Neuron, Vol. 46, 671–679, May 19, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.neuron.2005.04.021

Cognitive Modulation of Olfactory Processing

Ivan E. de Araujo,[1,2] Edmund T. Rolls,[1,2,*] Maria Inés Velazco,[3] Christian Margot,[3] and Isabelle Cayeux[3]
[1]Department of Experimental Psychology
University of Oxford
South Parks Road
Oxford OX1 3UD
United Kingdom
[2]Centre for Functional Magnetic Resonance Imaging of the Brain
John Radcliffe Hospital
Oxford OX3 9DU
United Kingdom
[3]Firmenich SA
1 Route des Jeunes
CH-1211 Geneva 8
Switzerland

Summary

We showed how cognitive, semantic information modulates olfactory representations in the brain by providing a visual word descriptor, "cheddar cheese" or "body odor," during the delivery of a test odor (isovaleric acid with cheddar cheese flavor) and also during the delivery of clean air. Clean air labeled "air" was used as a control. Subjects rated the affective value of the test odor as significantly more unpleasant when labeled "body odor" than when labeled "cheddar cheese." In an event-related fMRI design, we showed that the rostral anterior cingulate cortex (ACC)/medial orbitofrontal cortex (OFC) was significantly more activated by the test stimulus and by clean air when labeled "cheddar cheese" than when labeled "body odor," and the activations were correlated with the pleasantness ratings. This cognitive modulation was also found for the test odor (but not for the clean air) in the amygdala bilaterally.

Introduction

A central feature of odor perception is its hedonic or affective component. Most odors are labeled as "pleasant" (positive hedonic value) or "unpleasant" (negative hedonic value), and recent functional neuroimaging studies performed on humans have successfully demonstrated that the valence of odors is represented in particular in the orbitofrontal cortex. More specifically, pleasant odors preferentially activate medial orbitofrontal regions, whereas unpleasant odors activate more lateral regions (Anderson et al., 2003; Gottfried et al., 2002; Rolls et al., 2003; Zald and Pardo, 1997). In addition, the representation of the intensity of odors has been associated with activity in the piriform (primary olfactory) cortex (Rolls et al., 2003) and in the amygdala (Anderson et al., 2003). Anatomical investigations in nonhuman primates have shown that connections from the olfactory bulb reach the piriform cortex, corticomedial nucleus of the amygdala, and olfactory tubercle. From the piriform 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 and Price, 1994; Ongur and Price, 1998).

So far, little is known about how cognitive processing might modulate the neural representation of the affective value of odors. In a recent study, Gottfried and Dolan (2003) showed that activity in the human anterior hippocampus and medial orbitofrontal cortex is correlated with perceptual olfactory facilitation produced by presenting subjects with odors paired with semantically congruent pictures. In an earlier study using positron emission tomography (PET), Royet et al. (1999) showed that familiarity judgments were associated with activations in the right orbitofrontal and anterior cingulate cortices. Zatorre et al. (2000) reported that orbitofrontal cortex activation was related to hedonic judgements of a set of odors. However, none of these studies investigated the influences of cognitive information on the representations of pleasant and unpleasant odors in the human brain.

The aim of the event-related fMRI study described here was to measure the effects of cognitive (semantic) information on the neural responses to the (orthonasal) delivery of odors. The design consisted of presenting odors paired with descriptors (words) on a screen. A test odor (isovaleric acid combined with cheddar cheese flavor) was labeled on different trials as "cheddar cheese" or "body odor." Thus, a particular test odor was associated with labels describing stimuli with different reward values. The same labels were paired with delivery of clean air in different trials. Alpha-ionone (pleasant, labeled "flowers") and Octanol (unpleasant, labeled "burned plastic") were used as reference pleasant and unpleasant stimuli for the psychophysics and neuroimaging. This design allowed us to assess how the semantic labels modulate responses to the delivery of test odor (and clean air) by performing correlation analysis with the subjective pleasantness ratings and by performing direct comparisons between different experimental conditions.

Results

Psychophysical Data

The pleasantness ratings (obtained during the scanning on every trial) for the six stimulus conditions are shown in Figure 1. The α-ionone (labeled as "flowers") was rated as pleasant (mean ± SEM = 0.32 ± 0.06), and the octanol (labeled as "burned plastic") was rated as being unpleasant (–0.49 ± 0.06). The test odor when labeled as "cheddar cheese" was rated as being close to neutral (–0.10 ± 0.08) and when labeled as "body odor" was rated as being unpleasant (–0.86 ± 0.07). Statistical analysis showed that the test odor was rated as being

*Correspondence: edmund.rolls@psy.ox.ac.uk

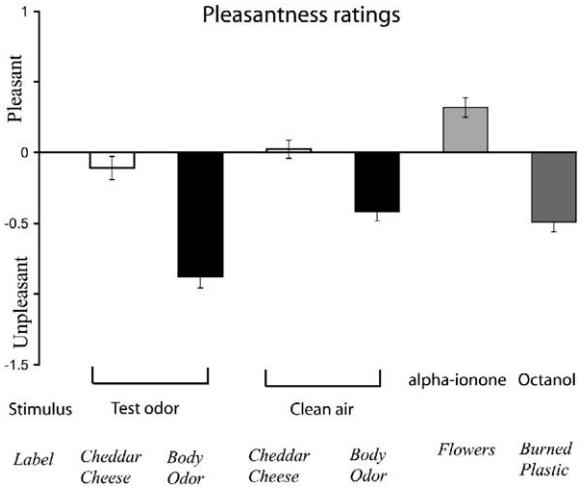

Figure 1. Subjective Pleasantness Ratings to Labeled Odors

The means ± SEM across subjects are shown. The corresponding stimulus and label to each bar are listed in the lower part of the figure. Note that the test odor and clean air were paired in different trials with a label of either "cheddar cheese" or "body odor."

significantly more pleasant when labeled as "cheddar cheese" than when labeled as "body odor" (paired t = 6.68, df = 11, p << 0.001). Interestingly, the clean air when labeled as "cheddar cheese" was rated as being more pleasant (0.02 ± 0.06) than when it was labeled as "body odor" (–0.40 ± 0.06) (paired t = 4.1, df = 11, p < 0.001). In contrast, the labels produced no effect on the intensity ratings, which were α-ionone, –0.10 ± 0.10; octanol, 0.20 ± 0.09; test labeled as cheddar, 0.55 ± 0.08; test labeled as body odor, 0.64 ± 0.08; clean air labeled as cheddar cheese, –0.38 ± 0.10; clean air labeled as body odor, –0.31 ± 0.09.

fMRI Data

Correlation of the BOLD Signal with the Pleasantness Ratings of the Test Odor

A correlation analysis was performed between the fMRI BOLD signal and the pleasantness ratings of the test odor when labeled as cheddar cheese and as body odor. Figures 2A and 2B show that significant correlations were found in a far anterior part of the anterior cingulate cortex and the adjoining medial orbitofrontal cortex (MNI coordinates [16 46 –4], Z score = 4.35, p < 0.05 corrected for multiple comparisons). (Although the peak voxel was on the right [Figure 2B], activations were found in a corresponding region on the left at a lower statistical threshold of p < 0.001 uncorrected.) Significant positive correlations were also found in the amygdala bilaterally (Figure 2C) (MNI coordinates [22 –2 –20], Z score = 3.41, p < 0.05 FDR corrected; and [–18 0 –16], Z score = 3.15, p < 0.001 uncorrected), which extended anteriorly to olfactory regions in or close to the olfactory tubercle (Figure 2D) (MNI coordinates [26 10 –22], Z score = 3.50, p < 0.05 FDR corrected). Thus, the pleasantness of the test odor measured by the ratings being given during the scanning, and being influenced by the verbal labels as shown in

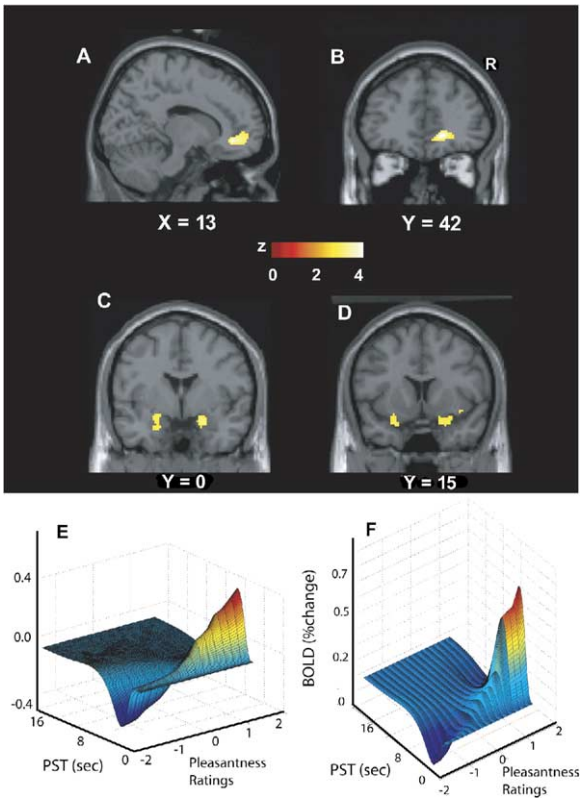

Figure 2. Group Random Effects for Correlation Analysis of BOLD Signal with Pleasantness Ratings Given to the Test Odor

(A) Activations in the rostral anterior cingulate cortex, in the region adjoining the medial OFC, shown in a saggital slice. (B) The same activation shown coronally. (C) Bilateral activations in the amygdala. (D) These activations extended anteriorly to the primary olfactory cortex. The image was thresholded at p < 0.0001 uncorrected in order to show the extent of the activation. (E) Parametric plots of the data averaged across all subjects showing that the percentage BOLD change (fitted) correlates with the pleasantness ratings in the region shown in (A) and (B). The parametric plots were very similar for the primary olfactory region shown in (D). PST, post-stimulus time (s). (F) Parametric plots for the amygdala region shown in (C).

Figure 1, was correlated with the activations produced by the odors in the brain areas shown in Figure 2.

We also examined the extent to which these brain areas had activations that were correlated with the pleasantness ratings produced by the clean air when labeled as "cheddar cheese" or "body odor." Figure 3 shows that the anterior cingulate and adjoining medial orbitofrontal cortex areas also had activations that were correlated with the pleasantness ratings given to clean air when it was labeled as "cheddar cheese" or "body odor" (MNI coordinates [10 38 –2], Z score = 3.95, p < 0.03 FDR corrected). The areas showing this correlation overlapped with the anterior cingulate areas showing a correlation with the rated pleasantness of the test odor. Significant correlations (even at the low threshold of p < 0.05 uncorrected) with the pleasantness ratings of the clean air were not found in the amygdala and adjoining olfactory areas.

The word labels used ("cheddar cheese" versus

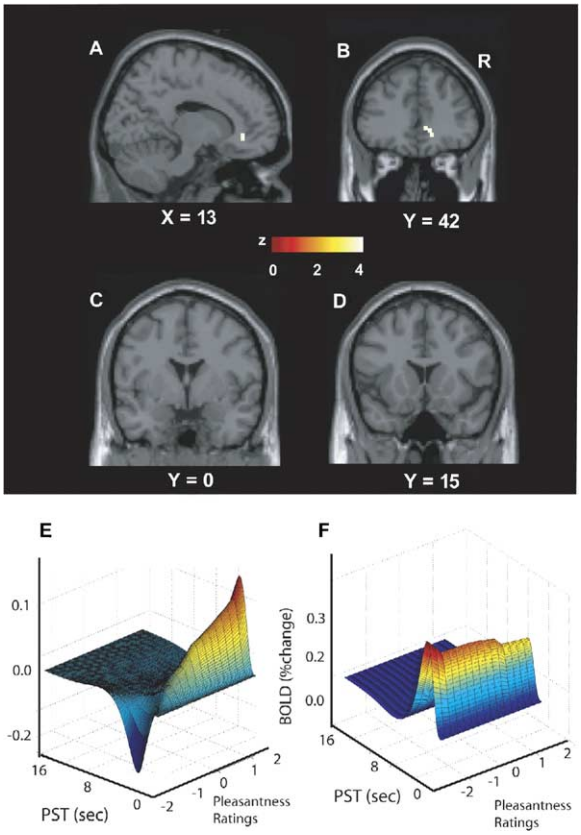

Figure 3. Group Random Effects for Correlation Analysis of BOLD Signal with Pleasantness Ratings Given to the Clean Air Odor

(A) Activations in the rostral anterior cingulate cortex, in the region adjoining the medial OFC, shown in a saggital slice. (B) The same activation shown coronally. No significant correlations were found with clean air (cf. Figure 2) in the amygdala (C) or primary olfactory cortex (D). The image was thresholded at $p < 0.0001$ uncorrected in order to show the extent of the activation. (E) Parametric plots of the data averaged across all subjects showing that the percentage BOLD change (fitted) correlates with the pleasantness ratings in the region shown in (A) and (B). PST, poststimulus time (s). (F) Parametric plots showing activation related to stimulus presentation but not related to the pleasantness ratings for the amygdala region shown in (C).

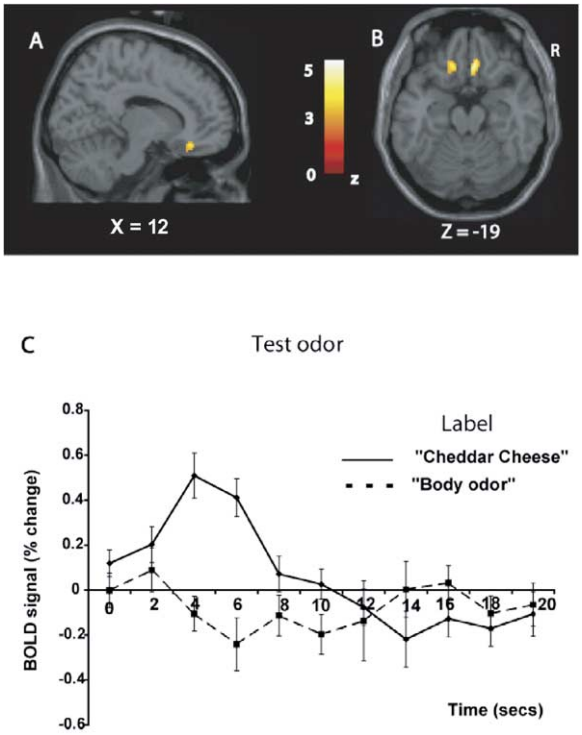

Figure 4. Activations in the Medial Orbitofrontal Cortex Produced by the Contrast [Test Odor When Labeled "Cheddar Cheese" – Test Odor Labeled "Body Odor"]

(A) Activations in the medial orbitofrontal cortex (shown in a saggital slice) produced by the contrast [test odor when labeled "cheddar cheese" – test odor labeled "body odor"]. (B) The same activations shown in an axial slice, illustrating bilateral activations. (C) The time course of activations in this region for these conditions, across trials and subjects (mean ± SEM).

"body odor") are prima facie more likely to influence representations of the pleasantness than of the intensity of the odor, and to check this we repeated the above analyses using the intensity ratings as regressors. No significant correlations ($p < 0.001$ uncorrected in the group analysis) were found between the BOLD signal in any brain area and the intensity ratings. As described in the psychophysics section, the intensity ratings were not influenced by the word labels, and the intensities of the different odorants used in this study were quite similar, so that the absence of a correlation of the BOLD signal with the intensity ratings is as might be expected. Thus, the word labels did influence the brain activations related to pleasantness ratings, and this result could not be attributed to effects arising from a correlation with intensity. Further confirmation of this is that the correlations of the BOLD signals with the pleasantness ratings were still the same when the analysis was repeated with the intensity ratings as an effect of no interest.

Brain Regions Where the Activation Was Influenced by the Word Label

Figure 4 shows brain areas in which more activation was found to the test odor when the label was "cheddar cheese" than when the label was "body odor." More activation was found in the medial orbitofrontal cortex where it adjoins the far anterior part of the anterior cingulate cortex (Figures 4A and 4B) (MNI coordinates [8 30 –18], Z score = 3.69, $p < 0.05$ FDR corrected; and [–12 30 –18], Z score = 3.26, $p < 0.001$ uncorrected). The time course (across all trials and subjects) of the activations is shown in Figure 4C, which makes it clear that there was strong activation in this region to the test odor when labeled as "cheddar cheese" but not when labeled as "body odor." A similar effect was found in the amygdala at a lower level of statistical significance ([18 8 –28], Z score = 3.06, $p < 0.001$ uncorrected). Interestingly, in this study there was no brain area that was consistent across subjects in showing more activation to the test odor when labeled as "body odor" than when labeled as "cheddar cheese." However, in 7 of the 12 individual subjects, more activation with this

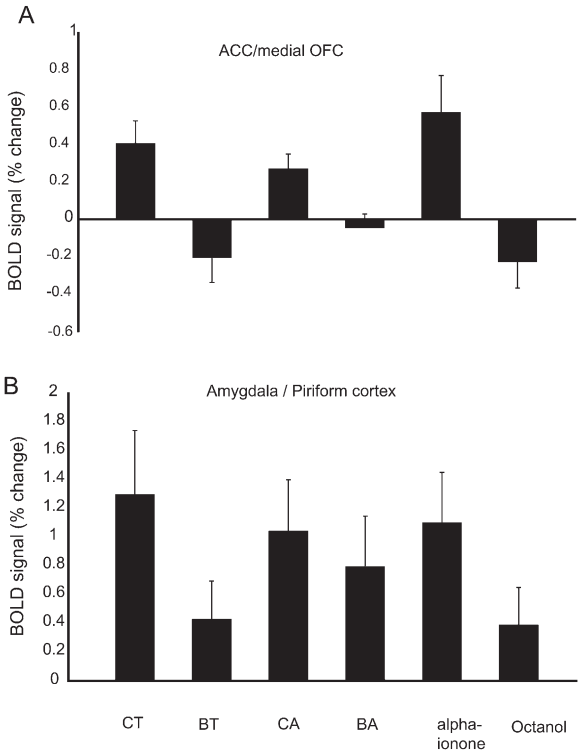

Figure 5. The BOLD Signal Shown as % Change from Control ± SEM in Different Brain Regions under the Different Experimental Conditions

(A) Anterior cingulate cortex ACC and medial orbitofrontal cortex OFC. (B) Amygdala/pyriform cortex under the different experimental conditions. C, "cheddar cheese" label; B, "body odor" label; T, test odor; A, clean air. (Thus, CT = cheddar cheese label and test odor delivery, etc.) Although the main statistical comparisons are those provided in the SPMs, supplementary statistical tests on the data shown in these histograms show the following, based on an ANOVA followed by post hoc corrected t test comparisons. For the ACC/medial OFC, CT > BT at $p < 0.005$; CA > BA at $p < 0.01$; α-ionone > octanol at $p < 0.002$. For the amygdala/pyriform cortex, CT > BT at $p < 0.03$; α-ionone > octanol at $p < 0.03$.

comparison was found in more lateral areas of the orbitofrontal cortex (at MNI coordinates close to [–20 40 –10]) (at least $p < 0.001$ uncorrected in each subject). Thus, although the test odor when labeled as body odor could produce more activation than when labeled as cheddar cheese, these activations were not significant in all subjects and moreover were not all in exactly the same part of the lateral orbitofrontal cortex.

We show the BOLD signal in these regions under the different experimental conditions in Figure 5. Activations in the anterior cingulate cortex/medial orbitofrontal cortex (ACC/medial OFC) were greater to the test odor (T) when labeled as "cheddar cheese" (C) than when labeled as "body odor" (B). In the clean air (A) condition, somewhat similar changes of activations, though of smaller magnitude, were produced when the label was cheese (C) versus body odor (B). In the clean air condition, the signal in these ACC/medial OFC regions could thus reflect effects of the word label in influencing the pleasantness of what was perceived even when there was no change in the olfactory stimulus at the time that the word label was given, as the air flow was clean air continuously throughout the trial. This interpretation, that the label is affecting the perceived pleasantness in the clean air condition, is supported by fact that the activations in the ACC/medial OFC to the (pleasant, flowery) α-ionone (FL) were greater than to the (unpleasant) octanol (see top right of Figure 5). In fact, the SPM analysis showed that this comparison was significant at $p < 0.001$ uncorrected in the medial orbitofrontal cortex at [8 42 –16], $Z = 3.54$.

Generally similar effects were found for the amygdala/olfactory cortex (see Figure 5B), except that the labels had smaller effects on the activations to clean air (compare CA and BA). It was also noticeable that in the amygdala, in most of the experimental conditions, activations above the baseline were found, as shown in Figures 5B and 3F.

Relation of Brain Areas Where Cognitive Modulation Is Found, to Olfactory Areas

We have identified, in the above analyses, areas of the human brain where the cognitive labels modulated the activations. To investigate further whether these are olfactory areas, Figure 6 shows a main effects analysis showing the activations revealed by the contrast odor – control. This main effects analysis shows for example strong activations bilaterally in primary olfactory cortical areas in or close to the pyriform cortex, as illustrated in Figures 6A and 6B (coordinates [–22 8 –26], Z score = 4.69, $p < 0.05$ corrected for multiple comparisons). (The odors included in this analysis were the test odor in both conditions, the α-ionone, and the octanol, each minus their respective control.) These activations extended in the anterior-posterior axis from Y = 15 (agranular insula) to Y = 2 (periamygdaloid cortex). There was also a small area of activation in the right lateral orbitofrontal cortex (illustrated in Figure 6B). Overall, the fact that strong activation of the orbitofrontal cortex and amygdala was not apparent in this main effects analysis is likely to be due to the fact that pleasant and unpleasant odors activate parts of these regions in opposite directions (Rolls et al., 2003), so that the effects partly cancel in the main effects analysis.

The time course of the activations in the pyriform cortex at Y = 8 is shown in Figure 6E. The odor was on for the period 0–8 s. Comparison of Figure 6 with Figure 2 shows that the region where word labels modulate olfactory processing is within the region of primary olfactory cortex where main effects of odor are found. However, the center of the odor main effects cluster was further forward (at Y = 8 as shown in Figure 6A) than the center of the region in which word labels modulated olfactory processing (at Y = 0 as shown in Figure 2C), providing a suggestion that not all primary olfactory cortical areas were modulated by the effects of the word labels. We show in Figure 6C a slice through Y = 0 for the main effects analysis, where Y = 0 was chosen because it is the center of the area with a correlation with the pleasantness ratings, as illustrated in Figure 2C. It can be seen from Figure 6C that the main effects (olfactory) contrast was located in an area that is probably the pyriform cortex, which is dorsal to the peak of the region in the amygdala shown in Figure 2C where correlations with pleasantness were found. Figure 6D

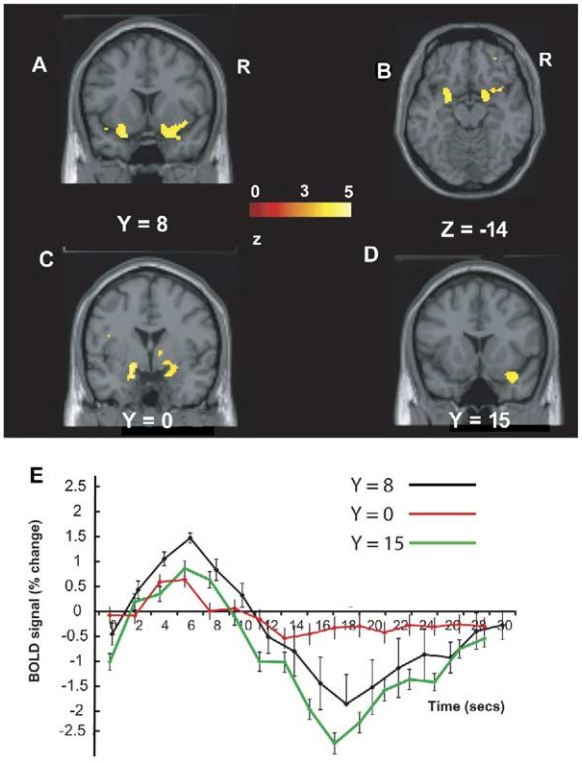

Figure 6. A Main Effects Analysis Showing the Activations Revealed by the Contrast Odor – Control

This main effects analysis shows (A and B) strong activations bilaterally in primary olfactory cortical areas in or close to the pyriform cortex (MNI coordinates [–22 8 –26], Z score = 4.69, $p < 0.05$ corrected for multiple comparisons). (C) shows a slice though Y = 0 for the main effects analysis with activation in the pyriform cortex ([–20 0 –12] Z = 3.23, $p < 0.001$ uncorrected), where Y = 0 was chosen because it is the center of the area with a correlation with the pleasantness ratings, as illustrated in Figure 2C. (D) shows the main effects activation at the slice Y = 15 (in or near the agranular insula ([36 15 –26] Z = 3.06, $p < 0.001$ uncorrected), for comparison with the region in Figure 2D at Y = 15 (in or near to the olfactory tubercle) where the activations were correlated with the pleasantness ratings. (E) shows that the peak of the main effects activations is at Y = 8 (means ± SEM are shown).

shows that the main effects (olfactory) activation at the slice Y = 15 (in or near the agranular insula) is lateral to the region in Figure 2D at Y = 15 (in or near to the olfactory tubercle) where the activations were correlated with the pleasantness ratings. Thus, Figure 6 shows that the main effects of odors are centered in areas such as the pyriform cortex (Figures 6A–6C) and agranular insula (Figure 6D), whereas the correlations with pleasantness shown in Figure 2 are centered in areas such as the ACC/medial orbitofrontal cortex, the amygdala, and a region in or close to the olfactory tubercle.

An additional analysis was performed to identify olfactory areas. We compared the activations of two of the odors to their nonodor (clean air) controls as follows (in which CT refers to the test odor labeled as cheddar cheese). With the contrast [(CT + α-ionone] – (CT control + α-ionone control)], activations were found bilaterally in the amygdala (e.g., [20 4 –25], Z = 3.99, $p < 0.001$ FDR corrected), in a posterior part of the orbitofrontal cortex extending to the ventral part of the far anterior cingulate cortex (peak at [–2 18 –24], Z = 3.34 $p < 0.001$ FDR corrected), and in the piriform cortex region described above to respond to the main effects of odor. These activations extended anteriorly to reach the agranular part of the insular cortex (at Y = 14 at $p < 0.001$ uncorrected).

Thus, overall, the results show that in human brain areas activated by olfactory stimuli, modulatory effects of the word labels are found. The cognitive modulation effects are clear in areas of the orbitofrontal cortex, amygdala, and anterior cingulate cortex and may include part but perhaps not all of the primary olfactory cortical areas such as the pyriform cortex.

Control Study for Sniffing

To check whether differential sniffing induced by the word labels might have contributed to the results (Zelano et al., 2005), we performed a control study in 11 participants in which the sniffing was measured outside the scanner. Inhalation and exhalation were measured by both inductance plethysmography and by temperature changes (measured with a miniature thermistor) reflecting the air flow in the nostrils. The plethysmography (and temperature measurements) showed that in the 2 s period after the onset of the visual and olfactory stimuli, there was no influence on the inhalation of the stimulus by the visual word label. Further evidence that altered sniffing did not account for the effects described here is that if subjects had altered their sniffing differentially to the word labels, then this should have affected the intensity ratings given, and no such effect was found, as shown in the psychophysics section. In addition, as described above, the correlations of the BOLD signals with the pleasantness ratings were present when the intensity ratings were included as an effect of no interest, and the BOLD signals were not correlated with the intensity ratings. Thus, altered sniffing and intensity changes are very unlikely to account for the effects of the word labels on the pleasantness ratings or on the fMRI activations described in this paper.

Discussion

We showed that a cognitive input, a word label, can modulate the pleasantness ratings to a test odor (Figure 1). We showed that in brain areas including the medial orbitofrontal/anterior cingulate cortex and amygdala, known to be activated by odors (as shown in this study, in a previous study with similar testing conditions [Rolls et al., 2003], and in many other studies referred to in the Introduction), the activation produced by a test odor could be modulated by cognitive inputs, visually presented words. In particular, more activation was found in these brain regions to the test odor when it was labeled as cheddar cheese than when it was labeled body odor (Figures 4 and 5). We also found that in the medial orbitofrontal/anterior cingulate area and in the amygdala, the activations to the test odor and its cognitive label were correlated with the pleasantness ratings (Figure 2). Use of a word label as the cognitive input ensured that the cognitive input was high level

and semantic. If we had used a picture of cheese or of a body part, this could have been a lower level association, in that neurons in the orbitofrontal cortex respond to visual stimuli such as the sight of food (Rolls and Baylis, 1994; Thorpe et al., 1983), probably as a result of associative learning implemented in the orbitofrontal cortex (Rolls et al., 1996). The results thus show that cognitive inputs can be very important in influencing subjective responses including affective responses to olfactory stimuli and show that some of the brain areas activated by odors, some of which are secondary olfactory cortical areas (Rolls, 2005), show an effect of this high-level cognitive influence.

We also found that the ratings of the pleasantness of clean air could be influenced by the word label (Figure 1). An influence of the cognitive label on the magnitude of the BOLD signals was found in the anterior cingulate/medial orbitofrontal cortex region illustrated in Figures 4 and 5, and a less significant cognitive effect was also found in the amygdala (see Results and Figure 5). Further, the activations in the anterior cingulate/medial orbitofrontal cortex region were correlated with the pleasantness/unpleasantness ratings given when the label was "cheddar cheese" versus "body odor." Clearly, when there is no odor present, the subjects may imagine a smell based on the word cue shown. Alternatively, the activations in the clean air condition might reflect an effect of the cognitive input on these areas that is independent of any imagined odor. However, in either case, the important new point being made in this paper is that high-level cognitive inputs, such as the sight of a word, can influence the activations in brain regions that are activated by olfactory stimuli such as the anterior cingulate and orbitofrontal cortex and the amygdala. Moreover, the high-level cognitive influence can modulate affective ratings of pleasantness and the brain regions such as the anterior cingulate/medial orbitofrontal areas where the activations are correlated with the pleasantness of odors (Rolls et al., 2003). The finding that the anterior cingulate/medial orbitofrontal region had activation correlated with the pleasantness ratings being given even in the clean air condition may indicate that this region is relatively close to the affective ratings being given. Given that the brain areas in which the word labels modulated the activations to the odors are areas where pleasant olfactory stimuli have been shown to produce activation (Rolls et al., 2003), it is likely that the modulations produced by the word labels in the present investigation reflect an altered perception of the pleasantness of the odors and not just a bias on the ratings being given.

Figure 3 shows that the BOLD change in the amygdala in the clean air condition does not correlate highly with the pleasantness ratings, and this is consistent with the evidence in Figure 5 that the magnitude of the activations in the amygdala are not affected greatly by the label in the clean air condition. In comparison, as just noted, even in the clean air condition, activations in the anterior cingulate/medial orbitofrontal cortex do correlate with the pleasantness ratings. When the test odor was present, the activations in both the amygdala and the cingulate/orbitofrontal cortex were modulated by semantic labels. The implication is that the activations in the amygdala are relatively closely coupled to effects on odor inputs, whereas the activations in the anterior cingulate/medial orbitofrontal cortex can be modulated even in the absence of the olfactory test stimulus.

The region shown in Figure 6 to be activated by the main effects contrast odor versus no odor includes the olfactory tubercle and extends to the pyriform/primary olfactory areas close to the medial amygdala. This was not the center of the region where cognitive influences had their effects, which were further posterior, as shown for example in Figure 2C. This may mean that the olfactory tubercle/pyriform cortex, which are primary olfactory areas, are less modulated by the word label or that they do not represent affect (Rolls et al., 2003), and so are not modulated by word labels that influence affect. Indeed, the reason that other olfactory areas were not activated in the main effects analysis shown in Figure 6 may well be because pleasant and unpleasant odors produce opposite effects in the medial orbitofrontal/anterior cingulate cortex areas (Rolls et al., 2003), so that the activations may cancel. However, the amygdala region shown in Figure 2C as being modulated by cognitive inputs did extend continuously to the region shown in Figure 2D, and, given the spatial resolution of the methods, some effect of cognitive inputs on representations in the pyriform/olfactory tubercle areas cannot be firmly rejected by the present investigation.

It has been well established by psychophysical methods that olfactory discrimination is rather inefficient in humans, in that successful odor identification depends heavily on attributes such as familiarity and a longstanding connection between an odor and its name (Cain, 1979). In particular, verbal or semantic information can strongly influence the perception of odor attributes (Herz, 2003). For example, Herz and von Clef (2001) presented subjects with a set of odors (including menthol and pine oil) paired with different labels in separate sessions and found a significant label × odor interaction for pleasantness ratings. One of the odors used was an ambiguous mixture of isovaleric acid and butyric acid, which was judged significantly more unpleasant when labeled "vomit" than when labeled "parmesan cheese." In the psychophysical part of the present study, we extended that observation by showing that semantic labels influence hedonic judgements even when clean air is paired with hedonically distinct labels.

The region of the far anterior cingulate cortex/medial orbitofrontal cortex with activations found to correlate with the pleasantness ratings given to the test odor basically coincides with a region previously found to correlate with the pleasantness ratings given to three pleasant and three unpleasant odors (Rolls et al., 2003). In addition, the medial orbitofrontal cortex has been reported to respond preferentially to pleasant but not unpleasant odors (Anderson et al., 2003; Gottfried et al., 2002; Rolls et al., 2003). Thus, the present findings are in agreement with current evidence that the medial part of the human orbitofrontal cortex represents the pleasantness of odors, but also provides evidence on the new finding that this representation holds even when the attributed hedonic properties are modulated by cognitive information. Moreover, this region has en-

hanced activity when subjects are making hedonic olfactory judgements about odors (Zatorre et al., 2000).

Gottfried and Dolan (2003) presented odors with congruent and incongruent pictures and found that activations in the anterior medial orbitofrontal cortex and the anterior hippocampus correlate with whether the picture is congruent with the odor. In the present investigation, knowing that pictures of food and similar stimuli can produce activation of orbitofrontal neurons in macaques (Critchley and Rolls, 1996; Thorpe et al., 1983) and orbitofrontal cortex and amygdala in humans (Morris and Dolan, 2001), we chose to use a much more high-level, semantic, cognitive cue, simply a word presented on a screen at the same time that the odor was presented. Moreover, it was affect in particular that was modulated by the type of label we used, as shown for example by the pleasantness ratings shown in Figure 1. Thus, the study described here is not of congruence, but instead of whether cognitive inputs can influence brain activations produced by affective properties of one and the same odor.

The study described here is also very different from the study described by Zatorre et al. (2000), who found more activation of the orbitofrontal cortex when subjects were making hedonic as contrasted with intensity judgements of a set of odors. In that study, there was no attempt to influence olfactory processing by a top-down biased competition cognitive influence, which is the framework investigated by Rolls and Deco (Deco and Rolls, 2003; Rolls and Deco, 2002), in which we understand the effects produced in the present investigation. The present study with olfactory stimuli is also very different from a recent investigation of flavor produced by drinks in which it was found that the rated preference of unlabeled drinks (i.e., without cognitive influences) was reflected in activations of a ventromedial part of the prefrontal cortex and that pictures of Coca-Cola versus Pepsi cans influenced activations in areas that are more cognitive than flavor-related areas, including the hippocampus and dorsolateral prefrontal cortex (McClure et al., 2004). They were unable to image the medial orbitofrontal cortex. In contrast, the present study used olfactory stimuli and showed that a more cognitive label, a word, could influence hedonic-related olfactory activations in the medial orbitofrontal/adjoining cingulate cortex (Figures 2A, 2B, and 4) and also in the amygdala and adjoining part of the olfactory tubercle as illustrated in Figures 2C and 2D.

The finding that modulation of activity in the amygdala by cognitive information depends on presentation of a detectable olfactory stimulus is in partial agreement with the Anderson et al. (2003) study, in which it was found that activity in the human amygdala represents the intensity dimension of olfactory perception. This finding has also been found to hold with respect to taste processing in humans (Small et al., 2003). However, we also provide evidence that activity in the amygdala correlates with the subjective pleasantness of odors at least when subjective pleasantness judgements are under the influence of semantic information. Thus, it is possible that the human amygdala is also involved in encoding some hedonic properties of olfactory stimuli (O'Doherty et al., 2001) and sexually related visual stimuli (Hamann et al., 2004). However, to what extent this covariation of amygdalar activity with hedonic judgements depends on a cognitive top-down type of influence remains to be determined by further studies.

In conclusion, high-level cognitive inputs, such as the sight of a word, can influence the activations produced by odors in brain regions activated by olfactory stimuli, such as the anterior cingulate and orbitofrontal cortex and the amygdala, and these effects cannot be attributed to altered sniffing, as shown at the end of the Results section. The top-down modulatory cognitive effects on olfactory processing are, we suggest, implemented by a top-down biased competition mechanism (Deco and Rolls, 2004; Deco and Rolls, 2005; Rolls and Deco, 2002). These cognitive effects can have profound influences on the pleasantness of an odor, implemented, we suggest, by influencing activations in the brain areas identified in this paper, such as the orbitofrontal cortex and the cingulate cortex.

Experimental Procedures

Subjects

Twelve healthy right-handed male subjects (age range 23–35) participated in the study. Written informed consent from all subjects and ethical approval (Oxfordshire Research Ethics Committee) were obtained before the experiment. Prior to the scanning sessions, subjects were exposed to each of the odors and trained to use a visual scale for rating the intensity and pleasantness of each of the odors.

Stimuli

The odors were chosen based on a previous fMRI study (Rolls et al., 2003) and preliminary psychophysical investigations in 35 subjects. The pleasant odor chosen was α-ionone, and the unpleasant odor chosen was octanol, both diluted at 5% in propylene glycol. The test odor was produced from a combination of isovaleric acid with cheddar cheese flavor (Firmenich SA, Switzerland), diluted at 5% and 1%, respectively, in propylene glycol.

Stimulus Delivery

A custom-built continuous airflow ten-channel computer-controlled olfactometer was used to allow odor 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 odor delivery. The flow of cleaned 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 odorant dissolved in the propylene glycol. Each washbottle is connected by its own Teflon tube (to provide for low adhesion) to a single delivery nozzle placed within 1 cm of the nose to minimize dead space. This provides seamless alternation between odorant and nonodorant conditions. The delivery nozzle provided two tubes, one for each nostril, to produce birhinal stimulation. The flow rate of the air supply was kept constant at 8 l/min, such that the same minimal degree of tactile somatosensory stimulation was delivered throughout. This system was used in a previous fMRI study of human olfaction (Rolls et al., 2003).

Experimental Design

The experimental protocol consisted of an event-related interleaved design using, in pseudorandom order, six experimental stimulus conditions that each consisted of pairing an odor with a word descriptor shown on a screen for the same duration as the odor delivery. Experimental conditions consisted of pairing the test odor with labels (in different trials) "cheddar cheese" and "body odor"; clean air with "cheddar cheese" and "body odor"; α-ionone

with "flowers"; and octanol with "burned plastic." As a baseline condition, we paired clean air with the label "air." All labeled odors were presented birhinally in a randomized block design during the imaging, with a total of nine presentations of each odor. The odor air stream, paired with a descriptor, was on for 8000 ms for any one odorant, 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 odorless air (passed through propylene glycol solvent) ensured the removal of the previous odorant before delivery of the next odorant. Subjects were instructed to keep their heads absolutely still, breathe normally, and to smell but not sniff the labeled odor. Subjects were pretrained on the procedure, whereby on every trial after the 8000 ms stimulation period, the odor was rated using a button box for first pleasantness and then intensity, using separate visual analog rating scales labeled from +2 (very pleasant/very strong) to −2 (very unpleasant/very weak) shown on the screen. The subject was given explicit instructions to rate the pleasantness and separately the intensity of the odor that had just been delivered.

fMRI Data Acquisition

Images were acquired with a 3 T VARIAN/SIEMENS whole-body scanner at the Centre for Functional Magnetic Resonance Imaging at Oxford (FMRIB), where 14 T2* weighted EPI slices were acquired every 2 s (TR = 2). We used a set of optimizing techniques to select the imaging parameters in order to minimize susceptibility and distortion artifact in the orbitofrontal cortex as described in Wilson et al. (2002) and in previous publications from this laboratory. The relevant factors include imaging in the coronal plane, minimizing voxel size in the plane of the imaging, as high a gradient switching frequency as possible (960 Hz), a short echo time of 25 ms, and global shimming to allow signal recovery in both frontal and temporal areas.

The matrix size was 64 × 64, and the field of view was 192 × 192 mm. Continuous coverage was obtained from +60 (A/P) to −38 (A/P). Acquisition was carried out during the task performance yielding 772 volumes in total. A whole brain T2* weighted EPI volume of the above dimensions and an anatomical T1 volume with slice thickness 1.5 mm and in-plane resolution of 1.5 × 1.5 mm was also acquired.

fMRI Data Analysis

The imaging data were analyzed using SPM2 (Wellcome Department of Imaging Neuroscience, University of London). Preprocessing of the data used SPM2 for realignment, reslicing with generalized interpolation (Thevanaz et al., 2000), normalization to the MNI coordinate system (Montreal Neurological Institute) (Collins et al., 1994), and spatial smoothing with a 10 mm full-width at half-maximum isotropic Gaussian kernel and global scaling. Time series nonsphericity at each voxel was estimated and corrected for (Friston et al., 2002), and a high-pass filter with a cut-off period of 156 s was applied.

A general linear model was then applied to the time course of activation where stimulus onsets were modeled as single impulse response functions and then convolved with the canonical hemodynamic response function (HRF, Friston et al., 1994). Time and dispersion derivatives were included in the basis functions set. Following smoothness estimation (Kiebel et al., 1999), linear contrasts of parameter estimates were defined to test the specific effects of each condition with each individual dataset.

Voxel values for each contrast resulted in a statistical parametric map of the corresponding t statistic, which was then transformed into the unit normal distribution (SPM z). The statistical parametric maps from each individual dataset were then entered into second-level, random effects analyses accounting for both scan-to-scan and subject-to-subject variability. More precisely, the sets of individual statistical maps corresponding to a specific effect of interest were entered as covariates in multiple regression models (ANOVA without a constant) as implemented in SPM2, and the corresponding group effects were assessed by applying linear contrasts (again following smoothness estimation) to the (second-level) parameter estimates generating a t statistics map for each group effect of interest. The above allowed us to perform conjunction analyses (Friston et al., 1999) at the second level. The correlation analyses of the fMRI BOLD signal with given parameters of interest (e.g., pleasantness ratings) were performed at the second-level through applying one-sample t tests to the first-level t maps resulting from performing linear parametric modulation as implemented in SPM2.

Reported p values based on this group analysis are either corrected for the number of comparisons (resels) in the entire volume ("whole-brain" multiple comparisons, Worsley et al., 1996) or controlled for false discovery rate (FDR correction, Genovese et al., 2002). We supplement these by describing a small number of further activations using uncorrected p values, in order to provide an indication of effects appearing in further brain areas shown to be of interest in prior studies (Rolls et al., 2003). Providing descriptions of these further regions in no way alters the interpretation of the results presented in the paper, but does allow some interesting extra effects to be described. We also only describe such uncorrected p values where they correspond to clusters of voxels significant when corrected for the number of comparisons made within each region (small volume correction S.V.C., Worsley et al., 1996). Checks were performed that the results were not influenced by motion artifact by rerunning the analyses using the estimated motion parameters as covariates of no interest in the design matrix and confirming that the results were unaffected.

Acknowledgments

This research was supported by grants from the Medical Research Council.

Received: December 1, 2004
Revised: February 28, 2005
Accepted: April 20, 2005
Published: May 18, 2005

References

Anderson, A.K., Christoff, K., Stappen, I., Panitz, D., Ghahremani, D.G., Glover, G., Gabrieli, J.D., and Sobel, N. (2003). Dissociated neural representations of intensity and valence in human olfaction. Nat. Neurosci. *6*, 196–202.

Cain, W.S. (1979). To know with the nose: keys to odor identification. Science *203*, 467–470.

Carmichael, S.T., and Price, J.L. (1994). Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. J. Comp. Neurol. *346*, 366–402.

Collins, D.L., Neelin, P., Peters, T.M., and Evans, A.C. (1994). Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. J. Comput. Assist. Tomogr. *18*, 192–205.

Critchley, H.D., and Rolls, E.T. (1996). Hunger and satiety modify the responses of olfactory and visual neurons in the primate orbitofrontal cortex. J. Neurophysiol. *75*, 1673–1686.

Deco, G., and Rolls, E.T. (2003). Attention and working memory: a dynamical model of neuronal activity in the prefrontal cortex. Eur. J. Neurosci. *18*, 2374–2390.

Deco, G., and Rolls, E.T. (2004). A neurodynamical cortical model of visual attention and invariant object recognition. Vision Res. *44*, 621–644.

Deco, G. and Rolls, E.T. (2005). Neurodynamics of biased competition and co-operation for attention: a model with spiking neurons. J. Neurophysiol. *94*, in press.

Friston, K.J., Worsley, K.J., Frackowiak, R.S.J., Mazziotta, J.C., and Evans, A.C. (1994). Assessing the significance of focal activations using their spatial extent. Hum. Brain Mapp. *1*, 214–220.

Friston, K.J., Holmes, A.P., Price, C.J., Buchel, C., and Worsley, K.J. (1999). Multisubject fMRI studies and conjunction analyses. Neuroimage *10*, 385–396.

Friston, K.J., Glaser, D.E., Henson, R.N., Kiebel, S., Phillips, C., and Ashburner, J. (2002). Classical and Bayesian inference in neuroimaging: applications. Neuroimage *16*, 484–512.

Genovese, C.R., Lazar, N.A., and Nichols, T. (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage *15*, 870–878.

Gottfried, J.A., and Dolan, R.J. (2003). The nose smells what the eye sees: crossmodal visual facilitation of human olfactory perception. Neuron *17*, 375–386.

Gottfried, J.A., O'Doherty, J., and Dolan, R.J. (2002). Appetitive and aversive olfactory learning in humans studied using event-related functional magnetic resonance imaging. J. Neurosci. *22*, 10829–10837.

Hamann, S., Herman, R.A., Nolan, C.L., and Wallen, K. (2004). Men and women differ in amygdala response to visual sexual stimuli. Nat. Neurosci. *7*, 411–416.

Herz, R.S. (2003). The effect of verbal context on olfactory perception. J. Exp. Psychol. Gen. *132*, 595–606.

Herz, R.S., and von Clef, J. (2001). The influence of verbal labeling on the perception of odors: evidence for olfactory illusions? Perception *30*, 381–391.

Kiebel, S.J., Poline, J.B., Friston, K.J., Holmes, A.P., and Worsley, K.J. (1999). Robust smoothness estimation in statistical parametric maps using standardized residuals from the general linear model. Neuroimage *10*, 756–766.

McClure, S.M., Li, J., Tomlin, D., Cypert, K.S., Montague, L.M., and Montague, P.R. (2004). Neural correlates of behavioural preference for culturally familiar drinks. Neuron *44*, 379–387.

Morris, J.S., and Dolan, R.J. (2001). Involvement of human amygdala and orbitofrontal cortex in hunger-enhanced memory for food stimuli. J. Neurosci. *21*, 5304–5310.

O'Doherty, J., Kringelbach, M.L., Rolls, E.T., Hornak, J., and Andrews, C. (2001). Abstract reward and punishment representations in the human orbitofrontal cortex. Nat. Neurosci. *4*, 95–102.

Ongur, D., and Price, J.L. (1998). Prefrontal cortical projections to the hypothalamus in macaque monkeys. J. Comp. Neurol. *401*, 480–505.

Rolls, E.T. (2005). Emotion Explained (Oxford: Oxford University Press).

Rolls, E.T., and Baylis, L.L. (1994). Gustatory, olfactory, and visual convergence within the primate orbitofrontal cortex. J. Neurosci. *14*, 5437–5452.

Rolls, E.T., and Deco, G. (2002). Computational Neuroscience of Vision (Oxford: Oxford University Press).

Rolls, E.T., Critchley, H.D., Mason, R., and Wakeman, E.A. (1996). Orbitofrontal cortex neurons: role in olfactory and visual association learning. J. Neurophysiol. *75*, 1970–1981.

Rolls, E.T., Kringelbach, M.L., and de Araujo, I.E.T. (2003). Different representations of pleasant and unpleasant odors in the human brain. Eur. J. Neurosci. *18*, 695–703.

Royet, J.P., Koenig, O., Gregoire, M.C., Cinotti, L., Lavenne, F., Le Bars, D., Costes, N., Vigouroux, M., Farget, V., Sicard, G., et al. (1999). Functional anatomy of perceptual and semantic processing for odors. J. Cogn. Neurosci. *11*, 94–109.

Small, D.M., Gregory, M.D., Mak, Y.E., Gitelman, D., Mesulam, M.M., and Parrish, T. (2003). Dissociation of neural representation of intensity and affective valuation in human gustation. Neuron *14*, 701–711.

Thevanaz, P., Blu, T., and Unser, M. (2000). Interpolation revisited. IEEE Trans. Med. Imaging *19*, 739–758.

Thorpe, S.J., Rolls, E.T., and Maddison, S. (1983). Neuronal activity in the orbitofrontal cortex of the behaving monkey. Exp. Brain Res. *49*, 93–115.

Wilson, J.L., Jenkinson, M., Araujo, I.E.T., Kringelbach, M.L., Rolls, E.T., and Jezzard, P. (2002). Fast, fully automated global and local magnetic field optimisation for fMRI of the human brain. Neuroimage *17*, 967–976.

Worsley, K.J., Marrett, P., Neelin, A.C., Friston, K.J., and Evans, A.C. (1996). A unified statistical approach for determining significant signals in images of cerebral activation. Hum. Brain Mapp. *4*, 58–73.

Zald, D.H., and Pardo, J.V. (1997). Emotion, olfaction, and the human amygdala: amygdala activation during aversive olfactory stimulation. Proc. Natl. Acad. Sci. USA *94*, 4119–4124.

Zatorre, R.J., Jones-Gotman, M., and Rouby, C. (2000). Neural mechanisms involved in odour pleasantness and intensity judgements. Neuroreport *11*, 2711–2716.

Zelano, C., Bensafi, M., Porter, J., Mainland, J., Johnson, B., Bremner, E., Telles, C., Khan, R., and Sobel, N. (2005). Attentional modulation in human primary olfactory cortex. Nat. Neurosci. *8*, 114–120.