Review article

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Functional role of the anterior olfactory nucleus in sensory information processing

Abstract: Olfaction, despite being evolutionarily one of the oldest senses, is complex in structure and function. It can distinguish between trillions of odorants, provides orientation, mediates social interactions, and serves as a warning system. Sensory signals from the periphery are first processed in the olfactory bulb (OB) and then distributed to several olfactory cortical structures. Unlike other sensory modalities, this primary sensory information is not relayed via the thalamus. One prominent olfactory cortical region is the anterior olfactory nucleus (AON), a two-layered structure located within the olfactory peduncle. The AON exerts strong reciprocal connections not only to the OB but also to higher brain areas, e.g., the piriform cortex (PCx), thereby serving as a hub for bottom-up and top-down information processing. However, the functional role of the AON is not well-understood. Here, we provide an overview of recent publications investigating the function of AON in olfactory processing and behavior and present a framework for future research on this fascinating archicortical structure.

Keywords: anterior olfactory nucleus; behavioral function; mouse; olfactory system; sensory processing.

Zusammenfassung: Der Geruchssinn, obwohl er evolutionär zu den ältesten Sinnen zählt, ist komplex in Struktur und Funktion. Er kann Billionen von Geruchsstoffen unterscheiden, gibt Orientierung, vermittelt soziale Interaktionen und dient als Warnsystem. Sensorische Signale aus der Peripherie werden zuerst im olfaktorischen Bulbus (OB) verarbeitet und dann an mehrere kortikale Strukturen verteilt. Im Gegensatz zu anderen sensorischen Modalitäten werden diese primären sensorischen Informationen nicht über den Thalamus geleitet. Eine besonders interessante kortikale Region ist der vordere olfaktorische Kern (AON), eine zweischichtige Struktur, innerhalb des olfaktorischen Pedunkels. Der AON hat starke wechselseitige Verbindungen zum OB, sowie auch zu höheren Hirnarealen, wie z. B. dem piriformen Kortex (PCx), und dient somit als Drehscheibe der olfaktorischen Informationsverarbeitung. Über die genaue funktionale Rolle des AON ist jedoch nur wenig bekannt. Hier geben wir einen Überblick über aktuelle Veröffentlichungen, die die Funktion des AON bei olfaktorischer Verarbeitung und Geruchsverhalten untersuchen, und einen Ausblick in die zukünftige Forschung an dieser faszinierenden archäkortikalen Struktur.

Schlüsselwörter: vorderer olfaktorischer Kern; Verhaltensfunktion; Maus; olfaktorisches System; sensorische Verarbeitung.

Introduction and objectives

Olfaction is of utmost importance for animals and can influence many behaviors, from social interactions and reproduction to foraging and predator avoidance. Despite its relevance for survival and well-being, olfaction remains one of the least studied sensory modalities. In contrast with other sensory systems, olfactory information is distributed directly to primary sensory cortices, bypassing the thalamus. The output cells of the olfactory bulb (OB), the first relay station of olfactory information in the brain, differentially project to several cortical areas. However, the exact nature of the received information and how it is processed and modulated within different areas is yet to be fully elucidated.

One prominent olfactory region is the anterior olfactory nucleus (AON), the most rostral portion of the olfactory cortex, located between the OB and the piriform cortex (PCx) in an area known as the olfactory peduncle. The AON exhibits a unique connection pattern with strong bilateral reciprocal interactions to olfactory areas as well as strong

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input from neuromodulatory and limbic centers. The integration of bottom-up and top-down inputs suggests a prominent role of the AON in olfactory processing. Furthermore, it shows histological changes in the earliest phases of neurodegenerative (Murray et al., 2020; Stevenson et al., 2020) as well as neurodevelopmental disorders (Eltokhi et al., 2021), pointing to the AON's strong potential for translational research. Still, the AON is one of the least understood structures in olfactory processing. Recent advances in neuronal data acquisition and optogenetic techniques have enabled new studies investigating the AON's functional role in different aspects of olfactory processing, leading to surprising results. Here, we provide a short overview of the recent literature and identify missing pieces of knowledge on this interesting olfactory brain area.

Anatomy and connectivity

The AON possesses neither a nuclear structure nor a characteristic three-layered cortical organization. The two AON layers are organized similarly and harbor principal cells that physiologically and anatomically resemble piriform neurons. Therefore, the AON is sometimes referred to as the anterior olfactory cortex, although AON remains the most widely used terminology.

Since the anatomy of AON has been reviewed extensively in an excellent review by Brunjes et al. 2005, we will only briefly summarize the most important features. Histologically, the AON consists of two zones, *pars externa* and *pars principalis* (Brunjes et al., 2005; Valverde et al., 1989). *Pars principalis* neurons comprise the majority of the AON cell population (Brunjes et al., 2011) and can be further subdivided into four regions based on their cardinal location, *pars dorsalis, pars medialis, pars lateralis, and pars ventralis* (also often referred to as *pars ventroposterioralis*). *Pars externa* and the subregions of *pars principalis* strongly diverge in terms of cytoarchitecture and connectivity, arguing that they might serve different olfactory processing functions. Similar to the PCx, the olfactory input to AON *pars principalis* is not topographically organized. By contrast, the sensory activation of *pars externa* resembles the topography of the OB, at least along the dorsoventral axis, i.e., dorsal OB regions target dorsally located cells in the AON (Schoenfeld and Macrides, 1984; Scott et al., 1985). On the functional side, *pars externa* was shown to represent changes in odorant concentration, whereas *pars principalis* does not (Kay et al., 2011). However, how other olfactory stimulus features are encoded within each subdivision is yet to be investigated, and there is, in general, little information about how the AON

responds to olfactory stimuli. One study showed that individual AON neurons can be activated by a wide variety of odorants and odor mixtures (Lei et al., 2006) both from the ipsilateral and the contralateral (via the anterior commissure) nostril (Kikuta et al., 2008). The broader response profile of the AON neurons when compared to OB output cells supports the synaptic convergence of differentially tuned OB projection neurons and the hypothesis that complex odor representations or "gestalts" are created at this level (Haberly, 2001).

Besides the input from the OB, AON's activity can be further shaped by cortical feedback from the PCx, neuromodulatory input from the basal forebrain (Rothermel and Wachowiak, 2014; Zaborszky et al., 2012), and limbic projections from the hippocampus (Aqrabawi and Kim, 2018a; Cenquizca and Swanson, 2007) and the amygdala (Petrovich et al., 1996; Pardo-Bellver et al., 2012) (Figure 1). Also here, differences between AON subdivisions can be observed, e.g., the ventral hippocampus preferentially targets the AON *pars medialis*. The AON represents the largest source of cortical glutamatergic feedback to the OB, and different subdivisions display distinct projection patterns. Most AON subdivisions project bilaterally, except for *pars externa*, sending projections almost exclusively to the contralateral OB. Conversely, *pars medialis* preferentially targets the ipsilateral side. Feedforward projections to the anterior PCx arise predominantly from *pars lateralis*, whereas the posterior PCx is mainly innervated by *pars medialis* (Haberly and Price, 1978). Despite these clear input–output differences of the AON subdivisions, so far, most functional studies have treated the AON as a single entity.

Functional roles of the AON

In recent years, the AON has been implicated in a variety of functions, mostly reflecting its connectivity within and outside the olfactory system. Here, we briefly introduce behaviorally relevant AON functions, including social odor processing, episodic odor memory, interhemispheric communication, and sensory gating (Figure 2).

Social odor processing

Social behavior, i.e., behavior toward conspecific animals, is mediated predominantly via the accessory olfactory system but several social behaviors could also be attributed to the main olfactory system. One of these behaviors is social recognition, the ability to remember an already encountered
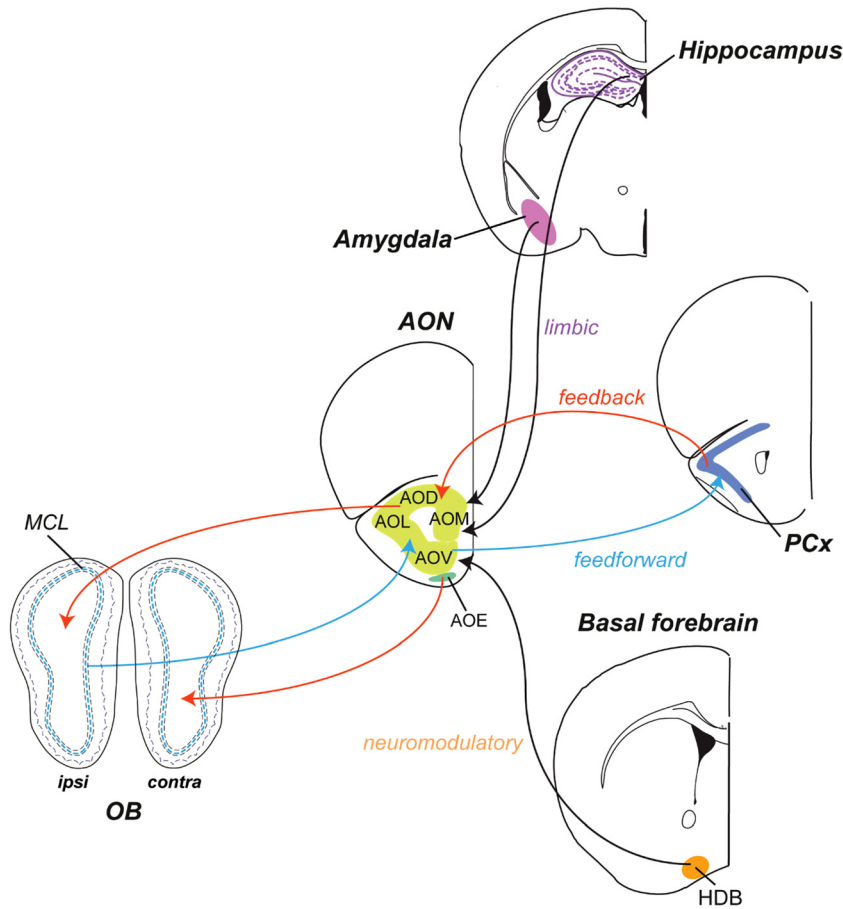
Figure 1: AON input-output connections. As part of the olfactory cortex, the AON is directly innervated by mitral and tufted cells, the principal neurons of the OB. The AON projects in a top-down fashion back to the OB. The AON is the only area sending projections to both the ipsi- and contralateral OB side. Within the bottom-up sensory pathway, the AON projects to other olfactory cortical structures, most notably the PCx with whom it also shares reciprocal connections. AON activity can be strongly regulated by neuromodulatory input from the basal forebrain and limbic projections originating from hippocampus and amygdala. AON, anterior olfactory nucleus; AOD, AON *pars dorsalis*; AOM, AON *pars medialis*; AOL, AON *pars* lateralis; AOV, AON *pars ventralis*; AOE, AON *pars externa*; PCx, piriform cortex; OB, olfactory bulb; MCL, mitral cell layer; HDB, horizontal limb of the diagonal band of Broca.

animal. Oxytocin and vasopressin are neuropeptides involved in the regulation of socially relevant olfactory behaviors including social recognition (Wacker and Ludwig, 2012). Receptors for both oxytocin and vasopressin have been found in the AON (Tribollet et al., 1988; Vaccari et al., 1998), rendering it a strong candidate for cortical integration of social contexts. Indeed, AON projections to the OB are activated in response to thalamic oxytocin release (Oettl et al., 2016) and are capable of modulating OB output activity. The deletion of AON oxytocin receptors had a detrimental effect on the recognition of conspecifics, supporting that this pathway is both physiologically and behaviorally relevant (Oettl et al., 2016).

Similar to oxytocin, vasopressin signaling in the AON has been implicated in social recognition (Wacker et al., 2011; Wacker and Ludwig, 2019). Whether vasopressin also regulates social processing via AON feedback to the OB remains to be investigated. The presence of vasopressin cells in the OB and the AON has also been reported, and vasopressin OB neurons have also been implicated in mediating social recognition (Suyama et al., 2021; Tobin et al., 2010).

Episodic odor memory

So far, most functional studies treated the AON as a single entity. The study by Aqrabawi et al. in 2016 was the first to focus on a specific AON subdivision (*pars medialis)*, almost exclusively projecting to the ipsilateral OB. The study revealed that the AON is capable of modulating olfactory-dependent behaviors via its OB projections, and that AON activity itself is influenced by limbic input from the ventral hippocampus, demonstrating a hippocampus-AON-OB pathway. Later studies demonstrated that hippocampal projections are not exclusive for *pars medialis*, but that these innervations are topographically organized, with ventral parts of the hippocampus targeting medial AON portions and dorsal/intermediate areas projecting more laterally in the AON (Aqrabawi and Kim, 2018a). Hippocampal projections were further shown to supply the AON with contextual information necessary for the recollection of odor memories associated with spatiotemporal cues (Aqrabawi and Kim, 2018b; Levinson et al., 2020), proposing the AON as a potential episodic odor memory storage site (Aqrabawi and Kim, 2020). These proposed higher order
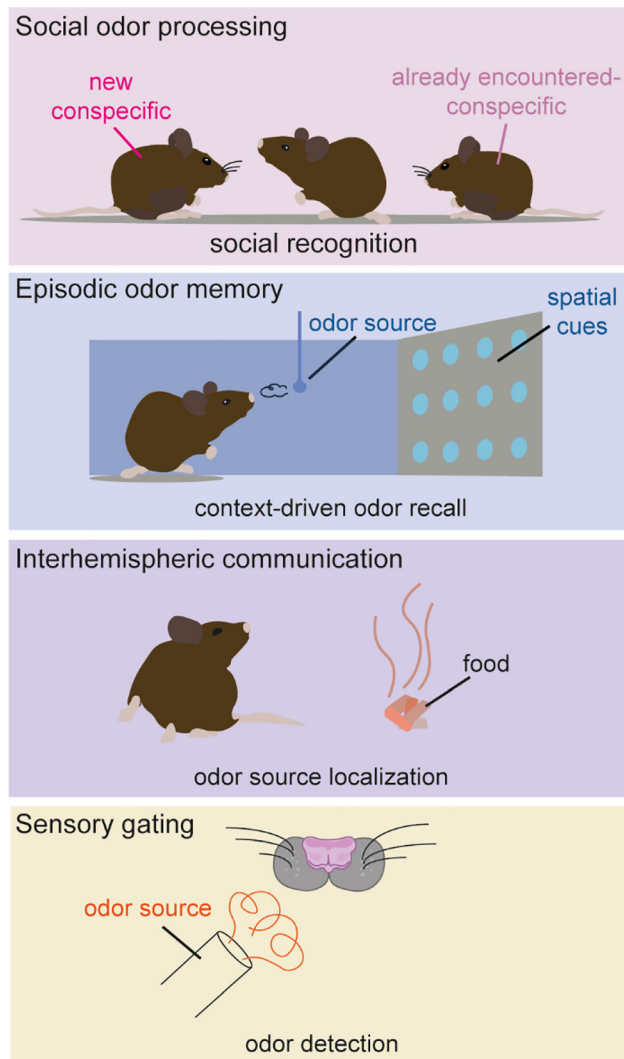
Figure 2: AON modulation of olfactory behaviors. The AON has been implicated in different functions, including regulation of social interactions, recollection of context-dependent odor memories, interhemispheric communication to support odor source localization, and influencing olfactory detection by gating olfactory signal transmission to the cortex.

AON functions are surprising, given that classically the PCx was believed to function as the first real olfactory associative cortex and the site of convergence for olfactory and multimodal information (Haberly, 2001). Only very recently, PCx was shown to also encode spatial information, however, to guide navigation, rather than memory recollection (Poo et al., 2022).

Interhemispheric communication

The AON is the only structure in the olfactory system that sends and receives information from the contralateral hemisphere (Brunjes et al., 2005). These interhemispheric projections might mediate perceptual unity (i.e., odors being perceived as the same, irrespective of the nostril the information is taken up) or direction sensing (i.e., locating odor objects based on differences between the inputs from the two nostrils). *Pars externa* projecting predominantly to the contralateral OB and the contralateral *pars dorsalis* (Illig and Eudy, 2009) is thought to interconnect mirror-symmetric OB output neurons, thus building a mechanistic basis for perceptional unity (Grobman et al., 2018). Furthermore, the AON *pars externa* compares ipsinostril to contranostril odor inputs (Kikuta et al., 2010), enabling odor source localization, and AON activation in awake animals led to a reorientation of the animal's nose toward an odor source (Esquivelzeta-Rabell et al., 2018). The AONs function in integrating odor and spatiotemporal cues argue for a role in odor orientation and foraging behavior.

Sensory gating

By demonstrating that the activation of *pars medialis* reduces olfactory detection sensitivity, Aqrabawi et al., 2016, provided first evidence that the AON is capable of gating olfactory signals. Our group reported that the AON activation impaired the trained behavioral response to olfactory stimuli. This strong behavioral inhibition was observed across a wide range of odorants and concentrations. Electrophysiological recordings supported these findings, as AON activation significantly reduced odor-evoked output activity in anesthetized as well as awake mice (Medinaceli Quintela et al., 2020). Thus, the AON seems capable of interfering with olfactory signal transmission to cortex, most likely through the direct activation of local OB inhibitory interneurons and subsequent inhibition of projection neurons (Markopoulos et al., 2012). Since AON projections to the OB are odor-specific (Rothermel and Wachowiak, 2014), their activation may support odor habituation, i.e., the active adaptation to continuously present odorants to favor the detection of novel stimuli (Li, 1990; Li and Hertz, 2000), a process that has been shown to depend on glutamate release onto OB cells (Chaudhury et al., 2010). However, AON projections to the OB are also modulated by input from higher brain areas such as the hippocampus (Aqrabawi et al. 2016) and neuromodulatory inputs from the basal forebrain (Rothermel and Wachowiak, 2014), a region strongly associated with attentional processes. Thus, the basal forebrain-AON-OB pathway might direct attention to relevant stimuli while suppressing the detection of known odorants.

Pathophysiological implications

Olfactory dysfunctions can be observed in neuro-developmental disorders (Hartig et al., 2021; Tonacci et al., 2017), mental health conditions (Daniels and Vermetten, 2016; Vermetten et al., 2007), and early stages of neuro-degenerative diseases. The AON has been linked to Alzheimer's (Saiz-Sanchez et al., 2010; Saiz-Sanchez et al., 2013) and Parkinson's disease (Pearce et al., 1995; Ubeda-Banon et al., 2017) in both animal models and postmortem human tissues, where an accumulation of misfolded proteins and cell loss was observed (Pearce et al., 1995). Aggregates were not only restricted to neurons but also found in non-neuronal AON cell types, especially microglia (Stevenson et al., 2020). The AONs contribution to neuro-developmental disorders and mental health conditions is a hot topic and currently under investigation.

Outlook

We have come a long way from the assumption of the AON being a unimodal feature correlator (Haberly, 2001) to the various higher order functions, as proposed of today. Recent research has implicated the AON in social context, odor memory, directional and interhemispheric sensing, and gating of the OB output. These different functions seem to be at least partially attributable to different AON subsections, e.g., *pars externa* with a strong connection to interhemispheric information exchange (Grobman et al., 2018) and *pars medialis* for the integration of contextual information (Aqrabawi and Kim, 2018b). Future studies will help to elucidate these functions further by specifically studying the differences between AON subsections.

Interestingly, many of the so-far proposed AON functions are connected to its projections to the OB, e.g., the role in oxytocin-mediated social recognition and odorant output gating. However, the AON has extensive projections not only to olfactory areas such as the PCx, olfactory tubercle, and lateral entorhinal cortex but also to the hypothalamus, basal forebrain, and striatum (Brunjes et al., 2005). So far, these connections have hardly been examined in a functional context. Doing so will provide further insight into the importance of the AON for behavior.

Increasing our knowledge of the AON is of great importance not only to understand olfactory behavior, but also to reveal its role in pathology including neuro-degenerative diseases or neurodevelopmental disorders.

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