Dissociated Representations of Irritation and Valence in Human Primary Olfactory Cortex

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Dissociated representations of irritation and valence in human primary olfactory cortex. J Neurophysiol 97: 1969–1976, 2007. First published January 10, 2007; doi:10.1152/jn.01122.2006. Irritation and negative valence are closely associated in perception. However, these perceptual aspects can be dissociated in olfaction where irritation can accompany both pleasant and unpleasant odors. Whereas the sensation of odor reflects transduction at olfactory receptors, irritation reflects concurrent transduction of the odorant at trigeminal receptors. Thus a stimulus can be either a “pure olfactant” activating the olfactory receptors only or a bimodal odorant activating both types of receptors. Using event-related functional magnetic resonance imaging and a 2 × 2 experimental design contrasting odorant valence (pleasant/unpleasant) and odorant type (pure olfactant/bimodal) we found activity in piriform cortex to be associated with valence, and not type, of odors. In contrast, activity in the olfactory tubercle was associated with type, and not valence, of odors. Importantly, this was found when perceived intensity was held equal across odors. These findings suggest that dissociable neural substrates subserve the encoding of irritation and valence in olfaction.

INTRODUCTION

In sensory experience, irritation and negative valence are typically positively correlated to the extent that they are seemingly indissociable. In olfaction, both unpleasant and pleasant odors can induce an irritating sensation, thus providing a framework for the dissociation of brain representations for valence and irritation. For example, both the unpleasant proprioic acid (smells acidic) and the pleasant citral (smells lemony) cause a sensation of irritation in the nose. This sensation reflects concurrent transduction of these odorants in the olfactory nerve and trigeminal nerve. It is the trigeminal activation that produces the sensation of irritation (Brand 2006; Doty and Kobal 1995; Hummel 2000). Thus an odorant can be either a “pure olfactant” that stimulates the olfactory nerve only or a “bimodal” odorant that simultaneously stimulates both the olfactory and trigeminal nerves (for review see Hummel and Livermore 2002). Most odorants are bimodal (Beidler and Tucker 1956).

The olfactory and trigeminal systems are not independent. Early observations on the interaction between the olfactory and trigeminal systems suggested that in bimodal odorants irritation was “masking” the effect of odor (Bain 1868; Katz and Talbert 1930). Later psychophysical investigations confirmed that trigeminal stimulation can inhibit olfactory sensations (Cain and Murphy 1980; Cometto-Muniz and Hernandez 1990; Kobal and Hummel 1988; Laska et al. 1997; Livermore et al. 1992). Concordantly, electrophysiological studies revealed trigeminal inhibition of neural activity in the olfactory system of amphibians (Bouvet et al. 1987), rodents (Stone et al. 1968), and humans (Kobal and Hummel 1988; Livermore et al. 1992). The site and mechanism of trigeminal inhibition on olfaction remain unclear. Whereas studies in amphibians suggested trigeminal inhibition on olfaction at the peripheral level (Bouvet et al. 1987), psychophysical and electrophysiological studies in rodents and humans pointed to central mechanisms of interaction (Cain and Murphy 1980; Kobal and Hummel 1988; Livermore et al. 1992; Stone et al. 1968). That central activity may be reduced in response to a trigeminal odorant was further evidenced in a positron emission tomography (PET) study comparing activity induced by smelling the pure olfactant vanillin and the bimodal odorant acetone (Savic et al. 2002). However, considering the significant hedonic differences between these two odorants (vanillin is pleasant and acetone is unpleasant), the influence of trigeminal activity alone remains unresolved and the specific neural substrates of this central interaction remain unknown.

In the present study we focused on primary olfactory cortex. This includes all brain regions that receive direct input from the olfactory bulb, including piriform cortex, the olfactory tubercle, entorhinal cortex, and the amygdala (Price 1987). We set out to ask whether valence and irritation (trigeminality) are dissociable qualities at this level.

METHODS

Subjects

Fourteen healthy subjects (nine women and five men, ranging from 20 to 39 yr of age) participated in the main functional magnetic resonance imaging (fMRI) study. An additional four healthy subjects participated in an identical control study using a different set of odors. Two anosmic female subjects, ages 40 and 25 yr, were tested in a functional magnetic resonance imaging (fMRI) study. An additional four healthy subjects (three men and one woman, ranging from 20 to 39 yr of age) participated in the main functional magnetic resonance imaging (fMRI) study.

Odorants and olfactometry

Odorants were delivered by a computer-controlled air-dilution olfactometer previously described in detail (Johnson and Sobel 2007). 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 pneumatotachograph that provides a highly accurate constant real-time measurement of airflow in the nose (Johnson et al. 2006a). The pneumatotachograph signal was processed with a spirometer (ADInstruments, Grand Junction, CO), amplified (ADInstruments, PowerLab 4SP), and digitally recorded at 100 Hz using Chart version 4.1 software (ADInstruments). This measurement was used to validate that subjects were following task instructions (i.e., sniffing at the tone and for its duration). 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 Reimann 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 (transistor–transistor logic) pulse that ensured accurate time-locking of all experimental components. Odors used included strawberry oil, peach oil, citral, eucalyptol, valeric acid, propionic acid, hydrogen sulfide, and mercaptoethanol. Concentrations of odors were individually adjusted so that perceived intensity was equal across all odorants within each subject and ranged from 5 to 7 on a 10-point perceptual scale across subjects (Fig. 1D).

### Experimental design

We used a 2 × 2 design, contrasting odorant type (pure olfactant/bimodal) and odorant valence (pleasant/unpleasant) within an event-related design. This yielded four trial types: 1) pleasant—pure olfactant; 2) pleasant—bimodal; 3) unpleasant—pure olfactant; and 4) unpleasant—bimodal. Trials were presented in a pseudorandom order, with each condition presented 24 times across four 12-min scans. The intertrial interval was 30 s (Fig. 1B). Each trial began when a digitized voice was heard through headphones instructing the subject to prepare to sniff for the duration of the tone. A 3-s countdown followed and then a tone lasting 1.7 s. The only task assigned to the subjects was to sniff consistently across all conditions at the tone. To maintain a generalized level of attention throughout participation, a randomly selected trivia fact was played through the headphones during the intertrial interval. Between scans, the intensity of the odors was assessed, and the continued equality of the intensity ratings verified. If needed, concentrations were adjusted before the next scan. Dilution of odorant was fine-tuned until each subject gave identical intensity ratings for all 4 odorants. Additionally, the intensity of the odors was assessed, and the continued equality of the intensity ratings verified. If needed, concentrations were adjusted before the next scan. Dilution of odorant was fine-tuned until each subject gave identical intensity ratings for all 4 odorants. Importantly, subjects also rated the intensity of odors before entering the scanner. Dilution of odorant was fine-tuned until each subject gave identical intensity ratings for all 4 odorants. All the raw data are available for download from the supplementary materials section at http://www.weizmann.ac.il/neurobiology/labs/sobel.

### Imaging parameters

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**FIG. 1.** Experimental design. A: odorant selection. Odorants were chosen such that they fell into one of 4 possible categories: pleasant and nontrigeminal, pleasant and trigeminal, unpleasant and nontrigeminal, or unpleasant and trigeminal. B: complete experimental session. Each subject participated in 4 functional scans of 24 trials each, with the 4 different odorants presented in random order. C: hedonic ratings. Before entering the scanner, each subject rated the pleasantness of the odorants on a scale from 1 to 10. Pleasant odorants were rated as significantly more pleasant than unpleasant odorants. D: intensity ratings. Importantly, subjects also rated the intensity of odors before entering the scanner. Dilution of odorant was fine-tuned until each subject gave identical intensity ratings for all 4 odorants. E: trigeminal-activity assessed by human anosmic ratings. An anosmic subject was presented with the odorants and was initially asked whether any sensation in the nose was felt. In the column labeled “sensation in nose reported,” an X indicates that the subject reported sensation in the nose. Subject then performed a 2-alternative forced-choice (2AFC) task for each odorant vs. clean air. Dilution of odorant was fine-tuned until each subject gave identical intensity ratings for all 4 odorants. E: trigeminal-activity assessed by human anosmic ratings. An anosmic subject was presented with the odorants and was initially asked whether any sensation in the nose was felt. In the column labeled “sensation in nose reported,” an X indicates that the subject reported sensation in the nose. Subject then performed a 2-alternative forced-choice (2AFC) task for each odorant vs. clean air. Dilution of odorant was fine-tuned until each subject gave identical intensity ratings for all 4 odorants. E: trigeminal-activity assessed by human anosmic ratings. An anosmic subject was presented with the odorants and was initially asked whether any sensation in the nose was felt. In the column labeled “sensation in nose reported,” an X indicates that the subject reported sensation in the nose. Subject then performed a 2-alternative forced-choice (2AFC) task for each odorant vs. clean air. Dilution of odorant was fine-tuned until each subject gave identical intensity ratings for all 4 odorants.
plane resolution was 3.5 mm. Twenty 3.5-mm-thick slices were obtained and used to probe sensory processing with fMRI (Boynton et al. 2003; Kennedy et al. 1998; Nieto-Castanon et al. 2003; Slotnick 2005). First, the fMRI images from each scan were tested for head movement. Where fMRI is often used within an exploratory setting for which arbitrary rules lead to errors of overlap between the olfactory and frontal piriform cortex and olfactory tubercle (Gottfried et al. 2002; Haberly 2001; Litiaudon et al. 2003; Zelano et al. 2005). It is important to note that these subregions have no clear anatomical borders visible on the MR image. Thus our demarcations were based on a set of rules extracted from an atlas that is particularly detailed in this respect (Mai et al. 1997). For example, to determine the border between the olfactory tubercle and the frontal piriform lateral to it, we drew a straight line up from the medial tip of the uncus within the coronal plane. It is certain that applying such rules restricted to include only voxels that responded hemodynamically to the union of all conditions. Specifically, we excluded all voxels whose correlation to the hemodynamic response function had a statistical significance value $P > 0.01$. A similar principle was applied to regions of interest created in the thalamus (dorsal medial, ventral medial, and ventral lateral portions) and orbitofrontal cortex (anterior, lateral, medial, and posterior portions). In this case, demarcation of the expected subdivisions of OFC was based on the Duvernoy atlas that is particularly detailed in this respect (Duvernoy 1991).

**Functional time series analysis**

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, 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 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 union of all conditions. This was calculated by correlating the response at each voxel after an event with a hemodynamic response function derived from the average responses of subjects in a separate study (Anderson et al. 2003). By calculating the correlation of each voxel to an expected hemodynamic response function, and the statistical significance of this correlation, we were able to produce a statistical parametric map of the responsiveness of each voxel to odorants. To restrict for all responsive voxels, we excluded all voxels whose correlation to the hemodynamic response function had a statistical significance value $P > 0.01$.

Subsequent analysis proceeded with these restricted ROIs. For each trial, a peristimulus time series (in an interval extending 10 s before sniff onset and 20 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 $= 2$ s) and detrended. Then, the time series was normalized by subtracting the average response from $t = 10$ s before odorant onset up to $1$ 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 4 to 8 s after odorant presentation. We then calculated the subdivisions in piriform cortex: frontal portion, temporal portion, and olfactory tubercle (Gottfried et al. 2002; Haberly 2001; Litiaudon et al. 2003; Zelano et al. 2005). It is important to note that these subregions have no clear anatomical borders visible on the MR image. Thus our demarcations were based on a set of rules extracted from an atlas that is particularly detailed in this respect (Mai et al. 1997). For example, to determine the border between the olfactory tubercle and the frontal piriform lateral to it, we drew a straight line up from the medial tip of the uncus within the coronal plane. It is certain that applying such arbitrary rules leads to errors of overlap between these two regions (olfactory tubercle and frontal piriform) across subjects. That said, all ROIs were drawn before functional analysis and thus any error was unrelated to functional condition. Data from all ROIs were then functionally restricted to include only voxels that responded hemodynamically to the union of all conditions. Specifically, we excluded all voxels whose correlation to the hemodynamic response function had a statistical significance value $P > 0.01$. A similar principle was applied to regions of interest created in the thalamus (dorsal medial, ventral medial, and ventral lateral portions) and orbitofrontal cortex (anterior, lateral, medial, and posterior portions). In this case, demarcation of the expected subdivisions of OFC was based on the Duvernoy atlas that is particularly detailed in this respect (Duvernoy 1991).
average across all trials of a given condition (in the same way described for the time courses) to attain an average area under the curve for each ROI and each condition of interest. These integrals are shown as the bar graphs in Figs. 4 and 5. All additional analyses were then performed using the integrals of blood oxygenation level-dependent (BOLD) activity for each trial. For each ROI, we performed a random-effects model three-way ANOVA with subject as the blocking variable and type (bimodal/pure olfactory) and valence (pleasant and unpleasant) as the grouping variables. We looked for main effects as well as second-order interactions between these factors. The additional control study was analyzed in the same way, but with directional tests to verify the results of the main study.

RESULTS

Behavior

To test the previously reported (Doty et al. 1978) trigeminality of the odorants used, we administered them to an anosmic subject in a two-alternative forced-choice (2AFC) detection task conducted in the psychophysics lab. The anosmic subject was able to detect all the bimodal odorants, but none of the pure olfactory odorants (Fig. 1E), thus verifying the reported trigeminality of these odorants. To test whether this result was influenced by the different testing conditions, we repeated the test with a second anosmic subject, this time in the MRI scanner. Results of this second test mirrored the first, further confirming the expected trigeminal/olfactory profile of these odorants.

Consistent with our intended perceptual space, odors in the pleasant conditions were rated as more pleasant than odors in the unpleasant conditions by all subjects \(F(1,13) = 97.1, P < 0.00001\), with no effect of odorant type \(F(1,13) = 1.3, P < 0.27\) and, critically, with no interaction between odorant valence (pleasant/unpleasant) and odorant type (pure olfactory/bimodal) \(F(1,13) = 1.7, P < 0.15\) (Fig. 1C). Given that the olfactometer was adjusted on a per-subject basis, perceived odorant intensity ratings were identical across all conditions \(F(3,13) = 1, P < 0.4\) (Fig. 1D). Finally, analysis of subjects’ sniffs revealed that they accurately followed instructions, sniffing equally across conditions (Fig. 3) [sniff duration: \(F(3,39) = 1.09, P < 0.36\); sniff max flow: \(F(3,39) = 1.42, P < 0.25\); sniff mean flow: \(F(3,39) = 0.92, P < 0.43\)]

Dissociated representations of valence and irritation in subregions of piriform cortex

In right pirF there was a main effect of valence (pleasant/unpleasant) \(F(1,13) = 6.54, P < 0.024\) no main effect of type

![Figure 3. Sniff trace analysis. A: sniff duration. Left: subject's normalized sniff duration is shown. There were no significant differences between conditions. Right: pairwise comparisons between all conditions. B: sniff maximum flow. Left: subject's normalized maximum flow. There were no significant differences between conditions. Right: pairwise comparisons between all conditions. C: sniff mean flow. Left: subject's normalized mean flow. There were no significant differences between conditions. Right: pairwise comparisons between all conditions.](image-url)
Olfactory tubercle had a main effect of type whereby pure olfactants elicited more activity than pleasant odorants regardless of trigeminality. Frontal piriform cortex had a main effect of valence whereby unpleasant odorants, regardless of trigeminality (Fig. 4) [pl-nt vs. pl-tr: \( t(13) = 1.7, P < 0.12 \)].

Overall levels of activity were significantly greater in right temporal piriform cortex than left \( [F(1,13) = 10, P < 0.008] \). The same was true in the tubercle \( [F(1,13) = 8.3, P < 0.01] \). However, in frontal piriform cortex, levels of activity were the same across sides \( [F(1,13) = 0.2, P < 0.89] \). Therefore it is possible that the lateralized nature of the observed effect arises partly from a greater signal on the right side regardless of condition.

To verify that this dissociation reflected the intended differences in type and valence across odorants rather than some other unidentified property of these stimuli, we repeated the study using four new odorants. We now selected the odorants peach oil (pure olfactory and pleasant), eucalyptol (bimodal and pleasant), mercaptoethanol (pure olfactory and unpleasant), and valeric acid (bimodal and unpleasant), whose trigeminal properties were verified by the anosmic subject, as with the previous odorants. Considering that this was a control to test the previous finding, we tested four new subjects, and used a directional one-tailed random effects test. Results from the second analysis mirrored the first.

In right pirF there was a main effect of valence \( [F(1,13) = 6.84, P < 0.05, \text{one-tailed}], \) no main effect of type \( [F(1,13) = 4.9, P < 0.12], \) and no interaction \( [F(1,13) = 0.14, P < 0.73] \). Follow-up tests mirrored the results from the first set of odorants: activity was greater for the unpleasant versus pleasant odorants, regardless of trigeminality (Fig. 4C). All tests were one-tailed: pl-nt vs. pl-tr: \( t(3) = 1.2, P < 0.14; \) pl-nt vs. un-nt: \( t(3) = 2.5, P < 0.04; \) pl-nt vs. un-tr: \( t(3) = 1.8, P < 0.07; \) pl-tr vs. un-nt: \( t(3) = 2.9, P < 0.03; \) pl-tr vs. un-tr: \( t(3) = 2.23, P < 0.05; \) un-nt vs. un-tr: \( t(3) = 1.28, P < 0.14. \)

In right olfactory tubercle there was a main effect of type \( [F(1,13) = 26.4, P < 0.01, \text{one-tailed}], \) no main effect of valence \( [F(1,13) = 0.23, P < 0.65], \) and no interaction \( [F(1,13) = 0.015, P < 0.91] \). Follow-up tests matched the results from the first set of odorants; activity was greater for pure olfactants versus bimodal odorants regardless of valence (Fig. 4C). All tests were one-tailed: pl-nt vs. pl-tr: \( t(3) = 9.4, P < 0.001; \) pl-nt vs. un-nt: \( t(3) = 0.67, P < 0.25; \) pl-nt vs. un-tr: \( t(3) = 3.03, P < 0.025; \) pl-tr vs. un-nt: \( t(3) = 9.4, P < 0.0025; \) pl-tr vs. un-tr: \( t(3) = 0.54, P < 0.3; \) un-nt vs. un-tr: \( t(3) = 4.1, P < 0.01. \)

Left hemisphere regions revealed no main effects of valence or type in pirT, pirF, or tu (all \( P > 0.07). \)

Together with the first set of odorants, this additional control suggested that the dissociation between irritation and valence in primary olfactory cortex was a reflection of these general properties—that is, irritation and valence—and not a unique aspect of the particular four odorants we first tested.

We next set out to ask whether this dissociation was maintained at the two main downstream components of primary olfactory cortex: the mediodorsal thalamus and orbitofrontal cortex.

**Fig. 4.** Activity in primary olfactory cortex. A: mean response by condition in subregions of piriform cortex. Left to right: right frontal piriform and right olfactory tubercle. Sniff onset occurred at time 0. B: binned response for each subregion. Error bars denote SE. Different regions exhibited different activity patterns. Frontal piriform cortex had a greater response to unpleasant than to pleasant odorants, regardless of type, whereas the olfactory tubercle had a greater response to pure olfactory than to bimodal odorants, regardless of valence. C: control study with 4 additional odorants. Binned response in pirF and tu is shown. Error bars denote SE. Activity mirrored the result found in A and B. Specifically, frontal piriform had a main effect of valence whereby unpleasant odorants elicited more activity than pleasant odorants regardless of trigeminality. Olfactory tubercle had a main effect of type whereby pure olfactants elicited more activity than bimodal odorants, regardless of valence.
FIG. 5. Activity in mediodorsal thalamus. A: mean response by condition in right mediodorsal thalamus. Sniff onset occurred at time 0. B: binned response in right mediodorsal thalamus. Error bars denote SE. In this region there was a main effect of type whereby smelling nontrigeminal odorants elicited more activity than smelling bimodal odorants, regardless of valence.

Representation of irritation in mediodorsal thalamus

Although the entire orbitofrontal region was within our anatomical acquisition, no portion of orbitofrontal cortex exhibited significant differences between conditions ($P > 0.05$). Orbitofrontal ROIs included left and right medial and lateral and anterior orbitofrontal cortex.

Because our acquisition was initially designed to cover only primary olfactory cortex, we had only limited coverage of the dorsomedial thalamus, fully covered in only seven subjects. In these subjects, there was a main effect of type [$F(1,6) = 6.23$, $P < 0.046$], no main effect of valence [$F(1,6) = 0.69$, $P < 0.4$], and no interaction [$F(1,6) = 0.2$, $P < 0.66$]. Follow-up tests revealed that Rdmt responded preferentially to pure olfactory odorants irrespective of their valence (Fig. 5) [pl-nt vs. pl-tr: $t(6) = 2.35$, $P < 0.036$; pl-nt vs. un-nt: $t(6) = 1.17$, $P < 0.26$; pl-nt vs. un-tr: $t(6) = 1.96$, $P < 0.07$; pl-tr vs. un-nt: $t(6) = 2.3$, $P < 0.04$; pl-tr vs. un-tr: $t(6) = 2.03$, $P < 0.06$].

No other portion of the thalamus exhibited any differences between conditions ($P > 0.1$). Coverage of the thalamus varied among subjects, depending on the location of slices. Thalamic nuclei included in analysis include right and left dorsomedial, right and left ventrolateral, and right and left ventrolateral.

**DISCUSSION**

We found clearly dissociable representations of irritation and valence in primary olfactory cortex. Whereas frontal piriform cortex responded preferentially to unpleasant over pleasant odorants, irrespective of trigeminality, the olfactory tubercle responded preferentially to nontrigeminal over trigeminal odorants, irrespective of valence. These findings demonstrate that, although negative valence and irritation are closely linked in perception, they have in fact dissociable neural representation. It is important to note in this respect that it remains possible for brain regions to also reflect an interaction between valence and irritation that would not be revealed in this study, but may be revealed after using additional odorants that clearly interact in perception.

Our findings offer a resolution to a previous apparent contradiction in the literature. On one hand we replicated previous fMRI findings of greater activity for unpleasant compared with pleasant odorants (Gottfried et al. 2002). However, we also replicated PET findings of reduced activity in response to a bimodal unpleasant odorant compared with a pleasant pure olfactory odorant (Savic et al. 2002). Critically, we found that these dissociable patterns of activity coexisted in neighboring subregions. These neighboring patterns would most likely be obscured and/or averaged together when using PET or fMRI parametric group maps.

All the above said, we should note two potential caveats regarding both the psychophysics and imaging data in our study. Regarding the psychophysics: first, although we determined which odorants were trigeminal and which were not, we did not determine the extent of trigeminality. For example, whereas citral and propionic acid were both trigeminal, it is reasonable to assume that propionic is in fact more trigeminal than citral. Second, apart from highly trained subjects, it can be difficult to distinguish odor intensity from odor trigeminality. Therefore if a subject thought that an odorant with high trigeminality were more “intense,” then the subject would tend to decrease the intensity rating, to account for the odorant’s irritative properties. These two psychophysical issues should be kept in mind when interpreting the data in Figs. 4 and 5.

Regarding the imaging data, first, as noted in METHODS, we have adopted an anatomical demarcation of the border between primary olfactory subregions that is not immune to error; and, second, is the unavoidable spatial error that arises from our coregistration of functional to structural data. Notwithstanding these concerns, our findings suggest parallel circuits of olfactory processing in primary olfactory cortex (Savic et al. 2000, 2001) and highlight the importance of considering functional heterogeneity in primary olfactory cortex when analyzing fMRI or PET studies.

In this, the current study joins a host of others (Caviness et al. 1996; Gaillard et al. 2002; Greicius et al. 2003; Kennedy et al. 1998; Nieto-Castanon et al. 2003; Slotnick 2005; Sterling et al. 2002; Zelano et al. 2005) in highlighting the value of an ROI approach when addressing targeted questions on the function of targeted regions. This is not to say that statistical parametrical mapping is an inappropriate tool in fMRI. In fact, it is a uniquely powerful tool to probe for involvement of novel brain mechanisms or activity across large homogeneous structures, two endeavors that were not part of the aims of this study, which focused on primary olfactory cortex.

Trigeminality was accompanied by reduced activity in the area of the olfactory tubercle. One may ask whether this reflected an upstream mechanism, an intrinsic mechanism, or a downstream centrifugal mechanism. A candidate upstream mechanism is the recently described trigeminal collaterals in the olfactory bulb (Schafer et al. 2002). Specifically, some trigeminal ganglion cells with sensory endings in the nasal epithelium also have branches reaching directly into both the olfactory bulb and the spinal trigeminal complex. This collat-
eral enervation of the epithelium and bulb may provide an avenue by which nasal irritants affect processing of concurrent olfactants.

A second possibility is that the activity pattern observed in the olfactory tubercle reflected a modulation of activity that took place within the tubercle itself. The tubercle receives direct olfactory input from the bulb (Carmichael et al. 1994; Haberly 2001) and may receive trigeminal input from somatosensory areas of the brain such as the thalamus (Heimer 1978; Zahn and Heimer 1987). This possibility is consistent with findings from numerous studies that implicate the olfactory tubercle as a multimodal region (Heimer et al. 1987; Ikemoto 2003; Mick et al. 1993; Zahn 1987; Zahn and Heimer 1985).

Finally, a third possible explanation for the observed patterns of activity is that they reflected a centrifugal input of a combined olfactory–trigeminal interaction that took place downstream of the tubercle (such as in the thalamus) that indeed projects to the tubercle (Zahn and Heimer 1987). We found a reduced response to bimodal odors in the dorsomedial thalamus. Similarly, single neuronal responses in dorsomedial thalamus were enhanced by blockade of the trigeminal nerve in rats (Inokuchi et al. 1993). Because the pattern of activity was identical in the olfactory tubercle and dorsomedial thalamus, we cannot determine which substrate represents the initial convergence of olfactory and trigeminal inputs. In other words, whereas we conclusively find trigeminal influence on activity in the earliest stage of cortical olfactory processing, we can only speculate that this is also the first site of olfactory–trigeminal interaction, although we cannot rule out any of the above three possibilities.

Our results were characterized by an overall limited extent of activity. Regarding the thalamus, both the observation of limited activity and the pattern of activity we reported should both be treated with caution because we had only limited coverage of this area. In contrast, we did have coverage of orbitofrontal cortex, yet no condition passed the criteria of the random-effects model in this region. We think that this reflects the absence of a behavioral task in this study. Active tasks always result in greater levels of fMRI activity (Hall et al. 2000; Lee et al. 1998; Nelson et al. 2004; Reddy et al. 2001; Zelano et al. 2005). Here, not only was there no task, but also odorant intensity and sniffing behavior were both carefully matched across trials and conditions. Thus the only difference across conditions was odorant identity. It is possible that limiting the difference to this alone accounts for the discrepancy between this study and previous work from our lab and others in which the hedonic value of odorants was reflected in the medial and lateral portions of orbitofrontal cortex (Anderson et al. 2003; Gottfried et al. 2002; Rolls et al. 2003). However, limiting the difference to this alone allowed us to conclude that there is a dissociation between irritation and valence across subregions of primary olfactory cortex. This dissociation was both statistically powerful within experiments and, critically, highly repeatable across experiments and odorants.

A C K N O W L E D G M E N T S

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R E F E R E N C E S


Inokuchi A, Kimmelman CP, Snow JB Jr. Convergence of olfactory and nasotrigeminal inputs and possible trigeminal contributions to olfactory

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