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Right Orbitofrontal Cortex Mediates Conscious Olfactory Perception

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Abstract

Understanding how the human brain translates sensory impressions into conscious percepts is a key challenge of neuroscience research. Work in this area has overwhelmingly centered on the conscious experience of vision at the exclusion of the other senses—in particular, smell. We hypothesized that the orbitofrontal cortex (OFC) is a central substrate for olfactory conscious experience because of its privileged physiological role in odor processing. Combining functional magnetic resonance imaging, peripheral autonomic recordings, and olfactory psychophysics, we studied a case of complete anosmia (smell loss) in a patient with circumscribed traumatic brain injury to the right OFC. Despite a complete absence of conscious olfaction, the patient exhibited robust “blind smell,” as indexed by reliable odor-evoked neural activity in the left OFC and normal autonomic responses to odor hedonics during presentation of stimuli to the left nostril. These data highlight the right OFC's critical role in subserving human olfactory consciousness.

Keywords

olfactory perception, consciousness, orbitofrontal cortex, lesion

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Environmental information continuously impinges on people's sensory organs in both sleep and wakefulness, but only a small fraction of this content ever reaches the level of conscious perception. Understanding how sensory stimulation culminates in conscious perceptual experience (as opposed to unconscious perceptual experience) has been a key challenge of neuroscience research (Crick & Koch, 2003). Much of this work, traditionally utilizing visual stimuli, has implicated sensory associative cortices and higher-order prefrontal association areas as brain structures critical for visual consciousness (Crick & Koch, 2003; Dehaene, Changeux, Naccache, Sackur, & Sergent, 2006; Zeki & Ffytche, 1998). By comparison, the neural underpinnings of olfactory consciousness are poorly understood.

One plausible candidate for the brain area in which odor inputs may give rise to conscious percepts is the orbitofrontal cortex (OFC). This brain region is the principal neocortical element of the olfactory system, and it has a pivotal associative role in olfactory information processing (Gottfried & Zald, 2005; Schoenbaum & Eichenbaum, 1995) and higher-order multimodal integration (Price, 2007). Posttraumatic anosmia is often accompanied by orbitofrontal pathology

(Eftekhari et al., 2006; Varney, Pinkston, & Wu, 2001); in a similar manner, orbitofrontal lesions are often paralleled by olfactory perceptual dysfunction (Jones-Gotman & Zatorre, 1988, 1993; Potter & Butters, 1980; Zatorre & Jones-Gotman, 1990, 1991). These observations suggest a possible functional link between the OFC and conscious olfactory experience. However, it is well recognized that lesion-based studies can both underestimate the extent of brain injury to other regions and overestimate the extent of brain injury to the region of interest. This is particularly true in the absence of functional brain measures, and it leaves open the possibility that a given brain area is neither necessary nor sufficient for the function in question.

The current study was designed to test the hypothesis that the human OFC is a key locus of olfactory conscious experience. Because prior lesion studies have emphasized a right-hemisphere dominance for olfactory perception (Abraham & Mathai, 1983;

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Jones-Gotman & Zatorre, 1988, 1993; Rausch, Serafetinides, & Crandall, 1977; Zatorre & Jones-Gotman, 1990, 1991), this study focused on a patient who developed complete anosmia following traumatic brain injury to the right OFC. The concurrent implementation of sensory psychophysics, autonomic recordings, and functional magnetic resonance imaging (fMRI) enabled us (a) to explore whether behavioral, physiological, and neural measures of olfactory processing were preserved despite the patient's dense smell loss in a manner that demonstrated unconscious olfactory processing ("blind smell") and (b) to exclude the possibility that the patient's olfactory deficits were due to a functional disruption in peripheral upstream structures or in central brain regions beyond the primary lesion site in the right OFC.

Method

Participants

Patient S. is a college-educated, right-handed, 36-year-old man with complete anosmia. Three healthy, college-educated, right-handed men (mean age = 27 years) were recruited as control subjects. None of the control subjects reported a history of neurological; psychiatric; or ear, nose, and throat problems.

Clinical case description of Patient S. Apart from his anosmia, Patient S. is healthy; prior to his brain injury, he had no history of smell or taste problems. At age 33, he sought treatment at Northwestern Memorial Hospital for an acute hemorrhagic contusion in the right inferior frontal lobe after falling down a flight of stairs. He was treated conservatively in the hospital, made a rapid recovery, and soon resumed his former routine without problem. However, over the next 2 months, S. completely lost his sense of smell. Magnetic resonance imaging (MRI) brain scans confirmed selective damage to the right OFC, with relative sparing of olfactory bulbs, medial temporal structures, and the left frontal lobe (Fig. 1). An MRI of the head and face revealed no fracture of the cribriform plate or other structural lesion within the nasal or sinus cavities. Nasal endoscopic examination conducted 1 year postincident indicated that the intranasal structures appeared healthy and the airways were patent. The subsequent evaluations reported in this article were conducted approximately 20 months after the initial injury.

Neuropsychological and psychophysical evaluations of Patient S. We administered a series of standard neuropsychological tests to Patient S. to assess his general cognitive abilities. The results were normal across all cognitive domains. (See Neuropsychological Assessment and Table S1 in Supplemental Results of the Supplemental Material available online.) S. showed some borderline normal performance in attention and executive function; such performance is in keeping with his sustained injury to the prefrontal cortex.

We assessed the extent of anosmia in S. using standard olfactory psychophysical tests administered separately to each nostril. A three-alternative, forced-choice odor detection test ("Sniffin' Sticks" test; Hummel, Sekinger, Wolf, Pauli, & Kobal, 1997) showed that Patient S. could not detect the target odor at the strongest concentration through either nostril. This indicated a severe odor-detection deficit. A four-alternative, forced-choice odor identification test (University of Pennsylvania Smell Identification Test; Doty, Shaman, Kimmelman, & Dann, 1984) indicated chance identification performance (left nostril: 10 correct out of 40; right nostril: 11 correct out of 40). Again, this result suggests markedly impaired olfactory function. Thus, despite unilateral orbitofrontal injury, S. was anosmic in both nostrils.

Stimuli

We selected two strongly unpleasant odors, trimethylamine (1%; rotten, fishy) and valeric acid (1%; sweaty, rancid), and two neutral odors, (+)-rose oxide (9%; vinous) and pinene (17%; woody). (For more information, see the Odor Valence Rating section in Supplemental Results of the Supplemental Material.) The odorants were well above the threshold of perception for healthy individuals and judged to be moderately intense. Each odor was delivered separately to each nostril on independent trials. Odors and air were delivered during scanning using an MRI-compatible, computer-controlled olfactometer, which is capable of delivering pulses of odorized air with a rapid on-off time (< 1 s) and without thermal, tactile, or auditory confounds (Gottfried, Winston, & Dolan, 2006; Li, Luxenberg, Parrish, & Gottfried, 2006).

Experimental paradigm

During the imaging study, subjects participated in an odor-detection task spread over four runs (Patient S.) or two runs (control subjects). Each run contained 12 trials for each of five conditions: unpleasant odor delivered to the left nostril, neutral odor delivered to the left nostril, unpleasant odor delivered to the right nostril, neutral odor delivered to the right nostril, and odorless air delivered to both nostrils. In the four odor conditions, an odor was presented to one nostril while odorless air was simultaneously delivered to the contralateral nostril; this procedure was intended to eliminate tactile and airflow confounds. The order of stimulus delivery was pseudorandomized such that no condition was presented more than twice in a row. Trials were separated by an interval of 12 s.

At the onset of each trial, a visual cue ("Sniff now") prompted subjects to sniff, at which time an odor or air was presented for 3 s. Subjects were then asked to report whether an odor was present or absent by pressing one of two buttons. Given that the five conditions were presented with an equal probability (20% each), and given that monorhinal odor stimulation is sufficient to generate conscious olfaction in normal individuals, the chance-level response of odor detection was 4 out of 5, or 80%.

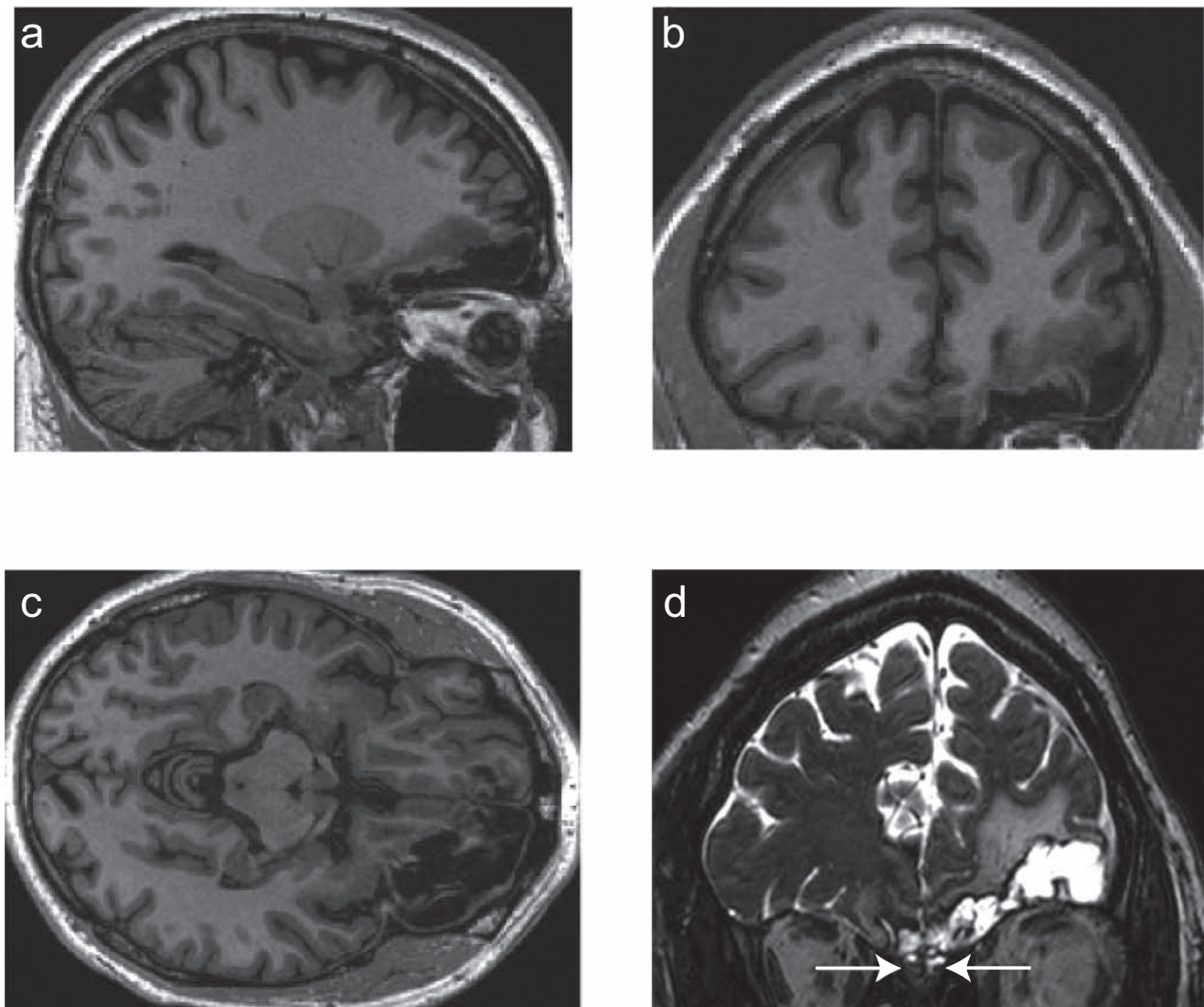


Fig. 1. Magnetic resonance imaging brain scans of Patient S. Sagittal (a), coronal (b), and axial (c) T1-weighted scans show the extent of lesions in the right orbitofrontal cortex (OFC). Bilateral olfactory bulbs (indicated by arrows) are clearly identifiable in a coronal T2-weighted scan (d). Approximate Montreal Neurological Institute coordinates for the scans are as follows: (a) $x = 28$, (b) $y = 32$, (c) $z = -16$, and (d) $y = 48$.

Respiratory and skin conductance response (SCR): monitoring and data processing

During scanning, participants were affixed with a pair of breathing belts connected to a differential-pressure transducer, the output of which was digitized and recorded using PowerLab data-acquisition systems (ADInstruments, Colorado Springs, CO). Sniff inspiratory volume, peak amplitude, and duration were computed for each condition and entered into repeated measures analyses of variance.

SCRs were continuously acquired from two Ag-AgCl electrodes placed on the first and second toes of the subject's left foot. The electrodes were connected to an SCR preamplifier module. Evoked SCRs were identified by the maximum of the SCR deflection in the interval between 1 s and 5.5 s after stimulus above a zero-slope baseline (identified within 2 s before

stimulus). In accordance with prior methods (Flykt, Esteves, & Öhman, 2007), we included only trials with a minimal evoked deflection of $0.02 \mu\text{S}$ in the SCR analysis. All SCR peak magnitudes were square-root transformed and then submitted to one-tailed Wilcoxon sign-rank tests.

Image acquisition

Gradient-echo T2-weighted echoplanar images (EPIs) were acquired during the experiment using a 3-T MRI scanner. Imaging parameters were as follows: repetition time = 1.51 s, echo time = 20 ms, slice thickness = 2 mm, gap = 1 mm, in-plane resolution = $1.72 \text{ mm} \times 1.72 \text{ mm}$, field of view = $220 \text{ mm} \times 206 \text{ mm}$, and matrix size = 128 mm. A total of 500 volumes (24 interleaved slices per volume, covering the piriform and orbitofrontal cortices) was obtained over each

run. A high-resolution (1 mm × 1 mm × 1 mm), T1-weighted anatomical scan and a whole-brain EPI were also obtained. For Patient S. only, a T2-weighted anatomical scan (0.31 mm × 0.31 mm × 0.60 mm) was obtained to further assist the examination of olfactory bulbs and olfactory tracts.

fMRI data processing

The imaging data were analyzed using the general linear model in Statistical Parametric Mapping Version 2 (SPM2; Functional Imaging Laboratory, 2003) software. Among healthy control subjects, we performed spatial normalization of EPIs to a standard EPI Montreal Neurological Institute (MNI) template available in SPM2, and this process resulted in a functional voxel size of 2 mm × 2 mm × 2 mm. Because of the potential for spatial distortion as a result of Patient S.'s brain injury, we first coregistered a whole-brain EPI (using three-dimensional rigid-body transformation to minimize image warping) to the MNI template. This was followed by coregistration of the patient's partial EPIs to the coregistered whole-brain EPI. Finally, all images were smoothed with a 6-mm (full width, half maximum) Gaussian kernel.

We used Patient S.'s data to build an anosmia model, and we pooled the 3 control subjects' data to construct a control model (fixed-effects analysis). For both models, five vectors of onset times were created to correspond with the four odor conditions and the air condition. Voxel-wise, condition-specific beta values were estimated for the anosmia and control models and then submitted to contrasts of interest. Activations were reported only in brain areas in which we had a priori regional hypotheses; these areas included the anterior and posterior piriform cortices, the OFC, and the amygdala (Gottfried et al., 2006; Li et al., 2006; Phelps, 2006).

We defined the centers of the putative olfactory OFC according to a meta-analysis of human olfactory neuroimaging studies—left: $x = -22$, $y = 32$, $z = -18$; right: $x = 24$, $y = 33$, $z = -12$ (Gottfried & Zald, 2005). For OFC activations, results were corrected for multiple comparisons across small volumes of interest (small-volume correction, SVC), which were spheres of 6-mm radius around the putative OFC centers. For piriform and amygdala activations, SVC was based on anatomical masks assembled in MRICro (Rorden & Brett, 2000) and drawn on the structural T1 image, with reference to a human brain atlas (Mai, Assheuer, & Paxinos, 1997). All reported voxels correspond to MNI coordinate space.

Results and Discussion

Patient S.

S.'s odor-detection accuracy during the fMRI experiment was no better than chance at either nostril (Fig. 2a). This result further corroborated anosmia. However, consistent with S.'s right OFC lesion and the predominantly ipsilateral mode of olfactory processing (Shipley & Ennis, 1996), odor-detection

accuracy was higher for stimulation to the left nostril than for stimulation to the right nostril ($p < .01$; binomial test, two-tailed). Comparisons with the air-only condition indicated that S. tended to endorse odor presence more frequently for odors delivered to the left nostril ($p < .05$) than for odors delivered to the right nostril ($p = .64$). Thus, although S. reported no subjective awareness of the odors, and despite his chance-level odor detection, these data suggest that S. had a reliable advantage in processing odors via the left nostril.

In parallel to these behavioral findings, S.'s left olfactory OFC exhibited greater fMRI responses in two contrasts: odor delivered to the left nostril compared with air only ($x = -18$, $y = 34$, $z = -22$; $Z = 3.12$, $p < .05$ SVC; Fig. 2b) and odor delivered to the left nostril compared with odor delivered to the right nostril ($x = -24$, $y = 32$, $z = -22$; $Z = 2.67$, $p < .005$, uncorrected). These loci of orbitofrontal activity overlap closely with the putative region of the olfactory OFC (Gottfried & Zald, 2005), and this overlap accentuates the residual preservation of left-sided olfactory sensory function in S. By comparison, responses to odor stimulation to the right nostril did not differ from responses induced by air only in any olfactory region (at $p < .05$, uncorrected). It is critical to note that the absence of significant differences in sniff volume, duration, or peak amplitude across odor conditions ($ps > .1$) makes it unlikely that the effects in these two contrasts were due to respiratory variations.

We next examined whether the emotional content of an odor might still be processed in S. despite a total lack of conscious aversion to malodorous substances. First, S.'s odor-detection performance was significantly better for neutral odors than for unpleasant odors ($p < .005$, binomial test, two-tailed; Fig. 2a); this result was suggestive of residual affective awareness, though the paradoxical direction of this effect implies some functional derangement of odor-affective processing as a result of right OFC damage. Second, the delivery of unpleasant odors augmented S.'s SCRs above the SCRs to neutral odors (Wilcoxon test, $p = .04$), but only when presented to the left nostril (Fig. 2c). Likewise, unpleasant odors enhanced activity (relative to neutral odors) in the left anterior OFC ($x = -22$, $y = 44$, $z = -16$; $Z = 3.03$, $p = .001$, uncorrected), but only on left-nostril stimulation (Fig. 2d). It is interesting that this activation spatially coincides with regions previously implicated in olfactory affective evaluation (Anderson et al., 2003; Gottfried, O'Doherty, & Dolan, 2002).

With regard to Patient S.'s piriform cortices, odor-related activity was observed in the comparisons of (a) odor stimulation with air only, (b) left odor stimulation with right odor stimulation, and (c) unpleasant odor stimulation to the left nostril with neutral odor stimulation to the left nostril; however, all of these comparisons were below the preset significance level of $p < .001$, uncorrected (Table 1). Nevertheless, an examination of the overall sniff-induced activity that compared odor trials and air trials together with the implicit baseline (i.e., the intertrial interval) revealed robust effects in the piriform cortex bilaterally ($p < .05$, whole-brain corrected;

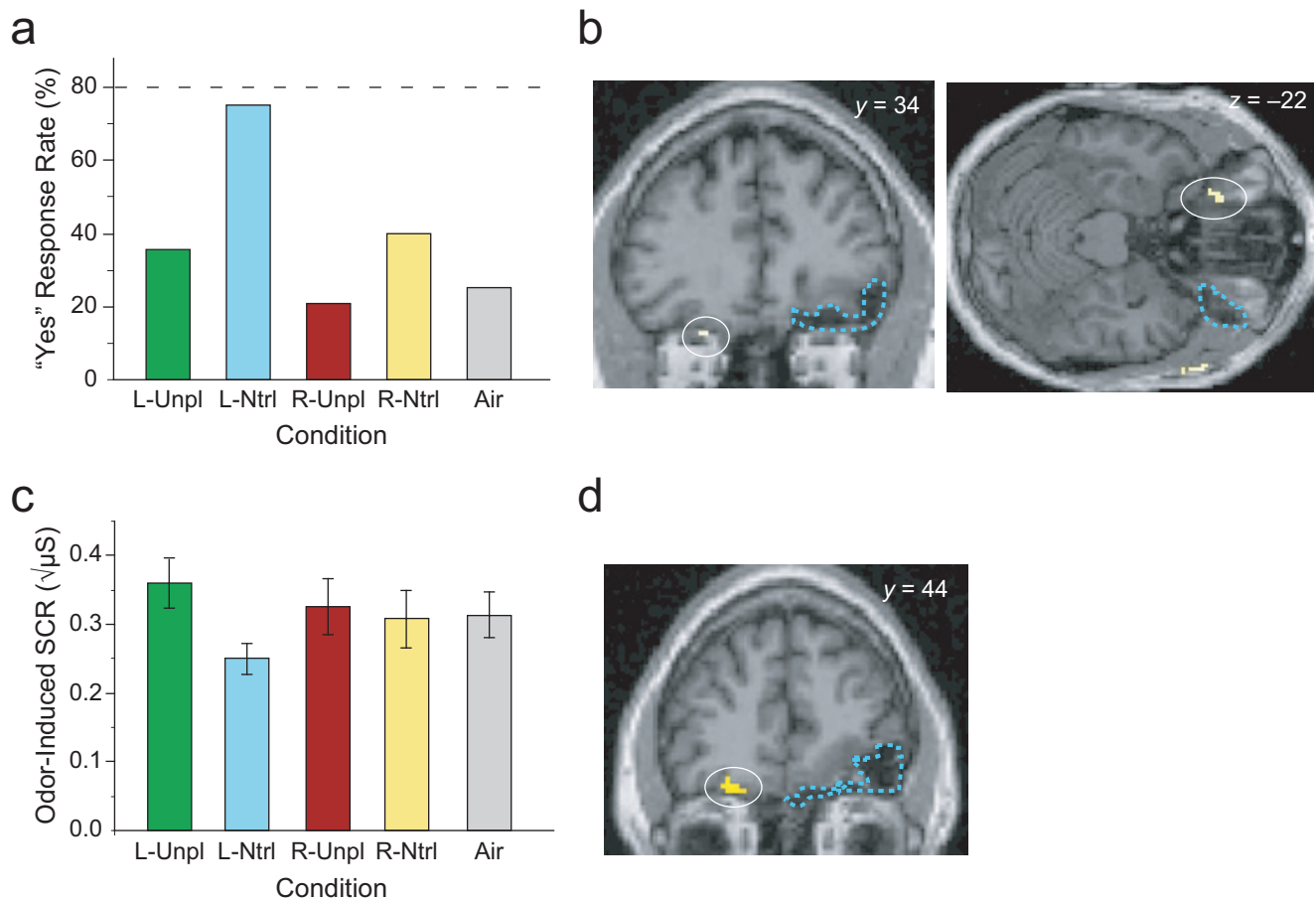


Fig. 2. Behavioral, physiological, and imaging evidence of unconscious olfactory processing in Patient S. The graph in (a) shows the percentage of "yes" responses (indicating that S. detected an odor) in each condition of the odor-detection task. Unpleasant odors ("Unpl"), neutral odors ("Ntrl"), and air only were delivered in separate trials to the left nostril (L) and the right nostril (R). The dashed line indicates the chance percentage of "yes" responses (80%), and it reflects the fact that 80% of trials contained odors. Areas in the left orbitofrontal cortex (OFC) showing greater activation in response to odors delivered to the left nostril, in comparison with air only, are shown in (b). Cyan curves demarcate the right OFC lesion. Amplitudes of the skin conductance response (SCR) to odor presentation are shown in (c), and areas showing greater left anterior OFC activity following unpleasant odors, compared with neutral odors, delivered to the left nostril are shown in (d). The display threshold for images in (b) and (d) is $p < .005$, uncorrected. Error bars in (c) represent standard deviations.

Table 1). This result corroborated the functional and structural integrity of the piriform cortex. Collectively, the behavioral and neural data presented here suggest that despite the patient's traumatic brain injury, the left olfactory pathway and the proximal right olfactory pathway are still preserved, allowing for reliable perceptual and affective responses that nevertheless reside outside of conscious awareness.

Control subjects

We subsequently performed the same olfactory fMRI (odor-detection) experiment in the 3 control participants to ensure that our paradigm had not introduced inadvertent biases favoring left-sided behavioral and neural responses. Control participants showed robust odor-detection accuracy ($p < .001$) and marginally heightened SCRs to unpleasant odors (as opposed to neutral odors, $p = .065$; Fig. 3a) regardless of whether the left nostril or the right nostril was stimulated ($ps > .70$). In

addition, unpleasant odors, compared with neutral odors, elicited greater responses in the bilateral OFC, right amygdala, and right anterior piriform cortex (as well as the left amygdala and left piriform cortex at a more lenient threshold of $p < .01$, uncorrected); these responses were independent of which nostril was stimulated (Fig. 3b¹; see Table 2 for all odor-related activity in control subjects).

Finally, a comparison of odor stimulation versus air-only stimulation (collapsed across valence and nostrils) revealed enhanced activity in the right piriform cortex (Fig. 3c), though odors delivered to the right nostril evoked greater responses in the right OFC than did odors delivered to the left nostril (Table 2). These additional results indicate that our protocol reliably induces autonomic and imaging responses with monorhinal stimulation to either side of the nose. To the extent that stronger right-sided piriform activity was observed in control subjects, this would align with previous reports suggesting a right-hemisphere predominance of odor processing in the

Table 1. Odor-Related and Sniff-Related Activity in the Piriform Cortex of Patient S.

Contrast and piriform cluster	Peak MNI coordinates			Z value
	x	y	z	
Odor – air (collapsed across right-nostril and left-nostril stimulation)				
Right anterior piriform	16	10	–22	1.54 [†]
Odor to left nostril – odor to right nostril				
Right anterior piriform	34	6	–12	1.92*
Right posterior piriform	30	0	–14	1.49 [†]
Unpleasant odor – neutral odor (left-nostril stimulation)				
Right posterior piriform	22	2	–30	2.75***
Left posterior piriform	–20	4	–30	1.89*
Sniff – rest				
Right posterior piriform	18	0	–24	6.18
Left posterior piriform	–26	2	–24	7.72

Note: Except as marked, Z values were significant at a threshold of $p < .05$, whole-brain corrected. MNI = Montreal Neurological Institute.

[†] $p < .1$, uncorrected. * $p < .05$, uncorrected. *** $p < .005$, uncorrected.

human olfactory brain (Abraham & Mathai, 1983; Jones-Gotman & Zatorre, 1988, 1993; Rausch et al., 1977; Zatorre & Jones-Gotman, 1990, 1991).

Control Experiment on Patient S.

It could be argued that Patient S.'s lack of affective physiological responses to right-nostril presentation was a general consequence of right orbitofrontal injury rather than an olfaction-specific phenomenon. In an effort to address this possibility, we conducted a visual analogue of the odor experiment using subliminal presentations of fearful faces and neutral-expression faces.

Method

Visual stimuli were presented on a CRT monitor. Stimuli consisted of two fearful and two neutral faces chosen from the Karolinska Directed Emotional Faces database (Lundqvist, Flykt, & Öhman, 1998), and two featureless faces generated from the two neutral faces by blurring the internal facial features (following prior methods in Li, Zinbarg, Boehm, & Paller, 2008). On each trial, a face and a featureless face were displayed simultaneously, with one face in the left visual field and the other face in the right visual field (with an eccentricity of 7°) for 17 ms. The faces were then replaced by two geometric images appearing at the same locations as the faces for 300 ms (followed by a central fixation cross for 1,500 ms). There were 12 trials each for four conditions (face in left visual field or right visual field × fearful face or neutral face). Patient S. reported on which side a face was displayed by pressing a button labeled “left” or “right,” while his SCR was monitored. (The experimental design is illustrated in Fig. S1 in the Supplemental Material.)

Results

In contrast to his asymmetrical SCR response profile in the case of unpleasant odors, S. demonstrated bilateral unconscious affective responses to fearful faces: Face detection was at chance level (hits = 21 out of 48, $p > .39$), but SCR magnitudes were higher for fearful faces than for neutral faces ($p < .05$), independent of the visual field in which they were presented (Fig. 4). The integrity of bilateral unconscious affective responses to nonolfactory sensory input underscores the olfactory specificity of S.'s perceptual impairments.

General Discussion

There are millions of nonmammalian vertebrate species that depend on the sense of smell but survive quite well in the absence of an OFC, and this fact plainly suggests that this structure is not necessary for basic olfactory functions (Gottfried, 2007). In the mammalian brain, one of the distinguishing neurobiological features is a frontal neocortex (Fuster, 1997), but the possible roles of the OFC, including the olfactory OFC, are still hotly debated (Shepherd, 2007). In rodents, ablation of the bilateral OFC does not critically impair odor processing and odor discrimination (Tait & Brown, 2007), whereas in dogs, such lesions can lead to severe olfactory malfunction (Allen, 1940). Further along the phylogenetic scale, monkeys exhibit systematic narrowing and refinement of odor tuning from the olfactory bulb through the piriform cortex to the OFC, and this fact suggests a specialized olfactory role for the OFC in primates (Tanabe, Iino, & Takagi, 1975). Coinciding evidence from human lesion studies has suggested that the OFC (especially the right OFC) plays a causal role in a variety of key olfactory-processing tasks (Jones-Gotman & Zatorre, 1988, 1993; Potter & Butters, 1980; Zatorre & Jones-Gotman, 1990, 1991).

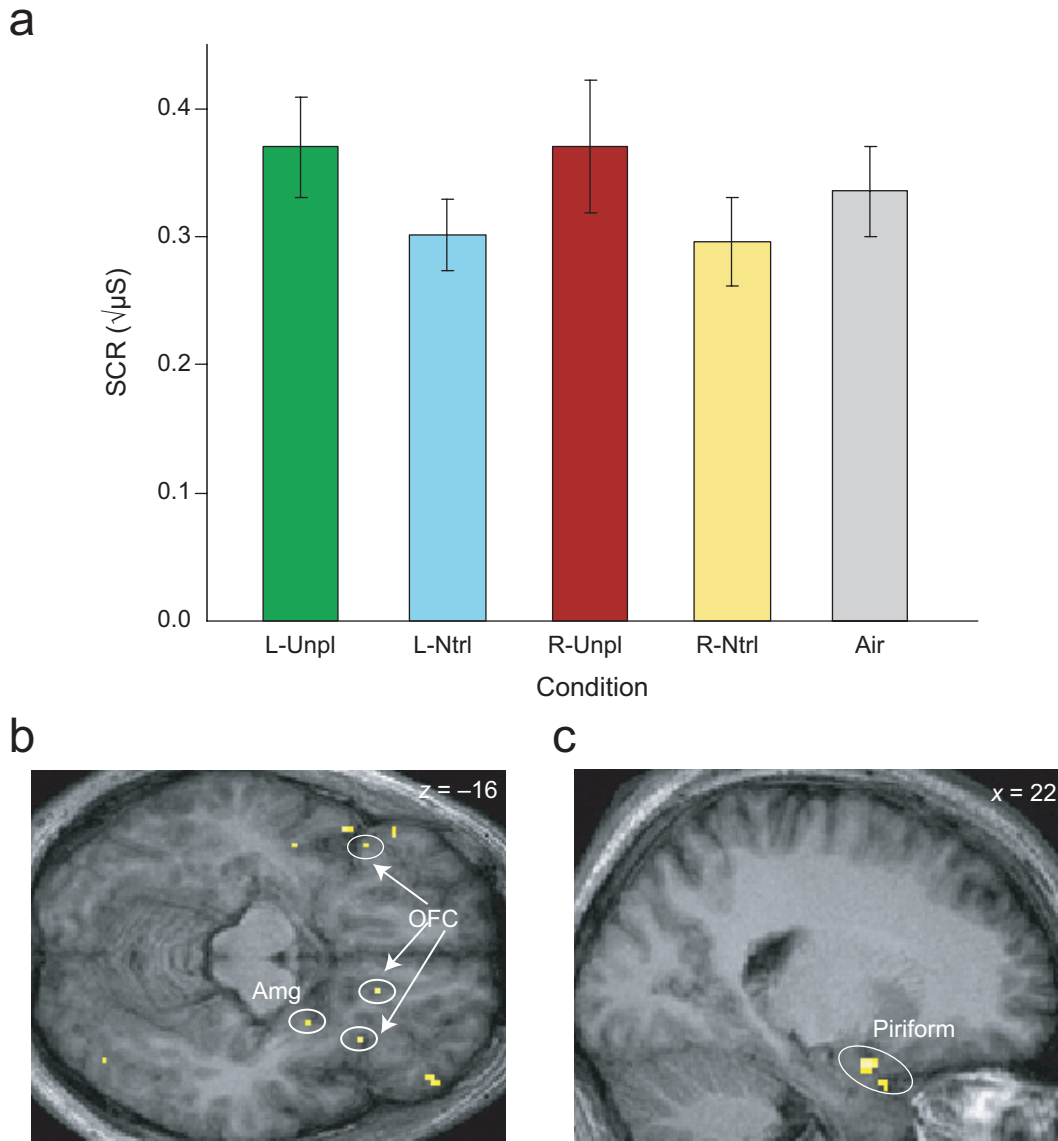


Fig. 3. Physiological and neuroimaging responses in control subjects. Magnitude of skin conductance responses (SCRs) to unpleasant odors (“Unpl”), neutral odors (“Ntrl”), and air only following monorhinal stimulation at either the left nostril (L) or the right nostril (R) is shown in (a). Error bars represent standard errors of the mean. Activations in the amygdala (“Amg”) and orbitofrontal cortex (“OFC”) in response to unpleasant odors (relative to neutral odors) are shown in (b). Clusters in the right piriform cortex with greater response to odor stimulation than air-only stimulation are shown in (c). Effects are overlaid on (b) axial and (c) sagittal sections of the mean T1-weighted anatomical scan; thresholds for display are $p < .001$ in (b) and $p < .005$ in (c).

The findings presented here offer new insights into the contributions of the OFC to the human sense of smell: Olfactory conscious experience does not transpire in the presence of brain injury largely limited to the right OFC. In the case of Patient S., the expression of odor-evoked responses across three different measurement modalities—behavioral, physiological (SCR), and fMRI—provides solid evidence that access to olfactory information is partially spared despite inaccessibility to conscious perceptual awareness. We suggest that these findings reasonably satisfy criteria for the phenomenon

of “blind smell”: An individual may be blind to (i.e., consciously unaware of) a smell, yet manifest reliable nonconscious responses to that smell (Sobel et al., 1999). Of course, it is evident that Patient S. has lost more than mere olfactory awareness and exhibits only a rudimentary preservation of odor-detection ability (Fig. 2a). However, the demonstration of odor-related activity in the left OFC (Figs. 2b and 2d) implies that the left olfactory pathway retains substantial functionality to implement olfactory sensory and affective analysis.

Table 2. Odor-Related Activity in Control Subjects

Contrast and brain region	Peak MNI coordinates			Z value
	x	y	z	
Odor – air (collapsed across right-nostril and left-nostril stimulation)				
Right anterior piriform	20	4	–28	3.04
Right posterior piriform	22	0	–22	3.31*
Odor to right nostril – odor to left nostril				
Right OFC	28	36	–12	3.23*
Right OFC	32	26	–16	3.32
Left OFC	–22	26	–16	2.86***
Unpleasant odor – neutral odor (collapsed across right-nostril and left-nostril stimulation)				
Right amygdala	26	–4	–14	3.32*
Left amygdala	–20	–10	–16	2.17**
Right OFC	38	40	–6	4.32
Right OFC	30	14	–12	4.22
Right OFC	12	22	–16	3.46
Left OFC	–42	18	–18	3.25
Right piriform	24	6	–22	3.39
Left piriform	–20	8	–26	2.35**

Note: Except as marked, Z values were significant at a threshold of $p < .001$, uncorrected. MNI = Montreal Neurological Institute; OFC = orbitofrontal cortex.

* $p < .05$, small-volume corrected. ** $p < .01$, uncorrected. *** $p < .005$, uncorrected.

With regard to the patient's relatively modest odor-related piriform activity, it is worth considering that sustainable piriform activation partially depends on odor-conscious awareness—perhaps via reentrant inputs from the OFC. A plausible account is that without conscious differentiation of trial types (such as odor trials compared with no-odor trials, or unpleasant trials

compared with neutral trials), the patient diverted equal amounts of attentional resources to the different conditions. It has been shown previously that attention to smell can enhance fMRI activity and connectivity within the piriform cortex (Plailly, Howard, Gitelman, & Gottfried, 2008; Zelano et al., 2005), so the lack of an attentional effect might serve to diminish differential piriform cortex activity in Patient S. Indeed, this possibility receives support from the demonstration of robust piriform activity in S.'s response to sniffing (as opposed to the baseline intertrial interval; see Table 1). This is a contrast in which strong attentional demands are embedded.

Notwithstanding the research shortcomings of single-case studies—shortcomings that include limited generalizability to the broader population and the risk of sampling error—two general implications can be inferred from our results. First, the right OFC appears to be necessary for mediating conscious perception of smell. Whether such a function is intrinsic to the right OFC or is instantiated via its connectivity with other brain regions and networks, such as the left OFC or thalamus (Carmichael, Clugnet, & Price, 1994; Ongur & Price, 2000; Plailly et al., 2008), remains to be determined. The notion that thalamocortical circuits (particularly those involving the right inferior frontal cortex) participate in odor awareness receives support from an earlier fMRI study in healthy subjects smelling perithreshold concentrations of an odorous steroid compound (Sobel et al., 1999).

Second, the left OFC (and, by implication, higher-level associative regions) is insufficient to sustain conscious olfaction. The fact that left-sided odor stimulation in Patient S.

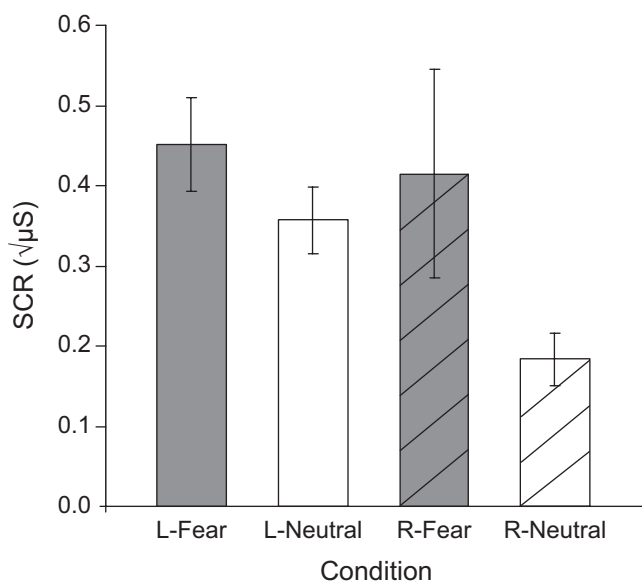


Fig. 4. Magnitude of Patient S's skin conductance responses (SCRs) to subliminal presentations of fearful faces and neutral faces. Faces were presented in either the left visual field (L) or the right visual field (R). Error bars represent standard deviations.

elicited appropriate peripheral and central responses suggests that the left olfactory system was largely preserved to support processing of the perceptual and emotional content of an odor, yet was unable to assign conscious awareness or feeling to that odor. Taken together, our data provide some of the first evidence to support the central role of the right OFC in facilitating the transformation of an upstream olfactory message into a conscious percept.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

Supplemental Material

Additional supporting information may be found at <http://pss.sagepub.com/content/by/supplemental-data>

Note

1. In Figure 3b, at a display threshold of $p < .001$ (uncorrected), the amygdala cluster contains 6 suprathreshold voxels, and the three OFC clusters contain 1, 3, and 22 voxels. At a less stringent threshold of $p < .005$ (uncorrected), there are 16 suprathreshold voxels in the amygdala cluster and 14, 54, and 74 voxels in the OFC clusters.

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