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Hemisperic Dominance of Cortical Activity Evoked by Focal Electrogustatory Stimuli

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Abstract

Functional magnetic resonance imaging was used to observe cortical hemodynamic responses to electric taste stimuli applied separately to the right and left sides of the tongue tip. In 11 right-handed normal adults activation occurred primarily in the insular cortex, superior temporal lobe, inferior frontal lobe, including premotor regions, and in inferior parts of the postcentral gyrus. Unexpectedly, the location and laterality of activation were largely identical regardless of the side of the tongue stimulated. Activation in the superior insula, the presumed location of primary gustatory cortex, was predominantly, but not exclusively, in the right hemisphere, whereas central (more inferior) insular activations were more evenly bilateral. Right hemispheric dominance of activation also occurred in premotor regions (Brodmann areas 6 and 44), whereas left hemispheric dominance occurred only in the superior temporal cortex (Brodmann areas 22/42). The electric taste-evoked hemodynamic response pattern was more consistent with activation of the gustatory system than activation of somatosensory systems. The results suggest that the sites for cortical processing of electric taste information are dependent on hemispheric specialization.

Introduction

Although the human primary gustatory cortex (PGC) is thought to be located in the dorsal insular cortex and adjacent frontal/parietal operculum, its precise location is not certain (Norgren, 1990). The PGC in macaques, defined as the taste-responsive regions receiving direct projections from the gustatory thalamus, is located in the above cortical regions and to a lesser extent in the precentral gyrus (Pritchard *et al.*, 1986; Ogawa, 1994). However, in macaques fewer than 10% of neurons in the PGC respond to taste stimulation and similar percentages of neurons in insular regions adjacent to the PGC (probable secondary cortical areas) respond to taste stimuli (Scott *et al.*, 1991). If the PGC is similarly organized in humans, it is not surprising that it has proven difficult to locate considering that the precise projections of the gustatory thalamus in humans are unknown. In humans modern imaging techniques have localized gustatory responses to the anterior insula/frontal operculum (Small *et al.*, 1999), as in macaques, or shifted posteriorly within the insula to lie close to the somatosensory representation of the tongue in parietal cortex (Kobayakawa *et al.*, 1999). Additional imaging studies are needed to clarify the localization of the PGC in humans.

It is not clear whether projections to the human PGC are all ipsilateral to the side of the tongue stimulated. Most anatomical evidence in vertebrates, including non-human primates, suggests ascending gustatory cortical inputs are primarily ipsilateral (Norgren, 1990), but evidence for humans is conflicting (Shikama *et al.*, 1996; Onoda and Ikeda, 1999). A central separation of right versus left tongue processing could account for the ability of humans to determine the side of stimulation based on taste information alone (Shikata *et al.*, 2000). Previous imaging studies have failed to address this issue, as gustatory stimuli were applied bilaterally. It has also been suggested that higher order cortical gustatory processing is associated with hemispheric specialization independent of side of stimulation (Small *et al.*, 1997). Imaging studies with unilateral tongue stimulation are needed to address these significant taste processing issues.

In the present study functional magnetic resonance imaging (fMRI) was used because of its non-invasiveness, high spatial resolution and the ability to evaluate the response to multiple stimuli during each experimental session. Blood oxygenation level-dependent (BOLD) fMRI has proved useful for the identification of activated areas in the human brain (Moonen and Bandettini, 1999). The present study addresses the question of the laterality of gustatory processing by applying focal stimulation of the left versus the right anterior tongue. We chose electric taste stimuli to facilitate control of stimulus location and timing. Weak anodal currents (≤50 μA) predominantly stimulate the gustatory system, whereas higher currents increasingly stimulate somatosensory systems (Frank and Smith, 1991).

Our results suggest that cortical gustatory processing shows hemispheric specialization independent of the side of stimulation.

Materials and methods

Subjects

Six female and five male right-handed volunteers ranging in age from 22 to 45 years and with no history of taste dysfunction were recruited from graduate students and staff at Yale University and the University of Connecticut Health Center. Handedness was assessed with the Edinburgh scale; mean 82.4 ± 4.5 (Oldfield, 1971). All procedures were approved by the Institutional Review boards at both institutions.

Stimuli

For electric taste stimulation in the fMRI scanner it was important to use metals that were non-magnetic. The probes were sintered Ag/AgCl half cells connected by twisted-pair copper conducting wires to the electrogustometer (Rion TR-06) in an adjacent room. Two 8 mm diameter anodes were placed on the anterior tongue tip ~1.0 cm apart straddling the midline; the 8 mm cathode was taped under the chin. The subjects used one hand to hold the anodes on the tongue surface. The subjects were free to swallow and reposition the tongue electrodes between runs of stimuli, but during a run the electrodes were not moved. An event-related protocol was used for the stimulations. The stimuli were 1 s square pulses of 25–50 μA generated by the electrogustometer. Stimulus strength (above 25 μA) was chosen for each subject to be consistently detectable, yet at least 2 dB (20%) below that causing mild tingling. A computer (Apple) controlled software program (Psyscope) and switching circuit controlled stimulus timing and side of stimulation. Single pulses were presented to the left or right sides in a pseudo-random pattern separated by 15–24 s variable intervals to make it difficult for subjects to anticipate stimulus location or timing. To avoid adaptation, the stimuli were presented in eight runs of ~4 min, separated by 2–3 min rest periods. In total, the stimuli were repeated 48 times for each side of the tongue. The subjects wore earplugs, but were allowed to open their eyes and the lights were left on. The subjects were instructed to try to direct attention to the stimuli.

Imaging

Imaging was performed with a 1.5 T scanner (General Electric Signa scanner equipped with Advanced NMR Systems echo-planar imaging hardware). For anatomical imaging, a T1-weighted mid-sagittal image was used to place 10 axial slice planes (7 mm thick, 0.5–2.5 mm skip distance) according to the Talairach coordinate system (Talairach and Tournoux, 1988). The 10 planes were centered at *z* levels from –16 to +56 mm. For functional imaging, fast T2*-weighted echo-planar gradient sequences (1.65 s repetition time for 10 slices) were used giving 3.1 × 3.1 mm in-plane resolution. All acquired images were then motion corrected using a modification of SPM96 (Friston *et al.*, 1996), which realigned the images as well as removed any signal variations correlated with the calculated motion.

Initial analysis

Activated cortical areas were identified in each individual using a cross-correlation technique (Leung *et al.*, 2000; Stevens *et al.*, 2000). This method of activation detection inherently removes any activation resulting from somatosensory stimulation due to the electrodes on the tongue or due to actions such as holding the stimulator, as these are constant throughout the experiment. Each voxel's signal time course for a run (4 min) was cross-correlated with a 4 min template function based on the timing of the stimuli and on model hemodynamic responses for a single stimulus derived from auditory sensory cortex (ASC) (Robson *et al.*, 1998) or that used in the SPM99 program (http://www.fil.ion.bpmf.ac.uk/spm/) (Figure 1). Specifically, each 4 min template was created by convolution of a vector containing delta functions at the time of each stimulus with a model of the ASC (or SPM99) hemodynamic response function (HRF). Separate templates were generated for right and left tongue stimuli or for all stimuli. For example, for right tongue stimuli a template would include the 15 s periods following each of the six stimuli, as well as periods with no stimuli. The results of the eight runs were averaged as follows: Pearson's correlation coefficients were normalized to *z* scores (Fisher's *z* transformation), averaged across runs and converted back to correlation coefficients. The template

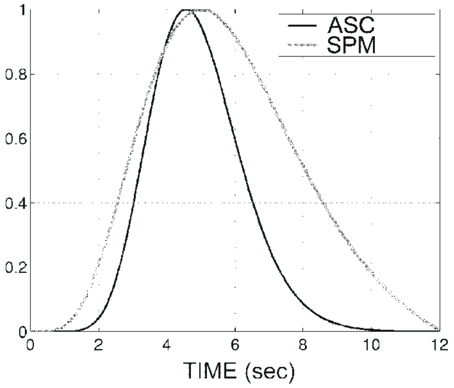

Figure 1 Plot of the HRFs that were used in the present study for 1 s stimuli that began at time 0. Hemodynamic response magnitude (relative) is plotted versus time following the stimulus. The SPM HRF (derived from the response of visual cortex) and the auditory cortex derived HRF (ASC) are shown (see Materials and methods).

(based on ASC) was also shifted in time by 1.65 s intervals so as to compute maps (see below) of delayed activation (delays of 0, 1.65 and 3.3 s were generated). A criterion of Pearson's $r > +0.5$ was used to define an activated voxel; negatively correlated voxels were not analyzed. In the figures R and L tongue stimulation refers to the combination of the data obtained from stimulating the right and left sides separately.

Group-averaged analysis

To identify common areas of activation across different individuals in a common stereotaxic space, group activation maps were generated by piece-wise linear warping transformation of each subject's T1-weighted anatomical images and corresponding functional maps into Talairach space. To identify activated voxels, correlation coefficients were normalized to z scores (Fisher's z transformation) and across-subject average z scores for each voxel were computed and compared using t-tests to a 'background' generated by a randomization procedure (uncorrected $P < 0.01$). The locations of centers of clusters of significantly activated voxels in Talairach space were computed. Identification of probable anatomical locations including Brodmann areas (BA) were determined by consulting the Talairach and Tournoux atlas (Talairach and Tournoux, 1988), the online atlas based on 305 normal brains at McGill University (http://www.bic.mni.mcgill.ca/) and the primary literature. Sites of activation are reported in Talairach coordinates. A list of abbreviations is provided in the caption to Figure 2 for the anatomical names listed in Table 1.

Comparison between model HRFs

The use of templates based on the ASC HRF at a delay of 0 versus 1.65 s resulted in slightly different amounts and locations of group-averaged activation: notably, right tongue stimulation activated more voxels at a delay of 0, whereas at a delay of 1.65 s there was no significant difference between stimulating the left and right tongue (see Results, Region of interest analysis). Thus, in the group-averaged images (Figures 5, 6) voxels activated based on the HRFs at delays of 0 and 1.65 s are combined to maximize the detection of active voxels. There was little group-averaged activation for templates based on the ASC HRF at a delay of 3.3 s. The SPM HRF generated similar but not identical patterns to the combined 0 and 1.65 s delay ASC HRF. This similarity is not surprising since the SPM HRF is broader than ASC at a delay of 0 (Figure 1). The largest difference between the results generated by the two HRFs was for the section centered at $z = 8$ mm (see Results).

Region of interest analysis

For statistical comparison of left versus right tongue activation of cortical regions in the left versus right hemisphere, regions of interest (ROIs) (Figure 2) were defined to include the activated areas in the group-averaged maps and to conform to general anatomical boundaries. The number of activated (correlation with the template based on ASC HRF, delay 0 or 1, $r > 0.5$) voxels in each ROI were counted in each individual and expressed as a ratio relative to the numbers of voxels in each ROI. For statistical analysis the ratios were normalized with an arcsin transformation, followed by repeated measures ANOVA (Statistica)

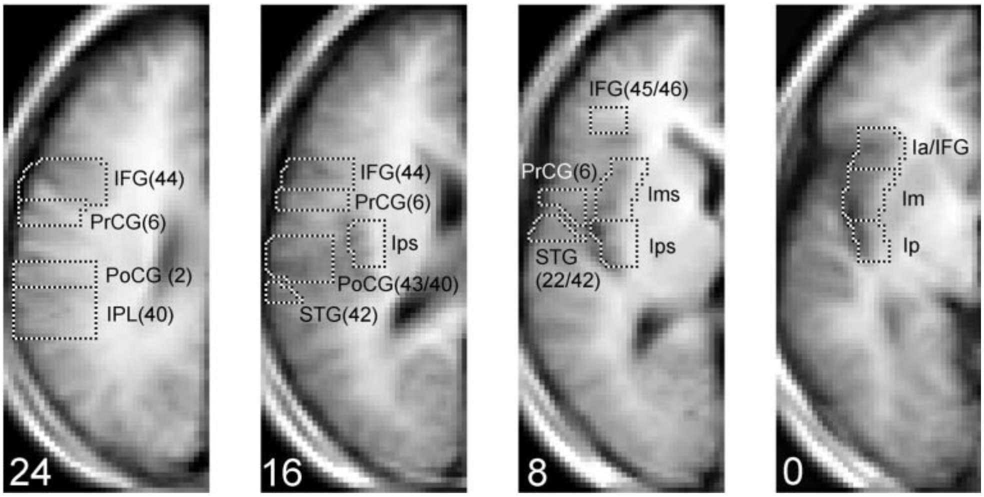

Figure 2 The outlines of ROIs that were used for statistical analysis are superimposed on the composite anatomical MRI scans of 11 subjects. The abbreviation of the anatomical region is followed by the probable Brodmann area(s) in parentheses. Frontal cortex: IFG, inferior frontal gyrus; MFG, middle frontal gyrus; PrCG, precentral gyrus. Insular cortex: Ia, anterior insula, superior and central parts; Im, mid insula, central part; Imi, mid insula, inferior part; Ims, mid insula, superior part; Ip, posterior insula, central part; Ips, posterior insula, superior part. Parietal cortex: IPL, inferior parietal lobule; PoCG, postcentral gyrus. Temporal cortex: STG, superior temporal gyrus. Occipital cortex: Occipital, occipital lobe. Non-cortical areas: Int Capsule, internal capsule; N Accumbens, nucleus accumbens; VL, ventrolateral thalamic nucleus; VPL, ventral posterolateral thalamic nucleus; VPM, ventral posteromedial thalamic nucleus. The numbers at the lower left of each section refer to the values (in mm) for the center of each section along the superior/inferior (z) axis of the brain according to the Talairach coordinate system.

Table 1 Activated brain regions in group-averaged data

Area ID[1]	Area name (BA)[b]	Talairach coordinates (*z*, *y*) of activation centers (mm)																		
		Left tongue							Right tongue						Left & right tongue					
		Left hemisphere				Right hemisphere			Left hemisphere			Right hemisphere			Left hemisphere			Right hemisphere		
		z	*x*	*y*	(ID)[a]	*x*	*y*	(ID)[a]	*x*	*y*	(ID)[a]	*x*	*y*	(ID)[a]	*x*	*y*	(ID)[a]	*x*	*y*	(ID)[a]
F	MFG(9/46)	24													–31.5	41	(F3)			
F	MFG(46)	24													–33	32.5	(F4)			
F	IFG(44)	24				53.5	12.5	(F1)										39	6	(F5)
F	IFG(44)/PrCG(6)	24										49.5	6	(F2)				53.5	5.5	(F6)
F	PrCG(6)	24																45	1	(F7)
P	IPL(40)	24	–60	–24	(P1)															
P	PoCG(2)/IPL(40)	24				43.5	–22	(P3)	–57	–27	(P6)				–60	–27	(P8)	52	–20	(P9)
P	PoCG(2)/IPL(40)	24				54.5	–20	(P4)												
P	PoCG(2)/IPL(40)	24																		
P	PoCG(2)	24										50	–19	(P7)						
P	Precuneus(31)	24	–11	–64	(P2)	13.5	–59	(P5)										6	–64	(P10)
O	Occipital(17/18)	24	–17	–64	(O1)															
F	MFG(46/10)	16				32.5	47.5	(F8)												
F	MFG(46)	16				39	43	(F9)												
F	MFG(10)	16										32.5	51	(F11)						
F	IFG(44)/PrCG(6)	16				50	4.5	(F10)										49.5	3.5	(F13)
F	PrCG(6)	16										50	2.5	(F12)						
I	Ips	16	–35.5	–16	(I1)	30	–7	(I2)												
P	PoCG(43)	16													–59.5	–10	(P14)	59.5	–10.5	(P16)
P	PoCG(43/40)	16				48.5	–14.5	(P11)												
P	PoCG(40)	16										52	–17.5	(P13)				52.5	–17	(P17)
P	PoCG(40)/STG(42)	16																–61	–20.5	(P15)
P	PoCG(43/40)/STG (42)	16							–58	–18.5	(P12)									
O	Occipital(17/18)	16	–13	–65.5	(O2)	7	–72.5	(O4)				15.5	–68.5	(O5)	–9.5	–71.5	(O6)	7.5	–71.5	(O8)
O	Occipital(17/18)	16	–8.5	–73.5	(O3)										–16	–79.50	(O7)			
F	IFG(46)	80							–37.5	36	(F17)				–40	37	(F21)			
F	IFG(45/46)	8				35.5	30	(F14)				36.5	30.5	(F18)				38.5	32.5	(F22)
F	IFG(45)/Ias	8				33	24.5	(F15)												
F	PrCG(44)	8										40	13	(F19)						
F	PrCG(6)	8				52	13	(F16)				48.5	3.5	(F20)						
I	Ims	8				37.5	8	(I3)				38.5	2.5	(I5)				35.5	9.5	(I6)
I	Ips	8				33	–10	(I4)										32.5	–7	(I7)
T	STG(22/42)/PrCG(6)	8	–52.5	–1.5	(T1)				–54.5	–3	(T2)				–53.5	–3	(T4)			
T	STG?	8							–32.5	–28	(T3)				–32.5	–28	(T5)			
O	Occipital(17/18)	8	–8.5	–71.5	(O9)										–6	–65.5	(O10)			
N	Caudate/ Int Capsule	8							–180	9	(N1)									
F	IFG	0							–32.5	37.5	(F23)									
I	Ia/Im/IFG	0				35.5	17.5	(I8)				33	20	(I10)				37.5	17.5	(I15)
I	Im	0							–37.5	5.5	(I9)	37.5	2.5	(I11)	–40	5.5	(I13)	41	2	(I16)
I	Ip	0										35.5	–10.5	(I12)	–40	–7.5	(I14)	35.5	–7.5	(I17)
T	STG(22)	0	–50	–1	(T6)															
T	STG(21/22)	0	–52	–13	(T7)															
O	Occipital(18/19)	0				9.5	–51.5	(O11)												
O	Occipital(18)	0				7.5	–65.5	(O12)												
N	Putamen	0	–20.5	9	(N2)															
N	Putamen/ Int Capsule	0										24.5	–17	(N5)						
N	VL/VPL/VPM	0																13.5	–14.5	(N6)
N	VPL/VPM	0				14.5	–17.5	(N4)												
N	VPL	0																18.5	–17.5	(N7)
N	Cerebellum	0	–1.5	–47.5	(N3)													6	–45.5	(N8)
I	Imi	–8							–35.5	2.5	(I18)									
O	Occipital(19)	–8							–19.5	–63.5	(O13)				–21.5	–53.5	(O14)			

Table 1 Continued

Area ID^1	Area name (BA)^b	Talairach coordinates (z, y) of activation centers (mm)																		
		Left tongue							Right tongue						Left & right tongue					
		Left hemisphere				Right hemisphere			Left hemisphere			Right hemisphere			Left hemisphere			Right hemisphere		
		z	x	y	(ID)^a	x	y	(ID)^a	x	y	(ID)^a	x	y	(ID)^a	x	y	(ID)^a	x	y	(ID)^a
N	Putamen/ N Accumbens	– 8							–15.5	12.5	(N9)									
N	Putamen	– 8										21.5	16	(N10)						
N	Cerebellum	– 8													–4.5	–39	(N11)			
N	Cerebellum	– 8													–15.5	–43.5	(N12)			

[a] See Figure 5 for description of area IDs; (ID) entries refer to labels of activated areas in Figure 5.

[b] For list of anatomical abbreviations see caption to Figure 2; area name describes the entire activated area(s), not just the center of activation; (BA), Brodmann areas.

with tongue side, hemisphere side and region (ROIs) as the repeated measures. For analysis of the combined right and left data activated voxels were identified if $r > 0.5$ for either left or right tongue stimulation. The ANOVAs were done once with the original 13 ROIs and a second time with the ROIs consolidated into eight regions based on commonality of response and region. A priori we expected that for many ROIs the activated hemisphere would depend on the side of stimulation. The level of significance was defined as $P < 0.05$.

Results

All subjects perceived the electric taste stimuli at the currents used, 25–50 μA, and did not report the buzzing or tingling sensations thought to be associated with trigeminal activation (Murphy *et al.*, 1995). Thus, the stimuli likely predominantly activated the gustatory system (see Discussion).

There was considerable individual variation in the number of voxels with a correlation (r) with the template of >+0.5. Activation was seen in many areas of the brain, but most prominently in the insular cortex and adjacent operculi. In individuals with the most activation, stimulation of either side of the tongue resulted in activation of these cortical areas in both hemispheres (Figure 3). Almost all activation was limited to four (centered at z = 0–24 mm) of the 10 horizontal slices examined. In the remaining six slices there was some scattered activation, but the locations of this activity were not consistent across subjects for templates based on different HRFs or for different stimulus paradigms. However, the slice centered at z = –8 mm is shown in Figure 4 and activation data are reported in Table 1, because this slice includes the most inferior part of the insula.

The insula was subdivided in order to relate the observed activation to specific subdivisions. Based on the patterns of activation and on the known cytoarchitectonic organization of the insula (Augustine, 1996) this region was divided into three arbitrary anterior to posterior divisions (anterior, middle and posterior) (Figure 4) and three superior to inferior divisions (superior, central and inferior) (Figure 2). The three superior to inferior divisions were designed to correspond roughly to the granular, dysgranular and agranular cytoarchitectonic divisions (Augustine, 1996), but we know of no studies that have related these divisions to Talairach coordinates. Note that the Talairach planes section the insula at an angle, thus the most superior part of the posterior insula is seen in the section centered at z = 16 mm, whereas the superior part of the anterior pole of the insula is more prominent at z = 8 mm (Figure 4). However, the z = 8 mm plane probably contains superior and central parts of the anterior insula, thus this part of the insula was designated simply anterior insula (Ia).

Group-averaged analysis

Significant group-averaged activation was seen in superior parts of the posterior (Figure 5, I1, I2, I4 and I7), middle (Figure 5, I3, I5 and I6) and anterior (Figure 5, I8, I10 and I15) insula, although the most posterior part of the superior insula showed little activation. The superior insular activation was predominantly in the right hemisphere independent of whether left or right tongue stimulation was delivered. In Figure 5 compare the superior right (I3–I7) and left insular cortical activation in the z = 8 mm slice. Similarly, for the slice centered at z = 0 compare activation in the right (I8, I10 and I15) and left anterior (superior) insula. In the superior insular cortex there appeared to be significant differences between the results of right versus left tongue stimulation. This difference may partially be a result of subtle differences in the time courses of response. In

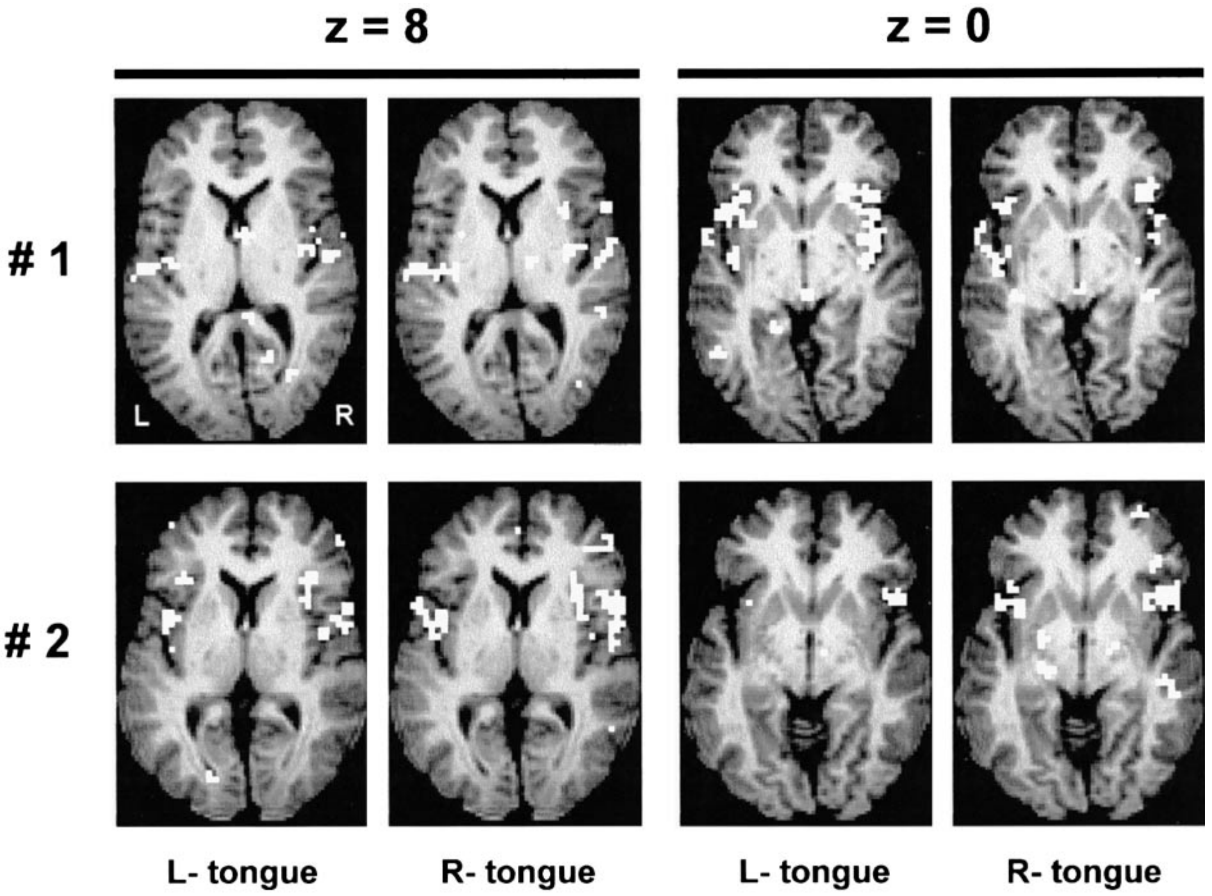

Figure 3 Examples of fMRI activation following electric taste stimuli from two individuals (nos 1 and 2) for two planes of section centered at $z = 8$ and $z = 0$ mm. The white voxels had an average Pearson $r > 0.5$ with the template function (based on the ASC HRF at a delay of 0). The right hemisphere (R) appears on the right in all figures.

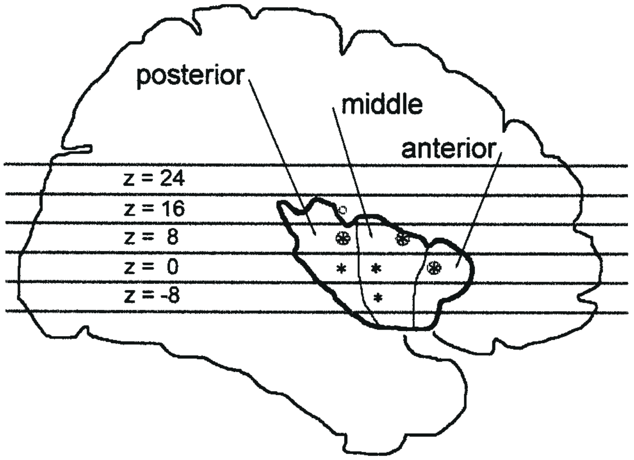

Figure 4 Diagram of a sagittal section through the right insula, to show how the insula was sampled by the slice planes shown in Figure 5 and used for Table 1. The circled asterisks indicate the locations of centers of the group-averaged activation in the right superior insula and plain asterisks in the right central insula resulting from combined left and right tongue stimulation. The small plain circle indicates another center of activity in or near the right superior insula evoked only from left tongue stimulation (Figure 5, I2). Anterior to posterior divisions of the insula used in this study are shown. See Figure 2 for depiction of the superior to inferior divisions used for the ROI analysis.

Figure 6 the group hemodynamic responses based on the ASC and SPM99 HRFs are compared for the $z = 8$ mm plane. Note that at this level the use of templates based on the SPM99 HRF identified three clusters with right side stimulation in right frontal and insular areas hardly detected with the ASC HRF.

In contrast to the right hemisphere dominance seen in the superior and anterior insula, the middle and posterior central insular cortex (Figure 5, I9, I11–I14, I16 and I17) had more bilaterally distributed activation. There was a small amount of activation following right tongue stimulation in the inferior part of the left insula at $z = -8$ mm (Table 1).

Outside the insula apparent right hemispheric specialization occurred in Brodmann areas 44 and 6 in the inferior frontal gyrus (Figure 5, F1, F2, F5, F6, F10, F12 and F13). Small areas of activation in parts of the middle and inferior frontal gyri (Figures 5, 6) were more bilaterally distributed. Activation occurred in inferior parts of the post-central

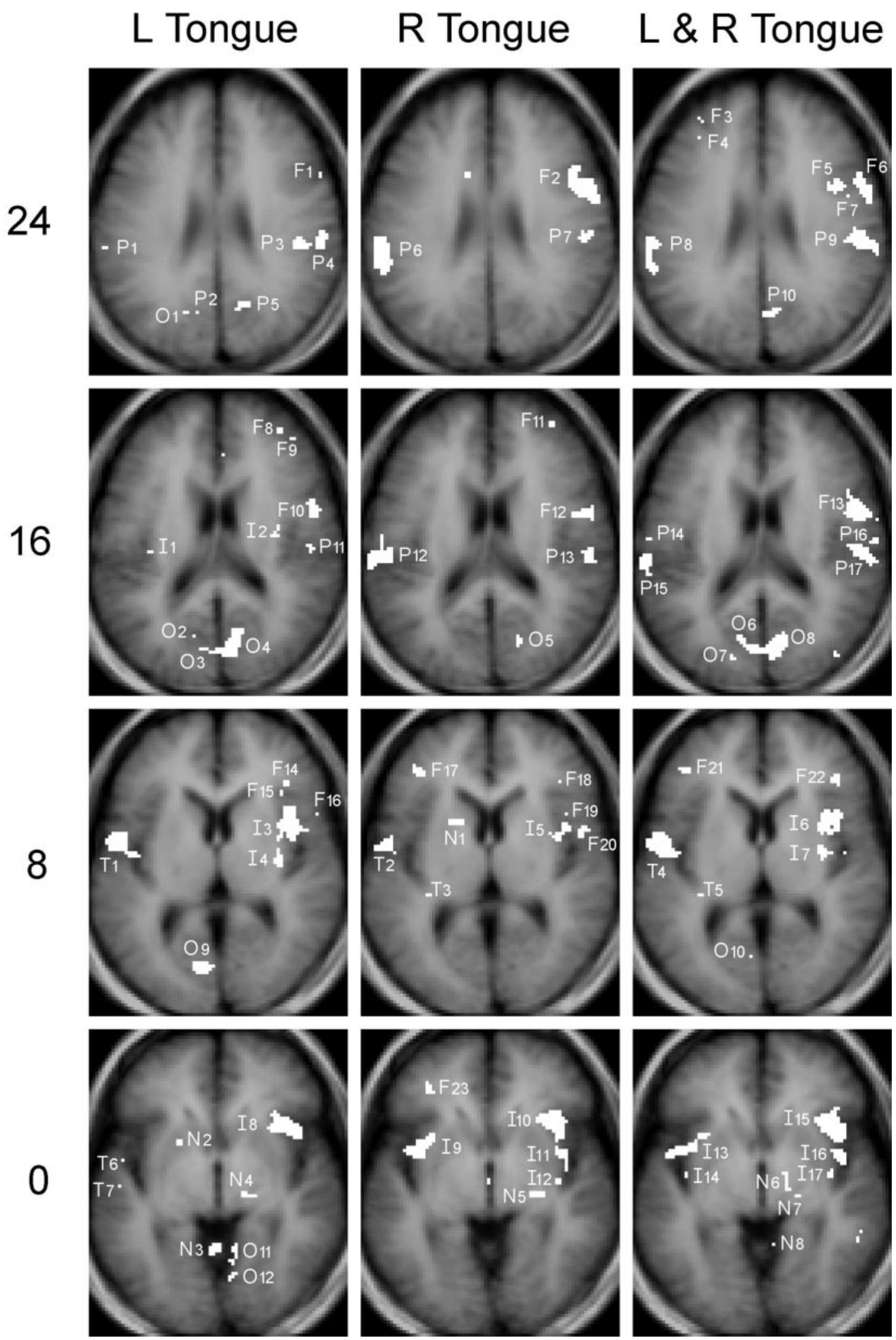

Figure 5 Composite images of the group-averaged hemodynamic responses to electric taste stimuli across 11 subjects. For each section voxels whose HRF showed a significant ($P < 0.01$) correlation across subjects with templates based on the ASC HRF (delay 0 or 1.65 s) are shown in white. The results of left tongue, right tongue and of left and right combined stimulation are shown separately. The labels next to the activated clusters of voxels correspond to entries in Table 1. The letters refer to regions of the brain as follows: F, frontal; I, insular; P, parietal; T, temporal; O, occipital; N, non-cortical. The numbers at left indicate the *z* value (in mm) of the center of each section in the Talairach coordinate system.

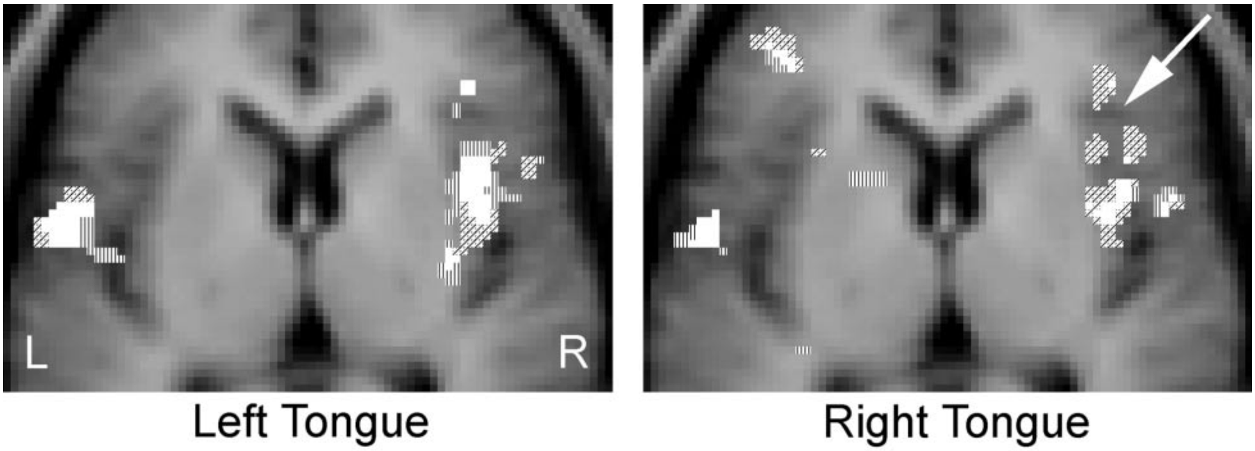

Figure 6 Comparison of the group-averaged hemodynamic responses based on the ASC versus the SPM99 HRFs for part of the $z = 8$ mm plane of section. Voxels whose HRF showed a significant ($P < 0.01$) correlation with templates based on one of the HRFs are marked as follows: vertical lines, correlated with ASC-based template (delay 0 or 1.65 s) alone; diagonal lines, correlated with SPM99-based template alone; white, correlated with both templates. With the SPM HRF for right tongue stimulation there were a few clusters of significant activation in the right anterior insula and frontal cortex (arrow) that were hardly seen for the ASC-based templates.

gyrus, Brodmann areas 2/40 (Figure 5, P3, P4 and P6–P8) and 43/40 (Figure 5, P11–P17). Based on the group-averaged data, left tongue stimulation activated primarily the right postcentral gyrus (Figure 5, P3, P4 and P11), while right tongue stimulation resulted in activation in both hemispheres (P6, P7, P12 and P13). For both right and left tongue stimulation a region of activation overlay both the anterior tip of the superior temporal gyrus and the most inferior remnant of the precentral gyrus (Brodmann area 6) in the left hemisphere only (Figure 5, T1, T2, T4, Figure 6). In individuals activation occurred in either or both these cortical areas. Activation was consistently seen in the visual areas of the occipital cortex (Figure 5, O1–O12) with a small amount of spread into the adjacent, most ventral part of the precuneus (P2, P5 and P10).

Region of interest analysis

In this ROI analysis we present results relevant to three topics. Is one cerebral hemisphere more strongly activated than the other? Is stimulation of one side of the tongue more effective in activating the brain than the other? How well do the ROI and group-averaged analyses relate to one another?

The ROI analysis revealed no relationship between the side of the tongue stimulated and the hemisphere of activation. Specifically, in the statistical analysis interactions between side and hemisphere were not significant for any individual ROI [$F(1,10) = 4.32$, not significant (ns)] except for Brodmann area 40 of the inferior parietal lobule [$F(1,10) = 12.8$, $P < 0.01$]. However, for the latter region further analysis revealed no significant differences between right and left tongue stimulation. For many brain regions, in agreement with the group-averaged analysis, one hemisphere was activated more than the other, independent of the side of stimulation (Figure 7, Table 2). The significant region by brain side interaction in the statistical analysis [$F(12,120) = 2.77$, $P < 0.01$, and $F(7,70) = 2.83$, $P < 0.05$, for consolidated ROIs] justified analysis for individual regions. Notably, in the superior insula (Figure 7) and Brodmann areas 44 and 6 (Table 2) there was significantly more activation in the right than left hemisphere, although there was some activation on the left side. We examined the difference in hemispheric activation by the right versus left tongues in Brodmann area

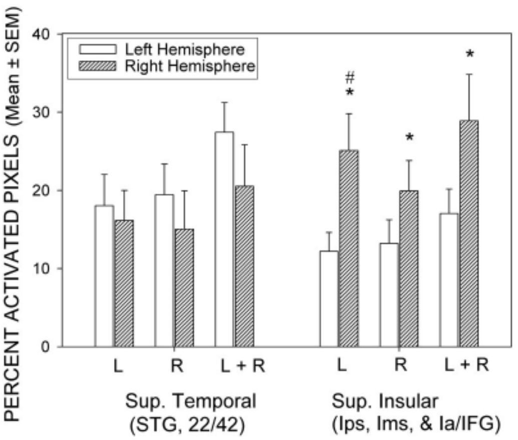

Figure 7 The mean number of activated voxels as a percentage of the number of voxels in each region for two consolidated ROIs shown in Figure 2. (Data for the other six ROIs are provided in Table 2.) For each ROI the results are shown for electrical stimulation of the left and right anterior tongue, as well as for the combined left and right stimulation data sets. In each instance the left hemisphere (white bars) and the right hemisphere (striped bars) are compared. The asterisks here and in Table 2 indicate a significant difference between the right and left hemispheres [$F(1,10) = 5.0–18.86$, $P < 0.05$]. The pound signs indicate a significant difference between right and left tongue stimulation for a single hemisphere [$F(1,10) = 6.23–23.94$, $P < 0.05$].

Table 2 Percent activated voxels (mean ± SEM) for six regions of interest (ROI)

ROI	Left tongue		Right tongue		Right & left tongue	
	Left hemisphere	Right hemisphere	Left hemisphere	Right hemisphere	Left hemisphere	Right hemisphere
IFG(45/46)	7.3 ± 2.4	8.3 ± 3.79	13.0 ± 5.38	10.1 ± 3.5	14.8 ± 5.21	15.8 ± 4.49
IFG(44)	7.9 ± 1.87	15.6 ± 3.7[a]	7.2 ± 2.18	18.4 ± 3.04[a]	8.8 ± 2.38	21.2 ± 4.64[a]
PrCG(6)	8.5 ± 1.86	13.4 ± 3.05	12.1 ± 2.58	19.0 ± 2.6[b]	13.8 ± 2.46	23.8 ± 3.87[a]
PoCG(2)	9.9 ± 3.8	23.5 ± 5.97[a]	18.9 ± 4.88	26.6 ± 3.38	16.9 ± 3.92	31.7 ± 4.5[a]
IPL(40) & PoCG(43/40)	9.8 ± 2.3	13.6 ± 2.81	19.8 ± 3.32[b]	17.7 ± 3.75	19.8 ± 4.09	19.1 ± 3.82
Ip & Im	16.6 ± 5.14	24.0 ± 7.01	21.4 ± 4.75	23.6 ± 6.78	24.6 ± 6.98	32.4 ± 8.02

[a] Significant difference ($P < 0.05$) between right and left hemispheres.

[b] Significant difference ($P < 0.05$) between right and left tongues.

2 of the postcentral gyrus, because of the group-averaged results. The ROI analysis showed greater activation of the right (contralateral) hemisphere only for left tongue stimulation (Table 2). Similar differences between right and left tongue stimulation in the superior and middle insula were not significant. In the superior temporal gyrus (STG) (Figure 7) the ROI analysis showed no significant hemispheric differences, although the directions of the differences were consistent with the left hemispheric dominance of activation seen in the group-averaged results.

The ROI analysis revealed a statistical trend for an overall greater activation following right than left tongue stimulation [$F(1,10) = 4.52$, $P = 0.059$] for correlations based on the ASC HRF at a delay of 0 s, but not at 1.65 s or when the data resulting from the use of the HRFs at both times were combined. However, right tongue stimulation evoked significantly more activation only in the postcentral gyrus [IPL (40) + PoCG (43/40), $F(1,10) = 9.82$, $P < 0.05$) and in the precentral gyrus [PrCG (6), $F(1,10) = 6.05$, $P < 0.05$]. Apparent right versus left tongue differences in the amount of group-averaged activation observed in the middle and posterior parts of the superior insular cortex and in Brodmann area 44 (in Figure 5, compare F1 with F2, I3 and I4 with I5) were not confirmed by the ROI analyses. When data from left and right tongue stimulation were combined, group-averaged activation in Brodmann area 44 and the superior insular cortex was substantial (Figure 5, F5, F6, I6 and I7). Since activation resulting from stimulation of only one side of the tongue is unlikely to produce a significant activation for the combined data, there may have been activation following stimulation of both sides of the tongue, but one side did not reach statistical significance in the group-averaged analysis.

Discussion

To our knowledge this is the first study to use functional imaging to investigate the central processing of electric taste stimuli. The observed activation following electric taste stimulation in the insular and frontal opercular cortex predominantly in the right hemisphere is consistent with positron emission tomography (PET) studies utilizing chemical gustatory stimuli (Small *et al.*, 1999). The activation that we observed in the postcentral gyrus was very different from the results of another PET study, where focal tactile stimulation of the tongue activated somatosensory cortex (Brodmann area 3/4) centered at z = 27–29 mm (Pardo *et al.*, 1997). The activity following electric taste stimulation was more ventral (z = 16, 24 mm) and in different Brodmann areas. Although for both types of stimuli the postcentral gyrus activity was largely contralateral, tactile stimulation tended to activate the left hemisphere, whereas electric taste activated the right hemisphere more. Similarly, touch-evoked activity in the precentral gyrus (Brodmann area 6) was largely in the left hemisphere regardless of side of stimulation, unlike the right hemispheric dominance with electric taste stimulation. Thus, in these respects the central processing of electric taste stimulation resembles processing of chemical stimuli rather than that of lingual touch. Electric taste activation of the postcentral gyrus and other somatosensory areas could be related to somatosensory components of the stimulus, but projections to inferior somatosensory cortex from the gustatory thalamic nuclei have been described in non-human primates (Pritchard *et al.*, 1986). Activation of the postcentral gyrus after chemical taste stimulation has been reported in some imaging studies (Van de Moortele *et al.*, 1997), although somatosensory components of the stimuli cannot be ruled out. In the present experiments tactile stimulation by the electric taste probe was present both during and between stimuli and so was controlled for in the experimental design. However, perhaps a taste stimulus in combination with the continuously present touch of the electric taste probe can activate somatosensory cortex, because of a shift in attention. Conversely, it is also possible that other types of oral somatosensory stimuli might be represented in many of the insular/opercular regions that were activated in the present study. The insular cortex is activated by non-oral somatosensory stimuli (Penfield and

Jasper, 1954), but temperature sensation may be represented in the insula more than other somatosensory stimuli (Gelnar *et al.*, 1999). Electric taste stimuli are not known to elicit thermal sensations, but cooling and warming are reported to activate taste sensations (Cruz and Green, 2000). The fMRI results did not bear directly on the question of whether electric taste stimulation is a complex stimulus that may have somatosensory as well as gustatory components. It is important to duplicate the focal stimulus paradigm employed here with chemical taste stimuli in order to explore any differences in central processing between electrical and chemical taste stimuli.

Considerable activation was observed in the insular cortex and adjacent operculi. The activation in the superior half of the insula (Ips, Ims and Ia) likely occurred in granular and dysgranular regions (Augustine, 1996), where the primary gustatory area (PGC) has been identified in non-human primates (Pritchard *et al.*, 1986). Within this superior zone activation in some individuals was spread over almost the entire anterior–posterior axis of the insula. However, in the group-averaged data there was little activation in the most posterior part of the superior insula (Figures 3 and 5). The consistent activation seen as far posterior as y = –7 to –10 mm (Figure 5, I4 and I7) is in agreement with the results of a recent PET study on chemical taste (Frey and Petrides, 1999), but not with earlier PET studies reviewed by Small *et al.* (Small *et al.*, 1999) and a recent fMRI study (Francis *et al.*, 1999). The very posterior localization of the PGC reported in a recent magnetoencephalography (MEG) study on the response to chemical taste (Kobayakawa *et al.*, 1999) is not consistent with any of the aforementioned studies. Although Talairach coordinates were not provided, we estimate, based on the figures provided, that their PGC is located from approximately y = –14 to –30 mm and appears to lie primarily in the parietal operculum rather than the insula. It is difficult to reconcile this MEG study relative to the fMRI and PET results, as the stimulus used in the MEG study was designed to eliminate somatosensory cues.

The electric taste-induced activation in more central regions of the insula likely corresponds to inferior parts of the dysgranular and the superior part of the agranular insular cortex (Augustine, 1996). These more inferior activations may be related to second order processing of the electric taste stimulus. Interestingly, they were more bilaterally symmetrical than was superior insula activation. Faurion *et al.* found that activation in the inferior insula occurred primarily in the dominant hemisphere (Faurion *et al.*, 1999). Although they did not provide z levels, their inferior insular activity appears to be centered between z = –8 and 0 mm, whereas our electric taste bilateral activation was centered at z = 0 to +8 mm. With electric taste we did observe some insular group-averaged activity at z = –8 mm in the left (dominant) hemisphere with right tongue stimulation, a finding which may be consistent with those of Faurion *et al.* Thus, there may be at least three types of taste-evoked insular activation seen with fMRI: superior, which predominates in the right (non-dominant) hemisphere; central, which is more bilateral; inferior, which is predominantly in the dominant hemisphere.

Cortical activation by electric taste stimuli applied to either the right or left side of the tongue was bilateral in some individuals, but overall was right hemisphere dominant in the superior insula and operculi, presumed primary gustatory cortical regions. Individual variation in the extent of right dominance may explain ipsilateral/contralateral effects following central lesions (Onoda and Ikeda, 1999). In vertebrates, including non-human primates, it is generally thought that taste pathways ascend mostly ipsilaterally (Norgren, 1990). Incoming gustatory afferent fibers terminate in the ipsilateral brainstem nucleus of the solitary tract and projections from the thalamus to the cortex are ipsilateral. However, some brainstem projections to the thalamus in rodents are contralateral (Halsell and Frank, 1991; Williams *et al.*, 1996). Latency and amplitude of taste-evoked human EEG recordings were reported to be identical in both hemispheres with unilateral stimulation (Genow *et al.*, 1998), but bilateral activation may represent second order cortical processing via inter-hemispheric projections. However, indirect activation would likely be smaller than direct activation from thalamic inputs (Simoes and Hari, 2000) and known prominent second order gustatory areas, orbitofrontal cortex and anterior-medial temporal lobe (Small *et al.*, 1997; Zald *et al.*, 1998), were not significantly activated in the present study. Yet it is possible that most of the activation seen was not from the PGC, but from nearby second order regions.

Unilateral stroke damage to the left or right anterior insula and frontal cortex resulted in significant gustatory deficits that were primarily on the side of the tongue ipsilateral to the brain damage (Pritchard *et al.*, 1999), whereas our results suggest a right-sided dominance of hemodynamic responses to electric taste in these regions. Moreover, damage to the left hemisphere in three right-handed people affected taste recognition similarly on both sides of the tongue, implicating the dominant left hemisphere. On the other hand, PET studies and other clinical lesion studies have implicated the medial right temporal lobe in taste recognition (Small *et al.*, 1997). The apparent differences in hemispheric taste specialization may relate to variations in test paradigms. Any taste test involving verbalization may activate the dominant hemisphere, but tests involving taste memory may activate the non-dominant hemisphere (Levy *et al.*, 1999). A critical test of a proposed relationship between dominant versus non-dominant hemisphere and taste hemispheric specialization would be to compare right-handed and left-handed people (Faurion *et al.*, 1999).

We did not expect to find hemodynamic changes evoked by electric taste in the visual cortex, the inferior precuneus, superior temporal cortex and scattered in frontal cortex.

Activation of premotor regions (Brodmann areas 6 and 44) predominantly in the right hemisphere would be consistent with the control of mouth movements unrelated to speech. It is possible that repressing temptations to move the mouth and tongue resulted in the premotor cortical activation. Precuneus activation has been associated with attentional shifts (Nagahama *et al*., 1999) such as may have occurred following electric taste stimuli, but the precuneus is also activated by hunger (Tataranni *et al*., 1999), memory retrieval (McDermott *et al*., 1999) and swallowing (Hamdy *et al*., 1999), any of which could have been associated with a taste stimulus. The group-averaged activation in the left superior temporal gyrus is centered near the anterior edge of Brodmann area 22 of auditory cortex, but does not appear in the adjacent area 38, which is thought to be a center for limbic processing (Kim *et al*., 2000). Activation in area 22 could be related to verbal thoughts elicited by the stimulus, but a non-auditory function of this activation, such as attentional control (Hopfinger *et al*., 2000), is possible. The small activation (Figure 5, T3 and T5) in more medial parts of the superior temporal gyrus overlaps with a broader activation reported for fasting subjects following tasting and ingestion of a liquid meal (Gautier *et al*., 1999). Visual cortex activation is puzzling, however, the subjects were not instructed to close their eyes and shifts of visual attention or eye blinking could well have occurred in conjunction with the electric taste stimulus.

It has been reported that the HRF seen with fMRI following gustatory stimuli is slow and is perhaps best related to the subject's perception of the duration and strength of the stimulus (Van de Moortele *et al*., 1997). However, the short electric taste stimuli used in the present study evoked hemodynamic responses with a similar time course to those seen in other sensory regions. The earlier findings were likely due to the nature of the chemical stimulus, which was delivered slowly by dripping solutions onto the tongue. We predict that pulsatile chemical stimulation will result in HRFs that resemble those seen with electric taste.

In conclusion, we report the first experimental fMRI study of the human brain in which focal taste stimuli were applied separately to the right and left side of the tongue. We found electric taste stimuli to effectively activate primary gustatory cortex as it is defined in other primates. The patterns of activation elicited by stimulating the right or left side of the tongue were nearly identical. Furthermore, the superior part of the insula, a key primary gustatory cortical region, was consistently activated more strongly in the right non-dominant cerebral hemisphere. Future experiments using focal chemical taste stimuli and left-handed as well as right-handed subjects would help clarify the implications of these results.

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