Sensory-specific satiety-related olfactory activation of the human orbitofrontal cortex

J. O'Doherty, E. T. Rolls,[CA] S. Francis,[1] R. Bowtell,[1] F. McGlone,[2] G. Kobal,[3] B. Renner[3] and G. Ahne[3]

Department of Experimental Psychology, University of Oxford, South Parks Road, Oxford OX1 3UD; [1] Magnetic Resonance Centre, University of Nottingham, Nottingham NG7 2RD2; [2]Unilever Research, Port Sunlight Laboratory, Wirral L63; [3]Department of Experimental and Clinical Pharmacology and Toxicology, University of Erlangen-Nuremberg, Germany

[CA]Corresponding Author

Received 13 October 1999; accepted 26 November 1999

Acknowledgements: A studentship was provided by the Medical Research Council and the Oxford McDonnell Pew Centre for Cognitive Neuroscience and Firmenich to J.O'D. This research is also supported by Unilever, MRC Special Project Grant G9302591 (Nottingham), MRC Programme Grant PG8513790 to E.T.R., and by the MRC Interdisciplinary Research Centre for Cognitive Neuroscience at Oxford.

When a food is eaten to satiety, its reward value decreases. This decrease is usually greater for the food eaten to satiety than for other foods, an effect termed sensory-specific satiety. In an fMRI investigation it was shown that for a region of the orbitofrontal cortex the activation produced by the odour of the food eaten to satiety decreased, whereas there was no similar decrease for the odour of a food not eaten in the meal. This effect was shown both by a voxel-wise SPM contrast ($p < 0.05$ corrected) and an ANOVA performed on the mean percentage change in BOLD signal in the identified clusters of voxels ($p < 0.006$). These results show that activation of a region of the human orbitofrontal cortex is related to olfactory sensory-specific satiety. *NeuroReport* 11:893–897 © 2000 Lippincott Williams & Wilkins.

Key words: Cingulate cortex; Emotion; Insula; Olfaction; Orbitofrontal cortex; Pleasant; Sensory-specific satiety

INTRODUCTION

When a food is eaten to satiety its reward value decreases to zero. This is operationally the case, in that a reward is anything that the organism will work to obtain. This decrease is usually greater for the food eaten to satiety than for other foods, an effect termed sensory-specific satiety [1]. The rated pleasantness of the taste and smell of foods show related changes. These changes in the reward value and rated pleasantness of the sensory input produced by food are one way in which food intake is controlled [1,2]. Sensory-specific satiety has been shown to occur to the odour of a food eaten to satiety [3]. In the brain of macaques, single neurons with olfactory responses in the orbitofrontal cortex decrease their responses to the odour of a food eaten to satiety, but much less to other foods not eaten in the meal [4,5]. To investigate the neural basis of the responses to food odours in humans and where in the brain these responses might be modulated by hunger, we performed the experiments described here in which fMRI was used to investigate the changes in the representation of a food-related odour after eating the corresponding food to satiety. Another reason for investigating the affective representation of odour in the brain is to advance our understanding of the brain mechanisms of emotion and its disorders, in that emotions can be considered as states elicited by rewards and punishers, of which pleasant odours are an example.

In previous neuroimaging studies in humans, Zatorre *et al.* [6] showed in a PET study that the right orbitofrontal cortex as well as structures that receive direct inputs from the olfactory tract such as the pyriform cortex are activated by odours. A number of other investigations have also reported olfactory activation of the orbitofrontal cortex [7–10]. Zald and Pardo [7] reported that aversive odours may be especially represented in the left orbitofrontal cortex and amygdala. It is an open question in humans about where in the olfactory system hunger influences the processing of food-related odours, although the neurophysiology described above suggests that the orbitofrontal cortex could be one such brain region.

The design of the experiments we performed was to measure changes in the BOLD signal in an on/off block design to the odour of banana and of vanilla, then to allow the subjects to eat banana to satiety, and then to repeat the measurements of brain activation produced by the two olfactory stimuli.

MATERIALS AND METHODS

Procedure: Imaging was conducted using a 3 T fMRI scanner at the University Of Nottingham. T2-weighted coronal images were obtained using echo-planar imaging (EPI) with a 128×64 matrix size, 23 ms echo time and gradient switching frequency of 1.9 kHz. Ten coronal T2*-weighted slices were acquired every 1.67 s (TR), with an in-plane resolution of 3 mm and slice thickness of 8 mm. This gave coverage from Y (anterior) = +40 (Talairach co-ordinates) to −40. Olfactory stimulation was produced using an olfactometer in which the stimulants are delivered without altering the mechanical or thermal conditions at the mucosa [11]. Pulses of odours were mixed in a constantly flowing air-stream (total flow rate 140 ml/s) with controlled temperature and humidity (36.5°C, 80% relative humidity). The olfactory stimuli were delivered in 334 ms bursts delivered 16 times throughout the on period which lasted 5 s in total (3 vol). The olfactory stimuli were delivered using velo-pharyngeal closure. Total cycle length was 20 s (including a 15 s rest period). Each run consisted of 30 cycles. The food-related odours used were vanilla (2.1 p.p.m.) and banana odour (Borthwicks Flavours) in an equivalent concentration. Five healthy subjects participated in this experiment. The subjects were scanned initially when hungry, and were presented with the two food-related odours in separate imaging runs. They were then taken out of the scanner, and provided with a lunch of bananas. After eating the banana lunch to satiety, the subjects were placed back into the scanner, and the two odour conditions were repeated. Subjective ratings of the pleasantness and intensity of the odours as well hunger and thirst ratings were taken before each scanning period.

Image analysis: The volumes from all four datasets (conditions) were registered to the first volume in the first dataset using a 3D AIR motion correction algorithm [12]. Spatial smoothing, intensity normalization and temporal filtering were then applied to the data. Brain areas activated by odour were identified by performing a model free one-way ANOVA on the full dataset for each subject to detect regions in which within-cycle variance of a voxel was significantly greater than the overall variance throughout the dataset [13]. The resulting F-maps were then converted to z-scores and thresholded using MEDx (Sensor Systems Inc) cluster analysis taking a minimum z threshold of 4.0 and a minimum cluster probability of $p < 0.01$. The z-maps were registered to the corresponding inversion recovery (IR) anatomical volume from each subject, and activation regions that corresponded across the subjects were obtained by registering each anatomical volume to that of an individual subject and combining the transformed z-maps (as described by Smith *et al.* [14]). The Talairach co-ordinates of each activated brain region were obtained by placing the individual subject IR anatomical volumes into Tailarach space [15] using a MEDx linear registration algorithm.

Brain areas showing changes of activation related to sensory-specific satiety were identified using SPM99b (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks, Inc., Sherborn, MA). A statistical parametric map was generated for each subject by fitting a box-car function to each combined dataset, convolved with the haemodynamic response function. A contrast was then performed which identified regions which had significantly decreased activation in the post-satiety banana odour (D) condition relative to the mean of the other three conditions: pre-satiety banana odour (A) , pre-satiety vanilla odour (B) and post-satiety vanilla odour (C). The contrast used was ([A + B + C]/3−D). This contrast was masked to include only those voxels which were significantly activated by the odour in conditions A, B and C compared to rest. This particular contrast was used rather than a two-way interaction contrast ([A−D]−[B−C]) because the latter contrast would also have detected voxels that showed a significant increase in the activation produced by vanilla in the post- *vs* pre-satiety condition. The resulting z-maps were then thresholded at $p < 0.05$ (corrected). The mean percentage change in the BOLD signal within each significantly activated cluster was measured for each subject. This was calculated in a time window when the olfactory-induced activation was maximal (by taking the mean percentage difference between the intensity values at the average of the three highest values within each cycle, corresponding to volumes 6–8 in the cycle, from the average of the three lowest values within each cycle, corresponding to volumes 11, 12 and 1 in the cycle. The z-maps were then registered to the corresponding IR anatomical volume for that subject. The simple contrast (A−D) was also performed to identify voxels which decreased their activation from the pre-satiety banana condition to the post-satiety banana condition (also thresholded at $p < 0.05$ corrected).

RESULTS

Brain areas activated by odour: The areas activated by odour (independent of the specific odour used or the satiety condition) are shown in Fig. 1 (the group combination of the individual thresholded z-maps) and Table 1 (the Talairach co-ordinates for each area that was activated in all five subjects). The orbitofrontal cortex was consistently activated in all five subjects (see Fig. 1, coronal section at y = +25; four subjects on the right and three subjects on the left). The anterior insula or agranular/dysgranular insula was activated in all five subjects. In some subjects the activated insula clusters also included part of the frontal operculum. Also activated was a part of the primary somatosensory cortex (perhaps corresponding to an area of somatosensory cortex representing oropharyngeal structures; see Fig. 1, coronal section at y = −20), pre-motor cortex (area 6), and a part of the dorsal anterior cingulate. These areas activated by odour are consistent with the results of previous imaging studies [6,10]. Significant activation was not found in primary olfactory areas such as the pyriform cortex (except in one subject). Activation was also found in areas of the dorsolateral prefrontal cortex including area 8 and areas 9/45 in some subjects, but as there did not appear to be a specific region of dorsolateral prefrontal cortex consistently activated across all subjects this area is not reported in Table 1. Other areas activated in some subjects were the posterior cingulate (three subjects) and posterior insula (three subjects).

Subjective ratings: The subjective ratings are summarized in Fig. 2. The average pleasantness rating (+2 = very

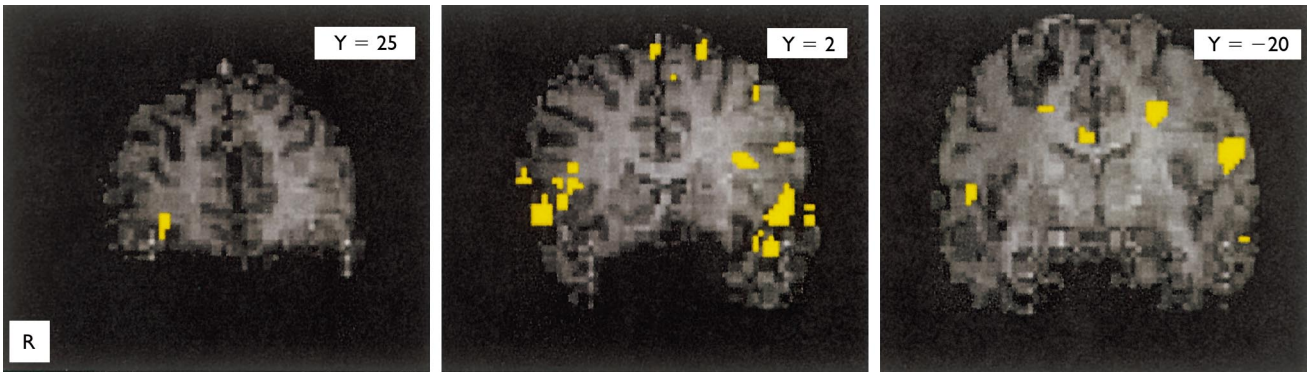

Fig. 1. Group combination of areas activated by odour (see text). The combinations of the activations across subjects are shown on coronal sections at Y = +25, y = +2, and y = −20 mm (Talairach coordinates).

Table 1. The mean co-ordinates of regions consistently activated across all five subjects (in either the left or right hemispheres). The co-ordinates given are averaged across the individual subjects and the standard deviations of the co-ordinate locations also given in brackets.

Brain area	Coordinates			Number of subjects
	X	Y	Z	
R orbitofrontal cortex	20 ± 9.6	25 ± 7.8	−7 ± 6.2	4
L orbitofrontal cortex	−26 ± 17.7	28 ± 5.6	−7 ± 7.8	3
R anterior/mid insula	41 ± 4.1	2 ± 5.6	0 ± 6.2	5
L anterior/mid insula	−45 ± 7.0	3 ± 5.1	0 ± 13.3	4
R dorsal anterior cingulate	3 ± 3.5	18 ± 14.8	35 ± 0.7	3
L dorsal anterior cingulate	−8 ± 3.3	15 ± 12.5	33 ± 9.5	5
R primary somatosensory	41 ± 14.1	−31 ± 4.7	30 ± 9.5	3
L primary somatosensory	−42 ± 7.8	−23 ± 4.9	30 ± 9.2	3
R pre-motor (area 6)	25 ± 29.8	−9 ± 8.6	55 ± 22.6	4
L pre-motor (area 6)	−20 ± 8.1	8 ± 14.7	34 ± 11.2	4

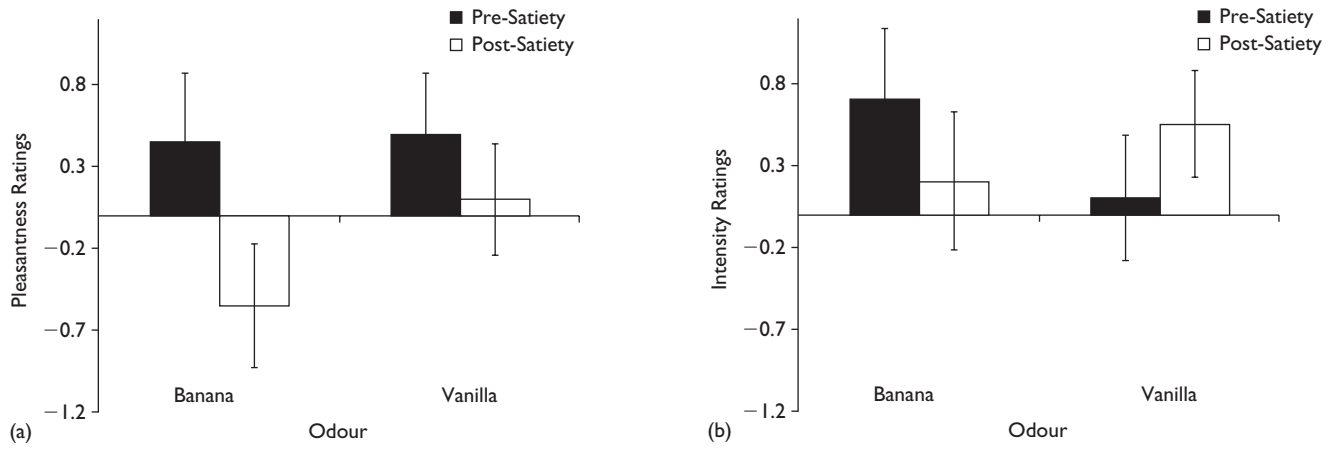

Fig. 2. Average (**a**) pleasantness and (**b**) intensity ratings of each odour before and after eating banana to satiety. (+2 = very pleasant; 0 = neutral; −2 = very unpleasant. For intensity, +2 = very intense; −2 = very weak).

pleasant, 0 = neutral, −2 = very unpleasant) for the banana odour decreased after the banana was eaten to satiety for lunch ($t = 3.6$, $df = 4$, $p < 0.05$ one-tailed). There was no significant decrease in the pleasantness of the vanilla odour. Thus the subjects showed olfactory sensory-specific satiety which was similar to that investigated in a much larger group [3]. There were no significant differences in the intensity ratings from pre- to post-satiety, also as found in a large group of subjects. The pleasantness ratings of the odour of the real bananas before eating was +0.63 and the pleasantness rating decreased to −0.75 after eating. The subjects' average hunger ratings before eating the bananas

were +0.58 while the ratings after eating the bananas had dropped to −0.75 (+2 = very hungry, −2 = not at all hungry). The average amount of banana eaten was 315 g (~3.5 bananas, range 180–450 g).

Brain areas with activation related to olfactory sensory-specific satiety: The orbitofrontal cortex contained regions in all the subjects in which the activation was related to the sensory-specific satiety as shown by the sensory-specific satiety related SPM contrast (significant in every subject at $p < 0.05$, corrected). These regions are shown in Fig. 3a for each individual subject. In four subjects the region was on the right (mean Talairach co-ordinates (x,y,z) = 18, 18, −17) and in one subject on the left (Talairach co-ordinates = −28, 20, −5). The effect is further illustrated by the mean percentage change in BOLD signal for this region in each condition across subjects shown in Fig. 3b. It is clear that the activation in this region to banana decreased by eating banana to satiety, while the activation to vanilla did not decrease (and if anything increased, as commonly occurs for the pleasantness of a food not eaten to satiety, see Rolls and Rolls [3]). A *post-hoc* repeated measures ANOVA carried out across subjects on the percentage change BOLD activation measures within the orbitofrontal cortex for each condition, revealed a significant satiety × odour interaction ($F(1,4) = 32.8$, $p = 0.006$).

No other brain area showed a similar olfactory sensory-specific satiety related change in activation in all or most subjects. Among the other areas that were activated by the main effect of odours described above, in one subject a sensory-specific satiety effect was found in the insula; in one in the amygdala, and in three in the dorsal anterior cingulate.

Brain areas modulated by satiety: For completeness, we also performed the simple contrast between banana odour pre-satiety vs banana odour post-satiety. In all subjects, there was less activation by the banana odour after banana had been eaten to satiety in the orbitofrontal cortex. This is consistent with the sensory-specific satiety effects just described. In addition, in four subjects there was a decrease in activation found either in the amygdala, or in a nearby medial temporal lobe area. In one subject there was a decrease in the insula.

DISCUSSION

The brain areas activated by odour, including the orbitofrontal cortex, were consistent with earlier studies [7–10]. The new finding described here is that activation of the orbitofrontal cortex is related to sensory-specific satiety. In particular, activation of the orbitofrontal cortex decreased to the odour of a food eaten to satiety (banana), but not to another odour that had not been eaten (vanilla). It was possible to complete the experiment on sufficient subjects

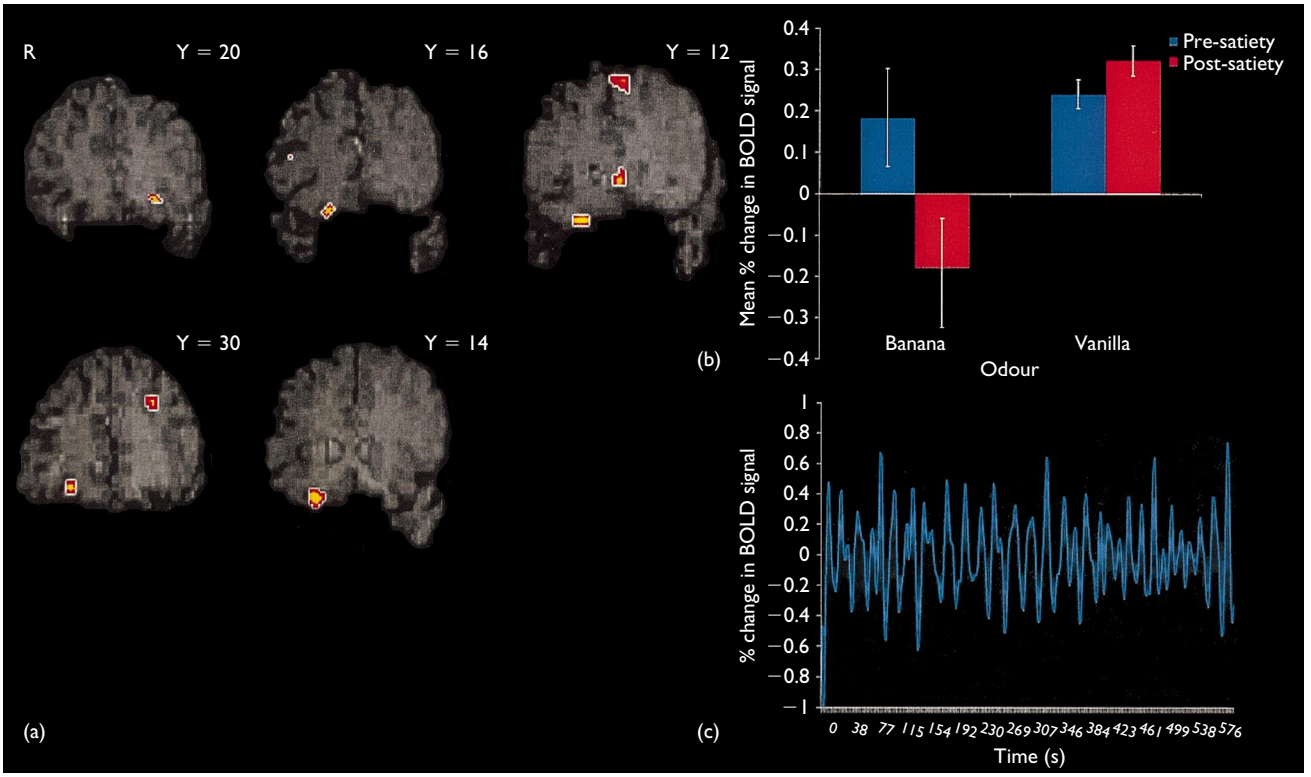

Fig. 3. (**a**) Regions of the orbitofrontal cortex in which the BOLD-measure activation was related to sensory-specific satiety. Coronal sections at the anterior (y) levels shown through the orbitofrontal cortex are shown for each subject. The activations that were significant ($p < 0.05$ corrected) in the SPM olfactory sensory-specific satiety contrast (see text) are shown in colour. (**b**) Mean percentage change in the BOLD signal across subjects of significantly activated clusters in the orbitofrontal cortex for each condition. (**c**) Time course of activation produced in one subject in the banana pre-satiety condition in the orbitofrontal cortex.

that the overall significance of the results for the orbitofrontal cortex was high ($p = 0.006$). The finding was also supported by the result of a separate statistical comparison which showed that the odour of banana produced less activation of the orbitofrontal cortex when satiated by banana than when hungry.

The effects did not appear to be related to general olfactory habituation. One point of evidence for this is that the BOLD activation measure did not decrease to the vanilla odour, which was not eaten as part of the meal (see Fig. 3b). A second point is that the olfactory system was in a generally steady state during these experiments, in that there was no sign of habituation of the BOLD signal in this region across the 30 repetitions of an odour (an example of such a time course is shown in Fig. 3c). Instead, the decrease of the BOLD-measured activation in the orbitofrontal cortex appeared to be related to sensory-specific satiety effects. The particular aspect of the sensory stimuli that alters most in sensory-specific satiety experiments when performed with large groups of subjects is the pleasantness of the taste or smell of the food, rather than its intensity [3,16].

The most likely interpretation of the sensory correlate of the orbitofrontal cortex activation described here is the pleasantness of the odour, although some relation to intensity cannot be ruled out. To investigate that particular issue further, one approach would be to test using a series of odours of different pleasantnesses in different concentrations, so that the change of BOLD-measured activation in different parts of the olfactory system can be correlated with both the pleasantness and the intensity of odours. However, the present results do show that when the sensory effects of the odour of food alter when the odour is of a food eaten to satiety, the alteration in the human orbitofrontal cortex shows the pattern of changes most closely associated with sensory-specific satiety effects. The implication of the present study is that the change in the orbitofrontal cortex is related to the change in pleasantness of the odour. The finding receives support from detailed single neuron studies in macaques, which show that the responses of orbitofrontal cortex neurons decrease to the odour of a food eaten to satiety in a sensory-specific way [4,5].

The results described here were obtained when olfactory stimuli were delivered in a highly controlled way using a carefully designed olfactometer, which maintained a constant air-stream when the odour was not being delivered, which switched to the odour without any change of pressure under computer control, and which maintained the temperature and humidity of the air-stream constant [11]. Moreover, a feature of the experiments described here is that only an olfactory stimulus was delivered, so that the nature of the food-related stimulus under investigation was well defined.

This study is of interest not only in relation to the issue of where affect is represented in the brain, which itself helps to identify brain systems involved in emotion (see [1]), but also in relation to how food intake is controlled. The experiments described here are consistent with neurophysiological evidence in primates that the orbitofrontal cortex is important in food intake because it is a brain region in which satiety signals and satiety-related processing modulate the sensory effects produced by food.

CONCLUSION

When a food is eaten to satiety, its reward value and its pleasantness, decrease. This decrease is usually greater for the food eaten to satiety than for other foods, an effect termed sensory-specific satiety. In an fMRI investigation it was shown that for a region of the orbitofrontal cortex the activation produced by the odour of a food eaten to satiety decreased, whereas there was no similar decrease for the odour of a food not eaten in the meal. These results show that the degree of activation of a region of the human orbitofrontal cortex is related to olfactory sensory-specific satiety. In humans, as in macaques, a part of the orbitofrontal cortex may thus represent the reward value and affective aspects of olfactory stimuli.

REFERENCES

1. Rolls ET. *The Brain and Emotion*. Oxford University Press: Oxford, 1999.
2. Cabanac M. *Science* **173**, 1103–1107 (1971).
3. Rolls ET and Rolls JH. *Physiol Behav* **61**, 461–473 (1997).
4. Critchley HD and Rolls ET. *J Neurophysiol* **75**, 1673–1686 (1996).
5. Critchley HD and Rolls ET. *J Neurophysiol* **75**, 1659–1672 (1996).
6. Zatorre RJ, Jones Gotman M, Evans AC and Meyer E. *Nature* **360**, 339–340 (1992).
7. Zald DH and Pardo JV. *Proc Natl Acad Sci USA* **94**, 4119–4124 (1997).
8. Small DM, Jones-Gotman M, Zatorre RJ *et al. Neuroreport* **8**, 3913–1917 (1997).
9. Sobel N, Prabhakaran V, Desmond JE *et al. Nature* **392**, 282–286 (1998).
10. Francis S, Rolls ET, Bowtell R *et al. NeuroReport* **10**, 453–459 (1999).
11. Kobal G and Hummel CS. *Electroencephalogr Clin Neurophysiol* **71**, 241–250 (1988).
12. Woods RP, Mazziotta JC and Cherry SR. *J Comput Assist Tomogr* **16**, 620–633 (1992).
13. Clare S, Humberstone M, Hykin J *et al. Magn Reson Med* In press (1999).
14. Smith SM, Matthews PM, Gurd JM and Slater A. *Neuroimage* **7**, 759 (1998).
15. Talairach J and Tournoux P. *Co-Planar Stereotaxic Atlas of the Human Brain*. Stuttgart: Thieme, 1988.
16. Rolls ET, Rolls BJ and Rowe EA. *Physiol Behav* **30**, 185–192 (1983).