

Interaction of Gustatory and Lingual Somatosensory Perceptions at the Cortical Level in the Human: a Functional Magnetic Resonance Imaging Study

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Abstract

The present study has investigated interaction at the cortical level in the human between two major components of flavor perception, pure chemical gustatory and lingual somatosensory perception. Twelve subjects participated in a functional magnetic resonance imaging study and tasted six stimuli, applied on the whole tongue, among which four were pure gustatory stimuli (NaCl, aspartame, quinine and HCl, pH 2.4 or 2.2) and two were both taste and lingual somatosensory stimuli, i.e. somato-gustatory stimuli (HCl, pH 1.6 or 1.5, and aluminum potassium sulfate). Functional images were acquired with an echo planar sequence on a 3 T system and were individually processed by correlation with the temporal perception profile. Both sets of stimuli showed activation in the same cortical areas, namely the insula, the rolandic operculum (base of the pre- and post-central gyri), the frontal operculum and the temporal operculum, confirming a wide overlap of taste and lingual somatosensory representations. However, the relative activation across areas and the analysis of co-activated areas across all runs for each set of stimuli allowed discrimination of taste and somatosensory modalities. Factor analysis of correspondences indicated different patterns of activation across the sub-insular and opercular regions, depending on the gustatory or somato-gustatory nature of the stimuli. For gustatory stimuli different activation patterns for the superior and inferior parts of the insula suggested a difference in function between these two insular sub-regions. Furthermore, the left inferior insula was co-activated with the left angular gyrus, a structure involved in semantic processing. In contrast, only somato-gustatory stimuli specifically produced a simultaneous and symmetrical activation of both the left and right rolandic opercula, which include a part of the sensory homunculus dedicated to the tactile representation of oral structures.

Introduction

Flavor is a complex perception, involving at least three sensory modalities: (i) taste, i.e. chemical stimulation of specific receptors on the tongue taste buds; (ii) lingual and oro-pharyngeal somatosensory sensitivity (touch, proprioception, temperature and trigeminal chemical sensitivity); (iii) olfaction, largely perceived by the retronasal pathway. Under natural conditions these three sensory systems are stimulated together and the resulting complex perception may be wrongly attributed to one or another sense (Murphy *et al.*, 1977; Todrank and Bartoshuk, 1991).

Taste and olfaction, dissociated by Chevreul in 1824, can be discriminated by the different location of the receptors, on the tongue and on the olfactory mucosa. Taste and somatosensory sensitivity resulting from tongue stimulation can be discriminated by the nerves that convey the signal. Taste results from the activation of taste bud sensory cells and is conveyed by the chorda tympani (a part of cranial nerve VII), the glossopharyngeal (IX) and the vagal

(superior laryngeal, X) nerves. Lingual somatosensory sensitivity, resulting from temperature and tactile stimulation, as well as chemical stimulation of chemosensory receptors localized on the perigemmal fibers, is conveyed by the trigeminal nerve (V) for the anterior two thirds of the tongue and by the glossopharyngeal nerve for the posterior third. The catalog of chemical trigeminal stimuli includes high concentrations of tastants (Beidler, 1953, 1965; Sostman and Simon, 1991; Wang *et al.*, 1993; Bryant and Moore, 1995; Pittman and Contreras, 1998), alcohols (Simon and Sostman, 1991) and other organic molecules, such as piperine from black pepper and capsaicin from chili pepper (Liu and Simon, 1996). Menthol (Kosar and Schwartz, 1990; Lundy and Contreras, 1994) can also elicit responses in the trigeminal nerve. The conscious perceptions elicited by these compounds vary from pungent to burning or noxious sensations. Other trigeminal sensations result in mild tingling or prickling, which are neither noxious, burning nor pungent.

Another supposed trigeminal sensation, the astringent sensation, may be described as a long-lasting puckering, shrinking and drying sensation on the tongue and oral mucosa and may be related to several compounds, such as polyphenols (e.g. tannic acid), aluminium salts, organic acids, ethyl alcohol, etc. Possible mechanisms for astringency include molecular binding with salivary proteins (Fischer *et al.*, 1994) or with proteins in the epithelium (Green, 1993), which may however be dependent on pH (Corrigan and Lawless, 1995; Peleg *et al.*, 1998). Psychologically, astringency has often been associated with touch or pain sensations (Joslyn and Goldstein, 1964; Lyman and Green, 1990; Green, 1993), although electrophysiological recordings did not confirm this in the rodent (Schiffman *et al.*, 1992).

Taste, olfaction and somatosensory stimuli are usually simultaneously present on food intake. Functional convergence between the three pathways has been already documented. Temperature interacts with taste at the neural level (Ogawa *et al.*, 1968) or at the psychophysical level (Paulus and Reisch, 1980; Bartoshuk *et al.*, 1982; Green and Frankman, 1988; Fontvieille *et al.*, 1989). In rodents Norgren found that 61 of 67 taste neurons in the first taste relay, the nucleus tractus solitarius (NTS), responded to cooling and that 60–70% were driven by mechanical stimulation (Norgren, 1984). However, because the chorda tympani fibers themselves are multimodal, responding both to taste and thermal stimulation, it was not clear whether the multimodal responses recorded in the NTS resulted from convergence with the trigeminal nerve or from the peripheral chorda tympani input itself. Nonetheless, the existence of bimodal neurons was further documented at the NTS level (Travers *et al.*, 1986, 1987; Travers and Norgren, 1995). Similarly, Halsell and Travers counted 55 bimodally responsive somatosensory and taste neurons out of 75 taste neurons in the parabrachial nucleus of the pons (PBN) (Halsell and Travers, 1997). Convergence between taste and olfaction was also found in the PBN (Di Lorenzo and Garcia, 1985). In primates taste and lingual somatic stimulation were found to elicit responses in the ventro-posteromedial nucleus of the thalamus (Emmers, 1966; Burton and Benjamin, 1971; Pritchard *et al.*, 1986), with somatosensory and taste cells localized more lateral to cells exclusively responding to chemicals and less lateral than pure somatosensory cells (Scott and Mark, 1986). In rodents neurons in the same thalamic taste area could also respond to odorants and to electrical stimulation of the tongue (Giachetti and MacLeod, 1977). Rat and monkey cortical insular neurons may respond simultaneously to chemical, touch and thermal stimulation of the tongue (Yamamoto *et al.*, 1981; Ogawa *et al.*, 1985) [(Pritchard, Hamilton and Norgren, unpublished data, quoted in Norgren (Norgren, 1990)] and also to olfactory stimulation (Giachetti and MacLeod, 1975). Moreover, a direct projection from the olfactory bulb was shown in the mouse insular cortex

(Shiple and Geinisman, 1984). Slightly different is the orbitofrontal projection. Rolls and co-workers (Rolls and Baylis, 1994; Rolls, 1995) found, in this more anterior region, integrative neurons responding to both taste and olfactory stimuli as a result of a multisynaptic taste projection (no direct taste projection has been shown in the orbitofrontal cortex to date).

Together these findings clearly document a functional neuronal convergence of the gustatory, lingual somatosensory and olfactory inputs which constitutes the neural substrate for a multimodal representation of flavor information at the very early stage of the direct cortical projection of taste. The aim of the present study was to examine, with functional magnetic resonance imaging (fMRI), whether pure taste and somatosensory components of flavor share a common cortical representation in humans and whether they could be dissociated.

Materials and methods

Subjects and stimuli

Twelve subjects aged 20–45 years (mean \pm SD 23.3 \pm 6.9), including nine women and three men, participated. All subjects were right-handed according to the Dellatolas test (Dellatolas *et al.*, 1988). A national ethics committee approved the study and all participants signed an informed consent agreement.

Four stimuli served as pure gustatory stimuli. Concentrations were adjusted according to the subjects' perceptions in order to elicit intensities equivalent to the sodium chloride solution. The concentration of this sodium chloride solution was adapted so that each subject's perception would be clear but not aversive when it was presented with the stimulation device used in the scanner (*vide infra*). Resulting solutions were: sodium chloride (NaCl), 4 or 5 g/l (70 or 86 mM); aspartame (Asp), 200 or 400 mg/l (0.7 or 1.4 mM); quinine hydrochloride (Qui), 100 or 300 mg/l (0.25 or 0.75 mM); weak hydrochloric acid (gHCl), pH 2.4 or 2.2 (4 or 6.3 mM). Two stimuli were chosen to stimulate both the taste and lingual somatosensory systems and will be referred to as somato-gustatory stimuli: pungent hydrochloric acid (pHCl), pH 1.6 or 1.5 (25 or 31 mM) (Simon *et al.*, 1992; Bryant and Moore, 1995; Corrigan and Lawless, 1995); astringent aluminium potassium sulfate (alum), 6 or 8 g/l (12.6 or 16.9 mM). Subjects were previously trained to evaluate acid taste, pungency and astringency and concentrations were chosen on the basis of their evaluations under experimental conditions corresponding to the scanner sessions. Stimuli were clearly pungent or clearly astringent, but never noxious nor painful. Stimuli were randomized except that pungent HCl and alum were presented after the gustatory stimuli.

Preliminary training

Psychophysical training

Each subject was familiarized with the stimuli and trained in magnitude estimation during four preliminary sessions. The magnitude estimation technique used a proportional scale with reference to 30 mM NaCl presented as 2 ml in a cup (reference = 10). Concentrations used in these sip and spit tests produced intensities in the range of those produced by the concentrations used in the scanner stimulation device.

Perception profile acquisition

Each subject also participated in six sessions, conducted outside the scanner, replicating the fMRI conditions, i.e. lying on their back and using the scanner stimulation device (*vide infra*). During these sessions all subjects were trained in the time–intensity matching technique by the finger span method (Berglund *et al.*, 1978; Larson-Powers and Pangborn, 1978; Yamamoto *et al.*, 1985). Subjects performed six runs in each session, as in the fMRI scanner. Each run lasted 5 min, including three stimulation and three rinsing periods, according to the paradigm used in the scanner. During these simulated runs the subject, using a linear potentiometer, was asked to continuously indicate the perceived intensity by the distance between his/her thumb, attached to the end of the potentiometer, and his/her forefinger moving on the cursor (Cerf *et al.*, 1996; Van de Moortele *et al.*, 1997). The resulting varying voltage was digitized by an analog–digital converter (frequency 1 Hz) and stored. The first two or three time–intensity perception profiles corresponding to learning were discarded. Then, profiles produced by every subject for six stimuli (12 subjects \times 3 repetitions \times 6 stimuli = 216 profiles) were averaged and used as a template to extract brain activations in fMRI images.

Magnetic resonance imaging

fMRI was performed at Service Hospitalier Frederic Joliot (CEA-DRM, Orsay France) with a 3 T whole body scanner (Bruker, Germany) equipped with a head gradient coil allowing echo planar imaging. Lying on their back in the scanner with their head maintained with foam pads and bands to limit motion artifacts, subjects tasted all six stimuli (six runs) in each fMRI session, which lasted 90 min, including acquisition of a structural image for anatomical reference. For each run, 22 contiguous functional slices, 5 mm thick, were repetitively acquired (resolution 64×64 voxels; field of view 20×20 or 22×22 cm² depending on subject; repetition time 5 s; echo time 40 ms). A high resolution three-dimensional anatomical image was also acquired to allow accurate localization of activated foci (inversion recovery sequence; matrix $19.2 \times 25.6 \times 25.6$ cm³; resolution $128 \times 128 \times 256$ voxels). Each run (309 s) was composed of a 30 s reference with water followed by three cycles including 18 s ON stimulation and 75 s OFF rinsing water. Each run was followed by a short resting period of

3–5 min. Water and stimuli were presented to the subject's mouth through polyethylene and silicon tubes as boluses of 50 μ l manually driven every 3 s with microsyringes. Subjects had previously been trained to swallow without head movement and functional images were further checked for evidence of head motion with Spm96 (Statistical Parametric Mapping) software. Subjects were asked to focus on their perceptions since they would be asked to report intensity and hedonic ratings after each run.

Data analysis

Each run was processed separately using the software package Spm96 (Friston *et al.*, 1991, 1995). The averaged time–intensity perception profile resulting from subjects' preliminary training was used as a template for the 'user specified function' (Spm96), which allowed extraction of brain activations by correlation with a template chosen by the user. Each individual run resulted in 62 temporal volumes (one volume = 22 slices). The first three temporal volumes were discarded to take into account the stabilization period of the magnetic resonance signal. The remaining 59 temporal volumes were then submitted to realignment procedures with first order adjustment, which corrected for small movements using an approach based on an approximate linear relationship between the temporal images and their partial derivatives (Spm96) (Friston *et al.*, 1995). The resulting realignment equations were examined and every run (functional time series) presenting a movement exceeding 1.5 mm in any direction was discarded. Temporal smoothing with an 8 s time constant was applied to each voxel time series to account for the hemodynamic rise time. A high pass filter (cut-off period 240 s) was used to eliminate instrumental and physiological low frequency signal variations. A low spatial smoothing with a 4 mm kernel (approximate size of one voxel) was applied to all functional images. Selected statistical thresholds for Spm96 processing were $P < 0.01$ on F and $P < 0.01$ on the Student t -test at the voxel level and $P < 0.2$ on the Student t -test at the cluster level (uncorrected).

The explored brain volume was limited in the reference anatomy of the subject by two planes at the inferior and superior limits of the insula, respectively (Figure 1). In this volume all activations were counted and anatomically identified according to brain atlases (Duvernoy, 1992; Talairach and Tournoux, 1993; Mai *et al.*, 1997) in 19 different regions (see Figure 4). Talairach coordinates were further calculated for all centers of clusters found in the explored brain volume with the Spm96 normalization algorithm.

Regions of interest were considered according to previous results (Cerf *et al.*, 1998; Faurion *et al.*, 1998, 1999), namely the insular lobe (INS), the frontal operculum (fOP), the base of the pre- and post-central gyri or rolandic operculum (rOP), mostly corresponding to Brodmann area 43, and the temporal operculum (tOP), mostly corresponding to

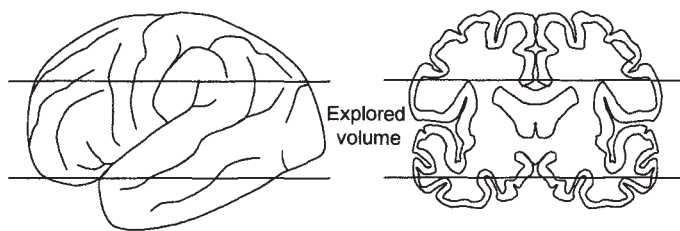


Figure 1 Explored brain volume. Two planes at the inferior and superior limits of the insula, respectively, limited the volume of brain in which activated voxels were localized and counted for this study.

Brodmann areas 22 and 38. Three sub-regions were furthermore discriminated within the insular lobe: the inferior anterior insula (iaINS), mostly corresponding to the part covered by the temporal operculum, the superior middle insula (smINS) and the superior posterior insula (spINS), both covered by the rolandic operculum. Talairach coordinates of activated clusters were averaged within each sub-region. Multidimensional analysis and ascending hierarchical classification (factor analysis of correspondences) (Benzecri, 1973) were conducted on the numbers of activated voxels collected for runs with gustatory stimuli and runs with somato-gustatory stimuli in the 19 regions.

Results

Intensity ratings were all above threshold and fell within the same range of magnitude estimates for all pure tastants and somato-gustatory stimuli (4–26 and 7–30, respectively), however, they were significantly higher for somato-gustatory stimuli (17.2 ± 6.7) than for tastants (11.4 ± 5.9 , $P < 0.01$, Student *t*-test). Of 72 possible runs planned (12 subjects \times 6 stimuli) one did not take place, six were discarded because the subject reported no perception during the fMRI session and three were discarded because of head movement greater >1.5 mm in translation (according to Spm96 realignment procedures). Among the remaining 62 processed runs 13 did not show any activated voxel with the parameters used. Forty-nine runs, i.e. 31 gustatory and 18 somato-gustatory, were available for further analysis.

Localization of activations

Individual fMRI activation maps obtained in several subjects are shown in Figure 2a for pure gustatory stimuli and in Figure 2b for somato-gustatory stimuli. Activations in response to pure gustatory stimuli and somato-gustatory stimuli were localized in the same areas and predominantly in the insular lobe, the rolandic operculum, the frontal operculum and the temporal operculum. Table 1 presents the number of subjects exhibiting activation in every region. For pure gustatory and somato-gustatory stimuli the insular lobe was activated in 11 and 10 subjects, the rolandic operculum was activated in nine and eight subjects, the frontal operculum was activated in nine and six subjects and

the temporal operculum was activated in five and two subjects, respectively.

Table 2 shows the averaged coordinates calculated on clusters extracted from Spm96 across all subjects and stimuli. Thirty-five percent of all activated voxels for gustatory stimuli and 38% for somato-gustatory stimuli were found in the insular lobes. In addition, 25 and 32% of all activated voxels for taste and somato-gustatory stimuli, respectively, were localized in the adjacent opercula, namely the frontal operculum (7.4 and 11%), rolandic operculum (13 and 17%) and temporal operculum (4.7 and 4.4%). Thus, 60 and 70% of activated voxels found in the explored volume for taste and somato-gustatory stimuli, respectively, were found in the insula and these three opercula (Figure 3), representing 13.4% of the explored volume on the basis of the standard brain model of Talairach and Tournoux (Talairach and Tournoux, 1993). These four regions thus appeared predominantly activated within the explored volume. In addition, 15 and 12% of all activated voxels were also found in the angular and supramarginal gyri for gustatory and somato-gustatory stimuli, respectively, 1.8 and 2.1% in the caudate nuclei, 2 and 4.8% in the temporal lobe, 7.6 and 8.4% in the occipital lobe, 5.4 and 0.5% in the frontal lobe and in other areas such as the thalamus, the gyrus rectus and the cingulate gyrus (8 and 6% for the latter).

Discriminating gustatory and somato-gustatory stimuli by quantitatively different distributions of activation

Table 2 shows that although gustatory and somato-gustatory stimuli activated equivalent areas in both hemispheres, the quantitative balance of these activations depended on the nature of the stimulus: taking into account the number of voxels activated in each area, the patterns of activation appeared significantly different for gustatory and somato-gustatory stimuli (Figure 3). Table 2 shows the statistical significance of differences between the right and left hemispheres (column 8) for each area and each sensory modality and the statistical significance of differences between both stimulus modalities (column 9) in each area. Some areas were more activated by taste than by somato-gustatory stimuli, for example the left and, above all, the right inferior anterior insula (iaINS, $P < 10^{-3}$, χ^2) and probably also the right superior posterior part of the insula (spINS, $P = 0.07$, χ^2). In contrast, the right part of the superior middle insula (smINS) was more activated by somato-gustatory stimuli than by taste ($P < 10^{-3}$, χ^2). The rolandic operculum was the most activated among opercula. In the case of somato-gustatory stimuli, activation was symmetrical, whereas in the case of taste stimuli the left rolandic operculum (rOPI) was significantly more activated than the right rolandic operculum ($P = 0.06$, χ^2). Both frontal opercula (fOP) and temporal opercula (tOP) were symmetrically activated in the case of taste. In the case of somato-gustatory stimuli the left frontal and temporal

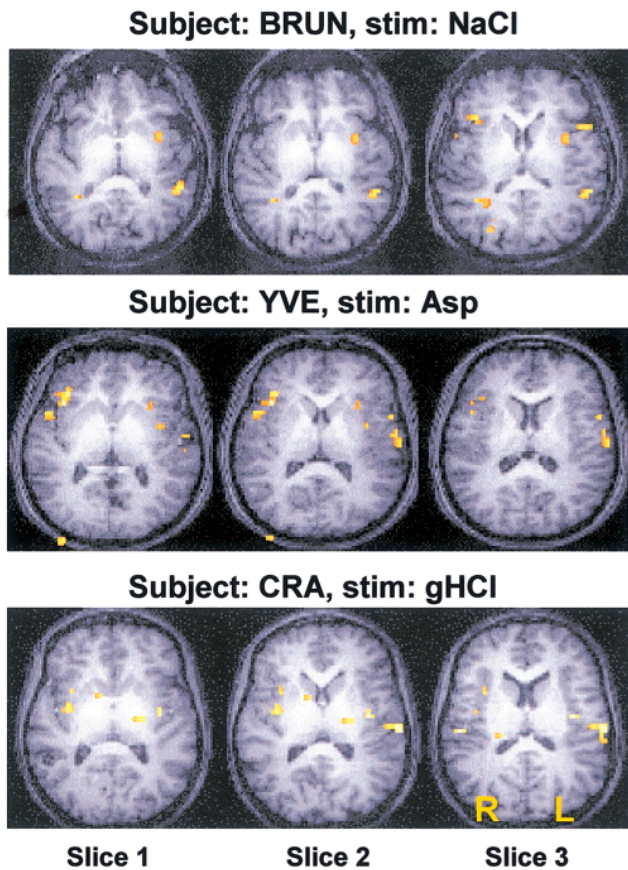


Figure 2a

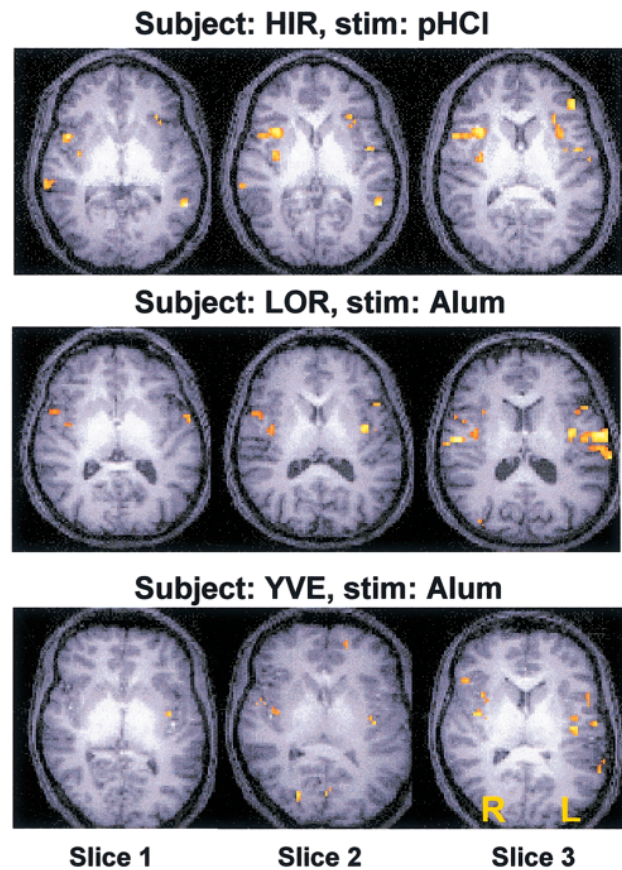


Figure 2b

Figure 2 Examples of activation maps for gustatory and somato-gustatory stimuli. Activations were extracted by correlation with an averaged perception profile obtained during the preliminary training (see Materials and methods) and were superimposed on the anatomical image. The left-hand side of the subject is represented on the right-hand side of the figure according to radiological convention. **(a)** Activation maps for gustatory stimuli. Activations may be seen in the superior insula (subjects BRUN and CRA, slice 3), the inferior insula (subjects BRUN, YVE and CRA, slice 1), the frontal operculum (subjects BRUN and CRA, slice 3), the rolandic operculum (subject YVE and CRA, slice 3) and the temporal operculum (subject YVE, slice 1). **(b)** Activation maps for lingual somato-gustatory stimuli. Activations may be seen in same areas as for gustatory stimuli: superior insula (subjects HIR, LOR and YVE, slice 3), inferior insula (subjects HIR, LOR and YVE, slice 1), frontal operculum (subjects HIR, LOR and YVE, slice 3), rolandic operculum (subjects LOR and YVE, slice 3) and temporal operculum (subjects HIR and LOR, slice 1).

opercula (fOPI and tOPI) were more activated than both the right frontal and temporal opercula ($P < 0.001$, χ^2).

Discriminating gustatory and somato-gustatory stimuli by different patterns of co-activated areas

Factor analysis of correspondences and ascending hierarchical classification (Benzecri, 1973) are descriptive analyses which display co-activated areas across runs in close proximity in a multidimensional vector space and discriminate areas with independent patterns of activation. In the case of gustatory stimuli (Figure 4a) the superior parts of the insula appeared grouped with the adjacent frontal, rolandic and temporal opercula and were

discriminated from the inferior parts of the insula. Moreover, the left inferior insula (iaINSI) was co-activated with the left angular gyrus (angl).

In contrast, in the case of somato-gustatory stimuli (Figure 4b) all parts of the insula were associated with frontal and temporal opercula: the left inferior insula was not dissociated and no specific co-activation was found between the left inferior insula and left angular gyrus. However, the left and right rolandic opercula appeared associated and strongly discriminated from all other areas. Hence, somato-gustatory stimuli activated the right and left rolandic opercula (including a part of the somatosensory area devoted to oral structures) in a different way than pure

Table 1 Number of subjects presenting activation for taste and somato-gustatory stimuli

Stimulus	No. of subjects	Region									
		INS	fOP	rOP	tOP	ang	cau	t	occ	f	Oth
Taste	12	11	9	9	5	7	8	4	8	6	7
Somato-gustatory	10	10	6	8	2	3	3	5	4	1	3

INS, insula; fOP, frontal operculum; rOP, rolandic operculum; tOP, temporal operculum; ang, angular and supramarginal gyri; cau, caudate nuclei; t, temporal lobe; occ, occipital lobe; f, frontal lobe; oth, others (thalamus, cingulate gyrus, gyrus rectus).

Table 2 Quantitative distribution of activation for gustatory stimuli and somato-gustatory stimuli

Area	Talairach coordinate (m \pm SD)			Stat Z (min-max)	nb activ. voxels	nb activ. voxels/nb total voxels (%)	χ^2 (left/right)	χ^2 (taste/som)
	x	y	z					
Gustatory stimuli								
iaINSI	-44 \pm 3.7	6 \pm 9.8	-2 \pm 4.4	3.24-4.05	41	4.42	<0.001	
iaINSr	40 \pm 8	19 \pm 13.7	-2 \pm 6.9	3.02-4.12	120	12.93		
smINSI	-41 \pm 5.7	11 \pm 14.5	10 \pm 6.6	3.04-3.94	60	6.47	n.s.	
smINSr	40 \pm 4.2	12 \pm 10.9	6 \pm 4.3	3.02-4.19	49	5.28		
spINSI	-45 \pm 0.5	-1 \pm 3.9	19 \pm 5.2	3.07-4	10	1.08	<0.001	
spINSr	42 \pm 4.3	-4 \pm 10.4	15 \pm 2.8	3.04-4.05	49	5.28		
fOPI	-52 \pm 9.4	25 \pm 25.4	4 \pm 15.8	3.07-4	33	3.56	n.s.	
fOPr	48 \pm 5.6	31 \pm 9.8	-7 \pm 7.6	3.14-4.35	36	3.88		
rOPI	-62 \pm 7.1	6 \pm 11.2	14 \pm 6.1	3.04-4.64	84	9.05	<0.001	
rOPr	58 \pm 5.8	4 \pm 10.5	11 \pm 11.4	3.15-4.03	34	3.66		
tOPI	-53 \pm 7.7	-9 \pm 21	2 \pm 17.6	3.02-3.47	18	1.94	n.s.	
tOPr	58 \pm 12	-18 \pm 17.8	15 \pm 15.9	3.1-4.07	26	2.80		
angl	-49 \pm 19.3	-60 \pm 10.7	38 \pm 7.8	3.12-4.54	87	9.38	<0.001	
angr	38 \pm 10.8	-63 \pm 9.6	42 \pm 8.2	3.17-3.87	35	3.77		
...					...			
Total voxel number in the explored volume					928			
Somato-gustatory stimuli								
iaINSI	-43 \pm 2.2	4 \pm 3	1 \pm 1.2	3.02-3.47	9	1.52	0.013	0.06
iaINSr	47 \pm 1.5	13 \pm 10.3	-6 \pm 4.9	3.01-3.65	23	3.89	<0.001	<0.001
smINSI	-41 \pm 1.8	5 \pm 15.4	13 \pm 5.9	3.06-4.55	52	8.78	<0.001	n.s.
smINSr	41 \pm 5	11 \pm 10.8	10 \pm 6.3	3.02-4.05	118	19.93	<0.001	<0.001
spINSI	-42 \pm 3.7	-6 \pm 2.5	20 \pm 4.9	3.08-3.96	13	2.20	n.s.	n.s.
spINSr	39 \pm 2.7	0 \pm 6.2	20 \pm 2.7	3.4-4.16	13	2.20		0.07
fOPI	-48 \pm 8.4	34 \pm 8.7	-2 \pm 10.2	3.01-4.74	50	8.45	<0.001	0.01
fOPr	52 \pm 6.7	33 \pm 10.4	3 \pm 7.6	3.16-3.34	13	2.20		n.s.
rOPI	-65 \pm 7	1 \pm 8.3	14 \pm 6.4	3.06-4.42	56	9.46	n.s.	n.s.
rOPr	58 \pm 6.3	4 \pm 7.5	13 \pm 4.3	3.1-4.59	43	7.26		0.06
tOPI	-64 \pm 8.2	-3 \pm 3.8	3 \pm 7.1	3.19-3.45	21	3.55	0.0017	n.s.
tOPr	48 \pm 0	14 \pm 0	-2 \pm 0	3.89	5	0.84		0.10
angl	-44 \pm 7.1	-56 \pm 10.1	50 \pm 10.2	3.07-3.72	67	11.32	<0.001	n.s.
angr	57 \pm 8	-58 \pm 3	47 \pm 15.3	3.04-3.12	8	1.35		0.09
...					...			
Total voxel number in the explored volume					592			

Anatomical identification was performed according to human brain atlases and Talairach coordinates of the centers of clusters (columns 2-4) were averaged across all subjects and relevant stimuli. Stat Z (column 5) refers to the average statistics on clusters (Spm96) found activated in the region considered. Percentages (%) of activated voxels (column 7) were calculated with reference to the total number of activated voxels in the explored volume. Statistical significance between numbers of activated voxels in the left and right hemispheres for each activated area (column 8, χ^2 left/right) and between numbers of voxels activated by gustatory and by somato-gustatory stimuli (column 9, χ^2 taste/som). r, right; l, left; iaINS, inferior anterior insula; smINS, superior middle insula; spINS, superior posterior insula; fOP, frontal operculum; tOP, temporal operculum; rOP, rolandic operculum; ang, angular and supramarginal gyri.

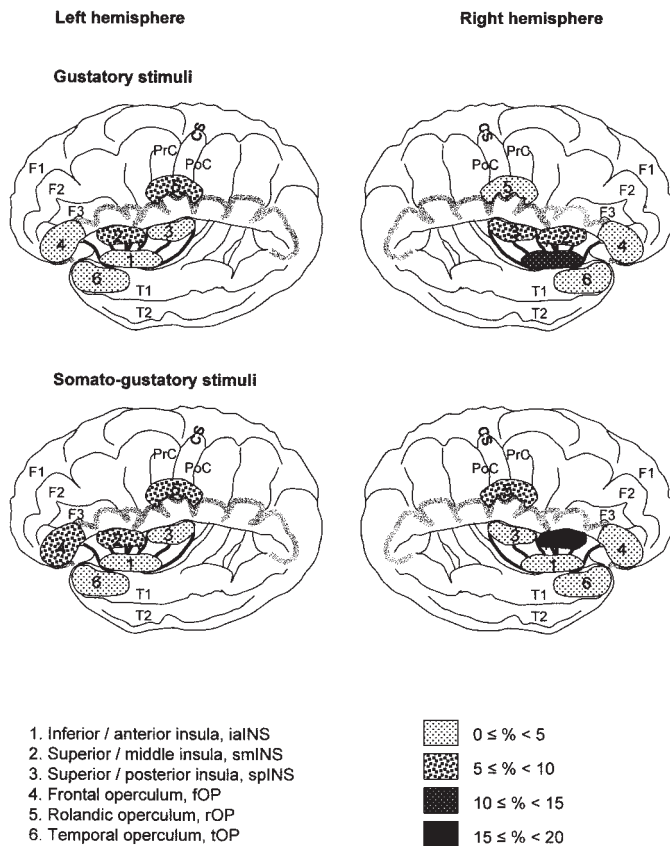


Figure 3 Schematic summary of cortical areas activated in response to gustatory and lingual somato-gustatory stimulation. Activations were consistently localized in the insular lobe, in the inferior and anterior part (1, ialNS), in the superior and middle part (2, smINS) and in the superior and posterior part (3, spINS), in the frontal operculum (4, fOP), the rolandic operculum (5, rOP) or the bases of the pre- and post-central operculum and in the temporal operculum (6, tOP) for both gustatory and somato-gustatory stimuli. Different degrees of activation are presented as percentages of activation (number of activated voxels in the considered region compared with the total number of activated voxels in the explored volume) for each region in each hemisphere (left hemisphere on the left, right hemisphere on the right) for gustatory stimuli (upper row) and somato-gustatory stimuli (lower row).

gustatory stimuli: they merely extracted them from the group of other areas, whereas gustatory stimuli associated all opercular and superior insular areas.

Discussion

The aim of the present study was to describe the cortical representation of two of the three components of flavor, i.e. taste and lingual somatosensory perception, to examine their degree of overlap and to determine whether these two components could be discriminated by fMRI. The use of pure taste stimuli served as a reference for comparing pure taste and somato-gustatory stimuli and allowed comparison with results on pure taste cortical representation. Comparison between pure gustatory and somato-gustatory

stimuli was achieved by two different and complementary approaches: (i) quantifying activated voxels in each area; (ii) analyzing patterns of co-activated areas by factor analysis of correspondences and hierarchical clustering for each set of stimuli.

The results of the present study identified differences in activation of cortical areas by pure taste and somato-gustatory stimuli and thus provided evidence for commonalities and differences between gustatory and lingual somatic components of flavor. The observation of a unique set of activated areas for pure gustatory stimuli and gustatory stimuli with a strong additional somatic component is not inconsistent with the hypothesis of a substantial overlap between cortical representations of gustatory and lingual somatic sensitivities. However, the differences in degree and lateralization of activation elicited by the pure taste and somato-gustatory stimuli facilitated extraction of patterns of activation for each modality and may represent the neurophysiological substrate for discrimination between the taste and lingual somatic components of flavor.

Activations related to pure taste stimuli

The localization of activations in response to pure taste stimuli described in the present fMRI study agrees with previous findings on primates and humans. In non-human primates lesion experiments showed that the anterior part of the insula, the rolandic operculum and the temporal operculum were all involved in the cortical representation of taste (Ruch and Patton, 1946; Bagshaw and Pribram, 1953). Benjamin and Burton (Benjamin and Burton, 1968) and, later, Pritchard *et al.* (Pritchard *et al.*, 1986) further demonstrated with electrophysiological recordings, retrograde degeneration and autoradiographic tracing that the insula and rolandic operculum both receive a direct projection from the thalamic gustatory relay through bifurcate neurons. On the basis of potentials evoked by electrical stimulation of the taste nerves, Burton and Benjamin considered both the post-central gyrus and the operculo-insular area as primary areas for taste (Burton and Benjamin, 1971). Further, responses to gustatory stimulation were recorded for several tastants in the frontal operculum (Scott *et al.*, 1986) and insula of primates (Scott and Plata-Salaman, 1999). Both posterior and anterior insula (Yaxley *et al.*, 1990) [reviewed by Norgren (Norgren, 1990)] were shown to respond to taste. Several sub-regions were identified with different functions in the insular lobe of rats, with the granular part more likely to be involved in fine taste discrimination and the dysgranular part more likely to play a role in the integration of taste information (Ogawa *et al.*, 1992).

In humans the rolandic operculum and the insular lobe were separately found to be involved in taste deficits following cortical lesions (Bornstein, 1940; Motta, 1959) and gustatory sensations could be elicited by electrical

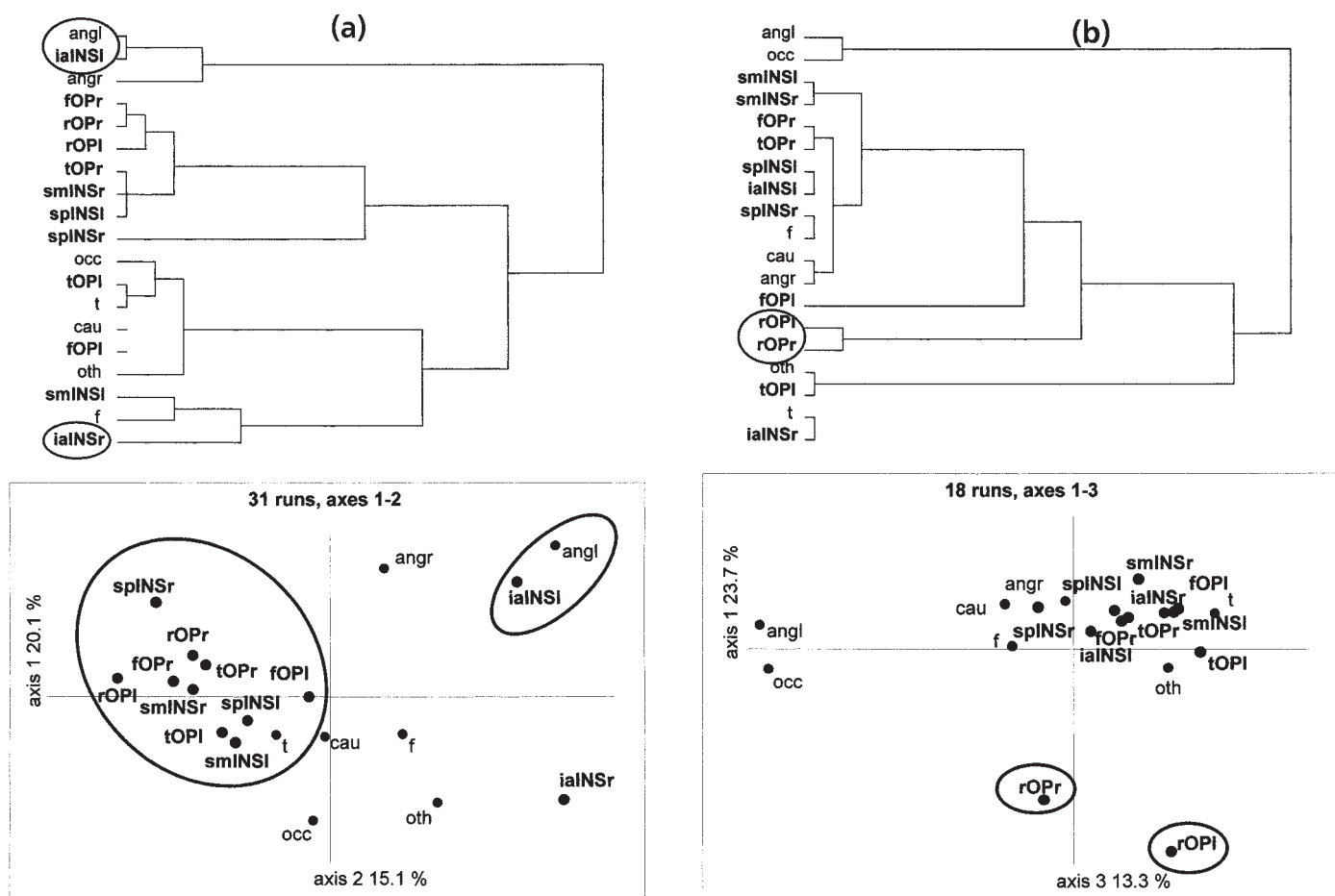


Figure 4 Factor analysis of correspondences (FAC) was performed on numbers of activated voxels collected in 19 regions (columns) across 31 runs (lines) with gustatory stimuli or 18 runs (lines) with somato-gustatory stimuli. Ascending hierarchical classification was then performed on the analysis factors. r, right; l, left; iaINS, inferior anterior insula; smINS, superior middle insula; spINS, superior posterior insula; fOP, frontal operculum; tOP, temporal operculum; rOP, rolandic operculum; ang, angular and supramarginal gyri; cau, caudate nuclei; t, temporal lobe; occ, occipital lobe; f, frontal lobe; oth, others (thalamus, cingulate gyrus, gyrus rectus). (a) (Upper) Hierarchical classification on results obtained with four gustatory (31 runs) stimuli in 12 subjects. (Lower) Plane 1–2 displaying axes 1 and 2 of the FAC. Axis 1 represents 20.1% of the information and axis 2 represents 15.1% of the information. Inferior insulae (iaINSr and iaINSi) appear strongly discriminated from superior insulae (smINSr, smINSi, spINSr and spINSi) on the first two factors of the analysis. Conversely, the left angular gyrus (angl) and left inferior insula (iaINSi) remain associated, indicating that both areas are co-activated across all runs and may be involved in some common function related to gustatory stimulation. (b) (Upper) Hierarchical classification on results obtained with two somato-gustatory stimuli (18 runs) in the same subjects. (Lower) Plane 1–3 displaying axes 1 and 3 of the FAC. Axis 1 represents 23.7% of the information and axis 3 represents 13.3% of the information. The left and right rolandic opercula (rOPr and rOPI) are strongly discriminated together from all other areas, suggesting a specific role of the rolandic operculum (basis of the somatosensory homunculus representing orofacial structures) for the lingual somatosensory stimuli.

stimulation of the insular lobe (Penfield and Faulk, 1955). The insula was consistently activated in response to gustatory stimulation in healthy subjects in neuroimaging by PET studies (Kinomura *et al.*, 1994; Small *et al.*, 1999) and fMRI (Cerf *et al.*, 1998; Faurion *et al.*, 1998, 1999; Francis *et al.*, 1999). Early activation of the insula in response to taste was also described with MEG (Kobayakawa *et al.*, 1996, 1999; Murayama *et al.*, 1996), thus reinforcing the notion of direct gustatory projections in the insular lobe (Norgren, 1977).

The present study confirmed the critical involvement of both the insula and the rolandic operculum in human taste cortical representation and thus reconciles early contra-

dictory clinical observations in humans (Bornstein 1940; Penfield and Faulk, 1955; Motta, 1959). The consistent activation recorded in the temporal operculum agrees with lesional studies on primates (Ruch and Patton, 1946; Bagshaw and Pribram, 1953) and more recent neuroimaging studies in humans (Kinomura *et al.*, 1994; Francis *et al.*, 1999) and suggests an important role of this region in taste processing. Other areas activated in response to taste stimulation certainly correspond to higher cognitive processes associated with taste perception and some of them, in particular the angular gyrus, will be considered further.

Activations related to lingual somato-gustatory stimuli

Clinical investigations on patients undergoing craniotomy and neuroimaging studies on healthy subjects both localized the sensorimotor representation of oral structures, including the tongue, at the base of the pre- and post-central gyri, i.e. the rolandic operculum. Van Buren evoked motor and sensory responses of the tongue in patients with implanted electrodes, eliciting electrical stimulation of the rolandic and sylvian regions (Van Buren, 1983). Conversely, McCarthy *et al.* recorded evoked potentials in the perirolandic cortex in response to tactile stimulation of the chin, lips, tongue and palate of patients (McCarthy *et al.*, 1993). Recent neuroimaging experiments using tactile stimulation of the face, the lips or the tongue confirmed the representation of oral structures at the base of the post-central gyrus in healthy subjects (Hari *et al.*, 1993; Sakai *et al.*, 1995; Pardo *et al.*, 1997; Nakamura *et al.*, 1998; Zald and Pardo, 2000).

The present study showed activation in response to somato-gustatory areas in a set of regions including the rolandic operculum, in agreement with the sensory and motor representation of oral structures described in this region in previous studies on patients and healthy subjects. Specific activation of the rolandic operculum by somato-gustatory stimuli, suggested by the comparison of co-activation patterns with factor analysis of correspondences, further agrees with the literature and reinforces the notion of a specific involvement of rolandic operculum activation in the somatosensory component of flavor.

A unique set of activated areas for two distinct sensory modalities localized on the same organ: the tongue

The present study has shown that the same areas were activated by both gustatory and somato-gustatory stimuli. No area was activated by only one of these two modalities. The insular lobe and the opercular part of the frontal, rolandic and temporal gyri were activated by both taste and lingual somatosensory stimuli and thus seem to process the lingual somatosensory components of flavor as well as pure taste. This result is in accordance with the literature. Electrophysiological studies on both monkeys and rodents report converging projections from gustatory and lingual somatosensory origins in several relays of the gustatory pathway, especially at the cortical level, where somatosensory and taste responses are found in intermingled cells or even within the same cells (Emmers, 1966; Burton and Benjamin, 1971; Norgren, 1977; Yamamoto *et al.*, 1981; Yamamoto, 1984; Ogawa *et al.*, 1985, 1989; Pritchard *et al.*, 1986; Norgren, 1990; Scott *et al.*, 1986, 1991) [Pritchard, Hamilton and Norgren, unpublished observations, quoted in Norgren (Norgren, 1990)]. The present imaging study thus illustrates in the human a strong association, at the cortical level, of the pure gustatory and somatosensory

components of flavor, as described in non-human animals and in psychophysical studies.

Comparison of taste and somato-gustatory activations

A balanced pattern of activation different for both modalities

The relative balance of activation in each sub-area appeared different for somato-gustatory and gustatory stimuli. Taste stimuli induced larger activations in the right inferior anterior insula (iaINSr) and in the right superior posterior insula (spINSr). Somato-gustatory stimuli induced larger activations in the right superior middle part (smINSr). In comparison, Small *et al.* have shown, by PET, a predominance of activations in response to taste in the right hemisphere (Small *et al.*, 1999), while Kinomura *et al.* reported only left insular activation (Kinomura *et al.*, 1994) and, more recently, Barry *et al.* showed predominant activation in the right insula in response to electrical taste (Barry *et al.*, 2000). From these results it appears that there is still no simple interpretation of the lateralization of activations for the cortical representation of taste and lingual somatosensory perception. Furthermore, consideration of the activation of different sub-regions in the insula and adjacent opercular areas may reveal subtle functional differences and different patterns of lateralization, which might explain discrepancies among studies. Neuroimaging techniques with high spatial resolution will probably soon allow such discrimination.

Activation of the rolandic operculum was symmetrical for somato-gustatory stimuli but was smaller in the right hemisphere (rOPl) for taste stimuli. In contrast, activation of the frontal operculum was greater in the left hemisphere (fOPl) for somato-gustatory stimuli but symmetrical for taste. Thus, although the areas of activation were globally similar for the two modalities, the distribution and extent of activation in the right and left hemispheres was dependent on the modality involved and the sub-region considered.

The predominance of activation in the right insula observed in the present study contrasts with previous fMRI results (Cerf *et al.*, 1998; Faurion *et al.*, 1999). In the preceding study subjects were neither familiarized with the experimental paradigm nor with the stimuli. Conversely, in the present study subjects were specifically familiarized with the stimuli and trained to the experimental paradigm. This choice was made on the basis of previous results showing a significant modification of the number of voxels in the areas of interest, i.e. the insula and adjacent opercula, with a familiarization process, depending on the evolution of hedonic ratings (Faurion *et al.*, 1998). The difference in lateral predominance in sub-regions between the two studies, in particular in the inferior insula, might be related to different cognitive strategies relative to familiar and unfamiliar stimuli, a hypothesis recently suggested by Savic and Berglund (Savic and Berglund, 2000). Other parameters may be considered as sources of variability in different

studies, such as the proportion of female and male subjects. In particular, we may note that the present study included nine females and three males, whereas the study reporting left insular predominance presented an opposite proportion, with seven males and three females. Differences related to gender in taste processing are not fully understood. Gender has been proposed as influencing the lateralization of some cognitive processes, including language (Reite *et al.*, 1995; Shaywitz *et al.*, 1995). Differences between males and females in number of gustatory receptors have been reported (Bartoshuk *et al.*, 1994) and gender differences in taste sensitivity appear during the aging process (Murphy, 1979), but seem to remain limited or absent under 40 years of age (Fikentscher *et al.*, 1977). Thus, the question of the influence of the proportion of males and females in studies of taste cortical representation remains open.

Co-activations

In addition to counts of activated voxels, multidimensional analysis and ascending hierarchical classification showed that the left inferior insula was strongly discriminated from superior insular sub-regions only for gustatory stimuli. This means that the left inferior insula was not co-activated with superior insular sub-regions across taste runs. This suggests a functional difference between the superior and inferior parts of the insula, with a specific role played by the left inferior insula in the case of pure gustatory perception. A specific role for the inferior insula was postulated in a previous fMRI study on an independent group of left- and right-handed subjects (Cerf *et al.*, 1998; Faurion *et al.*, 1999). In this study the superior part of the insula (including the two sub-regions considered in the present experiment) was bilaterally activated in response to pure taste stimulation, whereas the inferior insula was predominantly unilaterally activated in the subject's dominant hemisphere, i.e. the left hemisphere of right-handed subjects, and *vice versa*. This result led the authors to postulate that the superior insula, possibly including the primary cortical taste area, would receive direct taste projections from the gustatory thalamic relay and that, in contrast, the inferior part of the insula would be involved in higher cognitive processing, possibly integrating taste information into flavor (Cerf *et al.*, 1998; Faurion *et al.*, 1999). Recent clinical observations describing gustatory deficits related to lesion of the dorsal and rostral parts of the insula, but not to the ventral part of the insula, are consonant with this hypothesis (Pritchard *et al.*, 1999). Pritchard furthermore postulated a specific status of the left insula, on the basis of observations of bilateral deficits in recognition related to unilateral left insular lesions, and suggested that taste information from both sides of the tongue would pass through the left insula. The present study confirms the specific status of the left insula for taste and furthermore suggests that this specificity may be related to taste only and not to other oral sensory perceptions, since left insula

discrimination was not observed for somato-gustatory stimuli, i.e. when stimuli included a somatosensory component.

The present study also shows a close association, in right-handed subjects, between the left inferior insula and the left angular gyrus for pure gustatory stimuli. The angular gyrus was shown to be involved in semantic processing by cortical stimulation (Van Buren *et al.*, 1978) and functional imaging experiments (Binder *et al.*, 1996; Horwitz *et al.*, 1998). This observation suggests a hypothetical relationship between inferior insular activation and some semantic processing related to gustatory perception. Since we did not find this association in the case of somato-gustatory stimuli, it could furthermore indicate a semantic processing difference between the two modalities.

Factor analysis showed that the left and right rolandic opercula appeared closely associated with each other, i.e. were co-activated across runs, and strongly discriminated from all other areas for somato-gustatory stimulation only. The close association of the left and right rolandic opercula is in accordance with the bilateral nature of the stimulation. Furthermore, the discrimination of the rolandic operculum from other areas for somato-gustatory stimuli only seems to indicate a specific role of the rolandic operculum in cortical representation of the somatosensory component of flavor activations. This is in agreement with the description of primary projections of lingual somatosensory origin in this area in the primate (Benjamin *et al.*, 1968) and with the sensory representation of mouth structures in this region in the human revealed by electrocortical recordings (Van Buren, 1983; McCarthy *et al.*, 1993). The predominant status of the rolandic operculum in the lingual somatosensory modality also appears in several functional imaging studies (Hari *et al.*, 1993; Sakai *et al.*, 1995; Pardo *et al.*, 1997; Nakamura *et al.*, 1998; Zald and Pardo, 2000).

Conclusion

The present study illustrates the dual aspect of somato-gustatory sensation. During food intake, taste and somatic sensations, including texture and temperature, result from stimulation of the gustatory and somatosensory systems that originate simultaneously from the same location and combine to form a global sensation. Sensory pathways also widely overlap from the very periphery, so that the gustatory nerves, including the chorda tympani, may respond to both taste and temperature or tactile stimulation and the same chemical compounds may elicit responses in both the gustatory and somatosensory systems. However, although taste and lingual somatosensory modalities appear thoroughly intermingled, they can be discriminated by the brain and the global sensation may at least partially be analyzed introspectively. The present study has shown activation of one set of cortical areas in response to both pure taste and lingual somato-gustatory stimuli and thus

confirmed the wide overlap between taste and lingual somatosensory sensitivities. However, the comparison of the distribution of activation across areas and the different patterns of co-activated areas across subjects and stimuli allowed discrimination between the two modalities and thus illustrates the analysis process performed by the brain. This comparison furthermore suggested that taste cortical representation was characterized by a functional difference between the superior and inferior parts of the insula, with a hypothetical role in the semantic representation of taste perception of the left inferior insula associated with the left angular gyrus. On the other hand, the somatosensory component of flavor appeared to be characterized by the specific status of rolandic operculum activation, a primary projection area for lingual somatosensory information.

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