Odor-induced saltiness enhancement: Insights into the brain chronometry of flavor perception

Charlotte Sinding, Henri Thibault, Thomas Hummel, Thierry Thomas-Danguin

NEUROSCIENCE
INTERNATIONAL BRAIN IBRO RESEARCH ORGANIZATION
RESEARCH ARTICLE
C. Sinding et al. / Neuroscience xxx (2020) xxx–xxx

Odor-Induced Saltiness Enhancement: Insights Into The Brain Chronometry Of Flavor Perception

Charlotte Sinding,[a]* Henri Thibault,[a] Thomas Hummel[b] and Thierry Thomas-Danguin[a]

[a] *Centre des Sciences du Goût et de l'Alimentation, AgroSup Dijon, CNRS, INRAE, Université Bourgogne Franche-Comté, F-21000 Dijon, France*

[b] *Smell & Taste Clinic, Department of Otorhinolaryngology, TU Dresden, Dresden, Germany*

Abstract—Flavor perception results from the integration of at least odor and taste. Evidence for such integration is that odors can have taste properties (odor-induced taste). Most brain areas involved in flavor perception are high-level areas; however, primary gustatory and olfactory areas also show activations in response to a combination of odor and taste. While the regions involved in flavor perception are now quite well identified, the network's organization is not yet understood. Using a close to real salty soup model with electroencephalography brain recording, we evaluated whether odor-induced saltiness enhancement would result in differences of amplitude and/or latency in late cognitive P3 peak mostly and/or in P1 early sensory peak. Three target solutions were created from the same base of green-pea soup: i) with a ''usual" salt concentration (PPS2), ii) with ''reduced" salt (PPS1: −50%), and iii) with reduced salt and a ''beef stock" odor (PPS1B). Sensory data showed that the beef odor produced saltiness enhancement in PPS1B in comparison to PPS1. As the main EEG result, the late cognitive P3 peak was delayed by 25 ms in the odor-added solution PPS1B compared to PPS1. The odor alone did not explain this peak amplitude and higher latency in the P3 peak. These results support the classical view that high-level integratory areas process odor–taste interactions with potential top-down effects on primary sensory regions.

Key words: Olfaction, Taste, Integration, Perception, Food, Electroencephalography.

INTRODUCTION

We experience food as a unitary perception, which we commonly call ''taste". This common ''taste" is actually a holistic perception of at least olfactory and gustatory inputs, called ''flavor perception". Odor-induced taste enhancement (OITE) is a phenomenon that derives from the integration of taste and odor into flavor perception. For example, it was shown that a strawberry odor could increase the sweetness of a whipped-cream with sucrose. This result was first highlighted by Frank and Byram (1988). They also defined a fundamental principle of OITE, namely that only congruent odors and tastes would produce OITE, therefore pointing at the role of experience in shaping OITE. Indeed congruent, familiar, and complex flavor mixtures -which are more prone to be perceived as configural units- are more effective in producing OITE (Prescott et al., 2004; Small and Prescott, 2005; Labbe et al., 2006). Several independent labs have later replicated this finding and further demonstrated odor-induced taste enhancement of other tastes (Frank and Byram, 1988; Schifferstein and Verlegh, 1996; Sakai et al., 2001; Djordjevic et al., 2004; Prescott et al., 2004; Lawrence et al., 2009; Wang et al., 2019). OITE is, therefore, a reliable phenomenon. Other odor–taste interactions have also been established, such as the taste-induced odor enhancement (i.e., the reverse effect of OITE) (Lim et al., 2014; Linscott and Lim, 2016). In our study and the discussion of the results, we focused on the odor-induced saltiness enhancement only.

Most studies on OITE used water with sugar or salt and aroma, which produced non-ecologically relevant, unfamiliar and likely unpleasant perceptions (Prescott et al., 2004; Welge-Lüssen et al., 2005; Marshall et al., 2006; Prescott and Murphy, 2009; Welge-Lussen et al., 2009; Lim and Johnson, 2011, 2012; Seo et al., 2013). To overcome this issue, one can use close-to-real food models, which produce more familiar and holistic food representations. It may also facilitate the OITE with appropriate congruent aroma and smooth out significant hedonic variations that could mask subtle integration mechanisms (Prescott, 1999; Small, 2012; Mroczko-Wąsowicz, 2016; Thomas-Danguin et al., 2016). Other studies used more complex and familiar food models.

*Corresponding author.
E-mail address: charlotte.sinding@inrae.fr (C. Sinding).
Abbreviations: EEG, Electroencephalography; ERPs, event-related potentials; fMRI, functional magnetic resonance imaging; OISE, odor-induced saltiness enhancement.

https://doi.org/10.1016/j.neuroscience.2020.10.029
0306-4522/

Please cite this article in press as: Sinding C et al. Odor-Induced Saltiness Enhancement: Insights Into The Brain Chronometry Of Flavor Perception. Neuroscience (2020), https://doi.org/10.1016/j.neuroscience.2020.10.029

For example, ethyl 2-methyl butanoate was used in a fruit juice to enhance sweet perception (Barba et al., 2018). In another study, the authors used a sardine aroma to significantly enhance saltiness in a cheese model (Syarifuddin et al., 2016). In the present study, we studied odor-induced saltiness enhancement (OISE). A salty food model has been designed from a green-pea soup base, which was chosen for its composition with a negligible quantity of salt and an easily identifiable odor component. Five conditions with different salt and aroma quantities were selected to produce OISE according to previous results (Lawrence et al., 2009; Nasri et al., 2013). The first condition was the soup added with a standard (usual) level of salt (6.25 g/L), to record the most familiar level of saltiness in this kind of product and to test whether OISE could reinforce saltiness up to a ''normal" saltiness intensity. The second solution was 50% salt reduced. The third condition, which is the target beverage, was reduced in salt (50%) and supplemented with a ''beef stock" odor chosen for its potential to increase saltiness perception. Finally, two controls were tested, the base soup alone and the base soup with the odor component, to test the effect of added odor in the food model.

Endogenous mechanisms produce OITE in the brain. Several functional magnetic resonance imaging (fMRI) studies have investigated brain areas involved in flavor perception, leading to the identification of a relatively consensual flavor network (Rolls and Baylis, 1994; Rolls, 1997; De Araujo et al., 2003; Small and Prescott, 2005; Seo et al., 2013; Seubert et al., 2015). In these studies, supra-additive activations for the odorant-tastant mixture were found in high-level areas, in the orbitofrontal cortex, the dorsal mid-insula, and the perirhinal cortex (De Araujo et al., 2003; Seo et al., 2013; Small et al., 2013; Seubert et al., 2015). However, odor–taste convergence was also found in the primary gustatory cortex, more precisely in the anterior insula and frontal operculum (De Araujo et al., 2003; Seubert et al., 2015). Regarding these fMRI results, two views exist i) one consists in a hierarchical integration, starting with a parallel unimodal encoding of odor and taste in their respective cortices and further elaborated by higher-order unimodal zones, before converging onto multisensory integrative areas to form the flavor perception; ii) while the second proposed that odor and taste are already integrated into primary olfactory and gustatory cortices (Small and Prescott, 2005; Verhagen and Engelen, 2006; Verhagen, 2007; Prescott, 2012; Small et al., 2013).

To understand whether odor and taste already interact in the primary cortices or later in higher cortices, we need to study the chronometry of odor–taste integration and interaction. Electroencephalography (EEG) is of particular interest to gain insights into these questions. It permits quantitative measures of global brain activations with a resolution of milliseconds. Olfactory-gustatory event-related potentials (ERPs) give access to the chronometry of interactions between gustatory and olfactory cortices. To do so, one should select appropriate stimuli, which permit to isolate variables of interest (e.g., real saltiness or induced saltiness). An event-related potential (ERP) is a sequence of brain components identified by the maximum amplitudes of a series of positive and negative peaks, from P1 the earliest to P3 the latest measurable. ERP reflects the different steps of information processing in the cortex. The peak amplitude and latency provide a quantitative measure of the intensity and/or amount of neurons discharging in a synchronized way in response to the stimulus provided at t0. The early P1 peak mainly occurs in primary sensory areas and represents the processing of sensory and chemically related properties of food. The late P3 peak occurs mostly in high integratory and cognitive areas and illustrates endogenous processing such as emotional, semantic, decisional, and top-down mechanisms towards primary regions.

While an extensive literature exists on food-related visual event-related potentials (ERPs) (for review, see Carbine et al., 2018), very few studies were based on the senses directly involved in flavor perception: olfaction and gustation. To the best of our knowledge, no EEG studies showed the brain mechanisms of odor-induced taste enhancement. However, Welge-Lüssen et al. (2005), Welge-Lüssen et al. (2009) designed two studies to show the effect of taste (sucrose or lemon pulp) on odor (vanilla) or trigeminal perception (elicited by CO_2) respectively. In these studies, participants were sucking on a taste dispenser when an odor was sent orthonasally (Welge-Lüssen et al., 2005) or retronasally (Welge-Lüssen et al., 2009) with an olfactometer. This moment corresponded to the start of the ERP, which therefore highlighted the odor processing modulated by the taste. Although sensory results did not show odor or taste enhancement, ERPs tended to higher amplitude and reduced early and late peak latencies (P1 and P3), only when the taste matched the odor. These two peaks represent the earliest and latest observable brain mechanisms of the evoked potential measured with EEG. Therefore, Welge-Lüssen's studies showed that taste sped up the processing of a congruent odor from the very first processing mechanisms (P1 peak). Although these results did not permit observing supra-additive effects for a flavor mixture compared to its odorant-tastant components, they were interestingly discussed in terms of priming. To observe supra-additive effects, one should synchronously stimulate the olfactory and gustatory cortices and compare activation for the mixture to the single components. Recent electrophysiological results in animal reconsidered the classical view of late odor–taste integration. They indeed showed activations in a region of the primary olfactory cortex, i.e., the piriform cortex, in response to sucrose (sweet taste), which the authors considered early interactions (Maier et al., 2012, 2015; Maier, 2017). These results, therefore, challenge the classical theory of late brain interactions between odor and taste and suggest that primary olfactory and gustatory areas may interact as early as the primary EEG peaks such as P1 (100–200 ms).

Therefore, we addressed the chronometry of the integration of odor and taste into flavor perception, in

Please cite this article in press as: Sinding C et al. Odor-Induced Saltiness Enhancement: Insights Into The Brain Chronometry Of Flavor Perception. Neuroscience (2020), https://doi.org/10.1016/j.neuroscience.2020.10.029

humans, by studying the chronometry of brain mechanisms leading to OISE. The classical view, which consisted of a hierarchical integration of flavor, from primary gustatory and olfactory areas to secondary or tertiary integratory cortices, has been further expanded to explain OITE (Verhagen and Engelen, 2006; Verhagen, 2007; Small, 2008; Prescott, 2012). Following the integration of odor and taste into the flavor, top-down feedback may control activations in gustatory areas producing an increased endogenous perception of saltiness intensity. Following this reasoning, the odor-induced saltiness enhancement should be observed only on the ERP's late components. Therefore, we hypothesized that differences of amplitude and/or latency could be observed mostly on the latest peak of olfactory-gustatory ERP (the late P3 peak) and not on the P1 peak involving brain circuits responding to exogenous properties of the food such as tastant concentration. In the study, we did not address whether retronasal odor stimulation is necessary for the supra-additivity of the flavor solution. Still, to avoid any potential bias, we used only retronasal odor perception. Because of the presumed importance of oral referral in flavor perception (Small, 2008; Spence, 2016), which is supported by EEG results (Welge-Lüssen et al., 2009; Masaoka et al., 2010), participants should be stimulated in-mouth so that aromas could be perceived through the retronasal route. However, the aroma perception is supposed to be maximal when participants are swallowing. A dedicated paradigm was designed to account for the swallowing artifacts and the need for synchrony between odor and taste perceptions.

EXPERIMENTAL PROCEDURES

Participants

Twenty-one participants naïve to olfactory and gustatory testing were recruited (18–30 years old, 15 women). Data from 8 participants were discarded because of their low number of epochs after artifact rejection (less than 6 epochs in at least 2 stimulus conditions). The stimulation of participants in-mouth during EEG recording is tricky due to tongue and jaw movements during stimulation, which induce many artifacts. Power analysis (GPower) showed that 13 participants were sufficient to have adequate power on the amplitude and latencies of peaks (power = 0.82). Participants were asked not to drink or eat, at least 1 h30 min before the test sessions, to minimize food exposure. All participants were right-handed (self-reported) and normosmic (European Test of Olfactory Capabilities, ETOC; Thomas-Danguin et al., 2003). The experimental procedure was explained to each participant before recruitment and again before each test session. Participants signed an informed consent form to participate in the study. They received 10€ compensation for each hour spent performing test sessions. The study was conducted following the Helsinki Declaration and was validated by the ethics committee CPP EST 1N°2016/62 (ID RCB: 2016-A01732-49).

Solutions

Three stock solutions were prepared: (1) the base solution was a green-pea soup extracted from an unsalted green-pea puree (Nestlé®, green pea NaturNes). The puree was centrifuged at 15,000 RPM for 20 min at 20 °C (rotor JLA 16–250, Beckman Coulter), and the supernatant, which contained everything but the non-soluble particles, was collected and stored at −20 °C. (2) A salty solution was prepared at 12.5 g/L NaCl in Evian® water (Danone, France). (3) The aromatic solution (B) was prepared at 500 ppm of Beef Bouillon Flavor (YF 555,768 CB, Firmenich) in Evian water. Evian water was chosen because, in Dijon, it is the bottled water perceived as the most neutral (Teillet et al., 2010). Solutions 2 and 3 were prepared 24 h before the test and kept at 4 °C. The test's day, the base solution was defrosted in the microwave for 5 minutes (defrost position). All solutions were then heated at 35 °C (all tubes of the gustometer are water bath) in the gustometer to match the buccal temperature, 1 h before the test. Five target solutions were then mixed using the gustometer: PP (50% base solution + 50% Evian Water), PPB (50% base solution + 25% aromatic solution + 25% Evian water), PPS1 (50% base solution + 25% salty solution + 25% Evian water), PPS1B (50% base solution + 25% salty solution + 25% aromatic solution), PPS2 (50% base solution + 50% salty solution). Evian water, PP, and PPB contained negligible levels of salt (maximum 0.25 g/L), which are lower than the standard detection threshold in water (0.58 g/L) (Bartoshuk, 1974). Furthermore, B contained minimal salt (0.03 g/L).

Experimental procedure

The entire experiment took place in a ventilated air-conditioned room (23 °C), dedicated to EEG recording, with controlled light and acoustic insulation. The procedure was planned over two sessions: 1) a training session and 2) an EEG recording session, spaced by a maximum of 8 days, to keep the training effective.

Training session

Before the training session, participants were tested for their general olfactory abilities using the ETOC (Thomas-Danguin et al., 2003). This test consists of an odor supra-threshold detection task combined with an identification task for 16 different odors using a 4-alternatives forced-choice procedure (1 vial odorized among 4, then 1 correct odor descriptor among 4). The minimum score required to consider normal olfactory abilities was 12 (out of 16). All participants succeeded in the ETOC test.

The training session's objective was twofold: 1) to familiarize participants with the gustometer and the testing room and 2) train participants to breathe with the velum opened. Solutions were delivered with a GU002 gustometer (Burghart, Wedel, Germany). Initially, the gustometer is designed to spray raw taste solutions on the extended tongue; however, we delivered solutions directly in the mouth to produce the retronasal

Please cite this article in press as: Sinding C et al. Odor-Induced Saltiness Enhancement: Insights Into The Brain Chronometry Of Flavor Perception. Neuroscience (2020), https://doi.org/10.1016/j.neuroscience.2020.10.029

perception in the present study. To avoid movements that could cause artifacts during EEG recordings, excess solution and saliva were slowly and continuously withdrawn from the mouth, and participants did not need to swallow. A spray head was hand manufactured specifically for each participant to fit the mouth cavity (modification of the Burghart spray head and fixation on a piece of a hygoformic® Orsing tubing). The solutions were sprayed as a thin mist over a large part of the tongue, permitting homogeneous taste perception over the tongue and odorant diffusion. It also reduces somatosensory and motor artifacts that may occur when the participant has to drink from a glass or even when drops are delivered on the tongue. Furthermore, a salivary ejector head (hygoformic® Orsing) connected to a peristaltic pump permitted removing excess solution and saliva from the mouth to minimize swallowing artifacts during EEG recordings. Participants kept both tubes (external diameter: 4 mm) in the mouth by gently clenching the teeth around them. Participants were asked not to swallow during the sessions.

To trigger as much as possible odor and taste perception in a synchronous way, we trained participants during a dedicated session to inhale through the mouth and exhale through the nose while maintaining an open velum throughout the recording session (free circulation of aromas to the nasal cavity). The combination of in-mouth stimulation for retronasal perception and the open-velum breathing favored the passage of a maximum of odorant volatiles into the nasal cavity. It allowed an increased synchronization between odor and taste perception compared to velum closed (Buettner et al., 2002; Bonny et al., 2017). The participants were monitored with a breathing sensor (Burghart) coupled with an oscilloscope to receive feedback on their breathing during training. They had to maintain a constant amplitude and regular frequency of the sinusoid for 3 min. Finally, they were trained to maintain breathing while receiving in-mouth stimulations with each solution of interest (5 repeated stimulations for each solution).

EEG recording sessions

Participants started the EEG session by training again on the opened-velum breathing technique (3 min opened-velum breathing). EEG electrodes (Ag/AgCl) were fixed on the head with a conductive paste (EC2 electrode Cream, Natus®) after cleaning the skin (Everi, Spes medical®). Five electrodes were fixed on Fz, Cz, C3, C4, and Pz following a 10/20 system. Ground electrodes were positioned on the mastoids and reference electrodes on the ear lobes. One electrode was fixed above the right eyebrow to record vertical blinking artifacts. Impedance was kept below 30 kΩ. Participants were not notified of the stimulation. They received a flow of Evian water interrupted by air (400 ms water followed by 400 ms air) to limit the quantity of liquid in the mouth. Every 16 or 20 s, they received a target stimulation (400 ms); brain activity was recorded only for target stimulations (500 ms before and 1500 ms after the start of the stimulus). Air pressure was fixed at 850 mbar. This design permitted fast habituation to somatosensory stimuli (Plattig, 1989). Participants were stimulated 40 times in a row for each of the 5 solutions. Every 20 pulses, a 2 minutes break was made for the participants to relax. Solutions were presented in a counterbalanced order. To maintain a relatively low level of attention during the task, participants had to perform a tracking task (keeping a dot inside a slowly moving square). The game and the sensory evaluation questionnaire were displayed on a monitor (GustOlf custom-made software, adapted from "Tracking performance" software, from the Smell and Taste Clinic Dresden). The tracking task stopped one second after the stimulation, and participants were prompted to rate saltiness intensity after each trial on an unstructured visual analog scale anchored on the left with "low intensity" (corresponding to 0) and on the right side of the scale with "high intensity" (corresponding to 100). To control for noise, participants were listening to "brown noise" through earphones. Brain activity was sampled at 1000 Hz using an EEG Burghart system (OL026) (analog high pass filter 1st order: 0.072 Hz, analog low-pass filter 3rd order: 186 Hz). The recording was triggered by the gustometer and started 500 ms before stimulation and ended 1500 ms after stimulation.

Data analysis

Normality and homogeneity of variances were checked with QQplot and residuals vs. fitted values plots. Furthermore, the homogeneities of variances were confirmed for all models tested (Levene test, $p > 0.35$).

Sensory data analysis

Saltiness intensity was rated for each of the forty stimulations delivered during the EEG recording (R software, R package: nlme (Pinheiro et al., 2015)). A first linear mixed model tested the effect of repetitions to measure habituation to solution in the course of the recording (*repetitions*solutions*, with *participants* as a random factor), no interaction between solutions and repetitions, nor the main effect of repetitions were significant ($p < 0.05$). Therefore, in a second model, the variability of ratings across *participants* was modeled as a random factor, and *repetitions* were nested within each participant, thus taking into account repeated measures, while *solutions* were modeled as fixed factors. Finally, post-hoc tests were performed, pairwise comparisons between solutions were computed with a Tukey test, and *p*-values were corrected for multiple testing with the false discovery rate (FDR, pcorr < 0.05).

EEG preprocessing

Data were preprocessed in Letswave (open-source MATLAB EEG signal processing toolbox NOCIONS, Institute of Neuroscience, Université Catholique de Louvain). They were first filtered (Butterworth, bandpass filter: 0.01–30 Hz, filter order 4) and baseline corrected [yi = xi-mean(bl)] using the 500 ms recorded before the stimulation. Epochs contaminated by blinking artifacts

Please cite this article in press as: Sinding C et al. Odor-Induced Saltiness Enhancement: Insights Into The Brain Chronometry Of Flavor Perception. Neuroscience (2020), https://doi.org/10.1016/j.neuroscience.2020.10.029

were removed (amplitude criteria >90 μV). Finally, epochs with large alpha waves for most of the epoch duration were visually rejected. The mean number of epochs accepted was 21 ± 7. After computing the mean across epochs for each participant, a Grand Mean was calculated by weighting each participant's mean by the number of epochs accepted. This weighting, suggested by Mouraux (2015), allowed taking into account the number of epochs included in the individual means to reduce the noise effect on the Grand-Mean and linear mixed models.

EEG RESULTS ANALYSIS

Peak amplitudes and latencies were measured with ERPlab implemented in the EEGlab toolbox from MATLAB (Lopez-Calderon and Luck, 2014). We started the definition of time windows from the literature using gustatory ERPs for P1, which appeared between 120–180 ms (Mizoguchi et al., 2002; Franken et al., 2011), and on olfactory or gustatory ERPs for P3, which appeared between 550–750 ms (Pause et al., 1996; Welge-Lüssen et al., 2005; 2009;; Franken et al., 2011; Huart et al., 2012). We used relatively small windows (windows with a minimum of 100 ms and a maximum of 150 ms) to avoid overlaps between peaks. Local peak amplitude was searched in each time window within averages of 10 points on each local peak side. Local peak amplitude is defined as having a greater voltage than the average of the *n* number points on either side (Luck, 2014). When no peak was found, the NA value (non-applicable) was used. Time windows were checked and adapted to have as few as possible NA values on Cz, Fz, and Pz electrodes. Following these criteria, the P1 peak was analyzed within a 100–200 ms time window, and the P3 peak was analyzed within a 560–710 ms time window.

Before peak analysis, following Luck recommendations (Luck, 2014), data were filtered once more using a mild low-pass filter (half amplitude cutoff of 30 Hz, slope of 12 dB/octave). Finally, local peak amplitude and latency were measured for each participant at each electrode position. Data were analyzed with a linear mixed model (R package: nlme, lme function (Pinheiro et al., 2015)). The factor *participant* was modeled as a random factor, while solutions and electrodes were modeled as fixed factors. The interaction between solution and electrodes was also tested to highlight electrodes that may behave differently regarding solutions. The estimation of variance components followed the method of Restricted Maximum Likelihood (ReML) estimation. The variance of the response variables (amplitude or latency) measured on the peak of average ERP per participant and condition were weighted by the number of epochs accepted for each participant to reduce the impact of noisy mean, to correspond to grand-average ERP. Because no interactions between electrodes and solutions were found (cf. Results), electrodes that did not significantly differ were included in the models to highlight global brain responses and restrict the analysis to major effects. Only electrodes that did not vary from the electrode with the highest amplitude were analyzed. Finally, the effects of electrodes (used as a repeated measure) and solutions were tested without the interaction effect. Pairwise, Tukey's tests for defined contrasts were computed in cases of significant fixed effects. The contrasts were PPS1B vs. PPS1, PPS1B vs. PPS2, PPS2 vs. PPS1, PP vs. PPB, salted solutions vs. unsalted solutions, solutions with beef stock aroma vs. solutions without beef stock aroma. Pearson correlation was tested between P3 amplitude and the saltiness intensity evaluated for all participants and all conditions. Linear effects and correlation were considered significant at $p < 0.05$. Pairwise comparisons were FDR corrected for multiple comparisons (pcorr < 0.05).

RESULTS

Sensory results

Intensity evaluations did not decrease in the course of the 40 repetitions (F [39, 2548] = 0.19, $p = 1$). Moreover, no interaction between solutions and repetitions (F [156, 2388] = 0.74, $p = 0.99$), nor main effect of repetitions (F [156, 2388] = 0.46, $p = 0.99$) was significant. These results highlighted the lack of habituation to the different solutions in the course of the 40 repetitions.

Saltiness intensity differed significantly between solutions (F[4, 2076] = 939.21, $p < 0.0001$, sd random effects = 18.18). Sensory results revealed a small odor-induced saltiness enhancement (OISE) by the "beef stock" aroma in the salt-reduced green-pea soup (PPS1B). PPS1B (mean of intensity ratings of 40 repetitions across participants: M = 63.60, standard error of the mean: SEM = 0.86) was perceived as slightly more salty than PPS1 (M = 60.53, SEM = 0.96; $z = 2.72$, pcorr = 0.007, estimate = 3.06, sd = 1.13,), although not as salty as PPS2 (M = 72.80, SEM = 0.81; $z = 8.16$, pcorr < 0.0001 estimate = 9.20, sd = 1.13). All salt-added solutions (PPS1, PPS1B and PPS2) were perceived as more salty than the control solutions (PP, M = 17.87, SEM = 0.70, and PPB, M = 26.42, SEM = 1.05) (pcorr < 0.00001). PPB was rated as more salty than PP ($z = 7.59$, pcorr < 0.0001, estimate = 8.56, sd = 1.13) which support the odor-induced salty taste of the odor since no salt was added in this sample.

EEG results

No interaction was found between *electrode position* and *solution* for any of the peaks (P1, P3) regarding amplitude or latency (all comparisons: F [16, 282:288] < 1.06, $p > 0.39$). Therefore, this interaction was never included in the models. Because no interactions occurred, electrodes that did not significantly differ were included in the models to highlight global brain responses and restrict the analysis to major effects. P3 and P1 peaks were analyzed to determine whether odor-induced saltiness enhancement could be observed in early and/or later brain processing (Fig. 1).

Please cite this article in press as: Sinding C et al. Odor-Induced Saltiness Enhancement: Insights Into The Brain Chronometry Of Flavor Perception. Neuroscience (2020), https://doi.org/10.1016/j.neuroscience.2020.10.029

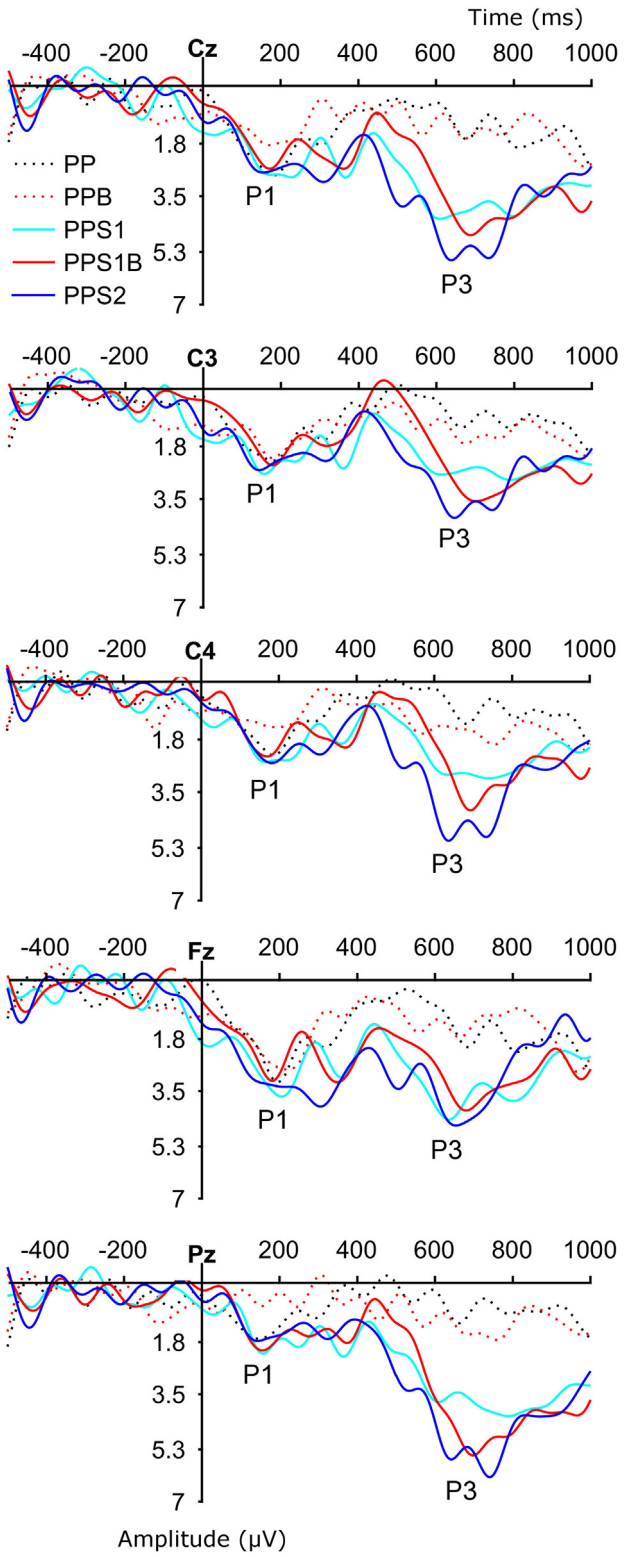

Fig 1. Event-related potentials for all solutions and all electrodes. The curves are Grand Mean weighted by the number of epochs finally accepted for each participant (amplitude (μV) as a function of time (ms) for each solution). The solutions were green-pea soup (PP), PP with beef stock aroma (PPB), PP with a reduced level of salt (3.125 g/L) (PPS1), PPS1 with beef stock aroma (PPS1B) and PP with a usual level of salt (6.25 g/L) (PPS2). The five recorded electrodes are shown (Cz, C3, C4, Fz and Pz). To improve graphical representation of ERPs, grand means were filtered with a Butterworth low-pass filter at 20 Hz and baseline was corrected.

P1 peak

There was a significant effect of channel on amplitude (F [4, 298] = 4.52, p = 0.002). Fz presented the highest P1 mean amplitude (M = 3.98, SEM = 0.33) and did not significantly differ from Cz (z = 1.45, pcorr = 0.26) but differed from Pz, C4 and C3 (for all comparisons: p < 0.02). Therefore, Fz and Cz were included as repeated measures in the following analyses.

There was no significant difference in the amplitude of P1 between solutions (F [4, 98] = 1.22, p = 0.31, sd random effects = 10.14) but the latency of P1 differed (F[4, 98] = 3.31, p = 0.01, sd random effects = 108.6029) (Fig. 2). P1 for PPS2 (M = 143 ± 5 ms) appeared earlier than PPS1B (M = 164 ± 4 ms) and PPB (M = 163 ± 5 ms). Indeed, P1 for PPS2 appeared respectively 21 ms (z = −3.22, p = 0.01, estimate = 21, sd = 6.45) and 20 ms (z = −3.05, p = 0.01, estimate = 20, sd = 6.44) earlier than PPS1B and PPB, which means that P1 for PPS2 appeared earlier than the two "aromatic" solutions (beef stock odor). Latency did not differ between PPS1B, PPS1, PPB and PP (p > 0.13, estimates < 13.6, sd < 6.99).

P3 peak

There was a significant effect of electrode position on the amplitude of P3 peak (F [4, 287] = 2.45, p = 0.05). Cz presented the highest mean amplitude of P3 (M = 5.03, SEM = 0.53) and did not significantly differ from the Fz, C4 and Pz electrodes (p > 0.75) but differed from C3 (z = 2.77, p = 0.05). Therefore, Cz, Fz, C4, and Pz were included as repeated measures in the analysis.

A significant difference was found on the amplitude of P3 peak between solutions (F [4, 204] = 18.52, p < 0.0001, sd random effects = 12.76). PPS1, PPS1B and PPS2 induced significantly larger P3 peaks than PP and PPB (contrast between unsalted and salted solutions, z = 8.443, pcorr < 0.0001, estimate = 9.02, sd = 1.07, Fig. 3A). A weak but significant positive correlation was found between saltiness intensity ratings and P3 peak amplitude (z = 3.05, p = 0.002, tau = 0.26) (Fig. 4). The P3 peak amplitudes for PP and PPB did not differ from a null amplitude (pcorr > 0.39, estimates < 0.16, sd < 0.55). There was no difference of P3 amplitude between PPS1, PPS1B and PPS2 (pcorr > 0.30, estimates < 0.69, sd < 0.56).

There was a significant difference on latency of P3 between the tested solutions (F[2, 102] = 9.05, p = 0.0003, sd random effects = 152.85). The P3 peak appeared later for PPS1B (M = 662 ± 6 ms) compared to PPS1 (M = 637 ± 5 ms, z = 3.93, pcorr = 0.0003, estimate = 26.3, sd = 6.70) and to PPS2 (M = 642 ± 4 ms, z = −3.24, pcorr = 0.002, estimate = 20.58, sd = 6.36) (Fig. 3B). In summary, the P3 peak was significantly different from zero amplitude only for the solutions PPS1, PPS1B and PPS2. The P3 peak, in response to PPS1B, was delayed of 25 ms and 20 ms compared with PPS1 and PPS2 respectively. Finally, the amplitude of the P3 peak increased as a function of the saltiness intensity rated.

Please cite this article in press as: Sinding C et al. Odor-Induced Saltiness Enhancement: Insights Into The Brain Chronometry Of Flavor Perception. Neuroscience (2020), https://doi.org/10.1016/j.neuroscience.2020.10.029

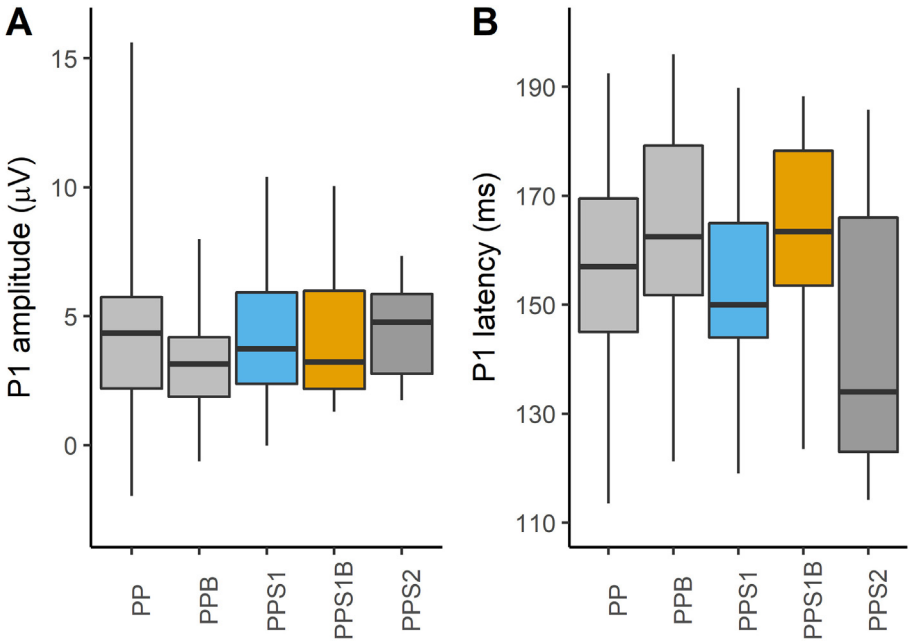

Fig 2. P1 peak amplitude and latency. Weighted mean P1 amplitudes **(A)** and latencies **(B)** (± CI95%) for electrodes Fz and Cz for each solution: green-pea soup (PP), PP with beef stock aroma (PPB), PP with a reduced level of salt (3.125 g/L) (PPS1), PPS1 with beef stock aroma (PPS1B) and PP with a usual level of salt (6.25 g/L) (PPS2).

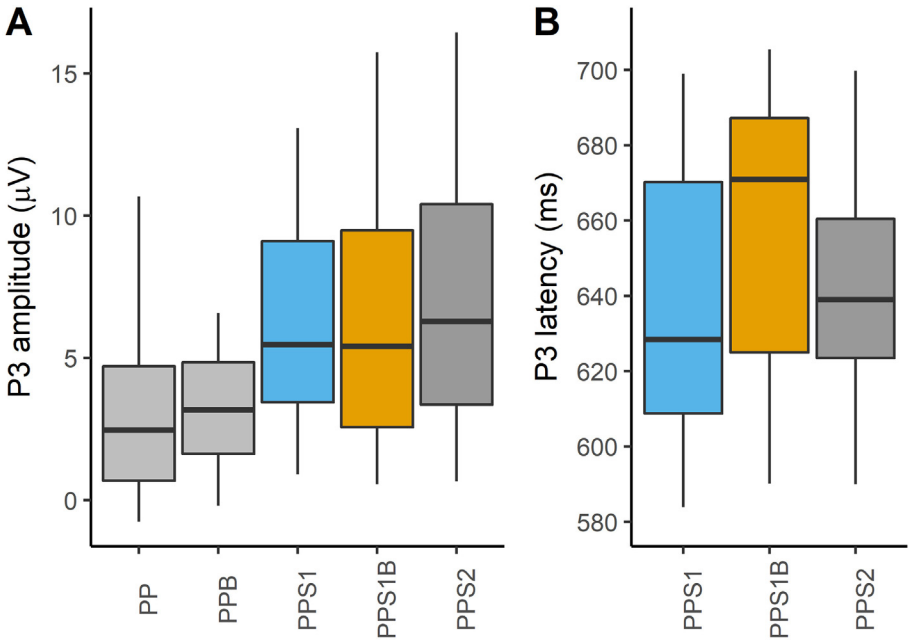

Fig 3. P3 peak amplitude and latency. Weighted mean P3 peak amplitudes **(A)** and latencies **(B)** (± CI95%) for electrodes Fz, Cz, C4, and Pz for each solution: green-pea soup (PP), PP with beef stock aroma (PPB), PP with a reduced level of salt (3.125 g/L) (PPS1), PPS1 with beef stock aroma (PPS1B) and PP with a usual level of salt (6.25 g/L) (PPS2). A P3 peak was not found for PP and PPB. Therefore, mean latencies were calculated only for PPS1B, PPS1, and PPS2.

DISCUSSION

The objective of the study was to highlight the brain chronometry of odor–taste integration using OISE. Our hypothesis, based on the classical view of odor–taste integration, was that differences of amplitude and/or latencies between solutions with and without OISE would be observed on the late P3 peak of olfactory-gustatory ERP, but no difference would appear on the early P1 peak. The sensory results showed a significant OISE using the "beef stock" aroma (PPS1B vs. PPS1) in the green pea soup. The ERP results showed an increased latency on the P3 peak with the same solutions (PPS1B vs. PPS1). No difference in amplitude or latency was observed on the P1 peak between PPS1B and PPS1. Therefore, our results support the hypothesis of late brain integration in the high cognitive areas as proposed in the classical view of flavor perception (Verhagen and Engelen, 2006; Verhagen, 2007; Small, 2008; Prescott, 2012).

The ERPs measured in our study mainly reflect the gustatory component (specifically the saltiness processing) of the solutions, and its modulation by the olfactory component. Indeed the grand-averages showed ERPs with proper peaks, well-differentiated from noise, for the salted solutions and small ones for the control solutions apart from the P1 peak (Fig. 2). These control solutions (PP and PPB) were mainly odorant and had a poor taste. Furthermore, as the P3 peak correlated to the saltiness intensity (Fig. 4), it also supports that the ERPs represent mainly the gustatory brain activations and their modulation by the olfactory component. Therefore, any effect observed on P1 or P3 peaks will be either explained by the concentrations of salt or by the modulation of the gustatory processing by the olfactory one (i.e., odor-induced saltiness enhancement). This modulation

Please cite this article in press as: Sinding C et al. Odor-Induced Saltiness Enhancement: Insights Into The Brain Chronometry Of Flavor Perception. Neuroscience (2020), https://doi.org/10.1016/j.neuroscience.2020.10.029

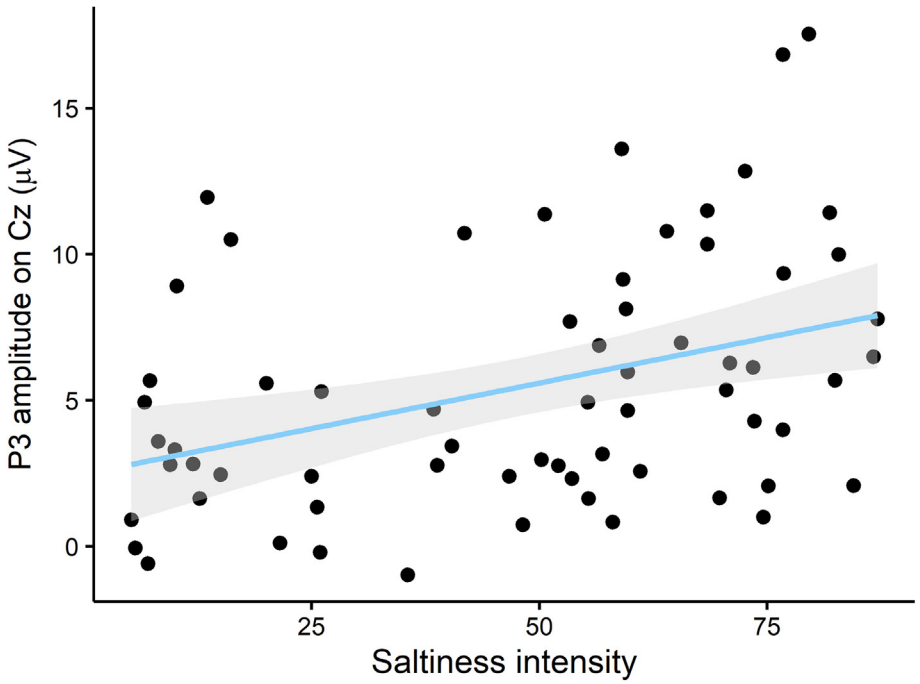

Fig 4. Correlation between the mean saltiness intensity ratings and the amplitude (μV) of the P3 peak at the Cz electrode. Each data point is the evaluation of one solution evaluated 40 times by one participant (13 participants and 5 solutions). The amplitude of the P3 peak increased as a function of the saltiness intensity. Kendall correlation: $z = 3.05$, $p = 0.002$, tau = 0.26.

can either intervene early in the processing by direct interactions between primary olfactory and gustatory areas (emerging view) or occur later in the processing through top-down pathways (classical view). Because the modulation observed appeared on the P3 peak and not on P1, the results confirmed OISE's classical view.

We observed a higher salty taste intensity in PPB compared to PP. However, the effect in PPB likely implied an odor-induced saltiness perception (OISP), but no enhancement (OISE) as salt was not present in the solution. Because gustatory responses mainly drive the ERPs here, although we observed a perceptual difference between PP and PPB (OISP), we did not observe brain correlates of such sensory response. It could be that OISP and OISE involve different brain circuits or that the number of neurons involved by the OISP may not be sufficient to be visible in ERP, on the contrary to OISE. The sensory effects may seem contradictory, but the low range of salt concentration may explain this result. The OISE effect is statistically significant in the PPS1B solution, but the OISE appeared small and lower than the OISP (Fig. 1). The enhancement of salty taste induced by an odor is usually observed in the range of 10 to 30% (Lawrence et al., 2009). In the present study, the percentage of enhancement (5%) might have been flattened because of the evaluation of no-salt-added samples (PP and PPB) in the sample set. Indeed, these two samples' saltiness intensity was likely low compared to the three other salt-containing samples, which could have reduced the discrimination between PPS1, PPS1B, and PPS2. This hypothesis is supported by the unexpected small difference between PPS1 and PPS2 that contained double salt.

One could think that rating saltiness intensity only at the end of each epoch recording would involve a dumping effect. A dumping effect occurs when "a salient attribute is not included on a ballot; the opinion about that aspect of the product may then be displaced onto another, sometimes inappropriate scale. In other words, if consumers are not given a rating scale in which they can voice some important opinion about a product, they will 'dump' this perception onto some other available rating scale or question" (Clark and Lawless, 1994). Dumping is usually considered as a bias in sensory rating because it could lead to perceived intensity overrating. However, several recent studies reconsider the dumping effect not as bias but as a proof of odor–taste integration, because flavor perception is by nature configural (Prescott, 2012; Onuma et al., 2018). Therefore, when participants have no clue about the elements (odor and taste), the configuration (flavor) is attended, and the OITE occurs. The configural perception is a typical integratory perception described in the significant contribution of the "unique cue theory" (Rescorla, 1972, 1973). This theory was further developed by Pearce (2002) and finally demonstrated in the context of odor-odor and odor–taste configural perceptions (Le Berre et al., 2008, 2010; Sinding et al., 2011; White et al., 2020).

P1 peak

P1 peak, in chemosensory studies (70–302 ms), is associated to brain circuits responding to exogenous properties of the food such as tastant concentration (Funakoshi and Kawamura, 1971; Kobayakawa et al., 1999, 2007; Mizoguchi et al., 2002; Ohla et al., 2010). Here, we did not find early changes in the brain processing of PPS1B compared to PPS1 when considering amplitude or latencies of the P1 peak. Therefore, no effect possibly linked to OISE could be observed on the P1 peak amplitude. We found a delay on the P1 peak, between PPS2 vs. PPS1B and PPB. These contrasts could not account for the OISE phenomenon, which would suppose a difference between PPS1 and PPS1B. Both PPS1B and PPB solutions contained a "beef stock aroma" and were delayed compared to the most salted solution PPS2. This polarization of the two types of solutions (high salt solution vs. high odorant solutions) regarding their P1 latencies could highlight the differential processing between salient gustatory solution (PPS2) and salient olfactory solutions

Please cite this article in press as: Sinding C et al. Odor-Induced Saltiness Enhancement: Insights Into The Brain Chronometry Of Flavor Perception. Neuroscience (2020), https://doi.org/10.1016/j.neuroscience.2020.10.029

(PPB and PPS1B). In the literature, it is reported that olfactory ERPs have a later P1 peak than gustatory ERP. In studies that showed a P1 peak in response to olfactory stimulation, this peak appeared between 200–280 ms (Tateyama et al., 1998; Iannilli et al., 2013), while it appeared at 120–140 ms for gustatory stimulation (Mizoguchi et al., 2002; Ohla et al., 2009, 2010; Jacquin-Piques et al., 2015).

Significant differences in P1 amplitude regarding salt concentration in PP, PPS1, and PPS2 were not found, although these solutions were perceived as significantly different. This result is inconsistent with Kobayakawa and colleagues (Kobayakawa et al., 1996, 1999, 2008). It is generally assumed that P1 amplitude is related to tastant concentration. Three studies from two independent labs showed that P1 latency is more likely to reflect a change in tastant concentration, with lower latencies for higher concentrations (Funakoshi and Kawamura, 1971; Kobal, 1985; Tateyama et al., 1998). In our study, the solution with the highest concentration of salt (PPS2) was processed with the lowest latency, but the result is not significant. Altogether, these results could be explained by the concentrations of salt used in our study, which are not sufficiently extreme to show the expected latency difference. Studies that tackle the brain peaks associated with the perception of tastant concentrations use steps of concentrations 5 times larger than those used in our study. In Kobayakawa et al. (2008), differences of P1 amplitude were observed between 100 mM (5.84 g/L) and 1 M (58.4 g/L), or between 30 mM (1.752 g/L) and 300 (17.52 g/L), but not between 100 mM and 300 mM. In our study, salt concentrations were in line with a usual soup that is 6.25 g/L for PPS2 and 3 g/L for PPS1 (soup with reduced-salt level). Likely, the low, but food relevant, salt concentrations used in our study could explain why we did not observe significant differences in either amplitude or latency for P1 peak as a function of salt levels.

P3 latency might be a marker of odor-induced taste enhancement

P3 peak might be linked to cognitive processing diversity, including emotions integration, attention allocation, and working memory, which have in common their endogenous origin. Furthermore, the P3 peak is elicited by multiple intracerebral generators revealing its integratory component (Picton, 1992; Li et al., 2015). In our study, the P3 peak was significantly delayed by 20 ms or more in response to PPS1B compared to PPS1 and PPS2. Moreover, the brain processing of PPB did not present a significant P3 peak; therefore, we could exclude an impact of the odor component on P3, and we could then directly compare PPS1B to PPS1 and PPS2. We can also exclude an earlier origin of this delay, as no significant delay was present at the early stages of brain processing (only 7 ms separated P1 peaks for PPS1B compared with PPS1). Although the interpretation of latencies, in terms of neuronal activity, is challenging, we might consider this delay as evidence for a higher number of synapses involved in processing the sensory information for solutions presenting an odor-induced taste enhancement (for review, see Woodman, 2010). This result would comply with the classical view of flavor integration proposed by Verhagen (Verhagen and Engelen, 2006; Verhagen, 2007). In this theory, inspired by visual studies, downstream areas activate heteromodal integration areas that then loop back to the primary sensory areas to form a refined activation pattern. The activation of these associative areas, and the back projections to primary gustatory regions, may explain the higher latency observed for the odor-induced taste enhancement solution. Heteromodal multisensory processing areas, such as the superior temporal sulcus (Calvert, 2001; Calvert and Thesen, 2004), were found to be activated between 518–730 ms after food odor stimulation, with magnetoencephalography (MEG) (Kettenmann et al., 1997). This timing is consistent with the latency of the P3 peak identified in the present study.

P3 peak amplitude might be a marker of conscious perception of the saltiness intensity

An intriguing result is that the amplitude of the P3 peak was significantly different from the null amplitude only in solutions with added-salt. Furthermore, looking at individual results, we found a small but significant correlation of this peak amplitude with salty taste intensity ratings. Several explanations may account for these results and may rely on different cognitive steps involved in the intensity rating task. These steps may be decomposed: i) non-conscious salt concentration processing, ii) conscious representation of saltiness intensity, and iii) evaluation of/decision on saltiness intensity. The difference in P3 amplitude did not correspond to the first step, as we did not find a significant difference in amplitude between PPS1 and PPS2. These results could be linked to the evaluation/decision on saltiness intensity rating, which occurred at least 320 ms after the P3 peak. As the participants were likely expecting to evaluate the saltiness intensity after each stimulation, the P3 peak could reflect their anticipatory evaluation. However, in this case, P3 would have also been observed for PP and PPB solutions. Finally, suppose these results are neither linked to ‘‘the non-conscious salt concentration representation” nor ‘‘to the evaluation/decision on the saltiness intensity”. In that case, it could be an intermediate state: ‘‘a conscious representation of the saltiness intensity”. Notably, the expectancy of the intensity scale could favor the conscious representation of the saltiness intensity. This late conscious perception has been shown in visual attentional blink studies (Sergent et al., 2005). This task permitted us to decipher the peaks involved in non-conscious processing versus conscious one. Although such results were not yet shown in taste sensory modality, we suggest that P3 might represent the conscious perception of the saltiness intensity.

The classical view of odor–taste integration supported by our results

Overall, our results support the odor–taste integration theoretical framework proposed by Verhagen (Verhagen

and Engelen, 2006; Verhagen, 2007), Prescott (2012), and Small (Small, 2008). In this framework, the integration of odor and taste occurs in high-level brain areas (OFC, perirhinal, and dorsal mid insula), as brain correlations of odor-induced saltiness enhancement were found only at the later stages of brain processing. More recently, Small and colleagues (Small et al., 2013) proposed an emerging model of odor–taste integration relying on animal studies and fMRI human studies (De Araujo et al., 2003; Maier et al., 2012, 2015; Seubert et al., 2015; Maier, 2017). They showed early interactions between primary olfactory and gustatory regions. They proposed: i) a densely connected system between olfactory and gustatory areas and ii) that flavor might be already integrated into primary chemosensory cortices. Although our study did not refute the dense connections between primary olfactory and gustatory cortices, it did not show early modulation in response to odor and taste presented together. However, we cannot completely exclude that our EEG design was not powered enough to detect early changes.

Our results provide the first insight into the brain chronometry of odor–taste integration, focusing on salty flavor. We found that olfactory-gustatory interactions mainly occur in the late brain processing of sensory information carried by a close-to-real food solution. We have developed an adequate stimulation method to understand the chronometry of odor–taste integration in the flavor system. Other converging results on similar questions would be necessary to comprehend flavor perception and underlying brain mechanisms further. The enhancing effect was small in our solution, likely due to the type of evaluation (intensity scales) and context (during EEG recording). Therefore, our results' reproducibility should be tested with a more reliable sensory evaluation method and several food models. Due to the long recording time, we could neither test several solutions presenting an odor-induced taste enhancement nor control solutions without such an effect. A study comparing enhancing and non-enhancing aroma would be of interest.

UNCITED REFERENCES

Geisler and Murphy (2000), Kobal et al. (1990), Lascano et al. (2010), Livermore et al. (1992), Lundstrom et al. (2006), Murphy et al. (2000), Murphy et al. (1998), Pause and Krauel (2000), , Spence et al. (2015), Stevenson et al. (2011), Thesen and Murphy (2002).

ACKNOWLEDGMENTS

This work was supported by a French INRA grant (ANS-COGITO). We would like to thank Jacques Maratray for setting up the GustOlf sensory evaluation software.

REFERENCES

Barba C, Beno N, Guichard E, Thomas-Danguin T (2018) Selecting odorant compounds to enhance sweet flavor perception by gas chromatography/olfactometry-associated taste (GC/O-AT). Food Chem 257:172–181. https://doi.org/10.1016/j.foodchem.2018.02.152.

Bartoshuk LM (1974) NaCl thresholds in man: Thresholds for water taste or NaCl taste? J Comp Physiol Psychol 87:310–325.

Bonny JM, Sinding C, Thomas-Danguin T (2017). In: modern magnetic resonance. Cham: Springer International Publishing. p. 1–20. DOI: 10.1007/978-3-319-28275-6_132-1.

Buettner A, Beer A, Hannig C, Settles M, Schieberle P (2002) Physiological and analytical studies on flavor perception dynamics as induced by the eating and swallowing process. Food Qual Prefer 13(7-8):497–504. https://doi.org/10.1016/S0950-3293(02)00052-6.

Calvert GA (2001) Crossmodal processing in the human brain: insights from functional neuroimaging studies. Cereb Cortex 11:1110–1123. https://doi.org/10.1093/cercor/11.12.1110.

Calvert GA, Thesen T (2004) Multisensory integration: methodological approaches and emerging principles in the human brain. Journal of Physiology-Paris 98(1-3):191–205. https://doi.org/10.1016/j.jphysparis.2004.03.018.

Carbine KA, Rodeback R, Modersitzki E, Miner M, LeCheminant JD, Larson MJ (2018) The utility of event-related potentials (ERPs) in understanding food-related cognition: A systematic review and recommendations. Appetite 128:58–78. https://doi.org/10.1016/j.appet.2018.05.135.

Clark CC, Lawless HT (1994) Limiting response alternatives in time-intensity scaling: an examination of the halo-dumping effect. Chem Senses 19(6):583–594. https://doi.org/10.1093/chemse/19.6.583.

de Araujo IET, Rolls ET, Kringelbach ML, McGlone F, Phillips N (2003) Taste-olfactory convergence, and the representation of the pleasantness of flavour, in the human brain. Eur J Neurosci 18 (7):2059–2068. https://doi.org/10.1046/j.1460-9568.2003.02915.x.

Djordjevic J, Zatorre RJ, Jones-Gotman M (2004) Odor-induced changes in taste perception. Exp Brain Res 159(3):405–408. https://doi.org/10.1007/s00221-004-2103-y.

Frank RA, Byram J (1988) Taste–smell interactions are tastant and odorant dependent. Chem Senses 13(3):445–455. https://doi.org/10.1093/chemse/13.3.445.

Franken IHA, Huijding J, Nijs IMT, van Strien JW (2011) Electrophysiology of appetitive taste and appetitive taste conditioning in humans. Biol Psychol 86(3):273–278. https://doi.org/10.1016/j.biopsycho.2010.12.008.

Funakoshi M, Kawamura Y (1971) Summated cerebral evoked responses to taste stimuli in man. Electroencephalogr Clin Neurophysiol 30(3):205–209. https://doi.org/10.1016/0013-4694(71)90055-1.

Geisler MW, Murphy C (2000) Event-related brain potentials to attended and ignored olfactory and trigeminal stimuli. Int J Psychophysiol 37(3):309–315. https://doi.org/10.1016/S0167-8760(00)00111-2.

Huart C, Legrain V, Hummel T, Rombaux P, Mouraux A (et) Time-frequency analysis of chemosensory event-related potentials to characterize the cortical representation of odors in humans. PLoS ONE 7:e33221. https://doi.org/10.1371/journal.pone.0033221.

Iannilli E, Wiens S, Arshamian A, Seo H-S (2013) A spatiotemporal comparison between olfactory and trigeminal event-related potentials. NeuroImage 77:254–261. https://doi.org/10.1016/j.neuroimage.2012.12.057.

Jacquin-Piques A, Gaudillat S, Mouillot T, Gigot V, Meillon S, Leloup C, Penicaud L, Brondel L (2015) Prandial states modify the reactivity of the gustatory cortex using gustatory evoked potentials in humans. Front Neurosci 9:490. https://doi.org/10.3389/fnins.2015.00490.

Kettenmann B, Hummel C, Stefan H, Kobal G (1997) Multiple olfactory activity in the human neocortex identified by magnetic source imaging. Chem Senses 22(5):493–502. https://doi.org/10.1093/chemse/22.5.493.

Kobal G (1985) Gustatory evoked potentials in man. Electroencephalogr Clin Neurophysiol/Evoked Poten Sect 62 (6):449–454. https://doi.org/10.1016/0168-5597(85)90055-3.

Kobal G, Hummel C, Nuernberg B, Brune K (1990) Effects of pentazocine and acetylsalicylic acid on pain-rating, pain-related evoked potentials and vigilance in relationship to pharmacokinetic parameters. Agents Actions 29:342–359.

Kobayakawa Ko, Kobayakawa R, Matsumoto H, Oka Y, Imai T, Ikawa M, et al. (2007) Innate versus learned odour processing in the mouse olfactory bulb. Nature 450(7169):503–508. https://doi.org/10.1038/nature06281.

Kobayakawa T, Endo H, Ayabe-Kanamura S, Kumagai T, Yamaguchi Y, Kikuchi Y, Takeda T, Saito S, Ogawa H (1996) The primary gustatory area in human cerebral cortex studied by magnetoencephalography. Neurosci Lett 212(3):155–158. https://doi.org/10.1016/0304-3940(96)12798-1.

Kobayakawa T, Ogawa H, Kaneda H, Ayabe-Kanamura S, Saito S, Endo H, Saito S (1999) Spatio-temporal analysis of cortical activity evoked by gustatory stimulation in humans. Chem. Senses 24:201–209. https://doi.org/10.1093/chemse/24.2.201.

Kobayakawa T, Saito S, Gotow N, Ogawa H (2008) Representation of salty taste stimulus concentrations in the primary gustatory area in humans. Chem Percept 1(4):227–234. https://doi.org/10.1007/s12078-008-9030-4.

Labbe D, Damevin L, Vaccher C, Morgenegg C, Martin N (2006) Modulation of perceived taste by olfaction in familiar and unfamiliar beverages. Food Quality Preference 17(7-8):582–589. https://doi.org/10.1016/j.foodqual.2006.04.006.

Lascano AM, Hummel T, Lacroix J-S, Landis BN, Michel CM (2010) Spatio–temporal dynamics of olfactory processing in the human brain: an event-related source imaging study. Neuroscience 167 (3):700–708. https://doi.org/10.1016/j.neuroscience:2010.02.013.

Lawrence G, Salles C, Septier C, Busch J, Thomas-Danguin T (2009) Odour–taste interactions: A way to enhance saltiness in low-salt content solutions. Food Quality Preference 20(3):241–248. https://doi.org/10.1016/j.foodqual.2008.10.004.

Le Berre E, Jarmuzek E, Béno N, Etiévant P, Prescott J, Thomas-Danguin T (2010) Learning influences the perception of odor mixtures. Chem. Percept. 3(3-4):156–166. https://doi.org/10.1007/s12078-010-9076-y.

Le Berre E, Thomas-Danguin T, Béno N, Coureaud G, Etiévant P, Prescott J (2008) Perceptual processing strategy and exposure influence the perception of odor mixtures. Chem Senses 33:193–199. https://doi.org/10.1093/chemse/bjm080.

Li F, Liu T, Wang F, Li He, Gong D, Zhang R, et al. (2015) Relationships between the resting-state network and the P3: Evidence from a scalp EEG study. Sci Rep 5(1). https://doi.org/10.1038/srep15129.

Lim J, Fujimaru T, Linscott TD (2014) The role of congruency in taste–odor interactions. Food Quality Preference 34:5–13. https://doi.org/10.1016/j.foodqual.2013.12.002.

Lim J, Johnson MB (2011) Potential mechanisms of retronasal odor referral to the mouth. Chem Senses 36(3):283–289. https://doi.org/10.1093/chemse/bjq125.

Lim J, Johnson MB (2012) The role of congruency in retronasal odor referral to the mouth. Chem Senses 37(6):515–522. https://doi.org/10.1093/chemse/bjs003.

Linscott TD, Lim J (2016) Retronasal odor enhancement by salty and umami tastes. Food Quality Preference 48:1–10. https://doi.org/10.1016/j.foodqual.2015.08.004.

Livermore A, Hummel T, Kobal G (1992) Chemosensory event-related potentials in the investigation of interactions between the olfactory and the somatosensory (trigeminal) systems. Electroencephalogr Clin Neurophysiol 83(3):201–210. https://doi.org/10.1016/0013-4694(92)90145-8.

Lopez-Calderon J, Luck SJ (2014) ERPLAB: an open-source toolbox for the analysis of event-related potentials. Front Human Neurosci 8:213. https://doi.org/10.3389/fnhum.2014.00213.

Luck SJ (2014) An introduction to the event-related potential technique (Gazzaniga MS, ed). Massachusetts: The MIT Press.

Lundstrom JN, Seven S, Olsson MJ, Schaal B, Hummel T (2006) Olfactory event-related potentials reflect individual differences in odor valence perception. Chem Senses 31(8):705–711. https://doi.org/10.1093/chemse/bjl012.

Maier J, Blankenship M, Li J, Katz D (2015) A multisensory network for olfactory processing. Curr Biol 25(20):2642–2650. https://doi.org/10.1016/j.cub.2015.08.060.

Maier JX (2017) Single-neuron responses to intraoral delivery of odor solutions in primary olfactory and gustatory cortex. J Neurophysiol 117(3):1293–1304. https://doi.org/10.1152/jn.00802.2016.

Maier JX, Wachowiak M, Katz DB (2012) Chemosensory convergence on primary olfactory cortex. J Neurosci 32 (48):17037–17047. https://doi.org/10.1523/JNEUROSCI.3540-12.2012.

Marshall K, Laing DG, Jinks AL, Hutchinson I (2006) The capacity of humans to identify components in complex odor-taste mixtures. Chem Senses 31:539–545. https://doi.org/10.1093/chemse/bji058.

Masaoka Y, Satoh H, Akai L, Homma I (2010) Expiration: The moment we experience retronasal olfaction in flavor. Neurosci Lett 473(2):92–96. https://doi.org/10.1016/j.neulet.2010.02.024.

Mizoguchi C, Kobayakawa T, Saito S, Ogawa H (2002) Gustatory evoked cortical activity in humans studied by simultaneous EEG and MEG recording. Chem Senses 27:629–634. https://doi.org/10.1093/chemse/27.7.629.

Mouraux A (2015) Average. NOCIONS/letswave6:1.

Mroczko-Wąsowicz A (2016) The unity and complexity of flavour perception. In: Proceedings of the 1st workshop on multi-sensorial approaches to human-food interaction - MHFI '16. New York, New York, USA: ACM Press. p. 1–4. DOI: 10.1145/3007577.3007583.

Murphy C, Morgan CD, Geisler MW, Wetter S, Covington JW, Madowitz MD, Nordin S, Polich JM (2000) Olfactory event-related potentials and aging: normative data. Int J Psychophysiol 36 (2):133–145. https://doi.org/10.1016/S0167-8760(99)00107-5.

Murphy C, Wetter S, Morgan CD, Ellison DW, Geisler MW (1998) Age effects on central nervous system activity reflected in the olfactory event-related potential: evidence for decline in middle age. Annals NY Acad Sci 855:598–607. https://doi.org/10.1111/j.1749-6632.1998.tb10630.x.

Nasri N, Septier C, Beno N, Salles C, Thomas-Danguin T (2013) Enhancing salty taste through odour–taste–taste interactions: Influence of odour intensity and salty tastants' nature. Food Quality Preference 28(1):134–140. https://doi.org/10.1016/j.foodqual.2012.07.004.

Ohla K, Hudry J, le Coutre J (2009) The cortical chronometry of electrogustatory event-related potentials. Brain Topogr 22 (2):73–82. https://doi.org/10.1007/s10548-009-0076-7.

Ohla K, Toepel U, le Coutre J, Hudry J (2010) Electrical neuroimaging reveals intensity-dependent activation of human cortical gustatory and somatosensory areas by electric taste. Biolo Psychol 85 (3):446–455. https://doi.org/10.1016/j.biopsycho.2010.09.007.

Onuma T, Maruyama H, Sakai N (2018) Enhancement of saltiness perception by monosodium glutamate taste and soy sauce odor: a near-infrared spectroscopy study. Chem. Senses 43:151–167. https://doi.org/10.1093/chemse/bjx084.

Pause BM, Krauel K (2000) Chemosensory event-related potentials (CSERP) as a key to the psychology of odors. Int J Psychophysiol 36(2):105–122. https://doi.org/10.1016/S0167-8760(99)00105-1.

Pause BM, Sojka B, Krauel K, Ferstl R (1996) The nature of the late positive complex within the olfactory event-related potential (OERP). Psychophysiology 33(4):376–384. https://doi.org/10.1111/j.1469-8986.1996.tb01062.x.

Pearce JM (2002) Evaluation and development of a connectionist theory of configural learning. Anim Learn Behav 30(2):73–95. https://doi.org/10.3758/BF03192911.

Picton TW (1992) The P300 wave of the human event-related potential. J Clin Neurophysiol 9(4):456–479. https://doi.org/10.1097/00004691-199210000-00002.

Pinheiro J, Bates D, DebRoy S, Sarkar D, R Core Team (2015) nlme: Linear and Nonlinear Mixed Effects Models. R Packag version 31-120 http://CRA.

Plattig K-H (1989) Electrophysiology of taste and smell. Clin Phys Physiol Measur 10(2):91–125. https://doi.org/10.1088/0143-0815/10/2/001.

Prescott J (1999) Flavour as a psychological construct: implications for perceiving and measuring the sensory qualities of foods. Food Qual Prefer 10(4-5):349–356. https://doi.org/10.1016/S0950-3293(98)00048-2.

Prescott J (2012) Multimodal chemosensory interactions and perception of flavor. In: Murray M, Wallace M, editors. The neural bases of multisensory processes. Boca Raton (FL): CRC Press/Taylor & Francis.

Prescott J, Johnstone V, Francis J (2004) Odor-taste interactions: effects of attentional strategies during exposure. Chem Senses 29:331–340. https://doi.org/10.1093/chemse/bjh036.

Prescott J, Murphy S (2009) Inhibition of evaluative and perceptual odour–taste learning by attention to the stimulus elements. Quarterly Journal of Experimental Psychology 62 (11):2133–2140. https://doi.org/10.1080/17470210903031169.

Rescorla RA (1972) Configural conditioning in discrete-trial bar pressing. J Comp Physiol Psychol 79:307.

Rescorla RA (1973) Evidence for "unique stimulus" account of configural conditioning. J Comp Physiol Psychol 85(2):331–338. https://doi.org/10.1037/h0035046.

Rolls ET, Baylis LL (1994) Gustatory, olfactory, and visual convergence within the primate orbitofrontal cortex. J Neurosci 14(9):5437–5452. https://doi.org/10.1523/JNEUROSCI.14-09-05437.1994.

Rolls ET (1997) Taste and olfactory processing in the brain and its relation to the control of eating. Crit Rev Neurobiol 11(4):263–287. https://doi.org/10.1615/CritRevNeurobiol.v11.i4.20.

Sakai N, Kobayakawa T, Gotow N, Saito S, Imada S (2001) Enhancement of sweetness ratings of aspartame by a vanilla odor presented either by orthonasal or retronasal routes. Percept Mot Skills 92(3_suppl):1002–1008. https://doi.org/10.2466/pms.2001.92.3c.1002.

Schifferstein HNJ, Verlegh PWJ (1996) The role of congruency and pleasantness in odor-induced taste enhancement. Acta Psychol 94(1):87–105. https://doi.org/10.1016/0001-6918(95)00040-2.

Seo H-S, Iannilli E, Hummel C, Okazaki Y, Buschhüter D, Gerber J, Krammer GE, van Lengerich B, Hummel T (2013) A salty-congruent odor enhances saltiness: Functional magnetic resonance imaging study. Hum Brain Mapp 34(1):62–76. https://doi.org/10.1002/hbm.21414.

Sergent C, Baillet S, Dehaene S (2005) Timing of the brain events underlying access to consciousness during the attentional blink. Nat Neurosci 8(10):1391–1400. https://doi.org/10.1038/nn1549.

Seubert J, Ohla K, Yokomukai Y, Kellermann T, Lundström JN (2015) Superadditive opercular activation to food flavor is mediated by enhanced temporal and limbic coupling: Food Flavor Enhances Temporal-Limbic Coupling. Hum Brain Mapp 36(5):1662–1676. https://doi.org/10.1002/hbm.22728.

Sinding C, Thomas-Danguin T, Crepeaux G, Schaal B, Coureaud G (2011) Experience influences elemental and configural perception of certain binary odour mixtures in newborn rabbits. J Exp Biol 214 (24):4171–4178. https://doi.org/10.1242/jeb.063610.

Small DM (2008) Flavor and the formation of category-specific processing in olfaction. Chem. Percept. 1(2):136–146. https://doi.org/10.1007/s12078-008-9015-3.

Small DM (2012) Flavor is in the brain. Physiol Behav 107 (4):540–552. https://doi.org/10.1016/j.physbeh.2012.04.011.

Small DM, Prescott J (2005) Odor/taste integration and the perception of flavor. Exp Brain Res 166(3-4):345–357. https://doi.org/10.1007/s00221-005-2376-9.

Small DM, Veldhuizen MG, Green B (2013) Sensory neuroscience: Taste responses in primary olfactory cortex. Curr Biol 23: R157–R159. https://doi.org/10.1016/j.cub.2012.12.036.

Spence C (2016) Oral referral: On the mislocalization of odours to the mouth. Food Qual Prefer 50:117–128. https://doi.org/10.1016/j.foodqual.2016.02.006.

Spence C, Smith B, Auvray M (2015) Confusing tastes and flavours. In: Stokes D, Matthen M, Biggs S, editors. Perception and its modalities. Oxford, UK: Oxford University Press. p. 247–274.

Stevenson RJ, Mahmut MK, Oaten MJ (2011) The role of attention in the localization of odors to the mouth. Atten Percept Psychophys 73(1):247–258. https://doi.org/10.3758/s13414-010-0013-6.

Syarifuddin A, Septier C, Salles C, Thomas-Danguin T (2016) Reducing salt and fat while maintaining taste: An approach on a model food system. Food Qual Prefer 48:59–69. https://doi.org/10.1016/j.foodqual.2015.08.009.

Tateyama T, Hummel T, Roscher S, Post H, Kobal G (1998) Relation of olfactory event-related potentials to changes in stimulus concentration. Electroencephalogr Clin Neurophysiol/Evoked Potent Sect 108(5):449–455. https://doi.org/10.1016/S0168-5597(98)00022-7.

Teillet E, Urbano C, Cordelle S, Schlich P (2010) Consumer perception and preference of bottled and tap water. J Sens Stud 25:463–480. https://doi.org/10.1111/j.1745-459X.2010.00280.x.

Thesen T, Murphy C (2002) Reliability analysis of event-related brain potentials to olfactory stimuli. Psychophysiology 39(6):733–738. https://doi.org/10.1111/1469-8986.3960733.

Thomas-Danguin T, Rouby C, Sicard G, Vigoroux M, Barkat S, Brun V... Rousseau F (2003) ETOC: A short olfactory test culturally validated across Europe. Chem Senses 28:E60.

Thomas-Danguin T, Sinding C, Tournier C, Saint-Eve A (2016) Multimodal interactions. In: Etiévant P, Guichard E, Salles C, Voilley A, editors. Flavor from food to behaviors, wellbeing and health. Woodhead Publishing Series In Food Science, Technology And Nutrition. p. 430.

Verhagen JV (2007) The neurocognitive bases of human multimodal food perception: Consciousness. Brain Res Rev 53(2):271–286. https://doi.org/10.1016/j.brainresrev.2006.09.002.

Verhagen JV, Engelen L (2006) The neurocognitive bases of human multimodal food perception: Sensory integration. Neurosci Biobehav Rev 30(5):613–650. https://doi.org/10.1016/j.neubiorev.2005.11.003.

Wang G, Bakke AJ, Hayes JE, Hopfer H (2019) Demonstrating cross-modal enhancement in a real food with a modified ABX test. Food Qual Prefer 77:206–213. https://doi.org/10.1016/j.foodqual.2019.05.007.

Welge-Lüssen A, Drago J, Wolfensberger M, Hummel T (2005) Gustatory stimulation influences the processing of intranasal stimuli. Brain Res 1038(1):69–75. https://doi.org/10.1016/j.brainres.2005.01.011.

Welge-Lussen A, Ebnother M, Wolfensberger M, Hummel T (2009) Swallowing is differentially influenced by retronasal compared with orthonasal stimulation in combination with gustatory stimuli. Chem Senses 34(6):499–502. https://doi.org/10.1093/chemse/bjp024.

Welge-Lüssen A, Husner A, Wolfensberger M, Hummel T (2009) Influence of simultaneous gustatory stimuli on orthonasal and retronasal olfaction. Neurosci Lett 454(2):124–128. https://doi.org/10.1016/j.neulet.2009.03.002.

White TL, Thomas-Danguin T, Olofsson JK, Zucco GM, Prescott J (2020) Thought for food: Cognitive influences on chemosensory perceptions and preferences. Food Qual Prefer 79:103776. https://doi.org/10.1016/j.foodqual.2019.103776.

Woodman GF (2010) A brief introduction to the use of event-related potentials in studies of perception and attention. Attenti Percept Psychophys 72(8):2031–2046. https://doi.org/10.3758/BF03196680.

(Received 9 September 2019, Accepted 26 October 2020)
(Available online xxxx)