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Human cortical gustatory areas: A review of functional neuroimaging data

Dana M. Small,[CA] David H. Zald,[1] Marilyn Jones-Gotman, Robert J. Zatorre, José V. Pardo,[1] Stephen Frey and Michael Petrides

Cognitive Neuroscience Unit, Department of Neurology and Neurosurgery, McGill University, Montreal Neurological Institute, 3801 University Street, Montreal, Quebec, Canada H3A 2B4; [1]Cognitive Neuroimaging Unit, Psychiatry Services, Veterans Affairs Medical Center, Minneapolis, MN, USA

[CA]Corresponding Author

IN an effort to define human cortical gustatory areas we reviewed functional neuroimaging data for which coordinates standardized in Talairach proportional space were available. We observed a wide distribution of peaks within the insula and parietal and frontal opercula, suggesting multiple gustatory regions within this cortical area. Multiple peaks also emerged in the orbitofrontal cortex. However, only two peaks, both in the right hemisphere, were observed in the caudolateral orbitofrontal cortex, the region likely homologous to the secondary taste area described in monkeys. Overall significantly more peaks originated from the right hemisphere suggesting asymmetrical cortical representation of taste favoring the right hemisphere. *NeuroReport* **10:7–14 © 1999 Lippincott Williams & Wilkins.**

Key words: Area 11; Area 13; Cerebral asymmetry; Human; Insula; Orbitofrontal cortex; Operculum; PET; Taste

Introduction

In non-human primates, single-cell recording [1–3], anatomical tracing [4,5] and evoked-potential mapping [6] studies have identified the dorsal anterior insula and adjacent frontal operculum as the primary gustatory area (PGA), and the caudolateral orbitofrontal cortical region (CLOF) as the secondary gustatory area (SGA). A limited number of taste-responsive cells have also been recorded from the precentral extension of the primary somatosensory area and a more ventral region of the insula [6]. However, according to Ogawa [7], these areas are likely to be supplementary rather than primary gustatory areas.

Until the advent of neuroimaging techniques, knowledge of human cortical gustatory representation derived entirely from studies of lesion sites in clinical populations. Such studies variably argued for cortical representation of taste either in the parietal opercular region (in the postcentral gyrus immediately adjacent to the somatosensory representation of the tongue) [8–10], the insula [11,12] or the anterior temporal lobe [13,14]. However, these early studies lacked information about the precise extent and location of lesion. More recent clinical studies using methods such as magnetic resonance imaging (MRI) [15,16] and stereoelectroencephalography [17], which allow more precise lesion localization, confirmed the importance of these regions in gustatory processing.

Functional neuroimaging techniques such as PET and fMRI provide powerful tools for localizing functional brain regions and have greatly expanded our ability to localize sensory representations in the normal brain. However, because of the small sample sizes and variable methodologies employed by these techniques, the most convincing demonstrations of functional localization emerge from the convergence of multiple studies. In the present study, we analyzed data from currently available neuroimaging studies of taste processing in humans in order to determine the localization of the human cortical taste areas.

Materials and Methods

This analysis included data from all published neuroimaging studies of taste for which coordinates in the standardized proportional Talairach stereotaxic space [18] were available [16,19–22] as well as from a number of as yet unpublished studies from our respective laboratories. All of the data used in the present analysis were generated using PET with either the $[O^{15}]H_2O$ bolus or the $[O^{15}]CO_2$ inhalation method with intra-subject averaging (Table 1).

Table 1. Studies, subjects, stimuli and methods.

Study	No. subjects	Stimulus and method
Frey and Petrides (unpublished work)	12	$H_2{}^{15}O$ bolus. Drops of 5% sucrose solution delivered to mouth via plastic pipettes every 4 s. Passive tasting. 60 s scans
Kinomura *et al.* [19]	10	$C^{15}O_2$ inhalation. 2 ml water or saline solution injected into mouth every 15 s through two plastic tubes. Discrimination required. 5 min scans.
Petrides *et al.* [20]	10	$H_2{}^{15}O$ bolus. 10% sucrose solution or water painted on tongue with a wooden stir stick. Passive tasting. 60 s scans.
Small *et al.* [1,21]	10	$H_2{}^{15}O$ bolus. Tongue-shaped filter papers soaked in liquid (either 0.023 M citric acid, 0.56 M sucrose and NaCl, 0.0001 quinine solutions, or water) delivered to tongue with tweezers and replaced every 7 s. Discrimination required. 60 s scans.
Zald *et al.* [22]	9	$H_2{}^{15}O$ bolus. 3 ml 5% saline solution or water injected into mouth via a cannnula ~5 s before scanning. Additional 2 ml fluid injected slowly over rest of scan. 3 g chocolate placed on tongue ~5 s before scanning. Discrimination required after scan. 90 s scan.
	9	Same method as above. 0.02 M quinine HCl solution or water.
	10	Same method as above. Water presented or subjects rest, or attempt to smell clean air.
	9	Same method as above. Subjects given lemon concentrate
	8	Same method as above. Fine grain salt presented on a stir stick by stroking one side of tongue at a rate of 1 stroke/s. Mechanical stimulation used same method but no salt.

fMRI has also been used to assess human gustation, but lacking coordinates in the Talairach proportional space, could not be included in this analysis [23]. Based on work performed in non-human primates [1–7] we targeted the insula, the frontal and parietal operculum, and the orbitofrontal cortex (OFC) as the regions of interest for this study.

The data were compiled from a total of 16 different comparisons (subtractions) of cerebral blood flow between two different scanning conditions. Most comparisons were between an experimental condition in which a gustatory stimulus was presented and a baseline condition in which the non-gustatory aspects of the experimental condition were presented as a control (Table 2). Data were also included from two subtractions in which both conditions involved presentation of a gustatory stimulus (all tastes-citric acid; aversive saline–chocolate, see Tables 1 and 2). Finally, data were included from a subtraction comparing a unimodal gustatory stimulation with a bimodal flavour stimulation. These subtractions yielded 22 activation peaks within the insula and opercular regions, and 19 activation peaks in the OFC (Tables 1 and 2). All published peaks were considered, but among unpublished peaks, only those with a t-value greater than alpha = 0.05 were included. Each laboratory used different stimuli and methods of stimulus presentation, the details of which are outlined in Table 1.

The standardized proportional Talairach stereotaxic coordinates representing each of the activation peaks were plotted onto an average MRI, generated from 12 subjects, none of whom participated in any of the neuroimaging studies reported in the current analysis. Talairach coordinates represent three dimensions within a proportional space that allows brains of different sizes to be compared in a common previously defined space. The x coordinate refers to the medial to lateral plane (sagittal), the y coordinate to the anterior to posterior plane (coronal), and the z coordinate to the inferior to superior plane (horizontal). The number of the coordinate represents millimeters from one of three different dimension defining lines [19].

Peaks were color-coded according to the laboratory from which they were generated, and grouped and displayed in the three planes. Peaks within the insula and the opercular region were grouped together and displayed in the sagittal plane (Fig. 1A,B). OFC peaks were grouped and displayed in the horizontal plane (Fig. 1C). In addition, all peaks were organized according to their position on the anterior to posterior axis and plotted onto coronal sections to give a better appreciation of their precise location (Fig. 2). On these coronal slices, the peaks were also labeled with numbers that correspond to those in Table 1, indicating the subtraction from which the peak was generated.

In order to display peaks relative to one another, the stereotaxic coordinates corresponding to the plane of interest were averaged so that peaks could be plotted onto an MRI section that would be most representative of the group. For example, all the x (i.e. medio-lateral) coordinates were averaged to give the value at which to plot the peaks in the sagittal plane. The resulting mean ($\pm$ s.d.) x coordinate (sagittal plane) was 36 ± 4. Peaks were then plotted by their y and z values onto an MRI sagittal slice at $x = 36$. This same procedure was carried out for the horizontal and coronal planes. The mean for the z coordinates (i.e. superior-inferior) was 15 ± 5 and those for the y (i.e. anterior to posterior) coordinates were $y = -7 \pm 3$, $y = 0 \pm 1$, $y = 6 \pm 1$), and $y = 15 \pm 2$, $y = 27 \pm 3$, and $y = 41 \pm 3$.

We used an additional method to display the OFC peaks. A surface-rendering was made from averaged

Table 2A. Insula and opercular peaks and conditions (y < 18).

	x	y	z	Group	Condition	Area
1	36	−11	15	Petrides	Water—tongue movement	DI/PO
2	42	−8	18	Zald	Water—eyes closed resting	PO
3	−39	−8	16	Zald	Water—eyes closed resting	PO
4	33	−6	11	Zald	Water—eyes closed resting	DI/FO
5	−37	−4	4	Zald	Water—odor	I
6	38	−4	6	Petrides	Sucrose—tongue movement	I
7	−36	−2	−3	Petrides	Sucrose—tongue movement	VI
8	38	−1	−6	Petrides	Water—tongue movement	VI
9	44	1	20	Small	All tastes—citric acid	FO
10	33	1	−2	Zald	Salt—mechanical stimulation of right tongue	VI
11	40	5	17	Small	All tastes—water	FO
12	36	5	−8	Petrides	Sucrose—tongue movement	VI
13	−46	6	12	Kinomura	Saline—water	FO
14	35	6	12	Zald	Aversive saline—water	DI/FO
15	40	8	0	Small	All tastes—citric acid	VI
16	−35	8	5	Small	All tastes—all tastes and smells	I
17	35	12	11	Zald	Salt—mechanical stimulation of right tongue	FO
18	30	14	16	Zald	Aversive quinine HCl—water	DI/FO
19	33	14	−7	Zald	Aversive saline—water	VI
20*	−28	14	−14	Zald	Water—eyes closed resting	I/OFC agranular
21	35	15	0	Small	All tastes—all tastes and smells	I
22	28	15	9	Petrides	Sucrose—water	DI/FO
23	−30	18	16	Zald	Aversive quinine HCL—water	DI/FO

*This peak is displayed in the horizontal section due to its inferior location. I, insula; DI, dorsal insula; VI, ventral insula; PO, parietal operculum; FO, frontal operculum

Table 2B. Orbitofrontal peaks and conditions (y > 18)

	x	y	z	Group	Condition	Area
24*	28	23	−18	Zald	Salt−mechanical stimulation of left tongue	CLOF
25*	34	24	−17	Small	All tastes−all tastes and smells	CLOF
26	25	24	−23	Small	Citric acid−water	Area 13
27	26	28	−16	Zald	Aversive quinine HCl−water	Area 13
28	−26	29	−18	Small	Citric acid−water	Area 13
29	−17	30	−22	Zald	Salt−mechanical stimulation of right tongue	Area 13
30	−21	36	−12	Small	All tastes−citric acid	Area 11
31	9	37	−26	Small	All tastes−water	Area 14
32	17	37	−20	Small	All tastes−citric acid	Area 11
33	−21	41	−7	Zald	Aversive saline−chocolate	Area 11
34	−44	39	−9	Zald	Salt−mechanical stimulation of left tongue	Area 47
35	−17	41	−17	Small	All tastes−citric acid	Area 11
36	−24	41	−7	Zald	Aversive saline−water	Area 11
37	21	41	−14	Zald	Salt−mechanical stimulation of left tongue	Area 11
38	−17	42	−12	Small	All tastes−water	Area 11
39	−15	44	−11	Zald	Lemon juice−water	Area 11
40	21	49	−5	Small	All tastes−water	Area 11

*These two peaks fall in the region homologous to the area identified as secondary gustatory area in the non-human primate. CLOF, caudolateral orbitofrontal cortex.

data composed of 27 MRI scans of a single subject's brain that had been placed into standardized proportional Talairach stereotaxic space. The anterior temporal lobe was removed from the surface rendering by means of a segmentation technique. Segmentation began at the point where the temporal lobe begins to separate from the insula and the OFC (y = 9 in the left and y = 8 in the right hemisphere). Thus, this procedure exposed the buried OFC surface, where the secondary gustatory cortex is postulated to be located [3,5]. Peaks were then projected onto the surface at their x (media to lateral) and y (anterior to posterior) stereotaxic coordinates (Fig. 3).

Results

Insula and operculum: A total of 22 peaks were located within the insula and frontal and parietal opercular region (Fig. 1A,B; Fig. 2A–D). These peaks were widely distributed both in the anterior to posterior (y) and inferior to superior (z) dimensions, reaching a maximum posterior value of y = −11, anterior value of y = 18, superior value of z = 20, and inferior value of z = −7. Of the 22 peaks, 16 fell in the right and six in the left hemisphere. A sign test showed this asymmetrical distribution to be significant ($p = 0.026$). Moreover, except for the peak reported by Kinomura *et al.* [19] (no. 13 in

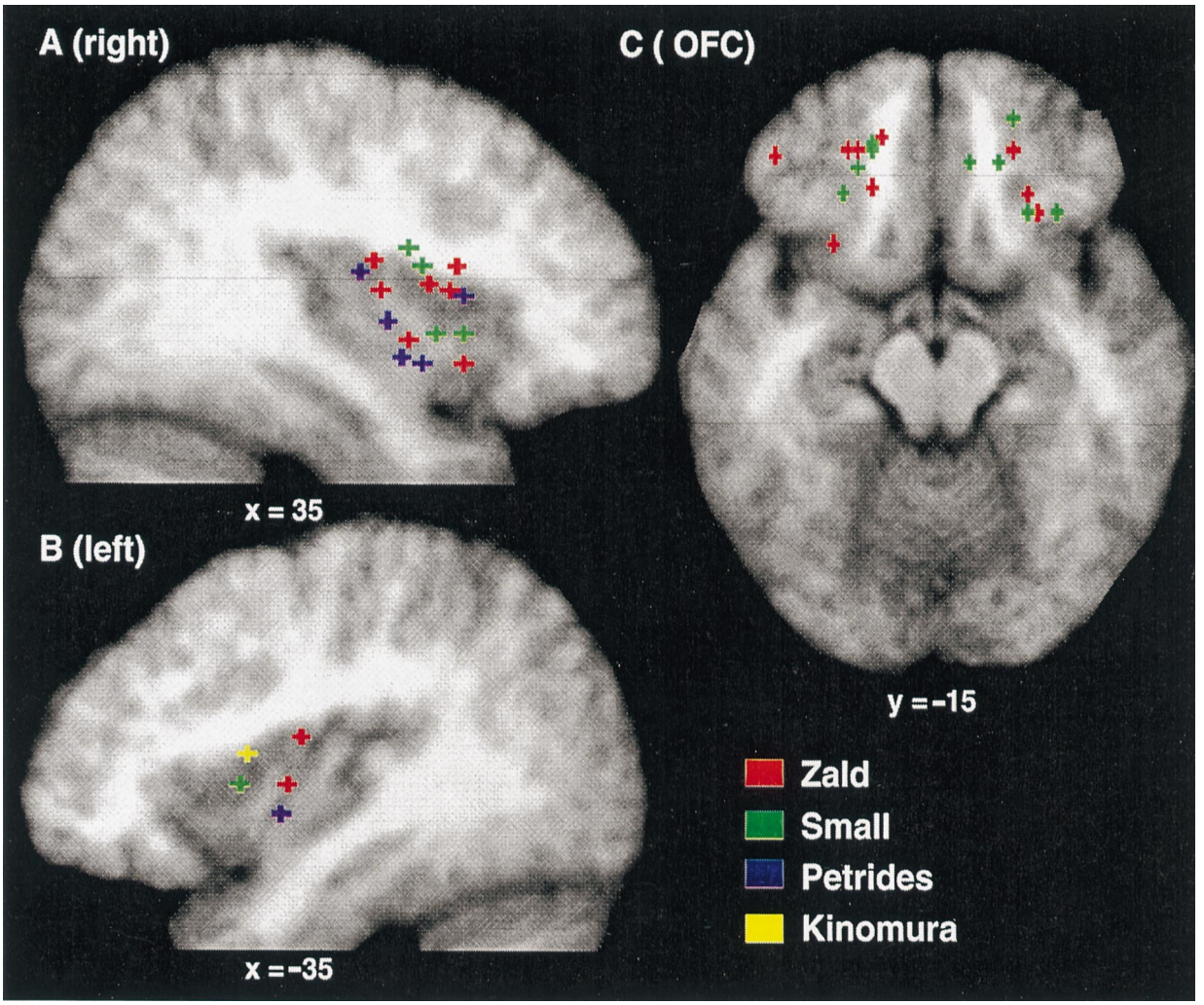

FIG. 1. (**A**) Right hemisphere insula and opercular peaks shown in sagittal section. (**B**) Left hemisphere insula and opercular peaks shown in sagittal section. (**C**) Orbitofrontal cortex peaks shown in horizontal section. Note that only two groups reported activity in this region (Zald *et al.* in red and Small *et al.* in green).

Fig. 2C), all left hemisphere foci resulted from subtractions that also yielded a corresponding homologous right hemisphere focus of a greater t-value.

Within the dorsal insula and the immediately adjacent frontal opercular cortex, the peaks clustered around a region that has recently been identified on the basis of comparative cytoarchitectonic analysis to correspond to the gustatory region in the monkey brain [24]. There were two additional clusters of peaks: one was situated in the more ventral part of insular cortex and the other, more caudally, at the junction of the parietal and frontal operculum.

Orbitofrontal cortex: A total of 18 peaks were located within the OFC (Fig. 1C; Fig. 2E,F; Fig 3A). Nine peaks fell in the left hemisphere and 10 fell in the right. To describe orbitofrontal cortical areas we use the terminology proposed by Petrides and Pandya [24], which was based on a study of comparative cytoarchitecture of the human and monkey brain. According to this terminology, the OFC peaks were distributed in areas 11, 13 and 14 and a caudolateral region of the OFC. This caudolateral region, which lies in a dysgranular part of the caudal orbital frontal cortex may correspond to a similar region that has been described as the secondary gustatory area on the basis of recording work in non-human primates [3,5]. In the monkey, this dysgranular region lies lateral to the most caudal part of the OFC, immediately anterior to the agranular insula. Thus, this region is the transition between the ventral agranular insular cortex and the caudal OFC at its lateral point. In an attempt to clarify the exact location of this area in the human brain, we compared non-human anatomical characteristics used to

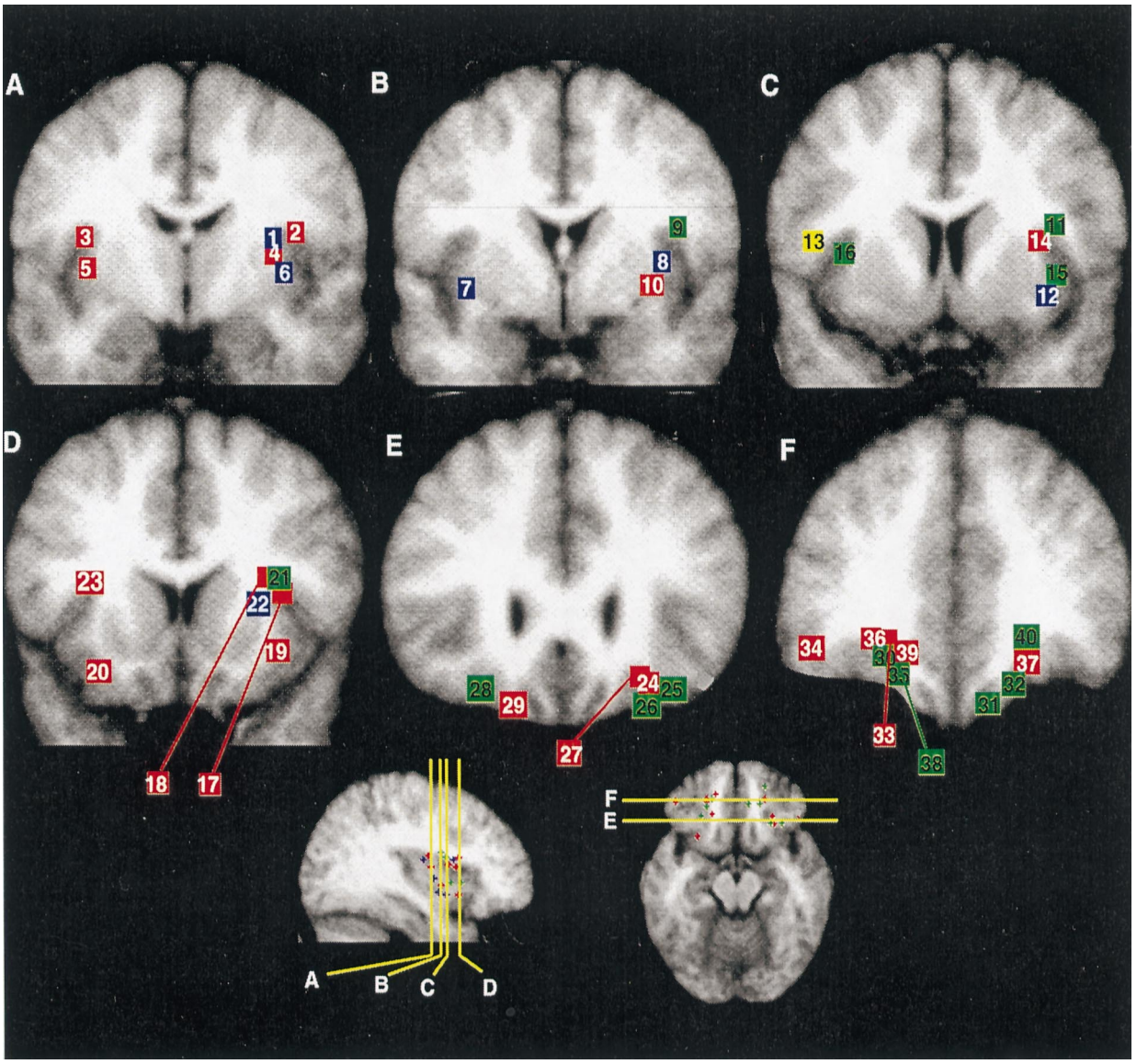

FIG. 2. Coronal sections. From posterior to anterior: (**A**) y = −7. (**B**) y = 0. (**C**) y = 6. (**D**) y = 14. (**E**) y = 27. (**F**) y = 41. Colours correspond to the legend in Fig. 1. Numbers represent those listed in Table 2, indicating subtraction from which the peak was generated. All peaks are displayed within these 6 coronal sections.

describe the secondary gustatory area by Rolls and colleagues [3,5] with the same averaged high resolution MRI that was used to create the surface rendering (see Fig. 3B). The transition zone at the most caudal part of the OFC and the ventral agranular insular region is indicated by the white arrow in Fig. 3. It extends caudally to a y value of approximately 13. Rostrally, this area extends to a y value of approximately 25. Interestingly, only 2 peaks (nos 24 and 25) were located within this region in the present analysis (Fig. 3A coronal section). The rest of the peaks observed in the OFC were localized to more anterior and medial regions.

Coronal sections: In the coronal sections the numbers correspond to those in Table 1 that identify the subtractions from which the peaks were generated (Fig. 2). This display clarifies the location of both the insular and the opercular peaks. In addition, the distinction between the dorsal and the ventral insular clusters can be appreciated. No single subtraction yielded peaks in all areas, although some produced peaks in several areas (e.g. subtractions 9 and 15). The position of the OFC peaks can be seen in the two most rostral sections (Fig. 2E,F).

Discussion

Compilation of PET data included in this analysis resulted in a wide distribution of peaks within the insula and parietal and frontal opercula. The specific

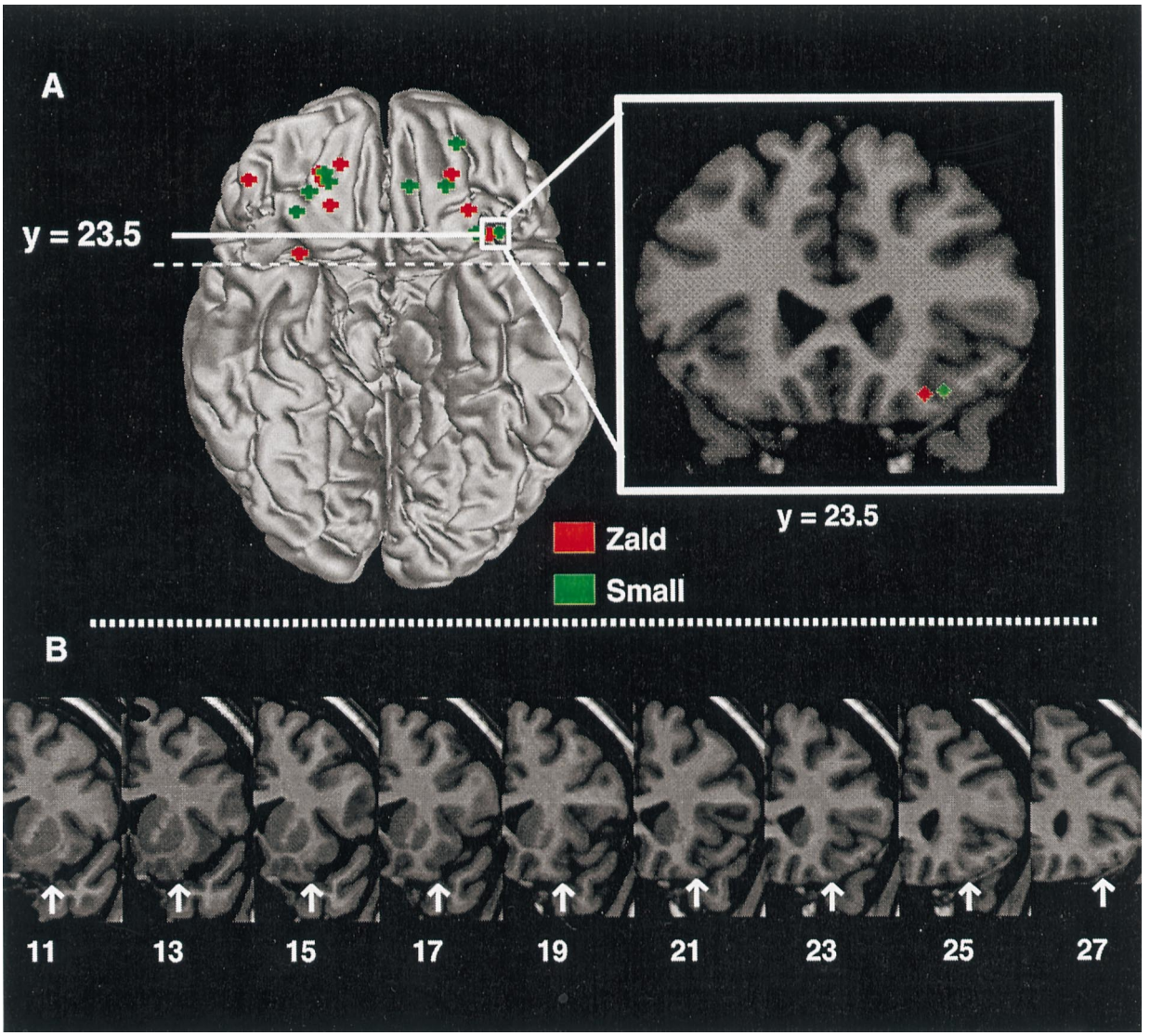

FIG. 3. (**A**) Peaks projected onto a surface rendering with anterior temporal lobes removed (see text for details). The white dotted line indicates the level to which the temporal lobes were removed. The two peaks in the small white box correspond to subtractions 24 and 25 in Table 2. A coronal section of their precise location demonstrates that they fall within the lower left bank of a fissure. As illustrated in Fig. 3B, this cortical region is probably the human equivalent of the caudolateral orbitofrontal cortex, described as the secondary gustatory area by Rolls and colleagues [3,5] (see Fig. 3B). The solid white line indicates the level from which the coronal section is taken (y = 23.5). (**B**) Based on anatomical descriptions in non-human primates, the proposed secondary gustatory area is located in dysgranular orbitofrontal cortex that is directly continuous with the agranular insular cortex [3,5]. These coronal sections, taken from an averaged high resolution MRI (see text), illustrate the transition from agranular insular cortex (at the level where temporal, insular and orbitofrontal areas are continuous) to the dysgranular cortex in the caudolateral orbitofrontal region. The numbers represent the y value at which each section is taken. The white arrows point to agranular cortex in sections 11–17, dysgranular cortex in sections 19–25, and the disappearance of this cortical region in section 27. We propose that the cortical area indicated by the arrows in sections 19–25 represents an analogous region to the secondary gustatory area described in monkeys.

regions of distribution (dorsal and ventral insula, frontal and parietal operculum) correspond to the three gustatory regions identifed in non-human animal studies [1,2,4,6,7] These data are also consistent with the results of clinical studies in humans [8–14] and an fMRI study with healthy human volunteers [23]. In monkeys, a region in the dorsal and rostral part of the insula, as well as the immediately adjacent frontal opercular cortex, has been described as the primary gustatory cortex on the basis of inputs from the gustatory region of the thalamus [4], single-cell recording studies [1,2] and cytoarchitectonic analysis [25]. A cytoarchitectonically homologous region has recently been identified in the human brain [24]. In the present analysis a clear cluster of peaks was located in this very region (nos 9, 11, 13, 14, 16–18, 21–23), providing strong evidence that it plays a functionally homologous role in monkeys and humans. However, there were also two other clusters of peaks, one in the ventral insula (nos 5–8, 10, 12, 15, 19) and the other at the junction of the parietal and frontal opercular cortex (nos 1–3). These latter regions have been implicated in gustatory processing in early clinical literature, as

well as in some non-human primate studies, although they have largely been ignored in recent discussion of gustatory processing. For instance, Penfield and Jasper reported eliciting taste sensations upon electrical stimulation of the ventral insula during surgery for intractable epilepsy [12]. More recently, Small *et al.* [16] reported an elevated detection threshold in a patient with an anterior temporal lobe removal that infringed upon the ventral insula. This patient's detection threshold was 5 s.d. above the mean of a group of patients with removal limited to the right anterior temporal lobe. With regard to the parietal opercular cortex, Bornstein [9,10] described deficits in gustatory processing following lesions to this area. Ogawa [7] concluded that the ventral insula and parietal opercular cortex represent supplementary as opposed to primary taste regions, since they do not receive direct projections from the gustatory thalamic nucleus. Taken together, these findings support the notion of multiple gustatory regions within the insula/opercular cortex.

This wide distribution of peaks is interesting in light of the recent demonstration of multiple somatosensory areas (including representations of the orofacial musculature) in the insular and opercular cortex [26,27]. Thus, the present analysis suggests that these multiple orofacial somatosensory areas may participate in some aspects of gustatory processing, in addition to the primary gustatory area as demonstrated in the monkey and the human brain. The proximal representation of gustatory and orofacial somatosensory modalities poses potential difficulties in interpreting peaks resulting from experiments using gustatory stimulation. It is possible that some cortical regions may be involved in both somatosensory and gustatory functions (although at the neuronal level the computations may be distinct), and therefore activity induced by gustatory stimuli may be in part obscured by the somatosensory components of the control condition when traditional subtraction paradigms are employed.

Similar issues arise in considering the frequent use of water as a control stimulus. As can be seen from Table 2 and Figures 1 and 2, water activates many of the same areas as taste stimuli (peaks 1–5, 8, 20). However, peaks resulting from comparison of water stimulation from a baseline condition tended to fall slightly more caudal than peaks resulting from stimulation with an actual taste. This was true regardless of whether a baseline controlling for somatosensory stimulation was employed. The caudal location of these peaks relative to the others may suggest a separate representation for the taste of water. The proximal location of the gustatory areas with orofacial sensory and motor representations and the ability of water stimulation to result in insular/operuclar activity, may substantially influence the localization of peaks within this region. These factors may have contributed to the variability in the location of the activity peaks observed in the studies reviewed here.

A total of 19 peaks fell in the OFC. It is interesting that only two laboratories observed OFC peaks, and that of the peaks they observed, only two fell in the area that is likely to be homologous to the secondary gustatory area identified in monkeys (Fig. 3). One interpretation of this result might be that the secondary taste area may be located more anteriorly in humans than in non-human primates. However most of the peaks observed were located in area 11 and area 13. These OFC areas have reciprocal connections with cortical gustatory areas [28], but are also connected to ventral lateral prefrontal areas [28]. We therefore favor the interpretation that activity in areas 11 and 13 is related to cognitive or motivational factors. For example, Small *et al*. observed OFC activity when they required subjects to discriminate the presence of a tastant from water, whereas Petrides *et al.* used a passive tasting paradigm that did not require a discrimination and did not see OFC activity. This difference in results caused by the different experimental paradigms is all the more striking considering that both of these studies were performed with the same PET scanner and followed the same methods for analysing the data. Unfortunately there is a dearth of clinical literature on the effects of OFC damage on taste processing in humans. Rolls and colleagues have emphasized the importance of the monkey OFC taste area in the motivational encoding of gustatory stimuli [29]. It thus remains to be seen whether the gustatory processing in this more anterior medial OFC region plays a similar role in the human.

Of the 22 insula/opercular peaks, a significant number fell within the right hemisphere (16 out of 22; $p = 0.026$). Moreover, the only two peaks that originated from the proposed human secondary gustatory area (caudolateral OFC) were in the right hemisphere. This is consistent with other reports in the literature, suggesting a functional specialization for the right hemisphere in both gustation [16] and olfaction [30]. Interestingly, the anatomical region that may represent the human secondary gustatory area (Fig. 3) also appears to be more prominent on the right.

There is no mention in the non-human primate literature of asymmetrical gustatory representation. One possible reason for functional asymmetry of taste favoring the right hemisphere in the human brain could be the specialization of the left hemisphere for language. Pardo *et al.* [31] performed a PET study in which they independently stimulated

the left and then the right half of the tongue with a wooden stir stick (tactile stimulation). They did not observe an effect for laterality. Instead they report bilateral activation in somatosensory tongue regions after stimulation of the left tongue. These authors interpreted this result as due to the tongue's involvement in language. It is also well established that the left frontal operculum represents Broca's speech production area, which is not present in the right hemisphere of normal human brains. Given the proximity of the primary gustatory cortex to both the frontal opercular speech area and to oral cavity somatosensory representations, it is possible that with the development of language these regions in the left hemisphere became more important for language at the expense of more basic gustatory processing. As a consequence, these regions in the right hemisphere may have become dominant or predominant for gustatory processing. An alternative explanation is that there is an effect of task such that the tasks used in the PET studies considered here somehow preferentially activate the right hemisphere.

Conclusion

The results of this study suggest the presence of multiple gustatory areas within the insula/opercular cortical region of the human brain. The exact location of activity within this region appears to be inconsistent across studies. However, when all the data are considered together in light of the gustatory literature, it seems clear that the observed peaks represent clusters in multiple gustatory areas. With regard to the OFC, some studies have observed peaks during gustatory stimulation and others have not. We suggest that OFC activity may depend upon cognitive or motivational features of individual gustatory tasks. Finally, in the proposed taste areas, the preponderance of right hemisphere peaks may be related to the specialization of the human left hemisphere for language, resulting in a cerebral dominance or predominance for taste in the right hemisphere.

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