

# Different representations of pleasant and unpleasant odours in the human brain

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## Abstract

Odours are important in emotional processing; yet relatively little is known about the representations of the affective qualities of odours in the human brain. We found that three pleasant and three unpleasant odours activated dissociable parts of the human brain. Pleasant but not unpleasant odours were found to activate a medial region of the rostral orbitofrontal cortex. Further, there was a correlation between the subjective pleasantness ratings of the six odours given during the investigation with activation of a medial region of the rostral orbitofrontal cortex. In contrast, a correlation between the subjective unpleasantness ratings of the six odours was found in regions of the left and more lateral orbitofrontal cortex. Moreover, a double dissociation was found with the intensity ratings of the odours, which were not correlated with the BOLD signal in the orbitofrontal cortex, but were correlated with the signal in medial olfactory cortical areas including the pyriform and anterior entorhinal cortex. Activation was also found in the anterior cingulate cortex, with a middle part of the anterior cingulate activated by both pleasant and unpleasant odours, and a more anterior part of the anterior cingulate cortex showing a correlation with the subjective pleasantness ratings of the odours. Thus the results suggest that there is a hedonic map of the sense of smell in brain regions such as the orbitofrontal cortex, and these results have implications for understanding the psychiatric and related problems that follow damage to these brain areas.

## Introduction

One of the most important features of odour perception is its hedonic or affective component. Most odours are labelled as ‘pleasant’ (positive hedonic value) or ‘unpleasant’ (negative hedonic value). The aim of this study is to investigate whether there are separate representations of pleasant and unpleasant odours in areas of the human brain that receive olfactory inputs, including in particular the orbitofrontal cortex, cingulate cortex, and subgenual cingulate cortex, as these areas are implicated in affect (Rolls, 1999). An additional aim is to investigate brain areas involved in emotion, for emotions can be defined as states elicited by rewarding (generally subjectively pleasant) and punishing (generally subjectively unpleasant) stimuli, and the representation of pleasant and unpleasant olfactory stimuli thus provides one part of a systematic study of the brain regions involved in affect (Rolls, 1999).

In primates, the projections from the olfactory bulb reach medial olfactory areas including the pyriform (primary olfactory) cortex, entorhinal cortex, cortico-medial nucleus of the amygdala, and olfactory tubercle. From the pyriform cortex, projections reach area 13a, a part of the caudal orbitofrontal cortex, and from there project on to area 13 of the caudal orbitofrontal cortex, and then on to further orbitofrontal areas (Carmichael *et al.*, 1994; Öngür & Price, 1998). Populations of neurons in the primate (macaque) orbitofrontal cortex have olfactory responses to odours (Tanabe *et al.*, 1975; Takagi, 1986; Rolls *et al.*, 1996b), which in many cases reflect the reward value of the odour (Critchley & Rolls, 1996a, b; Rolls *et al.*, 1996a).

In positron emission tomography (PET) neuroimaging studies in humans, Zatorre *et al.* (1992) and Zald & Pardo (1997) showed that the orbitofrontal cortex can be activated by odours such as vanilla and H<sub>2</sub>S. Another PET study found that the perception, discrimination and recognition of odours activate the orbitofrontal, cingulate and insula cortices (Savic & Berglund, 2000), while another PET study found that the right orbitofrontal cortex was associated with familiarity judgements (Royet *et al.*, 1999). Zatorre *et al.* (2000) showed in a PET study that orbitofrontal cortex activation was related to judgements of the hedonic value of a set of odours, but they did not describe any investigation of whether different brain regions were activated by pleasant and unpleasant odours, or covaried with subjective ratings of pleasantness vs. unpleasantness. A recent functional magnetic resonance neuroimaging (fMRI) study (Anderson *et al.*, 2003) found that activation of the amygdala was associated with intensity and of the orbitofrontal cortex with the valence of two odours, but only two different odours (citral and valeric acid) were used so that inferences about whether brain activations reflect pleasant odours in general, or instead citral vs. valeric acid, are unclear; and, also in contrast to the present study, subjects were asked to rate the odours for pleasantness and intensity *after* (and not during) collecting the neuroimaging data.

It is thus an open question in humans whether there are differences in the representation of pleasant and unpleasant odours. This issue was addressed in this investigation. We performed fMRI while three pleasant, and three unpleasant odours were delivered through an olfactometer. Each of the odours was a pure chemical, to ensure that the composition of each stimulus was constant throughout the experiment. To enable the brain activations to be directly related to the subjective affective value of the stimuli, pleasantness/unpleasantness

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ratings were taken during the neuroimaging, and we were able to perform a correlation between these ratings and the brain activations measured. Given the evidence from neurophysiological experiments (Rolls *et al.*, 1996b) and from neuroimaging experiments (O'Doherty *et al.*, 2000; Anderson *et al.*, 2003), we hypothesized that the orbitofrontal cortex and the anterior cingulate cortex would be activated by the odours. Moreover we used special methods to ensure that activations in the orbitofrontal cortex could be measured (Wilson *et al.*, 2002), as this region is implicated in the representation of the affective value of a variety of sensory stimuli.

## Materials and methods

### Experimental subjects

Eleven healthy right-handed subjects (six women and five men) participated in the experiment. Written informed consent from all subjects and ethical approval were obtained before the experiment. Prior to the scanning sessions subjects were exposed to each of the odours and trained to use a visual scale for rating the intensity and pleasantness of each of the odours.

### Stimuli and experimental design

The odours were chosen from a pool of 18 carefully selected odours, which had undergone meticulous psychophysical investigations in 35 subjects at Firmenich (Switzerland) such that the odour concentrations were matched for similar intensity. The pleasant odours chosen were linalyl acetate (floral, sweet), geranyl acetate (floral) and alpha-ionone (woody, slightly food-related). (Chiral substances were used as racemates.) The unpleasant odours chosen were hexanoic acid, octanol and isovaleric acid. All odours were diluted at 5% in propylene glycol.

A purpose-built continuous airflow 10-channel computer-controlled olfactometer was constructed to allow odour stimuli to be delivered in the MRI scanner. The control and metal components of the system are kept outside the scanner room, and the system is free of any auditory, tactile or thermal shifts that could cue the subject to the onset of odour delivery. The flow of clean pressurized medical air is controlled using a pressure regulator and flow meter. The air is directed using solenoid-operated valves controlled by the stimulus computer using TTL pulses to either a clean air washbottle containing only solvent, propylene glycol, or to one of seven other washbottles each containing one odourant dissolved in the propylene glycol. Each washbottle is connected by its own Teflon tube (to provide for low adhesion) to a delivery nozzle placed within 1 cm of the nose to minimize dead space. The delivery nozzle provided two types, one for each nostril, to produce birhinal stimulation. This provides seamless alternation between odourant and nonodourant conditions. The odour air stream was on for 8000 ms for any one odourant, and at all other times the clean air wash bottle and line were being used. The 24 000 ms intertrial interval with the stream of pure odourless air (passed through propylene glycol solvent) ensured the removal of the previous odourant before delivery of the next odourant. The flow-rate of the air supply was kept constant at 10 L/min such that the same degree of tactile somatosensory stimulation was delivered throughout. The olfactometer is the same design (apart from the longer Teflon tubes) as that used to analyse the responses of single neurons in the orbitofrontal cortex to odours (Critchley & Rolls, 1996b; Rolls *et al.*, 1996a, b). All odours were presented birhinally in a randomised block design during the imaging, with a total of ten presentations of each odour. Subjects were instructed to keep their heads absolutely still, breathe normally and to smell but not sniff the visually cued odour. Subjects were pretrained on the stimulation procedure where the onset of odour stimulation was visually cued and where after the 8000 ms stimulation

period, the odour was rated using a button box for both pleasantness and intensity, using a visual rating scale from +2 (very pleasant/very strong) to -2 (very unpleasant/very weak).

### fMRI data acquisition

Images were acquired with a 3.0-T VARIAN/SIEMENS whole-body scanner at FMRIB, Oxford. Local brain shim was performed using special weighting in the inferior frontal region before acquiring 840 volumes of 14 T2\* weighted coronal EPI slices with TR = 2 s and a TE of 25 ms. Slice thickness was 7 mm and in-plane resolution was 3 × 3 mm. Coverage was obtained from +60 (A/P) to -38 (A/P). The following parameters were carefully selected in order to minimize susceptibility and distortion artefact in the orbitofrontal cortex and are fully described in Wilson *et al.* (2002). Firstly, 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 helps to minimize through-plane dephasing. Secondly, the voxel resolution was minimized by using 3 mm in-plane resolution and a 7-mm slice thickness, which results in less phase cancellation than would be produced by lower voxel resolutions. Thirdly, a relatively low TE of 25 ms was selected to decrease the signal dropout, as less phase dispersion is created across the voxels. Fourthly, 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 specialist head insert gradient coil (Magnex SGRAD III) with a relatively high gradient switching frequency of 960 Hz.

### fMRI data analysis

Image preprocessing was performed with FLIRT (FMRIB Linear Registration Tool) (Jenkinson & Smith, 2001) for realignment, reslicing with sinc interpolation and normalization in MNI space (Collins *et al.*, 1994). SPM99 (Wellcome Institute of Cognitive Neurology) was then used first in applying spatial smoothing with an 8-mm full width half maximum isotropic Gaussian kernel and global scaling. The time series at each voxel were high-pass and low-pass filtered with a haemodynamic response kernel. A general linear model was then applied to the time course of activation of each voxel and linear contrasts were defined to test the specific effects of each condition.

Specific effects were tested by performing conjunction analysis (Friston *et al.*, 1999) on individual linear contrasts corresponding to statistical parametric maps of the *t* statistic (then transformed into the unit normal distribution SPM Z). Conditions were established for each of the six odours and for each of the six control periods with pure air following each odour. The main effects of pleasant odours were established by the conjunction of the contrasts: [linalyl acetate - control linalyl acetate] and [alpha-ionone - control alpha-ionone] and [geranyl acetate - control geranyl acetate]. The main effects of unpleasant odours were established by the conjunction of the contrasts involving the subtraction of the remaining three unpleasant odours minus their respective pure air control periods. In addition a correlation analysis based on the individual subjective ratings was performed in each subject revealing voxels representing a significant correlation between BOLD signal change and pleasantness ratings across all odours. Each individual subject-specific contrast was then entered into a second-level, random-effects group analysis (d.f. = 10). Reported *P*-values based on this group analysis for a *priori* regions of interest based on our prior hypothesis (i.e. that the orbitofrontal cortex and anterior cingulate cortex are involved in olfaction) were corrected by small volume correction (SVC) for the number of comparisons made within each region (Worsley *et al.*, 1996).

## Results

The mean pleasantness ratings given by the 11 subjects through the experiment were  $1.08 \pm 0.26$  (SEM) for the pleasant odours, and  $-0.79 \pm 0.27$  for the unpleasant odours ( $t = 3.91$ ,  $P < 0.006$ , two-tailed; the rating scale was from +2 very pleasant to -2 very unpleasant). No significant differences were found with respect to the intensity ratings, which (on a scale of +2 very intense to -2 very weak) were  $0.50 \pm 0.41$  (mean  $\pm$  SEM) for the unpleasant odours, and  $0.42 \pm 0.44$  for the pleasant odours.

Figure 1 shows the brain regions activated by each of the odours with respect to the clean air control in a group analysis across all 11 subjects. It was notable that a part of the medial orbitofrontal cortex was activated by each of the three pleasant odours, and that similar activations were not produced by any of the three unpleasant odours. Some activation of regions of the cingulate cortex was also found.

To investigate the common brain areas activated by all three pleasant odours, we performed a group conjunction analysis across all three pleasant odours (Friston *et al.*, 1999) (see Materials and methods). A large cluster of activated voxels (see Fig. 2) was found in the medial OFC with the voxel of highest significance located at MNI coordinates 0, 54, -12 and significance level  $Z = 5.23$  ( $P < 0.05$  corrected for multiple comparisons). Another significant cluster was found in the

anterior cingulate cortex with peak at 2, 20, 32 ( $Z = 5.44$ ,  $P < 0.05$  corrected for multiple comparisons). This analysis was confirmed and extended by another conjunction which tested for voxels significantly activated by the average of the pleasant odours and not activated by the average of the three unpleasant odours (i.e. [(Pleasant) and (-Unpleasant)]). This also revealed a large cluster of activated voxels in the same part of the medial OFC ( $P < 0.05$  corrected for multiple comparisons). This shows that this medial orbitofrontal cortex region is selectively activated by the pleasant with respect to the unpleasant odours, and that the anterior cingulate region is not significantly differently activated by the pleasant and unpleasant odours.

Conjunction analysis was similarly applied to reveal activations common to the three unpleasant odours (Fig. 2, below). A lateral part of the orbitofrontal cortex was activated ( $-36, 27, -8$ ;  $Z = 4.23$ ,  $P < 0.05$  SVC). In addition, the sagittal view (left) in Fig. 2 (below) shows an activated region of the anterior cingulate cortex ( $x, y, z = 0, 18, 36$ ;  $Z = 4.42$ ,  $P < 0.05$ , SVC), which is very similar to the region activated by the conjunction of the pleasant odours. Finally, a part of the anterior insula was activated by the conjunction of the three unpleasant odours with a peak at 45, 15, -9 ( $Z = 3.79$ ,  $P < 0.0001$  uncorrected), and the same region was activated by a conjunction of the three pleasant odours ( $Z = 4.69$ ,  $P < 0.05$  corrected for multiple comparisons).

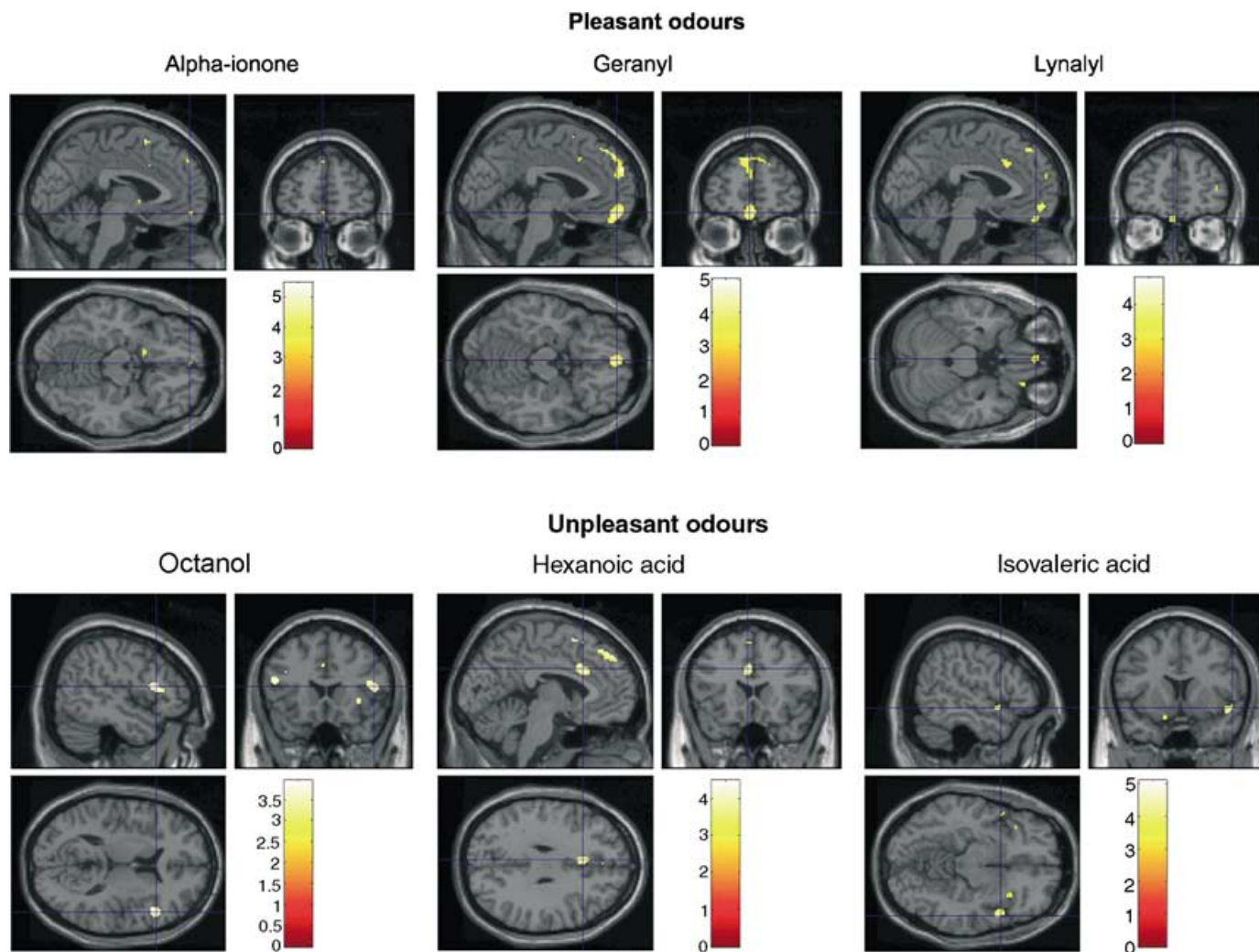


FIG. 1. Individual pleasant and unpleasant odour activations. The figure shows the group activations to each individual odour across 11 subjects with representative sagittal, axial and coronal slices. The activations were thresholded at  $P < 0.001$  to show the extent of the activations.

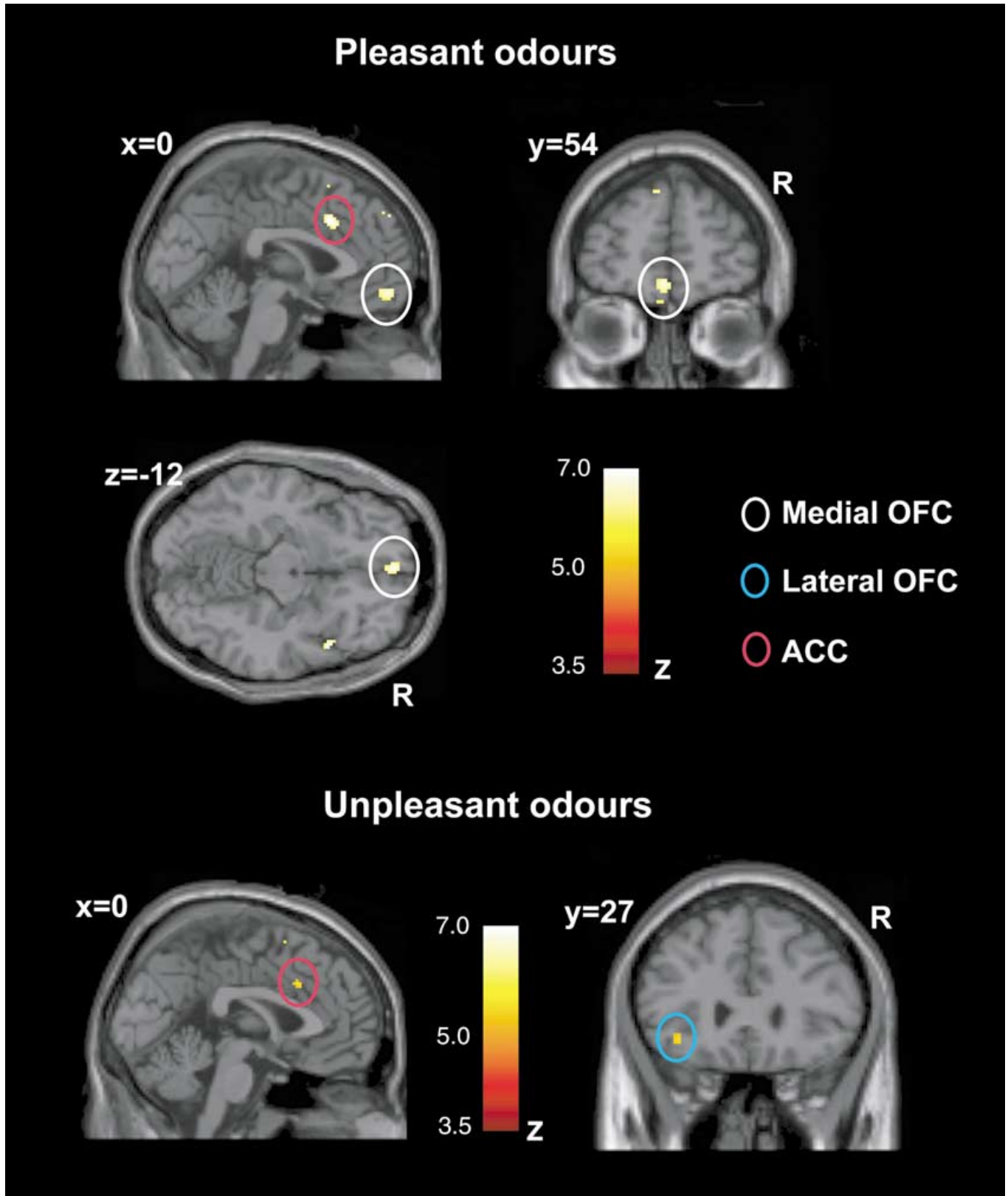


FIG. 2. Pleasant odours: group conjunction results for the three pleasant odours. Sagittal, horizontal and coronal views are shown at the levels indicated, all including the same activation in the medial orbitofrontal cortex, OFC ( $x, y, z = 0, 54, -12$ ;  $Z = 5.23$ ). Also shown is activation for the three pleasant odours in the anterior cingulate cortex, ACC ( $x, y, z = 2, 20, 32$ ;  $Z = 5.44$ ). These activations were significant at  $P < 0.05$  fully corrected for multiple comparisons. Unpleasant odours: group conjunction results for the three unpleasant odours. The sagittal view (left) shows an activated region of the anterior cingulate cortex ( $x, y, z = 0, 18, 36$ ;  $Z = 4.42$ ,  $P < 0.05$ , SVC). The coronal view (right) shows an activated region of the lateral orbitofrontal cortex ( $-36, 27, -8$ ;  $Z = 4.23$ ,  $P < 0.05$ , SVC). All the activations were thresholded at  $P < 0.00001$  to show the extent of the activations.

A direct comparison between pleasant and unpleasant odours revealed only a region of the medial OFC (peak at 2, 52, -18;  $Z = 3.92$ ,  $P < 0.05$ , SVC), which was very similar to the region found when performing a conjunction of the three pleasant odours. Likewise, the comparison between unpleasant and pleasant odours revealed a region of more lateral OFC (peak at 26, 28, -8;  $Z = 3.90$ ,  $P < 0.05$ , SVC).

#### Correlation analysis

The second part of the analysis concerns a correlation analysis of the BOLD signal (in each voxel) with the subjective pleasantness ratings given by the subjects after each odour presentation. The results show that BOLD responses in the rostral medial OFC correlate positively with the subjective ratings of pleasantness (see Fig. 3). The largest cluster of activation in a second-level random effects model extends bilaterally to the anterior portion of medial OFC, with peak activation at -2, 52, -10, and significance level  $Z = 4.28$  ( $P < 0.05$ , SVC). A second cluster was found in the anterior cingulate gyrus, with its peak at 4, 42, 12 and  $Z = 3.95$  ( $P < 0.05$ , SVC). On the right of Fig. 3 we show the relation between the subjective pleasantness ratings and the

BOLD signal from the first cluster (in the medial orbitofrontal cortex), together with the regression line.

Brain areas where activation correlated with the subjective unpleasantness ratings in a similar analysis are also shown in Fig. 3. It is shown that activation of the lateral OFC correlates with the unpleasantness ratings and thus related to the negative hedonic values of the odours. The random effects model shows that one cluster is located in the left anterior OFC (-20, 54, -14;  $Z = 4.26$ ,  $P < 0.05$ , SVC), and a second cluster is in a more posterior region in the left OFC (-16, 28, -18;  $Z = 4.08$ ,  $P < 0.05$ , SVC). On the right of Fig. 3 we show the relation between the subjective unpleasantness ratings and the BOLD signal from the first cluster (in the lateral orbitofrontal cortex at  $y = 54$ ), together with the regression line. No significant correlation with the unpleasantness of the odours was found in the cingulate cortex, but a correlation was found in a part of the right caudate nucleus (16, 8, 16;  $Z = 4.08$  below the statistical significance used in the paper but included here for descriptive purposes only), which receives from the prefrontal cortex.

A similar correlation analysis was performed for the intensity ratings. The results are shown in Fig. 4. There was no correlation

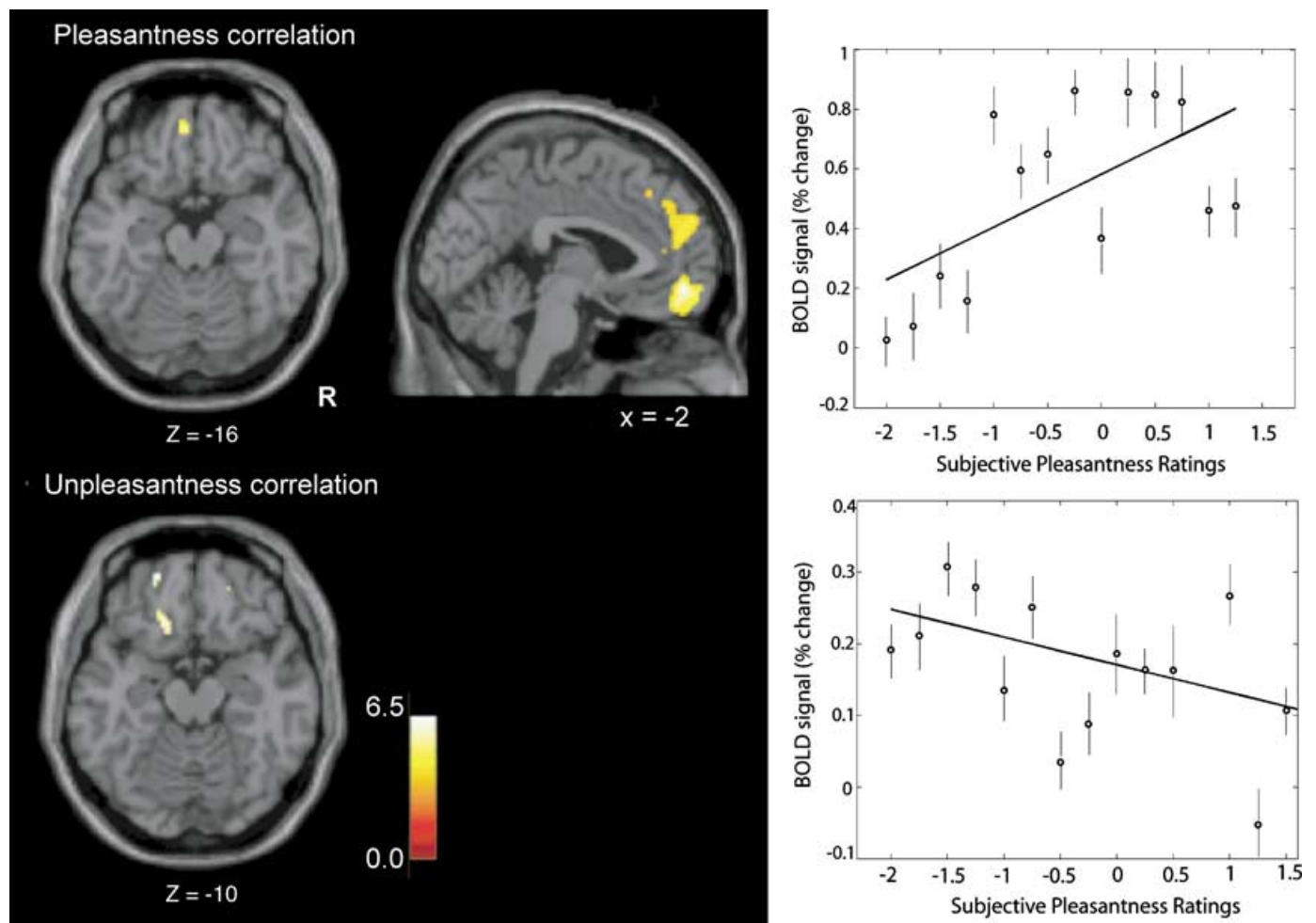


Fig. 3. Random effects group analysis correlation analysis of the BOLD signal with the subjective pleasantness ratings. On the top left is shown the region of the medio-rostral orbitofrontal (peak at -2, 52, -10;  $Z = 4.28$ ) correlating positively with pleasantness ratings, as well as the region of the anterior cingulate cortex in the top middle. On the far top-right of the figure is shown the relation between the subjective pleasantness ratings and the BOLD signal from this cluster (in the medial orbitofrontal cortex at  $y = 52$ ), together with the regression line. The means and SEM across subjects are shown. At the bottom of the figure is shown the regions of left more lateral orbitofrontal cortex (peaks at -20, 54, -14;  $Z = 4.26$  and -16, 28, -18;  $Z = 4.08$ ) correlating negatively with pleasantness ratings. On the far bottom-right of the figure is shown the relation between the subjective pleasantness ratings and the BOLD signal from the first cluster (in the lateral orbitofrontal cortex at  $y = 54$ ), together with the regression line. The means and SEM across subjects are shown. The activations were thresholded at  $P < 0.0001$  for extent.

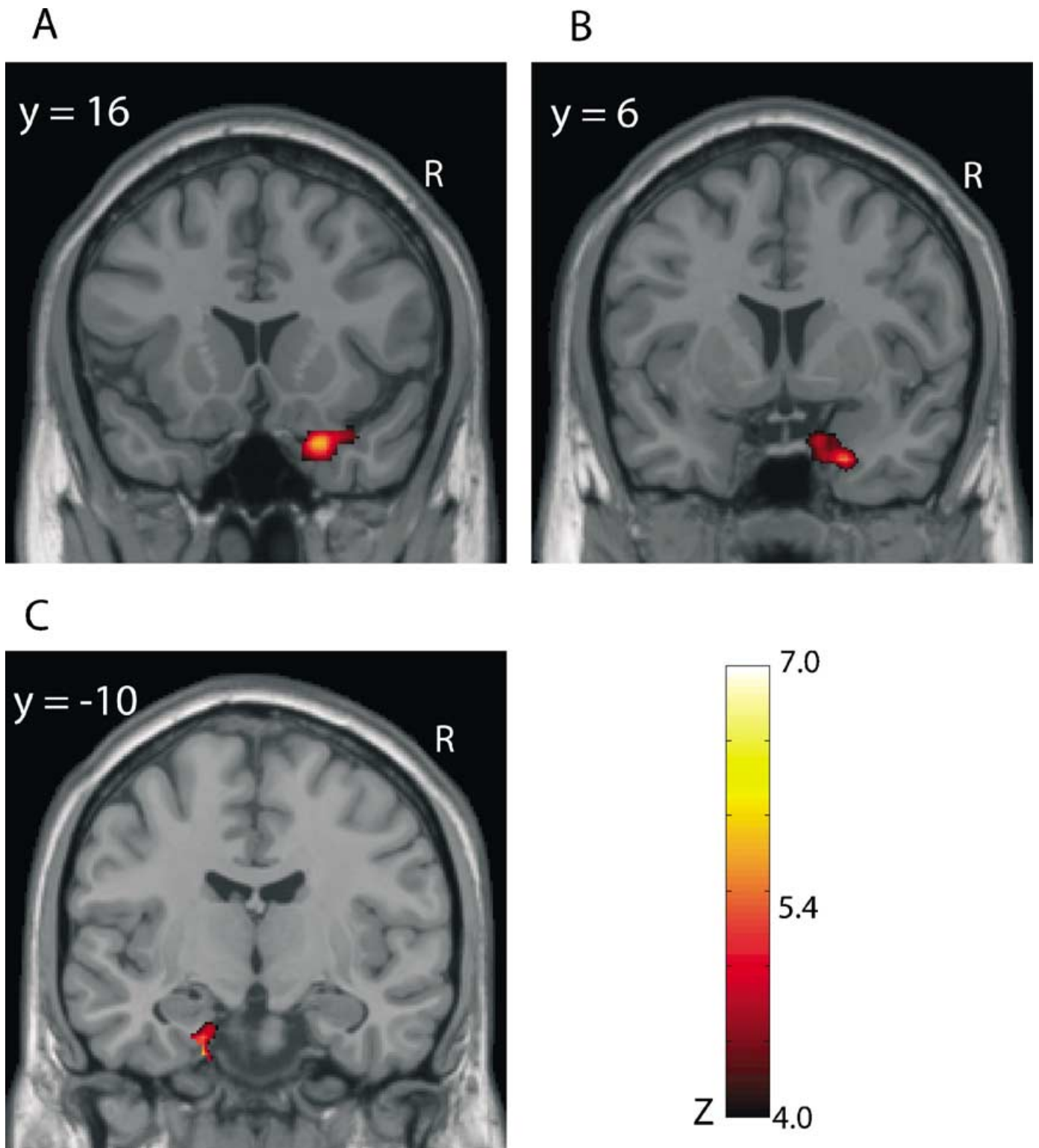


FIG. 4. Random effects group analysis correlation analysis of the BOLD signal with the subjective intensity ratings. (A) At the level  $y = 16$  the BOLD signal in the pyriform cortex and immediately adjacent areas is correlated with the intensity ratings (24, 16, -29;  $Z = 5.9$ ,  $P < 0.05$  corrected for multiple comparisons across the whole brain). (B) At the level  $y = 6$  the BOLD signal in the medial olfactory areas including parts of the pyriform cortex and olfactory entorhinal cortex which lie at the rostral and anterior border of the amygdala is correlated with the intensity ratings (20, 6, -31;  $Z = 5.2$ ,  $P < 0.05$  corrected for multiple comparisons). (C) A similar cluster was found on the left posterior to (B) in an entorhinal cortex/pyriform cortex area forming the ventral and medial border of the amygdala at its junction with the hippocampus (-17, -10, -29),  $Z = 5.5$ ,  $P < 0.05$  corrected for multiple comparisons.

between the intensity ratings and the activation of the orbitofrontal cortex. However, very interestingly, much of the pyriform cortex and related medial areas that receive direct connections from the olfactory bulb did show correlations of their activations with the intensity ratings. In Fig. 4A we show from the random effects model across subjects at the level  $y = 16$  that the BOLD signal in the pyriform cortex and immediately adjacent areas is correlated with the intensity ratings (24, 16, -29;  $Z = 5.9$ ,  $P < 0.05$  corrected for multiple comparisons across the whole brain). In Fig. 4B we show from the group random effects model at the level  $y = 6$  that the BOLD signal in the medial olfactory areas including parts of the pyriform cortex and olfactory entorhinal cortex which lie at the rostral and anterior border of the amygdala is correlated with the intensity ratings (20, 6, -31;  $Z = 5.2$ ,  $P < 0.05$  corrected for multiple comparisons). Although this cluster was on the right, a similar cluster was found (see Fig. 4C) on the left posterior to this in an entorhinal cortex/pyriform cortex area forming the ventral and medial border of the amygdala at its junction with the hippocampus (-17, -10, -29;  $Z = 5.5$ ,  $P < 0.05$  corrected for multiple comparisons). We note that because the intensity ratings were being given on every trial during the scanning by the subjects, any variation of intensity on a trial by trial basis, or any habituation effect, are being utilized in the correlation analysis to enable the results shown to be revealed.

## Discussion

The results of this study demonstrate that different brain areas were activated by the pleasant and the unpleasant odours. Pleasant odours activated a region of medio-rostral OFC, whereas no activity was observed in the OFC for the unpleasant odours (even when applying a much more liberal threshold of  $P < 0.001$ ).

The results of this study also show that there is a very significant correlation between a region of the medio-rostral OFC and the pleasantness ratings of the six different odours obtained a total of 60 times during the experiment for each of the 11 subjects. It is of interest that this region of medio-rostral orbitofrontal cortex is just anterior to the region found to correlate with monetary wins (O'Doherty *et al.*, 2001a). The present study also demonstrates that different and more lateral regions of the left OFC were correlated with the subjective unpleasantness ratings of the odours. This is the first time that dissociations have been found between brain areas encoding the pleasantness and unpleasantness of odours. The foci in the more lateral parts of the orbitofrontal cortex correlating with unpleasantness are not as lateral as those reported in O'Doherty *et al.* (2001a), but are clearly dissociable from the medial foci correlating with subjective pleasantness ratings.

The finding that the orbitofrontal cortex was activated by odour is consistent with neurophysiological findings that a population of neurons in the nonhuman primate orbitofrontal cortex has olfactory responses tuned to different odours (Rolls *et al.*, 1996b). The tuning of approximately 35% of these neurons is in terms of the affective value of the odour as it is influenced by whether the odour is associated with the taste of glucose reward or saline punishment in an olfactory discrimination task (Critchley & Rolls, 1996b). (Twelve per cent responded to the reward-related set of odours; 23% to the punishment associated set of odours; and 65% did not discriminate between odours based on their taste association.) Very direct evidence that the affective value of odours is represented in the orbitofrontal cortex is that many orbitofrontal cortex olfactory neurons alter the odour to which they respond when the association of the odour with sweet vs. salt taste is reversed during the reversal of an olfactory discrimination task (Rolls *et al.*, 1996a, b). Further evidence that the reward value of olfactory

stimuli is represented in the orbitofrontal cortex is that orbitofrontal cortex neurons that respond to the odour of a food decrease their responses (to zero) as the food is fed to satiety and the reward value of the food decreases to zero (Critchley & Rolls, 1996a). This decrease is even sensory-specific, occurring more for the smell of a food eaten to satiety than for other food odours. This olfactory sensory-specific satiety effect has been described and analyzed in humans (Rolls & Rolls, 1997), and indeed in humans it has been shown that activation of the orbitofrontal cortex mirrors this olfactory sensory-specific satiety (O'Doherty *et al.*, 2000). It is likely that activation of the orbitofrontal cortex is related to reward processing and the pleasantness of odours rather than to providing ratings about how rewarding an odour is, in that in the study by O'Doherty *et al.* (2000) ratings were not being given throughout the neuroimaging. [We do note though that in one PET study some difference was found that appeared to be related to giving ratings (Zatorre *et al.*, 2000)].

Both the pleasant and the unpleasant odours activated a middle part of the anterior cingulate cortex (Fig. 2). This was distinct from a more rostral part of the anterior cingulate cortex in which the activation was correlated with the subjective pleasantness ratings of the odours (Fig. 3). This is of interest, because the rostral part of the anterior cingulate cortex is activated by pleasant touch (Rolls *et al.*, 2003), and this has been called the affective division of the cingulate in a meta-analysis of imaging studies (Bush *et al.*, 2000). There is evidence from animal studies that it is involved in a range of motivationally orientated unconditioned behaviours and emotional learning (Devinsky *et al.*, 1995; Cardinal *et al.*, 2002). In addition, the anterior, ventral cingulate cortex (Brodmann's areas 24a/b and 25) in humans seems to be involved in the pathology of depression in humans, as well as in the control of normal mood (Drevets *et al.*, 1997), and in the response to emotionally significant stimuli, such as cocaine-associated cues in drug abusers (Childress *et al.*, 1999).

Some activation by pleasant odours was also found in the frontal operculum/anterior insula (with some activation also by some unpleasant odours, such as isovaleric acid as shown in Fig. 1). The far anterior insula is known to receive olfactory inputs from the primary olfactory cortices in nonhuman primates (Carmichael & Price, 1994; Carmichael *et al.*, 1994). The anterior insula of primates contains the primary taste cortex (Rolls *et al.*, 1985; Carmichael & Price, 1995), and it is of considerable interest that the part of the human insula activated by tastes such as glucose and umami as exemplified by monosodium glutamate (de Araujo *et al.*, 2003) is very close to the region found to be activated by odours in this paper, with the same imaging methods. This raises the possibility that at least part of the human anterior insula is a multimodal area, where taste and olfactory inputs may be brought together to represent flavour. It is known that in macaques such multimodal representations of the flavour of food are built by associative learning in the caudal orbitofrontal cortex (Critchley & Rolls, 1996b), and it is possible that these region is located topologically a little more posteriorly in humans. Activation of the right inferior frontal gyrus by olfactory stimulation has been reported previously (Zald & Pardo, 1997; Royet *et al.*, 1999; Royet *et al.*, 2001) and here we show that it is especially related to the delivery of unpleasant odours.

The activations described in this paper in the orbitofrontal cortex were related to the pleasantness and not to the intensity of the odours, in that the random effects group analysis described in the results section showed significant correlations in different parts of the orbitofrontal cortex with the pleasantness (medial OFC) or unpleasantness (lateral OFC) of the odours, whereas the corresponding analysis performed for intensity showed no BOLD signal correlation in the orbitofrontal or cingulate cortex (but did show a correlation with the

BOLD signal in other brain areas as described in the Results section). These findings show that the BOLD signal in the OFC reflected the pleasantness vs. the unpleasantness of the odours, but not their intensity. This conclusion is supported by the generally consistent evidence obtained by Anderson *et al.* (2003) that a pleasant odour activated the medial orbitofrontal cortex, and an unpleasant odour activated the left lateral orbitofrontal cortex. However, the study described here goes considerably beyond the study of Anderson *et al.* (2003) by testing whether it is generally the case that pleasant odours activate the medial orbitofrontal cortex, and unpleasant odours activate the lateral orbitofrontal cortex. With just one pleasant (citral) and one unpleasant odour (valeric acid), the localization found could have reflected just that the odours were different (Anderson *et al.*, 2003). However, by using three pleasant odours and three unpleasant odours in the present study, we were able to show using conjunction analysis that all the pleasant odours activated the medial orbitofrontal cortex, a region not activated by the unpleasant odours; whereas the lateral orbitofrontal cortex was activated by a conjunction of the three unpleasant odours, and this lateral region was not activated by the pleasant odours. Moreover, we were able to show that the activation in the medial orbitofrontal cortex correlated with the pleasantness taken across all three pleasant and three unpleasant odours, whereas activation of the lateral orbitofrontal cortex correlates with the unpleasantness taken across all six odours. This design and the results found makes it unlikely that the correlations with pleasantness reflected correlations with just the chance identity of the odours, but instead reflect correlations with pleasantness independently of any particular odour being used in the test.

The correlations with the intensity ratings completed the dissociation to produce a double dissociation of intensity and pleasantness ratings. In particular, the BOLD signal in the medial olfactory areas such as the pyriform and entorhinal cortex was correlated with the intensity ratings, and not with the pleasantness ratings of the olfactory stimuli. The strong conclusion is that the pyriform and entorhinal areas represent the intensity of odours, and the orbitofrontal cortex (at  $y = 52$  to  $y = 54$ ) represents the pleasantness (at  $y = 52$ , and medially) and the unpleasantness (at  $y = 54$  and 28, and laterally) of the olfactory stimuli. We note that Anderson *et al.* (2003) claimed that the amygdala itself (as well as a part of the pyriform cortex) represents the intensity of the odour. However, the correlations we found (see Figs 4 and 3) were much better confined to particular regions than those shown in the Anderson *et al.* (2003) paper (in which many activations are found outside the olfactory areas), and our results show rather clearly that it is the pyriform and entorhinal cortices which have activations correlated with intensity (see Fig. 4), rather than the body of the amygdala.

We note that 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 airstream when the odour was not being delivered, which switched to the odour without any change of pressure under computer control, so that the effects found are attributable to the odours being delivered, and not to somatosensory effects related to the presence or absence of an air stream.

The correlation of activation of the caudate nucleus with unpleasantness ratings has not been observed before. However, there are projections from the prefrontal cortex to the caudate nucleus (Berendse *et al.*, 1992; Öngür & Price, 2000), and we did find activations by unpleasant odours in a part of the orbitofrontal cortex, as noted above. A previous study has also found activation of the caudate nucleus to the main effects of odours (Poellinger *et al.*, 2001).

This study has demonstrated that the pleasant and unpleasant odours elicit activity in different parts of the human brain. One of the main findings of this study was that the brain activations produced by the

pleasant odours were similar to each other, and that the brain activations produced by the unpleasant odours were also similar to each other, and that these different brain regions can be dissociated with fMRI. Importantly, it has been demonstrated that dissociable regions of human orbitofrontal cortex correlate with subjective pleasantness and unpleasantness ratings of the odours. This is further evidence that the orbitofrontal cortex is involved in representing the affective valence of emotional stimuli such as odours. Taken together with similar data linking the orbitofrontal cortex with the representation and processing of the reward value of other primary and secondary reinforcers, including taste and monetary reward (O'Doherty *et al.*, 2001a, b), the orbitofrontal cortex is therefore a prime candidate for subjective emotional processing in the human brain (Rolls, 1999).

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## Abbreviations

fMRI, functional magnetic resonance neuroimaging; OFC, orbitofrontal cortex; PET, positron emission tomography; SVC, small volume correction.

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