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Flavor is in the brain

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ABSTRACT

Flavor is perhaps the most multi-modal of all of our sensory experiences. Here flavor is defined as a perception that includes gustatory, oral-somatosensory, and retronasal olfactory signals that arise from the mouth as foods and beverages are consumed. Although the sights, sounds and smells of foods that occur just before, or in the absence of eating, can impact flavor perception, it is argued that these sensory signals exert their influence by creating expectations based upon prior associations. The primary aim of the paper is to review anatomical and neurophysiological data towards an understanding of how the core sensory signals combine in the central nervous system of humans. Based upon the extant literature it is proposed that taste, oral-somatosensory and olfactory inputs are first integrated in the anterior ventral insula. The core flavor percept is then conveyed to upstream regions in the brainstem and thalamus, as well as downstream regions in the amygdala, orbitofrontal cortex and anterior cingulate cortex to produce the rich flavorful experiences that guide our feeding behavior.

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As Shepherd highlights in his book "Neurogastronomy", flavor is in the brain, not the food [1]. It is the brain that integrates the discrete sensory inputs from the food and drink we ingest to create flavor perceptions. This paper provides an overview of how the human central nervous system sets about the task of integrating taste, smell, and somatosensory inputs into a unitary flavor perception.

1. What is flavor?

Defining flavor is not as simple a task as it sounds. When we eat we simultaneously stimulate the gustatory, olfactory and somatosensory systems. As such, there is agreement that flavor is a multi-modal perception. However, there continues to be significant debate over just how many modalities should be included. Here the core flavor modalities are defined as those sensations that arise, or appear to arise from the mouth. This simple definition is inspired by a general principle of multisensory integration, which states that integration is favored when sensations from different modalities co-occur in time and space [2]. More specifically, multi-modal perceptions derive from the activity of neurons that respond to inputs from different sensory receptors. A critical feature of these multi-modal neurons is that they have overlapping receptive fields across modalities. A given cell in the cat superior colliculus that responds to flashes of light in the upper right quadrant of space will only respond to sounds that also appear to originate from the upper right quadrant of space. Moreover the response that the neuron produces to the sight and sound that co-occur in time and space is greater than the summed responses to either the sight or sound alone. Such responses "supra-additive" responses are the hallmark of multisensory integration because they indicate that two independent signals have not only been pooled but also transformed into an integrated product [2]. Here it is argued that the receptive field for flavor is the mouth, or particular locations within the mouth. Oral capture illusions serve to bring taste, touch, and smell into the common oral receptive field [3–6] so that information can be pooled and transformed into flavor percepts, indexed by supra-additive responses. The exact nature of the supra-additive response varies as a function of methodology employed; it could be perceptual (e.g. enhanced intensity or pleasantness ratings) or neural (e.g. increased neuronal firing or increased blood oxygen level dependent (BOLD) responses). Data will be presented suggesting that while integration occurs at many, if not most, levels of the neuroaxis, the independent sensory inputs that combine to create flavor sensations are first integrated in the anterior insula. It is then proposed that these neural signatures of flavor are communicated to higher and lower-order neural relays where they are enriched and integrated with appetitive circuits to guide feeding behavior.

The gustatory sense produces the sensation of sweet, sour, salty, bitter and savory. Taste receptors are located in discrete regions of the mouth but we perceive taste as arising from throughout the oral cavity. This is because tactile stimulation, which always co-occurs with taste, can capture taste. This capture illusion was first demonstrated by Todrank and Bartoshuk [6]. They asked subjects to report

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the intensity of a taste as it was painted onto the tongue with a cotton wand along a path that traversed regions of high and low taste bud density. When the path began in a region of low taste bud density, taste sensations started out weak. As the path intersected regions of greater taste bud density, taste sensations became stronger. However, when the path returned to low-density regions the sensation remained nearly as intense as it was in the high-density region, indicating that the taste sensation traveled with the touch. More recently, Green and colleagues confirmed this effect, showing that taste can be referred to a nearby but tasteless tactile stimulus [3,4]. This experiment is described in greater detail in Fig. 1. Thus an oral capture illusion co-localizes taste and touch to common regions of the mouth.

Slightly more problematic is the sensation of smell. Olfactory receptors are located in the olfactory epithelium, deep within the nasal cavity and far from the taste and tactile receptors in the mouth. Yet it is smell that provides the critical signal that defines the flavors we "taste". This is achieved because the volatiles that arise from foods enter the nasal cavity, bind to olfactory receptors and are then referred to the mouth. This type of smelling is referred to as retronasal olfaction. Retronasal olfaction is the critical sensory signal defining flavor objects because it is the retronasal odor that gives flavors their identity [7]. Although significant questions remain about how odors sensed retronasally are referred to the mouth, Lim and Johnson elegantly demonstrated that taste but not touch causes retronasally inhaled odors to be referred to the mouth [5]. In their experiment retronasally inhaled odors were significantly more likely to be perceived as arising from the mouth in the presence of overlapping presentation of a congruent taste (Fig. 2). Thus, touch is perceived where it is transduced, touch then captures taste and taste captures smell. The result is the co-occurrence of taste, touch and smell in space and time.

Interestingly, there is also recent evidence that orthonasally sensed odors can be referred to the mouth and that this too depends upon the presence of a taste and not on oral somatosensation [8–10]. This implies that orthonasal sensations, if referred to the mouth, may form part of the core flavor percept. A similar conclusion can be reached for aural stimulation that occurs during mastication (e.g. the crunch of a potato chip) [11]. Under most circumstances orthonasal olfaction (including inhalation of food aromas through the nose in the absence of an oral stimulus) and audition are not localized to the mouth and hence not part of the core flavor percept. However, during eating orthonasal odors emanating from the food and auditory inputs coming from the mouth may well contribute to the core flavor percept because they appear to arise from the mouth. In contrast, while the sight of foods clearly impacts flavor perception [12–14], it is not considered a core flavor sense because it is never localized to the mouth. Rather, the view taken here is that visual stimuli exert their influence by virtue of their effects on expectations and beliefs. This would also be true for the sound of the sizzle of a burger on the barbeque or the smell of a freshly baked pie cooling on the window sill.

In summary, flavor is defined as the unitary percept that results from the integration of oral somatosensation, gustation, retronasal olfaction and possibly audition and orthonasal smells, which occur during eating and drinking and are localized to the mouth. The question addressed below is: where are these distinct sensory inputs integrated?

2. Neural substrates

There is a significant body of literature from which to draw on to consider the central mechanisms of taste, oral somatosensation and olfaction. In contrast, virtually nothing is known about the neurophysiology of the integration of auditory cues with other oral sensations. The focus here is therefore on gustation, oral somatosensation and olfaction, and in particular, upon where these three signals combine. More specifically, since there is evidence that taste and oral somatosensation are integrated at virtually every level of the neuroaxis — beginning at the receptor [15] — the spotlight of the focus is on where olfaction joins taste and touch to create flavor objects. Where data are lacking in primates, we turn to the rodent literature.

2.1. Brainstem

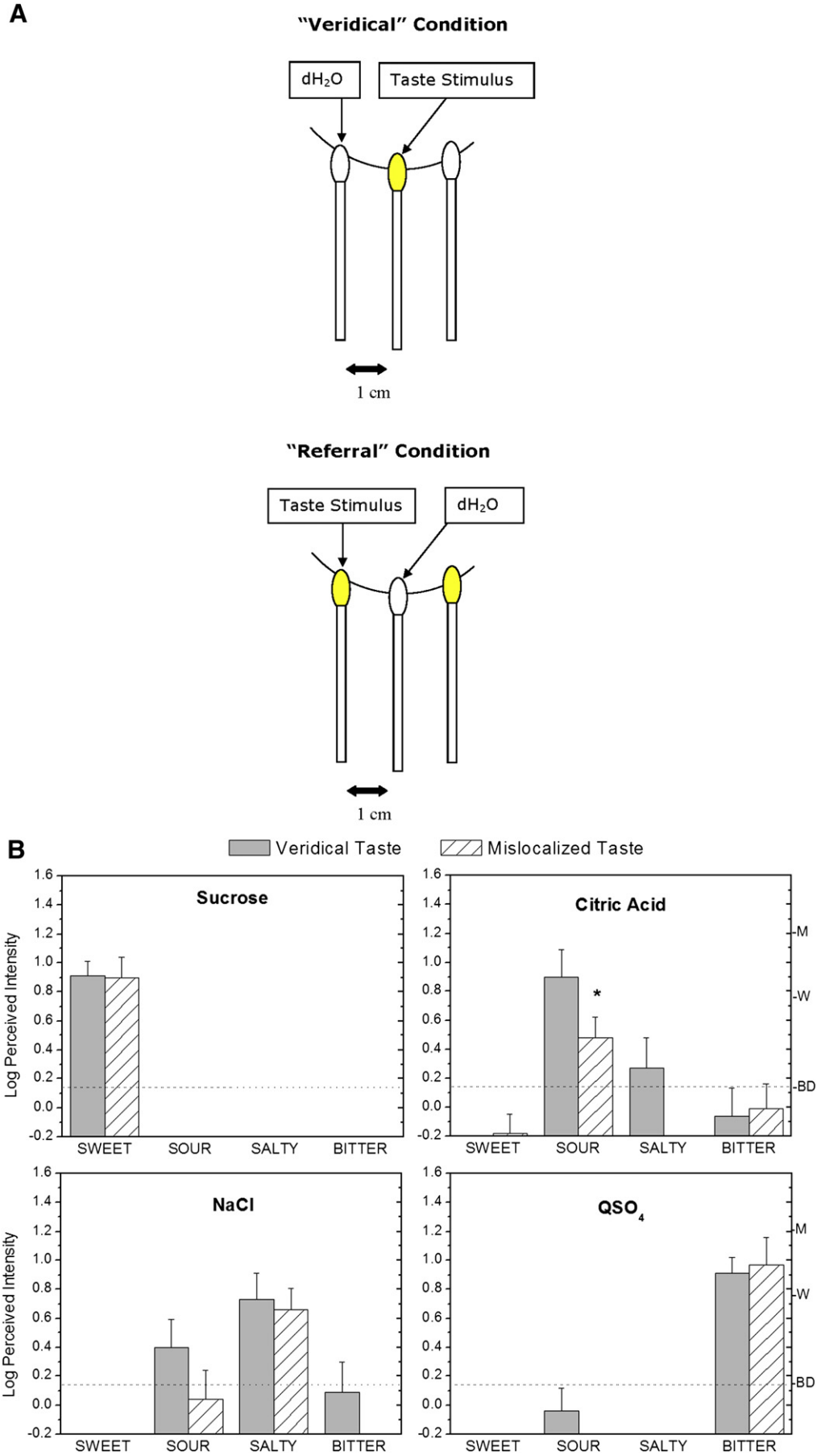
The taste signal is carried from taste receptors cells by cranial nerves VII, IX, and X to the nucleus of the solitary tract (NST) in the medulla, where they are joined by oral somatosensory projections from the spinal trigeminal nucleus. Although the precise locations of the trigeminal projections vary across species there is evidence of overlap with gustatory areas of the NST [16–20]. This overlap suggests that integration occurs. However, the hallmark of multisensory integration is the supra-additive response. To demonstrate supra-additivity two stimuli are delivered independently (i.e. unimodal stimulation) and then together (i.e., bimodal stimulation). If the summed response to unimodal stimulation is less than the response observed to the bimodal stimulation (i.e. it is supra-additive) then it is assumed that the signals have been integrated to create the supra-linear response. This procedure is problematic for flavor researchers because taste and touch almost always co-occur when food or drink comes into contact with the tongue. Achieving independent stimulation of taste and touch is therefore not trivial and perhaps not even ecological. For example, in humans pure taste stimulation achieved by adapting the somatosensory component using "flow" methods results in a much-reduced sensitivity [21]. This suggests that the brain is organized to detect and process taste and touch simultaneously, as they normally occur. What we do know about taste and tactile responses in the NST is that there are many cells that respond to taste and not to mechanical stimulation alone (i.e. unimodal taste) and a smaller portion of cells that respond weakly to mechanical stimulation alone (i.e. unimodal touch) and more robustly to mechanical stimulation plus taste (i.e. Bimodal taste/touch) [22]. This profile, while not definitive, supports the existence of taste-oral somatosensory integration in the NST, at least in rodents.

There is also some evidence that olfactory stimulation can drive NST single-unit responses. Van Buskirk and Erickson showed that 22 of 35 taste-responsive neurons in the NST also respond to olfactory stimulation [23]. Unfortunately, the odorants in this study were selected to be trigeminal, making it likely that somatosensory, rather than olfactory input was driving the response. Clearly, future work investigating whether pure olfactory responses occur in the NST is needed. However, even if overlapping and/or supra-additive responses are demonstrated here there is no evidence for a direct projection from the olfactory bulb to the NST [24,25]. Rather, it is likely that cortico-fugal projections from the insular cortex [26,27] are the source of olfactory signals. Thus the NTS may contribute to flavor perception but it is unlikely the first site of integration.

2.2. Thalamus

In rodents there is a gustatory projection from the NST to the pontine parabrachial nucleus [28–30]. This relay does not exist in nonhuman primates [31–34] or humans [35]. Thus in primates afferents conveying taste and oral somatosensory information travel from the NST directly to the ventroposterior medial (VPM) nucleus of the thalamus. Here unimodal taste, tactile and thermal, as well as bimodal tactile/taste and thermal/taste cells have been isolated in both rodent and nonhuman primate VPM [36,37]. Moreover supra-additive responses have been reported between taste and thermal stimulation [38], indicating that taste and thermal inputs are integrated in the thalamus.

Interestingly, an early study by Giachetti and Macleod reported that electrical stimulation of the lateral olfactory tract in rodents produced responses in VPM [39]. In fact, they reported that half of all gustatory neurons in VPM also responded to stimulation of the lateral olfactory tract. Remarkably, since that time no study has tested for


A
"Veridical" Condition
dH2O
Taste Stimulus
1 cm
"Referral" Condition
Taste Stimulus
dH2O
1 cm
B
Veridical Taste
Mislocalized Taste
Sucrose
Citric Acid
NaCl
QSO4
Log Perceived Intensity
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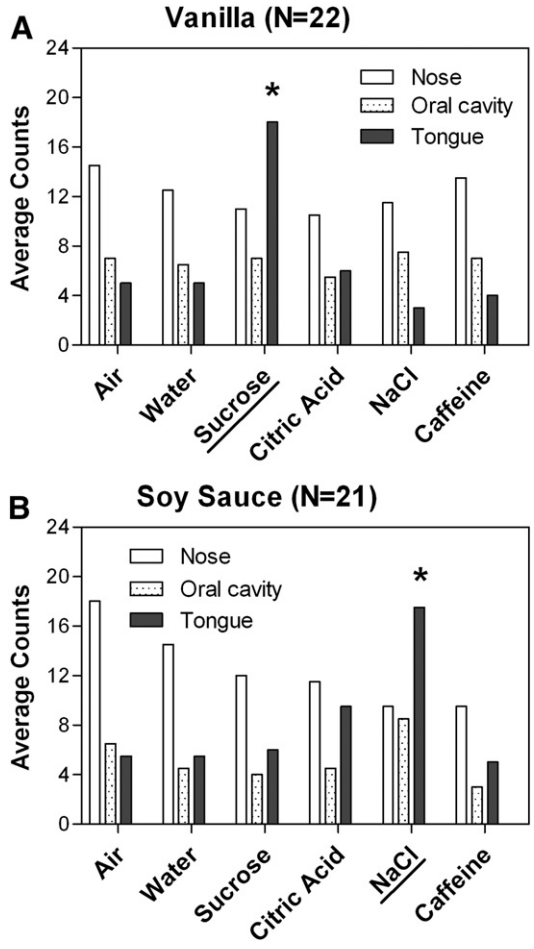

Fig. 2. Taste captures smell. In this experiment subjects inhaled odorants through a straw and the experimenter delivered a taste (or water) to the mouth with a pipette. Subjects consulted a diagram of the cross-section of the head with regions labeled nose, oral cavity, tongue, and throat, and indicated where they felt the vanilla (experiment 1) or the soy sauce odors (experiment 2) were coming from. They were allowed to endorse as many locations as they felt were appropriate. A. Results showing that retronasal perception of vanilla are referred to the mouth in the presence of a sweet taste but not in the presence of a salty, sour, or bitter taste, or a pure tactile stimulus. Average frequency responses for the odor localization tasks for each vanilla–air, vanilla–water, or vanilla–taste pair. Note that the subjects were allowed to report none, one location, or multiple locations for each test pair, and thus, the total frequency counts across the test pairs are not exactly the same. In one condition (air control), neither taste nor tactile stimulation was presented. In another condition, water was presented simultaneously in the mouth to provide tactile stimulation without any taste input. The frequency responses for each vanilla–taste pair were compared with those for vanilla–water pair by a 2-tailed chi-squared test. The asterisk indicates a significant difference at $P<0.0001$. B. Results showing that retronasal perception of soy sauce are referred to the mouth in the presence of a salty taste but not in the presence of a sweet, sour, or bitter taste, or a pure tactile stimulus. Average frequency responses for the odor localization tasks for each soy sauce–air, soy sauce–water, or soy sauce–taste pair. The frequency responses for each soy sauce–taste pair were compared with those for the soy sauce–water pair by a 2-tailed chi-squared test. The asterisk indicates a significant difference at $P<0.00001$.
Taken with permission from [5].

olfactory responses in the VPM and the role of this region in flavor remains very much unexplored. However, even if confirmed, in the absence of a known projection from the olfactory bulb, it is most likely that the olfactory responses represent cortico-fugal influences. Thus the VPM may contribute to flavor processing but, as is the case with the NST, it is not likely the site of first convergence.

2.3. Insula

Unlike the NTS and VPM, there is clear evidence for overlap and integration of taste, tactile and olfactory inputs in the insular cortex [40–50]. In primates gustatory fibers project from the VPM to the anterior opercular and insular regions of the granular and dysgranular insula and extend to the adjacent agranular region [51]. There are also projections from the granular and dysgranular region to a more extensive region of agranular insular cortex [52–54]. These regions respond to taste in rodents [47,55–61], nonhuman primates [46,62–65] and humans [66–70].

Oral somatosensory inputs reach all regions of primary gustatory cortex after synapsing in the primary somatosensory cortex of the pre- and post-central gyri [51]. As such, single unit recordings in primates [46] and neuroimaging studies in humans show insular responses not only to taste [66–70] but also to chemical stimuli with tactile components such as astringency [42] and burn [71], as well as to the temperature [72] and viscosity of oral stimuli [43,73].

Olfactory inputs are thought to project primarily to the agranular anterior insular cortex (reviewed in [47]). These projections either arrive directly from the bulb [74] or indirectly via piriform cortex [75,76]. As such, it has been concluded that the agranular insular cortex is the site of first convergence of taste, oral somatosensory and olfactory information — at least in rodents [47,55,77]. Human neuroimaging work is largely in agreement with this possibility. Although many regions of insula, operculum, and orbitofrontal cortex respond to olfactory and gustatory stimulation [38], it is in the anterior ventral insular region, which likely corresponds to agranular cortex in humans [76], where there is the strongest evidence for actual integration of these sensory signals.

First, Cerf-Ducastel and Murphy showed that the anterior ventral insula (among other regions) responded to retronasal olfactory stimulation[41]. Overlapping responses [44,49] and supra-additive responses [48] to taste and olfactory stimulation were then demonstrated. Using, using fMRI, de Araujo et al. demonstrated overlapping responses to tastes (sucrose and monosodium glutamate) and retronasally delivered odors (strawberry aroma and a chicken like flavor) in the anterior ventral insula [44] (Fig. 3). Overlap was also observed in the amygdala, caudal orbitofrontal cortex, and far posterior medial orbitofrontal cortex. In addition, a supra-additive response in the far anterior orbital cortex was identified, suggesting that this may be a critical sight for integration downstream of the anterior ventral insula. Unfortunately, while they were able to demonstrate perceptual supra-additivity, with subjects rating the consonance and pleasantness of sucrose + strawberry significantly greater than the summed ratings to sucrose alone or strawberry alone, these ratings did not

Fig. 1. Touch captures taste. A. This figure depicts the stimulus configuration used to measure referral of taste sensations to the site of tactile stimulation by [3]. On each trial, the experimenter touched three saturated cotton swabs simultaneously to the anterior edge of the tongue, producing identical tactile stimulation at each site. In the veridical condition (top), the taste stimulus was delivered only on the middle swab, with deionized water on the two outer swabs. In the referral condition, the taste stimulus was delivered only on the two outer swabs, with deionized water on the middle swab. In both conditions, subjects' task was to ignore any tastes on the outer swabs and to rate the intensity of the taste perceived at the middle swab. Significant taste sensations were reported at the middle swab in the referral condition for all four taste stimuli tested (sucrose, NaCl, citric acid, and quinine). B. Results from [3] showing that subjects judge the tasteless middle swab as having a taste (mislocalized condition) just as frequently as they do when a taste is actually present (veridical condition). Log-mean taste ratings of sweetness, sourness, saltiness and bitterness are shown for the middle swab as per the procedure described in A. The stimuli were 1.0 M sucrose, 0.5 M NaCl, 0.05 M citric acid, and 1.0 mM QSo_4. The gray bars show the results when the taste stimulus was applied to the middle swab (veridical condition), and the hatched bars show the ratings when the taste stimulus was applied only to the outer swabs (mislocalization or referral condition). Letters on the right y-axis represent semantic labels of the Labeled Magnitude Scale (BD = barely detectable; W = weak; M = moderate). Sensations below the horizontal dotted line were rated as less than "barely detectable". The only statistically significant difference between conditions was the lower sourness ratings for the citric acid in the referral condition ($P<0.05$). Vertical bars denote the standard errors of the means (SEMs).
Taken with permission from [3].

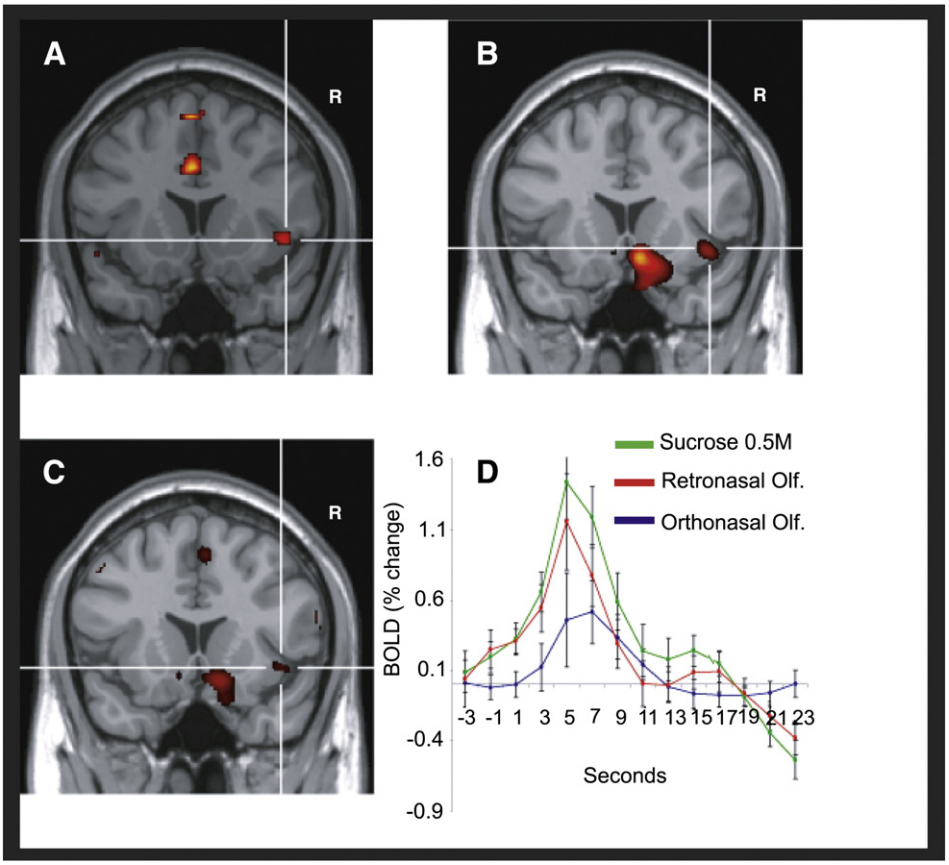

Fig. 3. Taste and olfactory convergence in the human anterior ventral insular cortex. The region of anterior ventral insular cortex showing overlapping responses to taste and odor in [44]. Coronal slices through the anterior insular cortex showing a small region found to receive convergent olfactory and gustatory input (MNI coordinates (45, 15, −9); this is the region marked by the cross-lines). (A) Responses to orthonasal olfactory stimuli as revealed in a conjunction analysis across a set of six odors corresponding to different affective values and compared to odorless air flow. (B) Responses to unimodal sucrose compared to a tasteless solution. (C) The same brain region is activated by a conjunctive comparison involving sucrose and a retronasally administered strawberry odor (both compared against tasteless). (D) Timecourses of activation corresponding to these effects, showing that these three different stimuli activate the same site in the far anterior (putatively agranular) insular cortex. The units on the abscissa are in seconds, and on the ordinate are percent of BOLD signal change.
From [44] with permission.

correlate with responses in the regions showing neurophysiological overlap or additivity.

In a subsequent study using a similar procedure as that employed by de Araujo and colleagues (2003) we demonstrated a supra-additive response to a congruent flavor in the anterior dorsal insula, anterior ventral insula, frontal operculum, anterior cingulate cortex, posterior parietal cortex and ventrolateral prefrontal cortex [48] (Fig. 4). Based upon the anatomy described above, we assume that the anterior ventral region is the initial site of convergence and that the supra-additive responses in other regions represent downstream processing. Unfortunately, in our study perceptual supra-additivity was not observed. Thus, how these neural supra-additive responses related to perceptual supra-additive responses could not be determined. Indeed, the link between perception and neurophysiology is still largely unexplored and constitutes an important avenue for future research. However, in that study we were able to demonstrate that the supra-additive response in most regions, including anterior ventral insula, to the bimodal congruent flavor (sweet vanilla), was significantly greater than the response to a bimodal incongruent flavor (salty vanilla), implying that integration is experience-dependent. This same conclusion was also reached by two evoked-related potential studies. In the first, Welge-Lussen et al. showed that the early P1N1 response to orthonasally presented vanillin was greater, and the latency shorter, when subjects simultaneously perceived a sweet as compared to a sour taste [78]. Then in a subsequent study from the same laboratory they demonstrated a similar effect but only if the odor was delivered retronasally [79].

Experience-dependent responses have also been reported from bimodal neurons in the caudolateral orbitofrontal cortex of the monkey; however, these same neurons do not appear to demonstrate supra-additive responses [80]. This raises the possibility that integration first occurs in anterior ventral insula and signals conveying the integrated flavor percept are relayed to the orbitofrontal cortex.

Further evidence for experience-dependent integration in human anterior ventral insula comes from a study by Veldhuizen et al. (2010). Since odors are often described as having taste-like qualities [81,82] we asked whether insular responses to odors were related to the perception of the taste-like quality of the odor [49]. Two concentrations of sucrose solution (perceptually judged as strong and weak) were delivered to subjects and a comparison of strong vs. weak sucrose was created to localize regions of the brain responding to sweet taste. The response map was then used as a "mask" in a contrast of the response to orthonasally presented sweet odors (chocolate cookie, strawberry and cream, rose and lilac) vs. odorless stimulation so that we could limit olfactory responses to those regions that responded to sweet taste. This analysis isolated one region: the anterior ventral insula, where responses to sweet taste and sweet odors overlapped. In addition, the magnitude of the response to the food, but not the nonfood odors, correlated positively with subject's

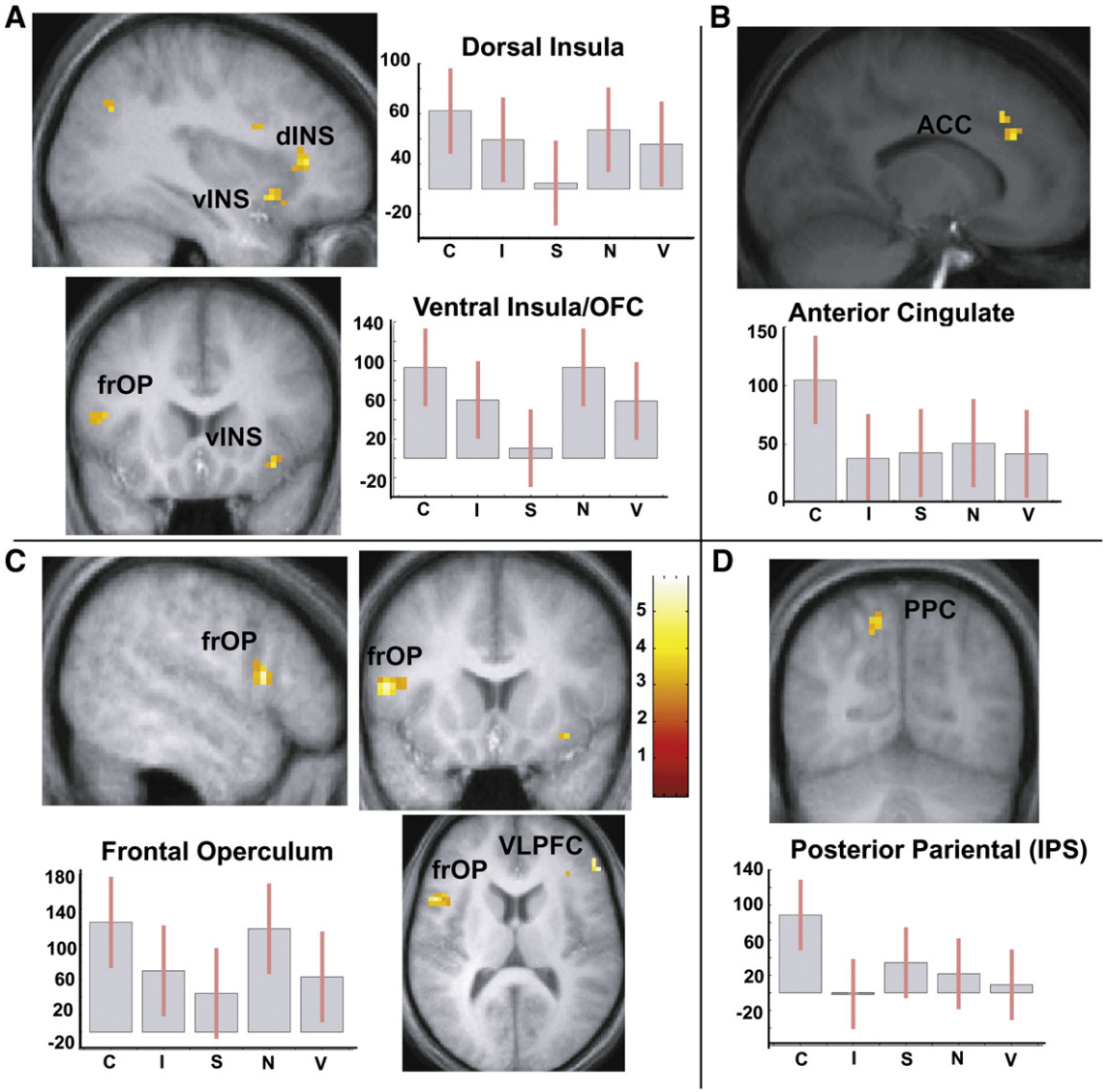

Fig. 4. Supra-additive responses to congruent taste–odor pairs in the human brain. Activations isolated in the group random effects analysis of [congruent − (taste + smell)] from [48]. Panel A shows activation in dorsal anterior insula (dINS) and ventral anterior insula/caudal orbitofrontal cortex (vINS). Graphs show parameter estimates associated with each of the 5 conditions (C = congruent, I = incongruent, S = sweet, N = salty, V = vanilla) in the dorsal insula (top) and ventral insual (bottom). Panel B displays activation in the anterior cingulate cortex (ACC) and the graph of parameter estimates from that region in the five conditions. Panel C displays activation in the frontal operculum and ventrolateral prefrontal cortex with the graph of parameter estimates in the frontal operculum for the five conditions. Panel D shows activation in the posterior parietal cortex (PPC) (intraparietal sulcus IPS) and parameter estimates at that location for each of the five conditions.
Taken with permission from [48].

ratings of odor sweetness (Fig. 5). This suggests that these responses are experience-dependent, since food but not nonfood odors have been experienced with sweet taste. As such, the findings accord well with a series of studies by Richard Stevenson and his colleagues demonstrating that the taste-like qualities of odors can be enhanced following the experience of that odor in solution with the taste [81,83–88]. Also of note was the fact that although there were robust responses to the odors in the piriform cortex and orbitofrontal cortex, these responses were not associated with odor sweetness perception. This suggests that the insula contributes to food odor quality coding, a conclusion that has also been reached by a recent experiment in which it was demonstrated that inactivation of insular taste cortex impaired rats ability to learn about or use olfactory information to guide food preference [89].

Taken together, these findings align with the proposal that the creation of flavor percepts depends upon processing in the anterior ventral insular cortex. However, definitive proof awaits future studies linking supra-additive perceptual and neural responses. For example, Dalton et al. demonstrated that when a sub-threshold taste is experienced simultaneously with a sub-threshold congruent sniffed aroma, subjects are able to perceive the bimodal stimulus [90] (Fig. 6). This effect was then replicated with retronasal odor/taste combinations by Delwiche and Heffelfinger [91]. If the anterior ventral insula is the critical site for flavor integration then response here should reflect this sub-threshold summation. Likewise, there are many reports in the literature of congruency effects on suprathreshold perceptual interactions between taste and smell. Most recently Green et al. showed that the enhancement of retronasal olfaction by taste is dependent on the perceptual congruence of the taste and odor [92]. It the anterior ventral insula is critical for integration then response here should be associated with perceptual enhancements.

A separate issue is the methodological short-comings of these early fMRI studies which may very well have limited their sensitivity [93]. Most critical is the fact that subjects were asked to refrain from

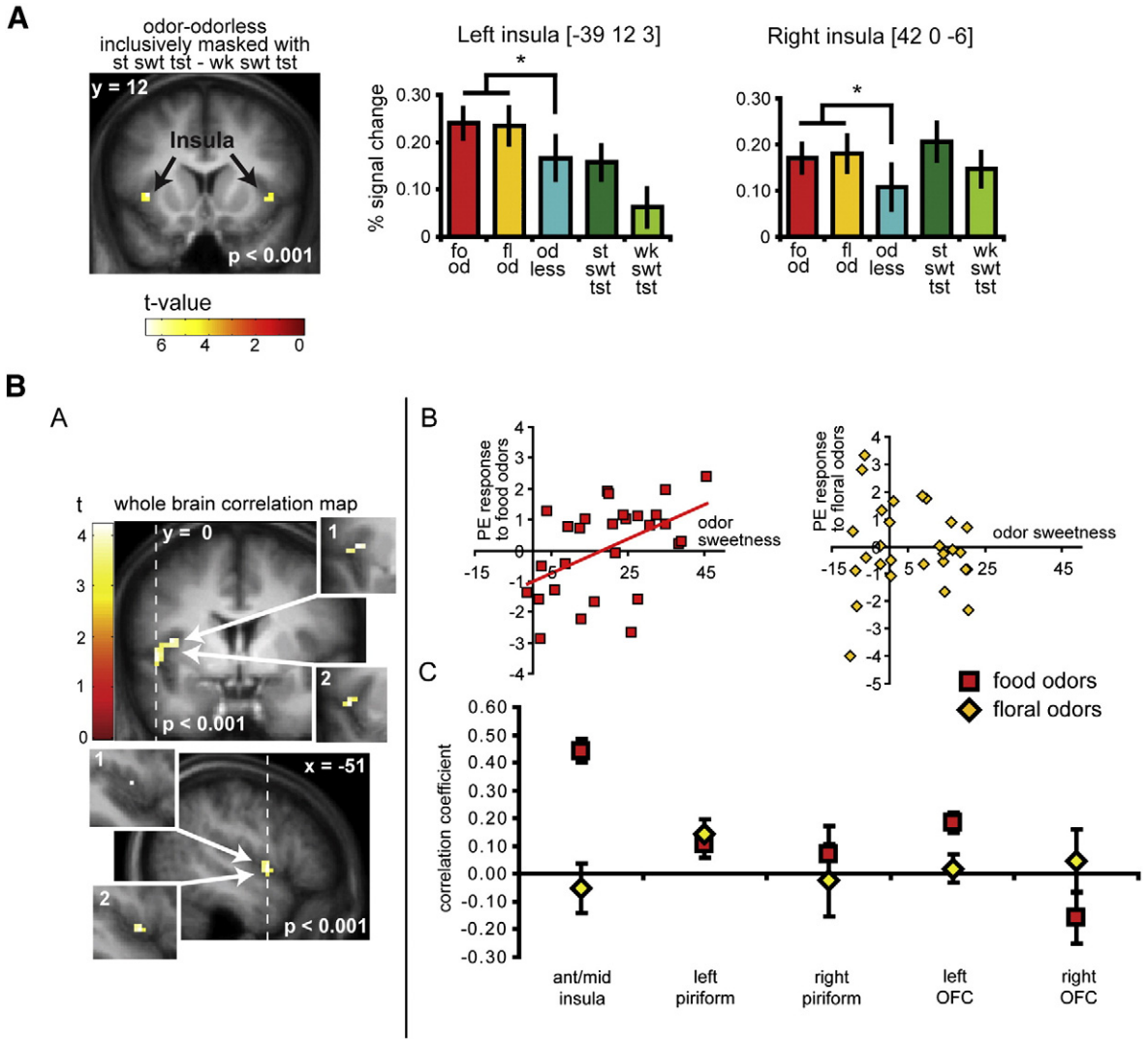

Fig. 5. Overlapping response to sweet taste and sweet odor in the human anterior ventral insula. A. Coronal section showing neural response to food and floral odors vs. odorless air in bilateral insula, inclusively masked by response to strong sweet taste minus weak sweet taste. The bar graphs show the percent signal change for the three odor conditions food (red), floral (yellow), and odorless air (blue), and the two taste conditions strong sweet taste (dark green) and the weak sweet taste (light green) (±s.e.m.), averaged over subjects. The line graphs display the timecourse of the signal extracted from the voxel responding maximally to odor–odorless, for food (red), floral (yellow), odorless air (blue), strong sweet taste (dark green) and the weak sweet taste (light green) (parameter estimates in arbitrary units (±s.e.m.) averaged over subjects). B. Panel (A). Coronal and sagittal sections of the area of insula where neural response to the food odors shows a positive correlation with the sweetness ratings of those odors. The main images display the unmasked regression maps while the insets labeled 1 depict the masked regressions (i.e. using the "sweet odors and sweet taste overlap" inclusive mask). The insets labeled 2 depict the analysis with the pleasantness and familiarity ratings as covariates. Panel (B) illustrates the magnitude of the correlation (averaged across all voxels ± standard deviation) in the insula for food odors (in red squares) and non-food odor (yellow diamonds) in comparison to the responses in other areas for food and non-food odors vs. odorless.
Taken with permission from [49].

swallowing the flavored liquids until cued. This procedure was followed to limit movement that threatens to produce artifact and to interfere with the ability to detect the event of interest (i.e. flavor). However, as Marciani et al. [93] elegantly confirmed with atmospheric pressure chemical ionization mass spectrometry, the volatile components of the flavor, upon which retronasal olfaction depends, traverse the nasophyarnx maximally following a swallow. This raises the possibility that retronasal olfaction was minimal during the modeled brain responses in the [44] and the [48] studies (as well as the McCabe and Rolls [143] paper described below). However, when Marciani et al. [93] performed an fMRI experiment in which subjects swallowed immediately after receiving a flavor comparison of a flavor vs. a control stimulus produced activation in the regions identified by the two earlier studies. Unfortunately, they did not investigate the possibility of supra-additive effects.

In summary, although there is evidence for overlapping responses to the sensory signals that give rise to flavor perception, the bulk of the evidence in rodents and in humans favor the conclusion that integration first occurs in the anterior ventral insula. Given that our definition of flavor includes the sounds made during mastication, it is also noteworthy that the insular cortex receives auditory inputs and has been proposed to be involved in the integration of auditory inputs with other sensory systems [94]. This work has focused primarily on phonological processing. Future studies aimed at exploring auditory, as well as oral somatosensory influences on oral sensory integration are needed.

3. Neural correlates of oral localization illusions

As reviewed above, touch captures taste and taste captures smell, resulting in the veridical perception that all the components of flavor emerge from a common location in the mouth. While it is likely that this perception depends critically upon sensory integration taking place in the anterior ventral insula, the peripheral or central neurophysiological mechanisms underlying the oral referral of retronasal odors remain largely unknown.

Early accounts of referral proposed three possible mechanisms: (1) a gating mechanism triggered by the presence of a palpable substance in the mouth or direction of movement of odorants across the olfactory mucosa; (2) olfactory input is combined with available oral inputs into an emergent percept in which the olfactory component loses its identity; (3) the input to the olfactory mucosa may be different under the two conditions [95]. The results of two recent psychophysical studies sway the evidence towards either a central gating mechanism or central integration of the olfactory input into an emergent percept — or likely both. First, Lim and Johnson demonstrated that the ability of taste to capture an odor depends strongly upon congruency [5]. Retronasally inhaled vanilla odor was more likely to appear to arise from the mouth in the presence of a sweet compared to a salty taste. In contrast, soy sauce odor was referred to the mouth more in the presence of a salty compared to a sweet taste (Fig. 2). This result strongly suggests that referral is learned and hence is the result of a central mechanism.

In the second study, Stevenson et al. investigated the role of attention on referral of orthonasal odors to the mouth [8]. Their hypothesis was that oral localization of smell may depend on the degree to which it can be distinguished from the taste component, such that greater perceptual similarity may make it harder to voluntarily attend to the olfactory channel. In addition, since tastes are typically more salient than odors, they proposed that tastes may be more effective at driving exogenous, or bottom-up, attention at the expense of odors. Consistent with this possibility they showed that modulating the saliency of a taste or an odor biased localization towards or away from the mouth. Since attention depends upon central mechanisms [96], it follows that oral capture is orchestrated centrally, in part by the canonical heteromodal attention network (e.g. intraparietal sulcus, temporal parietal junction, frontal eyefields and cingulate cortex) [97–104], working in concert with the relevant sensory cortices — and in the case of olfaction, the mediodorsal nucleus of thalamus [105]. Consistent with this possibility, in a subsequent study they showed that patients with medial dorsal thalamic lesions have impaired olfactory attention and enhanced oral capture [106]. One caveat to bear in mind is that these findings result from orthonasal not retronasal olfaction, and the ratings of localization are never clearly in the mouth, but rather reported as “less in the nose”. Nevertheless, the idea that attentional mechanisms are involved in oral referral is intriguing and deserves further exploration.

Finally, in a previous study conducted in collaboration with Thomas Hummel's group, we have suggested that neural processes in the oral somatomotor mouth area might be critical for referral [107]. In that study, four odors were presented to subjects in the MRI scanner orthonasally and retronasally via tubes endoscopically placed so that one tube ended at the nasopharynx to stimulate retronasal olfaction and the other tube ended at the external nares to stimulate orthonasal olfaction [108]. Response in the somatomotor mouth area was greater when the same odors were delivered retronasally compared to orthonasally, suggesting that this response reflected the referral of the retronasal odors to the mouth. However, it is equally possible that this response resulted from, rather than caused, referral. Another limitation of this finding is that odors were delivered in the absence of taste. Although some referral to the mouth occurs in the absence of taste [109], the effect is considerably weaker than when a congruent taste is present [5].

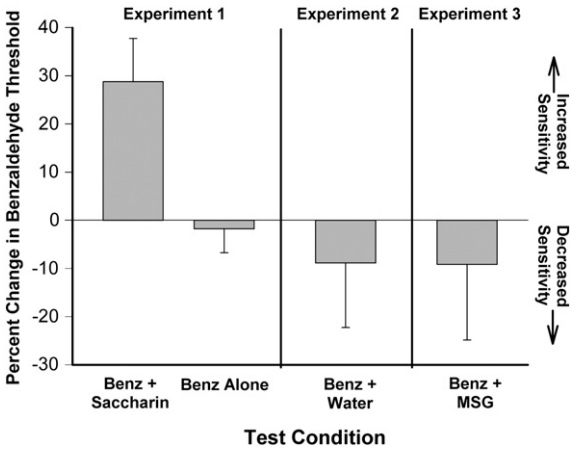

Fig. 6. Subthreshold summation of taste and smell. Median percent change from baseline benzaldehyde threshold in experiments 1–3. On each summation trial, subjects first placed 10 ml of the oral stimulus in their mouths, then sniffed through both nares from two bottles that contained either benzaldehyde solution in one bottle and diluent only in the second bottle (stimulus pair), or dilutent in both bottles (blank pair). Subjects then rinsed their mouths with deionized water. Next, subjects tasted the same oral stimulus while sniffing from the second set of two bottles. After rinsing their mouths, they indicated which set of two bottles contained the odorant (benzaldehyde). Negative numbers represent decreases in sensitivity; positive numbers represent increases. Single sample t-tests on the median change in each condition revealed that only the threshold change obtained when saccharin was in the mouth differed significantly from zero (saccharin, $p=0.01$; nothing, $p=0.71$; water, $p=0.52$; MSG, $p=0.57$). The two bars on the left depict the results from experiment 1, showing the significant change from baseline in benzaldehyde threshold with saccharin as the oral stimulus versus with nothing in the mouth (paired directional t-test, $t_{18}=2.66$, $p=0.001$). The changes from baseline in benzaldehyde threshold when water was the oral stimulus (experiment 2) and when MSG was the oral stimulus (experiment 3) were significantly different from the decreased threshold obtained with saccharin in the mouth (directional t-tests with Bonferroni corrections for multiple comparisons, $t_{18}=3.52$, $p=0.006$; $t_{18}=2.10$, $p=0.04$).
Taken with permission from [90].

4. Neural correlates of flavor liking

The reinforcing properties of foods and flavors depend upon oral-sensory and post-oral mechanisms [110,111]. Pure gustatory sensations provide reliable signals about the presence or absence of nutrients and/or toxins. Accordingly, affective responses to pure tastes are innate and stable [112] so that humans can avoid the perilous task of having to learn that bitter can signal poisons and be predisposed towards sweet tasting foods that contain calories. By contrast, affective responses to flavors are highly dependent upon learning [113]. This offers the distinct advantage of enabling organisms to learn to like what is available, which in turn motivates intake of accessible sources of energy. As such, mechanisms have evolved to optimize nutrient ingestion [110,111]. More specifically, once a flavor object has been created it is associated with its post-ingestive effects so that preferences can be formed to safe sources of energy.

Flavor–flavor learning and flavor–nutrient learning are two critical processes upon which flavor preference formation depends [114,115]. Critically, at least in rodents, post-oral mechanisms are thought to play a more significant role in controlling intake and in establishing long term flavor preferences than oral sensory mechanisms [116]. For example, nutritional content is a better predictor of sweet solution intake than the sweet taste response [117]; preferences for sucrose solutions can be established in the absence of sweet taste signaling [110]; and the addition of preferred flavors and textures to a balanced diet does not promote increased intake over an equi-caloric diet that lacks preferred flavors and textures [118]. In addition, consumption of high fat and high sugar diets, which are more energy dense than balanced meals consistently result in increased intake and weight gain [118–121], and preferences are readily formed for flavors associated with positive postingestive effects [111,122–127].

Thus, whereas oral sensory mechanisms enable the rapid identification of nutrients and, through their affective properties, promote acute consumption. Post-oral mechanisms drive long-term flavor preference formation and intake based on the positive postingestive effects of the nutrients being consumed [111,116]. Although there has been a recent surge in research aimed at understanding flavor preference formation in rodents, relatively little is known about this process in humans, and virtually nothing is known about the underlying neural processes in the human brain. This area represents an important area for future research.

What is known is that responses in the anterior ventral insula to oral stimulation preferentially interact with responses in the hypothalamus when the stimulus is potentially nutritive [71], and that this anterior ventral insular region is sensitive to modulation of internal state [128,129], with responses co-varying with changes in plasma insulin concentration [129] and circulating glucose levels [130]. It is therefore conceivable that flavor percepts are associated with their physiological significance in the anterior ventral insula [45]. Indirect support for this possibility comes from a recent study investigating the effect of artificial sweetener use on brain response to the caloric sweetener sucrose [131]. Based upon work in rodents showing that exposure to non-caloric sweeteners degrades the relationship between a sweet taste and its post-ingestive effect [132,133], we predicted that response to sucrose should be inversely related to artificial sweetener use in regions that represent the associations between tastes and their physiological significance. Consistent with this prediction, and with a role for the anterior ventral insula in associating flavors with post-ingestive effects, we observed inverse relationships between artificial sweetener use and response in the anterior ventral insula and amygdala (Fig. 7). Thus there is indirect support for a role of the anterior ventral insula in flavor preference formation based upon associations of oral sensations with post-oral effects.

More established is the role the orbitofrontal cortex plays in flavor hedonics. Human neuroimaging investigations have shown that the perceived pleasantness of taste [128,134,135], odor [136–139], oral somatosensory [140,141], flavor [44,142,143], and feeding [142,144,145] is correlated with response in orbitofrontal cortex. These findings accord well with electrophysiological studies in rodents [146] and

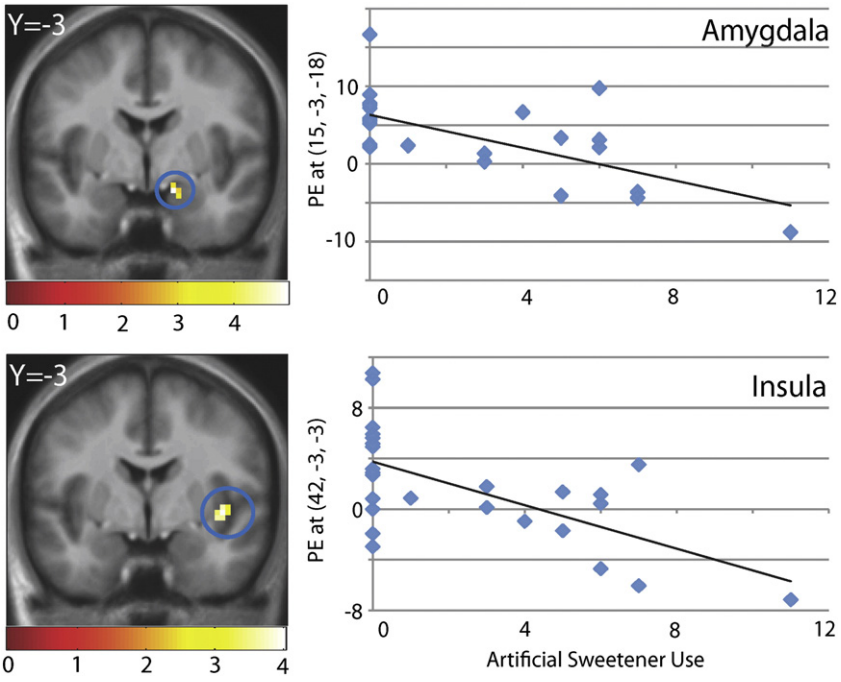

Fig. 7. Inverse associations between brain response to sucrose and artificial sweetener use. Coronal sections showing the regions of insula and amygdala in which response to sweet taste vs. tasteless (contrast of SS-tls) correlates with artificial sweetener use. The graphs show parameter estimates at the peak voxel in the circled region for the contrast of SS-tls plotted against NQ Artificial Sweetener Use scores. The color bar represents the T-scale for the activations shown. Images are displayed at $p \leq 0.005$ and $k \geq 5$ voxels. Post-hoc tests showed the strength of this correlation in the peak voxel to be $r^2 = 0.43$ (amygdala) and $r^2 = 0.38$ (insula).
Taken with permission from Rudenga and Small [131].

monkeys [147–149]. Of critical importance is the fact that supra-additive responses are observed in this region when the bimodal presentations are associated with increases in pleasantness [141,143]. For example, McCabe and Rolls [143] reported supra-additive pleasantness ratings to monosodium glutamate (MSG) and vegetable aroma and supra-additive neural responses to these stimuli in medial orbitofrontal cortex. Critically these perceptual and neural responses were positively correlated, providing strong support for this region in the effects of multi-sensory integration on the reward value of flavors (Fig. 8). The pleasantness of the combined MSG/vegetable odor stimulus also correlated with response in the adjacent perigenual cingulate cortex. This same region also produces supra-additive responses to the combination of high fat and pleasant sweet [141].

5. Top-down influences on flavor

Attention, expectations and beliefs have been shown to have a profound influence on neural/perceptual responses to tastes [102,103,150–153], odors [105,154–157] and flavors [158–161]. For example, simply attending to a taste or an odor can activate the respective primary sensory cortex in the absence of taste or smell input [102,157]. Similarly, response in the primary taste cortex to an intense bitter taste is reduced when subjects are told to expect a less intense solution [152]. Higher-order influences are also observed. The same wine thought to cost $90 per bottle produces greater pleasantness ratings and greater medial orbitofrontal cortex responses than when it is thought to cost $10 per bottle [161]. Such effects are clearly important for understanding flavor, feeding, overeating, and indeed how to use top-down strategies to promote healthy food choices [162,163]. However, an extensive review of this important literature is beyond the scope of this review, focused on sensory contributions to flavor perception and representation. Also important, but beyond the present scope is the influence of individual differences in perceptual and brain response to flavor (e.g. [140,164,165]). Instead, here we consider the neural correlates by which visual information influences flavor perception. We do so in a section termed "top-down" influences because it proposed that vision influences flavor by creating expectations and beliefs akin to those created by verbal labels or attentional orienting.

It has been well established that the colors of foods and drinks can impact upon the ensuing flavor experience. One of the most intriguing examples is the study by Morrot et al. that showed that adding red coloring to white wine induces a perceptual olfactory illusion that causes the wine to be described with olfactory terms typically used only for red wines [12]. However, color can also have a more fundamental influence on flavor perception. For example, Delwiche describes a general trend in the literature showing that darker colored drinks are rated as more intense than lighter colored drinks [166]. We know of no neuroimaging study that has investigated the influence of color on brain response to flavor or the integration of the sensory inputs that give rise to flavor. However, multi-modal, visual–odor, visual–taste, and visual–taste–odor neurons have been identified in monkey orbital cortex [80]. In addition, Österbauer et al. have demonstrated supra-additive responses to congruent color and orthonasal food odor combinations in the medial orbitofrontal cortex and they have shown that the congruency of the combination correlates positively with responses in multiple regions of orbitofrontal cortex, as well as the anterior ventral insular cortex [13]. This suggests that information about color is able to influence flavor processing in the earliest cortical integration centers. However, this is also true for other cues, such as verbal labels [152]. Thus, just as expectations about the presence or absence, identity, or intensity of an oral sensory stimulus can influence insular responses so too can visual information. In other words, it is argued that similar top-down mechanisms account for the influence of color, expectation, context, and brand on flavor by biasing the neural code towards expected experiences.

6. Summary

In summary, flavor is defined here as those sensations that arise, or appear to arise, from the mouth. This includes taste, oral somatosensation, retronasal olfaction, and in some cases audition and orthonasal olfaction. Although interactions, especially between taste and oral somatosensation, can occur at all levels of the neuroaxis, olfactory inputs appear to be integrated with taste and oral somatosensation, first in the anterior ventral insula. This point is critical because it is the olfactory input that most often defines the flavor identity.

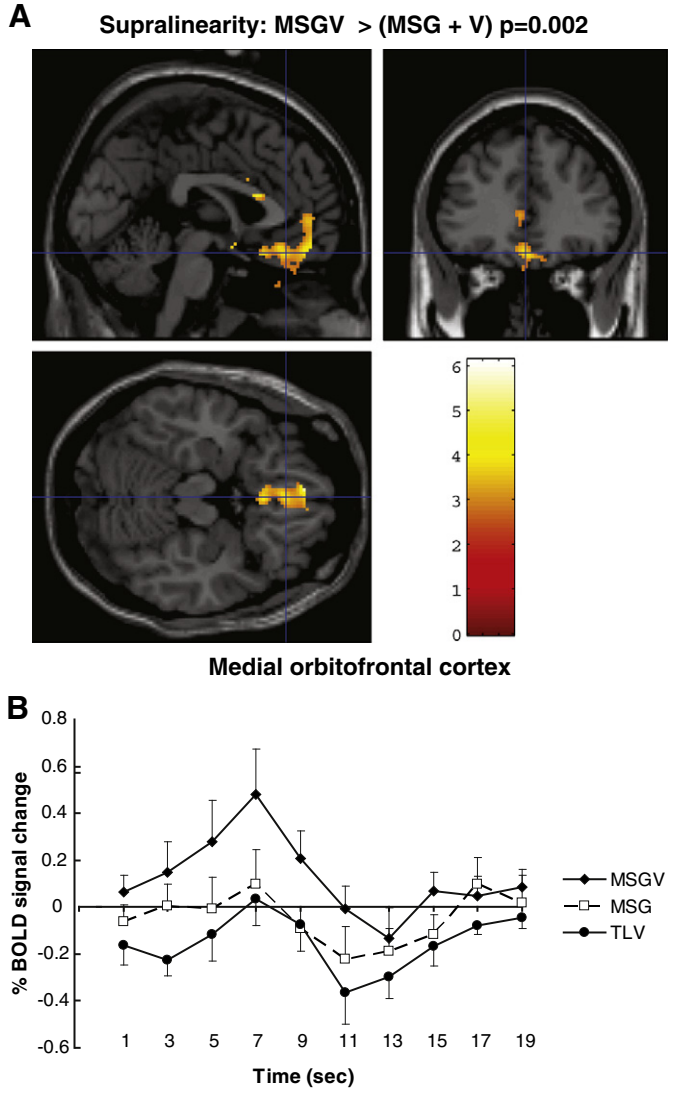

Fig. 8. Supra-additive responses in the caudomedial orbitofrontal cortex. Supralinear additivity between MSG and vegetable odor. A contrast of the mixture of MSG and vegetable (MSGV) with the sum of the activations to MSG and vegetable presented separately. This reveals a highly significant effect in the medial orbitofrontal cortex centered at [−6 52 −14] fc P = 0.002, with the activation extending up into the pregenual cingulate cortex. (B) Timecourse of the activations in the pregenual cingulate cortex at [−6 52 −14] produced by the combination of MSG and vegetable odor (MSGV), by MSG alone, and by the vegetable odor alone (tlV). The timecourses were computed across subjects using Marsbar for the region that showed significant effects in the supralinearity contrast at P = 0.002 shown in Fig. 4A. The mean across subjects percent BOLD for this analysis was MSGV = 0.485%, MSG = 0.097%, and tlV = 0.035%. The taste stimuli were delivered at time 0, and the means and SEM percentages are shown for 2-s bins.
Taken with permission from [143].

Thus it is proposed that flavor in the brain begins to emerge in the anterior ventral insula and continues to be modified and refined by projections and interactions with earlier (NTS and VPM) and later relays (e.g. orbitofrontal cortex, amygdala, and anterior cingulate cortex). Interactions between the nodes of this large-scale network can then take place to produce the rich and rewarding flavorful experiences that guide our feeding behavior.

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