# Peri-threshold Trigeminal Stimulation with Capsaicin Increases Taste Sensitivity in Humans

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## Abstract

**Introduction** Taste perception is affected by trigeminal stimuli, i.e., capsaicin. This has been studied at suprathreshold concentrations. However, little is known about taste perception at threshold level in the presence of low concentration of capsaicin. The aim of the study was to explore whether taste sensitivity for sweet, sour, salt, bitter, and umami is modulated by the presence of capsaicin in the peri-threshold range.

**Methods** Fifty-seven adults (age range 19–85 years; 32 women) with functional gustation participated in the study. Based on their perception of phenylthiocarbamide (PTC), the group was stratified into non-tasters ($n=20$) and tasters ($n=37$). Threshold for sweet (sucrose), sour (citric acid), salty (sodium chloride), bitter (quinine-hydrochloride), and umami (sodium-glutamate) tastes was estimated using a single-staircase paradigm (3-alternative forced choice; volume per trial 0.1 ml) with or without 0.9-μM capsaicin added. This capsaicin concentration had been determined in pilot studies to be in the range of oral perception thresholds.

**Results** The addition of capsaicin produced lower taste thresholds for sweet, sour, salty, and bitter but not for umami. In contrast, neither PTC taster status nor sex affected these results.

**Conclusion** The current results indicate that a low concentration of capsaicin increases gustatory sensitivity.

**Implications** The current findings provide evidence supporting different effects of capsaicin on taste perception at threshold level. It has implications for boosting taste sensitivity or flavor enjoyment with low concentration of capsaicin.

**Keywords** Taste · Irritation · Trigeminal · Mouth · Psychophysics · Thresholds

## Introduction

Growing evidence has shown that the perception of sensory cue from one modality is influenced by the simultaneous activation of other sensory modalities (Verhagen and Engelen 2006). The oral trigeminal-mediated sensation (including mechanical, thermal, chemical, and pain sensations) can affect taste perception (Braud and Boucher 2020; Mistretta and Bradley 2021). Trigeminal stimuli arising from food intake may impact on flavor perception. Certain foods are good examples of the trigeminal-taste interaction, such as carbonated sweetened beverages (Hewson et al. 2009) or spicy chili dishes. The most studied trigeminal stimulant is capsaicin, which is the main trigeminally active compound in chili pepper. Capsaicin produces irritative sensations such as tickling, stinging, burning, heat, or pain.

Previous studies have described suppressive effect of capsaicin (either in a capsaicin-taste mixture or prior mouth rinse) on the intensity of sweet, bitter, salty, and umami tastes in humans (Green and Hayes 2003; Green and Schullery 2003; Lawless and Stevens 1984; Narukawa et al. 2011; Prescott and Stevenson 1995; Simons et al. 2002), with few showing no effect of capsaicin on salty taste intensity (Lawless and Stevens 1984; Prescott et al. 1993). Conversely, studies have also demonstrated the effect of taste on the

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capsaicin-induced burning sensation. Prescott et al. (1993) showed the burning sensation produced by capsaicin solution (6.5 μM, 13.1 μM, or 26 μM) was uninfluenced by sucrose (0.1–0.4 M), but the burning sensation of 13.1-μM capsaicin was increased by NaCl (0.075–0.3 M), and that the effect of NaCl on burning sensation varied according to the capsaicin concentrations. However, another study showed that the presence of sweet taste decreases capsaicin irritation by approximately 50%, and the effect can be partially reversed by adding a sweet taste inhibitor (lactisole) (Smutzer et al. 2018). This results indicate that the effect of sucrose on capsaicin perception is mediated by the sweet taste receptor (Smutzer et al. 2018). In addition, several studies found suprathreshold level of capsaicin can elicit bitter (Green and Schullery 2003; Green and Hayes 2004; Just et al. 2007) or salty taste (Lawless 1984) sensations, although only found in part of the study participants and fade away shortly after capsaicin application. In fact, the co-localization of capsaicin receptors (vanilloid receptor subtype 1) with sweet or bitter taste receptors has been found in rat (Moon et al. 2010) and human (Jahng et al. 2010) taste papillae.

While extensive research had been done regarding the capsaicin-taste interaction at suprathreshold level, less has been investigated when both are presented at threshold levels. Taste threshold is defined as the lowest concentration of a compound that can be discriminated or recognized from the solvent. Both reflecting gustatory functions, the threshold (sensitivity) and suprathreshold intensity were poorly correlated for basic tastes, indicating each individual measure characterizes a separate component of the taste perception (Bartoshuk 1978; Keast and Roper 2007). Correlations were found between the sensitivity and preferences for certain types of taste in humans (Chamoun et al. 2019), suggesting the possibility of change taste (sensory)-based food preferences through taste sensitivity modulation. A few previous studies have demonstrated the threshold for capsaicin based on aqueous solutions, with a threshold range between 0.29 and 1.14 μM (in a 10-ml volume) (Lawless et al. 2000; Sizer and Harris 1985). Moreover, the coexistence of capsaicin receptors with sweet and bitter taste receptors in papillae (Jahng et al. 2010; Moon et al. 2010) also provides a molecular basis for potential interactions between stimuli from the two modalities at threshold levels (Mistretta and Bradley 2021).

Therefore, the primary aim of this study was to investigate the impact of capsaicin on taste sensitivity. Specifically, recognition thresholds of sweet (sucrose), salty (sodium chloride; NaCl), bitter (quinine-hydrochloride), sour (citric acid), and umami (monosodium glutamate, MSG) were assessed with and without addition of very low concentrations of capsaicin (peri-threshold level). Moreover, since the perceived capsaicin-induced irritation

intensity differs as a function of the participants' inherited sensitivity to bitter compounds (Prescott and Swain-Campbell 2000), the current study was also designed to explore the influence of phenylthiocarbamide (PTC) taster status on the postulated effects of capsaicin on taste sensitivity.

## Materials and Method

### Participants

Fifty-seven non-smoking healthy subjects participated (age mean = 33.0 years, SD = 17.8; range from 19 to 85 years; 25 men, 32 women; BMI mean = 22.2, SD = 2.7, range from 16.7 to 29.5). Participants' gustatory function was screened via taste sprays that consist of suprathreshold concentrations (diluted in 100-ml distilled water) of "sweet" (10-g D-saccharose), "sour" (5-g citric acid), "salty" (7.5-g NaCl), and "bitter" (0.025-g quinine-hydrochloride) solutions (Hummel et al. 2013). All participants were able to identify each of the four tastes correctly. Participants were asked to place a 3.80 cm × 1.43 cm strip of filter paper impregnated with 0.007 mg of phenylthiocarbamide (PTC; Sensonics, Inc., NJ, USA) in the mouth for a minimum of 5 s. Individuals who rated the bitterness intensity with score 1 = ''barely detectable'' were considered "non-tasters" (NT; $n = 20$, age mean = 45.8 years, SD = 22.4; 7 women), whereas those who detect a bitter sensation ( with ratings of 2 weak, 3 moderate, 4 strong, or 5 extremely strong) were classified as "tasters" (T; $n = 37$, age mean = 26.1 years; SD = 9.4; 25 women) (Bartoshuk et al. 1994). Participants (Table 1) reported whether they eat hot spices with a yes-or-no question. The study was conducted in accordance with the Declaration of Helsinki and its design was approved by the Ethics Committee at the TU Dresden. The power calculation using G*Power tool software (Faul et al. 2007) showed that a sample size in the present study of $n = 57$ would be adequate to detect significant differences (Wilcoxon signed-rank test, $a = 0.05$, power = 0.8) given a medium effect size of $d = 0.4$.

Table 1 Participants information of this study

| Category | Subcategory | No. of participant | Percentage |
|---|---|---|---|
| Gender | Females | 32 | 56.1% |
| | Males | 25 | 43.9% |
| PTC taste status | Taster | 37 | 64.9% |
| | Non-taster | 20 | 35.1% |
| Spicy food consumption[2] | Yes | 20 | 35.1% |
| | No | 37 | 64.9% |

## Capsaicin Concentration

A pilot test was carried out with 12 subjects who were not involved in later experiments to determine the capsaicin concentration which would not yield apparent trigeminal responses and to be used for taste sensitivity tests. Because the capsaicin is insoluble in water, the samples were prepared in 95% ethanol solutions. We dissolve the capsaicin (analytical standard of ≥ 99.0% by HPLC; Sigma-Aldrich, Steinheim, Germany; order number 12084) with ethanol first, and then we diluted the capsaicin-ethanol solution further into the water to reach the final concentrations, with the final ethanol concentration at a level imperceptible to participants (below 0.5%). A concentration of 0.9-μM capsaicin was determined to be in the range of peri-threshold level. The concentration was also comparable to that shown in previous research (Bovelet et al. 2015; Narukawa et al. 2011), which the capsaicin concentrations were 0.5 μM, 1 μM, and 0.9 μM, respectively.

## Taste Sensitivity Test

Gustatory recognition threshold was assessed in solutions with or without added capsaicin for five basic tastes: sweet (sucrose), sour (citric acid), salty (NaCl), bitter (quinine-hydrochloric acid), and umami (MSG). For each taste, six dilutions were prepared based on the work of Gudziol and Hummel (2007), and were identified using equivalence numbers 1 to 6 with highest concentration given to number "6" and lowest concentration given to number "1" (Table 2). Two series of dilutions were prepared for each taste. These differed only in the composition of the solvent. One was made with the solvent (distilled water) containing minute amounts of ethanol (0.00275%); these amounts of ethanol did not produce a noticeable taste when tried at volumes of 0.1 ml. The other was made with the solvent (distilled water with the 0.00275% alcohol) added with capsaicin (0.9 μM). All prepared samples were kept at room temperature and protected from light. All dilution series were tested per subject, i.e. the five series without capsaicin and the five series

**Table 2** Molar concentrations for taste solutions under each dilution step

| Dilution steps | Sucrose (mM) | Citric acid (mM) | NaCl (mM) | Quinine (mM) | MSG (mM) |
|---|---|---|---|---|---|
| 6 | 21.9 | 15.6 | 41.1 | 0.133 | 17.7 |
| 5 | 11.0 | 7.8 | 20.5 | 0.067 | 8.9 |
| 4 | 5.5 | 3.9 | 10.3 | 0.033 | 4.4 |
| 3 | 2.7 | 2.0 | 5.1 | 0.017 | 2.2 |
| 2 | 1.4 | 1.0 | 2.6 | 0.008 | 1.1 |
| 1 | 0.7 | 0.5 | 1.3 | 0.004 | 0.6 |

with capsaicin in the solvent. During experiments, half of the participants received the samples without capsaicin first, and the other half received the samples with capsaicin first. The test order for different taste qualities was the same for all participants.

Participants were asked to refrain from food, drink (except water), cigarette, or chewing gums from at least 30 min prior to the test. Taste recognition threshold test was performed following a single-staircase three-alternative forced choice procedure with four reversals, in which the subjects were provided with three samples (two controls and one containing the target stimuli) per trial, in ascending order from the lowest to the highest concentrations. In brief, a pipette triplet of drops (100 μl each) comprising two drops of the solvent (ethanol–water solution or ethanol–water-capsaicin solution) and one sample drop additionally containing one of the five tastes (sweet, salty, bitter, sour, or umami) were administered sequentially onto the middle of the anterior third of the extended tongue (Gudziol and Hummel 2007). For each trial, participants were asked to choose the sample that most likely contained one of the tastes and name the taste quality (sweet, sour, bitter, salty, or umami). The taste samples were administered in increasing concentrations, starting with the highest dilution and sorted according to taste. If a wrong sample was selected, the concentration was increased in the subsequent trial until two consecutive correct answers were given, the value of which was noted as the first turning point. Then, the concentration was lowered again until subjects did not identify the taste anymore. This concentration was noted as the next turning point. Afterwards, the concentration was increased again until the taste was recognized two times in a row (third turning point) which triggered a lowering of the taste concentrations until the taste was no longer identified (forth turning point). The average of the four turning points (the corresponding taste concentrations) was used as a threshold estimate. The interval between two trials was approximately 20 s, during which participants rinsed their mouth with tap water. During the test, if participants could not recognize the taste quality at the highest concentration (dilution step 6), they received a score of 7 (Gudziol and Hummel 2007). The total trial numbers and the whole duration of the test varied between participants, but in general, the whole test took approximately 40 min.

## Ancillary Tests

Two sequential ancillary tests were performed in a small sample (N = 10, mean age = 26.3 years; SD = 9.4; six females and four males) from the main experimental cohort on separate days. First, participants' recognition threshold for five tastes with no capsaicin was assessed. The first ancillary test was aimed to investigate whether irritation of the trigeminal nerve with capsaicin influences taste sensitivity

if the irritation occurred before the actual taste sample was administered. Participants kept 2 ml of a capsaicin solution (0.9 μM) in the mouth for 4 min and then spat it out. After a pause of 2 min, the same taste sensitivity test without capsaicin addition was performed again. The second ancillary test was to find out whether the capsaicin-induced irritation outside the oral cavity influences taste sensitivity. The Capsamol® ointment (WÖRWAG PHARMA, Böblingen, Germany) with the active ingredient cayenne pepper thick extract, corresponding to capsaicinoids calculated as capsaicin (50 mg/100 g ointment), was used for this test. According to the package leaflet, the ointment is used for the external treatment of muscle pain. A very low dose was applied, and the test subjects were only allowed to take part in the test if their skin was intact and free of open areas. A cotton swab was dabbed with the ointment. The subject was asked to use the cotton swab to spread some ointment on the skin of the left and right cheek. A few seconds after application, the subjects stated that they felt sharp and burning, but well tolerable sensations on the skin (intensity rating of 6 or 7 on a 10-point scale). This was followed by the determination of the threshold for the sweet (sucrose) and salty (sodium chloride) tastes without added capsaicin. A selection of two tastes was considered sufficient to receive some orientation of the potential distracting influence of external capsaicin treatment.

## Statistical Analyses

Data were analyzed using IBM SPSS Statistics version 21 (Chicago, IL). The effect of capsaicin on taste sensitivity was analyzed using repeated measures ANOVA. The influences of PTC taste status on taste sensitivity with and without added capsaicin were analyzed using mixed design ANOVA, with one between-subject factor (PTC taster and non-taster) and two within-subject factors (taste quality, capsaicin addition), including sex and age as co-variables of no interest. Post-hoc comparisons between independent variables were performed with Bonferroni corrections. All analyses were analyzed using SPSS (v. 21) and the significance threshold

was set to α ¼ 0.05. Effect sizes of the ANOVA terms are reported as $\eta^2$.

## Results

### Effect of Capsaicin on Taste Sensitivity

There was a significant effect of capsaicin addition ($F_{(1,55)} = 25.1$, $p < 0.001$, partial $\eta^2 = 0.31$) on taste sensitivity (Fig. 1). Pairwise comparisons revealed that the addition of capsaicin significantly decreased the threshold score for sweet ($p = 0.01$), salty ($p = 0.002$), bitter ($p = 0.01$), and sour ($p = 0.001$) tastes, but not for umami ($p = 0.15$). We observed no significant interaction between taste quality and capsaicin addition on sensitivity score ($F_{(4,220)} = 0.7$, $p = 0.59$).
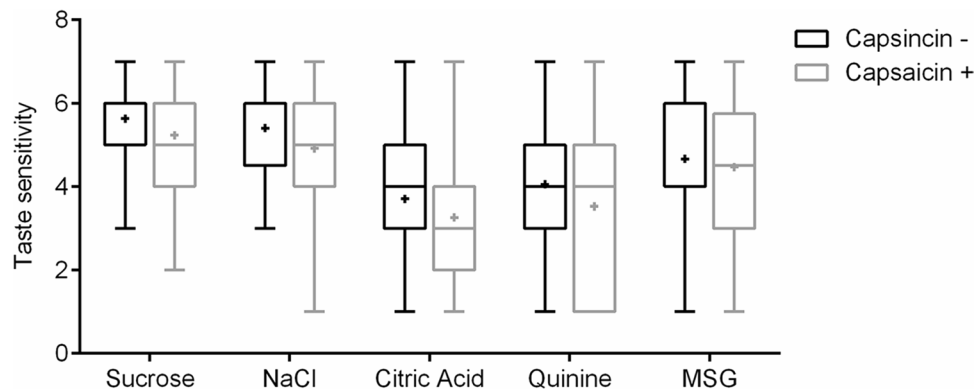
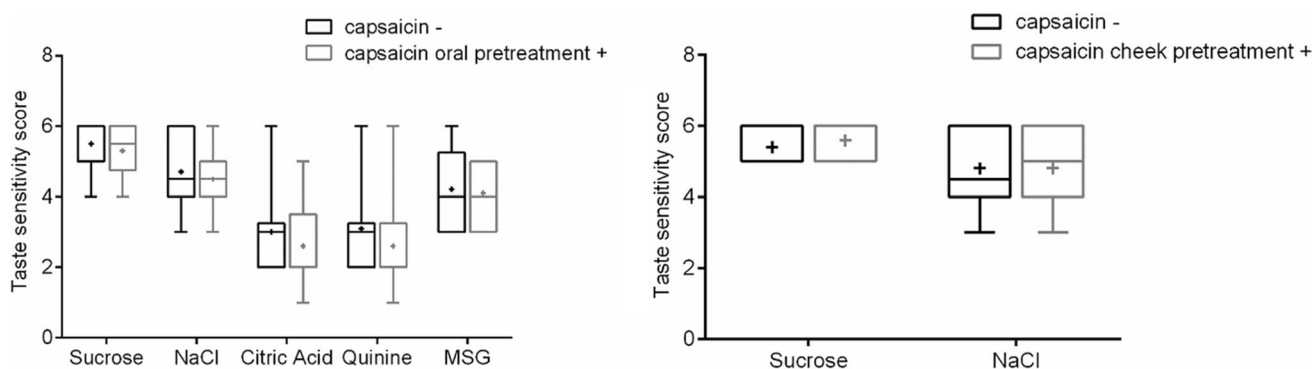### Effect of Oral and Cheek Capsaicin Pretreatment on Taste Sensitivity

The ancillary tests showed that there was a weak but significant effect of oral capsaicin pretreatment on taste sensitivity (Fig. 2) ($F_{(1,9)} = 5.13$, $p = 0.049$); however, none of the taste qualities survived the significant threshold after correction for multiple comparisons (for all $p > 0.05$). There is no significant interaction between taste quality and oral capsaicin pretreatment on taste sensitivity ($F_{(4,36)} = 0.26$, $p = 0.91$). In addition, compared to taste sensitivity without capsaicin, pretreatment with Capsamol® ointment on the cheek had no significant effect on taste sensitivity ($F_{(1,9)} = 0.13$, $p = 0.73$).

### Factors Influencing the Effect of Capsaicin on Taste Sensitivity

There was no significant interaction between PTC taster status and capsaicin addition on taste sensitivity ($F_{(1,52)} = 0.34$, $p = 0.56$). There was neither significant interaction between gender  capsaicin on taste sensitivity.

Fig. 1 Effect of 0.9-μM capsaicin (capsaicin+) on taste recognition threshold. In each box and whisker plot, the central line denotes the median and the plus (+) denotes the mean. The upper edge of the box represents the 75% quartile, the lower edge represents the 25% quartile, and the ends of the whiskers represent the maximum and minimum data points

**Fig. 2** Effect of oral (left panel) and cheek (right panel) pretreatment with capsaicin on taste recognition threshold in a subsample of participants ($N = 10$). In each box and whisker plot, the central line denotes the median and the plus (+) denotes the mean. The upper edge of the box represents the 75% quartile, the lower edge represents the 25% quartile, and the ends of the whiskers represent the maximum and minimum data points

## Discussion

Results from the current study showed that a low concentration of capsaicin increased taste sensitivity by lowering the recognition thresholds. Capsaicin may affect transmitter release, detection at a receptor level, transduction, and central-nervous integration. The capsaicin receptor (vanilloid receptor subtype 1) are co-localized with basic taste (sweet and bitter) receptors in human taste papillae (Jahng et al. 2010). Capsaicin itself is associated with bitter or sweet sensations (Green and Schullery 2003; Just et al. 2007). Besides, taste perception had been suggested to have a somatosensory component. For example, tactile stimulation of the taste papilla elicited chemical taste sensations (Cardello 1981), and strong cross-desensitization of the burning and stinging of NaCl and citric acid was mediated by activation of the capsaicin-sensitive fibers (Gilmore and Green 1993). Thus, capsaicin may affect taste transduction or taste receptor cell excitability and hence affect taste perception (Simons et al. 2003). Besides, oral pretreatment with capsaicin had a similar effect on decreasing taste threshold as compared to the capsaicin-taste mix, indicating a potential impact of capsaicin on taste perception, which lasts at least for several minutes. In contrary to multiple studies showing suppressive effect of capsaicin on taste intensity perception, one previous study had found that a low concentration of capsaicin (0.5 μM or 1 μM) increased the taste intensity of NaCl solution (Narukawa et al. 2011). It is likely that the concentration of capsaicin is important for its effect on capsaicin-taste binary mixture perception, which has been well-documented in taste-taste interactive effect (Wilkie and Phillips 2014). Previous study showed that capsaicin solution, when applied at high concentrations, were perceived as bitter by half of the study participants, whose perception of irritation was not different. This suggested independent transduction mechanisms for taste perception (bitter or sweet) and chemesthetic sensations (irritation) of capsaicin (Green and Hayes 2004). However, the current results may also be possibly related to the inter-papillary capsaicin-taste interaction caused by competition for receptor sites. Taken together, the trigeminal-taste cross-modal interplay could rely on multilevel interactions.

Central top-down modulation may also contribute to the effect. Brain imaging studies reported integration of capsaicin and taste perception in the anterior ventral insula (Rudenga et al. 2010). However, only limited portions of neurons in the primate's insula/operculum taste cortex respond to capsaicin stimulation (Verhagen et al. 2004). Thus, capsaicin elicited activation of the trigeminal system may gate or modulate gustatory processing at some stage in the taste pathway such as the solitary nucleus or thalamus. Presumably, the presence of trigeminal and taste stimuli increases the perceptual complexity which may produce an advantage in the processing of the gustatory information, similar to findings in bimodal odor perception (Pellegrino et al. 2017). One possible explanation may be that oral exposure to low concentrations of capsaicin produces an attentional capture of the taste sensation while high concentrations of capsaicin direct the attention away from taste to irritation that leads to a reduction of perceived intensity. However, considering the present ancillary experiments with capsaicin stimulation on the cheek, such attentional effects do not seem to be very strong. Taken together, the effect of taste sensitivity enhancement by low concentration of capsaicin could conceivably involve both peripheral and central neural interactions (Rhyu et al. 2021).

The null finding regarding the effect of PTC taster status may be due to the scaling method used for separating taster from non-tasters. A scale that is often used for determining these classifications is an adjective-labeled scale with ratio properties, such as the labeled magnitude scale (LMS) or the general labeled magnitude scale (gLMS), which were

recommended for comparison across groups (Bartoshuk 2000; Bartoshuk et al. 2004). Categorical scales, such as the one used in the current study, may have different properties, i.e., one person's rating of 4 cannot be assumed to be twice as intense as another person's rating of 2. Having said that, an advantage of the presently used scale was that it is easily comprehended by the participants. Future studies are needed to explore differences between the two types of scales in depth.

The 0.9-µM capsaicin used in the current study was determined as close to the threshold level, which means the sensation of irritation was not detectable or only barely detectable by the participants. This capsaicin concentration was comparable to the previously reported range for capsaicin threshold (0.29 to 1.14 µM in a 10-ml volume) (Sizer and Harris 1985), or the group mean capsaicin threshold of 1 µM (0.31 mg/l in a 10-ml volume) (Lawless et al. 2000). Although this concentration is higher compared to the capsaicin threshold level (e.g. a threshold between 0.16 and 0.49 µM) reported in other studies (Okamoto et al. 2018; Orellana-Escobedo et al. 2012), it is distinct from (far below) the concentration that could induce perception of irritation, for example, a concentration of around 0.36 µM (0.11 ppm) was barely detectable, and 0.9 µM of capsaicin (0.275 ppm) was barely detectable to weak sensation (Nolden and Hayes 2017). The variability between thresholds obtained in different studies may also be explained by different modes of stimulation and especially by differences in the volume of the administered stimuli. Also, because sensitivity of capsaicin varies between individuals and may be affected by multiple factors, a direct comparison of capsaicin threshold may be inappropriate.

The increased taste sensitivity by capsaicin may have nutritional implications. For example, generic taste loss (e.g. reduced taste sensitivity) is common among elderly people (Mojet et al. 2001). In addition, the decrement in food enjoyment among patients with chemosensory dysfunctions seems to be extremely high (from 60 to 90% of the patients) (Croy et al. 2014; Mattes et al. 1990). There is an trigeminal-taste interaction in palatability processing (Berridge and Fentress 1985); therefore, the addition of low concentrations of capsaicin in food product may constitute a potential approach to boost taste sensitivity, food palatability, and the enjoyment of foods (Ludy et al. 2015).

Several limitations to the current study need to be acknowledged. First, some participants failed to recognize the taste solution at the highest concentration, which limit the sensitivity of the gustatory test; future researches with broader range of concentrations are necessary. Second, although a pilot study suggested the concentration used was in the range of thresholds, future studies may include the assessment of individual capsaicin thresholds. This might be helpful to further understand the role of conscious capsaicin perception on taste sensitivity. Additionally, the taste solutions with added

capsaicin may have induced irritation among some participants whose capsaicin threshold was below 0.9 µM, which might be related to a negative emotional status. The emotions should be assessed and controlled in future research. Finally, the participants' age range was broad (19–85 years) which may have effect on the results; hence, the findings related to these analyses need to be validated for different age groups in future studies with large sample size.

In conclusion, the current study showed a peri-threshold concentration of capsaicin increases gustatory sensitivity when present in taste solutions. Given that taste perception at the threshold or suprathreshold levels reflect different aspects of the gustatory function (Webb et al. 2015), these findings suggested the complexity of oral perception of binary taste-trigeminal mixtures.

## Declarations

**Conflict of Interest** All authors declare no competing interests.

**Ethical Approval** The study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of TU Dresden.

**Informed Consent** Written informed consent was obtained from all participants prior to the experiment.

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