Representation of Pleasant and Aversive Taste in the Human Brain

J. O'DOHERTY,[1] E. T. ROLLS,[1] S. FRANCIS,[2] R. BOWTELL,[2] AND F. MCGLONE[3]
[1]*Department of Experimental Psychology, University of Oxford, Oxford OX1 3UD;* [2]*Magnetic Resonance Centre, School of Physics and Astronomy, University of Nottingham, Nottingham NG7 2RD2; and* [3]*Unilever Research, Port Sunlight Laboratory, Wirral L63, United Kingdom*

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O'Doherty, J., E. T. Rolls, S. Francis, R. Bowtell, and F. McGlone. Representation of pleasant and aversive taste in the human brain. *J Neurophysiol* 85: 1315–1321, 2001. In this study, the representation of taste in the orbitofrontal cortex was investigated to determine whether or not a pleasant and an aversive taste have distinct or overlapping representations in this region. The pleasant stimulus used was sweet taste (1 M glucose), and the unpleasant stimulus was salt taste (0.1 M NaCl). We used an ON/OFF block design in a 3T fMRI scanner with a tasteless solution delivered in the OFF period to control for somatosensory or swallowing-related effects. It was found that parts of the orbitofrontal cortex were activated ($P < 0.005$ corrected) by glucose (in 6/7 subjects) and by salt (in 6/7 subjects). In the group analysis, separate areas of the orbitofrontal cortex were found to be activated by pleasant and aversive tastes. The involvement of the amygdala in the representation of pleasant as well as aversive tastes was also investigated. The amygdala was activated (region of interest analysis, $P < 0.025$ corrected) by the pleasant taste of glucose (5/7 subjects) as well as by the aversive taste of salt (4/7 subjects). Activation by both stimuli was also found in the frontal opercular/insular (primary) taste cortex. We conclude that the orbitofrontal cortex is involved in processing tastes that have both positive and negative affective valence and that different areas of the orbitofrontal cortex may be activated by pleasant and unpleasant tastes. We also conclude that the amygdala is activated not only by an affectively unpleasant taste, but also by a taste that is affectively pleasant, thus providing evidence that the amygdala is involved in effects produced by positively affective as well as by negatively affective stimuli.

INTRODUCTION

The aims of this study are to investigate the representation of taste in the human brain and in particular to compare and contrast the representations of a pleasant and an aversive taste. The study of the affective representation of taste is important as a means of advancing our understanding of the neural mechanisms for the regulation of food intake as well as the mechanisms underlying emotional processing in the brain (Rolls 1999). Particular issues of interest are whether areas of the human brain such as the insula, orbitofrontal cortex, and amygdala implicated in taste are activated by both a pleasant and an aversive taste, or whether in contrast there is some specialization of different brain regions. If particular areas are activated by both pleasant and unpleasant tastes, it is then of interest to investigate whether the regions activated show topological separation.

Experimental investigations in macaques have shown that there is a primary taste cortical region in the anterior insula and adjoining frontal operculum, with a taste area in the orbitofrontal cortex that receives from this, and that is therefore defined as the secondary taste cortex (Baylis et al. 1994; Rolls 1997; Rolls et al. 1990; Scott et al. 1986). Neurons in this orbitofrontal secondary taste cortex region have been found to be modulated by the motivational state of the animal, responding to the sight or taste of food when the animal is hungry and not responding when the animal is satiated (Rolls et al. 1989). Furthermore, electrical stimulation of this brain region is rewarding when the animal is hungry and the reward value (as shown by whether the monkey will work for the stimulation) decreases as the animal is fed to satiety (Mora et al. 1979). These results suggest that the orbitofrontal cortex is involved in representing the affective aspects of taste in nonhuman primates. In addition, lesion studies and neuroimaging studies in humans have implicated the human orbitofrontal cortex in affective processing (Bechara et al. 1994; Elliot et al. 2000; Francis et al. 1999; Rolls et al. 1994). Consequently, it is suggested that the human orbitofrontal cortex is one region in which the affective aspects of taste are represented.

Previous neuro-imaging studies of the representation of taste in the human brain have found cortical areas activated to taste such as the frontal operculum/insula and the orbitofrontal cortex (Francis et al. 1999; Small et al. 1997, 1999; Zald et al. 1998). With the exception of Zald et al. (1998), the representations of pleasant and aversive tastes have not been compared within the same subject group. In the study by Zald et al. using positron emission tomography (PET), it was found that a region of the left orbitofrontal cortex was activated by aversive taste (salt solution). However, the interpretation of that study was complicated by the lack of consistent activation of the orbitofrontal cortex or other brain areas such as the amygdala by the pleasant stimulus used (solid chocolate). This may have been due to the fact that water was used as the control stimulus, a substance that itself has a taste and is known to activate neurons in the primate insular and orbitofrontal taste cortices (Rolls et al. 1990; Yaxley et al. 1990). Further, Zald et al. (1998) acknowledge that water is a positive reinforcer in its own right, so that it could have obscured activation to the pleasant stimulus in a subtraction paradigm. Also, that study was not designed to measure the effects of pleasant taste, in

Address for reprint requests: E. T. Rolls, Dept. of Experimental Psychology, University of Oxford, South Parks Road, Oxford OX1 3UD, UK (E-mail: edmund.rolls@psy.ox.ac.uk).

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that the positive stimulus used, chocolate, has taste, olfactory, and texture components.

The primate amygdala also receives gustatory inputs that activate single neurons (Sanghera et al. 1979; Scott et al. 1993). Moreover, it is of potential interest as an area containing an affect-related representation of taste, as its function in fear conditioning and thus in negative affect has been emphasized (LeDoux 1992). Indeed, many imaging studies of emotion reviewed by Davidson and Irwin (1999) have found amygdala activation related to negative affect. Further, there is evidence that patients with amygdala lesions have difficulties with identifying negative face expressions (Adolphs et al. 1994), and with aversive conditioning (LaBar et al. 1995). However, a few imaging studies have also found amygdala activation to affectively positive stimuli (Breiter et al. 1996; Schneider et al. 1997) and the amygdala has also been implicated in memory encoding of affectively positive as well as affectively negative events (Hamann et al. 1999). Another way to obtain evidence on the role of the human amygdala in affect is to measure its activation to tastes with different affective value. In the study by Zald et al. (1998), activation of the human amygdala was found to aversive saline, but there was no consistent activation to the pleasant chocolate stimulus, perhaps due to the reasons outlined above. However, in neurophysiological recordings made in nonhuman primates, amygdala neurons have been found that respond to rewarding tastes (such as glucose), while other neurons respond to other tastes, such as salt or sour (Scott et al. 1993). This raises the possibility that the amygdala is not only involved in processing affectively negative tastes, but also affectively positive taste. Indeed, testing whether the human amygdala is activated by affectively positive as well as by affectively negative tastes, as described here, is one way to obtain evidence on whether the human amygdala is involved only in negative emotions, or in both positive and negative emotions.

In this experiment, we used functional magnetic resonance imaging (fMRI) to investigate brain activation to pleasant and unpleasant tastes. The pleasant taste used in this study was sweet taste (1 M glucose), and the aversive taste salt (0.1 M NaCl). The neutral control stimulus used was designed to be a tasteless solution by being formulated to include the main ionic components present in saliva, and thus to overcome the pitfalls of using water alone as a control stimulus (see above). The aims of the study are to investigate whether the orbitofrontal cortex is activated by the pleasant and unpleasant tastes, and, if so, to show whether there is a functional anatomical separation between regions of orbitofrontal cortex involved in processing the two tastes, and to determine whether or not the amygdala can be activated by pleasant as well as by aversive tastes.

METHODS

Seven healthy human subjects participated in this experiment. Imaging was conducted using a 3.0 Tesla fMRI scanner at the University of Nottingham. Ten coronal T2* weighted EPI (Echo-planar imaging) slices were acquired every 2 s with a slice thickness of 8 mm (TR = 2 s). The matrix size was 128 × 64. The following parameters were carefully selected to minimize susceptibility and distortion artifact in the orbitofrontal cortex. First, the data were acquired in a coronal rather than axial slicing direction, as this aligned the slices to be perpendicular to the predominant direction of the intrinsic susceptibility-induced field gradients, and helped to minimize through plane dephasing. Second, the in-plane voxel resolution was set to 3 mm by 3 mm, which results in less phase cancellation than would be produced by a lower voxel resolution. Third, a relatively low TE of 23 ms was selected to decrease the signal dropout, as less phase dispersion is created across the voxels. Fourth, each subject was individually shimmed using both linear and second-order shimming to minimize static field inhomogeneities in the orbitofrontal cortex. Finally, geometric distortion was minimized by using a head insert gradient coil with very high gradient switching frequency of 1.9 kHz. The images were acquired beginning anteriorly at the orbitofrontal cortex (Talairach Y = +50) and moving posteriorly (to Y = −30) taking care to include the putative primary taste cortex (frontal operculum/insula). Anatomical localization was achieved by acquiring a multislice echo-planar dataset for each subject with isotropic 3-mm resolution using an inversion recovery (IR) sequence with the gray matter nulled (TI = 1,200 ms). Taste stimuli were delivered intra-orally by two polythene tubes held between the lips. The taste stimuli consisted of 1 M glucose, and 0.1 M NaCl. In the experiment, 0.5 ml of the taste stimulus (either glucose or saline) was delivered at the start of an 8-s ON period. This was followed by 0.5 ml of a tasteless control solution (with the main ionic components of saliva consisting of 25 mM KCl and 2.5 mM $NaHCO_3$) that was delivered at the start of an 8-s OFF period. This OFF period thus enabled nontaste-related activations such as swallowing or somatosensory effects to be subtracted out in the subsequent analysis (the subject was instructed to move the stimulus around the tongue and swallow once during each period). This protocol was repeated 24 times. In five subjects each taste was delivered separately in two separate runs. For the two additional subjects, an interleaved design was employed whereby both taste stimuli and the control stimulus were applied together in one imaging run using the same ON/OFF design but interleaving the application of the two taste stimuli. The subjects' subjective ratings of the pleasantness of the taste stimuli were also measured just before the imaging run using a rating scale ranging from +2 = very pleasant, 0 = neutral, −2 = very unpleasant, which has been validated in psychophysical experiments on the sensory factors that control food intake (O'Doherty et al. 2000; Rolls et al. 1981). The subjects were given practice in the use of the scale so that they knew the range of stimuli to be rated before the final ratings were taken.

Image analysis

The data were analyzed with MEDx (Sensor Systems). Motion correction [using automatic image registration (AIR)] (Woods et al. 1992), spatial smoothing (using a Guassian kernel with full width at half-maximum of 5 mm), intensity normalization (slice based ratio normalization), and temporal filtering (using a low-pass filter width of 2.8 s and a high pass filter set to twice the stimulus repetition period) were applied to the datasets. Significant changes of voxel intensity between each taste stimulus and the tasteless control condition were calculated by performing the following *t*-test comparisons using the standard Medx statistics and the appropriate time window given the hemodynamic response lags determined for this dataset as described previously (Francis et al. 1999): Glucose-Tasteless Control and Salt-Tasteless Control. To enable a single subject analysis, the thresholds in the resulting *z*-maps were then set at $P < 0.005$ (resel corrected) with a minimum cluster size of three contiguous voxels. For a more statistically sensitive analysis of activation in the region of the amygdala, a region of interest analysis (ROI) was also carried out, by defining two 84-voxel cubic ROIs centered on each amygdala within the medial temporal lobes, using the individual subjects' anatomical IR volume as a reference. The *z*-scores in the amygdala were then corrected for multiple comparisons (restricted to that region) at $P < 0.025$. The individual subjects' IR anatomical volumes were then registered to a standard high resolution (1 mm isotropic) anatomical volume, and the *z*-scores were rendered to that anatomical volume for better visualization. A group analysis was also carried out by setting

the threshold for significance of the *z*-maps from each subject for each of the two conditions at $P < 0.01$ (uncorrected) and identifying those voxels that were commonly activated (after transformation into Talairach space) in a minimum of six of seven subjects in each condition. The group analysis enabled voxels that were commonly activated at a significance level of $P < 0.01$ to be identified across subjects, and thus provided a measure of the reliability of the activation of particular voxels across subjects. Cluster sizes of <3 contiguous voxels in the group combined image were excluded from the analysis.

RESULTS

Pleasantness ratings

The average pleasantness rating (ranging from +2 = very pleasant, 0 = neutral, −2 = very unpleasant) for the Glucose condition, was +0.9 ± 0.49 (mean ± SE), whereas that for the Salt condition was −1.5 ± 0.16 (paired $t = 4.93$, df = 6, $P < 0.003$).

Orbitofrontal cortex

The single subject analysis showed that the orbitofrontal cortex was activated in six of seven subjects in the Glucose-Control condition and in six of seven subjects in the Salt-Control condition. Within each individual subject in the orbitofrontal cortex, different areas were activated by the Glucose and Salt tastes (the results from a single subject are presented in Fig. 1). The group analysis revealed common areas of activation across subjects in the orbitofrontal cortex for both glucose (pleasant) (Talairach coordinates: $X = 38$, $Y = 40$, $Z = -10$; $X = 47$, $Y = 38$, $Z = -6$; $X = -28$, $Y = 36$, $Z = -7$; $X = 12$, $Y = 42$, $Z = -1$) and salt (aversive) tastes (Talairach coordinates: $X = 13$, $Y = 36$, $Z = -8$; $X = -18$, $Y = 39$, $Z = -7$), and that the areas activated by each taste were nearby but showed little overlap (see Fig. 3). Taken together, the analyses show that there is some consistency of the areas activated across subjects, that the common area across subjects for glucose is separate from that for saline, and that in individual subjects the centers of mass of the activations were even further apart.

Insula and frontal operculum

The insula and frontal operculum were activated by the taste stimuli. The single subject analysis showed that the insula was activated in five subjects to glucose, and in three subjects to salt; the frontal operculum in five subjects to glucose, and three subjects to salt. The results for a single subject are shown in Fig. 2. The common areas across subjects (as revealed by the group analysis) showed that a considerable anterior-posterior extent of the insula/operculum could be activated by taste stimuli (Fig. 3). Some regions showed overlap of the activations to glucose and salt (Talairach coordinates: $X = 42$, $Y = 28$, $Z = 10$; $X = -48$, $Y = -5$, $Z = 0$), while other regions were activated by glucose (Talairach coordinates: $X = 46$, $Y = 11$, $Z = 17$; $X = 40$, $Y = 13$, $Z = -6$; $X = -33$, $Y = 17$, $Z = 2$). Both the group analysis and the single subject analysis did not provide clear evidence for chemotopography (with respect to glucose vs. salt) in the insular/opercular taste cortical areas.

Amygdala

The ROI analysis showed that pleasant taste (glucose) activated the left amygdala in five of the seven subjects (average Talairach coordinates: $X = -20$, $Y = -5$, $Z = -21$). Activation was also found to the taste of glucose in the right amygdala

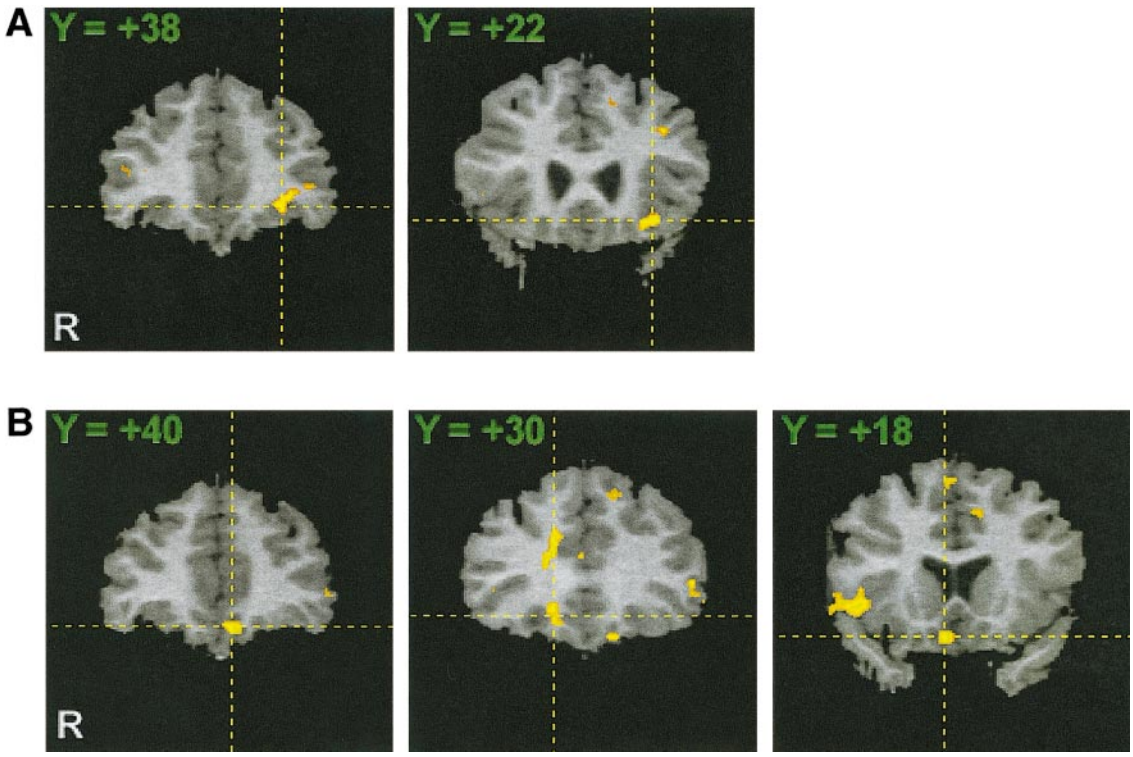

FIG. 1. Coronal slices through sections of orbitofrontal cortex at the anterior-posterior (*Y*) level indicated in Talairach space showing areas activated by (*A*) Glucose and (*B*) Salt in a single subject ($P < 0.005$ corrected).

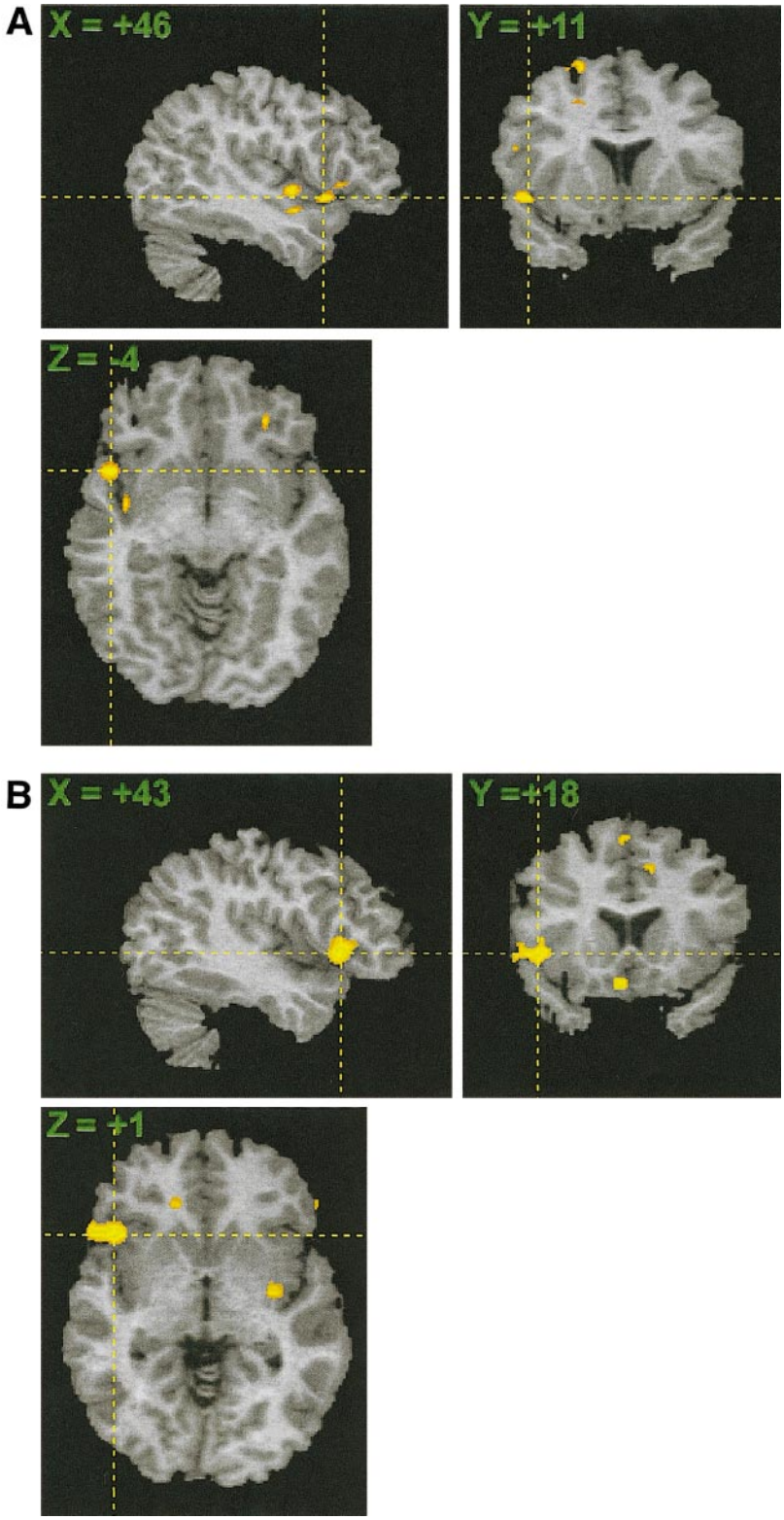

FIG. 2. Slices through the Insula/Operculum in Sagittal, Transverse, and Coronal planes at the Talairach coordinates indicated showing activation by (*A*) Glucose and (*B*) Salt in a single subject ($P < 0.005$ corrected).

in two of the seven subjects (Talairach coordinates: $X = 25$, $Y = -4$, $Z = -24$). Figure 4 shows not only the activations found in each subject, but also the median value of the activated voxels across subjects within the amygdala in the Glucose-Control condition. In the Salt-Control condition, the amygdala was significantly activated in four subjects in total, two subjects on the left side (Talairach coordinates: $X = -24$, $Y = -5$, $Z = -21$), and two subjects on the right (Talairach coordinates: $X = 18$, $Y = -4$, $Z = -14$).

Other areas

Activation was also found in the dorsal anterior cingulate (5 subjects to salt, 5 subjects to glucose). The Talairach coordi-

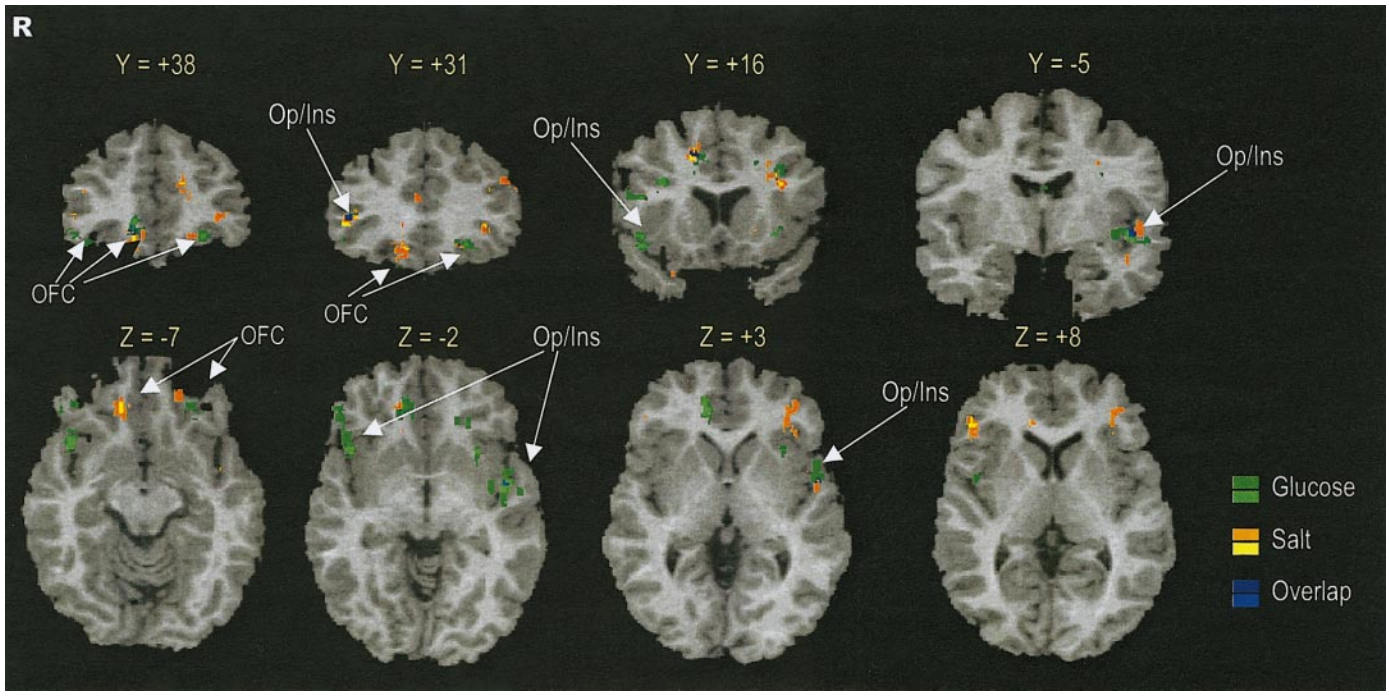

FIG. 3. Results from the group analysis. The thresholds for significance of the individual *z*-maps were set at $P < 0.01$ (uncorrected), and each *z*-map was transformed into Talairach space. Those voxels that were commonly activated in a minimum of 6 of 7 subjects were included in the group combination image (although clusters of <3 contiguous voxels were excluded). Glucose activations are depicted in green (voxels common to 6 subjects) and light green (voxels common to 7 subjects). Salt activations are depicted in orange (voxels common to 6 subjects) and yellow (common to 7 subjects). Areas of overlap between the 2 tastes are shown in blue. Coronal sections through regions of interest (ROIs) such as the orbitofrontal cortex and operculum/insula are shown in the *top row*, and transverse sections are shown in the *bottom row*, at the Talairach levels indicated. Arrows with labels point to some of the activated regions. OFC, orbitofrontal cortex; Op/Ins, frontal operculum/insula.

TABLE 1. *Talairach coordinates of areas activated in the group analysis for glucose and salt*

	Glucose			Salt			
Brain Region	Tal *X*	Tal *Y*	Tal *Z*	Tal *X*	Tal *Y*	Tal *Z*	Overlap
Orbitofrontal cortex							
Right	38	40	−10				
	47	38	−6				
	12	42	1	13	36	−8	*
Left	−28	36	−7	−18	39	−7	
Insula/operculum							
Right	45	9	17	45	30	10	*
	41	17	−7				
Left	−27	17	−1	−32	32	3	
	−48	2	−3	−45	−3	0	*
Anterior cingulate cortex							
Right	9	17	42	15	21	42	*
Left				−16	39	24	
Anterior temporal lobe cortex							
Right	50	5	−28	24	8	−22	
Inferior prefrontal cortex							
Right	32	14	27				
Left	−32	12	33	−33	16	25	
				−44	30	31	
L premotor							
Left	−19	5	54				
Striatum							
Left	−24	6	15				

* Areas in which there is an overlap in the activations produced by the 2 tastes (see text).

nates of the areas with activation in the group analysis are shown in Table 1.

DISCUSSION

The results from the single subject and the group analysis showed that the orbitofrontal cortex could be activated by sweet (pleasant) and salt (aversive) tastes. Moreover, the group analysis showed that the regions of the orbitofrontal cortex reliably activated across subjects by the sweet and salt tastes were adjacent. The separation between the two areas was more pronounced within individual subjects, as illustrated in Fig. 1. This is the first paper to investigate the effects of both pleasant and aversive taste stimuli (glucose and NaCl) against a tasteless control condition (as contrasted with previous studies that used substances such as citric acid or water that can activate neurons in the primate taste cortex) (Small et al. 1999) and thus provides clear evidence that pure gustatory stimuli (with nongustatory effects controlled for) activate the orbitofrontal cortex. We note that the sweet taste was rated as pleasant (+0.9) and the salt taste as aversive (−1.5). Thus we conclude that both a pleasant and an aversive taste are represented in the orbitofrontal cortex, and it follows, with respect to taste hedonics, that the orbitofrontal cortex is not concerned exclusively with the representation of only pleasant or aversive tastes. Although the two tastes were rated as pleasant or aversive, the study described here does not show directly that it is explicitly the hedonic value of the tastant that is represented in the orbitofrontal cortex. One way to address this issue would be to investigate the effects on the orbitofrontal cortex activation by

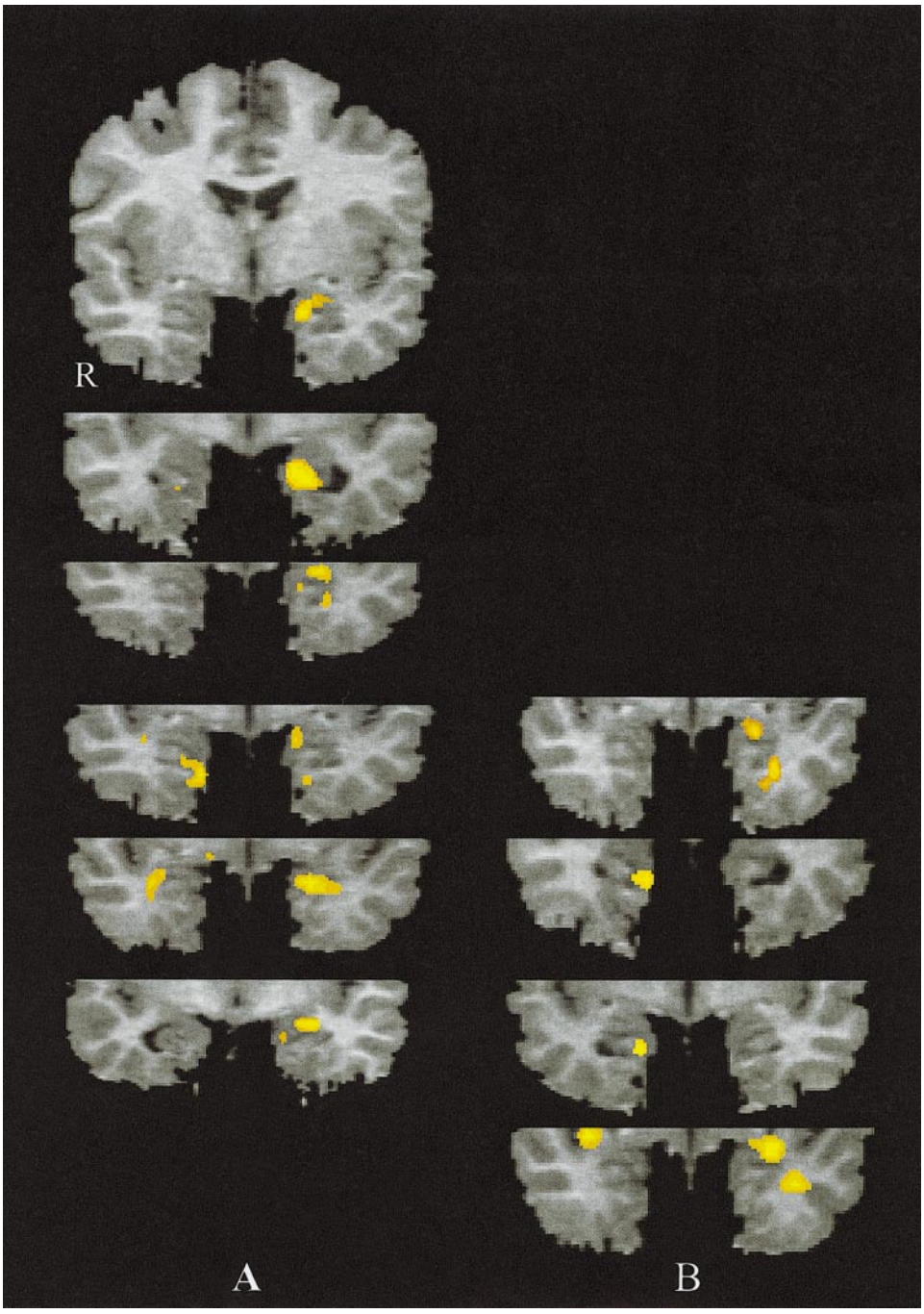

FIG. 4. Amygdala activation for the individual subjects shown for (*A*) Glucose and (*B*) Salt ($P < 0.025$ ROI corrected). Each of the horizontal pairs of images shows data from a single subject. The coronal slice on the *top left* depicts the voxelwise median across subjects with amygdala activation in the glucose condition.

glucose of feeding to satiety with glucose, which decreases the pleasantness of the taste of glucose but much less of its intensity (Rolls et al. 1983). However, we predict that this result would be found, because we have shown that in a nearby region of the orbitofrontal cortex the activation produced by a food odor is decreased by eating that food to satiety (O'Doherty et al. 2000). Given the results presented here for taste, it will be of interest to investigate further whether both pleasant and aversive stimuli in other modalities (including somatosensory, olfactory, and visual) can activate the human orbitofrontal cortex. Evidence on these issues is fundamental in understanding the functions of the human orbitofrontal cortex in emotion (Rolls 1999).

Another novel finding of this study is that the human amygdala can be activated by pleasant as well as by aversive tastes. The amygdala was activated in five of seven subjects in the pleasant taste condition, and in four of seven subjects in the unpleasant taste (salt) condition. These results provide new evidence to support the argument that the human amygdala is involved in pleasant as well as negative affect (Rolls 1999).

It is of interest that in humans the region of the insula and operculum that can be activated by taste does extend several millimeters back from the front of the operculum and insula. Although quite extensive, it is likely that this is the primary taste cortex of humans, with the orbitofrontal cortex containing the secondary taste cortex as in macaques (Baylis et al. 1994; cf. also Small et al. 1999). In previous neuroimaging studies of taste, activation has been reported over quite a wide region of

the anterior insular/opercular (primary taste) cortex, but in most studies only one taste stimulus was used or comparisons were not made between the effects of different tastants (Small et al. 1999). In our study, in the group analysis, it was found that in some parts of the anterior insula and frontal operculum there was overlap between the sweet and salt taste representations, while in other regions only one of the tastes produced activation. We know that in the primate (macaque) primary taste cortex there is some intermingling of neurons responsive to sweet and salt tastes (Rolls 1997; Scott et al. 1986). The present findings in humans are consistent with this but at the same time suggest that further exploration of whether there is in addition some chemotopography would be important.

To conclude, this study has shown that the orbitofrontal cortex can be activated by taste stimuli that are affectively positive and affectively negative, and there is some indication that the areas activated by pleasant and aversive tastes are topographically separate. Further, it was shown that the human amygdala can be strongly activated by affectively positive stimuli (sweet taste) as well as by affectively negative stimuli (salt taste). These stimuli are known to be positive and negative primary reinforcers, and the findings help to provide a basis for understanding the functions of the amygdala and the orbitofrontal cortex in positive as well as negative emotions (see further Rolls 1999, 2000a,b).

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