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ORIGINAL ARTICLE

Unpleasant olfactory and gustatory stimuli increase pain unpleasantness in patients with chronic oral burning pain: An exploratory study

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Abstract

Background: Despite mounting evidence for the powerful influence of smell and taste substances in experimental pain, our knowledge of their effects in the clinical context is scarce, especially for patients with chronic oral burning pain. To fill this gap, we investigated the effect of olfactory and gustatory stimuli on pain perception in patients with chronic oral burning pain, a disabling condition that is difficult to manage and treat.

Methods: Twenty-two patients with chronic oral burning pain underwent testing with a variety of olfactory and gustatory substances (pleasant, neutral, unpleasant) in multisensory interaction. The order of testing was randomized. Perception of pain intensity and unpleasantness was evaluated on a numerical rating scale at baseline and immediately after each test trial.

Results: Pain unpleasantness but not pain intensity was found to be modulated by chemosensory stimuli. Unpleasant olfactory and gustatory stimuli increased the perception of pain unpleasantness compared to pleasant and neutral stimuli. Pain unpleasantness after unpleasant olfactory and gustatory stimuli correlated with psychological questionnaire subscale scores for distress (CORE-OM) and emotional awareness (TAS-20).

Angela Sandri, Maria Paola Cecchini, Mirta Fiorio and Michele Tinazzi are contributed equally to this work.

Conclusions: Our findings suggest a role of unpleasant chemosensory stimuli in increasing the perception of pain unpleasantness in patients with chronic oral burning. The lack of an effect on pain intensity indicates a dissociation between sensory and affective pain components. Future research is needed to further study the association between chemosensory stimuli and emotional and subjective aspects in modulating chronic oral burning pain.

Significance: This exploratory work suggests that unpleasant smell and taste stimuli may have an adverse effect on the affective component of chronic oral burning pain. Future comprehensive large-scale research, also applying brain imaging investigations as well as full psychological analysis, is required to better understand the role of smell and taste stimuli on this chronic and disabling pain condition.

1 | INTRODUCTION

Oral burning pain is usually associated with the burning mouth syndrome (BMS), a chronic painful condition not universally accepted though diagnostic criteria have been proposed (Kim & Kho, 2018). Pathophysiological, neuropathological, and psychological factors have been suggested as contributory factors (Borsani et al., 2014; Feller et al., 2017; Galli et al., 2017; Kim & Kho, 2018; Yoo et al., 2018). Patients with oral burning pain demonstrate relevant comorbid psychological conditions (Freilich et al., 2020; Galli et al., 2017; Klasser et al., 2016). This multifactorial disorder has been variously described as burning mouth, stomatodynia, oral dysesthesia, glossopyrosis, and glossodynia (Klein et al., 2020; Périer & Boucher, 2019). It mainly affects menopausal or post-menopausal women and increases in prevalence with advancing age (Kohorst et al., 2015; Teruel & Patel, 2019). Generally, pain is continuous and of moderate/severe intensity, but can fluctuate, worsen late in the day, and remit at night. The tongue is most often involved, but the pain may be reported anywhere in the oral cavity. Patients may complain of dysgeusic phenomena (altered perception of taste or phantom tastes in the absence of gustatory stimuli) or xerostomia though salivation is normal (Jääskeläinen, 2012). Oral pain has a negative impact on daily life and general well-being (Sardella et al., 2006). Many different treatments are offered (e.g. chlorhexidine oral rinses, benzodiazepines, antihistamine medications, anti-inflammatory drugs, antifungal agents, vitamins, topical steroids, capsaicin, psychotherapy); despite advances in our understanding of the condition, it remains a challenge for clinicians (McMillan et al., 2016; Su et al., 2020).

Growing evidence has shown that smell and taste substances exert a strong influence on pain perception; however, the association between pain, smell and taste has not been extensively explored in the clinical context (Sandri et al., 2021). Multisensory integration is reported to reduce experimentally induced pain in healthy subjects (Bartolo et al., 2013; Cecchini et al., 2020; Kakeda & Ishikawa, 2011; Kakeda et al., 2008, 2010; Riello et al., 2019; Villemure & Bushnell, 2009; Villemure et al., 2003), and preliminary attempts have shown promise in some painful clinical conditions (Gossrau et al., 2020; Hirsch et al., 2011; Villemure et al., 2006). The effect of administration of smell and/or taste substances has not been systematically evaluated in chronic oral burning pain. To our best knowledge, only one pilot study involving three patients with oral burning pain reported a rapid reduction in pain intensity after the administration of sucralose, an artificial sweetener about 600 times sweeter than sucrose (Hirsch et al., 2011). Moreover, psychological and emotional factors could play a role in the relationship between pain, smell, and taste (Beauchamp, 2016; Krusemark et al., 2013).

With the above points in mind, we carried out an exploratory study on patients with chronic oral burning pain, as a first step in the research of this peculiar and clinical heterogeneous painful condition. All patients underwent detailed chemosensory and pain evaluation and psychological assessment by validated questionnaires before entering the experimental stage of the study. The main aim was to evaluate the effect of the administration of olfactory and gustatory substances on pain perception and to determine whether a correlation existed between psychological questionnaire scores and pain measures. The neutral conditions were used as control. We think

that this pioneering approach might shed light on the relation between the oral pain, smell and taste, poorly explored so far.

2 | METHODS

2.1 | Participants and study design

Patients eligible for the study were all those attending the Verona Hospital Maxillofacial Surgery Unit outpatient services in one year ($n = 30$). Inclusion criteria were: age >18 years, chronic oral burning pain for at least 3 months, no oral or systemic diseases that could explain the oral pain, no coexisting factors influencing olfactory and gustatory functions, no chemosensory deficit (normosmia and normogeusia). During the first of two sessions, the patients completed a detailed sensory interview and underwent smell and taste evaluation (Sniffin' Sticks Extended Test for smell and Taste Strips Test for taste, Burghart, Germany). During the second session (within 2 weeks from the first session), the patients completed the pain and the psychological questionnaire and underwent experimental testing (Figure 1). Two patients were excluded because they were deemed hyposmic and 6 withdrew after the first session for personal reasons. The final study sample was 22 patients (18 females; age range 46–79 years; mean 63.0 ± 9.9). Written, informed consent was obtained. The Ethical Committee of the University Hospital of Verona (Prot. no. 63032 of 2020/11/23) approved the study design and protocol.

2.2 | First session

2.2.1 | Sensory interview

A sensory interview was conducted by the same expert clinician to collect detailed information about the complaints: location, duration, main daily pain trend, qualitative and quantitative attributes, factors improving or worsening the pain.

2.2.2 | Smell and taste evaluation

Olfactory and gustatory functions were assessed with standardized procedures. Olfaction was assessed through the Sniffin' Sticks Extended Test (Burghart, Germany). This test uses felt-tipped, pen-like odour-dispensing devices; it has three individual subtests with a forced choice experimental paradigm (Hummel et al., 2007). The olfactory threshold subtest (T) indicates the concentration at which an odour (n-butanol) is reliably detected among triplets of dispensing pens (two containing the odourless solution and one containing the odour) presented in random order. Patients are asked to identify the odour-dispensing pen. The discrimination subtest (D) assesses the ability to discriminate between different odours: sixteen triplets of pens (each with two pens dispensing the same odour and one pen dispensing an odour different from the other two) are presented in random order; patients are asked to identify which pen smells different from the others. During the threshold and the discrimination subtest, patients are usually blindfolded to prevent

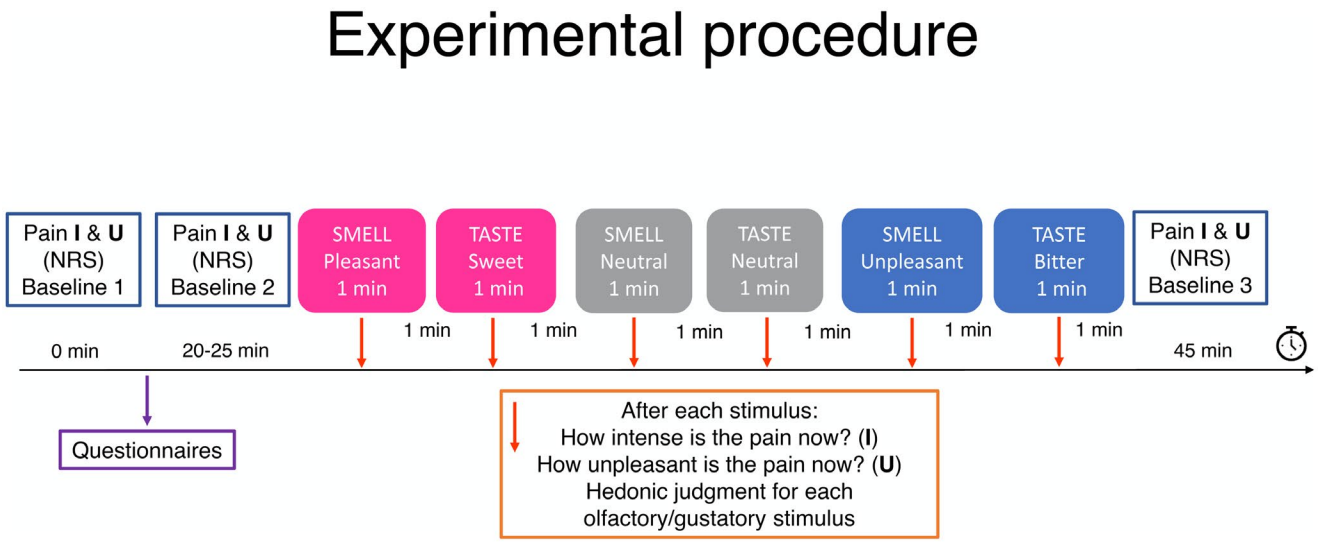

FIGURE 1 Experimental procedure. After two initial baseline measurements (at the beginning and at 20 min from the beginning), pain ratings were evaluated when pain was perceived in association with smell and taste stimulation of different valence (pleasant/sweet, unpleasant/bitter and neutral). Each stimulus (smell or taste) lasted 1 minute, and 1-minute break after each valence condition was given to collect the hedonic judgment on the olfactory or gustatory stimuli. The experiment ended at 45 minutes after the beginning. At the end, one last baseline measurement was collected

visual identification of the odour-dispensing pens. The identification subtest (I) entails the administration of sixteen different odours. For each odour, the patient chooses from a list of four odours in each trial. The combined threshold-discrimination-identification (TDI) score is the sum of each subtest. The total score is used to distinguish normosmia (TDI $\geq$ 30.3), hyposmia (30.3 > TDI $\geq$ 16) and functional anosmia (TDI < 16).

Gustatory function was assessed by means of the Taste Strips Test (TST) (Burghart, Germany) (Landis et al., 2009; Mueller et al., 2003). It consists of filter paper strips impregnated with gustatory solutions at four different concentrations for each taste (sweet, sour, salty, bitter). Because Europeans are not yet familiar with umami, it was not included in this taste evaluation (Cecchini et al., 2019; Landis et al., 2009). Patients rinse their mouth between each trial. The paper strips are placed on the tongue and patients are asked to identify the taste. A TST score ≥9 indicates normogeusia and a score <9 indicates hypogeusia.

2.3 | Second session

2.3.1 | Experimental procedure

Oral burning pain was evaluated by means of two pain measures (intensity and unpleasantness) at baseline and immediately after each smell and taste stimulation trial. Pain intensity ('How intense is the oral pain now?') was rated on a numeric rating scale (NRS) from 0 ('not at all painful') to 10 ('extremely painful') and pain unpleasantness ('How unpleasant is the oral pain now?') on a NRS from 0 ('not at all unpleasant') to 10 ('extremely unpleasant'). Pain intensity was defined as a measure of the sensory-discriminative component of pain and pain unpleasantness as a proxy of the affective-motivational pain component (Rainville, 2002).

Olfactory and gustatory stimuli were delivered according to a factorial design for the two senses and with different valences (pleasant, unpleasant, neutral) following the same design as described in our previous work (Cecchini et al., 2020; Riello et al., 2019). In detail, the chemosensory stimuli were delivered in three types of valence (pleasant, unpleasant, neutral) in random order of valence within the group and in a counterbalanced design (Figure 1). Patients were randomized to the order of testing of the chemical senses (smell and taste), and, for each sense, patients were randomized to the order of administration of valences. The choice of substances with pleasant and unpleasant valence was based on the idea of using stimuli with an opposite, phylogenetically archaic valence. Indeed, sweetness is related to energy intake and survival, whereas bitterness is linked to defense and alerts against poisonous substances (Beauchamp, 2016). Smell helps us process environmental cues associated with threatening or social stimuli (Stevenson, 2010). The neutral condition served as control.

The olfactory stimuli were orthonasally delivered through a single-use birhinal cannula (Intersurgical S.p.A., Italy) connected to a homemade manual olfactometer (built at the Anatomy Department according to the work of Lowen & Lukas, 2006). A banana extract solution constituted the pleasant odour and a fish extract solution the unpleasant one, neither of which are trigeminal odours (Cecchini et al., 2020; Riello et al., 2019). Odourless air was delivered as a neutral stimulus. In addition, during the interstimulus interval, nasal cavities were cleaned with odourless air.

Gustatory stimuli were administered manually by spraying a solution into the patients' mouth. For each trial, two aqueous saline solutions, the sweet (pleasant, sucrose 10%) and the bitter (unpleasant, quinine hydrochloride 0.05%), were continuously delivered by the experimenter to maintain stimulation in the oral cavity. These two suprathreshold solutions are generally used in the Whole Mouth Test (sucrose 10% for sweet, citric acid 5% for sour, sodium chloride 7.5% for salty, quinine 0.05% for bitter) as a rapid screening gustatory test for the four basic taste qualities (Cecchini et al., 2015). The sweet solution was delivered every 10 s, the bitter solution every 30 s, and the neutral solution every 20 s; the difference in timing is due to the physiological difference in duration of sensation between the two taste qualities. Natural oligomineral water was administered as a neutral stimulus. Besides, during the interstimulus interval oral cavity was rinsed with natural water.

Smell and taste stimulation lasted 1 min. Pain intensity and unpleasantness were rated on a NRS at the beginning of the session (first baseline), after questionnaire completion (second baseline), then in association with administration of the smell and taste stimuli at six-time points, and finally at the end of the session (third baseline) (Figure 1).

There was a 1-min interval between each smell and taste stimulation trial. After each olfactory or gustatory stimulation trial, the patients rated the substance ('How do you rate the substance?') on a NRS from −10 ('extremely unpleasant') to 10 ('extremely pleasant'), with 0 indicating 'neutral'.

2.3.2 | Pain and psychological questionnaires

At this regard, we collected measures of psychological distress (Clinical Outcomes in Routine Evaluation – Outcome Measures, CORE-OM; Palmieri et al., 2009), and alexithymia (Toronto Alexithymia Scale, TAS-20; Bressi et al., 1996).

In addition, other questionnaires that explore specific pain-related aspects were also administered: the Brief Pain Inventory (BPI) (Caraceni et al., 1996) to explore the interference of pain causes in daily life; the Pain Catastrophizing

Scale (PCS) (Monticone et al., 2012) to detect thoughts and feelings related to pain experience. The Italian Pain Questionnaire (QUID) (De Benedittis et al., 1988) was administered to highlight how the oral pain experience was perceived and to explore different classes (Sensory, Affective, Evaluative, Miscellaneous). We included a free translation of the items regarding pain facial interference, a section of the BPI-facial that has not yet been validated in Italian (Lee et al., 2010), to assess the relationship between oral pain and facial-related activities. Questionnaires were divided in two groups, administered in the first (BPI, PCS, CORE-OM) and second session (TAS-20, QUID) respectively.

2.4 | Statistical analyses

We described symmetrical and asymmetrical quantitative variables using means ± SD or median (Q1–Q3), respectively, and categorical variables using percentages. Statistical significance was set at $\alpha = 0.05$. Normality of data distribution was tested using the Shapiro–Wilk test; since it was violated for more than half of the variables, non-parametric analyses were performed, which are also robust to outliers.

Friedman's test (Friedman, 1940) was computed to analyse the three baseline ratings collected during the experimental trials to determine whether pain fluctuated overall during the procedure.

Patients' responses to each experimental condition were expressed as changes in pain intensity and unpleasantness relative to baseline value (normalized relative changes), calculated using the formula [1].

$$\Delta x_{\text{relative}} = \frac{X - Bx}{Bx} \quad (1)$$

where X represents the NRS rating for each experimental condition and Bx is the mean NRS rating for the three baseline sessions (assessed at the beginning, after questionnaire administration, at the end of the experimental trial). For sensitivity analysis, we also analysed patients' responses calculated as absolute changes in pain intensity and unpleasantness ($\Delta x_{\text{absolute}} = X - Bx$).

Two-way non-parametric Friedman's test was used to assess whether patients' responses varied as a function of valence (pleasant, unpleasant, neutral) separately for smell and taste substances. When an overall difference between valences was found ($p < 0.05$), post-hoc pairwise comparisons using Wilcoxon's signed-rank test were carried out, and p-values adjusted for multiple testing were calculated using the Benjamini-Hochberg correction (Benjamini & Hochberg, 1995). In addition, to have a more direct measure of the "effect size", we calculated the normalized relative changes for pain intensity and pain unpleasantness in response to pleasant and unpleasant experimental stimuli corrected for the neutral stimuli (i.e., intra-individual control conditions). We also tested whether patients' responses for a given valence varied as a function of sense (smell vs taste).

To assess whether baseline pain perception and disease duration modified patients' responses, the main analyses were repeated after stratification by median pain perception and median disease duration. Finally, since pain unpleasantness was the only pain measure modulated by smell and taste, we explored this aspect further. Using Spearman's rank correlation coefficients, we assessed the correlation of the modulation of pain unpleasantness with either the hedonic ratings assigned by the patients to the experimental substances and the psychological test scores. All statistical analyses were performed using RStudio software (Version 1.3.1093 © 2009–2020 Rstudio, PBC).

3 | RESULTS

3.1 | Pain features

The sensory interview revealed that all patients ($n = 28$) had a long history of oral symptoms (range: 4–192 months, median value: 22.5, interquartile range: 14.8–63 months), and none was taking any kind of treatment at the time of assessment. The mean age of recruited patients was 61.4 (range: 31–79) years and most of them were women (82%) (Table 1). The trigger events varied (e.g. oral diseases/oral surgery, stressful family or personal circumstances or events, medications, general surgery or no apparent event recalled). None of the female patients linked the menopause onset to the oral pain. Various pain patterns also emerged: worsening of pain over the course of the day, constant daily pain, and fluctuating pain perception with wide inter-individual variability. Generally, the pain did not interfere with sleep (Figure S1). Though the oral pain topography varied, the tongue was affected at least partially in almost all (89.3%) patients. Pain was defined as discomfort (85.7%), burning (67.9%) or mouth dryness (67.9%) (Table 1). Factors reported as worsening or increasing pain intensity are presented in Figure S2.

3.2 | Experimental trials

Perception of pain intensity did not vary significantly across the three baseline measurements ($p = 0.22$) nor did the perception of pain unpleasantness ($p = 0.93$), indicating that pain perception was stable during the experimental session and that it returned to the initial perception at the end of the experiment (Table 2). Mean ratings ± SD for each experimental condition are reported in Table 3.

TABLE 1 Sociodemographic, clinical and pain features ($n = 28$)

Gender	
Women (%)	23 (82%)
Men (%)	5 (18%)
Age (years)	
Range	31–79
Mean ± SD	61.4 ± 11.6
Work status	
Employed (%)	16 (57%)
Retired (%)	12 (43%)
Comorbidities	
Yes (%)	26 (93%)
No (%)	2 (7%)
Drug assumption (not for oral pain)	
Yes (%)	21 (75%)
No (%)	7 (25%)
Oral pain duration (months)	
Range	4–192
Median (Q1–Q3)	22.5 (14.8–63)
Oral pain trigger event	
Yes (%)	20 (71%)
No (%)	8 (29%)
Oral pain topography	
Tongue (%)	25 (89.3%)
Hard palate (%)	9 (32.1%)
Lips (%)	5 (17.8%)
Cheek mucosa (%)	1 (3.6%)
Gums (%)	1 (3.6%)
Oropharynx (%)	1 (3.6%)
Oral pain description	
Burning (%)	19 (67.9%)
Discomfort (%)	24 (85.7%)
Dryness (%)	19 (67.9%)
Pain in other sites	
Yes (%)	25 (89%)
No (%)	3 (11%)

3.3 | Effect of smell on pain perception

In the smell-pain trial, patients' responses (normalized relative changes) in unpleasantness scores significantly differed between the experimental conditions ($p = 0.006$, Figure 2a). Post-hoc comparisons suggested a significant difference of unpleasant vs. pleasant ($p_{adjusted} = 0.007$) and unpleasant vs. neutral odours ($p_{adjusted} = 0.023$) but not of pleasant versus neutral odours ($p_{adjusted} = 0.414$) The percentage of patients reporting an increase in pain unpleasantness were 41 and 18% for the unpleasant and neutral conditions, respectively (Table 4). No significant difference in response (normalized relative changes) was found between conditions (pleasant, unpleasant, neutral) and NRS pain intensity scores ($p > 0.05$, Figure 3a).

3.4 | Effect of taste on pain perception

Regarding the taste-pain trials, patients' response (normalized relative changes) in unpleasantness scores differed significantly between the experimental conditions ($p < 0.001$, Figure 2b). Post-hoc comparisons suggested a significant difference of unpleasant vs. pleasant ($p_{adjusted} = 0.008$) and unpleasant vs. neutral taste ($p_{adjusted} = 0.019$), but not of pleasant vs. neutral taste ($p_{adjusted} = 0.309$). The percentage of patients reporting an increase in pain unpleasantness were 55 and 18% for the unpleasant and neutral conditions, respectively (Table 4). Patients' response in pain intensity differed significantly between the experimental conditions ($p = 0.015$), but there were no significant differences in pairwise comparisons between trials (Figure 3b).

3.5 | Supplementary analyses

Consistent results were obtained with the analyses on the absolute values (Figure S3), and on patients' responses calculated as a difference from the neutral condition (Figure S4 and S5), both for smell and taste.

Patients' responses for a given valence did not vary as a function of sense ($p > 0.05$). The trend for a greater

TABLE 2 Baseline values (mean ± SD) for intensity and unpleasantness at three time points: at the beginning (1), after the questionnaires (2) and at the end of the experiment (3). Baseline all represents the mean of the three baselines

	Baseline 1 (Mean ± SD)	Baseline 2 (Mean ± SD)	Baseline 3 (Mean ± SD)	Baseline all (Mean ± SD)	Friedman's test
Intensity (NRS 0–10)	5.7 ± 2.6	5.4 ± 2.8	6.2 ± 2.4	5.6 ± 2.4	$\chi^2 = 3.0545$, $df = 2$ $p = 0.22$
Unpleasantness (NRS 0–10)	5.6 ± 3.2	5.6 ± 3.2	6.0 ± 3.0	5.7 ± 2.9	$\chi^2 = 0.15094$, $df = 2$ $p = 0.93$

TABLE 3 Mean values (±SD) of pain intensity and pain unpleasantness session for each smell and taste stimulus

	Smell (Mean ± SD)			Taste (Mean ± SD)		
	Banana	**Fish**	**Neutral**	**Sucrose**	**Quinine H**	**Neutral**
Intensity (NRS 0–10)	5.2 ± 3.1	6.5 ± 2.8	5.3 ± 3.0	4.7 ± 2.9	6.0 ± 3.1	5.4 ± 3.3
Unpleasantness (NRS 0–10)	5.0 ± 3.7	7.1 ± 3.4	5.3 ± 3.6	4.4 ± 3.4	6.8 ± 3.3	5.1 ± 3.6

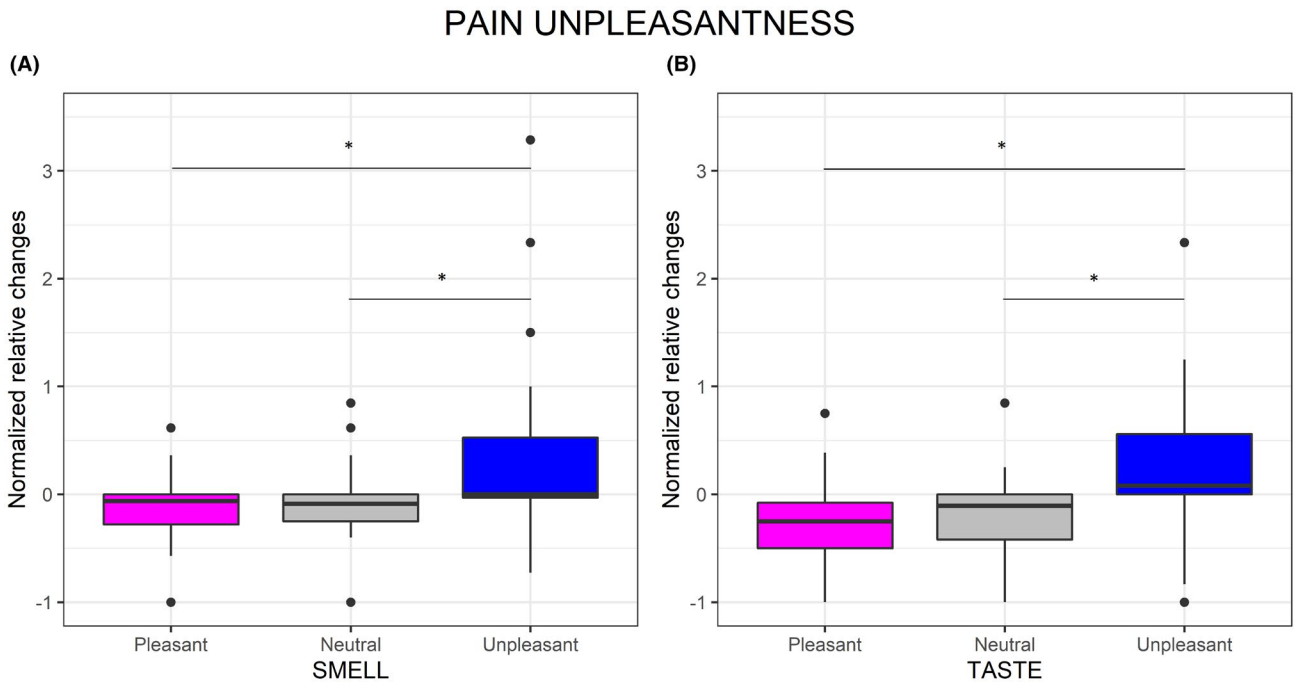

FIGURE 2 Pain unpleasantness. Box plots of normalized changes in pain unpleasantness ratings relative to baseline (mean of three baseline values) for pleasant (magenta), neutral (grey), unpleasant (blue) stimuli, for the smell (panel a) and taste stimulation trials (panel b). The horizontal black lines represent median values. Ratings were significantly higher in the unpleasant compared to the pleasant and neutral conditions, both for smell and taste. *=$p < 0.05$ after application of Benjamini-Hochberg correction

increment in pain unpleasantness after the unpleasant stimuli was confirmed for both patients with a lower (smell, $p = 0.023$; taste, $p = 0.020$) and higher (smell, $p = 0.047$; taste, $p = 0.031$) baseline pain unpleasantness, although responses were quite more pronounced for the former group (Figure S6). Responses to experimental conditions were also similar for patients with a shorter (smell and taste, $p > 0.05$) and longer (smell, $p = 0.02$; taste, $p < 0.001$) disease duration (Figure S7).

3.6 | Correlational analyses

We found a significant negative correlation between the hedonic ratings for fish odour and the normalized value of pain unpleasantness after fish odour stimulation ($R = -0.53$, $p = 0.011$) (Figure 4a). We also found a significant negative correlation between the hedonic rating for banana odour and the normalized value of pain unpleasantness after administration of the banana odour ($R = -0.58$, $p = 0.0057$) (Figure 4b). These findings suggest that individual perception of odour hedonicity correlates with modulation of pain unpleasantness: the more the odour (fish or banana) was rated unpleasant, the more pain unpleasantness increased, and vice versa, the more the odour was rated pleasant, the more the pain unpleasantness decreased. No correlations were found between the gustatory substances and modulation of pain unpleasantness (all $p > 0.05$).

3.7 | Pain and psychological questionnaires

Responses on the BPI and QUID pain questionnaires revealed a disabling effect of oral pain on daily life (Figures S8 and S9). Regarding anxiety and depression, during the sensory interview 22 (78.6%) out of 28 patients complained of anxiety, and 6 (21.4%) reported they had suffered depression, albeit not always clinically diagnosed. Regarding the

TABLE 4 Percentage of patients who had an increment in pain unpleasantness or intensity after the stimulus administration

Sense	Valence	Substance	Pain unpleasantness		Pain intensity	
			Any increment relative to baseline ($\Delta x_{relative} > 0$)	>50% increment relative to baseline ($\Delta x_{relative} > 0.50$)	Any increment relative to baseline ($\Delta x_{relative} > 0$)	>50% increment relative to baseline ($\Delta x_{relative} > 0.50$)
Smell	Pleasant	Banana	18%	4%	27%	9%
	Neutral (control condition)	Odorless air	18%	9%	27%	9%
	Unpleasant	Fish	41%	27%	41%	14%
Taste	Pleasant	Sucrose	14%	4%	14%	0%
	Neutral (control condition)	Natural water	18%	4%	23%	4%
	Unpleasant	Quinine H	55%	27%	41%	18%

psychological questionnaires, results from the CORE-OM indicated high general psychological distress in 3 (10.7%) out of 28 patients (with higher scores in all subscales), and particularly notable is the result on the symptoms subscale, over cutoff in comparison to the normal population in 7 of them (25%). At the TAS-20, 7 (31.8%) out of 22 patients scored as borderline or alexithymic (Bressi et al., 1996). Finally, responses to the PCS showed that 8 (28.6%) out of 28 patients had frequent thoughts and feelings of fear and catastrophizing compared to the normal population, and 14 (50%) had a high score on the Rumination subscale (Monticone et al., 2012).

Our sample did not differ from the normal population, on average. Such results could depend both on the small sample and also because psychological factors seem to have a different association with women and men in this condition (Yoo et al., 2018). Nevertheless, because we noted a tendency towards alexithymia and psychological distress, we explored the relationship between those variables and pain unpleasantness after the administration of unpleasant stimuli. To do this, we ran Spearman correlation analysis and focused on the affective component of pain and the unpleasant stimuli that emerged from the experimental trials. Given the exploratory nature of those correlations, we did not correct the results.

We found a positive correlation between modulation of pain unpleasantness after the administration of bitter substance and the life functioning subscale of CORE-OM ($R = 0.45$, $p = 0.036$): the more patients referred a general dysfunction (also in social and intimate relationships), the more the bitter taste increased the pain unpleasantness. In addition, we found a positive correlation between modulation of pain unpleasantness after administration of bitter substance and the describe feelings subscale of the TAS-20 ($R = 0.49$, $p = 0.020$): the more patients reported difficulty in describing their feelings, the more the bitter taste increased their perception of pain unpleasantness. Finally, we found a negative correlation between modulation of pain unpleasantness after administration of unpleasant odour and the external thinking subscale of TAS-20 ($R = -0.47$, $p = 0.029$): the less patients showed externally oriented thinking (were more internally oriented), the more the unpleasant odour increased the pain unpleasantness. Other correlations were not significant (all $p > 0.050$).

4 | DISCUSSION

With this exploratory experimental study we investigated the modulatory role of olfactory and gustatory stimuli in chronic oral burning pain, a disabling condition that is difficult to manage and treat (Klein et al., 2020). We aimed to determine whether smell and/or taste stimuli

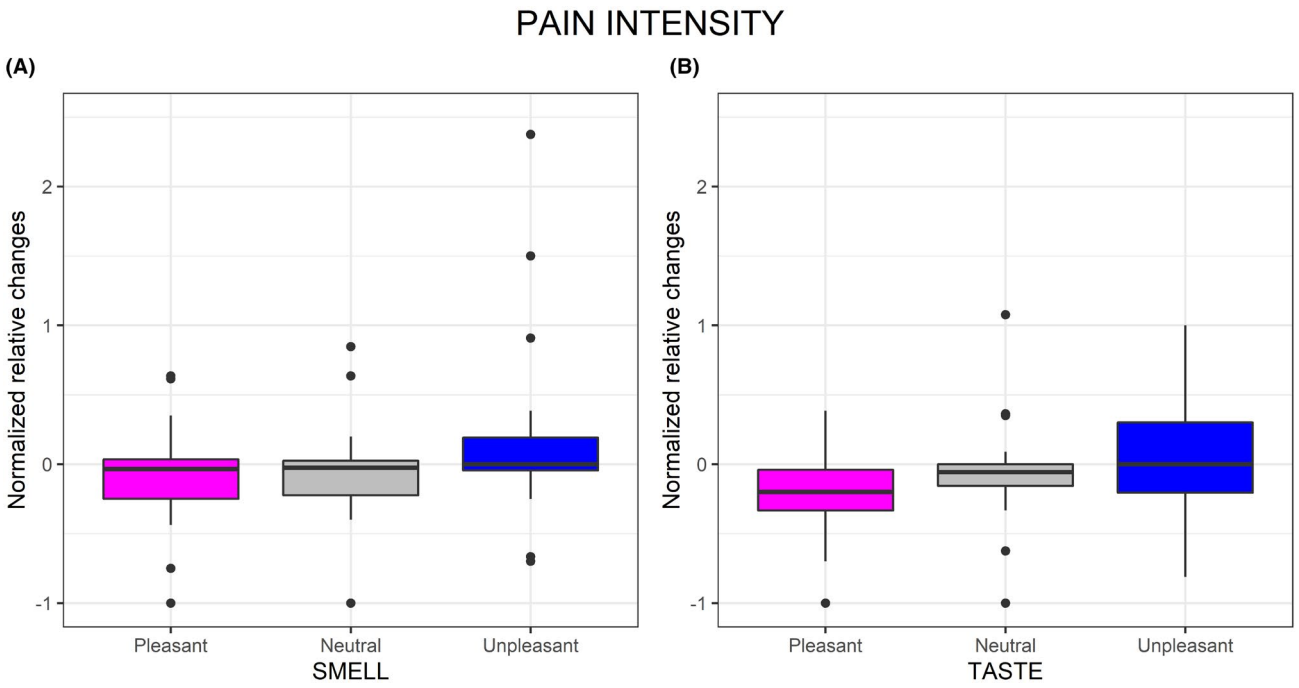

FIGURE 3 Pain intensity. Box plots of normalized changes in pain intensity ratings relative to baseline (mean of three baseline values) for pleasant (magenta), neutral (grey), unpleasant (blue) stimuli, for the smell (panel a) and taste stimulation trials (panel b). The horizontal black lines represent median values. No differences were found between conditions, both for smell and taste

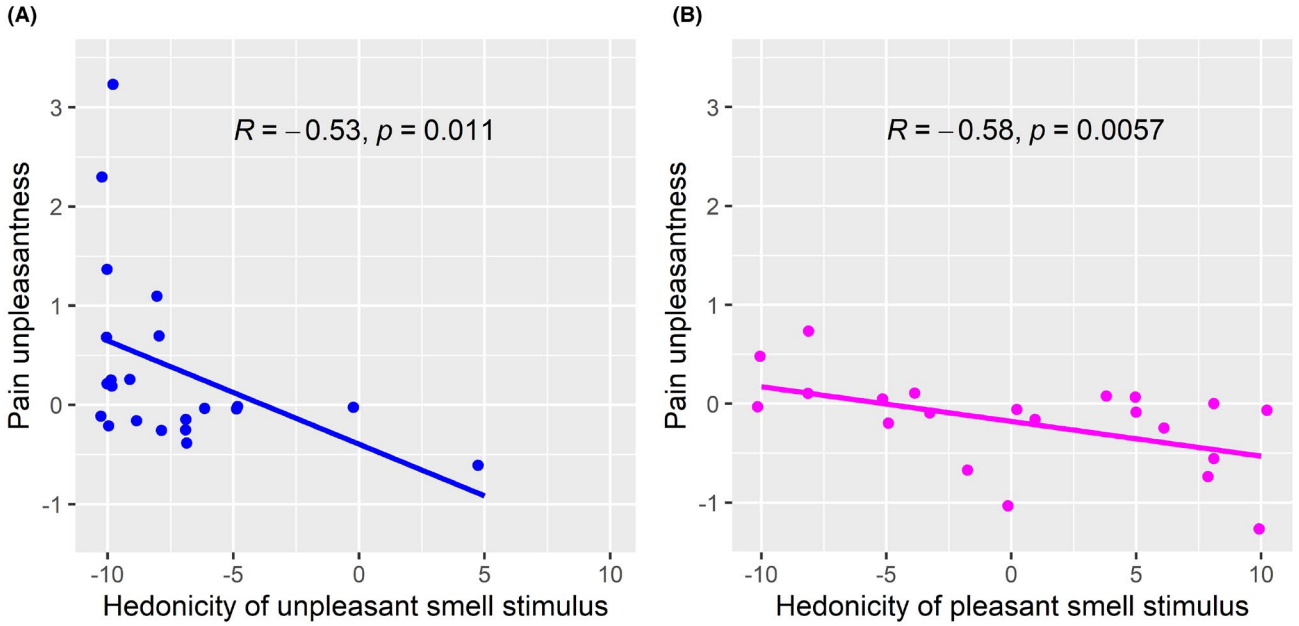

FIGURE 4 Correlations between smell stimuli and pain unpleasantness. Scatterplots with linear interpolation and Spearman's rank coefficients for the correlation between hedonicity of smell stimulus and normalized relative changes in pain unpleasantness ratings, for the unpleasant odour (panel a) and the pleasant odour (panel b). Likert scale of hedonic ratings is represented on x axis, from −10 (very unpleasant) to +10 (very pleasant), with 0 = neutral

might have an effect on the perception of pain intensity and unpleasantness. Two main findings emerged: (1) chemosensory stimuli had an effect on pain unpleasantness but not on pain intensity; (2) only the unpleasant stimuli (fish odour and bitter taste) increased pain perception, whereas the other stimuli (banana odour and sweet taste) did not decrease it. For smell, the effect seems to be related to subjective stimulus perception. Associations with

psychological distress (CORE-OM and TAS-20 scores) and clinical aspects were also noted.

We found that the unpleasant chemosensory stimuli altered pain unpleasantness without changing pain intensity perception, underlining the dissociation between the sensory and the affective dimensions of pain in this kind of chronic oral pain. Previous psychophysical studies showed that pain intensity and unpleasantness constitute two distinct dimensions of pain (Price, 2000). Similarly, in an experimental pain study using cutaneous capsaicin cream stimulation in healthy subjects there was a reduction in pain unpleasantness, but not pain intensity, after exposure to a pleasant odour (Cecchini et al., 2020). Only the emotional aspects of pain appear to be modulated by substances with different valences in patients with oral burning pain and in healthy subjects. This effect strengthens the rationale for the use of capsaicin cream as a model to mimic neuropathic pain (van Amerongen et al., 2016). While the unpleasant stimuli increased the pain in the patients, the pleasant smell reduced the perceived pain unpleasantness in the neuropathic pain model, although the substances were the same in both trials. In healthy subjects the pain experience is confined to the experiment itself, as a novel unexpected situation, whereas in patients with chronic pain the presence of an unpleasant stimulus may exacerbate the underlying pre-existing pain, shedding light on the differential effect of the substances.

In this context, an additive effect might arise from the negative pain condition and the unpleasant chemosensory stimulus, while a pleasant stimulus might not be adequate to exert any impact. In their psychophysical study, Villemure and Bushnell (2009) found by functional magnetic resonance imaging (fMRI) that an unpleasant odour increased the perception of pain intensity and unpleasantness in a patient with neuropathic pain (joint pain after surgery for spinal stenosis). They also reported an increase in neural activation after exposure to the unpleasant odour only in the patient but not in the controls, suggesting an underlying neural substrate linked to the odour effect (Villemure et al., 2006). Magnetic resonance imaging (MRI) studies in oral burning pain patients demonstrated alterations in cerebral blood flow and gray matter volume in pain-related brain regions (e.g. the anterior cingulate cortex, medial orbitofrontal cortex, pars orbitalis, insula, thalamus), suggesting a change at the central level of pain processing (Albuquerque et al., 2006; Su et al., 2020; Wada et al., 2017). Future studies are needed to better explore by means of fMRI the effect of chemosensory stimuli in patients with oral burning pain, for instance, in comparison with a neuropathic pain model.

Our results show that only the unpleasant stimuli had an effect on pain perception. The pathophysiology of chronic oral burning pain remains incompletely understood. To our best knowledge, only one pilot study has investigated the modulatory effect of a chemosensory stimulus in patients with burning mouth syndrome (Hirsch et al., 2011). Hirsch et al. (2011) reported a rapid analgesic effect on pain intensity after the administration of sucralose, an artificial sweetener 600 times sweeter than sucrose, in three patients with oral burning. Our results indicate that neither pain intensity nor pain unpleasantness was influenced by exposure to a sweet gustatory stimulus (sucrose). The lack of modulation in our sample might be due to the fact that the substance we used was not sweet enough to induce an effect. In addition, the three patients in Hirsch's study were found to have an impaired perception of sweet (sucrose) substances on preliminary evaluation, while our sample was normogeusic for all taste qualities.

A clinical study on chronic low back pain assessing pain thresholds for cutaneous stimuli found that regular exposure to pleasant odours (olfactory training for 4 weeks) raised pain thresholds and appeared to be useful for pain control (Gossrau et al., 2020). We found no effect for the banana olfactory stimulus on our sample. The difference might be due to the perceived valence of the odour itself, and so the modulatory effect might have been concealed. Correlation analysis showed that the more the odours (banana and fish) were rated as unpleasant, the more the pain unpleasantness increased; conversely, the more they were rated as pleasant, the less pain unpleasantness was reported. Because odours are strongly linked to the affective domain (Krusemark et al., 2013), they can differently influence individual perception: variability needs to be taken into account, for instance, by choosing the substances rated as most pleasant/unpleasant for each participant at preliminary evaluation, as described in previous studies (Gossrau et al., 2020; Villemure & Bushnell, 2009; Villemure et al., 2003, 2006).

A connection between pain perception, unpleasant chemosensory stimuli, and emotional aspects related to distress (CORE-OM) and emotions awareness (TAS-20) emerged from the correlations on the questionnaire subscales. Nevertheless, due to the exploratory nature of this study and the small sample size, these findings need to be confirmed by future wider investigations. Pain unpleasantness is known to be more strongly affected by emotions than pain intensity (Rainville et al., 2005). In their recent study, Chana and collaborators explored catastrophizing, pain self-efficacy, and acceptance in patients with oral burning pain and found that a personal belief in the ability to cope with or adapt to chronic burning pain plays a major role in the global pain experience (Chana et al., 2021). The negative orientation that emerged for the PCS responses (e.g. catastrophizing, rumination) may have had a role in directing attention to the unpleasant stimulus.

Moreover, the chronicity of painful sensation has a negative impact on general well-being (Sardella et al., 2006), and the distinctive features of the oral chronic painful status may offer a key element to investigate. Oral pain was reported as incessant during the day, as confirmed on the sensory interview and the baseline ratings during the trials. The oral cavity is one of the most richly innervated anatomical areas in the body and a wide variety of signals arises there (tactile, nociceptive, thermic, chemosensory). Accordingly, oral somatosensory awareness is a highly complex matter (Haggard & de Boer, 2014). Pain unpleasantness, when linked to unpleasant feelings (e.g. distress, fear, etc.) defined under the term secondary pain effect (Price, 2000), may increase the interference of an unpleasant stimulus in the modulation of pain perception. We observed that the more patients reported distress and difficulty in dealing with emotions, the more the unpleasant stimuli increased their perception of pain unpleasantness. An fMRI study involving patients with oral burning pain suggested different patterns of functional brain connectivity in relation to perceived pain. Increased brain functional activity was detected in affective-motivational neural circuits linked to depression and anxiety, supporting the link between psychogenic factors and chronic oral burning pain (Khan et al., 2014).

During the sensory interview, several patients reported having suffered from episodes of anxiety or depression. They also reported that emotional disturbances, as well as talking, dental care, and hot food or drinks exacerbated their oral pain (Figure S2), as described elsewhere (Grushka, 1987; Grushka et al., 2006; Klasser et al., 2016). Taken together, our findings suggest that pain, generally influenced by emotional states, might be exacerbated by an unpleasant chemosensory stimulus that typically conveys threatening cues (Beauchamp, 2016; Stevenson, 2010). Also, the patients reported sleep and resting, cold food and drinks as pain-relieving factors (Figure S2). Furthermore, distraction was also reported to bring pain relief. An fMRI study on attention and pain showed that diminished activity in the thalamocortical pain pathway was associated with decreased pain perception during distraction (Villemure & Bushnell, 2009). Future studies will need to disentangle the role of pain-relieving factors, attention, and emotions in oral pain.

The main limitations of this exploratory work are the lack of full psychological and functional neuroimaging evaluation which might have yielded more information about the role of chemosensory stimuli in pain perception, especially regarding the pleasant stimuli. Our results rise the question if unpleasant stimuli create a negative context increasing pain perception. A comparison with a neuropathic pain model or another chronic pain might represent the future step following this line of research, to yield more information about the role of chemosensory stimuli in pain perception, despite the challenge of comparing the very peculiar features of the oral pain with another painful condition. In addition, given the small sample size, the affective role of odours and the heterogeneity in the reported perception of daily pain, future studies in a larger patient sample will need to take subjective variability into account to better understand the modulatory effect of chemosensory stimuli on pain perception. Furthermore, this study involved brief manipulation. Assessing the effect of regular, constant exposure to chemosensory stimuli (similar to Gossrau et al., 2020) might unravel long-term beneficial effects. These limitations notwithstanding, our study findings suggest that unpleasant stimuli worsen the perception of pain unpleasantness in patients with oral burning pain.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

MT, MF and MPC conceived the idea. AS, MPC, AZ, GZ, MF and MT contributed to the study design. AS, MPC and FB worked for the Ethical Committee of Verona University Hospital approval. GZ, MPC, AS and RN were involved in patients' recruitment and selection. MPC, AS and AZ contributed to the acquisition and analysis of the data. AS, FB and AM contributed to the statistical analysis. AS, MPC, AM, MF and MT contributed to the data interpretation. AS, MPC drafted the first version of the paper. MPC, MF and MT revised the article for intellectual content. All authors provided approval for publication of the final content.

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