0.001***
Upper lip (warp)	Injection	2, 18	15.08	<0.001***
	Time	2.20, 19.76	6.45	0.006**
	Injection*time	8, 72	6.45	<0.001***

*significant at the 0.05 level
**Significant at the 0.01 level
***Significant at the 0.001 level

Table 5. Intra Class Correlation (ICC) for results about perceptual distortions of the face in the test-retest experiment

		Verbal subjective rating scale			Warping procedure		
Time	**Region**	**HS**	**LA**	**ISO**	**HS**	**LA**	**ISO**
30 sec	Infraorbital nerve region	0.88	0.99	0.69	0.81	0.82	0.04
	Upper lip	-*	0.97	-*	-*	0.91	-*
5 min	Infraorbital nerve region	0.72	0.96	-*	0.81	0.91	-*
	Upper lip	-*	0.81	-*	-*	0.95	-*
10 min	Infraorbital nerve region	-*	0.91	-*	-*	0.51	-*
	Upper lip	-*	0.84	-*	-*	0.91	-*
30 min	Infraorbital nerve region	-*	0.65	-*	-*	0.45	-*
	Upper lip	-*	0.94	-*	-*	0.76	-*

ICC <0.4 is considered poor, 0.4-0.59: fair, 0.6-0.75: good, and >0.75: excellent agreement
-* No calculation because data has zero variance

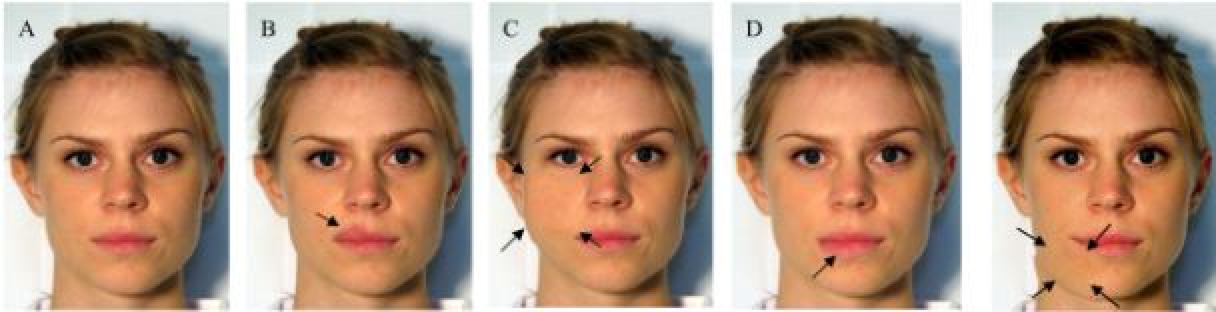
Table 6. Mean pain intensity (mean/SD) reported for all injection types and measurement times. Pain intensity was reported on a 0-10 NRS

Injection	Injection site	Time Baseline	30 sec	5 min	10 min	30 min
HS	Infraorbital nerve region	0.0/0.0	6.5/1.9	1.1/1.5	0.2/0.4	0.0/0.0
	Mental nerve region	0.0/0.0	5.3/2.6	1.1/1.7	0.0/0.0	0.0/0.0
ISO	Infraorbital nerve region	0.0/0.0	1.4/2.0	0.1/0.5	0.1/0.5	0.0/0.0
	Mental nerve region	0.0/0.0	1.8/1.7	0.0/0.0	0.0/0.0	0.0/0.0
LA	Infraorbital nerve region	0.0/0.0	0.2/0.5	0.0/0.0	0.0/0.0	0.0/0.0
	Mental nerve region	0.0/0.0	0.3/0.7	0.1/0.5	0.1/0.5	0.0/0.0

Table 7. Correlations between perceptual distortions of the face (calculated as the area under curve) and the psychological variable "dissociation".

		DES (total)		DES (÷ 19)	
Injection	**Region**	**r**	**p**	**r**	**P**
HS	Infraorbital nerve region	0.55	p=0.027*	0.57	p=0.022*
	Mental nerve region	0.10	p=0.713	0.10	p=0.707
LA	Infraorbital nerve region	0.35	p=0.185	0.37	p=0.165
	Upper lip	0.52	p=0.039*	0.52	p=0.040*
	Mental nerve region	0.58	p=0.020*	0.59	p=0.017*
	Lower lip	-0.09	p=0.731	-0.11	p=0.690

r = 0.1 (small correlation), r = 0.3 (medium correlation), r = 0.5 (high correlation).
*Correlation is significant at the 0.05 level.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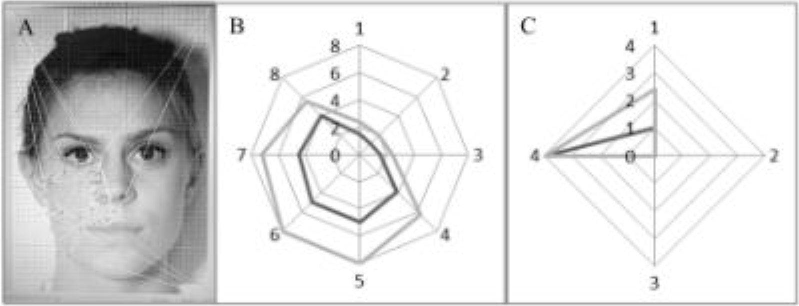
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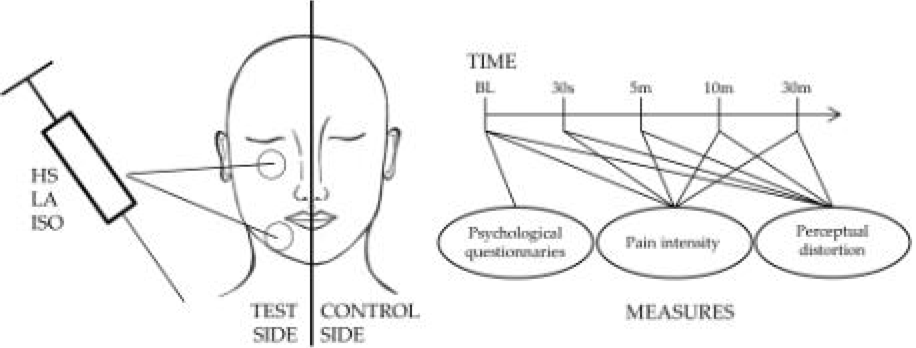
HS
LA
ISO
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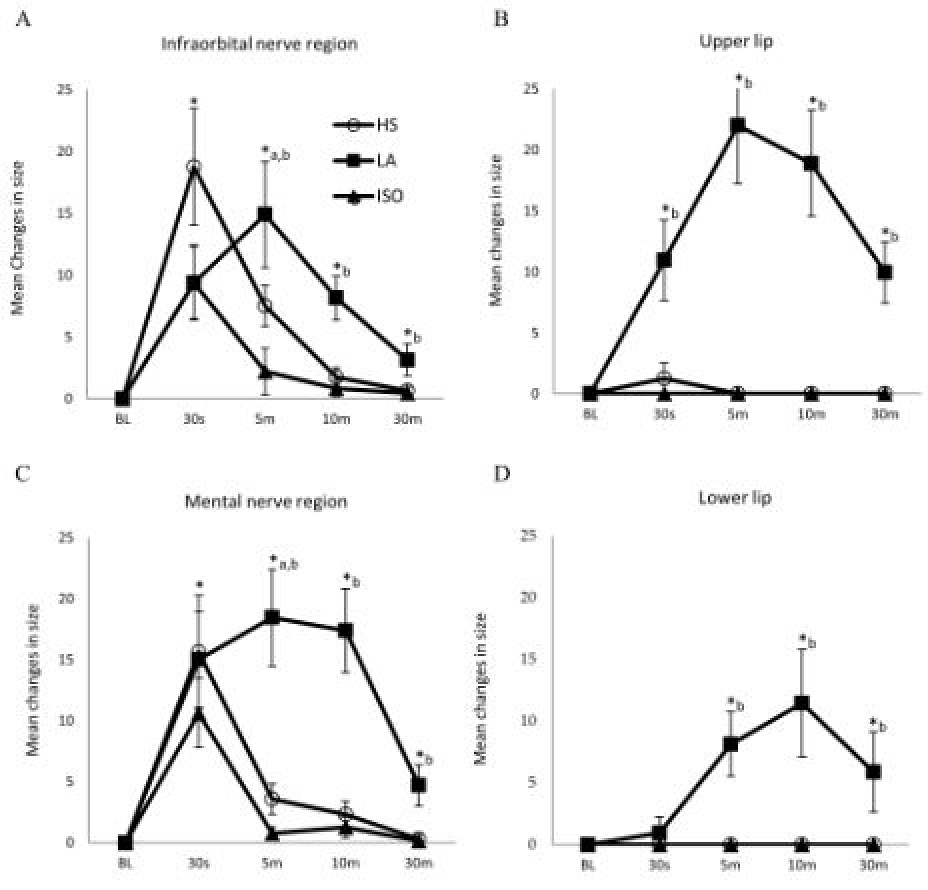
CONTROL SIDE
TIME
BL
30s
5m
10m
30m
Psychological questionnaries
Pain intensity
Perceptual distortion
MEASURES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Mean Changes in size
HS
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30s
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10m
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B
Upper lip
Mean changes in size
*b
*b
*b
*b
C
Mental nerve region
Mean changes in size
*
*a,b
*b
*b
D
Lower lip
Mean changes in size
*b
*b
*b
0
5
10
15
20
25