



Review

On the scent of human olfactory orbitofrontal cortex: Meta-analysis and comparison to non-human primates

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Abstract

It is widely accepted that the orbitofrontal cortex (OFC) represents the main neocortical target of primary olfactory cortex. In non-human primates, the olfactory neocortex is situated along the basal surface of the caudal frontal lobes, encompassing agranular and dysgranular OFC medially and agranular insula laterally, where this latter structure wraps onto the posterior orbital surface. Direct afferent inputs arrive from most primary olfactory areas, including piriform cortex, amygdala, and entorhinal cortex, in the absence of an obligatory thalamic relay. While such findings are almost exclusively derived from animal data, recent cytoarchitectonic studies indicate a close anatomical correspondence between non-human primate and human OFC. Given this cross-species conservation of structure, it has generally been presumed that the olfactory projection area in human OFC occupies the same posterior portions of OFC as seen in non-human primates. This review questions this assumption by providing a critical survey of the localization of primate and human olfactory neocortex. Based on a meta-analysis of human functional neuroimaging studies, the region of human OFC showing the greatest olfactory responsivity appears substantially rostral and in a different cytoarchitectural area than the orbital olfactory regions as defined in the monkey. While this anatomical discrepancy may principally arise from methodological differences across species, these results have implications for the interpretation of prior human lesion and neuroimaging studies and suggest constraints upon functional extrapolations from animal data.

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1. Historical background

More than 100 years ago, it was already well-recognized that the temporal lobe contributed to the human experience of smell. In the 1890s, Hughlings-Jackson and colleagues [36,37] described the occurrence of olfactory auras in patients with certain types of epilepsy and attributed these phenomena to ictal discharges in the medial temporal lobe (“uncinate fits”). Half a century later, Penfield and Jasper [56] discovered that focal electrical stimulation of the uncus or amygdala in awake patients could evoke olfactory perceptions typically described as smelling unpleasant in quality.

By historical comparison, a role for OFC in olfactory processing was slow to emerge. Throughout the 19th and early 20th centuries, anosmia (smell loss) was frequently documented as a result of post-traumatic head injury, but the inevitable damage to peripheral olfactory structures and olfactory bulb, along with the scarcity of detailed post-mortem studies, generally confounded efforts to relate these smell impairments to frontal lobe pathology (reviewed in [27]). During the 1930s and 1940s, Elsberg and colleagues developed a quantitative olfactory test (the so-called blast injection technique) to localize brain tumors in human patients [25,26]. Given the available alternatives at the time (including surgery, ventriculography, and of course autopsy), this method represented a non-invasive and diagnostically valuable approach. These investigators tested a total of 1000 neurological patients and demonstrated that reductions in odor sensitivity were particularly prevalent with “lesions in or around the frontal lobes.” While in retrospect this anatomical ambiguity makes it difficult to determine whether olfactory disruption arose from direct infiltration of olfactory neocortex or merely from compression of olfactory bulbs and tracts, the results certainly appeared to implicate the frontal lobes in the human sense of smell. These studies stand apart as the first methodical

attempt to utilize odors as a diagnostic tool in neurological disease. However, with the technical difficulties of implementing this procedure, the method eventually faded out, along with any imminent research investigations into the prefrontal basis of human olfaction.

Animal studies addressing a frontal lobe involvement in olfaction were also slow to materialize. Indeed, in 1933, Dusser de Barenne, the eminent Dutch physiologist, noted that smell-evoked reactions were preserved in a cat with complete extirpation of neocortex, suggesting olfactory function was independent of cerebral integrity [24]. This observation harmonized with the prevailing idea that olfaction was a phylogenetically primitive sensory modality, chiefly subserving reflexive behaviors related to feeding, reproduction, and threat and therefore under control of subcortical brain structures, without the requirement of a neocortical olfactory processor.

In the 1940s, Allen reported a pioneering set of studies that first established a critical role of frontal cortex in olfactory function [1–3]. Bilateral ablation of the frontal lobes in dogs caused a delay in learning an olfactory conditioned reflex (lifting the foreleg in response to an odor in order to avoid an electric shock) and interrupted the ability to discriminate between positive and negative conditioned odors [1]. In contrast, total ablation of parieto-temporal lobes (sparing piriform areas) or hippocampi had no effect on these responses, indicating that discrimination learning selectively relied on the structural integrity of prefrontal cortex. Parallel experiments revealed that prefrontal ablation had no impact on auditory, tactile, or visual conditioning [3], highlighting the olfactory specificity of this effect. In subsequent work, extracellular recordings in unoperated dogs showed that electrical stimulation of piriform cortex evoked short-latency spike activity in ventrolateral areas of prefrontal cortex [2], suggesting that this region might have rapid access to olfactory information. These physiological findings were complemented by a

series of strychnine neuronography experiments in monkeys emphasizing the presence of reciprocal connections between piriform, posterior orbital, and anterior insular areas [62,63]. However, following these studies, scientific interest in the subject of olfactory neocortex waned, and additional data did not become available for another two decades when electrophysiological and anatomical tracing studies definitively demonstrated the presence of secondary olfactory cortex in the OFC.

2. Anatomical overview of olfactory circuitry

In order to provide a context for understanding the position of the OFC in olfaction, it is useful first to outline the basic circuitry of the olfactory system in the mammalian brain. Most of the data presented below are based on anatomical and physiological studies in rodents and non-human primates, and it is generally presumed that this network of connections is similar in humans.

Odor-evoked responses are initially conducted from first-order olfactory receptor neurons at the nasal mucosa toward the olfactory bulb, where sensory axons make contact with second-order (mitral and tufted cell) dendrites within discrete glomeruli. Axons of the mitral and tufted cells of each bulb coalesce to form the olfactory tract, one on each side. This structure lies in the olfactory sulcus of the basal forebrain, just lateral to gyrus rectus, and conveys olfactory information ipsilaterally to a wide number of brain areas within the posterior orbital surface of the frontal lobe and the dorsomedial surface of the temporal lobe (Fig. 1). Collectively, these projection sites comprise “primary olfactory cortex,” signifying all of the brain regions receiving direct bulbar input [21,64,88]. These structures (from rostral to caudal) include the anterior olfactory nucleus, olfactory tubercle, anterior and posterior piriform cortex, amygdala (periamygdaloid region, anterior and posterior cortical nuclei, nucleus of the lateral olfactory tract, and medial nucleus), and rostral entorhinal cortex, all of which are substantially interconnected via associational intracortical fiber systems [14,35]. Note that because piriform cortex is the largest of the central olfactory areas and is the major recipient of inputs from the olfactory bulb, the term “primary olfactory cortex” (POC) is often used as a synonym for piriform cortex. Other regions of the basal forebrain, such as the taenia tecta, induseum griseum, anterior hippocampal continuation, and nucleus of the horizontal diagonal band, have been shown to receive direct bulbar input in animal models [14,77], although their specific role within the human olfactory system remains poorly defined.

Higher-order projections arising from each of these primary structures converge on secondary olfactory regions in OFC, agranular insula, additional amygdala subnuclei, hypothalamus, mediodorsal thalamus, and hippocampus. Together, this complex network of connections provides the

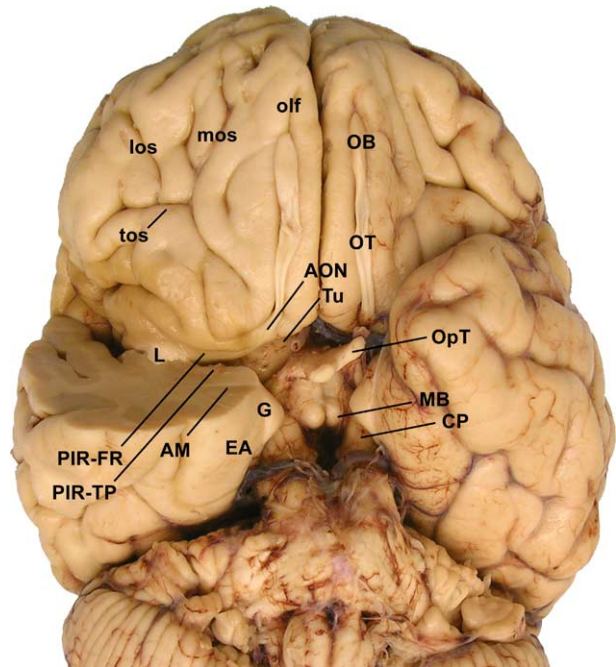


Fig. 1. Macroscopic view of the human ventral forebrain and medial temporal lobes, depicting the olfactory tract, its primary projections, and surrounding non-olfactory structures. The right medial temporal lobe has been resected horizontally through the mid-portion of the amygdala (AM) to expose olfactory cortex. AON, anterior olfactory nucleus; CP, cerebral peduncle; EA, entorhinal area; G, gyrus ambiens; L, limen insula; los, lateral olfactory sulcus; MB, mammillary body; mos, medial olfactory sulcus; olf, olfactory sulcus; PIR-FR, frontal piriform cortex; OB, olfactory bulb; OpT, optic tract; OT, olfactory tract; tos, transverse olfactory sulcus; Tu, olfactory tubercle; PIR-TP, temporal piriform cortex. Figure prepared with the help of Dr. Eileen H. Bigio, Dept. of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL.

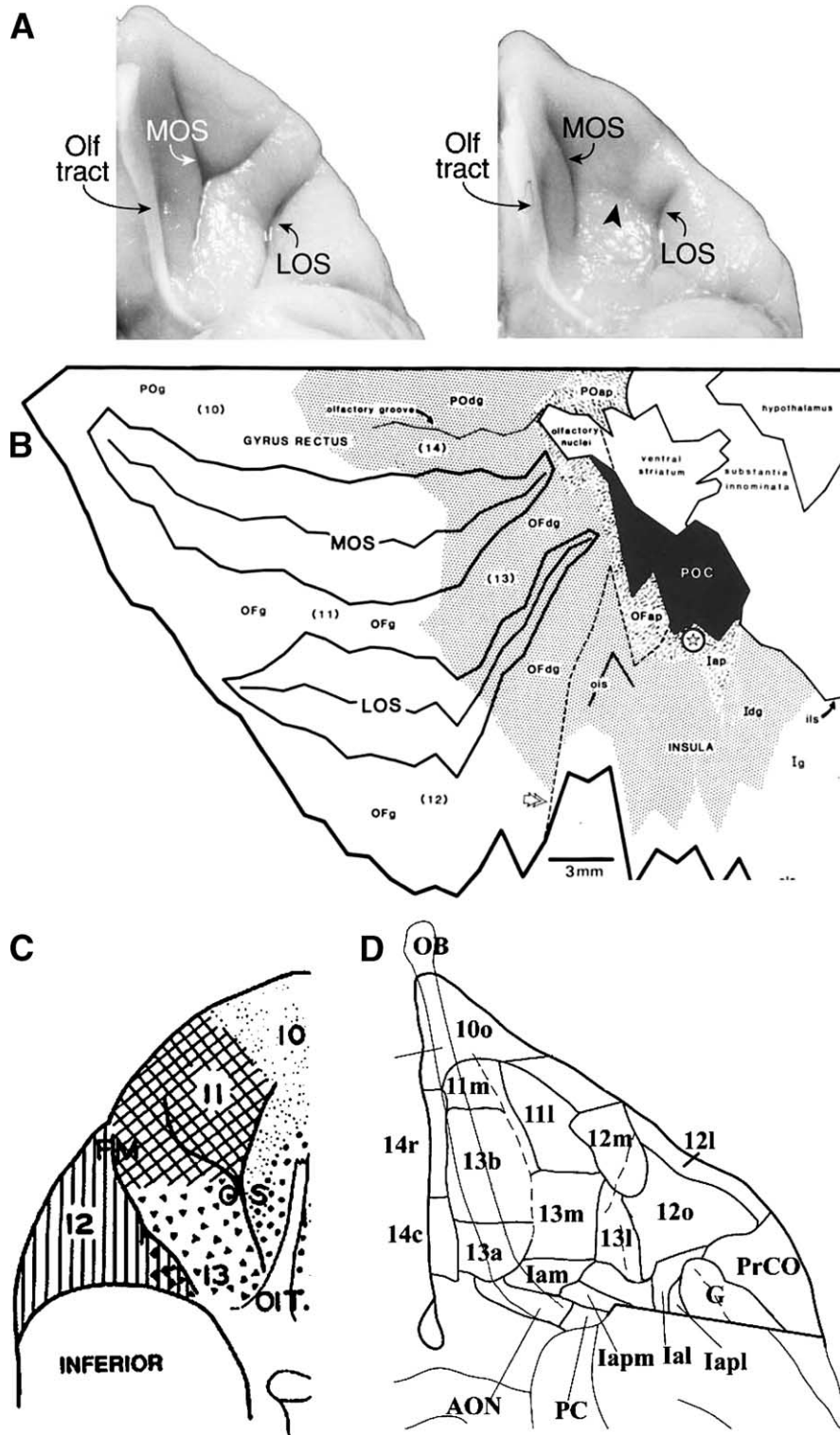
basis for odor-guided regulation of behavior, feeding, emotion, autonomic states, and memory. In addition, each region of primary olfactory cortex (except for the olfactory tubercle) sends dense feedback projections to olfactory bulb [14], supplying numerous physiological routes for central or “top-down” modulation of sensory processing as early as the second-order neuron in the olfactory hierarchy.

3. General anatomy of the OFC in non-human primates

The macaque OFC occupies the ventral surface of the frontal lobe and is comprised of several cytoarchitecturally heterogeneous regions. Three major sulci are identifiable in the macaque: a shallow olfactory sulcus (which lies immediately above the olfactory tract), a longer and deeper medial orbital sulcus, and a shorter and somewhat more variable lateral orbital sulcus (Fig. 2A). The gyrus rectus lies medial to the olfactory sulcus, the medial orbital gyrus occupies the area between the olfactory and medial orbital sulci, the middle orbital gyrus lies between the medial and lateral orbital sulci, and the lateral orbital gyrus lies lateral to the lateral orbital sulcus. There is additionally a variably

expressed horizontal sulcus or depression that bisects the middle orbital gyrus and runs between the medial and lateral orbital sulci [17]. Some investigators prefer to subdivide the middle orbital gyrus into anterior and posterior orbital gyri in order to indicate whether the cortex is specifically anterior or posterior to the incipient horizontal (transverse) sulcus.

At its broadest level, the OFC can be divided into three general cytoarchitectonic areas: a posterior agranular region, a middle dysgranular region, and an anterior granular region [47] (Fig. 2B). The more posterior sectors of OFC represent anterior medial extensions of the insula. Thus, agranular insula (referred to as Iap by Morecraft et al. [47]) is continuous with agranular OFC (referred to as OFap by



Morecraft et al. [47] or PAll by Barbas and Pandya [8]. Similarly, dysgranular insula (referred to as Idg by Morecraft et al. [47]) is continuous with dysgranular OFC (referred to as OFdg by Morecraft et al. [47] or Pro by Barbas and Pandya [8]). The agranular regions in both insula and OFC consist of a relatively undifferentiated two to three layer periallocortex and are contiguous medially with frontal piriform cortex, whereas the dysgranular regions are a more highly differentiated five- to six-layered cortex and are located rostral and dorsal to the agranular sector.

The anterior sectors of OFC, rostral to the insular extension, had previously been divided into 5 discrete cytoarchitectural regions by Walker [90], which he labeled areas 10–14. Area 10 reflects the ventral aspect of the frontal pole, area 11 occupies the anterior orbital gyrus, area 12 occupies the lateral orbital gyrus, area 13 is centered on the posterior orbital gyrus, and area 14 consists of the posterior gyrus rectus and the medialmost aspects of the medial orbital gyrus (see Fig. 2C). Since Walker's early work, this map has been largely confirmed in subsequent studies, with the primary alteration being that more recent surveys show area 13 extending medially into the posterior half of the medial orbital gyrus and area 14 being restricted to the gyrus rectus [8].

Based on analysis of cyto- and myelo-architectonic features, as well as immunohistochemical staining, Carmichael and Price [11] provided a more detailed map of the primate OFC, resulting in multiple subdivisions of the OFC (Fig. 2D). For instance, area 11 was divided into separate medial and lateral regions (11m and 11l). Area 12 was divided into 4 subregions, 12o, 12m, 12l and 12r, ranging from dysgranular to fully granular in nature. Area 13 was divided into three dysgranular areas, 13b, 13m and 13l (from medial to lateral), with a fourth agranular subregion at the posterior medial corner of area 13, which was labeled area 13a. Area 14 was divided into separate agranular (14c) and dysgranular (14r) regions. Finally, the insular extensions were divided into five territories, Iam, Iapm, Iai, Ial, Iapl.

4. Localizing olfactory neocortex: monkey

Until recently, most of our knowledge regarding the location of olfactory neocortex was based on studies in non-

human primates. This section summarizes converging electrophysiological and histochemical evidence showing that discrete portions of monkey OFC receive afferent inputs directly from POC.

4.1. Electrophysiological studies

The first systematic investigation of an olfactory projection area in primate OFC was carried out by Takagi and his colleagues using electrophysiological techniques [85–87]. These researchers demonstrated that in awake unanesthetized monkeys, electrical stimulation of olfactory bulb or anterior piriform cortex elicited local field potentials (LFPs) in lateral portions of the posterior OFC, substantiating Allen's earlier findings in canine prefrontal cortex [2]. This area was named the lateral posterior orbitofrontal area, or LPOF, encompassing the posterior part of Walker's [90] area 12, the lateroposterior part of area 13, and more posteriorly the frontotemporal junction and frontal operculum (Fig. 3A).

In the same study, damage to either the anterior piriform cortex or the hypothalamus abolished the bulb-evoked potentials in LPOF, leading to the conclusion that olfactory projections to the OFC were conducted via piriform and hypothalamic relays [87]. In contrast, ablation of the mediodorsal thalamus (MD) had no effect on the evoked potentials in LPOF nor did direct MD stimulation elicit potentials within the LPOF region of the OFC. These findings were a surprise at the time as it was generally assumed that the primate MD was an obligatory checkpoint through which all afferent fibers must pass en route to the orbitofrontal surface [51,62,89]. Moreover, the medial subdivision of MD was already known to receive direct olfactory projections in both rodents [61] and primates [9], so it seemed plausible that this region should form a node in the projection pathway from olfactory bulb to LPOF. The seemingly heretical idea that olfactory information in OFC could bypass the thalamus prompted a retrograde tracer study in primates intended to characterize the afferents to LPOF [60]. Neurons were labeled in many regions, including MD thalamus and prohinal (entorhinal) cortex, implying that LPOF was accessible by dual olfactory fiber systems: a thalamocortical pathway via piriform cortex/MD and a cortico-cortical pathway via piriform/entorhinal cortex.

Fig. 2. Anatomy of the monkey OFC. (A) Two examples of the macaque OFC demonstrate the most commonly observed orbitofrontal sulcal patterns. In the right side of the panel, a horizontal indentation (arrowhead) denotes the rudimentary transverse orbital sulcus. MOS, medial orbital sulcus; LOS, lateral orbital sulcus. [Reproduced from Fig. 10 of: M.M. Chiavaras, M. Petrides, Orbitofrontal sulci of the human and macaque brain, *J. Comp. Neurol.* 422 (2000) 35–54. Copyright 2000 by Wiley-Liss. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley and Sons, Inc.] (B) A two-dimensional flattened cytoarchitectonic map of monkey OFC demonstrates the concentric organization of these paralimbic structures. The open double arrow indicates approximate border between OFC and insula. Iap, agranular-periallocortical insula; Idg, dysgranular insula; Ig, granular insula; ils, inferior limiting sulcus; OFap, agranular-periallocortical OFC; OFdg, dysgranular OFC; OFg, granular OFC; ois, orbital insular sulcus; POC, primary olfactory cortex; POap, agranular-periallocortical paraolfactory cortex; POdg, dysgranular paraolfactory cortex; POg, granular paraolfactory cortex; sls, superior limiting sulcus. [Reproduced and modified from Fig. 1 of: R.J. Morecraft, C. Geula, C., M.M. Mesulam, Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey, *J. Comp. Neurol.* 323 (1992) 341–358. Copyright 1992 by Wiley-Liss. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley and Sons, Inc.] (C) Walker's map of cytoarchitectural areas in the macaque [90]. (D) A detailed cytoarchitectural map of the macaque ventral frontal lobe. [Reproduced from Fig. 2 of: D. Ongur, A.T. Ferry, J.L. Price, Architectonic subdivision of the human orbital and medial prefrontal cortex, *J. Comp. Neurol.* 460 (2003) 425–449. Copyright 2003 by Wiley-Liss. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley and Sons, Inc.]

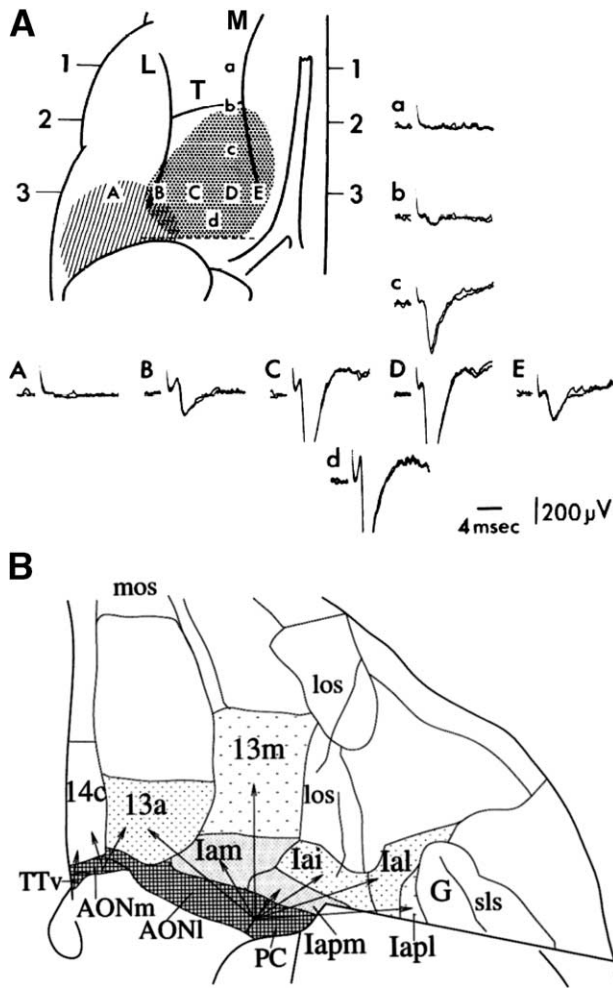


Fig. 3. Localization of olfactory OFC in monkeys. (A) A diagram of the left ventral frontal lobe shows the approximate locations of regions LPOF (hatched lines) and CPOF (stippled area). Note the CPOF area as defined is based not on olfactory responses but on antidromic field potentials elicited in portions of mediadorsal thalamus that are also responsive to olfactory bulb stimulation. The orbital sulci comprise of medial (M), lateral (L), and transverse (T) segments and show a classic “H”-shaped pattern. Numbers and letters refer to electrode stimulation sites within these regions. Evoked antidromic responses in the thalamus were largest when evoked at electrode positions C, D, and d, intermediate at electrode c, and substantially smaller at electrodes B, E, and b, indicating the focus is primarily in the posterior half of the stippled area. [Modified from Fig. 3 of: T. Tanabe, H. Yarita, M. Iino, Y. Ooshima, S.F. Takagi, An olfactory projection area in orbitofrontal cortex of the monkey, *J. Neurophysiol.* 38 (1975) 1269–1283. Used with permission of the American Physiological Society, copyright 1980.] (B) A summary of the primary olfactory inputs to monkey OFC on this ventral view of the macaque brain shows that projection density (indicated by the density of dots) is highest in regions adjacent to POC (e.g., 13m) and decreases with distance (e.g., 13m). Note, while this illustration depicts a homogenous distribution of projections in each subregion, the olfactory inputs to area 13m were actually concentrated in its posterior half. [Adapted from Fig. 22 of: S.T. Carmichael, M.C. Clugnet, J.L. Price, J.L., Central olfactory connections in the macaque monkey, *J. Comp. Neurol.* 346 (1994) 403–434. Copyright 1994 by Wiley-Liss. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley and Sons, Inc.]

The same research group that initially characterized LPOF later identified a second olfactory projection area in primate OFC that was in fact mediated by a transthalamic

pathway [92]. This region was situated in between the medial and lateral orbital sulci, within Walker’s area 13 (Fig. 3A). As this region was positioned medial and slightly anterior to LPOF, it was labeled the centroposterior orbitofrontal area (CPOF). It must be noted that the CPOF as displayed in Fig. 3A does not necessarily reflect the boundaries from which one easily detects odor-evoked responses. Rather, the area was defined based on the ability of stimulating electrodes placed in the posterior orbital gyrus to invoke antidromic potentials in the same areas of the medial (magnocellular) division of MD thalamus (MDmc) that were engaged by orthodromic olfactory bulb stimulation. Electrodes placed more posteriorly in the CPOF produced the most robust activation in MDmc, suggesting that the focus of the projection was in the posterior part of the CPOF. The Takagi group interpreted their findings as direct evidence that the MD thalamus provides a critical relay for olfaction in the CPOF. While complementary studies confirmed the ability to directly record responses to olfactory stimulation in the CPOF [92], it did not indicate the extent to which responses were limited to more posterior aspects of the CPOF or extended into the more anterior portions of the CPOF that were more weakly associated with MDmc stimulation.

Takagi and colleagues further presented evidence that areas LPOF and CPOF exhibit different activity patterns in response to odor stimulation [85–87,92]. Out of 44 neurons analyzed during single-cell recordings of LPOF, 50% responded to just one of eight different odors, and no cell responded to more than four odors [86]. This stimulus specificity was striking insofar as it was higher than that seen in either the olfactory bulb or POC, suggesting a selective role of the LPOF in odor identification. In contrast, out of 12 neurons recorded in CPOF, none responded to less than three of the eight odorants [92]. Although recordings in CPOF were limited, the data suggested that odor tuning and discrimination were highly specialized and selective in LPOF, but much more generalized in CPOF. However, subsequent data have not fully supported the idea that the LPOF and CPOF possess clearly distinguishable response patterns. For instance, in a series of single-unit recording studies, Rolls and Baylis [66] reported the presence of both broadly tuned and finely tuned olfactory-responsive cells throughout the posterior orbital surface.

4.2. Anatomical tracer studies

While the work of Takagi and colleagues suggested the presence of two discrete olfactory areas (LPOF, CPOF) in monkey OFC, specific details regarding the underlying projection pathway remained somewhat uncertain, with conflicting evidence for involvement of hypothalamus, thalamus, entorhinal cortex, substantia innominata, and amygdala [50,60,87,92]. Recent advances in histochemical and anatomic tracer techniques have made clear that the OFC is no more than three synapses removed from the nasal

periphery. Mesulam and Mufson first showed that projections to anteroventral insular regions (agranular Iap and dysgranular Idg) on the monkey posterior orbital surface arise directly from POC [44,45,48]. Subsequent work has documented analogous olfactory projection patterns in agranular (OFap) and dysgranular (OFdg) sectors of caudal OFC [6,47], which themselves represent rostromedial continuations of Iap and Idg. Together, these insular and orbital territories comprise concentric rings emanating from an allocortical piriform “root” (Fig. 2B) and appear to provide the substrate for convergence of olfactory, gustatory, visceral, autonomic, endocrine, and emotional information [45,47].

In 1994, Price and colleagues conducted further investigations of POC and its projections to primate OFC using anterograde and retrograde tracers, as well as electrophysiological recordings [14]. These experiments showed that a total of 9 different orbital areas received direct input from virtually all portions of POC, including anterior and posterior piriform cortex, anterior olfactory nucleus, periamygdaloid cortex, and entorhinal cortex. Olfactory neocortical targets included areas Iam, Iapm, Iapl, Iai, and Ial in the agranular insula, areas 13a, 13m, and 14c in the medial OFC, and area 25 along the inferior medial wall (Fig. 3B). These areas broadly overlap the previously identified representations in Iap/OFap and Idg/OFdg [6,47,48]. Among the cytoarchitectural subregions identified by Carmichael and Price, areas Iam and Iapm received the highest density projections from olfactory regions and were the only areas with significant inputs into deep layers of cortex (with labeling extending from layer I–VI). The next highest area of labeling was area 13a, but, unlike area Iapm and Iam, labeling was limited to layers I–III. All three areas showed action potentials in response to electrical stimulation of the olfactory bulb. Area Iam was notable for the presence of rapid (4–10 ms latency) single-unit action potentials, which were not characteristic of Iapm or 13a responses. The only dysgranular area demonstrating direct olfactory input was the posterior half of area 13m. However, projections to this area were light and limited to layer I of cortex. Importantly, examination of the labeling maps provided by Carmichael and Price indicates that these POC projections do not reach the more anterior portions of area 13m (a feature that will be returned to later in the article). No evoked activity was observed in area 13m, although the region was not sampled enough to draw firm conclusions regarding its responsiveness to olfactory bulb stimulation.

Four general principles emerged out of this work. First, despite the broad pattern of distribution, neocortical projections were most heavily concentrated in regions nearest to POC (in areas Iam and Iapm) and progressively declined with distance from POC. It was concluded that Iam and Iapm are the principal neocortical sites of olfactory information processing, though the role of Iapm may subsume a more general visceral function, given its substantial input from the ventroposteromedial nucleus of the thalamus [12]. Second, there is overall preservation of

olfactory topography, such that more anterior–medial portions of OFC received olfactory inputs from anterior–medial POC (e.g., anterior olfactory nucleus), whereas posterior–lateral portions of OFC received inputs from posterior–lateral POC (e.g., posterior piriform cortex, periamygdaloid cortex). Third, projections between POC and Iam/Iapm are typically bidirectional, consistent with previous findings [45,48], apart from the olfactory tubercle, which lacks input to OFC [14]. Finally, most of the olfactory areas identified in agranular insula and posterior OFC are connected to the region of MD thalamus that receives input from POC [65,72], substantiating the presence of both direct and indirect (thalamic) pathways to olfactory neocortex.

In comparing their findings to the prior physiology data from the Takagi laboratory [87,92], Carmichael et al. [14] suggested that area LPOF roughly corresponded to their projection sites in Iam, Iai, and Ial, and area CPOF corresponded to 13m and portions of Iam and 13a. A few issues warrant attention before fully accepting that the areas defined by Carmichael et al. are necessarily synonymous with the CPOF defined by Takagi and colleagues. First, whereas the Takagi group focused on an obligatory thalamic pathway to this region, the areas thought by Carmichael et al. to be equivalent to CPOF receive either heavy (Iam) or light (13m, 13a) projections directly from POC. Second, area Iam actually lies posterior to the area that Takagi et al. recorded from, and therefore it is somewhat tenuous to consider it synonymous with the CPOF. Nevertheless, even if Iam is distinct from CPOF, it would still provide an additional nonthalamic route through which area 13m and 13a receive olfactory information.

Price and colleagues also argued that similarities in the structure and connections of posterior orbital and agranular insular areas in the rodent and macaque “suggest a high degree of homology” between the rat and monkey ([14], p. 403). For instance, they note a broad correspondence between the agranular insula in the rodent and the primate. They also note that area VLO in the rodent appears similar to area 13a in the primate in that both are agranular, receive projections from anterior piriform cortex, and respond with multiunit action potentials to olfactory bulb stimulation [19,43]. Finally, they point out that dysgranular area LO in the rodent may correspond with area 13m in the monkey. Such cross-species similarities provide support for the use of rodent models of olfaction since it is reasonable to assume that similarities in structure and connections will lead to similarities in the processing capabilities of these regions in rodents and monkeys (e.g., see [75]). However, the ability to make similar inferences regarding humans rests on whether or not the same areas show similar structural, connectational, and functional features in the human OFC.

4.3. Functional imaging studies

To date, there have been just a handful of olfactory fMRI studies in primates [10,28,29]. Work by Boyett-Anderson et

al. [10] specifically examined olfactory responses in the OFC. In this paradigm, 40-s epochs of odor (alternating with odorless air) were delivered via a cotton-tipped applicator to six squirrel monkeys. Odor-evoked neural responses were detected in rostromedial OFC (along with cerebellum, hippocampus, and piriform cortex), overlapping ventromedial prefrontal cortex. While this anterior pattern of findings contradicts the electrophysiological and anatomical data indicating posterior OFC involvement, we suggest that these fMRI data should be regarded as preliminary, as: (1) they are based on a small subject sample; (2) the neural responses are based on a fixed-effects analysis, whereby the OFC responses may be predominantly driven by one or two outliers; (3) the studies were conducted in a highly non-physiological context, in which the monkeys were sedated and the odorants were delivered out of phase with respiration; and (4) the piriform activations may have also spanned caudal regions of OFC.

5. General anatomy of the OFC in humans

The topography of the human OFC retains the basic features of the macaque OFC. However, unlike the macaque, there is always a deep horizontally running sulcus (the transverse orbital sulcus) that bisects the middle orbital region between the medial and lateral orbital sulci [17]. In about a quarter of samples, the pattern formed by the medial, lateral, and transverse orbital sulci forms a clear H-shape, and indeed this H-shape was identified as early as the 1850s [34,46]. However, in the majority of cases, the shape is less clearly an H [17]. Frequently, this occurs because either the lateral or medial orbital sulci are interrupted such that they can be divided into separate rostral and caudal segments. Additionally, humans typically possess one or two intermediate orbital sulci in the anterior orbital gyrus region, and it is not uncommon for one of these intermediate gyri to intersect the transverse orbital sulcus. This pattern frequently appears in cases where the medial orbital sulcus is divided into two segments.

Data from humans indicate a substantial degree of cytoarchitectural convergence between monkeys and humans. Early work by Petrides and Pandya [57] indicated a gross correspondence between monkey and human features. More recent work by Ongur, Ferry, and Price [55] indicates additional convergence in terms of both staining and cellular features at the subregion level. The Ongur et al. map is displayed in Fig. 4. As can be seen, the basic pattern is similar to that seen in the macaque, but there is a substantial elongation of subregions. One important discrepancy must be noted between this map and previous studies of human OFC cytoarchitectonics. Specifically, Ongur et al. [55] limit area 13 to the medial orbital gyrus and the medialmost sections of the posterior orbital gyrus. This contrasts dramatically with work by Petrides and Pandya [57] and Semendeferi et al. [76], who indicate that

area 13 extends throughout the posterior orbital gyrus as far as the lateral orbital sulcus. The source of the discrepancy is unresolved.

In order to make their system translatable to neuroimaging researchers, Ongur et al. [55] provided a sample map for a brain within the conventional Talairach coordinate system. In considering the location of specific boundaries, it should be noted that many of the transitions between areas are relatively gradual, making precise demarcation of boundaries difficult. Moreover, the authors studied too few brains to provide a clear picture of the variability in the positioning of these transitions. Nevertheless, the map is likely to provide a reasonable approximation of the location of cytoarchitectural regions and represents the clearest attempt to date to provide a precise map of OFC architecture within a standardized coordinate system.

6. Localizing olfactory neocortex: human

The cytoarchitectural similarities between the human and macaque OFC lead to direct predictions regarding the location of olfactory zones in the human OFC. If the areas are homologous in terms of both architecture and connections, it follows that the greatest olfactory responsivity should occur in the same cytoarchitectural areas as in the macaque. Specifically, the most robust responses are predicted to arise in agranular regions, particular Iam and Iapm, since these areas show the heaviest input from POC and show robust responses to olfactory bulb stimulation. Based on the Ongur et al. [55] map, such an area would be centered about 8 mm anterior to the anterior commissure in the most posterior aspect of the OFC. Based on the work of Takagi and colleagues [87,92], one would expect an additional slightly more anterior focus in the posterior portions of area 13 (13a and posterior 13m). If centered in area 13a, this would still be quite posterior ($y < 15$) mm. If centered in posterior area 13m, one would expect this focus to be centered between roughly 15–20 mm anterior to the anterior commissure.

Direct information regarding the location of olfactory responsive sites in human OFC has understandably lagged behind the monkey data due to technological constraints. As reviewed below, studies of patients with focal brain lesions have implicated the OFC in olfactory functions but have been less instructive in terms of where in the OFC these processes are being mediated. After reviewing these data, we turn our attention to more recent efforts to define the putative olfactory OFC with the aid of functional neuroimaging techniques.

6.1. Patient lesion studies

A general role for human OFC in olfactory processing was initially inferred from studies of patients with focal lesions of prefrontal cortex. In particular, surgical excisions

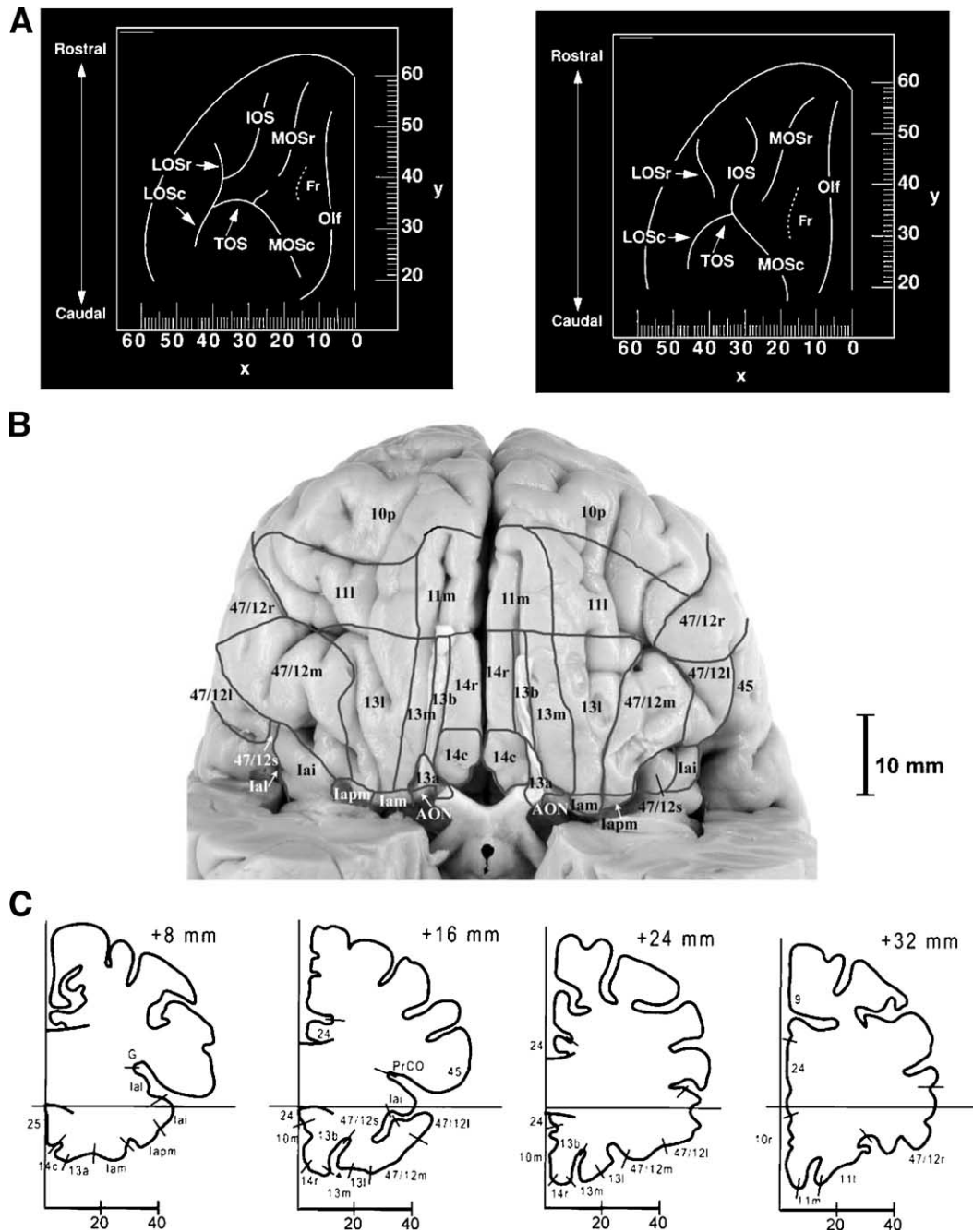


Fig. 4. Anatomy of the human OFC. (A) These diagrams show the two most common patterns of orbital sulci in humans. Fr, sulcus fragmentosus; IOS, intermediate orbital sulcus; LOS, lateral orbital sulcus; MOS, medial orbital sulcus; TOS, transverse orbital sulcus; (r), rostral, (c), caudal. The scales on the bottom and the right refer to *x* and *y* positions in Talairach space. [Reproduced from Figs. 5 and 6 of: M.M. Chiavaras, M. Petrides, Orbitofrontal sulci of the human and macaque brain, *J. Comp. Neurol.* 422 (2000) 35–54. Copyright 2000 by Wiley-Liss. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley and Sons, Inc.] (B) A human cytoarchitectural map drawn on the surface of the OFC and shown alongside coronal slices transformed into Talairach space (C), where the number in the corner represents the number of mm anterior to the anterior commissure. [Reproduced from Figs. 2 and 4 of: D. Ongur, A.T. Ferry, J.L. Price, Architectonic subdivision of the human orbital and medial prefrontal cortex, *J. Comp. Neurol.* 460 (2003) 425–449. Copyright 1994 by Wiley-Liss. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley and Sons, Inc.]

of the prefrontal lobe, either as a result of tumor, hematoma, or medically intractable epilepsy, were shown to be associated with impairments of odor identification [38], odor quality discrimination [59,96], and olfactory memory [39]. For example, in a study of odor identification [38], post-surgical epileptic patients were asked to identify

common odors using the University of Pennsylvania Smell Identification Test (UPSIT) [23], a “scratch-and-sniff” test that requires matching each of 40 different odors to different lists of 4 verbal descriptors. Compared to a normal control group, only those prefrontal patients whose excisions involved OFC were impaired on this task. Interestingly,

patients with temporal lobe excisions (frontal sparing) also performed poorly, though they were relatively less impaired than the OFC group. These effects were generally observed in the presence of normal detection thresholds, excluding any primary loss of smell, although there was a significant negative correlation between right-nostril odor detection values and identification performance in patients with right frontal damage. Complementary studies on odor quality discrimination have demonstrated similar effects. Potter and Butters [59] asked patients with prefrontal damage to rate the similarity of odor quality between successive pairs of stimuli. Performance impairment appeared to be specific to the olfactory modality as visual hue discrimination was left intact. Curiously, odor detection thresholds were lower (more sensitive) in the prefrontal subgroup than in controls, though the overall younger age of the prefrontal patients might have accounted for this finding.

Two important patterns emerged from these studies. First, the results clearly documented a role for human OFC in sustaining higher-order cognitive operations related to odor discrimination, though the exact contribution of OFC to these functions remained unclear. Successful performance on an identification test such as the UPSIT, for example, relies on accurate odor detection and recognition, working memory, lexical comprehension, and cross-modal (odor–verbal) matching, any of which could be compromised by prefrontal damage. Second, and perhaps more notably, the lesion data indicated that low-level markers of olfactory function (such as odor detection thresholds) were relatively preserved with orbital lesions. The absence of a lesion effect on elementary odor processing implies that the olfactory projection site in human OFC may not have direct access to unadulterated representations of the original odor percept but instead may receive only highly refined and abstracted sensory inputs in the service of more complex olfactory behaviors.

Although the patient lesion data provide convincing evidence for the involvement of human OFC in olfactory processing, there are several important caveats. Lesion-based approaches are necessarily limited by the large size and spatial extent of the surgical resection. Especially given the close proximity of so many heterogeneous regions within the ventral frontal lobe, this confound effectively precludes a more precise anatomical delineation of olfactory OFC. In addition, as presurgical olfactory performance was not available in these patients, it remains difficult to establish whether the olfactory impairments directly followed from the prefrontal excision or were a consequence of pre-existing pathology located elsewhere. Finally, it is possible that at least some of the lesions actually spared the olfactory projection areas in OFC, giving a misleading impression that elementary olfactory functions do not localize to orbital neocortex. For example, based on the tracing studies in primates, one would not predict that anteromedial or anterolateral lesions of the OFC would disrupt basic olfactory

processing since these regions do not receive direct input from POC.

6.2. Functional neuroimaging studies

In 1992, Zatorre and colleagues published the first imaging (PET) study of human olfaction [97]. Healthy volunteers were asked to inhale during birhinal presentation of an odorless cotton wand (first scan) or during presentation of 8 different odorants (second scan). Comparison of odor to no-odor scans revealed significant neural activity in left and right piriform cortex and right OFC. The right OFC activation was located centrally within the orbital cortex, in between the medial and lateral orbital sulci, but more rostral than would be predicted from the monkey data. Odor-evoked OFC activity was also observed on the left side, albeit at reduced statistical threshold. The greater right-hemispheric OFC activity, combined with evidence of greater impairments in olfactory function following right vs. left OFC lesions, led to a hypothesis of a right frontal dominance for olfaction.

Since this groundbreaking work, numerous investigators using both PET and fMRI techniques have further examined the location of an olfactory representation in OFC. These studies have spanned a creative variety of experimental paradigms, involving manipulations of odor stimulus duration, stimulus quality, multisensory effects, and motivational state. To document the localization of human olfactory OFC more definitively, we compiled the OFC voxel coordinates reported in all imaging studies where: (a) the neural characterization of basic olfactory processing was a central aim; (b) odor-evoked activity was not complicated by the use of aversive odorants; and (c) subjects were not asked to make cognitive olfactory judgments (other than odor detection) during scanning. Given the data from monkeys, this analysis was broadly constrained to OFC activations posterior to $y = 45$ along the anterior–posterior axis (Talairach coordinate space). Data came from the following 13 studies (5 PET, 8 fMRI): Zatorre et al., 1992 [97]; Small et al., 1997 [78]; Sobel et al., 1998 [81]; Zald and Pardo, 1998 [94]; Francis et al., 1999 [30]; O’Doherty et al., 2000 [52]; Savic and Gulyas, 2000 [73]; Savic et al., 2000 [74]; Sobel et al., 2000 [82]; Poellinger et al., 2001 [58]; Gottfried et al., 2002 [31]; Gottfried and Dolan, 2003 [32]; Kareken et al., 2004 [40]. A total of 26 coordinates were identified, including 15 on the right and 11 on the left. Seven of these studies reported significant bilateral activation, five reported significant right-sided activation only, and one reported significant left-sided activation only. To reduce inconsistencies across studies, MNI coordinates were converted to Talairach space, using Matthew Brett’s “mni2tal” function (<http://www.cla.sc.edu/psyc/faculty/rorden/mriicro.html>) as implemented in Matlab 6 (The Mathworks, Inc., Natick, MA). Finally, voxel coordinate means (with standard deviations) and medians were computed separately for

Table 1
Functional localization of putative human olfactory OFC averaged across 13 neuroimaging studies

Coordinates *	Mean (+/- S.D.)			Median		
	x	y	z	x	y	z
Right OFC	23.9 (5.4)	33.8 (5.6)	-12.1 (5.3)	24.0	33.0	-12.0
Left OFC	-21.2 (5.7)	30.8 (4.2)	-15.5 (4.6)	-21.8	30.0	-17.0

* Coordinates are in Talairach space in mm, where x = media/lateral from the midline (+ = right), y = posterior/anterior from the anterior commissure (+ = anterior), and z = inferior/superior from the intercommissural plane (+ = superior).

right and left sides. The results are shown in Table 1 and Fig. 5.

These findings indicate that the localization of human olfactory neocortex is highly consistent across studies, with negligible between-study variation, especially given the inherent spatial limitations of neuroimaging. It is evident that the neural substrates of odor stimulation reliably converge upon bilateral areas along the medial orbital sulcus close to its intersection with the transverse orbital sulcus (i.e., the horizontal limb of the “H”-shaped sulcus). While the data generally confirm a right-hemisphere predominance, it is important to note that left hemisphere involvement arose in almost two-thirds of the studies.

7. Reconciling the monkey and human data

Comparison of the consensus neuroimaging activation locus to the human architectonic maps delineated by Price and colleagues [55] suggests that the putative human olfactory OFC roughly corresponds to the posterior portion

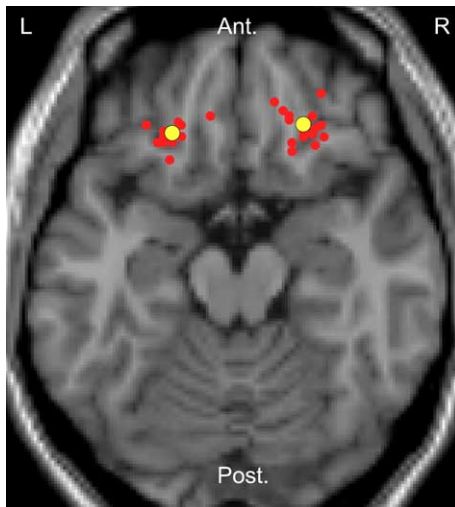


Fig. 5. Localization of olfactory OFC in humans. The peak activation coordinates (23 voxels: red dots) from 13 neuroimaging studies of basic olfactory processing are plotted on a canonical T1-weighted anatomical MRI scan in Talairach space. The yellow circles indicate the mean voxel coordinates for right and left sides. For presentation, coordinates are collapsed across the z axis (superior–inferior) in order to depict all voxels on a single image.

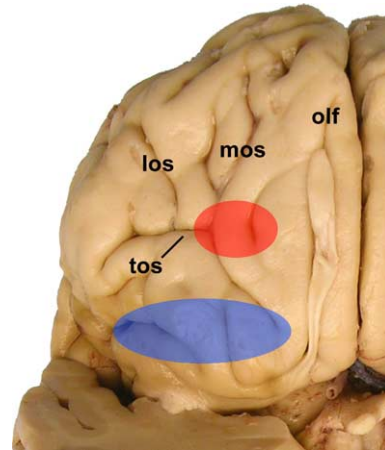


Fig. 6. Cross-species mismatch between predicted and observed olfactory OFC. The blue area signifies the olfactory projection area in monkey OFC, as based on electrophysiological [87,92] and anatomic tracer [14] studies, whereas the red area denotes the putative human olfactory projection area, as based on the neuroimaging meta-analysis presented here and recent cross-species anatomical comparisons of OFC [17,55]. See Fig. 1 for key to abbreviations. The diagram clearly indicates that the human olfactory region is located considerably more anterior than the monkey counterpart. Possible explanations for this anatomical discrepancy are discussed in the text.

of area 111, a location that is strikingly more anterior than one would predict on the basis of the animal data discussed above [14,47,92]. Regardless of specific cytological subdivisions, it is clear that the putative human region is situated at least 2 cm rostral to the monkey counterparts in areas Iam and Iapm in the posterior OFC (Fig. 6). Indeed, the posteriormost (agranular) segment of the orbital surface is rarely activated in human olfactory neuroimaging. Among the 13 studies cited above, only three reported insular activations that could be considered to lie properly within agranular portions of OFC [31,32,58]. A complete survey of the olfactory imaging literature shows that, if anything, agranular insula is preferentially activated during higher-order tasks involving explicit hedonic judgments [69,71] or cross-modal integration [20,80].

The OFC region nearest to area 111 that receives direct POC projections (according to [11]) would be area 13m, which receives a light projection to layer 1. The posterior–medial corner of area 111 abuts the anterior–lateral corner of area 13 m, and it is certainly possible that variability in the precise locations of cytoarchitectural boundaries has led to the misidentification of a focus that is actually in the anterior–lateral corner of area 13 m. However, given that the POC projection to this area in monkeys is concentrated in the posterior portion of area 13m, one would expect that such projections would be focused posterior to y = 20 in humans (according to [55]). Thus, even if the neuroimaging focus is labeled as area 13m, it still does not appear to correspond well with predictions based on the monkey literature. On the other hand, if one considers the CPOF boundaries as defined by Takagi’s group, based on MDmc connections rather than POC projections, the boundaries do indeed include the more anterior part of area 13m. However, as already noted, the

CPOF is centered in the posterior aspects of area 13m in the macaque, not in its anterior–lateral aspect.

What might account for the anatomical discrepancy between the monkey and human locations of olfactory OFC? One way to approach this question is to ask why the *human* imaging studies do not show activation of *caudal* orbital areas. As discussed in Sections 7.1–7.6, a combination of technical and experimental factors may render fMRI insensitive to this region and together is likely to bias the detection of more anterior OFC loci in the human data. In Section 7.7, we consider the inverse question, namely, to ask why the *monkey* studies do not show activation of *rostral* orbital areas. Finally, methodological issues notwithstanding, we speculate in Section 7.8 that biological differences in olfactory processing between monkeys and humans might account for some of the cross-species differences in functional anatomy detailed here.

7.1. Methodological differences between fMRI and electrophysiology

Direct comparison of the human and non-human primate data regarding olfactory representations is complicated by the simple fact that the human data derive from fMRI studies whereas the animal data arise primarily from electrophysiological and anatomical tracer studies. Preferably, cross-species comparisons should rely on the same method in both species; with the improvement in fMRI, it may become possible to obtain adequate imaging data in monkeys that could be directly compared to the human data. Indeed, the data by Boyett-Anderson et al. [10] suggest that, when matched for methodologies, there may in fact be considerable overlap in the functional localization of primate and human olfactory OFC. However, the small sample size of this particular study will require replication, preferably with non-sedated monkeys smelling in a more physiologically relevant context.

This issue aside, a consideration of the neuronal basis of the fMRI signal (technically, blood oxygen level-dependent [BOLD] contrast) may bear on how best to relate human imaging and animal electrophysiological data. Recent work indicates that both single-unit responses and local field potentials (LFPs) correlate with fMRI BOLD effects [42], though the LFPs are better predictors. Given the greater correspondence of BOLD signal to LFPs, it is important to note that LFPs and single-unit recordings reflect fundamentally different aspects of neuronal processing [41]. Single-unit (and multi-unit) studies focus on the cell spiking (action potentials) of pyramidal neurons and thus reflect the output of a region. However, they do not capture subthreshold inputs, integrative processes, or associational operations of the cortical area under study. In contrast, LFPs are markers of aggregate extracellular activity spanning a wider cortical territory (typically on the order of a few hundred micrometers to a few millimeters), generated by a combination of postsynaptic potentials, afterpotentials of somatodendritic

spikes, and voltage-gated membrane oscillations, which together reflect the input of a cortical area as well as its local processing (including the activity of excitatory and inhibitory interneurons). Because the fMRI signal is more closely tied to the LFPs, it has been interpreted as being more representative of local integrative processing than regional output.

The idea that fMRI BOLD activity is a truer reflection of neuronal inputs and local processing suggests that the animal studies using LFPs (rather than single- or multi-unit recordings) may be more comparable to the human imaging data, providing at least partial validity for comparisons between these particular methods. The most extensive studies in this regard are the early studies by Takagi and colleagues [85,87,92], which do indeed show a pattern of localization that extends more anteriorly into dysgranular OFC cortex than into the agranular insular areas showing short-latency single-unit responses described by Carmichael et al. [14]. While the human data still appear somewhat more anterior to what would be predicted from the focus of the Takagi LFP studies, the discrepancy is certainly smaller than when one limits comparison to the anatomical tracing and short-latency single-cell data.

Actually, in many instances, the output of a region and the level of regional processing are similar, in which case LFPs, spike firing, and fMRI BOLD signal are likely to produce convergent results [42]. However, there are situations in which spiking activity is relatively transient, but LFPs are more prolonged [41], so that the LFP and fMRI data will diverge from the single-unit data. To the extent that posterior OFC regions show short-lived output without engaging in prolonged local processing (an open question), their activity may not be strongly detected by neuroimaging. In contrast, the information fed forward from these areas might engage substantial levels of local processing in more anterior OFC regions, resulting in their being detected by fMRI.

7.2. Spatial insensitivity of functional neuroimaging

It is certainly plausible that human olfactory OFC is actually located more posteriorly, akin to the primate anatomy, but that fMRI is simply insensitive to the caudal OFC olfactory region. In particular, conventional fMRI sequences can be associated with signal distortion and dropout (susceptibility artifact) at air–tissue interfaces, reducing image quality in olfactory-specific areas of the basal frontal and ventral temporal lobes [53]. Such an artifact would explain the absence of caudal OFC activations in the human fMRI studies. However, this explanation seems unlikely since a similar distribution of responses is observed in the PET studies of basic olfactory processing, which are not susceptible to these technical artifacts. It is also possible that olfactory representations in posterior OFC are simply too sparse to be detected reliably by human imaging modalities, particularly due to the small size of this region in the human brain. Nevertheless, there are at least a few

instances where odor-evoked activation has been documented in these regions [20,31,32,58,69,71,80], as described above, suggesting that low neuron counts may not entirely explain the findings. Moreover, based on the anatomical data, assuming the intrinsic cortico-cortical connections within the OFC are essentially preserved across species, then olfactory representations in human OFC should be sparser in anterior (vs. posterior) areas so that odor-evoked activation should be more difficult to elicit in rostral OFC, yet this prediction is opposite to the pattern described here.

7.3. Temporal insensitivity of functional neuroimaging

The insensitivity of fMRI to rapid (millisecond) temporal changes may be particularly relevant in considering the olfactory system. The critical role of temporal dynamics in olfactory processing has been demonstrated across both vertebrate and non-vertebrate species (e.g., [16,18,22,84]). For example, in a recent study using voltage-sensitive dyes in the rodent olfactory bulb, odorants activated specific sequences of glomeruli with unique temporal firing patterns and respiratory phase shifts that evolved over just a few hundred milliseconds [83]. Therefore, if the neural analysis of olfactory sensory information depended more on the pattern (rather than the amount) of activity in caudal OFC, there would be no difference in the overall response between control and stimulus conditions, and there would be no detectable signal with PET or fMRI. It must be emphasized, however, that at present there is little direct evidence suggesting that the sorts of rapid temporal dynamics that characterize olfactory bulb processing are specifically implemented in secondary olfactory regions. Nevertheless, such a pattern would certainly explain the dearth of posterior OFC responses observed in imaging studies.

7.4. Differential effects of habituation

Data from both animals [91] and humans [58,82] have demonstrated that the POC shows a rapid pattern of habituation to odorants, such that the initial response is brief and is not sustained even in the face of prolonged odorant exposure. In contrast, it appears that more anterior OFC regions lack this rapid habituating response [58]. However, neither animal nor human data have specifically addressed issues of habituation in areas such as Iapm, Iam, and posterior 13m. Whether habituation effects are pronounced in the posterior OFC remain unclear, although they might help explain the relative absence of odor-evoked neuroimaging responses in this region.

7.5. Differential effects of sniffing

Participants in olfactory imaging studies are commonly asked to pace their breathing during olfactory paradigms and/or make sniffs in response to an instruction cue. However, Sobel et al. [81] indicate that the posterior OFC (consistent

with the agranular insular regions) is sensitive to the effects of respiration, whereas more anterior OFC regions are not. This would appear consistent with its close relationship to the POC where a similar effect of sniffing has been observed. Experiments by Sobel et al. [81] further indicate that it is not the motoric act of sniffing that is critical to this activation but rather the stimulation of air flow through the naris. This association with sniffing may critically limit the ability to observe signals specifically correlated with olfaction in the posterior OFC region, leading to signal detection only in areas that are insensitive to air flow effects. Indeed, a similar argument has been made for why far more olfactory neuroimaging studies observe OFC activity than POC activity, despite the primacy of the POC in the olfactory pathway [95].

7.6. Cognitive factors

Another possible source of cross-species discrepancies may relate to fundamental cognitive differences between humans and monkeys during a given experiment. For example, in human studies, it is likely that subjects actively attend to the odorants even if they are not told to make any specific judgments (apart from odor detection). Such interactions between attention and olfaction could theoretically alter the underlying response patterns and favor the activation of more rostral OFC regions. Along these lines, it is notable that, in macaques, area 11 receives input from both ventral area 46 and ventral area 10, as well as input from cingulate cortex [5], which may make the region far more sensitive to attentional and top-down control than agranular areas. It also cannot be ruled out that human participants automatically engage in certain judgments about odorants in these studies, even when not explicitly told to. For instance, in a study of olfactory judgment tasks, Royet et al. [70] found that odor detection, intensity, hedonicity, familiarity, and edibility judgments were all associated with activity in the right OFC (at 26, 30, –12 in MNI space; or 26, 29, –12 in Talairach space), which is very close to our reported olfactory coordinates. Whether this concordance of results simply reflects the fact that attended odorants routinely engage this region, or that this area is explicitly involved in judgment processes, remains to be explored.

7.7. Limitations of approaches in monkeys

Thus far, we have focused on why functional neuroimaging may be less sensitive to detecting posterior OFC activations. At the same time, one may ask why animal studies have failed to detect more rostral activations. In general, the use of anatomical and electrophysiological techniques (as in monkeys) favors the identification of monosynaptic short-latency pathways. Yet, this can come at the expense of detecting important areas that are less directly connected. The anatomical data are clear that more rostral OFC areas are devoid of direct connections in the macaque,

but the extent to which they are responsive to less direct routes is less well studied. The seminal work of Takagi and colleagues provides the strongest support for the importance of thalamic input into the OFC, and this work specifically suggests that thalamic projections extend anterior to the areas defined by heavy direct POC input. Electrophysiological studies have consistently focused on more posterior OFC areas where olfactory signals have been the easiest to detect. Thus, anatomical constraints and sampling biases may have limited thorough examination of more rostrally focused olfactory processing in non-human primates. These biases may have led to a less than complete picture of the subregions involved in olfaction in monkeys.

7.8. Ascendancy of rostral olfactory processing

In the preceding sections, we have listed numerous features that might influence some of the anatomical differences between monkey and human data. The fact that human OFC shows an olfactory responsive region in a location anterior to what would be predicted from the monkey data may be simply ascribed to technical and methodological issues, as outlined above. However, it has yet to be definitively established that this discrepancy is due to the abovementioned technical factors, and in a number of instances, the explanations are not completely convincing. For example, PET is protected against susceptibility artifacts that might limit fMRI sensitivity, and event-related fMRI designs are protected against habituation effects. Furthermore, the demonstration of caudal activations in a handful of fMRI studies provides face validity that neither regional size nor atypical activity patterns necessarily preclude the detection of odor-evoked activity in caudal OFC. Finally, although the neural basis of cell spiking and fMRI signals may lead to differential sensitivity in caudal vs. rostral OFC regions, this is only likely to occur if there is a dissociation between regional output and local processing in the OFC, which remains to be seen.

Without dismissing the importance of technical factors, we feel it is valuable to introduce other possible interpretations for why the human data emphasize an area that is anterior to what would have been predicted from the monkey literature. One provocative idea is that rostral OFC has gained ascendancy in its importance for olfactory processing to a degree that it is now a critical node for human olfactory processing. In contrast, the importance of this region for olfactory function in primates may have been more limited in scope, with the posterior OFC playing a more dominant role. Below, we provide three highly speculative scenarios, in keeping with the concept of system reorganization in olfactory OFC, though we readily acknowledge that specific data supporting these ideas remain limited.

7.8.1. Evolutionary expansion

Perhaps the most radical hypothesis for the emergence of more rostral olfactory processing in humans is that evolu-

tionary expansion of prefrontal cortex has led cell types in human Iam/Iapm to shift more anteriorly while maintaining their connectivity with POC. This possibility seems unlikely, given that comparative cytoarchitectonic analyses indicate that OFC subdivisions are generally conserved across human and primate species [45], with only minor anatomical variations. Certainly, the cross-species differences that have been observed anatomically cannot adequately account for a 2-cm shift in the location of olfactory OFC.

7.8.2. Translocation of afferent connections

An alternative, but equally radical, hypothesis is that the wiring between the POC and OFC has changed, such that the secondary olfactory neocortex has undergone an anterior translocation of position, involving a population of target neurons with different cytoarchitectural and functional features. If true, this would raise problematic questions regarding attempts to infer function on the basis of shared anatomical (cytological) features across species. Specifically, it would call into question whether such relations are a sufficient means of characterizing the response properties in human prefrontal cortex, with respect not only to olfactory processing, but also to non-olfactory computations. Such a hypothesis would require specific anatomical characterization of olfactory projections to human OFC. Perhaps with the help of olfactory-specific immunohistochemical stains in post-mortem material, this issue can be answered in the future. However, at present, additional data regarding changes in regional connectivity are lacking.

7.8.3. Emergence of late-stage processing

A third more modest hypothesis is that the connectional patterns have not dramatically changed across species but that in humans, an area that was originally more tertiary in olfactory function has taken on a more pivotal role. If this has occurred without a profound alteration in connections, it would indicate that this area operates exclusively on olfactory information received either through the thalamus or through feed-forward projections from the posterior OFC. Indeed, the caudal orbital areas are linked in an extensive network of cortico-cortical connections with more rostral orbital areas, integrating multisensory inputs in the service of feeding, emotion, and homeostatic control. This network undoubtedly propagates odor information at least as far rostrally as area 11l, which is the region activated in the human imaging studies and which in single-unit recordings has been shown to contain a variety of olfactory multisensory neurons [66].

8. Potential implications

The more rostral location of the putative human olfactory OFC has a number of interesting implications for understanding the general role of OFC in olfaction. Many of these conclusions apply regardless of whether we entertain the

radical possibility of an anterior translocation of cell position or afferent connectivity or accept the more conservative hypothesis that the networks have remained similar across species, but the relative importance of anterior vs. posterior OFC regions has changed. Even if the apparent species differences are artifact, the neuroimaging data make it evident that a more rostral area appears to be heavily involved in human olfactory processing, and its presence requires reevaluation of certain assumptions about olfactory processing in the OFC.

First and foremost, there is no reason to assume that the functional responsiveness of the anterior region resembles that of the posterior regions from which most of our (animal) physiological understanding derives. The more rostral region possesses significantly different cytoarchitectural features and connectivity patterns than the agranular regions that have been the primary focus of olfactory research in animals. Thus, the wisdom of extrapolating from studies based on a different region in animals seems questionable. In other words, even if the cross-species differences are nothing more than methodological artifact, it still remains that existing models of human olfactory OFC function that are based on current data from the posterior OFC of primates are likely to prove insufficient.

If the putative olfactory OFC area had actually taken over or superseded functions that previously depended on the posterior OFC, this would fundamentally alter aspects of olfactory experience and its role in human behavior. As discussed above, the posterior OFC receives olfactory input from both direct and indirect (via MD thalamus) pathways [60,87,92], providing cortical access to dual sources of olfactory information. However, the more rostral OFC olfactory region in humans almost certainly has a different balance of thalamic vs. nonthalamic pathways. A greater reliance on thalamic input could have both advantages and disadvantages. On the one hand, it would allow the advantages of thalamic gating and allow processing features that are more similar to those seen in other sensory systems. On the other hand, it would lose the effects of synchronous or desynchronous input between thalamic and POC afferents. In primates, Price and colleagues have described a hierarchical flow of information transfer in OFC that underlies progressive functional complexity, whereby sensory afferents (olfactory, gustatory, visceral) terminating upon caudal OFC then converge upon more anterior medial orbital regions, allowing for information synthesis and the construction of higher-order perceptual representations, particularly those related to flavor [12,13,54]. If olfactory afferents actually bypass caudal OFC, this would substantially alter aspects of sensory integration. Alternatively, if the projection pathways described by Price and colleagues are intact, it may suggest that humans are actually dependent upon areas where stimuli are already highly multimodal and integrated, perhaps leading to some of the confusion between olfactory and gustatory experiences that are frequently

described in humans [49]. One can also imagine how such changes might lead to a reduction in stimulus specificity in this more heteromodal region. This might provide a biological explanation for why the human sense of smell seems so impoverished beside that of other mammalian species. In other words, the ascendancy of more rostral areas may have come at the cost of certain olfactory abilities, even leading to a narrowing of the human repertoire of odor-guided discriminations and behaviors.

Second, the rostral region has dramatically different connections with the amygdala. Areas Iai, Iapm, and Ial receive heavy projections from the amygdala. In contrast, both areas 13m and 11l receive far less direct input from the amygdala [7,12]). This would lead to a degree of olfactory processing far less influenced by amygdalar output than is seen in the posterior agranular regions. Similarly, anterior 13m and posterior 11l have substantially weaker outputs to the hypothalamus. In many mammals, odorous stimuli are the primary means of motivating behavior. Maternal bonding, kinship recognition, food search, mate selection, predator avoidance, and territorial marking are all guided by smells [15]. Given the convergence of olfactory, visceral, and amygdalar input and hypothalamic output in the posterior OFC of non-human primates, it is easy to see where the posterior OFC would be critical in regulating these functions. In contrast, to the extent that olfactory processing extends outside of the amygdalar input and hypothalamic output zones, the end product of olfactory processing would likely be less directly related to emotional responses.

The discussion of amygdalar connectivity focuses attention on a key feature of the present meta-analysis—this analysis was restricted to neutral or only mildly valenced conditions. Previous studies of emotionally valenced odorants have shown more variably located responses [4,32,67,68,70,93]. In several cases, more posterior OFC activations have actually arisen in these studies, particularly in response to pleasant odorants. However, activations that were equally anterior, or even more anterior, than the region identified in the meta-analysis have also emerged. Thus, if anything, inclusion of emotional stimuli suggests an even broader scope of olfactory processing beyond the posterior OFC.

Finally, the current observations might directly impact the interpretation of patient lesion studies. Whether the lesions encompass the posteriormost aspects of the OFC or the area described here may critically influence the results of neuropsychological studies of olfaction. In contrast to models based on animal studies that would argue that deficits should only arise from lesions to the agranular insula and perhaps posterior 13m, we assert that lesions in the central OFC encompassing anterior 13m and posterior 11l might produce substantial deficits on olfactory tasks. Indeed, variations in whether or not this area were lesioned may account for some of the disparities previously seen across different studies (e.g., [59,96]).

9. Summary

Our understanding of olfactory processing in the OFC has advanced remarkably in the last 20 years. Systematic improvements in basic methodology, the development of modern human neuroimaging techniques, and an increasing awareness and interest in olfaction as a viable neuroscience discipline have combined to enhance our knowledge regarding the neural basis of smell. In monkeys, olfactory projection areas have been identified in posterior OFC and portions of agranular insula that are situated along the orbital surface. In humans, the secondary olfactory areas in OFC appear to be located more rostral than the corresponding sites in monkeys, though the significance of this disparity is unclear. While we have articulated several different possible explanations for this difference, future research will be necessary to determine the true source and impact of this apparent difference. Interestingly, a similar pattern of more-anterior-than-predicted activations has been observed in the gustatory modality, where taste stimuli frequently engage OFC areas significantly anterior to the caudolateral OFC region that has been defined as a secondary taste region in monkeys [79].

While not a specific focus of this article, converging physiological and imaging data indicate that, at least at a gross level, the monkey and human OFC respond to similar properties of olfactory stimuli, especially those related to affective, motivational, and associative features (see [33], in press). However, the specific details of where in the OFC these processes are carried out may reveal some significant differences. The most important of these may be a level of processing in more developed areas of cortex that are less directly linked to output pathways associated with species-typical motivated behavior and perhaps more linked to higher-order cognitive operations. Curiously, despite routine claims that the human sense of smell is highly degenerate, the data reviewed here suggest a possibly uniquely human modification or extension of the olfactory pathway. Future efforts to clarify cross-species differences in the localization of olfactory OFC will set important constraints upon the extent to which we can extrapolate between animal and human data and should lead to a better understanding of the role of odor in human brain function and behavior.

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