nature neuroscience

Attentional modulation in human primary olfactory cortex

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Central to the concept of attention is the fact that identical stimuli can be processed in different ways. In olfaction, attention may designate the identical flow of air through the nose as either respiration or olfactory exploration. Here we have used functional magnetic resonance imaging (fMRI) to probe this attentional mechanism in primary olfactory cortex (POC). We report a dissociation in POC that revealed attention-dependent and attention-independent subregions. Whereas a temporal subregion comprising temporal piriform cortex (PirT) responded equally across conditions, a frontal subregion comprising frontal piriform cortex (PirF) and the olfactory tubercle responded preferentially to attended sniffs as opposed to unattended sniffs. In addition, a task-specific anticipatory response occurred in the attention-dependent region only. This dissociation was consistent across two experimental designs: one focusing on sniffs of clean air, the other focusing on odor-laden sniffs. Our findings highlight the role of attention at the earliest cortical levels of olfactory processing.

Humans continually respirate through the nose but are not constantly attending to the content of their sniffs. We set out to identify the neural substrates of attentional modulation that dissociate respiration from olfactory exploration and to determine whether these substrates are evident at the earliest cortical processing stage of olfaction, namely POC. According to its cytoarchitectual definition, POC encompasses all cortical regions that receive direct input from the olfactory bulb[1]. Although this definition incorporates an expansive neural substrate[2], it is often used to refer only to piriform cortex, the chief component of POC that is situated at the junction of the ventral temporal and frontal lobes (**Fig. 1** and **Supplementary Figs. 1** and **2** online). Lord Adrian was the first to describe activity in piriform cortex that reflected sniffs of non-odorized air[3]. This phenomenon has been also recorded at the level of olfactory bulb[4] and replicated in the cortex of rodents[5] and humans[6].

In experiment 1 in this study, we probed for attentional modulation of this activity in piriform cortex by comparing sniff-induced activity after sniffs in search of an odorant that was not present to sniff-induced activity after similar sniffs created without the expectation of odor. The use of no-odorant stimuli in this study enabled us to focus on the effects of attention unencumbered by the effects of odorant habituation. In experiment 2, we examined attentional modulation in the presence of odorants. Subjects sniffed odorants for the duration of a tone under two conditions: in one, they were making judgments on the odorants; in the other, they were making judgments on the tone. Tones and odorants were equal across both conditions.

The results of both experiments converged to show that there was pronounced attentional modulation in a subregion of POC consisting of the olfactory tubercle and PirF. They also showed that auditory instructions to prepare for an olfactory task were alone sufficient to induce a significant response in this attention-dependent region. This anticipatory response was not present when the auditory instructions did not predict an ensuing odorant event. By contrast, activity in a second subregion of POC consisting of PirT was constant regardless of attention and did not reflect an anticipatory response to instructions. These findings point to the existence of attentional modulation at the earliest cortical phase of olfactory processing.

RESULTS

Experiment 1: attentional modulation of odorant-free sniffs

Subjects sniffed no-odorant air in three conditions that were equal in sensory content but hierarchically ordered in terms of attentional demand (**Fig. 2**). In a random-ordered event-related experimental design, subjects performed either 'task detection,' in which they took one sniff and tried to detect an odorant (which was absent on 50% of trials), or 'task inhalation,' in which they took one sniff but knew no odorant would be presented. Thus, the same no-odorant air was sniffed with and without an attentionally directed olfactory search. In 'task inhalation 2,' subjects sniffed the same no-odorant air as in the two other conditions, but in a scan that did not contain task detection and thus did not require constant shifting of the attentional focus; in other words, this task required less attention to sniff content. Subjects were instructed to maintain a constant sniff in terms of nasal airflow across conditions.

Levels of activity in piriform cortex reflected attentional demands (**Fig. 3**). No-odorant sniffs in task detection differed from sniffs in

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Published online 19 December 2004; doi:10.1038/nn1368

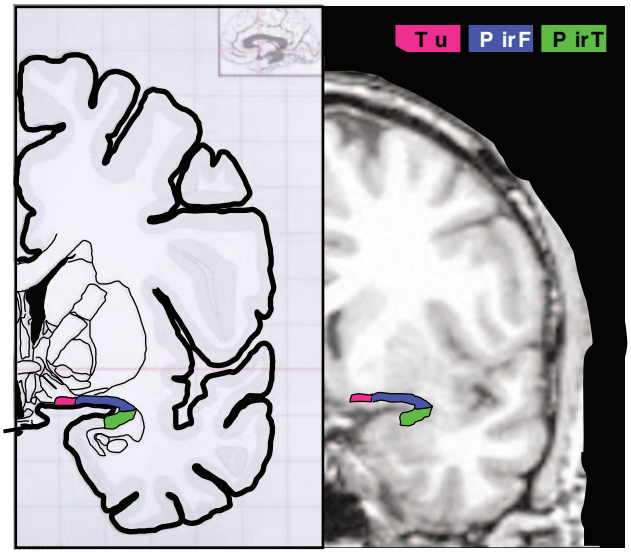

Figure 1 Structural outline of piriform cortex. Left, the relevant slice from the atlas used to define regions[10]. Right, a T1 image showing the ROI of one subject. The piriform ROI is indicated in different colors denoting its separation into PirF, PirT and the olfactory tubercle (Tu). The PirF, PirT and Tu ROIs of each subject were drawn over 19 slices traversing from 12.5-mm anterior to the anterior commissure to 2.7-mm posterior to the anterior commissure. In total, 76 ROIs were summed per subject, all of which were drawn before functional analysis (see **Supplementary Fig. 1** online).

task inhalation and inhalation 2 only in behavioral context and not in sensory content. These sniffs, however, induced different levels of activity in piriform cortex that mirrored their attentional demand ($F_{2,621} = 3.1053$, $P < 0.05$). The no-odorant sniffs in task detection induced more piriform activity than did the no-odorant sniffs in task inhalation (mean % change: no-odorant task detection = 1.34 ± 0.166 versus task inhalation = 0.737 ± 0.171, $T_{446} = 1.9932$, $P < 0.05$; bootstrap, 1,000 replications, $P < 0.057$), and significantly more activity than the no-odorant sniffs in task inhalation 2 (mean % change: task inhalation 2 = 0.452 ± 0.186 versus no-odorant task detection, $T_{411} = 2.073$, $P < 0.039$; bootstrap, 1,000 replications, $P < 0.002$).

In addition, before the response to the sniff, there was a small but significant anticipatory response in piriform cortex to the auditorily presented instructions ($F_{2,621} = 5.3556$, $P < 0.0049$). This effect was observed for task detection (mean % change: task detection = 0.255 ± 0.116, $T_{238} = 3.0804$, $P < 0.0023$; bootstrap, 1,000 replications, $P < 0.036$), but not for task inhalation (mean % change: task inhalation = 0.129 ± 0.14, $T_{208} = 0.1411$, not significant (NS); bootstrap, 1,000 replications, NS) or inhalation 2 (mean % change: task inhalation 2 = 0.146 ± 0.154, $T_{173} = 1.9604$, NS; bootstrap, 1,000 replications, NS).

Subdivisions of piriform cortex

Considering the proposed heterogeneity in piriform cortex[7–9], we used previously defined landmarks[8,10] to divide piriform cortex into the olfactory tubercle, PirF and PirT (**Fig. 1** and **Supplementary Figs. 1** and **2**). Distinct response profiles were observed across these subregions (**Fig. 4**). Attentional modulation was evident in PirF ($F_{2,592} = 3.4255$, $P < 0.0332$) and the olfactory tubercle ($F_{2,505} = 7.0356$, $P < 0.00097$), but not in PirT ($F_{2,550} = 0.7269$, NS). In the olfactory tubercle, task detection sniffs elicited significantly more activity than task inhalation 2 sniffs (mean % change: task detection = 1.42 ± 0.28 versus task inhalation 2 = 0.136 ± 0.269, $T_{334} = 3.303$, $P < 0.0011$; bootstrap, 1,000 replications, $P < 0.001$), and than task inhalation sniffs (mean % change: task inhalation = 0.822 ± 0.318, $T_{358} = 2.0602$, $P < 0.0401$; bootstrap, 1,000 replications, $P < 0.07$). In PirF, task detection sniffs resulted in significantly more activity than task inhalation 2 sniffs (mean % change: task detection = 1.25 ± 0.162 versus task inhalation 2 = 0.533 ± 0.178, $T_{393} = 2.1846$, $P = 0.0295$; bootstrap, 1,000 replications, $P < 0.001$) or than task inhalation sniffs

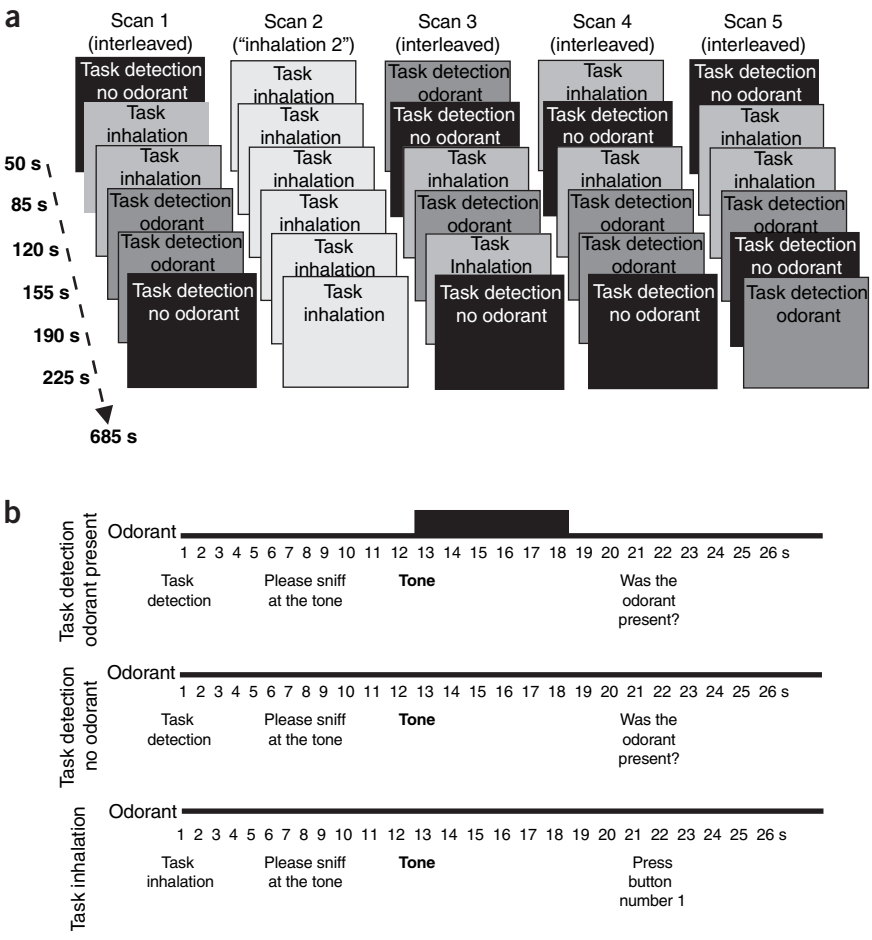

Figure 2 Experimental design. (**a**) Complete experimental session. Each box represents a single trial. Subjects participated in five scans: four with trial conditions interleaved, and one with only the inhalation 2 condition. (**b**) Events in each of the four types of trial. The instructions that subjects received via earphones are indicated. Odorants were presented for a 5-s pulse starting at the tone only during odorant trials of task detection.

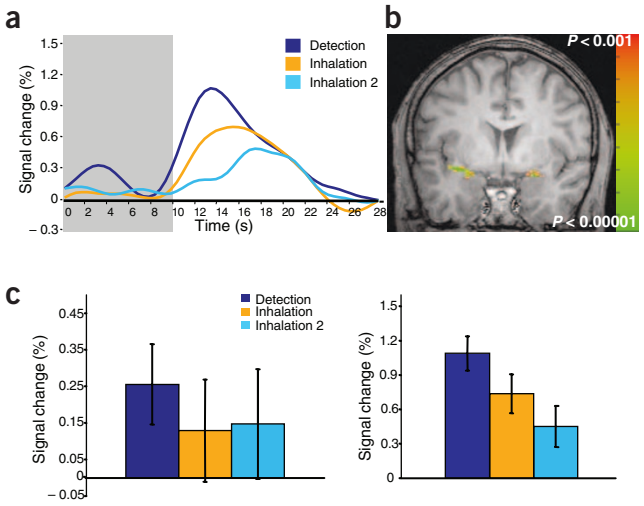

Figure 3 Activity in piriform cortex. (**a**) Mean raw response by condition obtained in the piriform ROI. The gray area represents the period of auditory instructions (**Fig. 1**). Although no odorant, inhalation and inhalation 2 had identical stimuli, activity across these conditions differed as a reflection of attentional demands. In addition to the sniff response, a small but significant response was seen after task instructions for task detection but not task inhalation or inhalation 2. (**b**) Random-effects group image of all ten subjects. This analysis complemented the ROI analysis as it showed piriform activity, extending here into the left insular area. (**c**) Binned response during the period of task instructions (left) and after the sniff (right). Error bars represent the s.d. Notably, we also observed condition- and region-specific differences in the latency of the fMRI signal response (see **Supplementary Fig. 4** online).

(mean % change: task inhalation = 0.884 ± 0.198, T_{417} = 2.2009, $P < 0.0283$; bootstrap, 1,000 replications, $P < 0.075$). In other words, whereas activity in PirF and the olfactory tubercle was modulated by attention, activity in PirT was not.

Concordantly, the three subregions showed different patterns of activity in response to task instructions. In PirF, different task instructions produced significantly different levels of activity ($F_{2,592} = 7.582$, $P < 0.000562$), which were greatest in task detection ($T_{220} = 3.624$, $P < 0.0004$; bootstrap 1,000 replications, $P < 0.016$), small but statistically significant in task inhalation 2 ($T_{173} = 2.8679$, $P < 0.005$; bootstrap 1,000 replicates, NS), and insignificant in task inhalation ($T_{197} = 1.6474$, NS; bootstrap 1,000 replications, NS).

In the olfactory tubercle, we observed a similar pattern of response, in that all three task instructions produced significantly different levels of activity ($F_{2,505} = 6.7528$, $P < 0.0013$), with task detection producing the largest response ($T_{189} = 3.555$, $P < 0.0005$; bootstrap, 1,000 replications, $P < 0.02$), task inhalation producing a small but significant response (mean % change: task detection = 0.413 ± 0.176 versus task inhalation = 0.108 ± 0.269, $T_{169} = 2.409$, $P < 0.0171$; bootstrap 1,000 replications, NS), and a significant response in task inhalation 2 (mean % change: task inhalation 2 = 0.095 ± 0.24, $T_{145} = 1.9983$, $P < 0.0476$; bootstrap 1,000 replications, NS).

In PirT, by contrast, bootstrap analysis showed no significant response to the instructions in any condition ($P > 0.1$ in all, bootstrap, 1,000 replications). In this one comparison, the parametric result differed from the nonparametric result in that it suggested a small but significant overall response to instructions ($T_{214} = 3.384$, $P < 0.0008$). Notably, however, this response did not differ across conditions ($F_{2,550} = 1.4432$, NS).

It was possible that the pattern of activity observed across subregions was due to differences in size between regions. To address this issue, we examined the relative number of voxels in each subregion. PirF consisted of 723 voxels, PirT consisted of 260 voxels and the olfactory tubercle consisted of 266 voxels. Thus, the sizes of PirT and olfactory tubercle were almost identical, but their activity patterns were different, indicating that differences in size between regions were not solely responsible for the observed activity patterns.

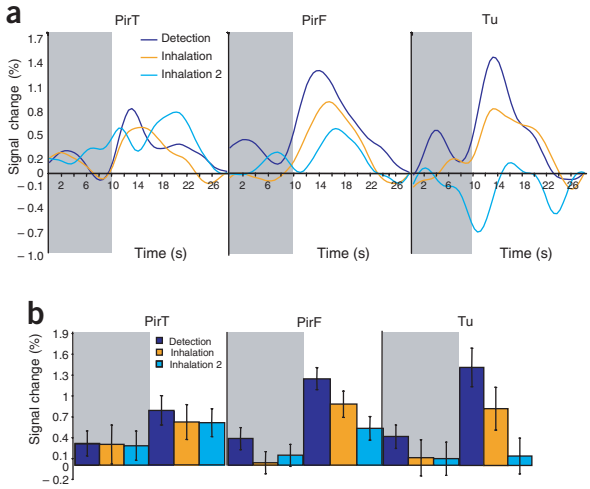

Figure 4 Activity in piriform subdivisions. (**a**) Mean raw response by condition obtained in the PirT, PirF and olfactory tubercle (Tu) ROIs (**Fig. 1**). The gray area represents the period of auditory instructions (**Fig. 2**). Attentional modulation was greatest in Tu, reduced in PirF and not apparent in PirT. (**b**) Binned response during the period of task instructions (left) and after the sniff (right). Error bars represent the s.d.

Effects of airflow

It was also possible that, despite instructions to maintain a constant sniff, subjects sniffed more in the no-odorant trials of task detection than in the similar no-odorant trials of tasks inhalation and inhalation 2. Under such conditions, an increase in activity in the no-odorant trials of task detection might reflect an increase in airflow rather than an increase in attentional demand.

To address this issue, we analyzed the sniff airflow patterns that were continuously measured throughout the scans (**Fig. 5a**). In the no-odorant conditions, sniffs were uniform, showing differences that did not reflect the sniff-induced activity patterns in piriform cortex. Sniffs in task inhalation 2 that induced the lowest level of piriform activity had greater volumes than sniffs in task inhalation that induced greater piriform activity (inhalation 2 versus inhalation sniff volume, $T_9 = 3.5$, $P < 0.006$). A similar trend was evident in maximum airflow rate ($T_9 = 1.8$, $P < 0.1$). Concurrently, a regression analysis on levels of activity in piriform cortex and airflow patterns in all conditions revealed no significant relationship (**Supplementary Fig. 2** online). These analyses showed that the activity patterns were not due to differences in airflow between the trials.

Additional odorant-responsive regions

To determine whether the pattern of attention-dependent activity observed in piriform cortex was prevalent throughout the brain, we created a random-effects parametric map of odorant-induced activity in all subjects. The group image revealed significant odorant-

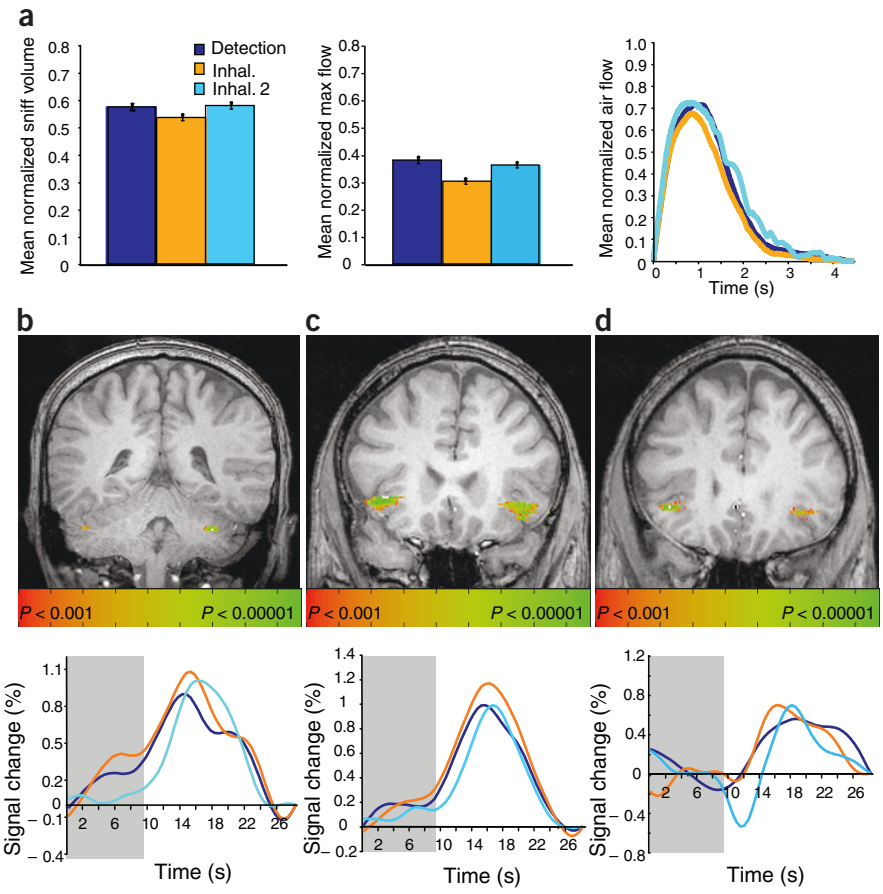

Figure 5 Control analyses. (**a**) Left, normalized sniff volume by condition for all sniffs. Sniff volume did not reflect piriform cortex activity patterns. Specifically, inhalation 2 induced significantly less activity but had equal or greater volume than inhalation or no odorant. Right, normalized sniff maximum airflow rate by condition for all sniffs. Similarly to sniff volume, sniff airflow rate did not reflect piriform cortex activity patterns. (**b–d**) Statistical parametric group maps. (**b**) The posterior portion of the quadrangular lobule of the cerebellum. Activity was greater on the right. A robust response is seen to sniffs in all conditions and to all instructions except those for inhalation 2. (**c**) The short insular gyri, bilaterally. Activity was equal across conditions. (**d**) The border of the posterior and lateral orbitofrontal gyri in the area of the basal operculum. An early negative deflection was evident for inhalation 2. These activity patterns contrast with those in piriform cortex (**Fig. 4a**).

induced activations in piriform cortex, amygdala, entorhinal cortex, superior temporal gyrus, insular gyri, insula, orbitofrontal gyri and cerebellum, consistent with previous fMRI and positron emission tomography studies[11].

In brief, activity in the insula was independent of attention as equal activity was induced by all conditions. Activity at the border of the posterior and lateral orbitofrontal gyri was equal in amplitude across all no-odorant conditions, but it showed a sharp early negative deflection for inhalation 2, possibly reflecting an inhibitory process. Activity in the quadrangular lobe of the cerebellum was also equal for all sniffs, and for task instructions for all conditions except for inhalation 2 instructions, which showed no response. Whereas task instructions in the interleaved scans required attention to be directed in a trial-specific manner, instructions in the inhalation 2 scans did not. The fact that cerebellar activity reflected this difference in the instructions is in keeping with the proposed role of the cerebellum in attentional modulation and task preparation[12].

This analysis of regions outside piriform cortex was not an attempt to provide a full-brain account of attentional modulation in olfaction, but rather was a control that enabled us to conclude that the pattern of activity measured in piriform cortex was not the only, or even the dominant, pattern of activity across the acquired neural substrate (**Fig. 5b–d**).

Experiment 2: attentional modulation of odorant sniffs

Probes of attentional modulation usually involve tasks that require subjects to make decisions about one stimulus while ignoring others. Input stimuli and task demands are typically maintained at a constant level across conditions. In experiment 1, input stimuli were indeed constant across conditions ('no odorant'), but task demands were not. Task identification was more difficult than task inhalation. To address the possibility that this difference in motivation and effort across conditions might have been responsible for the patterns of activity that we observed, we conducted experiment 2.

In an event-related study, subjects performed either 'task audition' or 'task olfaction'. In task audition, subjects sniffed odorized air for the duration of a tone and were then cued to rate the pitch of the tone; in task olfaction, subjects sniffed odorized air for the duration of a tone and were then cued to rate the intensity of the odorant (**Fig. 6a**). Tones and odorants were equal across tasks and, importantly, both the concentration of the medium intensity odorant and the degree of change in pitch were individually adjusted for each subject such that the performance accuracy was about 75%; thus, the difficulty, or effort, of the two tasks was equated. Finally, subjects were instructed to take an equally vigorous sniff in both task audition and task olfaction.

In agreement with experiment 1, this control study revealed attention-dependent patterns of activity in PirF and the olfactory tubercle, and attention-independent patterns in PirT. The response to the identical odorants was greater during task olfaction than during task audition in both PirF and the olfactory tubercle (PirF: $F_{1,558} = 6.9505$, $P < 0.0087$; mean % change task olfaction = 6.62 ± 0.4769, mean % change task audition = 4.272 ± 0.3192, $T_{557} = 2.548$, $P < 0.011$; the olfactory tubercle: $F_{1,557} = 6.3827$, $P < 0.0118$; mean % change task olfaction = 5.2865 ± 0.3972, mean % change task audition = 3.2178 ± 0.2402, $T_{556} = 2.3294$, $P < 0.0202$), but was equal across tasks in PirT ($F_{1,501} = 0.0467$, NS; mean % change task olfaction = 5.7329 ± 0.6922, mean % change task audition = 5.5795 ± 0.5814, $T_{500} = 0.1872$, NS; **Fig. 6b**). In addition, a double dissociation was evident whereby tone-induced activity in auditory cortex was greater during task audition than during task olfaction (**Fig. 6c**).

Also in agreement with experiment 1, there was a significant anticipatory response to task instructions in the olfactory tubercle and PirF, but not in PirT (**Fig. 6b**). In the olfactory tubercle, a significant response was seen to instructions for both conditions, but the response to task olfaction instructions was significantly greater than that for task audition ($F_{1,557} = 5.9762$, $P < 0.0148$; mean % change task olfaction = 2.333 ± 0.1519, mean % change task audi-

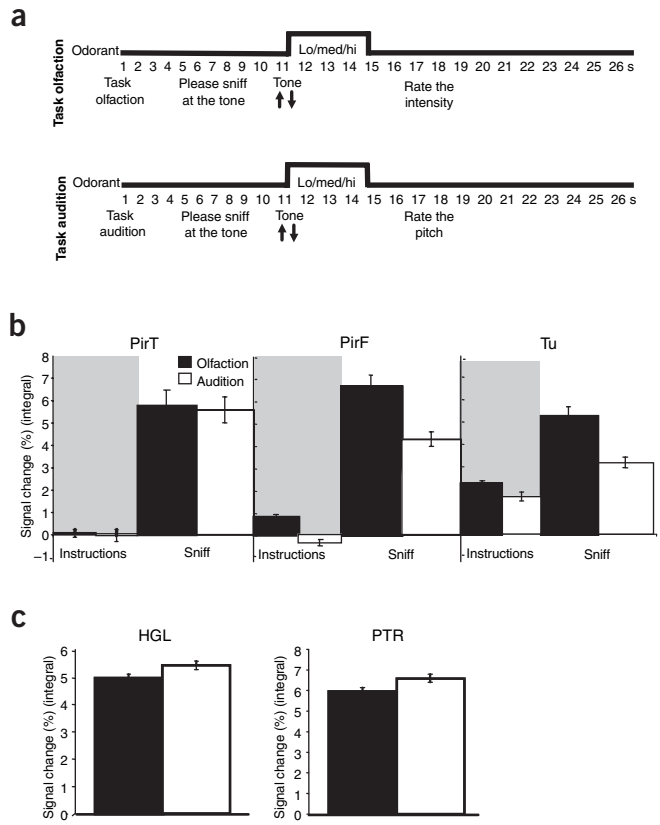

Figure 6 Study controlling for effort. (**a**) Experimental design. Events in each of the two types of trial. The instructions that subjects received via earphones are indicated. Odorants were presented for the duration of the tone in all trials. Odorant concentration and tone pitch were randomized across trials. (**b**) Activity in piriform subdivisions. Bar graphs represent the integral under the response curve for each region (note that a comparison of the peaks yielded nearly the same picture). Error bars represent the s.e.m. Gary areas represent responses to task instructions. Attentional modulation was evident in the olfactory tubercle (Tu) and in PirF, but not in PirT. (**c**) Activity in auditory cortex: Heschl's gyrus (HGL) and planum temporale (PTR). Bar graphs represent the integral under the response curve for each region. Attentional modulation was evident in both HGL and PTR, and was greater in the auditory than in the olfactory condition (HGL, $F_{2,551} = 4.7859$, $P < 0.0291$; PTR, $F_{2,550} = 4.1802$, $P < 0.0414$).

tion = 1.747 ± 0.0999, $T_{556} = 2.3093$, $P < 0.0213$). PirF also showed a greater response to task olfaction instructions than to task audition instructions. ($F_{1,558} = 139.6135$, $P < 0.0001$; mean % change task olfaction = 0.7869 ± 0.0527, mean % change task audition = −0.4003 ± 0.0513, $T_{557} = 11.767$, $P < 0.0001$). By contrast, in PirT there was no significant response to task instructions for either of the conditions (olfaction, $T_{240} = 0.1137$, NS; audition, $T_{236} = 0.7668$, NS; mean % change task olfaction = 0.011 ± 0.0969, mean % change task audition = −0.0462 ± 0.1558). The above differences in activity patterns were not related to any differences in sniff airflow, which was nearly identical across tasks ($F_{1,6} = 0.07$, $P = 0.8$; see **Supplementary Fig. 3** online).

In addition, to address the concern that even though performance was objectively equated across the tasks audition might have been subjectively easier (thereby accounting for the reduced activity), we reran the psychophysical aspect of the experiment in seven subjects, who were then asked to rate the subjective difficulty of the task on a visual analog scale. Although the fMRI signal in piriform cortex was significantly lower during task audition, there was a trend towards the association of greater subjective effort with this task than with task olfaction (mean subjective difficulty ratings: task olfaction = 34 ± 8, task audition = 62 ± 10, $T_6 = 2$, $P = 0.09$). Thus, we conclude that the observed patterns of activity reflect attentional modulation in piriform cortex and not motivation or effort.

DISCUSSION

Attention to olfaction can modulate behavioral response latency[13,14] as well as the latency of early odorant-induced electrophysiological components[15,16]. Concordantly, several findings have pointed to the existence of olfactory attentional modulation in human secondary olfactory regions and the amygdala[17,18]. Here, in agreement with the emerging view of selective attention in human primary sensory processing of vision[19–21], audition[22,23] and somatosensation[24], and with findings in POC of rats[25], we have found strong attentional modulation at the earliest cortical phase of sensory processing. Our findings, however, diverge from observations in audition and vision in that they point to heterogeneity of the attentional modulation in primary cortex.

Heterogeneity in POC is consistent with findings in rats[9,26] and in humans[8]. For example, activity in human PirF strongly reflects odorant valence, but activity in PirT does not[8]. Similarly, the anticipatory response that we measured after instructions was primarily evident in PirF and Tu. This anticipatory response was similar to that seen in rats[27] and may reflect the functional significance of the robust centrifugal connectivity from cortex to bulb[28], which possibly prepares the bulb for particular representations[27]. Taken together, these findings suggest that there is higher order processing in human PirF and Tu than in PirT.

Considering the dissociation in fMRI signal that we observed between the temporal and frontal portions of POC, it is tempting to localize the mechanisms of olfactory attention to the interaction between these regions—an interaction that may substitute for the precortical thalamic and geniculate connections that might modulate attention in vision[29] and audition[30], but are absent in olfaction. Such deductions regarding our results are limited, however, by our understanding of the relationship between neural activity and the fMRI signal. The current view is that the fMRI signal primarily reflects the input and local processing of the 'activated' region, rather than its output[31]. This gives rise to two possibilities.

First, under the assumption that the fMRI signal primarily reflects input, the condition-independent activity in PirT suggests that the bulbar input to this region is equal across attentional conditions. By contrast, the condition-dependent activity in PirF and the olfactory tubercle suggests that attentional modulation occurs in the structures that target these regions. One possibility is that these targeting regions are in fact PirT. In this case, it could be claimed that PirT is the site of the attentional mechanism in olfaction. By contrast, the signal in PirF and the olfactory tubercle may reflect direct input from the olfactory bulb, thus placing the attentional mechanisms there[32]. Second, under the assumption that the fMRI signal primarily reflects local processing, the condition-independent activity in PirT suggests that this region processes all input equally, regardless of attentional state. By contrast, the condition-dependent activity in PirF and the olfactory tubercle places the mechanisms of olfactory attention in this frontal portion of POC.

Our findings also shed light on an apparent discrepancy in the literature concerning the imaging of olfaction. Sniffs of odorless air temporally drive activity patterns in the olfactory bulb[4], which in turn drive activity patterns in piriform cortex[5,33]. This process was

originally described by Lord Adrian[3], who, when electrically recording from piriform cortex, noted that "in spite of their olfactory origin the waves seem to depend more on the mechanical effect of the air current than on its smell". Thus, it is no surprise that fMRI reveals similar sniff-induced activity in humans[6,34]. Another study using positron emission tomography (PET) did not, however, record sniff-induced activity in piriform cortex[35]. In that study, subjects were specifically told before the no-odorant condition that no odors would be presented. Such a condition is analogous to inhalation 2 in our study, in which very little activity was indeed measured. In other words, the effects of attention and expectation can explain the apparent discrepancy in imaging results. If the subjects are told in advance about the absence of odor, then the response to inhalation, not olfactory sniffing, will be measured.

Mammalian sensory processing does not consist of a one-sided transform from sensory content to neural representation. Anticipation and attentional focus modulate activity patterns in primary sensory regions from vision[19,20], to audition[22], to somatosensation[24] and olfaction[25]. In our study, the neural image represented both the expectation alone (response to instructions) and the stimulus (sniff content) as a function of this expectation (the difference between the same sniff content in task detection versus task inhalation). These aspects of the neural representation combine to show that sensation is not a passive process. POC actively mediates the process of olfaction not only by coding odorant quality[36], but also by coding the anticipation of relevant stimuli, thereby determining when the attentional focus shifts from merely breathing in air to smelling the world around us.

METHODS

Subjects. Twelve subjects (six women and six men, mean age 29.8 ± 4.8 years) participated in the main experiment and eight participated in the control experiment. All subjects gave informed consent to procedures approved by the University California Berkeley Committee for the Protection of Human Subjects.

Odorants and olfactometry. Odorants were delivered by a computer-controlled air-dilution olfactometer, which also provided an ongoing real-time measurement and recording of airflow in the nostrils[37]. This olfactometer switches between odorant presence and absence in less than 2 ms, with no non-olfactory cues about the switch. We used the odorants citral, phenyl ethyl alcohol (PEA), eugenol, propionic acid and limonene at suprathreshold concentrations. In the control study, we used amyl acetate at a concentration of 9 ppm (low), between 12 and 18 ppm (medium), and 27 ppm (high).

Experimental design. Each of the four types of trial was presented 22 times across five 685-s long scans with an intertrial interval of 35 s. Three of the trial types (task detection, odorant; task detection, no odorant; and inhalation) were randomly mixed in four of the scans, and the fourth trial type (inhalation 2) was the only trial type in the fifth scan. Inhalation 2 trials were identical in all respects to inhalation trials, but they occurred repeatedly throughout a scan and were not interleaved with other trial types. The temporal order of the five different functional scans was counterbalanced across subjects.

Through earphones, subjects received task instructions generated by a digitally recorded voice. Each trial began with an auditory primer for task detection or task inhalation. In task detection, subjects took one sniff at the tone and determined whether or not an odorant was present. Odorants were present in half of these trials, generating odorant and no-odorant task detection trials. In task inhalation, subjects took one sniff but they knew in advance that an odorant would not be present during task inhalation. Thus, the only difference between sniffs in task inhalation and the no-odorant sniffs in task detection was that in the latter condition subjects were exploring for the presence of odor.

Control study. Each experiment began with a passive (no task) block-design olfaction scan that was later used to restrict the POC region of interest (ROI) functionally. This scan was followed by five scans comprising an event-related design, in which subjects performed task olfaction and task audition (randomized order, interstimulus interval = 35 s). The sensory content of these two tasks was identical. In both tasks subjects sniffed an odorant (one of three concentrations, randomized across trials and equal across tasks) for the duration of a tone (one of three pitches, randomized across trials and equal across tasks). The only differences between task olfaction and task audition were the auditory primer that preceded the task (either 'task olfaction' or 'task audition') and the question after the task (either 'rate the intensity' or 'rate the pitch').

Imaging parameters. All of the raw magnetic resonance data are available on the authors' website. We used a 4T Inova magnet (Varian) with a custom-built full-head receive coil. A T2* sensitive echo planar sequence was used with the parameters of repetition time (TR) = 500 ms, echo time (TE) = 28 ms and flip angle = 20°. The functional in-plane resolution was 3 mm and the through-plane resolution was 3.5 mm. Two interleaves were collected for each frame, with a total acquisition time of 1,000 ms per frame. The interleaves were interpolated during reconstruction, resulting in an effective resolution of 500 ms per frame. Eight 3.5-mm thick slices were acquired at an oblique plane traversing from frontal pole to temporal pole (typically 30° clockwise to the anterior commissure–posterior commissure plane). To prevent head motion, a custom-formed bite bar was fitted to the individual dental impression of each subject. This bite bar was fitted with a pyrolitic graphite implant that significantly reduces ventral temporal susceptibility artifacts[38]. 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.

Imaging analysis. Data were analyzed using MrVista[39,40]. Two subjects were excluded from analysis owing to head motion. We combined a structural and functional restriction to define the ROI. We first outlined the expected piriform on the basis of an atlas10 and then functionally restricted this region to only voxels that responded hemodynamically to the odorant condition ($P < 0.01$). Because we used the odorant condition to define our ROI, this condition was treated as a reference condition on which we did not make statistical inferences (in the control study, we restricted ROIs to areas that were responsive to odors presented in a separate reference scan). We then analyzed the data in this fROI twice. In one analysis, we used parametric methods used by others to analyze fMRI data[41,42]; in the other, we used nonparametric bootstrapping—a modern resampling technique that makes no distributional or parametric assumptions[43] and has been applied to fMRI data[44]. The results from the bootstrap analysis are presented throughout this manuscript with the parametric analysis; in general, the two analyses were in good agreement. We also did the parametric analysis twice: once using the peak response values, and once using the integral values. There was no significant difference between the results. Additional details of the methods used in this study are given in the **Supplementary Methods** online.

URLs. MrVista, http://white.stanford.edu/software/. For raw magnetic resonance data, see socrates.berkeley.edu/~borp/supp.htm.

Note: Supplementary information is available on the Nature Neuroscience website.

ACKNOWLEDGMENTS

We thank Arak Elite. This work was supported by a grant from the National Institute of Deafness and Communication Disorders (R01 DC005958). C.Z. is supported by a predoctoral fellowship from the National Science Foundation.

COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

Received 1 September; accepted 21 October 2004
Published online at http://www.nature.com/natureneuroscience/

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