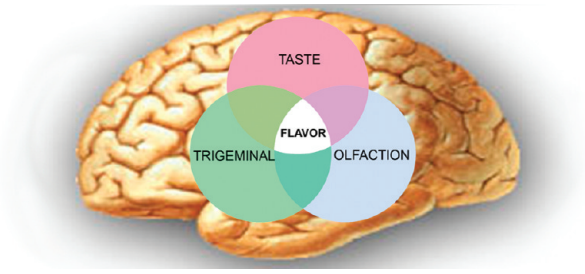
Central Processing of the Chemical Senses: An Overview

Johan N. Lundström,*[,†,‡,§] Sanne Boesveldt,[†,∥] and Jessica Albrecht[†]

[†]Monell Chemical Senses Center, Philadelphia, Pennsylvania, United States, [‡]Department of Psychology, University of Pennsylvania, Pennsylvania, United States, [§]Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden, and [∥]Division of Human Nutrition, Wageningen University, Wageningen, The Netherlands

Abstract



Our knowledge regarding the neural processing of the three chemical senses has been considerably lagging behind that of our other senses. It is only during the last 25 years that significant advances have been made in our understanding of where in the human brain odors, tastants, and trigeminal stimuli are processed. Here, we provide an overview of the current knowledge of how the human brain processes chemical stimuli based on findings in neuroimaging studies using positron emission tomography and functional magnetic resonance imaging. Additionally, we provide new insights from recent meta-analyses, on the basis of all published neuroimaging studies of the chemical senses, of where the chemical senses converge in the brain.

Keywords: Olfaction, smell, taste, trigeminal, neuroimaging, fMRI

1. Introduction

One can easily argue that the three chemical senses are the most frequently enjoyed, but least appreciated, of our senses. It is true that the vibrant colors of a beautiful painting, the soft touch of a loved one, and the joy brought by a nice piece of music are all cherished experiences. However, the chemical senses have the ability to regularly bring out a fantastic flavor experience where the first bite has the capacity to block every other sensory experience for the duration of its time inside the mouth. Although this flavor experience happens on a regular basis for most of us, when people rate which sense they would find least upsetting to lose, the olfactory, gustatory, and the trigeminal sense are consistently rated as the least valuable. Similarly, this notion of a hierarchy among the senses is evident in the amount of funding allocated to research and with that the level of knowledge. A search on ISI-Web of Knowledge (from where >99% of the literature on basic science is accessible) reveals that in 2009 alone, more than 100,000 articles were published using the keywords visual or auditory processing, individually. In contrast, there were 49,481 articles published using the keyword olfaction, 30,786 using gustation, and 17,655 using trigeminal processing. This considerable scientific tilt toward the more classical sensory fields of vision and audition also becomes clear when we view the progress in the respective fields. Whereas the visual and auditory systems are relatively well understood, we are still struggling to understand even the more basic steps of how the chemical senses operate. Nowhere is this disparity as evident as in our lack of understanding of the neurobiological substrates of chemical stimuli.

The last twenty-five years have, however, brought notable and rapid advances in our understanding of the basic cerebral processing of the human chemical senses. This progress has largely been owed to the advances in methods of stimulus delivery and an increased interest in the topic. The invention of the modern olfactometer (*1*) and gustometer (*2*) allowed the use of advanced electroencephalogram recordings (EEG) when exploring how the brain processes chemical stimuli and, later, the techniques of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). In this review, we will provide a general overview of the latest knowledge regarding the central processing of the three chemosensory stimuli, odors, taste, and intranasal irritants in humans. Since no sensory system is an island, entire of itself, we will first review the current knowledge for each sensory system in isolation and end with a brief overview of how the chemical senses interact in the brain to form the flavor percept. We will be providing a general overview, rather than in-depth analyses, and instead refer the interested reader to more focused material elsewhere. It is our hope that this review will provide the reader with a good overview of where the various research domains stand today and the problems that they face.

Received Date: September 14, 2010
Accepted Date: November 4, 2010
Published on Web Date: November 16, 2010

DOI: 10.1021/cn1000843 | *ACS Chem. Neurosci.* (2011), *2*, 5–16

2. Olfactory Sense

It is a common assumption that humans have a generally poor sense of smell. Indeed, there is a valid scientific basis for this assumption. Studies have demonstrated that humans, in comparison to other species, have fewer functional olfactory receptor genes (*3*). However, recent behavioral studies repudiate the notion of labeling the human sense of smell as near residual by demonstrating that our ability to extract information from our olfactory sense is far greater than we are consciously aware of (*4*, *5*). There are now several lines of evidence supporting the view that the number of olfactory receptors in the periphery does not directly translate into sensitivity (*6*) and that the peripheral disadvantage that humans seem to possess in comparison to other animals might be compensated for by our comparably larger olfactory brain. As we will review below, the parts of the human brain that are directly involved in olfactory processing are much larger than commonly assumed. This allows us to benefit from an increase in cognitive processing that is relatively independent of the number of peripheral receptors, a form of additional processing that other nonprimate animals are believed not to possess in such rich fashion (for a more detailed discussion of how human olfaction compare to other animals, see refs *7* and *8*).

2.1. Neuroanatomy of the Olfactory Network

The anatomical organization of the olfactory pathway has several features that are unique among our senses. First, the most frequently stated difference of the olfactory pathway is the lack of a thalamic relay to transfer peripheral input into the brain (but see ref *9* for an alternative view); the functional implications of this "negative" feature of the olfactory system remains unknown (*10*). Second, whereas all other senses project contralaterally from the sensory organs into the brain, the olfactory sense projects ipsilaterally, i.e., the signal originating in the left nostril projects to the left hemisphere. Third, the spatial organization of the olfactory system is much more dispersed than that of other sensory systems. Whereas the primary cortical region in other senses typically consists of one discrete cortical area, the primary olfactory cortex includes a set of structures (*11*), some of which are subcortical. The secondary sensory cortex in other senses usually includes a cortical area immediately adjacent to the primary sensory cortex. However, as we will review below, this is not the case in olfaction.

The olfactory sensory pathway starts with olfactory receptor cells where volatile molecules activate receptors embedded in the olfactory mucosa at the roof of the nasal cavity. From here, the olfactory signal projects via the olfactory nerve (CN I) through the cribriform plate to the first relay station in the brain, the tufted and mitral cells within the olfactory bulb (*12*). The largest recipient of input from the olfactory bulb is the piriform cortex; however, several other structures also receive direct projections from the olfactory bulb. These structures include the anterior olfactory nucleus, the olfactory tubercle, the anteromedial part of the entorhinal cortex, the periamygdaloid cortex, the anterior cortical nucleus, and the nucleus of the lateral olfactory tract of the amygdala.

Figure 1. Schematic overview of the basic steps of the central processing of odorous stimuli. Odorants are first detected by receptors at the top of the nasal cavity, and from there, the signal travels to the olfactory bulb (1). This signal is then routed to the piriform cortex (2) and subsequently to the orbitofrontal cortex (3), among other structures. Note the dual route that odorants can take to reach the receptors at the top of the nasal cavity. The route via the nostrils is known as orthonasal olfaction, whereas the route via the back of the throat is known as retronasal olfaction. See the text for further details.

From this set of structures, often defined as the primary olfactory sensory areas, inputs are sent to another series of structures, including the caudal orbitofrontal cortex (OFC), the agranular insula, the hippocampus, but also the dorsomedial nucleus of the thalamus, medial and lateral hypothalamus, and ventral striatum and pallidum (*11*, *13*). The region that receives the major cortico-cortical projections from the piriform cortex in primates is the caudal OFC (*11*). In addition to this direct link, the OFC also receives indirect projections from several areas of the primary olfactory cortex through a relay in the dorsomedial nucleus of the thalamus (*14*) (see Figure 1).

DOI: 10.1021/cn1000843 | *ACS Chem. Neurosci.* (2011), *2*, 5–16

2.2. Neural Substrates of Olfactory Perception

Zatorre and colleagues (*15*) were the first to outline the olfactory brain in humans using PET imaging. According to their findings, smelling odors results in brain activations in an area lying in the junction of the frontal and temporal lobes, corresponding to the piriform cortex, and in the right OFC. These findings have withstood the test of time, and the piriform and orbitofrontal cortices are still considered to be key nodes in the olfactory system. What has shifted, however, is how the contribution of these regions to the olfactory percept is interpreted. Zatorre and colleagues, as well as the authors of subsequent early publications (*16*, *17*), originally postulated that the piriform cortex was the primary olfactory cortex, primarily responsible for odor detection, whereas the OFC was named as the secondary olfactory cortex, primarily responsible for higher-order cognitive processing such as quality formation (*16*, *17*). Whereas the OFC is still considered as a center for cognitive odor processing, more recent data have brought the interpretation of the piriform cortex as the primary olfactory cortex into question. Increasing amounts of evidence suggest that computations that characterize functioning of primary sensory cortices in other senses actually happen at the level of the olfactory bulb (*18*, *19*). This value-added computation already at the level of the olfactory bulb, one synapse away from the receptors, has led some to argue that the olfactory bulb is the equivalent of an olfactory thalamus (*9*) and others to argue that the olfactory bulb constitutes the defacto primary olfactory cortex. The latter stems from new knowledge that the processing that takes place in the piriform cortex is more complex than the processing seen in any other primary sensory cortex including attention (*20*), recognition, and memory (*21*, *22*), as well as valence-dependent responses to odors (*23*, *24*).

Whereas the exact location of the primary olfactory cortex is still under debate, an emerging view is that the anterior and posterior portions of the piriform cortex should be viewed as two functionally, as well anatomically, separate entities (*25*). According to this view in its most simplified version, the conscious odor percept is created in an additive fashion. Central processing is initiated in the olfactory bulb, where the signal is condensed (*26*), amplified, and basic cognitive processing takes place (*27*). The anterior portion of the piriform cortex, which resides in the frontal lobe, then merges the chemical information obtained from the olfactory bulb into an initial representation of the odor identity by separating and organizing the odorants, i.e., the individual chemicals, into individual odors, i.e., perception of the chemical (*28*, *29*). The odor object formation is then subsequently accomplished by the posterior portion of the piriform cortex, where the perceptual quality of the odor is shaped (for a more detailed review of how the piriform cortex shapes the odor percept, see ref *25*). The final role in the formation of the odor percept seems to be assigned to the OFC. Within the OFC, higher-order cognitive processes, such as experience-dependent modulation, affective coding (*30*, *31*), and influences from our other senses (multimodal convergence) (*32*, *33*) help shape the odor signal coming from the piriform cortex into the final conscious percept that we experience when we lean over to smell the roses. Support of this view of the OFC as a central node in the making of the final olfactory percept can be found in its dense connectivity, with input from most sensory systems (*34*). In other words, the OFC seems to handle value-added processing based on input from the many cerebral regions responsible for basic odor processing as well as cognitive information. For a more thorough discussion of the role of the OFC in creating the odor percept, see ref *35*. The neural organization of how the brain processes odors, however, seems to be true mainly for common, but not socially related, odors. Recent data, from animals and humans alike, suggest that certain social odors are processed mainly outside the piriform cortex by other parts of the olfactory system (*4*, *36*−*38*).

As reviewed above, the complete olfactory system consists of many more components than just the piriform and orbitofrontal cortex. Therefore, the question arises, which regions are contributing what to the final olfactory percept? The simple answer is that little is known about how the various regions are collaborating to shape the percept; however, we can gain some insights from viewing the neural processing of what is arguably one of the most basic perceptual dimensions, odor pleasantness. It was originally suggested that unpleasant odors are processed by the amygdala in conjunction with the lateral OFC (*30*, *31*). The role of the amygdala was later brought into question by demonstrations that there was no difference in how the amygdala processed pleasant versus unpleasant odors, but there was a clear difference between weak and strong odors, thus suggesting that the amygdala codes for odor intensity and not pleasantness (*39*). However, a recent emerging view is that odor pleasantness is processed in the medial parts of the OFC, whereas unpleasantness is coded in the lateral parts of the OFC around the agranular insula (*40*−*42*). The role of the amygdala in this network is then not to code for pleasantness per se but rather to signal the emotional salience of the stimulus, independent of its pleasantness (*43*). More recent data support this view by demonstrating that the amygdala, in conjunction with posterior piriform cortex, shapes the signal sent to the OFC on the basis of its emotional valence (*44*). As can be seen from the example of pleasantness processing, even the most basic perceptual olfactory characteristics are handled by a complex neural system, of which little is known.

DOI: 10.1021/cn1000843 | *ACS Chem. Neurosci.* (2011), *2*, 5–16

The exact role of the various anatomical regions of the olfactory system is yet to be discovered. The future is ripe for discoveries of what functions the entorhinal cortex (*45*), the hypothalamus (*46*), the olfactory tubercle (*38*), and the other cerebral areas have and how they interact with the mechanical sniff mechanism to form the final odor percept (*47*).

3. Gustatory Sense

Among the flavor senses, taste attracts the most attention in everyday conversation. The gustatory sense, or taste, consists of only 5 primary qualities, namely, sweet, sour, salty, bitter, and umami or savory (glutamate). Nevertheless, flavor sensations, independent of whether they are mediated by an odor or a trigeminal stimulus, are almost always perceived as a taste. What mediates this so-called oral referral, i.e., that flavor perception is localized to the oral orifice, is not known. Compared to olfaction, taste seems to be a more functionally oriented sense, with each taste domain tuned to identify specific nutrients or poisons and associated with particular physiological functions, such as detecting energy content (sweet, umami), maintaining electrolyte balance (salt), guarding pH level (sour), or avoiding toxins (bitter).

Taste perception begins with stimulation of the tongue, where three types of gustatory papillae, are found: circumvallate, foliate, and fungiform papillae. Besides on the tongue, similar receptors were recently discovered in the epithelium of the palate, oropharynx, larynx, and the upper esophagus; the functions of these remain to be determined.

3.1. Neuroanatomy of the Gustatory Network

Already in the second century A.D., Claudius Galenus described correctly and in detail the innervations of the tongue and how the taste signal is conveyed to the brain, via the chorda tympani of the facial nerve (CN VII), the lingual branch of the glossopharyngeal nerve (CN IX), and the superior laryngeal branch of the vagus nerve (CN X). Gustatory axons then terminate in the rostral part of the nucleus of the solitary tract (NTS), the first gustatory relay in the brainstem (*48*). In primates, second-order gustatory fibers ascend from the NTS to project directly to the ventroposteromedial and mediodorsal nuclei of the thalamus (*49*−*51*). From here, main projections lead to the anterior region of the insula and overlying frontal operculum (AIFO), typically regarded as the primary gustatory cortex (*52*, *53*). Signals from the AIFO project to the medial and lateral OFC (sometimes referred to as the secondary gustatory cortex) (*34*, *54*), and the amygdala (*55*). Further areas that connect to the primate's OFC are the hypothalamus, hippocampus, and striatum (*50*); see Figure 2 for an overview of the taste system's basic components.

Figure 2. Schematic overview of the basic steps of the central processing of taste stimuli. Tastants are first detected by receptors situated on the tongue as well as taste-like receptors lining the gastrointestinal system. The signal from these two receptor locations is sent to the solitary tract in the brainstem (1) and from there to the insular cortex (2) and subsequently to the orbitofrontal cortex (3). See the text for further details.

3.2. Neural Substrates of Gustatory Perception

The very first study exploring the neuronal underpinnings of taste processing, by means of PET, found an increase of regional cerebral blood flow (rCBF) in the thalamus, insular cortex, anterior cingulate gyrus, the parahippocampal gyrus, lingual gyrus, caudate nucleus, and the temporal gyri (*56*). Since then, many more imaging studies have confirmed these areas as part of a neuronal network involved in taste perception. Moreover, according to a recent meta-analysis of all available human gustatory functional imaging papers (*57*), there was a significant and widespread probability of activations in the bilateral insula and overlying operculum, left lateral OFC, right medial OFC, the pregenual cingulated cortex (prACC), and right mediodorsal thalamus. This indicates that these regions are reliably and consistently activated in response to gustatory stimuli (see Figure 3). However, such an analysis does not clarify which specific taste functions these areas regulate or how these different regions interact to produce behavioral responses to gustatory stimuli.

DOI: 10.1021/cn1000843 | *ACS Chem. Neurosci.* (2011), *2*, 5–16

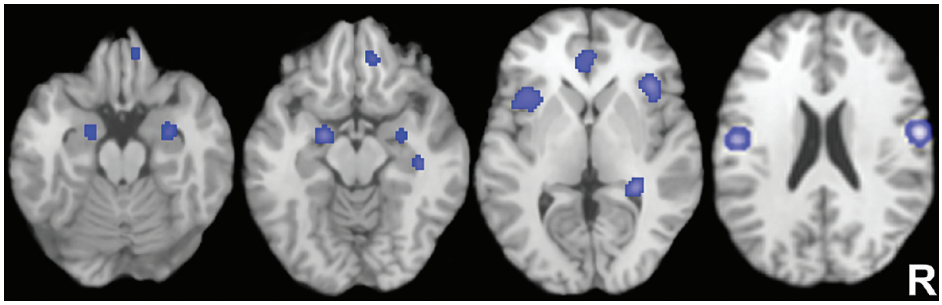


Figure 3. Localization of significant activation likelihood estimation (ALE) values ($p < 0.05$) of taste stimulation projected onto a standard template in Talairach space. These represent the areas commonly activated by taste stimuli. For a more detailed description and naming of anatomical locations, please see ref *57*. R in the figure indicates the right hemisphere.

Since taste consists of only five primary qualities, a remaining question is whether the different qualities are represented differently in the brain. Haase and colleagues (*58*) found that sucrose produced significantly greater global activation, than did other taste qualities, irrespective of intensity, and postulated that this was related to sucrose's ecological importance for eating behavior. Schoenfeld and colleagues (*59*) analyzed the topography of hemodynamic activity elicited by five taste stimuli in six single subjects, and a group analysis revealed regions that were activated more by one specific taste than by any of the other tastes. However, these studies do not give new insight on the underlying neuronal pathways of taste quality coding or recognition, and other studies state that different taste qualities activate similar cortical regions (*60*, *61*).

Neural responses in the medial OFC and the prACC appear to correlate with taste pleasantness and preferentially occur when the focus is on the pleasantness of a taste rather than on intensity or other tasks (*62*, *63*). It has therefore been suggested that these areas constitute a part of the gustatory cortex that functions as an intermediate area between the AIFO and lateral OFC (*64*) and are primarily involved in the affective evaluation of the stimuli to produce goal-directed behavior (*65*, *66*). As for olfaction, the amygdala has been shown to respond to aversive gustatory stimuli (*67*, *68*) and was therefore originally suggested to be involved in encoding the salience of gustatory stimuli. However, a more recent study suggested that the amygdala, as reviewed above for olfaction, is involved in the coding of perceived intensity (*63*). Whether the amygdala codes for pleasantness or intensity, rather than the emotional salience of the stimulus, independent of its pleasantness and intensity, remains to be determined.

As described above, depending on the context in which a taste is presented, the brain responds differently to a taste: a shift in attentional focus on a taste stimulus (pleasantness vs intensity) can result in a shift in neuronal activation (*62*). Neuronal responses also differ between implicit and explicit processing of taste. Connectivity analyses show that the AIFO and amygdala are maximally connected during passive tasting compared to task-related processing of a taste stimulus (*69*), indicating the effect of selective attention on sensory processing. Furthermore, trying to detect taste in a tasteless solution also results in enhanced activity in the insula and overlying operculum (*70*), thus suggesting that, as for olfactory processing, attention to the taste modality can produce neural responses similar to those for a real stimulus.

Although women outperform men in both taste identification and detection (*71*, *72*), no studies have been performed to determine the possible neuronal correlates of this finding. With respect to aging and gustation, we face a similar problem: behavioral studies report that the sense of taste declines with age (*72*), but we have only a very tentative understanding of the underlying neural mechanisms (*73*).

As alluded to above, the sense of taste is of vital importance for food intake and eating behavior, and part of the gustatory cortex is also implicated in the so-called reward network. For instance, the OFC is thought to be the region dedicated to the reward value of the food and responds to changes in pleasantness associated with eating (*74*). In addition, significantly greater activations are found in parts of the primary (insula) and secondary (OFC) gustatory cortices, ACC, and amygdala, when comparing responses to pure taste stimuli in hungry versus sated subjects (*58*, *75*). Several recent neuroimaging studies also suggest that obese individuals show greater activation of the gustatory cortex (insula/frontal operculum) and oral somatosensory regions (parietal operculum and Rolandic operculum) in response to anticipation and intake of food, compared to lean subjects (*76*). For a more detailed review on the association between taste and hunger/satiety or eating behavior, see ref *77*.

Much remains to be elucidated regarding the central processing of taste. However, as reviewed above, the sense of taste seems to be tightly interlinked with both satiety and eating disorders, much more so than the

DOI: 10.1021/cn1000843 | *ACS Chem. Neurosci.* (2011), *2*, 5–16

other senses. This suggests that the sense of taste might be a good stepping stone, by itself or in conjunction with other senses, in our struggle to understand the explosion in obesity rates and eating disorders.

4. Trigeminal Sense

The trigeminal system is responsible for multiple facets of chemosensory perception, such as burning, stinging, tingling, prickling, and itching, but also touch, pressure, and temperature sensations. Examples of sensations mediated by the trigeminal system are the cool and fresh feeling while chewing peppermint gum, the burning hot sensation caused by chili peppers, or the pleasing prickling experience on your tongue during the consumption of a carbonated drink. Although humans are usually not aware of this, almost all odorants, in a concentration-dependent manner, do not only evoke a clear olfactory but also some aspect of the aforementioned trigeminal sensations (*78*). The two anatomically separate, yet colocalized and intimately connected, intranasal systems conveying those sensations work together in order to integrate the single percepts into a unique flavor experience. They interact by suppressing or enhancing each other (*79*), and this interaction takes place on multiple processing levels (*80*). Of the three chemosensory systems, the human trigeminal system is the least understood, even though it is of great importance not only during food consumption but also for the perception of nasal airflow during breathing and the detection and avoidance of potentially toxic substances.

4.1. Neuroanatomy of the Trigeminal Network

The face is innervated by the trigeminal nerve, which is the largest cranial nerve (CN V). Its name (tri = latin for three, and geminus = latin for twin, thus thrice twinned) originates from the fact that the nerve divides into three branches on each side of the face, namely, the ophthalmic, the maxillary, and the mandibular nerve. Both the olfactory and respiratory intranasal mucosa are innervated by free nerve endings of the ophthalmic and the maxillary branches (*81*). Information about intranasal trigeminal stimulation is transferred through these two branches into the trigeminal ganglion. From there, sensory nerve fibers enter the brainstem at the level of the pons, where they form different trigeminal nuclei and extend into the thalamus. Cerebral pain processing takes place in two parallel organized networks: the lateral pain system transmits information through lateral thalamic nuclei to the primary and secondary somatosensory cortices (SI and SII), and the medial pain system conveys information through medial thalamic nuclei to brain regions including the prefrontal cortex, insula, cingulate gyrus, and the limbic system (see Figure 4) (*82*, *83*).

Figure 4. Schematic overview of the basic steps of the central processing of trigeminal stimuli. Irritants are first detected by nerve endings lining the nasal and oral cavities, and signals are then sent to the trigeminal nucleus in the brainstem (1). From here, a dual stream is projected. One stream to the somatosensory cortices (2, primary; 3, secondary somatosensory cortex) and the other to the insular (4) and orbitofrontal cortices (5). See the text for further details.

4.2. Neural Substrates of Trigeminal Perception

As mentioned previously, pain in general is mediated by two parallel systems. The lateral pain system is responsible for the basic processing of pain perceptions; those areas are responsible for evaluation and discrimination of the sensory aspect of pain sensation, e.g., detection and localization of the stimulus, as well as the determination of stimulus quality and duration. The medial pain system is responsible for higher-order cognitive processing, such as the emotional evaluation of pain as well as the affective and motivational responses to a painful stimulus. The latter system also helps us to predict and to avoid potentially noxious stimuli (*82*, *83*).

Only a handful of functional imaging studies have explored the central correlates of intranasal trigeminal stimulation. One of the main reasons is the difficulty in selectively stimulating the trigeminal nerve fibers without concomitant olfactory stimulation. One of the few stimuli that selectively activates the trigeminal system is the gas carbon dioxide (CO_2). The first study to map the neural substrates of intranasal trigeminal processing demonstrated that the trigeminal stimuli activated some of the areas associated with nociceptive processing as well as cortical regions attributed to the olfactory system (*84*). Moreover, during a recent meta-analysis of all available imaging data on intranasal trigeminal processing, we were able to show that intranasal trigeminal stimulation activated the full nociceptive processing network (*85*) (see Figure 5). On the basis of this,

DOI: 10.1021/cn1000843 | *ACS Chem. Neurosci.* (2011), *2*, 5–16

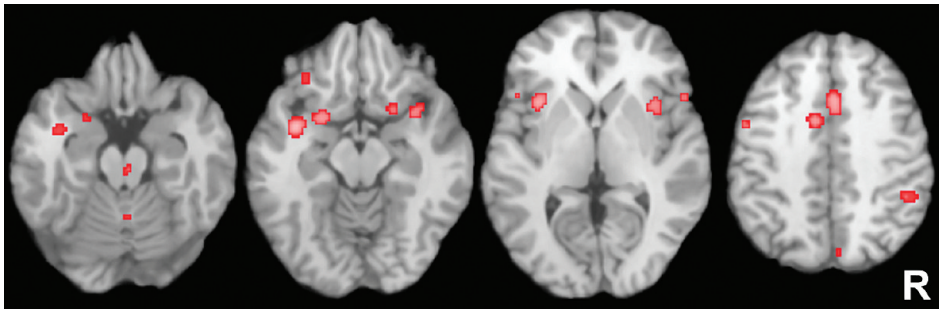


Figure 5. Localization of significant activation likelihood estimation (ALE) values ($p < 0.05$) of trigeminal stimulation projected onto a standard template in Talairach space. These represent the areas commonly activated by the intranasal trigeminal stimulus. For a more detailed description and naming of anatomical locations, please see ref *85*. R in the figure indicates the right hemisphere.

we hypothesize that the processing of intranasal trigeminal stimulation does not utilize a separate network but rather accesses the general pain processing network, also known as the pain matrix (*86*−*88*). However, there is evidence that peri-insular regions act as a central node in the network that processes intranasal trigeminal stimuli (*85*, *89*). The central role of the insular cortex might be caused by an involvement of this area in the processing of pain-related feelings such as arousal but also empathy and compassion, or by the responsibility of the insula in mediating an attentional shift toward the source of pain, resulting in a heightened awareness of the sensation (*90*). Functional connectivity analyses demonstrate that the anterior insula is connected to attentional and emotional brain areas in frontoparietal and temporal areas (*91*), areas that were also implicated in the aforementioned meta-analysis (*85*). Moreover, the role of the insula in pain processing might be caused by its integrative function that links information from different functional systems (*92*) and may therefore be of greater importance than the somatosensory cortices and the traditional pain network in intranasal trigeminal processing.

Interestingly, even though they are substantially interlinked, intensity coding of trigeminal stimuli is different from the olfactory intensity coding system. Subregions of the cingulate cortex, which are also involved in emotion and fear processing as well as avoidance behavior, are responsible for intensity coding of trigeminal stimuli (*93*). However, pain intensity ratings are usually related to emotional or hedonic ratings (e.g., unpleasantness) of the stimulus. This leads to a difficulty in dissociating whether the activated brain areas are processing the stimulus intensity or the emotional response to the stimulus.

CO_2 is known to induce a pure trigeminal stimulation and is therefore often used when a trigeminal stimulus is needed. In light of this, the finding that brain areas associated with olfactory processing, such as the piriform cortex and adjoining orbitofrontal cortex, are commonly activated in trigeminal brain imaging studies is puzzling (*85*). What mechanisms could explain olfactory-like activations for the intranasal trigeminal stimulus? First, activation of the piriform cortex may be due to a subset of human olfactory receptors that respond to odorous and CO_2 stimulation alike. The possibility that CO_2 has an odor and thus activates olfactory receptors provides a second, though unlikely, hypothesis for trigeminal stimulation-derived cortical olfactory activations. Third, activation of the piriform cortex is spurious in that it is mediated by potential differences in sniff characteristics, a factor known to activate the piriform cortex (*94*). Fourth, the piriform cortex has a role in the integration of chemosensations, possibly due to the known strong behavioral links between the chemical senses. This latter hypothesis is supported by an array of studies showing that the piriform cortex seems to process chemosensory stimuli from all three chemical senses independent of whether or not a chemosensory perception is detected (*85*). Which one of the above-mentioned hypotheses explains the activation of the piriform cortex, commonly associated with trigeminal processing, remains to be determined.

Although the advances in neuroimaging methods during recent years have led to a great enhancement of knowledge about chemosensory processing in general, there are still many questions that need to be answered about the processing of intranasal trigeminal stimuli in particular. Future studies in this field should focus on the interconnection between brain areas activated by trigeminal stimuli using advanced statistical analysis methods, such as dynamic causal modeling or diffusion tensor imaging.

5. Neural Processing of Flavor in the Chemical Senses

The three chemical senses are naturally bound to each other by their shared anatomical location, and seldom is one of them activated without an accompanying signal from one or two of the others. The ease with which these unimodal percepts are interlinked to form a flavor percept

DOI: 10.1021/cn1000843 | *ACS Chem. Neurosci.* (2011), *2*, 5–16

is clear if one considers how we experience a plate of spicy chicken wings. Although each bite activates the olfactory receptors (via the retronasal and orthonasal passage), the taste receptors on the tongue, as well as the trigeminal nerve endings, the sensation we obtain is not that of three individual sensations coming together, but rather that of a uniform flavor. As reviewed above, although the exact function is not well understood, the neural network of each of these senses has been documented by both anatomical and functional imaging studies. However, surprisingly few studies have been done exploring how the brain transforms the individual chemosensory perceptions into a flavor sensation, and existing studies have all focused on the integration of only two modalities at a time (*95*, *96*) (for an extensive review of the neural bimodal integration of the chemical senses, see ref *97*). To the best of our knowledge, no neuroimaging study exploring integration between the three chemical senses exists.

Multisensory perceptual integration is characterized by a supra-additive neural response. This mechanism is dependent on the coactivation of neurons by the underlying unimodal senses (*98*). In an attempt to explore where a potential overlap between the three chemical senses occurs, and thus possibly determine which brain regions are involved in the integration of the three senses, we compared the results of separate ALE meta-analyses of the individual senses, two of which are mentioned above, and one analysis of all olfactory imaging studies is yet to be published (*57*, *85*, *99*). The three ALE maps, together consisting of all of the published neuroimaging experiments exploring the chemical senses in isolation, were merged in a conjunction analysis using the software MANGO (http://ric.uthscsa.edu/mango/). This conjunction analysis reveals voxels in the brain that are commonly activated in all three senses: only one area, the dorsal−anterior portion of the insular cortex and the overlying frontal operculum, bilaterally (see Figure 6), was commonly responsive to stimuli, independent of chemosensory modality. This region can thus be viewed as the ideal area of integration of the three chemical senses and has previously been implicated as involved in the integration between orthonasal odor and taste sensations (*60*). However, this is the first time it can also be demonstrated that the trigeminal sense shares neural resources with both other chemical senses. It is worth noting that this integration area is located within an area commonly associated with basic taste processing (*57*), which could explain why the perception of all flavor sensations originates from the oral cavity (oral referral) and in the form of a taste. This could be mediated either through classical Hebbian learning (*100*), through configural learning, thus transforming sensations originating in the other chemical senses into a taste percept (for an extensive review of flavor formation, see ref *101*), or simply via experience-dependent

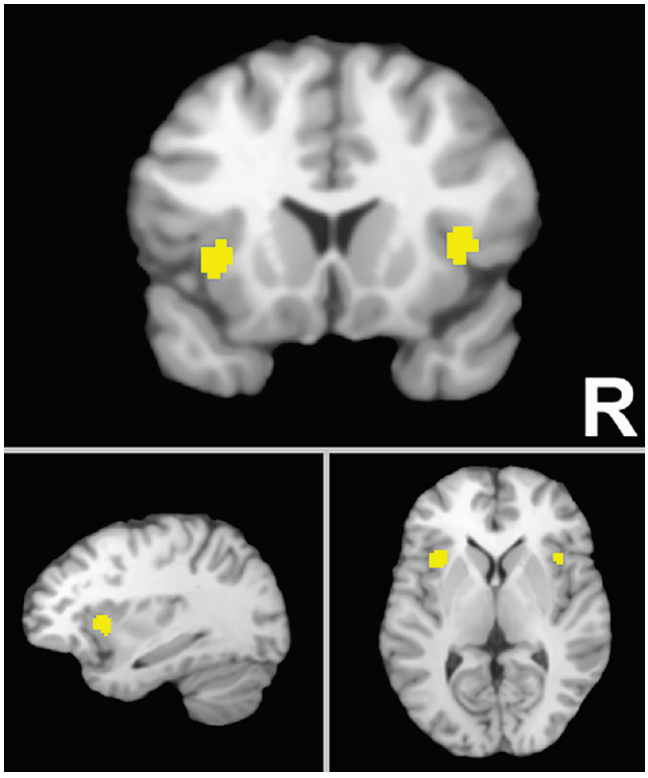


Figure 6. Conjunction map of activation likelihood estimation analyses originating from the available literature on taste, trigeminal, and odor stimulation. The yellow markings in the figure demonstrate that all of the three sensory modalities conjointly activate bilateral anterior portions of the insular cortex. R in the figure indicates the right hemisphere.

synthesis (*102*). What the implications for this shared neural connection are, and what the mediating mechanism behind oral referral is, remains to be elucidated in neuroimaging experiments directly exploring the integration of the three chemical senses.

6. Summary

We have tried here to summarize where science stands in our knowledge of the central processing of the three chemical senses. As is evident by this brief overview, important first steps have been made toward an understanding of how the human brain processes chemical stimuli. It is clear that major anatomical areas of the brain are involved and that these regions have been identified and well mapped out. However, it is also clear that many questions remain and that knowing which areas are involved is a mere first step. More important and more challenging is the knowledge of how these areas collaborate and possibly compete to form the final percept. Research has already started to chip-away at this important question, and it is likely that a successful effort will follow the constant improvement in imaging methods.

Even though there is strong interest regarding flavor perception and its mechanisms from academic and

DOI: 10.1021/cn1000843 | *ACS Chem. Neurosci.* (2011), *2*, 5–16

regulatory scientists, as well as companies alike, no study has yet directly investigated the neural processing of all of the three chemical senses. Since a perceptual sense is seldom experienced in isolation, research merging the chemical senses in one experiment is long overdue. The naturally multimodal sensation of flavors demands studies employing more of our senses. Only when true multimodal flavor experiences are explored will we begin to understand how the human brain forms the supramodal sensation of flavor.

Our ability to answer more specific and advanced questions will improve as the spatial and temporal resolution of the current imaging methods improve. The widespread network involved in the processing of odorants, tastants, and chemical irritants recruits several key cerebral areas, including those responsible for emotions, memories, and reward. This fact suggests that future studies will likely discover that the chemical senses hold a more dominant position in our everyday life than presently thought. With the stage set by our basic knowledge of the neuroanatomical substrates of the three chemical senses, the future is ripe for discoveries of how the odor, taste, and trigeminal perception is formed and how these are merged to create the flavor percept.

Author Information

Corresponding Author

*Monell Chemical Senses Center, 3500 Market Street, Philadelphia, PA 19104. Phone: +1-267-519-4690. E-mail: jlundstrom@monell.org.

Author Contributions

All authors contributed toward the Introduction and Summary sections. J.N.L. worked on olfactory processing and flavor processing, S.B. on gustatory processing, and J.A. on trigeminal processing.

Funding Sources

J.N.L. is partly supported by the National Institute on Deafness and other Communication Disorders (NIDCD R03DC009869) and J.A. by a fellowship within the postdoctoral program of the German Academic Exchange Service (DAAD D/08/40252).

Acknowledgment

We are grateful to George Retseck and the Monell Chemical Senses Center for providing us with Figures 1, 2, and 4 and Dr. Karen Yee for her help with modifying them to our needs. We thank Dr. Johannes Frasnelli and Andrea Ponting for providing valuable feedback.

References

1. Kobal, G. (1981) *Electrophysiologische Untersuchungen des menschlichen Geruchssinns*, Thieme Verlag, Stuttgart, Germany.

2. Plattig, K. H., Dazert, S., and Maeyama, T. (1988) A new gustometer for computer evaluation of taste responses in men and animals. *Acta Otolaryngol. Suppl. 458*, 123–128.

3. Rouquier, S., Taviaux, S., Trask, B. J., Brand-Arpon, V., van den Engh, G., Demaille, J., and Giorgi, D. (1998) Distribution of olfactory receptor genes in the human genome. *Nat. Genet. 18*, 243–250.

4. Lundstrom, J. N., Boyle, J. A., Zatorre, R. J., and Jones-Gotman, M. (2009) The neuronal substrates of human olfactory based kin recognition. *Hum. Brain Mapp. 30*, 2571–2580.

5. Porter, J., Craven, B., Khan, R. M., Chang, S. J., Kang, I., Judkewitz, B., Volpe, J., Settles, G., and Sobel, N. (2007) Mechanisms of scent-tracking in humans. *Nat. Neurosci. 10*, 27–29.

6. Laska, M., Genzel, D., and Wieser, A. (2005) The number of functional olfactory receptor genes and the relative size of olfactory brain structures are poor predictors of olfactory discrimination performance with enantiomers. *Chem. Senses 30*, 171–175.

7. Laska, M., Seibt, A., and Weber, A. (2000) 'Microsmatic' primates revisited: olfactory sensitivity in the squirrel monkey. *Chem. Senses 25*, 47–53.

8. Shepherd, G. M. (2004) The human sense of smell: are we better than we think? *PLoS Biol. 2*, E146.

9. Kay, L. M., and Sherman, S. M. (2007) An argument for an olfactory thalamus. *Trends Neurosci. 30*, 47–53.

10. Plailly, J., Howard, J. D., Gitelman, D. R., and Gottfried, J. A. (2008) Attention to odor modulates thalamocortical connectivity in the human brain. *J. Neurosci. 28*, 5257–5267.

11. Carmichael, S. T., Clugnet, M. C., and Price, J. L. (1994) Central olfactory connections in the macaque monkey. *J. Comp. Neurol. 346*, 403–434.

12. Firestein, S. (2001) How the olfactory system makes sense of scent. *Nature 413*, 211–218.

13. Price, J. L. (2003) The Olfactory System, in *The Human Nervous System* (Paxinos, G., Ed.) pp 1198−1212, Academic Press, San Diego, CA.

14. Powell, T. P., Cowan, W. M., and Raisman, G. (1965) The central olfactory connexions. *J. Anat. 99*, 791–813.

15. Zatorre, R. J., Jones-Gotman, M., Evans, A. C., and Meyer, E. (1992) Functional localization and lateralization of human olfactory cortex. *Nature 360*, 339–340.

16. Savic, I., Gulyas, B., Larsson, M., and Roland, P. (2000) Olfactory functions are mediated by parallel and hierarchical processing. *Neuron 26*, 735–745.

17. Zald, D. H., and Pardo, J. V. (2000) Functional neuroimaging of the olfactory system in humans. *Int. J. Psychophysiol. 36*, 165–181.

18. Cleland, T. A., and Linster, C. (2005) Computation in the olfactory system. *Chem. Senses 30*, 801–813.

19. Haberly, L. B. (2001) Parallel-distributed processing in olfactory cortex: new insights from morphological and physiological analysis of neuronal circuitry. *Chem. Senses 26*, 551–576.

DOI: 10.1021/cn1000843 | *ACS Chem. Neurosci.* (2011), *2*, 5–16

20. Zelano, C., Bensafi, M., Porter, J., Mainland, J., Johnson, B., Bremner, E., Telles, C., Khan, R., and Sobel, N. (2005) Attentional modulation in human primary olfactory cortex. *Nat. Neurosci. 8*, 114–120.

21. Dade, L. A., Zatorre, R. J., and Jones-Gotman, M. (2002) Olfactory learning: convergent findings from lesion and brain imaging studies in humans. *Brain 125*, 86–101.

22. Gottfried, J. A., Smith, A. P., Rugg, M. D., and Dolan, R. J. (2004) Remembrance of odors past: human olfactory cortex in cross-modal recognition memory. *Neuron 42*, 687–695.

23. Gottfried, J. A., O'Doherty, J., and Dolan, R. J. (2002) Appetitive and aversive olfactory learning in humans studied using event-related functional magnetic resonance imaging. *J. Neurosci. 22*, 10829–10837.

24. Zelano, C., Montag, J., Johnson, B., Khan, R., and Sobel, N. (2007) Dissociated representations of irritation and valence in human primary olfactory cortex. *J. Neurophysiol. 97*, 1969–1976.

25. Gottfried, J. A. (2010) Central mechanisms of odour object perception. *Nat. Rev. Neurosci. 11*, 628–641.

26. Maresh, A., Rodriguez Gil, D., Whitman, M. C., and Greer, C. A. (2008) Principles of glomerular organization in the human olfactory bulb: implications for odor processing. *PLoS One 3*, e2640.

27. Chaudhury, D., Manella, L., Arellanos, A., Escanilla, O., Cleland, T. A., and Linster, C. (2010) Olfactory bulb habituation to odor stimuli. *Behav. Neurosci. 124*, 490–499.

28. Barnes, D. C., Hofacer, R. D., Zaman, A. R., Rennaker, R. L., and Wilson, D. A. (2008) Olfactory perceptual stability and discrimination. *Nat. Neurosci. 11*, 1378–1380.

29. Gottfried, J. A., Winston, J. S., and Dolan, R. J. (2006) Dissociable codes of odor quality and odorant structure in human piriform cortex. *Neuron 49*, 467–479.

30. Royet, J. P., Hudry, J., Zald, D. H., Godinot, D., Gregoire, M. C., Lavenne, F., Costes, N., and Holley, A. (2001) Functional neuroanatomy of different olfactory judgments. *Neuroimage 13*, 506–519.

31. Zald, D. H., and Pardo, J. V. (1997) Emotion, olfaction, and the human amygdala: amygdala activation during aversive olfactory stimulation. *Proc. Natl. Acad. Sci. U.S.A. 94*, 4119–4124.

32. Gottfried, J. A., and Dolan, R. J. (2003) The nose smells what the eye sees: crossmodal visual facilitation of human olfactory perception. *Neuron 39*, 375–386.

33. Rolls, E. T., and Baylis, L. L. (1994) Gustatory, olfactory, and visual convergence within the primate orbitofrontal cortex. *J. Neurosci. 14*, 5437–5452.

34. Carmichael, S. T., and Price, J. L. (1995) Sensory and premotor connections of the orbital and medial prefrontal cortex of macaque monkeys. *J. Comp. Neurol. 363*, 642–664.

35. Gottfried, J. A., and Zald, D. H. (2005) On the scent of human olfactory orbitofrontal cortex: meta-analysis and comparison to non-human primates. *Brain Res. Brain Res. Rev. 50*, 287–304.

36. Lundstrom, J. N., Boyle, J. A., Zatorre, R. J., and Jones-Gotman, M. (2008) Functional neuronal processing of body odors differ from that of similar common odors. *Cereb. Cortex 18*, 1466–1474.

37. Lundstrom, J. N., Olsson, M. J., Schaal, B., and Hummel, T. (2006) A putative social chemosignal elicits faster cortical responses than perceptually similar odorants. *Neuroimage 30*, 1340–1346.

38. Wesson, D. W., and Wilson, D. A. (2010) Sniffing out the contributions of the olfactory tubercle to the sense of smell: hedonics; sensory integration; and more? *Neurosci. Biobehav. Rev.*, published online Aug 26, 2010.

39. Anderson, A. K., Christoff, K., Stappen, I., Panitz, D., Ghahremani, D. G., Glover, G., Gabrieli, J. D., and Sobel, N. (2003) Dissociated neural representations of intensity and valence in human olfaction. *Nat. Neurosci. 6*, 196–202.

40. Winston, J. S., Gottfried, J. A., Kilner, J. M., and Dolan, R. J. (2005) Integrated neural representations of odor intensity and affective valence in human amygdala. *J. Neurosci. 25*, 8903–8907.

41. Grabenhorst, F., Rolls, E. T., Margot, C., da Silva, M. A. A. P., and Velazco, M. I. (2007) How pleasant and unpleasant stimuli combine in different brain regions: odor mixtures. *J. Neurosci. 27*, 13532–13540.

42. de Araujo, I. E., Rolls, E. T., Velazco, M. I., Margot, C., and Cayeux, I. (2005) Cognitive modulation of olfactory processing. *Neuron 46*, 671–679.

43. Dolan, R. J., and Vuilleumier, P. (2003) Amygdala automaticity in emotional processing. *Ann. N.Y. Acad. Sci. 985*, 348–355.

44. Sacco, T., and Sacchetti, B. (2010) Role of secondary sensory cortices in emotional memory storage and retrieval in rats. *Science 329*, 649–656.

45. Rolls, E. T., Kringelbach, M. L., and de Araujo, I. E. (2003) Different representations of pleasant and unpleasant odours in the human brain. *Eur. J. Neurosci. 18*, 695–703.

46. Savic, I., Berglund, H., Gulyas, B., and Roland, P. (2001) Smelling of odorous sex hormone-like compounds causes sex-differentiated hypothalamic activations in humans. *Neuron 31*, 661–668.

47. Sela, L., and Sobel, N. (2010) Human olfaction: a constant state of change-blindness. *Exp. Brain Res. 205*, 13–29.

48. Witt, M., Reutter, K., and Miller, I. J. J. (2003) Morphology of the Peripheral Taste System, in *Handbook of Olfaction and Gustation* (Doty, R. L., Ed.) Marcel Dekker, New York.

49. Beckstead, R. M., Morse, J. R., and Norgren, R. (1980) The nucleus of the solitary tract in the monkey: projections to the thalamus and brain stem nuclei. *J. Comp. Neurol. 190*, 259–282.

50. Cavada, C., Company, T., Tejedor, J., Cruz-Rizzolo, R. J., and Reinoso-Suarez, F. (2000) The anatomical connections of the macaque monkey orbitofrontal cortex. A review. *Cereb. Cortex 10*, 220–242.

51. Pritchard, T. C., Hamilton, R. B., and Norgren, R. (1989) Neural coding of gustatory information in the thalamus of Macaca mulatta. *J. Neurophysiol. 61*, 1–14.

DOI: 10.1021/cn1000843 | *ACS Chem. Neurosci.* (2011), *2*, 5–16

52. Ogawa, H., Ito, S., and Nomura, T. (1985) Two distinct projection areas from tongue nerves in the frontal operculum of macaque monkeys as revealed with evoked potential mapping. *Neurosci. Res. 2*, 447–459.

53. Pritchard, T. C., Hamilton, R. B., Morse, J. R., and Norgren, R. (1986) Projections of thalamic gustatory and lingual areas in the monkey, *Macaca fascicularis*. *J. Comp. Neurol. 244*, 213–228.

54. Baylis, L. L., Rolls, E. T., and Baylis, G. C. (1995) Afferent connections of the caudolateral orbitofrontal cortex taste area of the primate. *Neuroscience 64*, 801–812.

55. Aggleton, J. P., Burton, M. J., and Passingham, R. E. (1980) Cortical and subcortical afferents to the amygdala of the rhesus monkey (*Macaca mulatta*). *Brain Res. 190*, 347–368.

56. Kinomura, S., Kawashima, R., Yamada, K., Ono, S., Itoh, M., Yoshioka, S., Yamaguchi, T., Matsui, H., Miyazawa, H., and Itoh, H.; et al. (1994) Functional anatomy of taste perception in the human brain studied with positron emission tomography. *Brain Res. 659*, 263–266.

57. Veldhuizen, M. G., Albrecht, J., Zelano, C., Boesveldt, S., Breslin, P., and Lundstrom, J. N. Identification of human gustatory cortex by activation likelihood estimation, *Hum Brain Mapp.*, in press.

58. Haase, L., Cerf-Ducastel, B., and Murphy, C. (2009) Cortical activation in response to pure taste stimuli during the physiological states of hunger and satiety. *Neuroimage 44*, 1008–1021.

59. Schoenfeld, M. A., Neuer, G., Tempelmann, C., Schussler, K., Noesselt, T., Hopf, J. M., and Heinze, H. J. (2004) Functional magnetic resonance tomography correlates of taste perception in the human primary taste cortex. *Neuroscience 127*, 347–353.

60. de Araujo, I. E., Rolls, E. T., Kringelbach, M. L., McGlone, F., and Phillips, N. (2003) Taste-olfactory convergence, and the representation of the pleasantness of flavour, in the human brain. *Eur. J. Neurosci. 18*, 2059–2068.

61. Rudenga, K., Green, B., Nachtigal, D., and Small, D. (2010) Evidence for an integrated oral sensory module in the human anterior ventral insula. *Chem Senses. 35*, 693–703.

62. Grabenhorst, F., Rolls, E. T., and Bilderbeck, A. (2008) How cognition modulates affective responses to taste and flavor: top-down influences on the orbitofrontal and pregenual cingulate cortices. *Cereb. Cortex 18*, 1549–1559.

63. Small, D. M., Gregory, M. D., Mak, Y. E., Gitelman, D., Mesulam, M. M., and Parrish, T. (2003) Dissociation of neural representation of intensity and affective valuation in human gustation. *Neuron 39*, 701–711.

64. Pritchard, T. C., Edwards, E. M., Smith, C. A., Hilgert, K. G., Gavlick, A. M., Maryniak, T. D., Schwartz, G. J., and Scott, T. R. (2005) Gustatory neural responses in the medial orbitofrontal cortex of the old world monkey. *J. Neurosci. 25*, 6047–6056.

65. Kringelbach, M. L. (2005) The human orbitofrontal cortex: linking reward to hedonic experience. *Nat. Rev. Neurosci. 6*, 691–702.

66. Rolls, E. T. (2008) The Anterior and Midcingulate Cortices and Reward, in *Cingulate Neurobiology and Disease* (Vogt, B. A., Ed.) Oxford University Press, New York.

67. Zald, D. H., Lee, J. T., Fluegel, K. W., and Pardo, J. V. (1998) Aversive gustatory stimulation activates limbic circuits in humans. *Brain 121* (Pt 6), 1143–1154.

68. O'Doherty, J., Rolls, E. T., Francis, S., Bowtell, R., and McGlone, F. (2001) Representation of pleasant and aversive taste in the human brain. *J. Neurophysiol. 85*, 1315–1321.

69. Bender, G., Veldhuizen, M. G., Meltzer, J. A., Gitelman, D. R., and Small, D. M. (2009) Neural correlates of evaluative compared with passive tasting. *Eur. J. Neurosci. 30*, 327–338.

70. Veldhuizen, M. G., Bender, G., Constable, R. T., and Small, D. M. (2007) Trying to detect taste in a tasteless solution: modulation of early gustatory cortex by attention to taste. *Chem. Senses 32*, 569–581.

71. Landis, B. N., Welge-Luessen, A., Bramerson, A., Bende, M., Mueller, C. A., Nordin, S., and Hummel, T. (2009) "Taste Strips": a rapid, lateralized, gustatory bedside identification test based on impregnated filter papers. *J. Neurol. 256*, 242–248.

72. Boesveldt, S., Tessler-Lindau, S., McClintock, M. K., Hummel, T., and Lundstrom, J. N. (2010) Gustatory and olfactory dysfunction in older adults: a national probability study, *Rhinology*, in press.

73. Jacobson, A., Green, E., and Murphy, C. (2010) Age-related functional changes in gustatory and reward processing regions: An fMRI study. *Neuroimage 53*, 602–610.

74. Kringelbach, M. L., O'Doherty, J., Rolls, E. T., and Andrews, C. (2003) Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. *Cereb. Cortex 13*, 1064–1071.

75. Uher, R., Treasure, J., Heining, M., Brammer, M. J., and Campbell, I. C. (2006) Cerebral processing of food-related stimuli: effects of fasting and gender. *Behav. Brain Res. 169*, 111–119.

76. DelParigi, A., Chen, K., Salbe, A. D., Reiman, E. M., and Tataranni, P. A. (2005) Sensory experience of food and obesity: a positron emission tomography study of the brain regions affected by tasting a liquid meal after a prolonged fast. *Neuroimage 24*, 436–443.

77. Stice, E., Spoor, S., Ng, J., and Zald, D. H. (2009) Relation of obesity to consummatory and anticipatory food reward. *Physiol. Behav. 97*, 551–560.

78. Doty, R. L., Brugger, W. E., Jurs, P. C., Orndorff, M. A., Snyder, P. J., and Lowry, L. D. (1978) Intranasal trigeminal stimulation from odorous volatiles: psychometric responses from anosmic and normal humans. *Physiol. Behav. 20*, 175–185.

79. Hummel, T., and Livermore, A. (2002) Intranasal chemosensory function of the trigeminal nerve and aspects of its relation to olfaction. *Int. Arch. Occup. Environ. Health 75*, 305–313.

80. Silver, W. L. (1991) Psychological Factors in Nasal Trigeminal Chemoreceptions, in *Chemical Senses* (Green, B. G., Mason, J. R., and Kare, M. R., Eds.) pp 21−37, Marcel Dekker, New York.

DOI: 10.1021/cn1000843 | *ACS Chem. Neurosci.* (2011), *2*, 5–16

81. Anton, F., and Peppel, P. (1991) Central projections of trigeminal primary afferents innervating the nasal mucosa: a horseradish peroxidase study in the rat. *Neuroscience 41*, 617–628.

82. de Leeuw, R., Albuquerque, R., Okeson, J., and Carlson, C. (2005) The contribution of neuroimaging techniques to the understanding of supraspinal pain circuits: implications for orofacial pain. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 100*, 308–314.

83. Treede, R. D., Kenshalo, D. R., Gracely, R. H., and Jones, A. K. (1999) The cortical representation of pain. *Pain 79*, 105–111.

84. Boyle, J. A., Heinke, M., Gerber, J., Frasnelli, J., and Hummel, T. (2007) Cerebral activation to intranasal chemosensory trigeminal stimulation. *Chem. Senses 32*, 343–353.

85. Albrecht, J., Kopietz, R., Frasnelli, J., Wiesmann, M., Hummel, T., and Lundstrom, J. N. (2010) The neuronal correlates of intranasal trigeminal function-an ALE meta-analysis of human functional brain imaging data. *Brain Res. Rev. 62*, 183–196.

86. May, A. (2007) Neuroimaging: visualising the brain in pain. *Neurol. Sci. 28* (Suppl. 2), S101–S107.

87. Seifert, F., and Maihofner, C. (2009) Central mechanisms of experimental and chronic neuropathic pain: findings from functional imaging studies. *Cell. Mol. Life Sci. 66*, 375–390.

88. Tracey, I. (2008) Imaging pain. *Br. J. Anaesth. 101*, 32–39.

89. Iannilli, E., Del Gratta, C., Gerber, J. C., Romani, G. L., and Hummel, T. (2008) Trigeminal activation using chemical, electrical, and mechanical stimuli. *Pain 139*, 376–388.

90. Craig, A. D. (2009) How do you feel--now? The anterior insula and human awareness. *Nat. Rev. Neurosci. 10*, 59–70.

91. Ploner, M., Lee, M. C., Wiech, K., Bingel, U., and Tracey, I. (2010) Flexible cerebral connectivity patterns subserve contextual modulations of pain, *Cereb. Cortex* [online early access], DOI: 10.1093/cercor/bhq146.

92. Kurth, F., Zilles, K., Fox, P. T., Laird, A. R., and Eickhoff, S. B. (2010) A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. *Brain Struct. Funct. 214*, 519–534.

93. Bensafi, M., Iannilli, E., Gerber, J., and Hummel, T. (2008) Neural coding of stimulus concentration in the human olfactory and intranasal trigeminal systems. *Neuroscience 154*, 832–838.

94. Sobel, N., Prabhakaran, V., Desmond, J. E., Glover, G. H., Goode, R. L., Sullivan, E. V., and Gabrieli, J. D. (1998) Sniffing and smelling: separate subsystems in the human olfactory cortex. *Nature 392*, 282–286.

95. Boyle, J. A., Frasnelli, J., Gerber, J., Heinke, M., and Hummel, T. (2007) Cross-modal integration of intranasal stimuli: A functional magnetic resonance imaging study. *Neuroscience 149*, 223–231.

96. Small, D. M., Jones-Gotman, M., Zatorre, R. J., Petrides, M., and Evans, A. C. (1997) Flavor processing: more than the sum of its parts. *Neuroreport 8*, 3913–3917.

97. Small, D. (2008) Flavor and the formation of category-specific processing in olfaction. *Chemosensory Perception 1*, 136–146.

98. Calvert, G. A., Campbell, R., and Brammer, M. J. (2000) Evidence from functional magnetic resonance imaging of crossmodal binding in the human heteromodal cortex. *Curr. Biol. 10*, 649–657.

99. Lundstrom, J. N., Albrecht, J., and Djordjevic, J. (2010) The localization of human olfactory cortex: an ALE meta-analysis of functional neuroimaging studies, submitted for publication.

100. Cruikshank, S. J., and Weinberger, N. M. (1996) Evidence for the Hebbian hypothesis in experience-dependent physiological plasticity of neocortex: a critical review. *Brain Res. Brain Res. Rev. 22*, 191–228.

101. Verhagen, J. V., and Engelen, L. (2007) The neurocognitive bases of human multimodal food perception: Sensory integration. *Neurosci. Biobehav. Rev. 53*, 271–286.

102. Stevenson, R. J., and Tomiczek, C. (2007) Olfactory-induced synesthesias: a review and model. *Psychol. Bull. 133*, 294–309.

DOI: 10.1021/cn1000843 | *ACS Chem. Neurosci.* (2011), *2*, 5–16