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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.

Theme: Sensory systems
Topic: Olfactory senses

Keywords: Olfaction; Smell; Orbitofrontal cortex; Comparative neuroanatomy; Functional neuroimaging; Meta-analysis

Contents

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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