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Identification of Human Gustatory Cortex by Activation Likelihood Estimation

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Abstract: Over the last two decades, neuroimaging methods have identified a variety of taste-responsive brain regions. Their precise location, however, remains in dispute. For example, taste stimulation activates areas throughout the insula and overlying operculum, but identification of subregions has been inconsistent. Furthermore, literature reviews and summaries of gustatory brain activations tend to reiterate rather than resolve this ambiguity. Here, we used a new meta-analytic method [activation likelihood estimation (ALE)] to obtain a probability map of the location of gustatory brain activation across 15 studies. The map of activation likelihood values can also serve as a source of independent coordinates for future region-of-interest analyses. We observed significant cortical activation probabilities in: bilateral anterior insula and overlying frontal operculum, bilateral mid dorsal insula and overlying Rolandic operculum, and bilateral posterior insula/parietal operculum/postcentral gyrus, left lateral orbitofrontal cortex (OFC), right medial OFC, pregenual anterior cingulate cortex (prACC) and right mediodorsal thalamus. This analysis confirms the involvement of multiple cortical areas within insula and overlying operculum in gustatory processing and provides a functional "taste map" which can be used as an inclusive mask in the data analyses of future studies. In light of this new analysis, we discuss human central processing of gustatory stimuli and identify topics where increased research effort is warranted. *Hum Brain Mapp 32:2256–2266, 2011.* © 2011 Wiley Periodicals, Inc.

Key words: activation likelihood estimation; functional brain imaging; fMRI; gustation; taste; PET

INTRODUCTION

Taste stimulation has consistently activated the same brain regions across multiple imaging studies [Faurion et al., 2005; Small et al., 1999], activating the insula and overlying operculum, large portions of cortex. However, it is unlikely that these entire regions are taste-responsive. Small et al. [1999] have proposed in their review that there may be multiple sub-areas within the insula and operculum that process gustatory inputs. In the past decade, more reports of taste imaging have been published that

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report activity in various areas in insula and operculum. However, disagreement across studies in the precise location of these subareas makes their identification difficult. In this study, we conducted a meta-analysis of 15 peer-reviewed studies using activation likelihood estimation (ALE) to identify which brain areas are activated by taste solutions with a high probability. ALE gives a quantitative estimate of activation based on coordinates of foci reported in each study. Each focus is weighted for the number of subjects participating in the study. The resulting ALE value is submitted to formal statistics and corrected for the observation of false positives. Through the use of ALE we identified brain sub-regions that are reliably activated by taste stimuli across studies.

Anatomy and Neurophysiology of the Primate Gustatory System

Sensations of taste, which are qualitatively labeled as sweet, salty, sour, bitter, or savory, originate from molecules interacting with taste receptor cells and presynaptic cells within taste buds in the oral cavity [Chandrashekar et al., 2006; Tomchik et al., 2007]. The taste signals are conveyed to the brain via branches of the facial (CN VII), glossopharyngeal (CN IX), and vagus (CN X) nerves to the nucleus tractus solitarius (NTS), the first gustatory relay in the brainstem [Witt et al., 2003]. In primates, second-order gustatory fibers ascend from the NTS to project directly to the ventroposteromedial (VPMpc) nucleus of the thalamus [Beckstead et al., 1980; Cavada et al., 2000]. From VPMpc thalamus there are two main projections. The primary and larger projection is located in an anterior region of insula and overlying frontal operculum (AIFO) and extends rostrally into the lateral orbitofrontal cortex (lOFC) [Mufson and Mesulam, 1984; Ogawa et al., 1985; Pritchard et al., 1986]. A second, less extensive, primate thalamic projection terminates in the precentral extension of Brodmann Area 3, along the ventral part of the precentral gyrus in primate [Ogawa, 1994; Pritchard et al., 1986]. Thus, anatomically, there are two "primary" thalamo-cortical gustatory projections; in terms of anterior/posterior orientation, one would be located anteriorly and one in a more middle/posterior region of the insula/operculum area. However, the latter's existence and exact location is controversial and relatively little is known about gustatory coding in this area (but see [Hirata et al., 2005]. Signals from the AIFO project to medial orbitofrontal cortex (mOFC) and lOFC [Baylis et al., 1995; Carmichael and Price, 1995; Pritchard et al., 2005], and the amygdala [Aggleton et al., 1980; Mufson et al., 1981]. The pregenual cingulate cortex (prACC) is connected to the thalamus, insula, and the OFC [Carmichael and Price, 1996; Vogt et al., 1987], and recently taste responsive neurons have been identified in the macaque prACC [Rolls, 2008b]. Further areas that connect to the macaque's OFC are the hypothalamus, hippocampus, and striatum [Cavada et al., 2000].

Many of the regions that contain taste-responsive cells are remarkably heteromodal (or multi-sensory), containing only a small portion of cells that respond to taste stimuli in primates: 6–27% in insula and overlying operculum [Hirata et al., 2005; Scott and Plata-Salaman, 1999], 20% in caudomedial OFC [Pritchard et al., 2005], 1.6% in pregenual ACC [Rolls, 2008b], and 2–8% in caudolateral OFC [Rolls et al., 1990]. This differs from the responsiveness of sensory cortex cells for other modalities, which are mostly unimodal in that a majority of neurons respond to stimulation from the principal modality; for example, ~99% of neurons in primary auditory cortex respond to tones [Phillips and Irvine, 1981]. As such, the cellular representation of taste processing in the primate brain can be characterized as both distributed and sparse [Scott and Plata-Salaman, 1999].

Human Clinical and Neuroimaging Studies

Early studies with patients confirmed the involvement of the insula and overlying operculum, and amygdala in gustatory representation in the human brain. Electrical stimulation of brain tissue in the insula and overlying operculum, amygdala, and hippocampus in patients with epilepsy led to (mostly unpleasant) gustatory sensations, [Hausser-Hauw and Bancaud, 1987; Penfield and Faulk, 1955]. Lesions in the amygdala (as a result of stroke or resection for the treatment of epilepsy) led to changes in taste recognition and intensity perception [Henkin et al., 1977; Small et al., 1997b, 2001b,c, 2005]. Damage to the insula and operculum resulted in impaired taste identification and discrimination, as well as changes in intensity perception [Börnstein, 1940a,b; Cereda et al., 2002; Mak et al., 2005; Pritchard et al., 1999; Stevenson et al., 2008]. Although the damage often encompasses large portions of the brain, the variation in locations across patients in these studies confirms the extensive representation of gustation in a distributed network in human cortex, involving the insula and the overlying operculum.

Taste neuroimaging studies commonly report activations throughout the insula and overlying operculum, including: anterior insula and overlying frontal operculum, mid insula at the base of the precentral sulcus and overlying Rolandic operculum, and posterior insula and overlying parietal operculum—the latter frequently extending into postcentral gyrus [Barry et al., 2001; Bender et al., 2009; Cerf-Ducastel and Murphy, 2001; De Araujo et al., 2003b; Faurion et al., 1999; Grabenhorst et al., 2008; Haase et al., 2007, 2009; Kinomura et al., 1994; Kobayakawa et al., 1999; McCabe and Rolls, 2007; Mizoguchi et al., 2002; O'Doherty et al., 2001, 2002; Veldhuizen et al., 2007]. Activations of medial and lateral OFC are also frequently observed in response to gustatory stimulation [De Araujo et al., 2003b; Francis et al., 1999; Haase et al., 2007; O'Doherty et al.,

2001; Small et al., 1997a,b; Veldhuizen et al., 2007; Zald et al., 1998, 2002]. Neuroimaging studies of taste have also indicated the involvement of amygdala, prACC, and thalamus [De Araujo et al., 2003b; Grabenhorst et al., 2008; Haase et al., 2007; O'Doherty et al., 2001].

Reviews and meta-analyses of neuroimaging studies confirm widespread activations in insula and operculum, diverging from posterior to the most anterior junction of insula and operculum [Faurion et al., 2005; Small et al., 1999]. These reviews have not, however, been able to precisely localize or identify subregions within the insula and operculum. This raises the question whether the emergence of an increasing number of new taste neuroimaging studies and new meta-analysis techniques might provide data for a more precise localization of gustatory cortex. Here, we employ a meta-analytic technique to estimate the likelihood of brain activations across multiple taste studies [Eickhoff et al., 2009; Laird et al., 2005; Turkeltaub et al., 2002] and to create a map of activation likelihoods which can be used in the data analyses of future taste studies. The ALE algorithm identifies common activations, and thereby factors out effects not related to the process of interest, such as different methodologies that are used by different research groups. In this analysis, we modeled the foci reported in several published taste studies as the centers of a Gaussian probability distribution of activation and pooled them to create a statistical whole-brain image of gustatory representation.

The ALE technique has three important advantages over traditional label-based regional reviews and meta-analyses. First, foci of activation are the input into the analysis, instead of labels. Labeling of anatomical areas does not occur until after data pooling, and thus is independent of differences in labeling among studies. Second, the foci that serve as the input for the analysis are weighted by the number of participants in each study. Third, this method yields a quantitative estimate of the probability of activation, which is statistically analyzed for significance and corrected for the observation of false positives. Although gustatory representation is sparse and distributed, we hypothesized that there is concordance in activation among neuroimaging studies of taste, and we expected to observe a high probability of gustatory activation in the "classical" regions of insula, overlying operculum, and the OFC with the emergence of various subregions within these larger areas.

METHOD

Identification of Papers

Two different methods were used to identify suitable papers investigating neural processing of gustatory stimuli. First, we searched the PubMed Medline database as well as the PsycINFO database to identify human gustatory functional imaging journal articles appearing prior to May 2010. Databases were probed with the keywords: positron emission tomography and functional magnetic resonance imaging (including acronyms and synonyms such as PET, fMRI, regional cerebral blood flow, BOLD, etc.) and cross-referenced with the terms: taste, gustatory, gustation, tastants, and flavor. Second, the reference list of original papers reporting cortical signals in humans for gustatory stimuli using either PET or fMRI were then explored using tools accessible in Web of Science (Version 4) to find additional articles that were not identified by the Medline and PsycINFO searches.

Inclusion Criteria

We only included contrasts in the meta-analysis that fulfilled six individual criteria:

First, the stimulus was a pure gustatory stimulus (without ortho- or retronasal olfactory components, i.e., flavors and foods were excluded) and was contrasted against a "taste free" baseline (such as artificial saliva, distilled water, etc.). If the individual experimental conditions appeared in more than one contrast, i.e., the contrast (sucrose vs. tasteless) also appeared in a joint contrast (sucrose + NaCl vs. tasteless), we only included the basic and not the combined contrast. Moreover, direct comparisons between two conditions, which both included a taste stimulus, were excluded.

Second, the included studies only reported data obtained in young healthy subjects, i.e., contrasts using a special population were excluded. Several papers included contrasts under hungry or satiated conditions; only data obtained from satiated conditions were included.

Third, imaging data reported in a direct contrast, i.e. correlated functional data with other measures, such as behavior, were excluded. Deactivations and contrasts with between-group comparisons were omitted.

Fourth, we included contrasts regardless of task required during or after scanning, since the inclusion of contrasts independent of task allows a maximum benefit from the use of statistical probability methods. Activations not mediated by gustatory processing will be identified as outliers by the ALE analyses due to the inconsistency in their activations across studies.

Fifth, we only included results which were reported in a standardized stereotaxic space, i.e., in either Montreal Neurological Institute (MNI) or Talairach spaces.

Sixth, signals must have been acquired from, and averaged across, a minimum sample size of seven subjects, i.e., we only included contrasts originating from group based comparisons and not single subject analyses.

Procedure

To allow comparisons of anatomical locations between subjects and studies, most functional neuroimaging studies are spatially normalized to a standardized anatomical template. The most commonly used are the Talairach and the

MNI brain templates. Since these anatomical templates are not directly comparable due to minor anatomical differences, all data included in the meta-analysis were transformed into Talairach space, the algorithm for this transformation is provided by the ALE software package (GingerALE 2.0.1; http://www.brainmap.org/ale). The ALE software does an automated analysis that has been described in detail elsewhere [Eickhoff et al., 2009; Laird et al., 2005; Turkeltaub et al., 2002]. A whole brain ALE map was created by modeling the activation foci for each included experiment using a full-width half-maximum (FWHM) Gaussian filter to produce model activation volumes (MA maps). The radius of the Gaussian filter was adjusted for empirical estimates of between-subject variance within a study, and between-study variance. As a result, ALE does not weigh the studies and foci equally, but controls for the number of subjects in each of the included studies. In the current analysis, the median FWHM of the Gaussian was 10 mm (minimum of 9.3 mm and a maximum of 10.6 mm). These MA maps were then compared and the activation probabilities were calculated based on known gray matter areas (voxels where the probability for gray matter is >10%) as well as computations of the appropriate null-distribution for this specific data set. This modeling renders arbitrary ALE values whose statistical significance was determined by using permutation testing of randomly generated foci. Seven thousand permutations were performed using the same FWHM value as used in computing the ALE scores and corrected for multiple statistical comparisons using the false discovery rate (FDR) method [Genovese et al., 2002]. Importantly, this method produced ALE scores based on a random-effects model thus allowing an inference about the population to be drawn from these sets of studies, much like analyses of multiple subjects in an individual imaging study [Eickhoff et al., 2009]. Only corrected ALE scores reaching significant levels ($P < 0.05$) are reported in the figures, and only clusters exceeding 100 cubic mm (~6 mm cube) in size were included in the tables and labeled in Figure 1 below.

For visualization purposes, the anatomical template provided on the Ginger ALE website [colin1.1.nii, Kochunov et al. [2002], http://brainmap.org/ale] was overlaid with the thresholded ALE map using MRIcron (version beta 3.1, http://www.sph.sc.edu/comd/rorden/mricron/).

Local maxima of activation clusters were anatomically labeled using diverse anatomical atlases [Duvernoy, 1999; Mai et al., 2004] and visually cross-referenced within MRIcron.

RESULTS

A total of 15 studies were included in this meta-analysis. Ten of these studies were functional magnetic resonance imaging (fMRI) studies and five were positron emission tomography (PET) studies (Table I). The included studies yielded brain activations in a total of 179 foci (Table II), resulting in nine significant clusters (see Fig. 1). To facilitate the use of these meta-data for independent regions of interest analyses (ROI) or as an inclusive mask in imaging analyses, the complete activation map is enclosed both as supplementary material and made available at http://flavor.monell.org/~jlundstrom/ale/. We observed high ALE values within bilateral insula and overlying operculum. In the left hemisphere, we observed a large cluster that encompasses a peak in the postcentral gyrus/parietal operculum/posterior insula and one in the mid dorsal insula and overlying rolandic operculum. We also observed a cluster in the left anterior insula and overlying frontal operculum. In the right hemisphere, we observed significant ALE values in similar insular and opercular areas as in the left hemisphere; in postcentral gyrus/parietal operculum, mid dorsal insula and overlying rolandic operculum, anterior insula and overlying frontal operculum with a more anteroventral extension of the activation in anterior insula as compared with the left hemishpere. As can be seen in Figure 1, these activations were generally symmetric across the hemispheres.

In the orbitofrontal cortex, we observed two clusters: in the right medial orbital gyrus and in the left anterior orbital gyrus (covering the lateral part of Brodmann area 11 and 47/12). Additionally, we observed significant values medially in the prACC and in right mediodorsal thalamus.

DISCUSSION

The present meta-analysis used an ALE procedure to obtain a quantitative map of the probability of activations in the human brain by gustatory stimuli among 15 neuroimaging studies that investigated activations associated with taste stimulation. In the resulting probability map, we observed widespread and significant ALE values in bilateral insula and overlying operculum, in left lateral OFC, in right medial OFC, in the prACC, and right mediodorsal thalamus. Other regions known to be activated by taste stimulation but not observed in the present meta-analysis, such as the amygdala and hippocampus, may not be commonly observed across multiple studies. The regions reported here constitute the significant taste-activation foci that appear consistently across multiple taste imaging studies.

Gustatory Representation Within Insula and Overlying Operculum

Recently, two important characteristics of gustatory representation have emerged: (1) taste cells are sparsely and extensively distributed in the central nervous system, and (2) conscious taste perception emerges from activations in insula and overlying operculum [Faurion et al., 2005; Small et al., 1999]. However, these studies leave unclear the precise location and number of subregions of within these large portions of cortex. Here, we observed

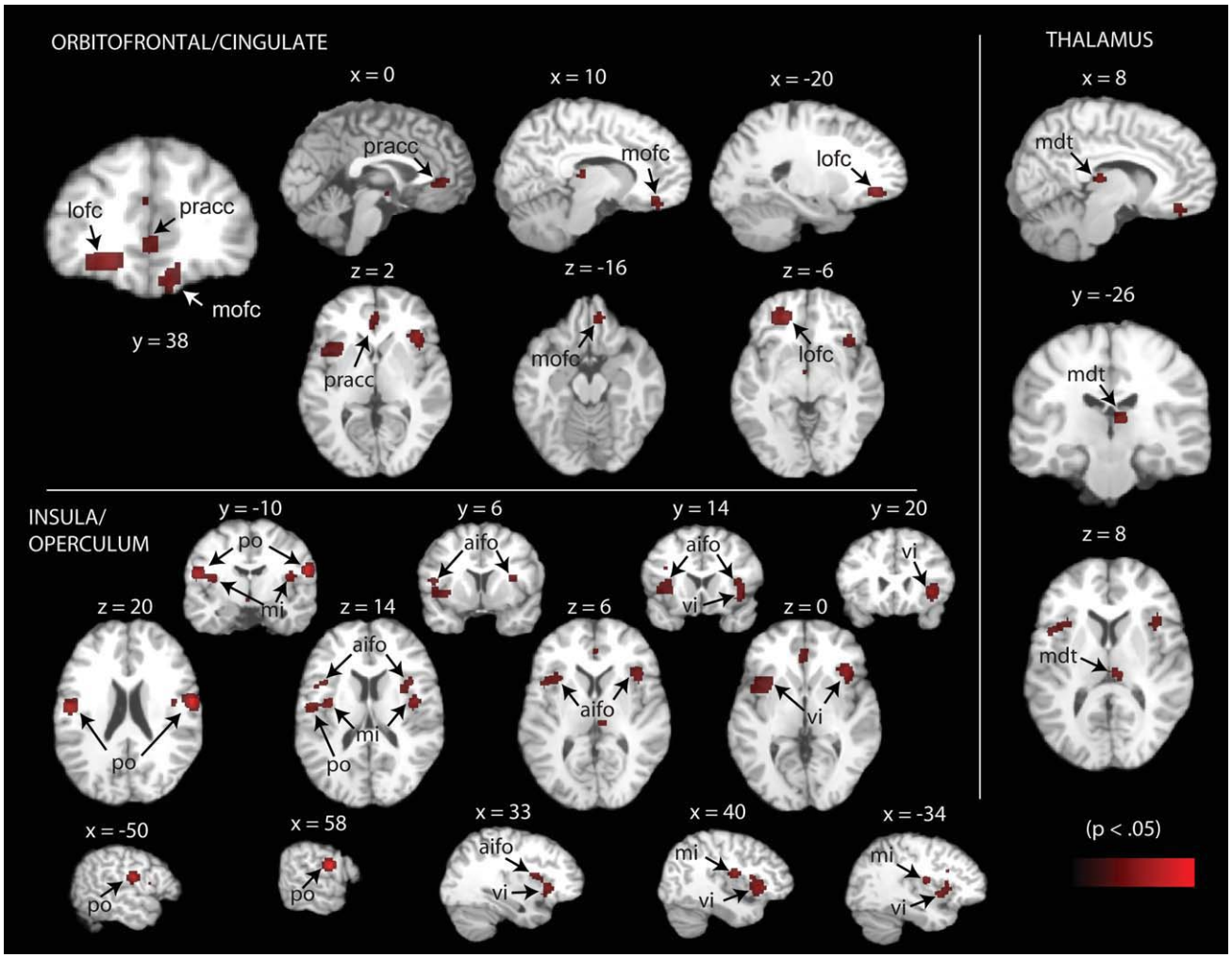

Figure 1.

Localization of significant ALE values ($P < 0.05$) of gustatory stimulation projected onto a standard template (colin1.1.nii) in Talairach space. Location of selected slice is denoted with stereotactic coordinates above each of them. Only clusters exceeding 100 cubic mm in size are labeled. Abbreviations of anatomical areas: mdt = mediodorsal thalamus, pracc = pregenual anterior cingulate cortex, mofc = medial orbitofrontal cortex, lofc = lateral orbitofrontal cortex, aifo = anterior insula and overlying frontal operculum, po = postcentral gyrus, posterior insula and overlying parietal operculum, mi = mid insula and overlying Rolandic operculum, and vi = ventral insula.

significant ALE values bilaterally at the junction of anterior insula and overlying frontal operculum. We also observed a high likelihood of activations in other areas of insula and operculum: (1) bilaterally in the mid dorsal insula and overlying rolandic operculum, and (2) bilaterally in a slightly more lateral and superior area in the parietal operculum/postcentral gyrus/posterior insula. The observation of the cluster in the anterior insula and overlying frontal operculum is consistent with the most extensive projection from VPMpc as reported in primate neuroanatomy literature [Mufson and Mesulam, 1984; Ogawa et al., 1985; Pritchard et al., 1986]. In agreement with this, our analysis shows that the regions in anterior insula and overlying frontal operculum have the highest probability of being observed across studies, e.g., in both hemispheres this area has higher ALE values than the other areas within insula and overlying operculum.

The second (more controversial) afferent from VPMpc [Ogawa, 1994; Pritchard et al., 1986] projects to the base of precentral sulcus in primate. There is disagreement about the location of this projection in the human neuroimaging literature. Some researchers believe the activation by taste

TABLE I. Studies included in the meta-analysis

Reference	Imaging modality	*n*	Age of the subjects	Contrasts (stimuli)	Number of foci
Bender, 2009	fMRI (3 T)	15	Mean 25.4 yr (22–31 yr)	Taste (sucrose/citric acid/NaCl)-tasteless	5
Cerf-Ducastel and Murphy, 2001	fMRI (3 T)	12	Mean 23.3 yr, SD 6.9 yr (20–45 yr)	Taste (NaCl/aspartame/quinine hydrochloride/hydrocholic acid)-tasteless	14
De Araujo et al., 2003b	fMRI (3 T)	11		Sucrose-tasteless	8
Haase et al., 2007	fMRI (3 T)	18	Mean 20.7 yr, SD 0.99 yr (19–22 yr)	Sucrose-tasteless	14
Haase et al., 2009	fMRI (3 T)	18	Mean 20.7 yr, SD 0.99 yr (19–22 yr)	Sucrose-tasteless, citric acid-tasteless, saccharin-tasteless, caffeine-tasteless, GMP-tasteless, NaCl-tasteless	10
Kinomura et al., 1994	^{15}C-O_2-PET	10	(18–21 yr)	NaCl-tasteless	10
McCabe and Rolls, 2007	fMRI (3 T)	12		MSG-tasteless, NaCl-tasteless	7
O'Doherty et al., 2002	fMRI (2 T)	8	Mean 24.5 yr (18–35 yr)	Glucose-tasteless, NaCl-tasteless	4
O'Doherty et al., 2001	fMRI (3 T)	7		Glucose-tasteless, NaCl-tasteless	24
Ogawa et al., 2005	fMRI (1.5 T)	11	Mean 23.8 yr (21–31 yr)	NaCl-tasteless	8
Small et al., 1997b	^{15}O-H_2O-PET	10	(22–41 yr)	Citric acid—water	11
Small, 2003	fMRI (1.5 T)	9	Mean 24 yr	Sucrose-tasteless, quinine sulfate-tasteless	40
Small et al., 1997a	^{15}O-H_2O-PET	10	(22–41 yr)	Taste (citric acid/sucrose/quinine sulfate/NaCl)—tasteless	6
Zald et al., 1998	^{15}O-H_2O-PET	9		NaCl-tasteless	8
Zald et al., 2002	^{15}O-H_2O-PET	9	24 yr (18–34 yr)	Quinine hydrochloride-tasteless, sucrose-tasteless	10

Abbreviations: NaCl, sodium chloride; GMP, guanosine monophosphate; MSG, monosodium glutamate.

TABLE II. Localization of significant FDR corrected ALE values for gustatory stimulation (whole and partial brain volume analyses)[a]

Cluster number	Cluster volume (mm^3)	ALE extrema value ($\times 10^{-3}$)	Talairach coordinates			Brain region
			x	*y*	*z*	
1	3,168	2.05	−36	6	−2	Anterior insula/ventral insula
		1.99	*−32*	*14*	*6*[b]	Anterior insula/frontal operculum
		1.79	*−42*	*10*	*8*	Frontal operculum
2	3,136	3.14	38	20	2	Anterior insula/frontal operculum/ventral insula
		1.83	*32*	*6*	*14*	Anterior insula/frontal operculum
		1.80	*36*	*12*	*12*	Anterior insula/frontal operculum
3	2,296	3.52	−50	−12	20	Postcentral gyrus/parietal operculum
	264	2.33	−36	−10	14	Mid insula/rolandic operculum
4	2,096	5.31	58	−6	22	Postcentral gyrus/parietal operculum
5	2,024	2.71	−20	38	−6	Lateral orbitofrontal cortex
6	848	2.86	40	−8	16	Mid insula/rolandic operculum
7	776	2.01	0	38	2	Pregenual anterior cingulate gyrus
		1.82	*−2*	*30*	*0*	Pregenual anterior cingulate gyrus
8	752	2.26	10	38	−16	Medial orbitofrontal gyrus
9	480	2.26	8	−26	8	Mediodorsal thalamus

[a]Significant values are reported together with stereotaxic coordinates in Talairach space (Talairach and Tournoux [1988]), cluster volume, and activation likelihood estimation of the local activation maximum.
[b]Italics indicate that a peak falls under the same cluster as the preceding peak.

in the posterior insula and overlying parietal operculum/postcentral gyrus [Faurion et al., 2005; Kobayakawa et al., 1996, 1999; Ogawa et al., 2005] reflects this secondary projection. Others believe that the activations in mid dorsal insula and overlying Rolandic operculum [Faurion et al., 1998, 1999; Veldhuizen et al., 2007] represent the secondary projection from VPMpc in humans. Note that these two areas are in close proximity. Since some authors reported brain activation in a non-standardized stereotaxic space [Faurion et al., 1998, 1999] and/or obtained them with techniques that have limited spatial resolution such as magnetoencephalography (MEG) [Kobayakawa et al., 1996, 1999], distinguishing among these activations may be difficult. As a result, it is unclear if there is disagreement among reports about regional labeling or the actual locus of activation. Here we observed gustatory representation across multiple studies in both the parietal operculum/posterior insula and the mid dorsal insula and overlying Rolandic operculum. The present ALE analysis suggests that both these areas play a role in gustatory processing, besides the area in anterior insula and overlying frontal operculum.

Interestingly, one of the hallmarks of primary sensory representation, baseline increases during attention to a stimulus in the absence of a sensory stimulus itself, was observed for the gustatory modality in mid dorsal insula and overlying Rolandic operculum [Veldhuizen et al., 2007]. We cannot, however, readily identify the "primacy" of the different areas within insula and operculum. The current analysis suggests that all subregions are involved in gustatory representation, but future studies into the specific contributions from each are warranted.

Contribution of Somatosensory Stimulation to Gustatory Representation

The controversy over which area in insula and overlying operculum has primacy in encoding taste sensations revolves around disagreements regarding the somatosensory contributions to these activations. Taste and oral somatosensory cortical processing regions either overlap or lay beside each other [Hirata et al., 2005; Kadohisa et al., 2005; Pritchard et al., 1989; Smith-Swintosky et al., 1991; Yamamoto et al., 1985], including the areas in mid-dorsal insula and overlying Rolandic operculum and the posterior insula/parietal operculum/postcentral gyrus. This latter area has been proposed to be the site for oral somatosensory cortical representation in humans [Boling et al., 2002].

In a natural situation, taste stimulation is always concurrent with oral somatosensory stimulation. Most neuroimaging taste studies rely on the subtraction of a baseline (water or tasteless trial) to eliminate non-gustatory components from the taste signal. Also, different methods have been developed to minimize oral somatosensory stimulation (see for example [Haase et al., 2007; Kobayakawa et al., 1999; Veldhuizen et al., 2007]). Although the current analysis should show gustatory representation irrespective of somatosensory control methods, we also know that oral touch and taste are inherently related [Green, 2003; Simon et al., 2008]. As we normally experience taste sensations, oral somatosensation is almost perfectly correlated. This raises the issue of whether taste can be isolated from somatosensory representations, unless directly addressed by the design of a study [Shikata et al., 2000]. Indeed, taste is captured by concurrent touch in the mouth, leading to the illusion of taste sensation at the locus of somatosensory stimulation [Delwiche et al., 2000; Green, 2003; Todrank and Bartoshuk, 1991]. On the basis of this phenomenon, we have suggested that attention to taste may automatically evoke attention to the mouth, including attention to somatosensory components [Veldhuizen et al., 2007], resulting in recruitment of somatosensory areas during "pure" taste presentation. Thus, the oral somatosensory system may still have contributed to the activations reported in the current meta-analysis. The combined contributions of somatosensation and gustation to the activation of human insula and overlying operculum remain an important outstanding issue in the imaging of gustatory representation.

Gustatory Representation in Orbitofrontal Cortex

We observed several clusters in the OFC; in left lateral anterior orbital gyrus and right medial orbital gyrus. Functional dissociation in areas within the OFC have been made on the basis of: (1) pleasantness of taste stimuli (with preferential response in the left hemisphere for unpleasant and in the right hemisphere for pleasant stimuli, [Small et al., 2003; Zald and Pardo, 2000]), and (2) motivation to consume chemosensory stimuli (with activity in the medial and lateral OFC associated with increased and decreased motivation for consumption [Kringelbach et al., 2003; Small et al., 2001a]). Neural responses in medial OFC are graded with increasing stimulus pleasantness and are activated during attention to pleasantness rather than to intensity [Grabenhorst and Rolls, 2008; Grabenhorst et al., 2008]. Hence, the medial OFC is thought to constitute a part of the gustatory cortex that functions as an intermediate area between the AIFO and lateral OFC [Pritchard et al., 2005], possibly involved with affective evaluations of the stimuli.

Gustatory Representation in Pregenual ACC

The prACC is connected to gustatory insular cortex and overlying operculum and OFC; it has frequently been observed in gustatory studies, but the prACC is not considered part of primary gustatory cortex. Together with the recent observation of taste-responsive cells in this area [Rolls, 2008b], the high activation likelihood in this analysis confirms the involvement of the prACC in gustatory

processing. This area of prACC is also frequently coactivated with mOFC [Kringelbach, 2005]. It has been shown that responses in prACC, like responses in mOFC, correlate with taste pleasantness and, similar to the mOFC, responds preferentially with attention to the pleasantness of a taste compared with other tasks [Grabenhorst and Rolls, 2008; Grabenhorst et al., 2008]. Thus, it has been suggested that the prACC interacts with the OFC to produce goal-directed behavior (or behavioral planning) on the basis of pleasantness information [Kringelbach, 2005; Rolls, 2008a], consistent with its purported role in attention to the pleasantness of a taste stimulus [Grabenhorst and Rolls, 2008].

Absence of Gustatory Representation in Amygdala

The amygdala has connections with gustatory cortex in insula and overlying operculum and OFC, and is frequently activated in gustatory studies. However, we did not observe significant ALE values in the amygdala, which has traditionally not been considered gustatory cortex. The amygdala has not shown a graded response to varying pleasantness of intraoral stimuli [De Araujo et al., 2003a,b; Kringelbach et al., 2003; McClure et al., 2004]. Rather, it responds to strongly pleasant or unpleasant gustatory stimuli [Small et al., 2003] and has been proposed to encode the salience of gustatory stimuli [Small et al., 2003]. Although only half of the studies included in the ALE analyses reported foci located within the amygdala, the amygdala is often mentioned in relationship with taste processing.

Therefore, we lowered the cutoff threshold in an exploratory effort to investigate whether amygdala activation would appear with a less stringent approach. Indeed, using a less stringent statistical approach, left sided amygdala activation was observed [centered at (x, y, z) 26, −14, −20]. The failure of amygdala to appear in the more conservative analyses reported above is probably due to the low number of individuals scanned within the studies that did report significant amygdala activation. ALE 2.0 takes into account the number of participants within each included study where the between-subject variance is inversely scaled by the square root of the sample size.

Gustatory Representation in Mediodorsal Thalamus

We observed significant likelihood of activation in mediodorsal thalamus, an area connected to the OFC [Cavada et al., 2000]. We did not, however, observe activity in the traditional gustatory region of the thalamus, the parvocellular portion of the ventral posterior medial nucleus (VPMpc). Only 10% of neurons in this area respond unimodally to gustatory stimulation [Verhagen et al., 2003]. Gustatory representation in the VPMpc may be too sparse to be observed with fMRI, particularly if, in parallel with other early cortical gustatory areas, attention to taste is also represented in this area [Veldhuizen et al., 2007]. It has recently been proposed that the thalamus plays a dynamic role in sensory processing, possibly contributing to selective relaying of sensory signals to enable an organism to engage in goal-directed behavior [Guillery and Sherman, 2002]. In a recent study, the connection between the mediodorsal thalamus and OFC was strengthened under attention to odors compared with attention to tones [Plailly et al., 2008]. This suggests that there are indirect pathways from primary olfactory cortex to higher order areas via the mediodorsal thalamus that play a role in olfactory perception. It is possible, therefore, that the connection between gustatory cortex and mediodorsal thalamus [Cavada et al., 2000] also plays an important role in the awareness of tastes. Consistent with this, the mediodorsal thalamus has been implicated in attention to gustatory stimuli [Veldhuizen et al., 2007; Veldhuizen and Small, 2008].

Lateralization of Gustatory Representation

It has been suggested that gustatory representation is dominant in the right hemisphere as a result of left-hemisphere dominance in processing of language [Small et al., 1999]. However, inconsistencies have been observed, for example right-handed subjects have left hemisphere activations in response to taste stimulation, left-handed subjects have the reverse pattern [Faurion et al., 1999]. Most of the studies included in this meta-analysis used right-handed subjects. In general, the current meta-analysis produced symmetry in activation in response to gustatory stimulation across the two hemispheres, indicating a relatively balanced hemispheric representation of gustatory processing.

Limitations

ALE is a powerful technique to conduct coordinate-based meta-analyses on functional imaging data when one wishes to concatenate the often disparate results obtained within individual studies [Albrecht et al., 2010]. However, as with all data reduction techniques, including meta-analyses, ALE suffers from some inherent drawbacks. The underlying data originate from individual studies which all use slightly different methods and settings when analyzing their data. These differences will invariably produce differences in outcome, even between seemingly identical studies, often resulting in a difference in the number of reported significant foci. The ALE analyses software utilized during this study (version 2.0) partly controls for this study bias by factoring in the sample size. Moreover, it has been demonstrated that individual studies reporting many activation foci do not bias the ALE analyses in a significant way [Turkeltaub et al., 2002].

As can be seen in Table I, contrasts using sweet or salty taste are overrepresented, certainly compared with savory taste (MSG and GMP). In some of the studies, stimuli were specifically manipulated to be aversive or attractive. Of those studies, three studies used strong and aversive sodium chloride concentrations that were likely trigeminal in addition to gustatory. Thus, it is conceivable that the results are slightly skewed toward specific stimuli or tasks. However, with the ALE analysis, variations across studies are parceled out and the common denominators are reflected in the final ALE maps. As a result, this analysis is most likely not skewed by one particular task or stimulus. For example, when we inspected the clusters resulting from the ALE analyses, we observed that four clusters resulted from foci that included all five taste qualities (clusters 1, 3, 4, and 8), and that the remaining five clusters resulted from foci that included the four taste qualities sweet, salty, sour, and bitter, indicating that each cluster represents at least four taste qualities. This indicates that while sweet taste and salty taste may dominate the input, which is in agreement with the state of the research in the field, they are far from the sole mediator of the output. Nevertheless, when the number of future studies including other taste qualities become more prolific and balanced, quality-specific representations may turn out to influence ALE analyses in such a way that the present probability map of the gustatory cortex might be subjected to revisions.

Because of the low number of total published taste studies and low statistical power, we have not divided the included articles according to behavioral tasks or taste stimuli used, which would be of great interest. Future meta-analyses of central taste processing need to assess these questions when the total number of published taste articles is significantly higher.

CONCLUSIONS

By using the meta-analytical method of activation likelihood estimation, we mapped the recruitment of cerebral areas for gustatory processing. We confirmed the involvement of several areas in OFC, in bilateral insula and overlying operculum following gustatory stimulation. In addition, we observed significant ALE values in the prACC and right mediodorsal thalamus confirming the contribution of these areas to gustatory processing. These areas potentially represent associative or tertiary processing stages. It remains to be determined how these different regions interact to produce behavioral responses to gustatory stimuli, and which tissues are necessary and sufficient for taste sensations. Nevertheless, this meta-analysis provides a comprehensive overview of the brain areas activated by taste stimuli. By including studies independent of task and taste stimuli, the analyses will isolate those tissues that commonly activate to taste stimulation in general. In conclusion, we show that gustatory processing recruits a wide network of cerebral areas. These activation likelihood estimates could also serve as independent values for ROI analyses or serve as a mask in analyses of future imaging studies. To this extent, the complete activation map (note the Talairach space) is enclosed as supplementary material and can be downloaded from the web address mentioned above.

The field of gustatory neuroscience is now faced with an important and difficult challenge to understand the contribution of oral somatosensory and gustatory stimulation to neural activities and their interactions and to determine which of these tissues are critical for the generation of gustatory sensation.

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