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Orosensory and Homeostatic Functions of the Insular Taste Cortex

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Abstract

The gustatory aspect of the insular cortex is part of the brain circuit that controls ingestive behaviors based on chemosensory inputs. However, the sensory properties of foods are not restricted to taste and should also include salient features such as odor, texture, temperature, and appearance. Therefore, it is reasonable to hypothesize that specialized circuits within the central taste pathways must be involved in representing several other oral sensory modalities in addition to taste. In this review, we evaluate current evidence indicating that the insular gustatory cortex functions as an integrative circuit, with taste-responsive regions also showing heightened sensitivity to olfactory, somatosensory, and even visual stimulation. We also review evidence for modulation of taste-responsive insular areas by changes in physiological state, with taste-elicited neuronal responses varying according to the nutritional state of the organism. We then examine experimental support for a functional map within the insular cortex that might reflect the various sensory and homeostatic roles associated with this region. Finally, we evaluate the potential role of the taste insular cortex in weight-gain susceptibility. Taken together, the current experimental evidence favors the view that the insular gustatory cortex functions as an orosensory integrative system that not only enables the formation of complex flavor representations but also mediates their modulation by the internal state of the body, playing therefore a central role in food intake regulation.

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Keywords

Energy homeostasis; Feeding; Flavor; Insular cortex; Multisensory integration; Orosensation; Taste

Introduction

Whenever we place foods in the mouth, an array of sensory inputs almost simultaneously reaches the central nervous system via gustatory, olfactory, and somatosensory peripheral pathways (Green 1993; Small et al. 1997; Verhagen 2007). However, the ultimate decision to ingest or reject a food relies not only on the sensory properties associated with each separate modality but also on the actual combination of segregated inputs arising from the oral cavity. The ability of the central nervous system to integrate intra-oral inputs is clearly exemplified by two sensory “illusions” associated with multisensory stimulation of the intra-oral cavity. The first, known as the olfactory localization illusion, causes olfactory stimulation to appear to originate from the mouth (Murphy et al. 1977). This illusion has been recently shown to be strongly influenced by the presence of a taste in the mouth, suggesting that taste captures odor (Lim and Johnson 2011). The second causes gustatory stimulation, which depends upon transduction from taste receptor cells located in discrete regions of the tongue, to appear to originate from the site of somatosensory stimulation—even if it is devoid of taste receptor cells (Green 2002). This illusion represents the “capture” of taste by touch (Green 2002). Together, these two mechanisms of illusory co-localization reflect an ability of the central nervous system to rapidly integrate segregated inputs arising from the oral cavity to form the representation of a single flavor percept (Small 2009; Small and Green, In Press). However, since the integration is one of fusion rather than synthesis (McBurney 1986; Auvray and Spence 2008), the flavor percept becomes associated not only with the overall flavor (e.g., the unique multimodal experience of eating strawberries) but also with the unimodal properties of that particular food (e.g., the strawberry’s sweet taste or soft texture). Therefore, it becomes immediately clear that a thorough understanding of how the brain controls food intake as a function of chemosensory cues presupposes the characterization of the brain regions operating the integration of segregated orosensory inputs.

Which brain regions might control ingestive behaviors based on these multiple, parallel orosensory inputs? Much progress has been made recently on the signaling cascades required for gustatory transduction in the periphery (Roper 2007). However, while molecular studies indicate that orosensory inputs might reach the brain via segregated, dedicated pathways, a different picture is unveiled by studies assessing brain responses to food-related stimuli. In fact, the results of electrophysiological and functional neuroimaging investigations make a strong case in favor of the existence of brain circuits devoted to processing the convergence of segregated orosensory inputs (Small 2004; Simon et al. 2006). In the following, we will review evidence from the animal physiology and the human neuroimaging literatures favoring both the presence of multisensory responses in the gustatory aspect of the insular cortex and their modulation by internal physiological cues. We will also evaluate the existence of regional functional specializations within the insular

cortex that might reflect a functional map associated with the sensory and homeostatic roles of this region.

Food Selection Is Guided in Part by Oral Somatosensory, Olfactory, and Gustatory Inputs

As mentioned previously, in addition to taste, other sensory properties of intra-oral stimuli contribute to the organisms' decision to ingest or reject a given aliment. For example, the texture of foods can function as an important cue to their state of conservation; otherwise, palatable foods, like meats or fruits, might be rejected if associated with excessive sogginess or dryness. A usually preferred treat will most likely be rejected if served at excessively high temperatures, since nociceptive stimulation in the mouth might warn against eminent harm to the digestive tract. On the other hand, volatile particles detected via the olfactory system might function as cues to the availability of nutrients and often become themselves appetitive stimuli that alone are sufficient to engage an organism in ingestive behaviors. In general, an array of inputs arising from the oral cavity via peripheral lines ascending in parallel to taste will reach the central nervous system and give rise to a complex, multi-sensory percept (McBurney 1986; Green 1993; Small et al. 1997; Small and Prescott 2005). A full explanatory model of food selection based on taste quality must therefore take into consideration the influence of other sensory inputs that accompany gustatory stimulation.

Chemical sensors for a variety of different compounds lie throughout the epithelium of the oral cavity. In the case of gustatory transduction, the oral chemosensory epithelia contain onion-shaped structures known as taste buds, which, in turn, host approximately 50–100 taste receptor cells (henceforth "TRCs"; Roper 2006). TRCs are bipolar cells (i.e., display identifiable apical and basolateral regions) that have been usually classified into different types according to their morphological and histological properties (Finger et al. 2002). In mammals, TRCs are typically embedded in stratified epithelia and distributed throughout the oral cavity, more specifically on the tongue, palate, epiglottis, and esophagus (Scott and Verhagen 2000; Finger et al. 2002). The transduction of taste information essentially starts with the binding of taste chemicals to their corresponding receptors, which, in turn, will activate intra-cellular pathways that eventually cause TRC depolarization followed by release of chemical messages to proximal nerve afferents (Roper 1989). Neural afferents originating from branches of cranial nerves innervate the basolateral aspect of taste cells and transmit to the brain information on the identity and quantity of chemicals detected by the membrane taste receptors (Zotterman 1935; Spector and Travers 2005). The chorda tympani and the greater superior petrosal branches of the VIIth (facial) cranial nerve innervate TRCs present on the anterior tongue and palate, respectively (Norgren 1995). On the posterior tongue, epiglottis, and esophagus, TRCs are innervated by the lingual branch of the glossopharyngeal nerve and the superior laryngeal branch of the vagus nerve (Simon et al. 2006). The chemical pathways linking TRC activation to the transmission of electrical messages through cranial nerves seem to involve the release of ATP from TRCs upon depolarization (Finger et al. 2005) (and possibly other transmitters, including serotonin) to their P2X2/P2X3 purinergic receptors located on the postsynaptic membrane of the nerve afferents (Bigiani et al. 1997; Ogura 2002; Huang et al. 2005; Roper 2006).

Recent progress on the molecular identity of taste receptors unveils what has been dubbed a "labeled-line model" (Chandrashekar et al. 2006), in which different taste qualities are encoded by separate peripheral circuits defined by subsets of taste cells expressing chemically specific receptors in connection with the afferent neurons to which they synapse. Therefore, different ingestive responses (e.g., acceptance or rejection) seem to be mediated by separated transduction pathways in the periphery. While it is true that the existence of broadly tuned gustatory neurons has been argued to give support to an alternative "across-fiber model" where taste sensations arise from combinatorial arrangements of TRC activation patterns (Boudreau et al. 1985; Frank et al. 1988; Caicedo et al. 2002), evidence is mounting in favor of the existence of dedicated lines transducing taste signals to the central nervous system (for a different perspective, see Lemon and Katz 2007).

Among such evidence is the actual pattern of taste receptor expression throughout the tongue for the five "classical" taste qualities (sweet, umami, bitter, sour, and salty). In fact, it has been established that none of the taste receptors mediating different taste qualities are co-expressed in TRCs (Chrandrashekar et al. 2000). This corresponds to say that, for example, T1R (the family of G-protein coupled receptors mediating the transduction of attractive sweet and umami tastants) receptors and T2Rs (the family of G-protein coupled receptors mediating the transduction of aversive bitter tastants) do not co-express on the same TRC. Such pattern provides the anatomical substrate to support a network of dedicated, labeled lines of taste transduction for sweet (via heterodimeric T1R2/T1R3 receptors), L-amino acids (via heterodimeric T1R1/T1R3 receptors), and bitter (Damak et al. 2008) even if these different receptors may utilize the same intra-cellular signaling pathways in order to depolarize its host taste cell (Zhang et al. 2003). Finally, recent advances have been made towards understanding the transduction mechanism of sour (which seems to utilize proton-sensitive channels of the Polycystic Kidney Disease family; Huang et al. 2006) and sodium (which seems to utilize the epithelial sodium channel, "ENaC"; Chandrashekar et al. 2010) tastants.

However, while taste receptor activation is sufficient to elicit stereotyped appetitive/aversive behaviors, sensors for stimuli other than tastants populate the oral cavity and are as efficient in transducing chemical and physical signals from the oral cavity to the brain (Prescott et al. 1999). In this regard, a prominent role is played by the transient receptor potential (TRP) family of ion channels, which are ubiquitously expressed in sensory fibers innervating the oral cavity (Eid and Cortright 2009). Let us take the exemplar case of the influence of temperature on taste perception (Moskowitz 1973; Breza et al. 2006). Strikingly, warming the anterior end of the tongue might evoke the sensation of sweetness, whereas cooling can be associated with different taste sensations, including sourness or saltiness (Cruz and Green 2000). On the tongue, the effects of temperature on taste transduction seem to be mediated by a temperature-sensitive TRP channel, TRPM5 (Talavera et al. 2005), which is found in G-protein coupled receptor-expressing taste cells (Perez et al. 2002). In fact, besides being required for the depolarization of taste cells upon activation of T1R and T2R receptors (Zhang et al. 2003), TRPM5 also displays temperature dependence, with increasing temperatures triggering channel activation (Liman 2006). Likewise warm temperature, information on cooling is also transmitted to the brain via specialized TRP channels expressed in sensory fiber terminals within the oral cavity. TRPM8 is a transducer of cool to

cold temperatures (McKemy et al. 2002), and the mint leaves-extract menthol activates TRPM8 (Peier et al. 2002). In fact, application of menthol into the oral cavity excites cold-sensitive neurons in the trigeminal subnucleus caudalis (Zanotto et al. 2007). Overall, specialized temperature sensors located within the oral cavity convey information on the current temperature of foods concomitantly to gustatory transduction whenever food is placed in the mouth.

Irritation and astringency constitute yet other dimensions to intra-oral stimuli capable of modulating taste perception (Green 1993; Lim and Green 2007). An intriguing exemplar case regards the ability of irritant compounds such as cap-saicin, the pungent or “burning” substance present in chili pepper, to elicit the sensation of bitterness. More specifically, the ability of capsaicin to not only evoke but also desensitize bitter taste suggests a close perceptual relation between irritation (burning) of the oral cavity and bitterness (Lim and Green 2007). Interestingly, in those individuals prone to taste capsaicin as bitter, reports of bitterness from structurally similar irritants are also observed (Green and Hayes 2004). Such perceptual association between bitterness and irritation might serve an adaptive function that contributes to the selection of stereotyped avoidance responses to a variety of chemically diverse toxic and poisonous compounds (Green 1993; Lim and Green 2007).

Irritant compounds present in pungent substances are rapidly recognized via specialized sensors, the activation of which might trigger immediate aversive responses by the brain. TRPV1 is found in trigeminal nociceptors and, in addition to being activated at temperatures above 40°C, displays high affinity to capsaicin (Caterina et al. 1999). Other pungent substances commonly used as food spices also produce their salient effects via TRP channels. For example, cinnamaldehyde, the sharp chemical present in cinnamon oil, activates the TRPA1 channel (Bandell et al. 2004), which, in turn, is known to be richly expressed in sensory fibers innervating the mouth epithelium, including the tongue (Nagatomo and Kubo 2008). Likewise, the chemical components responsible for the pungent note of garlic are also known to activate TRPA1 (Bautista et al. 2005). The pungency of mustard oil, on the other hand, is mediated by the ANKTM1 member of the TRP superfamily (Jordt et al. 2004). Overall, pungent compounds provide a compelling illustration of the regulatory role of multisensory integration in food intake: At first eliciting irritant sensations, these compounds may eventually acquire appetitive value via association with nutrient-related sensory cues such as taste (“flavor-nutrient conditioning”; Holman 1968).

Olfactory cues constitute yet another critical source of food-related sensory inputs to the brain, usually accompanying taste stimulation. Volatile molecules present in foods can reach the olfactory epithelium either via the nostrils (“orthonasal” olfaction) or via the nasopharynx upon drinking or mastication (“retronasal” olfaction; Rozin 1982; Pierce and Halpern 1996). Depending on the route being activated, olfactory stimulation may provide qualitatively different types of feeding-related information: On one hand, olfactory stimuli detected via the orthonasal route can function as predictive cues to the quality of the food about to be ingested, whereas molecules detected via the retronasal route signal the consummatory act itself (Small et al. 2005). In fact, psychophysical measurements reveal that a given odor might elicit different perceptual experiences depending on the delivery

route (Rozin 1982; Small et al. 2005; Hummel and Welge-Luessen 2006; Hummel 2008). More generally, the modulatory role played by olfactory cues during food intake is illustrated by the ability of specific combinations of tastants and odors to enhance flavor perception (Frank and Byram 1988; Prescott 1999).

Finally, it must be noted that physical properties of foods conveyed by mechano-sensitive somatosensory fibers also play a regulatory role in food acceptance (Green 2002; Cook et al. 2003). One obvious example is fat, whose particular rheological properties critically depend on the perception of texture and viscosity (Mattes 2005); even if after being degraded by lingual lipases to produce free fatty acids, fat can activate lipid sensors in taste cells (Abumrad 2005). Taste localization constitutes another interesting example of how information from a different sensory modality (i.e., touch) shapes gustatory perception. In an elegant experiment (Green 2002), touch–taste interactions were demonstrated by showing that when the tongue is touched simultaneously by three cotton swabs, while only the outer two swabs contain a taste, the psychophysical reports given by tested subjects pointed to a referral of the taste sensation to the middle swab. Such robust interaction between oral touch and taste perception, as was the case for the other modalities reviewed previously, strongly favors the view that specific groups of brain circuits operate the convergence between oral mechano-sensitive and taste inputs from the oral cavity.

The critical question hereby posed regards the characterization of the brain circuits capable of performing the simultaneous representation of these different sensory properties in such a way that each separate orosensory input appropriately weighs its influence on the regulation of ingestive behaviors. In the following, we will review evidence in favor of the view that the insular taste cortex functions as an oral integrative system, where taste-responsive regions also show heightened sensitivity to olfactory and somato-sensory cues present in foods.

Anatomical Location of the Taste Insular Cortex in Rodents and Primates

Cranial nerves VII, IX, and X transmit electrical signals that convey the chemical properties and quantity of tastants to the rostral division of the Nucleus of the Solitary Tract (NST) of the medulla, the principal visceral sensory nucleus of the brainstem (Norgren 1995; Scott and Plata-Salaman 1999). In rodents, second-order fibers (i.e., NST afferents) project ipsilaterally to the gustatory parabrachial nuclei (PBN) in the pons, proceeding then to the parvicellular part of the ventroposterior medial nucleus of the thalamus (VPMpc, Norgren 1995).

It must be noted at this point that current anatomical evidence strongly indicates that the PBN is not part of the central taste pathways in primates. In fact, it has been shown that in the Old World monkey, projections from the gustatory portion of NTS bypass the PBN only to terminate directly into the gustatory thalamic center (Beckstead et al. 1980). This was further confirmed by more recent experiments showing that in cynomolgus monkeys, retrograde tracer injections into the taste thalamic nucleus primarily labeled neurons within the NST rather than the PBN (Pritchard et al. 2000). Thus, in primates, PBN circuits seem to

be dedicated to convey general visceral information (e.g., from the vagus nerve) to specialized thalamic nuclei, including the VPM (Scott and Small 2009).

The primary taste cortex (Fig. 1) can be defined in terms of VPMpc afferents (Scott and Plata-Salaman 1999). In rodents, a group of projections from the gustatory aspect of PBN reaches the insular cortex via the taste thalamic relay (Norgren and Wolf 1975; Kosar et al. 1986a), whereas second, separate pathway reaches the amygdala, lateral hypothalamus, and the bed nucleus of the stria terminalis bypassing the thalamic relay (Norgren 1976; Li et al. 2005). In primates, the efferent projections of the VPMpc in the monkey, *Macaca fascicularis*, have been studied with tritiated amino acid autoradiography (Pritchard et al. 1986). Two discrete cortical areas were characterized as targets of VPMpc projections. First, labeled cells were located in the ipsilateral insular-opercular cortex adjacent to the superior limiting sulcus and extending as far rostrally as the caudo-lateral orbitofrontal cortex. Moreover, further projections were located within the primary somatosensory cortex, in the precentral gyrus subjacent to the anterior subcentral nucleus (i.e., a precentral extension of the primary somato-sensory cortex). This area is anterior to the VPM projection sites representing somatosensory information and is adjacent to or overlapping with the cortical somatotopic sites for the face and oral cavity (Jain et al. 2001). This region might be a target of somatosensory VPM and VPMpc projection fibers and thus implement the convergence in the cortex of the somatosensory and gustatory aspects of stimuli delivered in the mouth (see the following discussion).

The gustatory cortex of rats (Fig. 1a) has been localized by Kosar et al. (1986b) to the insula, more precisely to its agranular cytoarchitectural aspect, in contrast to the previously conventional assignment to granular insular cortex. This gustatory region of the insular cortex was found to be more anterior and dorsal to the areas targeted by visceral and nociceptive inputs (Cechetto and Saper 1987). The middle cerebral artery and the rhinal veins provide anatomical landmarks helping to locate precisely the insular gustatory cortex (Yamamoto et al. 1984; Kosar et al. 1986b). In the case of primates (Fig. 1b), Scott and Plata-Salaman (1999) defined the anterior limit of the primary taste cortex in the macaque as the junction of the orbitofrontal and opercular cortices, from which it extends 4.0 mm posteriorly. The mediolateral extension is defined ~16–19 mm lateral to the midline in an average adult macaque. The dorsal limit is defined as ~6 mm above the lateral fissure. The insular cortex, in the depth of the Sylvian fissure, was divided into four rostrocaudal subdivisions: The most rostral portion has been designated as the insular proisocortex; adjacent to it is the agranular subdivision of the insula, followed caudally by the dysgranular and granular insular areas. In these terms, the VPMpc nucleus projects to the opercular and insular regions of the granular and dysgranular insula and extends to adjacent agranular portions of the insula (Scott and Plata-Salaman 1999).

In both rodents and primates, attempts have been made to functionally locate the gustatory aspect of the insular cortex. In rats, early electrophysiological studies consistently reported single neuron responses to prototypical tastants (Yamamoto et al. 1984; Kosar et al. 1986b; Yamamoto et al. 1988). More recently, new techniques have confirmed that the sensitivity to tastants in this region can be attributed to entire neuronal populations. Simultaneous electrophysiological recordings from multiple channels demonstrate that chemosensory

information is encoded by populations of neurons in the insula according to the temporal patterns associated with the taste responses (Katz et al. 2002a; Katz et al. 2002b). Furthermore, in vivo optical imaging studies confirmed at the population level that tastants consistently activated a region estimated 3 mm^2 within the gustatory portion of the insular cortex, i.e., within the borders defined by middle cerebral artery and rhinal veins landmarks (Accolla et al. 2007).

In primates, early electrophysiological recordings were performed in a dysgranular region of the primary taste cortex, which was localized to the rostral and dorsal parts of the insula of the cynomolgus macaque monkey (Yaxley et al. 1988; 1990). The area recorded was part of the dysgranular field of the insula and was bordered laterally by the frontal opercular taste cortex, and displayed single neuron responses to prototypical tastants that were described as more stimulus specific compared to those found in NTS (Yaxley et al. 1990). Further electrophysiological studies in the macaque monkey have confirmed the sensitivity of the insular taste cortex to prototypical tastants (Scott et al. 1991). In this particular study, neural thresholds for each taste quality closely reflected those found in human psychophysical investigations (Scott et al. 1991). More specifically, the mean firing rate associated with taste-responsive neurons closely reflected stimulus concentration for glucose, NaCl, and quinine HCl. In addition, although no clear evidence of a chemotopic map was found, taste quality representation was associated with specific patterns of neuronal responses, with sweet stimuli evoking patterns of activity that were distinct from those associated with non-sweet chemicals. Overall, these early studies described previously contributed to shape the view that the response characteristics of cortical taste cells imply a homology between gustatory thresholds and intensity-response functions in the non-human primate and those reported in psychophysical studies of humans (Scott et al. 1991).

Studies making use of functional neuroimaging methods, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), enabled the localization of the taste-responsive regions of the human insular cortex (Fig. 1c). In fact, both PET and fMRI studies strongly suggest that homologous gustatory areas to those of primates are responsive to gustatory stimuli in humans, including the anterior insular and overlaying frontal opercular cortices (Small et al. 1999; Small et al. 2003). This includes responses to prototypical taste qualities such as glucose (sweet) and NaCl (sweet and salty; O'Doherty et al. 2001), umami, savory (de Araujo et al. 2003b), caffeine, and citric acid (bitter and sour, Schoenfeld et al. 2004). The functional neuroimaging depiction of the insular taste cortex is consistent with earlier findings assigning changes/impairments in taste recognition in humans sustaining lesions to the anterior dorsal part of the insula (Pritchard et al. 1999) and ageusia in patients sustaining bilateral lesions to the insular and adjacent opercular cortices (Mathy et al. 2003).

However, while these electrophysiological and neuroimaging studies clearly indicate that insular gustatory cortex neurons produce robust responses to prototypical tastants, they also show that a large population of neurons in this same region responds as reliably to non-gustatory properties of the stimuli. As will be explored in the following sections, such ability to respond to non-gustatory components of intra-oral stimuli appears to be an intrinsic property of the insular taste areas, possibly reflecting a multimodal dimension to gustation

that might be intrinsic to its perception (Green 1993; Small 2004; de Araujo and Simon 2009)

The Insular Gustatory Cortex and Multisensory Processing

Scott et al. (1991) analyzed the activity of single neurons in gustatory cortex of awake cynomolgus monkeys in response to a range of taste stimuli, including water, fruit juices, and the four prototypical taste stimuli (glucose, NaCl, HCl, and quinine HCl) presented at various concentrations. While taste-responsive cells constituted only 3.7% of the neurons tested, non-gustatory cells turned out to provide a more accurate representation of the response profiles in this cortical gustatory area. In fact, non-gustatory cells were mainly associated with mouth movement (10.1%), somatosensory stimulation (2.2%), and approach or anticipation (0.9%).

More generally, an overview of the electrophysiological recordings in monkeys provides clear evidence for multisensory neuronal responses in primary taste cortex (Ogawa et al. 1989; Scott and Plata-Salaman 1999). While relatively small numbers of cells in primary taste cortex did actually respond exclusively and consistently to taste stimuli (~6.5%), a significantly higher proportion (~23%) tends to respond during tongue or jaw movements, for example. In addition, somatosensory coding in gustatory cortex neurons can be parametrically assessed by varying the degree of viscosity of a tasteless stimulus. In fact, groups of neurons in the taste insular cortex recorded from non-human primates display sensory responses to tasteless carboxymethylcellulose solutions prepared within specific ranges of viscosity, but no responses to solutions with viscosity values outside this range (Verhagen et al. 2004; Kadohisa et al. 2005). Taken together, the data from electrophysiological studies in primates suggest that the primate primary taste cortex is a brain region where convergence of taste and oral somatosensory inputs associated with intra-oral stimuli takes place.

Like sniffing and whisking, licking produces stereotyped responses at theta frequencies, in such a way that consummatory behaviors will concurrently engage neuronal populations in both somatosensory and taste central pathways (Gutierrez et al. 2006). Somatosensory as well as gustatory responses of neuronal ensembles in the taste insula of rats were observed using multiple array electrophysiology, while animals licked nutritive solutions from a spout (Stapleton et al. 2006). The results of these investigations reveal that groups of neurons in the gustatory cortex of the rat could be divided in different types according to their sensitivity to somatosensory responses (Stapleton et al. 2006). One type seemed to reflect orosensory responses in preparation to consumption, given its temporally precise activation before a lick burst. A second type of neuron response was associated with licking a dry sipper. Finally, a different type of stimulus-responsive neurons produced responses to licking combined with tastant detection, showing significant increases in firing rate whenever chemosensory information was present.

In addition to such straightforward superposition of firing rate activity, individual neurons or ensembles in insular taste cortex might store information on the multisensory properties of tastants in the temporal patterns of spike trains. In fact, it has been shown that gustatory

cortex ensembles uncover sensory-specific responses to the somatosensory, chemosensory, and hedonic components of tastants in a way that is consistent with a temporal code (Katz et al. 2002b; Katz 2005). These insular cortex ensembles are possibly modulated by temporal patterns arising from earlier gustatory relays in the brainstem (Di Lorenzo 2003; Di Lorenzo et al. 2003). In any event, whatever is the coding strategy being used, the available electrophysiological data suggest that neurons in insular gustatory cortex show evidence of convergence of different modal inputs arising from the oral cavity, including oromotor and somatosensory information.

In line with the animal electrophysiological data, human studies also provide evidence that the taste insular cortex not only responds to the major perceptual categories of taste but also supports the encoding of the multisensory aspects of taste stimuli. Specifically, a robust sensitivity to oral somatosensory inputs (Cerf-Ducastel et al. 2001) seems to hold true for the human taste insular cortex to an extent comparable to the rat and monkey cases. In fact, it has been shown that activation produced by a tasteless viscous stimulus (carboxymethylcellulose) was proportional to the log of the viscosity in an insular taste cortex region that overlaps with glucose-responsive areas, providing evidence of somatosensory/gustatory integration in this region (de Araujo and Rolls 2004). In addition, the same region was activated by the oral delivery of fatty vegetable oil (de Araujo and Rolls 2004), suggesting that the human insular taste cortex might use inputs from different sensory modalities to detect biologically (in this case nutritive) relevant stimuli in the oral cavity.

Olfactory representations do also converge and interact with gustatory inputs in the human insular taste cortex. Evidence for significant interactions between these two modalities comes from studies where tastants and odorants were paired and compared according to their degree of congruency and familiarity. In a demonstration of supra-additive effects of taste–olfactory combinations, both congruent and incongruent taste–odor pairs were compared against the sum of their constituent unimodal stimuli (Small et al. 2004). Supra-additive responses during the perception of the congruent, but not incongruent, taste–odor pairs were observed in both dorsal and antero-ventral aspects of the insular cortex (Small et al. 2004). These results demonstrate that taste-responsive regions of the human insula have the ability to selectively encode for associative relations formed between tastants and odorants. Consistent with this possibility, the magnitude of insular response to an odor correlates positively with the intensity of the sweet “taste” of food but not non-food odors (Veldhuizen et al. 2010), which suggests that when taste and odor are perceived during the course of eating and drinking, associations are formed and represented in the insula. Accordingly, insular lesions impair sensations of the taste-like qualities of odors, such as sweet (Stevenson et al. 2008).

In fact, it has been shown that taste and olfactory inputs to the human brain converge in the far anterior (putatively agranular) insular cortex (Fig. 2 and de Araujo et al. 2003a). This region of the far anterior (agranular) insula is proximal to the insular cortex region where it adjoins the caudal orbitofrontal cortex, a region where electrophysiological responses in monkeys have revealed the existence of neurons encoding for sensory-specific taste–odor associations (Rolls and Wiggins 1989). The evidence for integration of taste and olfactory

representations in the human insular cortex, particularly regarding its anterior, agranular aspect, strongly suggests inter-species similarities regarding the cortical sites where taste–olfactory associations are formed. In fact, a homology between the rodent and primate cases with respect to the central anatomy of taste and olfactory integration (which would take place in the anterior agranular insula) has been previously suggested (Sewards and Sewards 2001), and the currently available data obtained using functional neuroimaging techniques indicate that such homology should extend to humans to encompass at least three different mammal species. However, the possibility must be considered that olfactory and taste representations extend further posteriorly into the primate insular cortex since posterior insular lesions result in perceptual changes in both olfactory and gustatory tasks (Mak et al. 2005).

Another example of responses in the human primary taste cortex that are independent of the major perceptual categories of taste is activation to water in the mouth, when subtracted from activations produced by artificial saliva at the same level of viscosity (de Araujo et al. 2003c). Noticeably, the insular regions activated by water in the mouth strongly overlapped with those found to be responsive to a prototypical sweet tastant (1-M glucose) in the same subjects (de Araujo et al. 2003c). This finding has later been confirmed in rats where neurons in insular gustatory cortex were found to respond to water but not to some tastants, ruling out purely somatosensory effects (Stapleton et al. 2006). Therefore, not only the stimulation of taste receptors but also substances generally relevant for behavior and survival seem to elicit responses in the insular gustatory cortices.

Interestingly, such taste-like responses in human insular cortex produced by water seem to depend on stimulus temperature, providing evidence for the more general idea that changes in intra-oral temperature levels also seem to modulate activity in the human taste insular cortex. It has, in fact, been shown that the same regions of the insular cortex activated by a prototypical taste stimulus (1-M glucose) were also activated by thermal stimuli (Guest et al. 2007). For example, following delivery of intra-oral thermal stimuli (i.e., distilled water at different temperatures), activations in this anterior insula region were found in Guest et al. (2007) for the contrasts “hot” (50°C–RT) and “cold” (5°C–RT), and “cold–hot” (5–50°C) (RT = water at room temperature).

Overlapping insular representation is also observed following independent stimulation with the irritant capsaicin and pure taste stimuli (sweet, salty, and bitter tastes) (Rudenga et al. 2010). In this study, subjects underwent fMRI scanning while sampling two potentially nutritive solutions (sucrose and NaCl), two potentially harmful solutions (quinine and capsaicin), and a tasteless baseline control. Consistent with a role of the human anterior insula in multisensory oral integration, this region responded significantly to all four stimuli compared to the tasteless control.

It is important to note here that the insula, including the taste cortex, integrates sensory inputs from many, if not, all modalities in the internal milieu, beyond the oral cavity, with those coming from the outside world (Saper 2002). For example, Hanamori et al. (1998) found that the majority of taste neurons in the rat gustatory cortex also respond to painful pinch and visceral input. In addition, Cechetto and Saper (1987) identified gustatory neurons

in the rat dysgranular insula responding to both visceral and gustatory input. Direct stimulation of different parts of the insula during surgical treatment for epilepsy or epileptic activity localized to the insular cortex has been shown to elicit gustatory as well as visceral sensations in addition to somatic and motor responses (Penfield and Fulk 1955; Hausser-Hauw and Bancaud 1987). It has also been shown that rodents with bilateral insular lesions that include gustatory cortex have difficulty updating the incentive value of food (Balleine and Dickinson 2000), detecting its novelty (Lin et al. 2009a), or integrating taste and odor cues to guide the choice of ingested nutrients (Lin et al. 2009b; Fortis-Santiago et al. 2010). Therefore, the role of the insula, including the gustatory cortex, is not simply a reflection of peripheral input but also multimodal integration where gustation is processed among sensory and visceral inputs from other modalities to inform feeding behavior relevant to survival. In fact, a recent study in rodents showed that olfactory social transmission of food preference in rodents depends upon insular cortex processing (Fortis-Santiago et al. 2010), indicating its involvement in the regulation of intake based upon social factors.

In summary, available evidence from both animal electrophysiological studies and human functional neuroimaging experiments places the insular gustatory cortex as the main candidate associated with the neural integration of multimodal, including non-gustatory, inputs from the oral cavity. As such, we assert that the neural machinery in the insular cortex is responsible for representing unitary flavor percepts or “flavor objects” (Small and Green In Press). In addition, given the evidence for a role for this same region in representing physiological state and reward value, we suggest that flavor percepts are associated with their biological meaning in the insular cortex. One caveat to this proposal is that we cannot definitively rule out the possibility that the responses that we interpret as markers of neural integration, such as supra-additive responses, also reflect epiphenomenon associated with related events, such as cephalic phase responses, which may depend on brain circuits outside insular cortex. However, in our view, this possibility is unlikely given that insular lesions disrupt both unimodal (Mak et al. 2005) and multimodal (Stevenson et al. 2008) perceptions of oral stimuli and therefore underscore a causal role for processing in this region in flavor perception.

Higher-Order Inputs to GC

In addition to the basic sensory modalities of taste, olfaction, oral somatosensation, and temperature, higher-order, cognitive influences associated with specific behavioral states also function as strong modulators of gustatory perception (Marks and Wheeler 1998).

Ensemble recordings performed in rats suggest that the current level of attention and expectation of the animal might modulate taste processing in insular gustatory cortex (Fontanini and Katz 2009). For example, coherent oscillations in the theta range are observed in this region during tasks in which rats progress through different behavioral states associated with task engagement and attentional demand (Fontanini and Katz 2004). Interestingly, such rhythmic episodes are inhibited through fluid delivery and consumption, suggesting that oscillatory signals in insular cortex did not merely reflect chemosensory processing.

Cognitive modulation of insular taste cortex activity is also observed in humans. To demonstrate the influence of cognitive states on gustatory cortex activity in an fMRI setting, Veldhuizen et al. (2007) asked subjects to sample solutions that could, with equal probability, contain or not a weak taste and subsequently indicate whether or not a taste was detected. The authors reported significant responses in insular gustatory cortex when subjects attempted to detect the presence of a tastant in a tasteless solution, compared to when they passively sampled the same solution. This active searching for taste also recruited circuits involved in attentional processing, including the intraparietal sulcus and anterior cingulate cortex. Thus, selective attention to taste mediated by the canonical attention networks is sufficient to engage the insular taste circuitry even when no concomitant gustatory stimulation is provided. Such a mechanism may underlie the modulatory effects of selective attention on gustatory sensitivity (Marks and Wheeler 1998).

In another human fMRI study on cognitive influences on taste responses, Nitschke et al. (2006) found that the taste responses in the insular and opercular gustatory cortices are modulated by expectation of a tastant, in line with previous demonstrations that the insular cortex responds to arbitrary cues that had previously been associated with tastants via Pavlovian conditioning (O'Doherty et al. 2002). In their study, Nitschke et al. (2006) found that when cue-based expectancies were manipulated in such a way to mislead subjects into believing that the upcoming taste would be less unpleasant than it actually was, the responses in the insular cortex were likewise blunted. Consistent with the possibility that taste expectation and reward value interact to modulate gustatory responses in insular cortex, Berns et al. (2001) have found that insular responses to juice or water were maximal for the unpredicted and preferred solutions.

Cognitive modulation also appears to influence how insular taste responses interact with other brain regions. Bender et al (2009) used fMRI to identify a region of anterior insular cortex that responded preferentially to taste vs. tasteless irrespective of whether subjects tasted passively, performed a basic detection task, quality discrimination (sweet, sour, salty) or affective evaluation. However, while the BOLD response within this region appeared to be task insensitive, the effective connectivity between the anterior insula and amygdala was the most significant during passive tasting, whereas the connectivity between the insula and orbitofrontal cortex was the most significant during affective evaluation (Bender et al. 2009).

There is also evidence that the sight or mere thought of food is sufficient to activate insular taste cortex (Pelchat et al. 2004; Simmons et al. 2005). Using fMRI, Simmons et al. (2005) had subjects to view pictures of appetizing foods and, for comparison, pictures of locations. Compared to "location pictures" that also activate the visual pathway, food appearance specifically activates gustatory processing areas, including the insular and opercular cortices. Therefore, the mere presentation of food pictures, independently of concomitant gustatory activation, is sufficient to evoke neural activity in insular cortex. Importantly, the locations of the activations reported were highly coincidental with those known to be activated by prototypical tastants (Simmons et al. 2005). These results are consistent with an earlier demonstration that (visual and olfactory) food presentation of favorite foods was sufficient to significantly increase metabolism in the whole brain as detected by PET

imaging, with largest changes observed in the anterior insular and orbitofrontal cortices (Wang et al. 2004). Altogether, the aforementioned data indicate that the perceived appearance of foods directly influences the neural responses associated with their chemical composition.

Besides appearance, another psychological dimension strongly affecting the affective properties of tastants relates to its motivational value or “desirability.” For example, food cravings, which tend to be very stimulus specific, are thought to be supported by imagination of the object of desire (Pelchat et al. 2004; Kavanagh et al. 2005). Through diet manipulation and cue-induction techniques, cravings were induced in an fMRI setting by having subjects imagine the sensory properties of their favorite foods (Pelchat et al. 2004). Increasing craving for a particular food using this protocol enhanced activity levels in reward processing areas such as the caudate nucleus, as expected, but also in the insular cortex (Pelchat et al. 2004). This particular study therefore supports the view that craving a desired food object activates the insular oral sensory region and, as such, may modulate the perception of its actual chemical properties.

Postingestive and Homeostatic Influences on Insular Gustatory Activity

It has been long determined that the gustatory zone of the insular cortex is required for associations to be formed between the sensory and postingestive aspects of foods. Thus, in the so-called conditioned taste aversion paradigms (CTA; Garcia et al. 1955), pharmacological manipulations (Gutierrez et al. 1999), protein synthesis inhibition (Rosenblum et al. 1993), or irreversible lesions (Bermudez-Rattoni 2004) to gustatory cortex disrupt the formation of a “memory trace” linking a conditioned taste cue to ensuing visceral malaise.

In line with these earlier findings, a recent intrinsic imaging study of the rat insular gustatory cortex showed that taste-activated areas of the rat gustatory cortex varied their responses according to whether the animal was infused with a malaise-producing agent following exposure to saccharin (Accolla and Carleton 2008). The imaging map of the saccharin response became more similar to the one evoked by the bitter tastant quinine. Upon extinguishing the CTA, the topography of the responses was partially reversed (Accolla and Carleton 2008). These experiments reveal that insular gustatory cortex sensory maps are formed according to the associative history of a taste stimulus and the internal state of the animal.

However, the gustatory cortex also seems to be important for the control of food intake by postingestive factors when those are rewarding to the animal. In appetitive conditioning paradigms, bilateral lesions to the gustatory cortex abolished the assignment of incentive value to food outcomes in instrumental tasks (Balleine and Dickinson 2000). While early studies using mice lacking sweet taste transduction indicated that the insular cortex is involved in the representation of caloric sugar intake independently of sweet taste (de Araujo et al. 2006b), insular neuronal responses to palatable compounds such as sucrose are modulated by postingestive satiation in rats (de Araujo et al. 2006a). In fact, it has been shown that while ensembles of simultaneously recorded neural units reflect more efficiently

the hunger/satiation state of the animal compared to their constituent single units, it was observed that neurons in insular cortex contributed to approximately the same extent to the coding of the physiological state of the animal as other forebrain regions known to be involved in the homeostatic control of feeding (de Araujo et al. 2006a). Overall, this study provided evidence for an involvement of insular taste cortex neurons in the homeostatic control of food intake and more specifically to the neural encoding of the nutritional state of the animal.

The insular cortex does also represent hunger and satiety states in humans. In a PET study where volunteers ate chocolate to beyond satiety, Small et al. (2001) demonstrated regional cerebral blood flow changes according to variations in ratings of pleasantness given by subjects after eating each chocolate piece. When subjects were highly motivated to consume chocolate—i.e., when pleasantness ratings were the highest, different groups of structures had their activity levels significantly increased, including the insular and adjacent opercular cortices, striatum, and midbrain (see Fig. 3). Interestingly, a different pattern of activity was observed when subjects consumed chocolate while being sated, suggesting lowered activity thresholds in human insular cortex while subjects experience physiological states of mild deprivation. In any event, modulation of brain activity by motivation to eat squares of caloric Lindt© chocolate was observed in insular cortex chemosensory areas, suggesting the representation of the reward value of a food in this region of the human brain (Small et al. 2001). Moreover, modulation of insular responses to pure taste by internal state changes has been further supported by Haase et al. (2009). It is interesting to note that such internal state-dependent insular responses may be modulated by the subject's gender. In fact, the insular cortex of male subjects seems to produce greater contrasts between hunger vs. satiety upon taste stimulation, when compared to the insular cortex of female subjects; similar effects were observed in the middle frontal gyrus and cerebellum (Haase et al. 2011).

Interestingly and consistent with the aforementioned findings, imaging subjects at rest during hunger vs. satiety states also produced differential patterns of cortical activity (Tataranni et al. 1999; Del Parigi et al. 2002). Physiological states of hunger activated a complex network of brain regions that included not only the hypothalamus but also the insular and orbitofrontal cortices; on the other hand, satiation was associated with increased neuronal activity in more dorsal regions of prefrontal, but not insular, cortex (Del Parigi et al. 2002). These studies therefore provide evidence that in humans, the insular cortex regions, including its chemosensory aspect, display heightened levels of activity during states of nutritional deficit. Consistent with a role for the insular cortex in homeostatic regulation, Tataranni et al. (1999) found that insular cortex activity at rest correlates positively with plasma insulin concentrations. Insular responses to the sight and thought of food may also be modulated by internal state (Hinton et al. 2004; Malik et al. 2008). For example, Malik et al. (2008) demonstrated that insular responses to pictures of foods decrease with satiety and then increase following intravenous infusions of ghrelin, an orexigenic gut hormone.

Intriguingly, the currently available rodent and human data seem to digress from what has been observed in non-human primate studies, where it has been reported that feeding an animal to satiety from an initial state of hunger does not modulate firing rate activity of

neurons located in either insular (Yaxley et al. 1988) or adjacent opercular taste areas (Rolls et al. 1988). However, it must be noted that primate electrophysiological studies are based on relatively small samples that are usually confined to restricted cortical regions. Therefore, while hunger-dependent taste responses in monkey insular areas might exist, the investigation of which probably will demand the use of newly available techniques such as multiarray electrophysiological recordings or functional neuroimaging.

Functional Maps Within Insular Cortex

As was described in “Food Selection Is Guided in Part by Oral Somatosensory, Olfactory, and Gustatory Inputs”, the currently available data on the molecular bases of taste transduction in the periphery would suggest that attractive (e.g., sweet, umami) and aversive (e.g., bitter) elicit separate neuronal central representations. This might, in fact, be the case in particular for the insular gustatory cortex. By selectively expressing a transsynaptic tracer in either T2R (bitter)-or T1R3 (sweet and/or umami)-expressing taste receptor cells, Sugita and Shiba (2005) reported segregated representations for appetitive vs. aversive taste receptor fields in insular cortex by comparing the locations of the tracer-labeled neurons. Despite the limitations associated with the fact that the T2R- and T1R3-synaptically labeled neurons were compared across different animals (Sugita and Shiba 2005), similar results were partially obtained by intrinsic optical imaging of the rat gustatory cortex (Accolla et al. 2007). In fact, stimulating the tongue of the animal during imaging showed that while no gustatory region was specific to a single taste modality, tastants of similar hedonic value produced greater overlap between their corresponding activated areas compared to tastants with opposite hedonic value (Accolla et al. 2007). Therefore, sensory-specific spatial patterns of cortical activity in the rat insular gustatory cortex might signal differential representations of taste quality as a function of hedonic value. Furthermore, a recent study reports that gustatory maps may show segregation between taste qualities in gustatory cortex when analyzed at the cellular level (Chen et al. 2011).

The picture might, however, turn out to be more complex for the human case. Early fMRI studies on the representation of pleasant and unpleasant tastes in the human brain indicate that while reward-processing regions such as the orbitofrontal cortex and the amygdala display segregated responses to a pleasant (e.g., glucose) vs. an unpleasant taste (e.g., NaCl), the insular and adjacent opercular cortices seem to respond similarly to these two stimuli (Small et al. 1999; O’Doherty et al. 2001). Furthermore, middle regions of the insular cortex were found to respond to tastants as a function of intensity independently of valence (Small et al. 2003). Finally, a study comparing the representations of attractive vs. aversive (including bitter and irritant compounds) stimuli revealed robust overlapping activations across stimuli in the anterior insular region (Rudenga et al. 2010). However, responses within this insular region were shown to preferentially modulate activity in the hypothalamus, ventral pallidum, and striatum when subjects tasted the potentially nutritive, rather than the potentially harmful, stimuli. This suggests that while there may be overlapping responses to oral stimuli of different affective valences within the human anterior insular cortex, it is also true that these stimuli of opposing valence engage different circuits among those having the ability to interact with the insular cortex. An additional consideration is that the spatial resolution afforded by standard fMRI analyses may preclude

the isolation of quality-specific responses. In fact, Schoenfeld et al. (2004) analyzed the topography of BOLD activity elicited by sweet, sour, salty, bitter, and savory stimuli on a flattened map of the human insula. A high inter-individual topographical variation was noted, but stable tastant-specific patterns of activity were identified for individual subjects. One caveat is that although these data are intriguing, since affective value and stimulus intensity (which both influence insular taste responses) were not matched, it is not possible to rule out these factors as contributing to the quality-specific responses. Nonetheless, these data suggest that this approach holds future promise for clarifying whether or not chemotopy exists in the insular cortex.

While no clear chemical map has so far been reported in the human gustatory cortex, future investigations on patients sustaining injury to the insular cortex might eventually reveal that this region contains specialized neuronal circuits differentially controlling chemosensory vs. homeostatic functions associated with food intake and body weight. Whereas atrophy in the anterior ventral region of the insula has been associated with compulsive binge eating in patients with frontotemporal dementia (Fig. 4a–b; Woolley et al. 2007), a single case study investigated by Small et al. revealed a patient with a posterior insular lesion who reported losing 25 lb without actively attempting to control body weight (Fig. 4c; Mak et al. 2005). Follow-up interviews with this very patient revealed a sustained maintenance of postsurgical weight associated with little effort at controlling appetite.

The Insula and Obesity

In addition to the patient data described previously, neuroimaging studies comparing brain responses in lean vs. overweight subjects implicated the insular cortex in the regulation of body weight. It has been hypothesized that individual differences in brain representation of food and/or of internal state predispose some to overeat in an environment where energy dense foods abound (Del Parigi et al. 2002; Berthoud 2004; Volkow and Wise 2005; Small 2009). Consistent with this hypothesis, Gautier et al. (2001) showed that reduced resting insular responses, which accompany satiety in lean subjects (Tataranni et al. 1999), are attenuated in obese subjects. Moreover, in postobese subjects, whereas most abnormal responses return to “normal” levels, response in the insula (and hippocampus) does not (Del Parigi et al. 2004). Similarly, individuals carrying the Prader–Willi syndrome, which is characterized among other symptoms by hyperphagia, show greater responses in the insular cortex to pictures of foods in the post- but not premeal condition (Holsen et al. 2006). These data implicate the insular cortex in homeostatic regulation during abnormal food intake. Regarding the sensory representation of food, obese relative to lean individuals also show greater insular responses to pictures of high-calorie foods (Rothemund et al. 2007) and to the anticipated as well as actual ingestion of milkshake (Stice et al. 2008). Taken together, the lesion and neuroimaging human data strongly support the view that the insular integration of sensory and homeostatic inputs associated with food stimulation plays a critical role in regulating energy intake. As such, it is plausible to assume that individual variations in insular representations of food and internal state might represent a biomarker for weight-gain susceptibility.

Conclusion

We have reviewed evidence from functional neuroimaging and electrophysiological studies supporting the view that the insular taste cortex functions as an integrative circuit by forming associations between sensory modalities arising from the oral cavity. Furthermore, both animal and human studies demonstrate that taste responses in this brain region are regulated by fluctuations in energy homeostasis. Taken together, these findings suggest that the insular taste cortex has a more general function than merely representing the gustatory aspects of intra-oral stimuli. A general function that could therefore be attributed to this circuit is to operate as a multisensory system dedicated to evaluating the biological significance of intra-oral stimuli. Future research must determine which physiological cues function as critical molecular signals allowing for the modulation of flavor representations by fluctuations in energy homeostasis.

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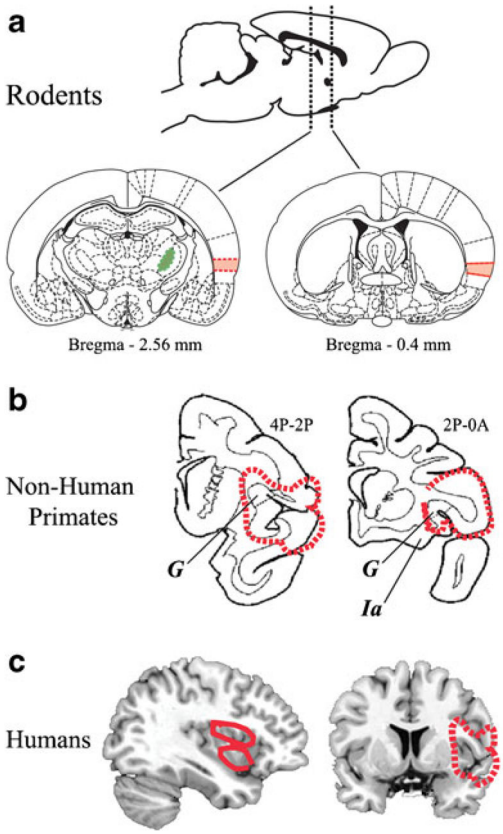

Fig. 1.

Schematic diagrams of the putative locations of gustatory cortex in rodents, non-human, and human primates. **a** Sagittal section of the rat brain showing the approximate extension of the gustatory cortex as delimited by the *dotted vertical lines* with corresponding coronal sections shown below it. The coronal section on the *left* depicts a posterior region of the gustatory cortex in the granular/dysgranular insula (delimited by the *red rectangular area*), immediately dorsal to the agranular insular cortex. This region is a target of efferent projections from the gustatory thalamus, originating from the ventral posterior medial nucleus (shown in *green* in the same section). It also projects anteriorly to the granular/dysgranular insular regions, shown in the coronal section on the *right*, immediately ventral to the secondary somatosensory cortex and dorsal to the pyriform cortex (adapted from Paxinos and Watson (1998)). **b** Coronal sections of the rhesus monkey brain. The slice on the *left* shows a posterior section of the anterior insula. The region delimited by the *red dotted line* includes gustatory cortex as well as adjacent frontal and temporal operculae, where taste-responsive cells are also described. The coronal slice on the *right* depicts a section through the more anterior insula in the rhesus monkey, including parts of the primary taste cortex. *Coordinates* shown to the *upper right* of the sections are in the anterior-posterior direction with respect to the sphenoid (as in Aggleton and Passingham, 1981). *G* indicates the primary taste cortex, and *Ia* indicates the agranular part of the insula, as defined with the nomenclature of Carmichael and Price (1994). The region delimited by the *red dotted line* includes gustatory cortex as well as adjacent frontal operculum (adapted from de

Araujo et al. (2003a, b, c)). **c** MRI images of the human insular cortex showing, on the *left*, sagittal and, on the *right*, coronal sections; the dorsal insular area delimited on the *left* consistently responds to unimodal taste stimulation in human imaging and PET studies. This region likely corresponds to the human homologue of the primary taste cortex that has been anatomically identified in non-human primates (Small et al. 1999). The insular area encircled more ventrally is activated in response to many oral sensations. Here, supra-additive responses to congruent taste and odors are found (Small et al. 2004). This same area also shows preferential connectivity with the hypothalamus when the oral stimulus represents a nutritive versus a non-nutritive food or drink (Rudenga et al. 2010). The *right* coronal section delineates within the *dotted line* the insular and opercular cortical areas where taste responses are observed in humans. Note the homology with non-human primate brain as shown in **b**

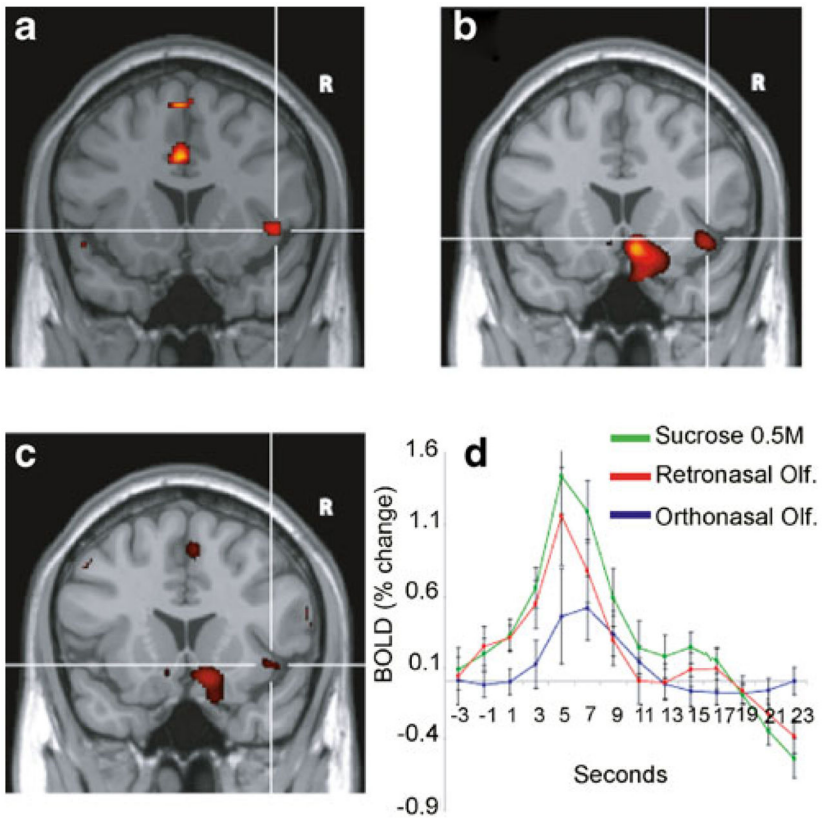

Fig. 2.

Taste and olfactory convergence in the human insular cortex. Coronal slices through the anterior insular cortex showing a small region found to receive convergent olfactory and gustatory inputs (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 the units on the *ordinate* are percent of BOLD signal change. From de Araujo et al. (2003a)

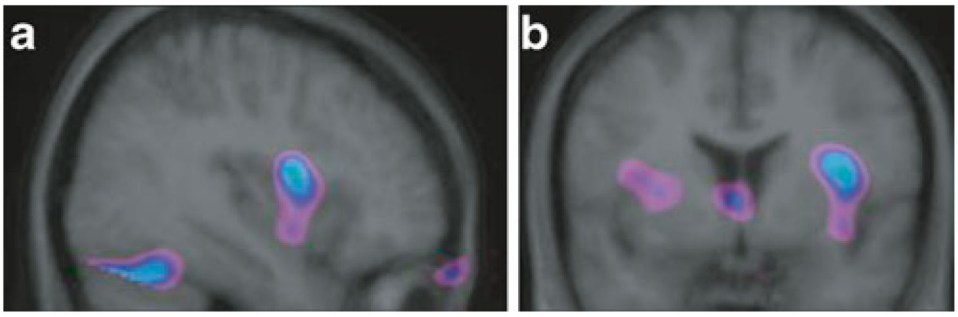

Fig. 3.

Regions in the human taste insular cortex reflect physiological states and motivational properties of food stimuli. **a**–**b** Insular cortical regions demonstrating significant regional cerebral blood flow (rCBF) correlations with affective ratings chocolate squares. Regression analyses were used to correlate rCBF from averaged PET data with the subjects' affective ratings that were taken immediately after scanning. Correlations are shown as *t* statistic images superimposed on corresponding averaged MRI (**a**, sagittal; **b**, coronal) scans. Data from the PET study performed by Small et al. (2001)

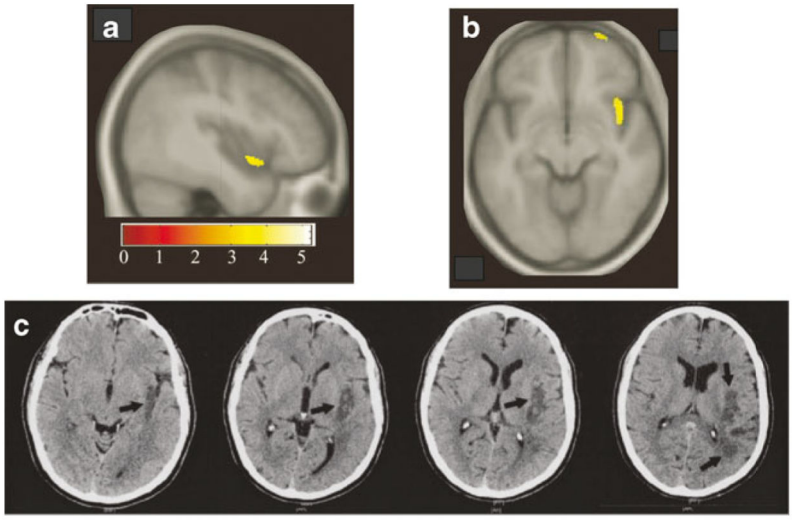

Fig. 4.

Lesions to the posterior regions of the insular cortex are associated with significant weight loss in humans. **a**–**b** Voxel-based morphometry on high-resolution magnetic resonance images reveal that the right inferior insula of overeating patients is significantly atrophied compared to control subjects. Insular regions of significant atrophy are displayed on sagittal (**a**), and axial (**b**) sections of the mean across all subjects' brains and thresholded at $p<0.05$, corrected for multiple comparisons (*color bars* representing observed Z-scores). From Woolley et al. (2007). (**c**) MRI scans from a stroke patient sustaining posterior insular lesions. The patient reported losing 25 lb without actively attempting to control body weight. *Arrows* indicate location of insular lesions displayed in axial images. From Mak et al. (2005)