Hedonic-Specific Activity in Piriform Cortex During Odor Imagery Mimics That During Odor Perception

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Bensafi M, Sobel N, Khan RM. Hedonic-specific activity in piriform cortex during odor imagery mimics that during odor perception. J Neurophysiol 98: 3254–3262, 2007. Although it is known that visual imagery is accompanied by activity in visual cortical areas, including primary visual cortex, whether olfactory imagery remains controversial. Here we asked whether cue-dependent olfactory imagery was similarly accompanied by activity in olfactory cortex, and in particular whether hedonic-specific patterns of activity evident in olfactory perception would also be present during olfactory imagery. We used functional magnetic resonance imaging to measure activity in subjects who alternated between smelling and imagining pleasant and unpleasant odors. Activity induced by imagining odors mimicked that induced by perceiving real odorants, not only in the particular brain regions activated, but also in its hedonic-specific pattern. For both real and imagined odors, unpleasant stimuli induced greater activity than pleasant stimuli in the left frontal portion of piriform cortex and left insula. These findings combine with findings from other modalities to suggest activation of primary sensory cortical structures during mental imagery of sensory events.

INTRODUCTION

Although mental imagery is well documented in the visual (Fletcher et al. 1995; Kosslyn et al. 1995), auditory (Halpern and Zatorre 1999; Zatorre and Halpern 1993), and motor (Jeannerod 1995; Jeannerod and Frak 1999) systems, its existence in olfaction remains controversial (Bensafi and Roubey 2007; Elmes 1998; Herz 2000; Stevenson and Case 2005). The existence of mental imagery for smells is supported by studies showing similarity in the relative contributions of real and imagined odors to the perception of an odor mixture (Cain and Algom 1997) and similarity in perceptual grouping of perceived and imagined smells (Carrasco and Ridout 1993). Additional support comes from the observed improvement of recognition memory (Lyman and McDaniel 1990), taste detection (Djordjevic et al. 2004a), and odor detection (Djordjevic et al. 2004b) when tested concurrently with odor imagery. Furthermore, psychophysical evidence suggests that during odor imagery, humans spontaneously activate the olfactomotor system in an odorant-specific manner: when imagining a pleasant smell, humans spontaneously take a large sniff and when imagining an unpleasant smell they take a smaller sniff. When sniffing behavior is modified by either preventing or encouraging sniffing, olfactory imagery is modulated accordingly (Bensafi et al. 2003a, 2005).

A prevalent theme in mental imagery research is the idea that the neural mechanisms underlying imagery generation are shared with those that process corresponding real sensations (Farah 1989). Psychophysical (Laeng and Teodorescu 2002), neuropsychological (Farah 1988), and imaging (Kosslyn et al. 1999) methods have all demonstrated similarities between perception and mental imagery, to the extent that common neural substrates are implied in both processes (Kosslyn et al. 1995, 1999, 2001). Similarly in olfaction, Djordjevic et al. (2005) used positron emission tomography (PET) to show that mental imagery of odors is associated with increased activation in a number of regions associated with the processing of odors including orbitofrontal cortex, anterior insula, and piriform cortex.

A potential barrier to the interpretation of imaging of imagery results (in all modalities) has to do with task demands and attention. Trying to imagine an odor may drive the olfactomotor system (Bensafi et al. 2003a, 2005), which alone is sufficient to drive activity in olfactory cortex (Sobel et al. 1998, 2000). Furthermore, merely shifting attention to olfaction may further modulate patterns of neural activity throughout the olfactory system (de Araujo et al. 2005; Geisler and Murphy 2000; Sabri et al. 2005; Zelano et al. 2005).

To address this issue, we took advantage of the hedonic-specific patterns of neural activity evident in olfactory cortex (Anderson et al. 2003; Gottfried et al. 2002a; Heining et al. 2003; Rolls et al. 2003; Royet et al. 2003; Wicker et al. 2003). We hypothesized that attention to olfaction and general task demands can be held equal when imagining either pleasant or unpleasant odorants. Thus if olfactory imagery is generated through activation of sensory circuits, then differences in neural activity between imagining pleasant versus unpleasant odors should mimic the differences between smelling the same pleasant versus unpleasant odorants.

METHODS

Subjects

Sixteen subjects (8 women and 8 men, mean age 26.8 ± 4.38 yr) participated in the experiment after giving informed consent to procedures approved by the UC Berkeley Committee for the Protection of Human Subjects. Participants were screened for abnormal olfaction,
history of neurological disease or injury, history of nasal insult (broken nose or surgery), or magnetic resonance (MR) contraindications. Due to technical and motion-related problems, 2 of the 16 subjects were excluded from further analysis.

Odorants and olfactometry

Odorants were delivered by a computer-controlled air-dilution olfactometer described in detail elsewhere (Johnson and Sobel 2007; Johnson et al. 2003). This olfactometer switches between odorant presence and absence in <2 ms, with no nonolfactory cues as to the alteration. The endpoint of the olfactometer is a nasal mask where the odorant is vacuumed away at the same rate at which it is supplied. The mask is coupled to a pneumotachograph that provides a highly accurate constant real-time measurement of airflow in the nose. The pneumotachograph signal was processed with a spirometer (AD Instruments, Grand Junction, CO), amplified (PowerLab 4SP, AD Instruments) and digitally recorded at 100 Hz using Chart version 4.1 software (AD Instruments). This measurement was used to validate that subjects were following task instructions (i.e., sniffing at the tone and for its duration, and otherwise orally respirating), and as a potential measure of interest in later analysis (i.e., comparing sniffing parameters across conditions). Sniffs were preprocessed by removing baseline offsets and aligned in time by setting the point where the sniff entered the inspiratory phase as time 0. Sniff inspired volume, sniff duration, and maximum flow rate were calculated for all sniffs. Volume was calculated by the trapezoidal Riemann sum method. Both the volume integration and sniff duration ended at the first data point where the sniff returned to zero flow. To allow cross-subject comparison, each subject’s airflow values were divided by the maximum value within that subject, resulting in normalized values reaching a maximum of one. The olfactometer, digitized auditory instruction generator, recording of respiratory data, and the MRI scanner itself, were all linked through one TTL pulse that ensured accurate time-locking of all experimental components. The two odorants that were used were ammonium sulfide (4 × 10⁻⁴ vol/vol; Sigma–Aldrich, St. Louis, MO), which smells like rotten eggs, and strawberry oil (10⁻² vol/vol; Lhasa Karnak, Berkeley, CA), which smells like strawberries.

Experimental design

We used an event-related design consisting of five conditions distributed across five functional scans. The five conditions were a no-odorant event, consisting only of clean air (“Clean” condition) and distributed across five functional scans. The five conditions were a presence and absence in Odorants and olfactometry with Hedonic Value (“Pleasant” vs. “Unpleasant”). The pleasant odor was “Strawberry” (strawberry oil) and the unpleasant odor was “Rotten Eggs” (ammonium sulfide). Thus the five conditions were Clean (no odorant), Sensory-Pleasant (“strawberry”), Sensory-Unpleasant (“rotten eggs”), Imagery-Pleasant (“strawberry”), and Imagery-Unpleasant (“rotten eggs”). To avoid the risk of any residual odors in the masks during imaging scans that would contaminate our results, we divided the five scans into two types: “sensory” scans (three scans) and “imagery” scans (two scans) that were run in blocks. Subjects wore new, unused masks during each of the blocks. Three of the trial types (the Clean and the two Sensory conditions) were pseudorandomized across the “sensory” scans block. The temporal order of the “sensory” and “imagery” scans block was counterbalanced across conditions. Conditions were randomized with the constraint that each scan should contain equal numbers of trials of each condition.

During each trial subjects received task instructions through earphones generated by digitally recorded voice (Fig. 1). During the “sensory” scans, each trial began with an auditory primer “Please prepare to sniff,” followed by a countdown (“3, 2, 1”) and a tone. Subjects were asked to sniff for the duration of the tone (1.67 s) during which odorants were diffused into the mask subjects wore. The odorants were diffused for 3 s. During the “imagery” scans, each trial began with an auditory primer “Please prepare to sniff,” followed by a countdown (“3”, “2”), the name of the stimulus to be imagined (“Rotten Eggs” or “Strawberry”) and a tone. Here also, subjects were asked to sniff for the duration of the tone (1.67 s). There were 22 trials per condition type and the stimulus onset asynchrony (SOA) was 30 s.

At the end of the scanning session each subject gave ratings of odor intensity and pleasantness as well as ratings of imagery vividness and imagery pleasantness using a scale from 1 (not at all “intense,” “pleasant,” or “vivid”) to 9 (extremely “intense,” “pleasant,” or “vivid”).

Imaging parameters

All the raw structural and functional imaging data, along with corresponding files describing the temporal structure of the data for each subject, will be made publicly available at http://www.weizmann.ac.il/neurobiology/worg/materials.html.

The experiment was conducted on a 4-T Varian Inova magnet. A custom-built full-head receive coil was used for signal reception. A T2*-sensitive echo planar sequence was used with parameters of TR = 500 ms, TE = 28 ms, and flip angle = 20°. The spatial resolution was set by a 64 × 64 voxel matrix covering a 19.2 × 19.2-cm field of view, resulting in a functional in-plane resolution of 3 mm and through-plane resolution of 3.5 mm. Two interleaves were collected for each frame, with total acquisition time of 1,000 ms per frame. The interleaves were interpolated during image reconstruction, resulting in an effective temporal resolution of 500 ms per frame. Fifteen frames were collected before task onset at the beginning of each scan to achieve dynamic equilibrium. Eight 3.5-mm-thick slices were acquired at an oblique plane traversing from the frontal pole to the temporal pole (typically 30° clockwise to the anterior commissure–posterior commissure plane) with a 0.5-mm gap between slices. This slice orientation was chosen to cover the entire primary olfactory cortex while minimizing partial voluming artifacts (Sobel et al. 1997). To prevent head motion, a custom-formed bite bar was fit to the individual dental impression of each subject. This bite bar was also fit with a pyrolitic graphite implant aimed at reducing ventral temporal susceptibility artifacts (Wilson et al. 2002). Full brain T1-weighted flow compensated spin-warp anatomy images (TR = 500 ms, minimum TE, isotropic 0.875-mm voxels) were acquired as a substrate on which to overlay functional data.

Image analysis

Data were analyzed using mVista software (http://white.stanford.edu/software/). This analysis package has been extensively developed and used to probe sensory processing with fMRI (Boynton et al. 1996; Engel et al. 1994), and has been used by us for olfaction (Porter et al. 2005; Zelano et al. 2005). First, in-plane anatomical images were aligned to the high-resolution anatomical volume of each subject’s brain so that all MR images (across multiple scanning sessions) from a given subject were coregistered to an accuracy of 1 mm (Nestares and Heeger 2000). The fMRI images from each scan were tested for
head movements. We then defined regions of interest (ROIs) anatomically for each subject.

Defining ROIs

We combined a structural and functional restriction to define ROIs. We first outlined the expected subdivisions in piriform cortex (PIR; frontal portion, “PIrF”; temporal portion, “PIrT”; and olfactory tubercle, “Tu”) based on an atlas that is particularly detailed in this respect (Mai et al. 1997). This delineation was performed before any further analysis and in the absence of functional results (see Fig. 4A). To eliminate voxels within the anatomical boundary that are functionally unresponsive (e.g., white matter, cerebrospinal fluid, etc.) we further functionally restricted this region to only those voxels that responded hemodynamically to the control “Clean” condition (see next section for details). A similar principle was applied to ROIs created in the insula (anterior and posterior portions) and orbitofrontal cortex (anterior, lateral, medial, and posterior portions). In this case, demarcation of the expected subdivisions of insula and orbitofrontal cortex was based on the Duvernoy atlas (Duvernoy 1991).

Functional time series analysis

The average time series for each trial within each ROI for each subject was calculated using three steps:

First, for each subject we calculated an activation mask to filter out voxels for which we had no signal. We produced images of the average response across all time points at each voxel. Because voxels in gray and white matter have a significantly different mean response than that of voxels in bone or air, we were able to filter voxels based on their mean response to include only voxels for which we had signal. This eliminated voxels that were in regions of high susceptibility, particularly near the ventral frontal and temporal surface of cortex.

Second, for each subject we produced a noise mask similar to the first that calculated the SD of the response at each voxel. This mask also discriminated between regions of high susceptibility and brain tissue, and further excluded voxels with high noise, such as voxels on large blood vessels.

Third, we restricted each subjects’ anatomical ROI to those voxels that responded to the control “Clean” trials. This was calculated by correlating the response at each voxel after an event with a hemodynamic response function (HRF) derived from the average responses of subjects in a separate study (Anderson et al. 2003). This HRF is derived from a large number of subjects and has been used as a standardized HRF in previous studies (Anderson et al. 2003; Porter et al. 2005; Zelano et al. 2005). Because it is data derived, it is likely to be a better representation of the actual HRF observed in our data than the use of an idealized HRF based on a gamma or Poisson density function as is sometimes done (Friston et al. 1994). By calculating the correlation of each voxel to an expected hemodynamic response function as is sometimes done (Friston et al. 1994). By calculating the correlation of each voxel to a gamma or Poisson density function, we were able to produce a statistical parametric map of the responsiveness of each voxel to the functional condition. To restrict for “Clean” responsive voxels, we excluded all voxels whose correlation to the HRF had a statistical significance value higher than \( P = 0.01 \). Supplementary Fig. 8 and Table 1 show example ROIs and the effects of this restriction procedure.

Subsequent analysis proceeded with these restricted ROIs. The time series at each voxel were filtered to remove low-frequency drift. The average time series were converted into percentage signal change by dividing each time series by its mean response and multiplying by 100. Then, for each trial, a peristimulus time series (in an interval extending 15 s before sniff onset and 30 s after it) was calculated by averaging together activity across all voxels in the ROI. This time series was then smoothed with a Gaussian kernel (full width at half-maximum = 3 s) and detrended. Then, the time series was normalized by subtracting the average response from \( t = 15 \) s before odorant onset \( \leq 10 \) s before the time of odorant onset, for the whole time series (the baseline response before sniff) so that all time series had comparable baselines. Finally, we calculated the average of all trials of a certain condition to derive an average time series for that ROI. fMRI response was defined as the area under the hemodynamic response curves in the window 2 to 8 s after odorant presentation. We then calculated the average across all trials of a given condition (in the same way described for the time courses) to get an average area under the curve for each ROI and each condition of interest. Thus, for each event and ROI we had a single number, the area under the time series curve, as a measure of the magnitude of fMRI response. To account for small variations in sniffing from trial to trial, this value was adjusted for the sniff parameters of sniff volume, maximum flow rate, and sniff duration, which were modeled out of the fMRI response before the ANOVA by linear regression on a subject-by-subject basis. For each subject in each ROI, we regressed fMRI response against these three sniff parameters and took the residual values as our adjusted fMRI response. Thus, the adjusted fMRI response data are that part of the fMRI response that cannot be explained by the sniff data. These adjusted numbers are used in subsequent analyses. These adjusted integrals are shown as the bar graphs in Figs. 4, 5, and 7. For each ROI, we performed a three-way ANOVA with subjects as the blocking variable and Task (“sensory” or “imagery”) and Hedonic Value (“pleasant” or “unpleasant”) as the grouping variables. We looked for main effects as well as second-order interactions between these factors.

RESULTS

Odor ratings

As expected, “Strawberry” was rated as more pleasant than “Rotten Eggs” during both odor imagery \( F(1,13) = 55.513, P < 0.0001 \) (Strawberry: mean = 6.10, \( SE = 0.28 \); Rotten Eggs: mean = 3.03, \( SE = 0.32 \)) and real sensation \( F(1,13) = 101.409, P < 0.0001 \) (Strawberry: mean = 6.30, SE = 0.17; Rotten Eggs: mean = 2.60, \( SE = 0.27 \)). Stimuli were not different in odor intensity \( F(1,13) = 0.902, P > 0.05 \) (Strawberry: mean = 5.21, \( SE = 0.29 \); Rotten Eggs: mean = 5.19, \( SE = 0.27 \)) and imagined odor vividness \( F(1,13) = 1.644, P > 0.05 \) (Strawberry: mean = 4.21, \( SE = 0.40 \); Rotten Eggs: \( m = 4.60, SE = 0.33 \)) (Fig. 2). It is possible that grouping the imagery scans and the perception scans may have had an impact on the experience of vividness depending on the order in which the two blocks were presented. To address this concern, we

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1 The online version of this article contains supplemental data.
The statistical analysis did not reveal any significant difference between groups [F(1, 12) = 3.083, P > 0.05], suggesting that the order of scans did not affect the experience of vividness in perception versus imagery across these orderings.

Effects of airflow

Figure 3A illustrates the average sniff trace during the five experimental conditions. A significant main effect of conditions was observed for sniff volume [F(4, 1535) = 7.873, P < 0.001], reflecting a 14.16% increase in sniff volume for the pleasant odor relative to the unpleasant odor following real odor sensation [t(614) = 3.287, P < 0.001] and a 10.94% increase in sniff volume for the pleasant odor relative to the unpleasant odor following odor imagery [t(614) = 2.392, P < 0.017] (Fig. 3B). Significant main effects of these conditions were also observed for maximum flow rate [F(4, 1535) = 22.782, P < 0.0001] and sniff duration [F(4, 1535) = 17.250, P < 0.0001], reflecting a 9.95% increase in maximum flow rate for the pleasant odor relative to the unpleasant odor following odor imagery [t(614) = 3.962, P < 0.017] (Fig. 3C) and a 7.30% increase in sniff duration for the pleasant odor relative to the unpleasant odor following real odor sensation [t(614) = 4.126, P < 0.001] (Fig. 3D). Airflow parameters (sniff volume, maximum flow rate, and sniff duration) were collected for every trial and were used to adjust the fMRI data on a subject-by-subject basis.

Activity induced by the sensory and the imagery conditions in subdivisions of piriform cortex

As described in METHODS, we used previously defined landmarks to divide PIR into the olfactory tubercule, frontal PIR and temporal PIR (Fig. 4A). Distinct response profiles were observed across these subregions (Fig. 4, B and C). In all analyses, the fMRI response measurements were adjusted with covariates for the sniff data, so that the differences in sniff volume, sniff duration, and maximum flow rate were factored out.

Consistent with previous results, there was significant functional heterogeneity across the three subregions of piriform cortex (Gottfried et al. 2002a; Porter et al. 2005; Zelano et al. 2005). Left and right regions were analyzed separately for all ROIs. The only region that showed a significantly different response for real and imagined stimuli was PirF. In both right [F(1, 13) = 27.22, P < 0.05] and left [F(1, 13) = 32.75, P < 0.05] PirF, the effect of Hedonic Value was accompanied by an effect of Task with greater activity in the sensory than that in the imagery trials. A significant effect of Hedonic Value was observed in left PirF [F(1, 13) = 15.51, P < 0.05] with greater activity, in both sensory-pleasant and sensory-unpleasant conditions. Maximum flow rate during the imagery-pleasant condition was significantly greater than that observed during both the sensory and imagery-unpleasant conditions. Maximal flow rate during the imagery-pleasant condition was significantly greater than that observed during the imagery-unpleasant condition. D: means and SEs of sniff duration during the 5 conditions. Sniff duration during the sensory-pleasant condition was significantly longer than that during the sensory-unpleasant condition. * signifies a statistically significant difference at the threshold 0.05.
sensation and mental imagery induced in the unpleasant trials (Fig. 4D). Such effects were not observed in left (Fig. 5A) and right (Fig. 5B) PirT and left (Fig. 5C) and right (Fig. 5D) olfactory tubercule (P > 0.05 in all cases). In the right PirF, a significant Hedonic Value × Task interaction reflected that the effect of Hedonic Value was mostly carried by the sensory condition [F(1,13) = 5.27, P < 0.05] (Fig. 4E).

In sum, the unpleasant perceived odor induced greater activity than the pleasant perceived odor in both left and right frontal PIR, whereas the unpleasant imagined odor induced greater activity than the pleasant imagined odor in the left frontal PIR.

Activity induced by the sensory and the imagery conditions in additional regions

Next, we examined the responses of a number of odor responsive regions outside piriform cortex. We created ROIs within subregions of orbitofrontal cortex (OFC) and insula (INS) (Fig. 6, A and B) based on anatomical landmarks, and measured responses separately within each ROI. Left and right regions were analyzed separately. In all analyses, the fMRI response measurements were adjusted with covariates for the sniff data, so that the differences in sniff volume and maximum flow rate were factored out.

Insula ROIs

Two insula regions were defined in each hemisphere: a posterior region (pINS) and an anterior region (aINS). Parts of these regions in a single slice are shown in Fig. 6B. Average responses in these ROIs showed effects of both Task and Hedonic Value (Fig. 7, A–D).

Effects of Task were observed in both right aINS [F(1,13) = 8.84, P < 0.05] and right pINS [F(1,13) = 11.57, P < 0.05], with greater activity during Sensory than during Imagery conditions, but not in either region in the left hemisphere. Conversely, effects of Hedonic Value were observed in both

FIG. 4. Response in primary olfactory cortex. A: piriform cortex was subdividing anatomically into a tubercle region (Tu), frontal region (PirF), and temporal region (PirT). Left: Coronal slice from a single subject showing anatomical subdivisions. Right: Atlas coronal view (Mai et al. 1997). B and C: time course of blood oxygen level–dependent (BOLD) activity in the left (B) and right (C) frontal piriform to each of the 4 experimental conditions (sensory-pleasant, sensory-unpleasant, imagery-pleasant, and imagery-unpleasant). Sniff-adjusted functional magnetic resonance imaging (fMRI) response in left (D) and right (E) frontal piriform. Error bars represent the SE. Hedonic value–dependent activity in left frontal piriform cortex during odor imagery is similar to that during odor perception. * signifies a statistically significant difference at the threshold 0.05. ns, nonsignificant difference at the statistical threshold of 0.05.

FIG. 5. Activity in subdivisions of the piriform cortex. Sniff-adjusted fMRI response in left (A) and right (B) temporal piriform, and in left (C) and right (D) olfactory tubercule from t = 2–8 s. Error bars represent the SE.
left aINS \[ F(1,13) = 16.09, P < 0.05 \] and left pINS \[ F(1,13) = 11.25, P < 0.05 \] but not in the right hemisphere regions. In both regions, responses were greater for unpleasant than for pleasant stimuli for both real and imagined odors.

A general characterization of the insula response suggests a left versus right hemisphere dissociation in which the left regions reflected odor content of an odor percept, regardless of its source (real vs. imagined) and the right hemisphere regions were responsive more to real odors.

**Orbitofrontal ROIs**

Four orbitofrontal regions were defined in each hemisphere: an anterior region (aOFC), a lateral region (lOFC), a medial region (mOFC), and a posterior region (pOFC). Parts of these regions in a single slice are shown in Fig. 6A. Average responses in these ROIs showed effects of both Task and Hedonic Value (Fig. 6, E–L).

Effects of task were observed in all OFC regions in both hemispheres: left aOFC \[ F(1,13) = 18.42, P < 0.05 \], right aOFC \[ F(1,13) = 21.36, P < 0.05 \], left lOFC \[ F(1,13) = 7.43, P < 0.05 \], right lOFC \[ F(1,13) = 15.32, P < 0.05 \], left mOFC \[ F(1,13) = 26.81, P < 0.05 \], right mOFC \[ F(1,13) = 62.88, P < 0.05 \], left pOFC \[ F(1,13) = 7.97, P < 0.05 \], and right pOFC \[ F(1,13) = 15.5, P < 0.05 \]. In all instances the response to real odors was greater than that for imagined odors.

Effects of Hedonic Value were observed in left \[ t(13) = 2.19, P < 0.05 \] and right \[ t(13) = 2.52, P < 0.05 \] pOFC and in left mOFC \[ t(13) = 2.45, P < 0.05 \] for the real but not the imagined odors.

FIG. 6. Structural regions of interest were drawn, subdividing the orbitofrontal cortex (OFC) (A) into anterior (“a”), lateral (“l”), medial (“m”), and posterior (“p”) regions, and subdividing the insula (B) into an anterior region (“a”) and a posterior region (“p”).

FIG. 7. Activity in insula and OFC. Sniff-adjusted fMRI response in left (A) and right (C) aINS, in left (B) and right (D) pINS, in left anterior (E), lateral (F), medial (G), posterior (H) OFC, and in right anterior (I), lateral (J), medial (K), posterior (L) OFC. Error bars represent the SE. Hedonic Value–dependent activity in left anterior and posterior insula during odor imagery is similar to that during odor perception (A and B). Activity during perception was significantly greater than that during imagery in right anterior and posterior insula, in left and right anterior, lateral, medial, and posterior OFC (C–L). * signifies a statistically significant difference at the threshold 0.05. ns, nonsignificant difference at the statistical threshold of 0.05.
DISCUSSION

Our main result was that odor-imagery-induced activity paralleled odorant-induced activity in primary olfactory cortex and insular cortex. In particular, similar patterns of hedonic-value–specific activity were evident in a frontal portion of the left piriform cortex as well as in the left anterior and posterior insula during both real and imagined olfaction. Whereas simple activations during imagery can be attributed to task demands and attention toward the task, the demonstration of parallel activations across equal task demands and attention in our study suggests more strongly that the observed-imagery–induced neural activity reflects imagery itself rather than concomitant factors. That imagery-induced activity was valence specific in a manner that resembled perception, combined with the findings of Djordjevic et al. (2005), suggests that some form of odor imagery exists and that it relies in part on neural mechanisms common with real olfactory perception.

This observed greater neural activity in primary sensory areas, during both perception and imagery of the unpleasant odor, may reflect the primacy of hedonic judgments—and particularly judgments of negative hedonic value—in olfactory processing (Rouby et al. 2002). Hedonic categorization at an early processing stage (i.e., in frontal piriform cortex) may reflect the survival value in deciding very quickly whether the environmental stimulus is noxious or dangerous. This view is consistent with the fact that humans react more rapidly to aversive and dangerous odors than to appetitive odors (Bensafi et al. 2003b; Jacob et al. 2003) and that unpleasant stimuli have a greater impact on everyday life and are usually more arousing than pleasant stimuli (Lang et al. 1993).

The heterogeneity of response within piriform cortex during odor perception and odor imagery seen here was consistent with previous results of heterogeneity during odor imagery (Djordjevic et al. 2005) and during hedonic processing of odorants (Gottfried et al. 2002a; Zelano et al. 2007). Together, these findings support the notion of generally higher-order top-down processing in frontal piriform, and more bottom-up stimulus-driven and attention-independent activity in temporal piriform (Gottfried et al. 2002a; Zelano and Sobel 2005; Zelano et al. 2005).

Beyond piriform cortex we observed activity in a number of regions, notably OFC and insula. Real sensation of odorants induced more activity than odor imagery in all regions of the OFC in both hemispheres. In posterior OFC, unpleasant odorants induced more activity than pleasant odorants. This is consistent with one previous study (Gottfried et al. 2002a), but may be inconsistent with several others that did not find hedonic-value–dependent activity in posterior OFC (Anderson et al. 2003; Gottfried et al. 2002b; Rolls et al. 2003). However, considering that OFC activity is modulated by a considerable variety of factors, such as sensory-specific satiety (O’Doherty et al. 2000), motivation (Small et al. 2001), and lexical knowledge (de Araujo et al. 2005), the differences between our results and those of previous studies may be the result of methodological variables or differences in study design. For example, whereas subjects in the studies reported by Anderson et al. (2003) and Rolls et al. (2003) performed respectively a detection task and hedonic and intensity judgments during scanning, in our study subjects did not perform any task after odorant onset.

Whereas OFC activity was driven mainly by perception and not imagery, activity in the insula was nearly identical in its extent and power under both conditions. Furthermore, the left insular activity in this study was strongly valence dependent, being greater during unpleasant real and imagined odors. This hedonic-specific pattern is consistent with previous findings of increased left insular activity during identification of unpleasant odors (Royet et al. 2003), during unpleasant emotions evoked by odors, and during perception of the same unpleasant emotion in others (Wicker et al. 2003). It is also consistent with electrical stimulation results that report that stimulation of the anterior insula through implanted depth electrodes produced unpleasant sensations in the throat spreading up to the mouth, lips, and nose (Krolak-Salmon et al. 2003). Although when taken together these results highlight an increased insular response related to unpleasant stimuli, further work is necessary to determine whether this preferential insular response to unpleasant stimuli reflects valence alone or whether it is confounded by related entities such as valence-independent arousal, which contribute to the general insular role in flavor processing (Small et al. 2001).

Another general feature of our data was that imagery-induced brain activity was strongly lateralized to the left in piriform cortex. This is consistent with previous results in olfaction (Djordjevic et al. 2005) and resembles similar lateralization observed during visual imagery (Sack et al. 2005). The relatively greater response in these left lateralized regions to unpleasant than pleasant odors seen in our study is in line with emotion theories that suggest a more general left hemisphere dominance for unpleasant stimuli (Royet et al. 2003) and support the notion of an overall leftward lateralization in imagery generation (D’Esposito et al. 1997). It is tempting to link the lateralization in imagery-induced activity to lateralization in language mechanisms. The role of language in olfactory cortex activity was recently studied by Gonzalez et al. (2006), who observed that reading words with strong olfactory associations activates olfactory regions. Our study, however, cannot answer the question of the role of linguistic labels on piriform cortex activity in that all stimuli were easily namable.

Although our results present evidence of olfactory imagery in primary olfactory cortex, it is possible that additional brain regions outside of our image acquisition were also involved. We could have opted to scan the entire brain, at the cost of significantly increased susceptibility artifacts in the ventral portion of the brain that contains primary olfactory cortex. Rather, we elected to optimize our scanning parameters to obtain good signal in the classic olfactory areas, at a cost of scanning only a limited portion of brain. Thus ours is not a comprehensive study of brain mechanisms involved in odor imagery, but is a targeted investigation of olfactory cortex. What role additional regions such as parietal and more dorsal regions may play during olfactory imagery is a topic for further investigation.

A second caveat about our results is the possible effect of other factors that may have been fortuitously correlated with hedonic value in our study. Any pair of odors will differ along a large number of dimensions, such as hedonic valence, familiarity, edibility, linguistic associations, and so forth, and whereas we designed our study with the intention of comparing hedonic value, it is possible that it was some other...
difference between the pair we used that created the pattern of differences we observed. Whereas such a concern limits interpretation of our results regarding the larger issue of odor hedonics, it does not undermine our main result, which is that patterns of behavioral and neural activity during imagery of odors paralleled that during perception.

Although subjects were asked to maintain constant sniffs across conditions, sniffs during imagery and sensation of the pleasant odor were slightly but significantly larger than those for the unpleasant odor. That this behavioral difference persisted despite instructions to the contrary points to the robustness of this behavioral mechanism (Bensafi et al. 2003a, 2005). Although the differences in sniffing were small, we nevertheless entered these differences as regressors into our brain imaging analysis, to prevent any possible related confounds. An additional finding here was that although increased sniff volume for the pleasant odor was found for both odor sensation and imagery conditions, increased sniff duration for the pleasant odor was found only during sensory trials. Moreover, increased sniff flow rate for the pleasant odor was found only during imagery trials. One explanation of this may be that during the sensory trials, participants did not know until after they encountered the odor whether it was pleasant or unpleasant. Thus they increased sniff volume (for the pleasant odor) by increasing sniff duration for pleasant rather than unpleasant odors. In contrast, during the imagery trials participants knew beforehand the hedonic value of the odor they had to imagine, and thus increased their sniff volume (for the pleasant odor) at the beginning of the trial, by increasing their inspired flow rate.

Another issue worth considering in interpreting our results is a potential bias introduced in our procedure for selecting voxels of interest to analyze. In our procedure, we analyzed voxels responsive to the “clean” no-odor condition for their response to the pleasant and unpleasant stimuli. This strategy could be a potential problem if there are voxels that respond to odors that do not respond during sniffing. This question has been the subject of several studies (Sobel et al. 1998; Zelano et al. 2005) that suggest that although active sniffing (sniffing in which a potential odor is sought and processed) leads to neural activity in olfactory cortex (including primary olfactory cortex)—even when no odor is actually present—passive inspiration, where the subject has no interest or anticipation of a potential odor, leads to significantly less activity in these regions. Because the sniffing in the sensory conditions of our study was active in this sense (subjects had no cue as to which odor was to be presented on any given trial), we would expect activity in olfactory cortex even during the “clean” trial when no odor was presented. Indeed, we found significant activity in response to sniffing alone (no odorant) in all olfactory brain areas we examined; had we not, our procedure would have led to the selection of a random and extremely small set of voxels, which would have shown a random pattern of response in the other conditions. The fact that this was not the case, that in fact the pattern of response (in terms of its hedonic-value response) was consistent with that in previous reports (Royet et al. 2003; Wicker et al. 2003) and was paralleled during imagery suggests that the voxel selection procedure based on clean trials was meaningful.

A final question concerns how our findings relate to competing theories of mental imagery. The two main theories are the “perceptual anticipation theory,” in which mental images may arise when one anticipates an object or scene so strongly that a depictive representation of the stimulus is created in early sensory cortex (Kosslyn and Thompson 2003) and the “propositional theory,” in which mental images are not images, but descriptions (Pylyshyn 2003). Under the propositional theory, one might argue that propositional representations are not expected to activate the earliest stage of olfactory processing because they are essentially linguistic. Our finding of a parallel hedonic-value–dependent pattern of neural activity at the earliest stage of processing in both olfactory sensation and olfactory mental imagery is consistent with the perceptual anticipation theory. Nevertheless, because linguistic odor labels may modulate patterns of activity in human primary olfactory cortex (Gonzalez et al. 2006), we cannot claim that the current findings weigh definitively against the propositional theory. Ultimately, absent detailed mechanistic models of sensory processing and imagery, these competing theories are irresolvable. That said, our findings lend support to the view that olfactory imagery exists and that generating imagery of sensory events involves activation of neural substrates common to real perception. This has been well documented in vision (Kosslyn and Thompson 2003), and its current iteration in olfaction suggests that this is a general principle in brain function.

REFERENCES


