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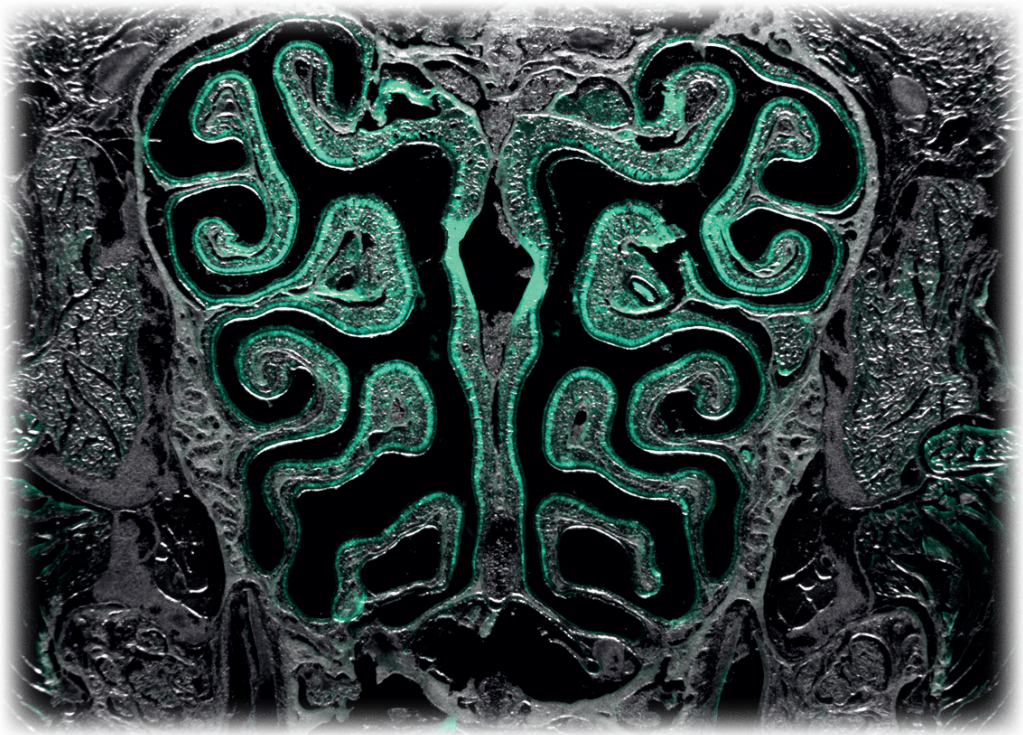

SPECIAL ISSUE:
OLFACTORY PROCESSING

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2023

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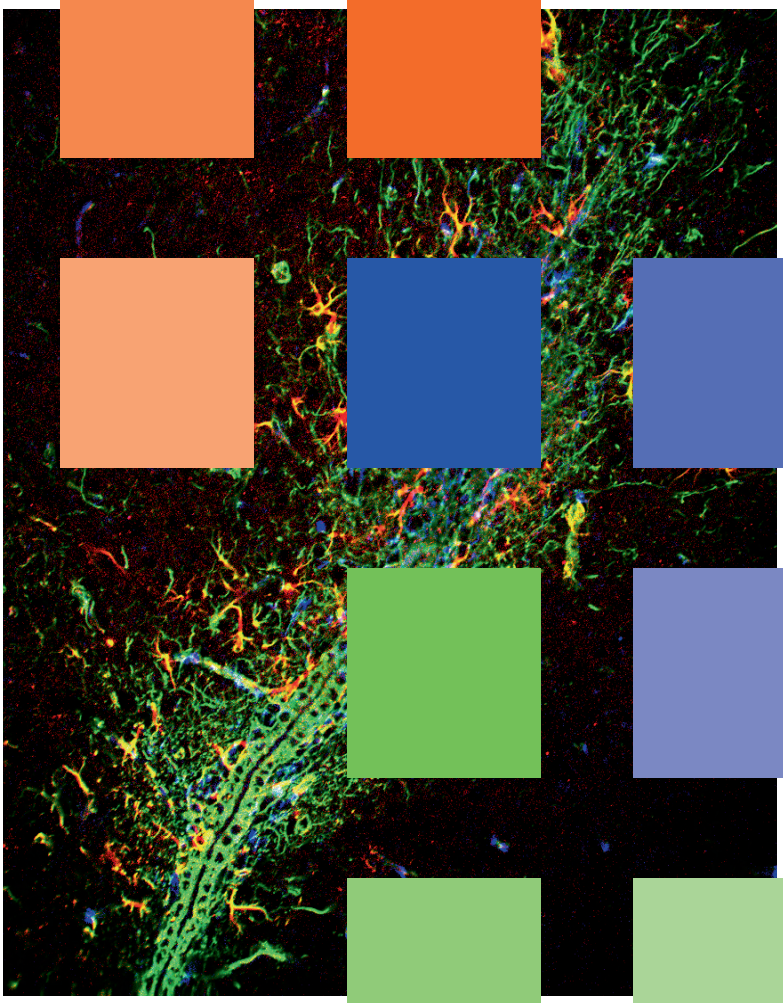

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Translational Neuroscience Lecture
of the Gertrud Reemtsma Foundation
Mathias Jucker | **Tübingen, Germany**
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COVER ILLUSTRATION Coronal cryosection of the head of an adult OMP-GFP mouse. Mature olfactory sensory neurons express GFP (turquoise). Fluorescence along both the nasal septum and endoturbinates illustrates the vast surface of sensory epithelium the lines the mouse nasal cavity. Cover illustration provided by Prof. Dr. Marc Spehr.

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Contents

Marc Spehr* and Ileana L. Hanganu-Opatz*

Editorial

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The air around us is full of information. With every inhalation, we (as well as other mammals) constantly sample our environment to make sense from the scents that surround us. The nose is an exquisite sensor and our brain, of course, is still the most powerful processing unit known. Obviously, the olfactory system faces a daunting task in detecting and discriminating a virtually limitless number of odor molecules – from the rich bouquet of a full-bodied red wine, to the distinctive stench of decaying flesh. Olfaction also is an evolutionary success story. Probably our most ancient sense, olfactory processing bypasses the conventional thalamocortical route. Instead, projection neurons from the main (and, in most mammals, accessory) olfactory bulb directly target phylogenetically old allocortical areas and limbic regions. Thus, our sense of smell lacks thalamic sensory filtering and, instead, provides a direct gateway to our emotional brain and access to subconscious memories. Developmentally, olfaction is among the very first senses functionally mature at birth. And while it is crucial for any mammalian neonate to navigate towards the nipple to locate its first food source, any parent will concur that the smell of a newborn is almost addictive. Olfaction, therefore, can teach us an awful lot about general sensory processing, but also about early development of sensory circuits, information processing in ancient cortical and limbic structures, and how odors guide social and reproductive interactions.

This Special Issue aims to provide a state-of-the-art overview on recent discoveries in mammalian olfaction and to highlight multiple aspects of olfactory processing from the periphery to neocortical areas. Moreover, the six articles in this issue of neuroforum cover a broad span of olfaction research and approach this topic from different perspectives. The authors identify several open questions of critical relevance and, accordingly, this Special Issue is intended as a point of inspiration for future investigations.

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Already at the level of the olfactory epithelium inputs are modulated. An article by Ivan Manzini highlights the contributions of diverse olfactory epithelium cell types to odor processing in vertebrates. Ivan Manzini pays special attention to the modulatory mechanisms that profoundly shape odor signals before they are relayed to the olfactory bulb. At this first stage of central odor processing, information is transformed into neural activity maps with unique spatiotemporal features. Here, the ability of mammals to recognize a known conspecific by its individual body odor, generally described as social memory, is rooted. The article by Hajime Suyama, Veronica Egger and Michael Lukas reviews how olfactory processing contributes to social memory. The authors' focus is laid on the vasopressin system, as an example of how neuromodulation improves olfactory perception of conspecific signatures.

Not only since the pandemic and the link between COVID-19 and hypo-/anosmia, a wealth of studies documented the modulation of olfactory perception and the consequences for day-to-day life. In her article, Annika Cichy summarizes our current knowledge about this topic and documents how metabolic, endocrine and social states impact olfactory abilities. While most available data originates from work in mice, findings are instrumental for understanding the relationship between olfactory impairment and human disorders, such as infections or neurodegenerative diseases.

Considering the behavioral relevance of olfactory cues for 'tracking tasks' such as food or mate localization, or escape from predators, the need to discern spatial information from odor cues becomes obvious. Tobias Ackels reviews how dynamically fluctuating odors enable navigation. Such complex behaviors require information processing not only in the olfactory bulb, but also within several downstream areas. The role of the anterior olfactory nucleus, the most rostral part of the olfactory cortex that links olfactory bulb and piriform cortex, is addressed by Renata Medinaceli Quintela, Daniela Brunert and Markus Rothermel. Moreover, the article by Johanna Kostka and Sebastian Bitzenhofer reviews how olfactory stimuli activate large scale neuronal networks involved in cognitive processing throughout life and highlights the underestimated value of olfactory processing for neurodevelopmental disorders.

This Special Issue provides a comprehensive overview on the still rapidly expanding field of olfactory research and identifies future directions. The non-specialist reader might be surprised by how much we still have to learn about signal detection, transduction, and modulation in peripheral olfactory sensory tissues. In addition, numerous questions on input-output transformation in the olfactory bulb network remain to be answered, with odor-guided navigation just representing the tip of the iceberg. The coming decades in olfactory research will aim to reveal the link(s) between olfactory deficits and devastating diseases such as Alzheimer's or Parkinson's, uncover the roles of olfactory input in determining neonatal brain development, and dissect the individual functions exerted by the many mitral cell target regions that collectively comprise the olfactory cortex. Clearly, the future is bright for olfactory research.

Review article

Ivan Manzini*

Perireceptor events and peripheral modulation of olfactory signals in the olfactory epithelium of vertebrates

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Abstract: The olfactory epithelium (OE) and its associated perireceptor space, i.e., the mucus layer (ML) covering the epithelium, are the most peripheral parts of the vertebrate olfactory system. The olfactory receptor neurons (ORNs), one of the cell types of the OE, are the odorant detectors of the olfactory system. These bipolar neurons extend their apical appendages, which express odorant receptors, into the ML. The binding of odorants to odorant receptors is the initial step of odor processing. The vast majority of research on the peripheral olfactory system has focused on the ORNs and the molecular components of the olfactory transduction cascades. Less attention has been directed to the other cell types of the OE and their physiological functions. For a long time, it was assumed that the olfactory signals detected in the OE are transmitted to the olfactory bulb without preprocessing, but this view turned out to be oversimplistic. It has been shown that the olfactory signals are critically modulated already in the OE. Despite compelling evidence, many descriptions of the olfactory system still ignore the existence of these peripheral modulatory mechanisms. The importance of peripheral modulation of the olfactory signals, the physiological functions of the other epithelial cell types, the extrinsic innervation of the olfactory mucosa, and the perireceptor space are only slowly coming into focus in the olfactory research. Furthermore, several intraepithelial signaling pathways that signal epithelial damage and initiate regenerative processes have recently been discovered. This review provides a concise overview of the current knowledge of peripheral events in the olfactory mucosa and the perireceptor space.

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Keywords: modulatory substances; mucus; odorant binding proteins; olfactory system; xenobiotic metabolizing enzymes.

Zusammenfassung: Das olfaktorische Epithel und der zugehörige Perirezeptorraum, d. h. die Schleimschicht, die das Epithel bedeckt, sind die peripheren Teile des olfaktorischen Systems der Vertebraten. Die olfaktorischen Rezeptorneuronen, eine der Zellarten des olfaktorischen Epithels, sind die Geruchsdetektoren des olfaktorischen Systems. Diese bipolaren Neuronen erstrecken ihre apikalen Fortsätze, die Geruchsrezeptoren exprimieren, in die Schleimschicht. Die Bindung von Geruchsstoffen an Geruchsrezeptoren ist der erste Schritt der Geruchsverarbeitung. Der Großteil der Forschung über das periphere olfaktorische System hat sich auf die olfaktorischen Rezeptorneuronen und die molekularen Komponenten der olfaktorischen Transduktionskaskaden konzentriert. Den anderen Zelltypen des olfaktorischen Epithels und ihren physiologischen Funktionen wurde weit weniger Aufmerksamkeit geschenkt. Lange Zeit ging man davon aus, dass olfaktorische Signale, die im olfaktorischen Epithel erkannt werden, ohne Vorverarbeitung an den Bulbus olfactorius weitergeleitet werden, doch diese Ansicht erwies sich als zu vereinfacht. Es hat sich gezeigt, dass olfaktorische Signale bereits im Epithel entscheidend moduliert werden. Trotz überzeugender Beweise vernachlässigen viele Beschreibungen des olfaktorischen Systems immer noch die Existenz dieser peripheren Modulationsmechanismen. Erst sehr langsam rückt die Bedeutung der peripheren Modulation von olfaktorischen Signalen, die physiologischen Funktionen der anderen Zelltypen des olfaktorischen Epithels, die extrinsische Innervation der olfaktorischen Mukosa und der Perirezeptorraum in den Fokus der Riechforschung. Darüber hinaus wurden in den letzten Jahren mehrere intraepitheliale Signalwege entdeckt, die Epithelschäden signalisieren und Regenerationsprozesse einleiten. Dieser Übersichtsartikel gibt einen prägnanten Überblick über den aktuellen Wissensstand zu peripheren Ereignissen in der olfaktorischen Mukosa und dem Perirezeptorraum.

Schlüsselwörter: Enzyme des xenobiotischen Stoffwechsels; Geruchsstoffbindeproteine; modulatorische Faktoren; Mukus; olfaktorisches System.

Introduction and objectives

The sense of smell is fundamental to the vast majority of animal species. For most species, it is important for orienting in space, finding food and mating partners, avoiding potential predators, and/or detecting any kind of danger (Ache and Young, 2005). The cellular system underlying the sense of smell, i.e., the olfactory system, is optimally designed to detect odorant molecules in the environment, process the information received, and, in turn, trigger behavioral changes and/or hormonal responses (Ache and Young, 2005; Manzini et al., 2022).

The anatomy, cellular and molecular composition, and functioning of the olfactory system of different vertebrate species are remarkably similar (Ache and Young, 2005; Manzini et al., 2022). In vertebrates, olfactory systems generally consist of an olfactory epithelium (OE; peripheral detector), an olfactory bulb in the anterior telencephalon (relay and processing center), and various higher olfactory centers (terminal processing areas; Manzini et al., 2022). Although most fishes have a single OE and olfactory bulb, later diverging vertebrates generally have two or more anatomically segregated olfactory subsystems, the most prominent being the main and the accessory olfactory systems (Manzini et al., 2022).

For a long time, it was assumed that the olfactory receptor neurons (ORNs) in the OE merely function as odorant detectors and transmit the olfactory signals to the olfactory bulb without preprocessing. During the last decades, however, it has become increasingly clear that an initial processing and modulation already occur in the periphery, i.e., within the OE (Bryche et al., 2021; Hall, 2011; Lucero, 2013; Palouzier-Paulignan et al., 2012; Rotermund et al., 2019). Despite this proven evidence, the vast majority of studies about the olfactory system still infer that the olfactory information leaves the OE unprocessed. A variety of perireceptor events (Getchell et al., 1984b; Heydel et al., 2013, 2019; Pelosi and Knoll, 2022; Schilling, 2017), i.e., crucial events that occur in the mucus layer (ML) of the OE in close proximity to the odorant receptors are also not considered in most descriptions of the olfactory system.

In future research, it will be necessary to focus more on the olfactory periphery and the peripheral processes that take place in the olfactory system. The aim of this review is to provide an up-to-date and concise overview of the diverse modulatory and processing pathways within the OE and the processes occurring in the perireceptor space of the ML.

Anatomy and cellular composition of the peripheral olfactory organ

Vertebrate olfactory epithelia are composed of three main cell types: (i) ORNs, (ii) supporting cells, and (iii) neuronal stem cells, so-called basal cells (Manzini et al., 2022; see Figure 1).

The ORNs are the primary detectors of odorants. Upon binding of an odorant to an odorant receptor (for detailed information about vertebrate odorant receptors, please see Manzini et al., 2022), a transduction cascade is initiated,

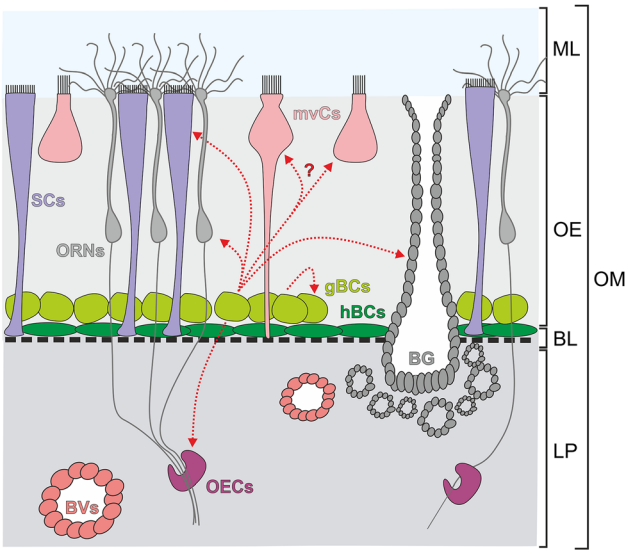

Figure 1: Structure and cell types of the vertebrate olfactory mucosa. The olfactory mucosa (OM) is made up of the olfactory epithelium (OE) and the underlying lamina propria (LP), a thin layer of connective tissue. The OE and the LP are separated by a basal layer (BL) (dotted line). The OE is covered by a sizable mucus layer (ML). The ML contains the apical appendages of olfactory receptor neurons (ORNs) and supporting cells (SCs) and the openings of the Bowman's glands (BGs). The main cell types of the OE are ORNs, SCs, and horizontal basal cells (hBCs) and globose basal cells (gBCs). The OE also contains several nerve terminals (shown in Figure 3). The OE of rodents additionally contains different subtypes of the so-called microvillar cells (mvCs). The ORNs have a limited life span and are constantly replaced by the pool of proliferative gBCs. Basal cells are probably also capable of replacing all other cell types of the OE (see red dotted arrows). The LP contains axons of ORNs, olfactory ensheating cells (OECs), blood vessels (BVs), and nerve terminals (shown in Figure 3). The figure has been adapted from (Manzini et al., 2022).

the ORN typically depolarizes and, in turn, sends olfactory signals toward the olfactory bulb encoded in action potentials (Manzini et al., 2022). While up to five morphological subtypes of ORNs can be present in the OE of fishes, the OE of terrestrial vertebrates harbors up to three morphological ORN subtypes (Manzini et al., 2022).

The supporting cells have structural functions, insulate ORNs, and are responsible for different maintenance tasks within the OE (Manzini et al., 2022). Lately, it has become increasingly evident that in addition to the abovementioned functions, supporting cells are also critically involved in the modulation and processing of odorant responses, i.e., they are drastically involved in the fine-tuning of odorant-induced responses of ORNs (Bryche et al., 2021; Lucero, 2013). Various subtypes of supporting cells have been described in vertebrates, and especially in aquatic species, some subtypes are essential for the production of the olfactory mucus (Manzini et al., 2022; Weiss et al., 2021).

Basal cells are the stem cells of the OE that give rise to new ORNs, as well as other epithelial cell types, throughout the life of an animal. This way, the dying epithelial cells are replenished (Brann and Firestein, 2014). In rodents, at least two subtypes of basal cells, i.e., globose basal cells and horizontal basal cells, have been reported (Brann and Firestein, 2014).

In addition to these invariably present cells, depending on the species, olfactory epithelia often include additional cells types (e.g., microvillar cells in rodents; Hansen and Finger, 2008; Lucero, 2013), olfactory glands (Bowman's glands in terrestrial species; Getchell and Getchell, 1992; Getchell et al., 1984a), and numerous nerve terminals (Getchell and Getchell, 1992; Lucero, 2013; see Figures 1, and 3).

The surface (apical side) of the OE of both aquatic and terrestrial vertebrates is covered by an ML (Manzini et al., 2022; Menco, 1980; see Figures 1, 2, and 3). The ORNs extend their apical appendages that express odorant receptors into the ML. In this layer, often also named perireceptor space (Getchell et al., 1984b; Heydel et al., 2013, 2019; Pelosi and Knoll, 2022; Schilling, 2017), the odorant–odorant receptor interactions take place (Manzini et al., 2022). On its basal side, the OE terminates at the basal lamina, a protein layer that divides the OE from the lamina propria. The lamina

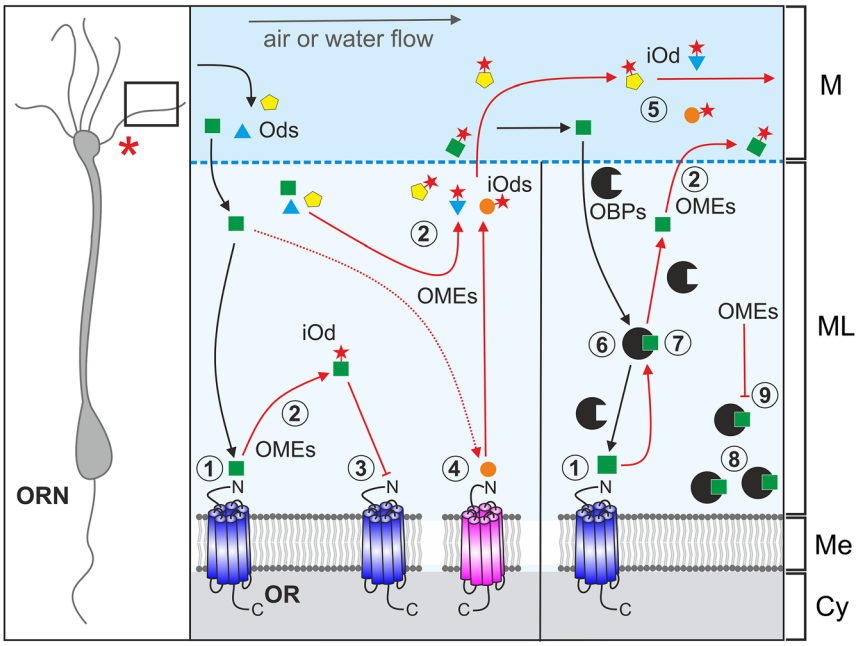

Figure 2: Perireceptor events in the mucus layer of the vertebrate olfactory epithelium. Schematic representation of an olfactory receptor neuron (ORN; left part of the figure). The black rectangle (red asterisk) indicates the area within the mucus layer (ML) of the olfactory epithelium (OE), which is schematically shown on the right side of the figure. Odorants (Ods) reach the olfactory mucus within an air or water stream (terrestrial or aquatic species; M, olfactory medium) that flows over the ML. Odorants dissolve in the mucus [but see the probable contribution of olfactory binding proteins (OBPs)] and activate an appropriate odorant receptor (OR) expressed in the ciliary membrane (Me) of ORNs (1; black arrows; Cy, ciliary cytoplasm). The odorant metabolizing enzymes (OMEs) present in the mucus catalyze odorant transformations. Some transformations lead to inactivated odorants (iOds; 2; red arrows) that no longer bind to any OR (3; red line). Other transformations produce new odorants that activate different ORs (4; red dotted arrow). Inactivated odorants leave the ML and are eliminated from the perireceptor space via the air or water stream (5; red arrows). In air-breathing animals, most odorants are volatile and hydrophobic molecules that only hardly dissolve in the aqueous mucus and are hindered from reaching the ORs. OBPs present in the mucus probably facilitate the diffusion of odorants to and from ORs (6, black arrows, and 7, red arrows, respectively). The OBPs possibly also concentrate certain odorants in the mucus (8) and protect odorants against degradation by OMEs (9; red line).

propria is a thin layer of connective tissue containing axons of ORNs, the edges of Bowman's glands, cells (e.g., olfactory ensheathing cells; Chuah and West, 2002), and blood vessels. In addition, several nerve endings of different nerves terminate in the OE and the lamina propria. Together, the OE, the basal layer, and the lamina propria form the olfactory mucosa (Manzini et al., 2022; see Figure 1). The OE is typically surrounded by nonsensory/respiratory epithelium that lacks ORNs and is composed of many other cell types and glands (Menco, 1980, 1983).

Perireceptor events in the mucus layer of the OE

Depending on the habitat of an animal, the odorants reach the OE dissolved in air or water. Thereby, the variations in the amount of air or water flowing over the olfactory surface critically change the concentration of odorants that reach the ORNs in the OE (Wachowiak, 2011). By changing the sniffing rate (terrestrial species) or the swimming velocity (aquatic species), animals can modulate the number of odorant molecules that reach the OE (Wachowiak, 2011). By this way, it is possible to increase or decrease odorant-induced responses of ORNs. In this context, it has been shown that ghrelin, a hormone that is produced to an increasing degree when animals are hungry, enhances the sniffing frequency. It is supposed that this mechanism enhances the detection of food-related odorants (Tong et al., 2011). Once at the ML of the OE, odorants must dissolve in the mucus and find their way to the odorant receptors (Getchell et al., 1984b). Numerous and only poorly understood events take place in the ML before an odorant reaches a suitable odorant receptor and the transduction cascade within ORNs is initiated (Getchell et al., 1984b; Heydel et al., 2013, 2019; Pelosi and Knoll, 2022; Schilling, 2017).

In both aquatic and terrestrial vertebrates, the OE is covered by an ML, having a diameter that ranges from 10 to 35 µm (Menco, 1980). The presence of an ML in terrestrial species is certainly more intuitive as it forms a fluid compartment that separates the olfactory medium (air) from the OE. Most importantly, the mucus protects the epithelium from drying out. Also, the apical appendages of ORNs, which are embedded in the ML, require an aqueous environment to function properly (Yoshikawa et al., 2018). The presence of the ML in aquatic species is less intuitive as the olfactory medium is water and strongly supports the view that the olfactory mucus not only forms a fluid compartment but that it must have additional important functions. The thickness and composition of the ML, without a doubt, influence how fast odorants and potentially toxic substances diffuse in the mucus and reach odorant receptors and the OE. Toxic substances trigger intraepithelial signaling pathways involving different cell types and nerve endings of the OE, leading to increased mucus secretion and thus, exerting a protective effect (Getchell et al., 1988; Lucero, 2013; Yoshikawa et al., 2018). Although in terrestrial vertebrates, the olfactory mucus is mainly produced by Bowman's glands (Getchell and Getchell, 1992; Getchell et al., 1984a), in fishes, the main source of mucus are the so-called goblet cells, characteristic cells that are present throughout the nonsensory and sensory epithelium of the nose (Getchell and Getchell, 1992). The supporting cells are primarily involved in the production of mucus in many fishes and amphibians, but the mucus-secreting supporting cells have also been described in other vertebrate classes (Getchell and Getchell, 1992; Weiss et al., 2021). The olfactory mucus contains lysozyme, glycoproteins, antibodies (Heydel et al., 2013), different water-soluble proteins (the so-called odorant binding proteins (OBPs; Heydel et al., 2013; Pelosi and Knoll, 2022), and a series of xenobiotic metabolizing enzymes (Heydel et al., 2013, 2019; Figure 2). Also, the mucus has a

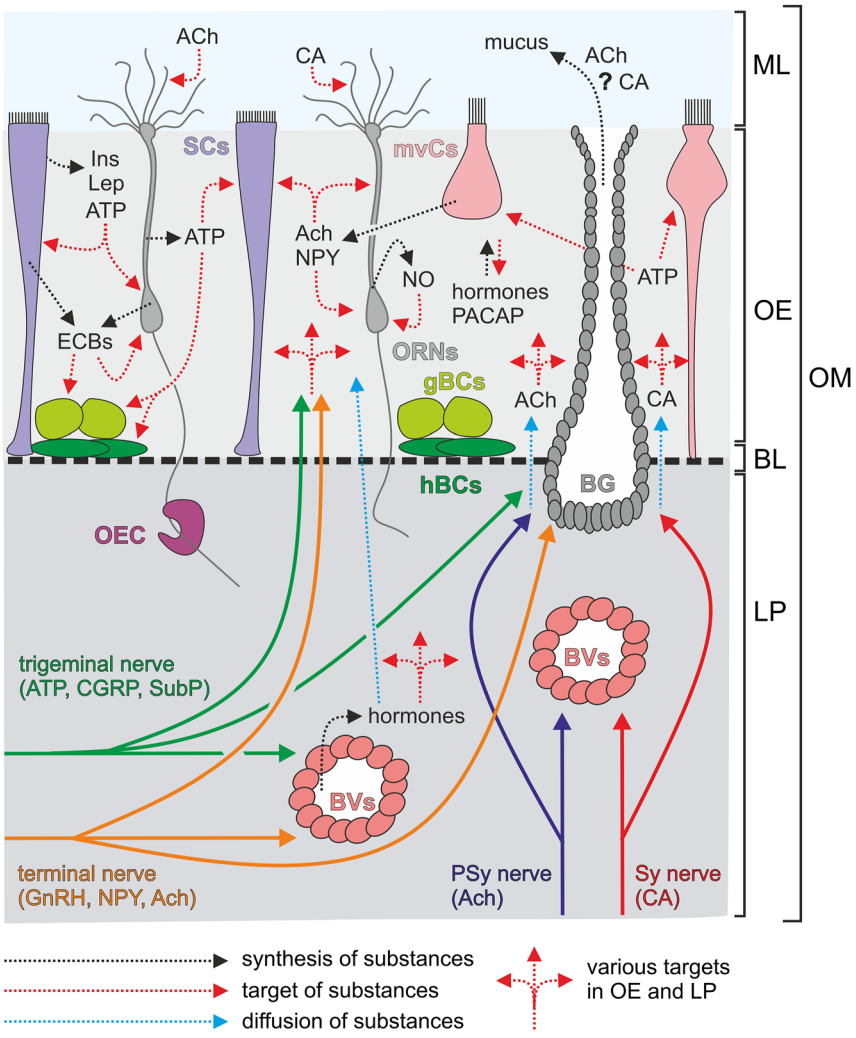

Figure 3: Extrinsic innervation and modulatory signaling pathways in the vertebrate olfactory mucosa. Schematic diagram of the olfactory mucosa (OM), the extrinsic innervation of the olfactory epithelium (OE) and the lamina propria (LP), and the several mucosal modulatory substances. Black dotted arrows indicate the source of modulatory substances, and red dotted arrows indicate the target of the substances. The orange, green, red, and blue arrows represent the extrinsic innervation of the OE and the LP. Hormones and neurotransmitters released in the LP from blood vessels (BVs) and autonomic nerve fibers, respectively, probably diffuse into the OE (cyan dotted arrows). More detailed information about the extrinsic innervation and several mucosal modulatory pathways are given in the main text of the review. The figure has been adapted from (Manzini et al., 2022). Abbreviations: mucus layer (ML); basal lamina (BL); supporting cells (SCs); olfactory receptor neurons (ORNs); globose basal cell (gBCs); horizontal basal cell (hBCs); microvillar cells (mvCs); Bowman's gland (BG); olfactory ensheathing cells (OECs); Sy (sympathetic); PSy (parasympathetic); adenosine triphosphate (ATP); insulin (Ins); leptin (Lep); gonadotropin-releasing-hormone (GnRH); endocannabinoids (ECBs); pituitary adenylate cyclase-activating polypeptide (PACAP); calcitonin gene-related peptide (CGRP); acetylcholine (ACh); catecholamines (CA); nitric oxide (NO); Neuropeptide Y (NPY); substance P (SubP).

characteristic ionic composition that is essential for the proper functioning of olfactory transduction (Manzini et al., 2022).

The OBPs are members of the lipocalin superfamily, a family of proteins dedicated to the transport of hydrophobic molecules (Heydel et al., 2013; Pelosi and Knoll, 2022). Within vertebrates, OBPs have only been found in mammals and an amphibian species (Millery et al., 2005; Pelosi and Knoll, 2022). Data obtained from different mammalian species suggest that OBPs are secreted into the nasal mucus by different nasal glands located in the non-sensory nasal epithelium, the lateral nasal glands, and glands of the nasal septum (Pelosi and Knoll, 2022). Also, it is known that OBPs are synthesized in the vomeronasal organ of rodents, but not in their main OE (Miyawaki et al., 1994). To date, there is no indication that in mammals, OBPs are synthesized in the main olfactory area of the nose, i.e., in the main OE (Pelosi and Knoll, 2022). By contrast, in

the amphibian *Xenopus laevis*, it has been shown that OBPs are synthesized by Bowman's glands of the main OE (Millery et al., 2005). Similar proteins, also named OBPs but having a completely different sequence and structure, are also found in the olfactory system of insects (Pelosi and Knoll, 2022). The presence of OBPs in the olfactory system of species from different animal phyla suggests that these proteins must be involved in ubiquitous olfactory functions. It has been shown that OBPs are able to bind odorants with a rather low affinity (Pevsner et al., 1990). Nevertheless, the exact function(s) of OBPs in the olfactory system of vertebrates are still far from being conclusively clarified. They could be involved in (i) solubilizing volatile (hydrophobic) odorants in the olfactory mucus, (ii) shuttling odorants through the aqueous ML to the odorant receptors, and (iii) eliminating odorants from the ML (Manzini et al., 2022; Pelosi and Knoll, 2022). It has also been proposed that OBPs could protect odorants against degradation by xenobiotic metabolizing enzymes present in the ML (see below) and concentrate certain odorants in the ML (Figure 2).

A very recent review (Pelosi and Knoll, 2022) provides a very comprehensive and extensive overview of mammalian OBPs. This review goes far beyond OBPs and deals with the occurrence and function of lipocalins in general. The authors of this review propose that in contrast to insect OBPs, vertebrate OBPs might be solely involved in the detection of volatile pheromones rather than general odorants, and that some OBPs might act as pheromones themselves. This review is recommended to all readers interested in the physiologic function of these very interesting and highly enigmatic proteins.

Xenobiotic metabolizing enzymes are a large family of enzymes that are involved in the elimination of toxic exogenous substances (e.g., drugs; Heydel et al., 2013) or endogenous substances (e.g., hormones; Heydel et al., 2013). The OE is in direct contact with the external environment, and it is constantly exposed to a plenitude of substances/molecules (Getchell et al., 1984b; Minn et al., 2002). As some substances are potentially harmful to the epithelial cells, the presence of numerous xenobiotic metabolizing enzymes in the OE and the olfactory mucus is not surprising (Heydel et al., 2013, 2019; Schilling, 2017). The supporting cells, Bowman's glands, and ORNs of different vertebrate species have been shown to express various xenobiotic metabolizing enzymes, including cytochrome P450s, glutathione transferase, UDP-glucuronosyltransferases, alcohol dehydrogenases, aldehyde dehydrogenases, etc. (Heydel et al., 2013, 2019; Schilling, 2017). In addition to the xenobiotic metabolizing enzymes, cells of the OE express a broad range of proteins involved in protein folding, antiaggregation, and oxidative stress regulation (Heydel et al., 2019). Those xenobiotic metabolizing enzymes that are capable of also metabolizing odorant molecules are often collectively named odorant metabolizing enzymes (Heydel et al., 2016, 2019). This group of enzymes probably contributes to the clearance of odorants from the OE and helps prevent odorant saturation in the perireceptor space (Heydel et al., 2010, 2019; Figure 2). The activity of odorant

metabolizing enzymes, however, inevitably inflicts changes in the chemical structure of odorant molecules while processing them and thus produces several metabolites of odorants. Some metabolites no longer act as odorants and are, in turn, eliminated from the perireceptor space (Heydel et al., 2013; Thiebaud et al., 2013; Figure 2). Some odorant metabolites can, however, act as new odorants, often on different odorant receptors as the original odorants (Heydel et al., 2013, 2019). This way, the odorant metabolizing enzymes can significantly affect the activation of odorant receptors and the cellular network of the olfactory bulb and thus, significantly affect and shape the perception of odors (Asakawa et al., 2017; Nagashima and Touhara, 2010; Oka et al., 2006; Thiebaud et al., 2013; Figure 2).

Vertebrate tissues and biofluids, including MLs, are generally populated by numerous microorganisms. The composition and function of the microbiomes of various tissues and organs, e.g., the gut, have been extensively studied during the last decades (Berg et al., 2020). By contrast, the knowledge about microorganisms inhabiting the ML of the OE is still limited. Only recently, some studies have dealt with the impact of mucosal microorganisms in the development and functioning of the OE. Epithelial microorganisms have been shown to influence the normal development of the OE, affect the detection of odorants by ORNs, and change the turnover rate of ORNs (François et al., 2016). The metabolites produced by certain microorganisms themselves are odorants, and the presence of microorganisms can influence the expression of xenobiotic metabolizing enzymes (François et al., 2016; Koskinen et al., 2018). In humans, the composition of the nasal microbiome can critically affect the olfactory performance (Koskinen et al., 2018; Kumpitsch et al., 2019). Interestingly, in mice, differences in the gut microbiome can also influence the olfactory preferences and the functioning of the OE (Naudon et al., 2020). Together, the above studies have unambiguously shown that microorganisms present in the ML affect the perireceptor events and modulate the olfactory function.

The question of how odorants and their metabolites are eliminated from the perireceptor space is also still far from being fully understood. Several routes of elimination are plausible. Odorants could be excreted with the help of OBPs, eliminated via the internal nostrils by mucociliary transport (Getchell et al., 1984b), taken up and metabolized by supporting cells and possibly other epithelial cells (Getchell et al., 1984b), or internalized into ORNs together with their specific odorant receptors and then conclusively metabolized in the cytoplasm of these cells (Getchell et al., 1984b; Mashukova et al., 2006; Figure 2).

Processing of odor information and modulation mechanisms in the OE

During the last decades, a growing number of studies have described several intramucosal signaling pathways and modulatory substances that are critically implicated in the processing of olfactory information in the OE (Bryche et al., 2021; Hall, 2011; Lucero, 2013; Palouzier-Paulignan et al., 2012; Rotermund et al., 2019). Also, it has been shown that the different cell types of the OE express specific receptors for several modulatory substances (Bryche et al., 2021; Hall, 2011; Lucero, 2013; Palouzier-Paulignan et al., 2012). Some of these substances directly target ORNs, others exert their effects on other epithelial cell types, and others signal epithelial damage. Together, these signaling molecules and signaling pathways profoundly impact odorant signals before they are transmitted to the olfactory bulb and influence the turnover of epithelial cells (Figures 1 and 3).

The adult olfactory epithelia of vertebrates are generally avascular (Cuschieri and Bannister, 1975). Therefore, substances with potential modulatory effects cannot directly reach the OE via the bloodstream. However, modulatory substances are released into the OE and the subepithelial lamina propria by nerve terminals (Figure 3). In various vertebrates, the lamina propria and its blood vessels, the OE, and the olfactory glands are extrinsically innervated (Getchell and Getchell, 1992; Hall, 2011; Lucero, 2013). The ophthalmic and maxillary branches of the trigeminal nerve and the terminal nerve innervate the lamina propria and the OE (Lucero, 2013; Manzini et al., 2022; Figure 3). The trigeminal nerve endings can release calcitonin gene-related peptide, substance P, and ATP, and the axons of the terminal nerve can release gonadotropin-releasing hormone, acetylcholine, and neuropeptide Y (Getchell and Getchell, 1992; Lucero, 2013; Manzini et al., 2022). In addition, the lamina propria but not the OE, receives sympathetic and parasympathetic nerve endings that release catecholamines (adrenaline, dopamine, and acetylcholine; Getchell and Getchell, 1992; Lucero, 2013; Manzini et al., 2022; Figure 3). The activity of these nerves changes in response to varying physiological or environmental conditions, and correspondingly fine-tunes the responsiveness to odorants of the olfactory system and trigger various epithelial signaling pathways. The released neuropeptides and neurotransmitters (see above) act on cells, blood vessels, and olfactory glands in the lamina propria and affect cells in the OE. In the OE, they activate supporting cells and microvillar cells (see below for more information about this cell type, also see Figures 1 and 3) or

directly modulate the activity of ORNs (Bryche et al., 2021; Hall, 2011; Lucero, 2013; Palouzier-Paulignan et al., 2012; Rotermund et al., 2019). The activation of supporting cells and microvillar cells can, in turn, lead to a release of additional modulatory substances, which in turn can additionally influence the various epithelial cell types (Bryche et al., 2021; Lucero, 2013; Figure 3).

Some elegant studies have contributed to the understanding of how the peptides and transmitters released from nerve endings influence the activity of ORNs. In rodents, odorant-induced responses are enhanced by autonomic neurotransmitters that activate adrenergic receptors expressed on cilia and/or the soma of ORNs (Hall, 2011; Kawai et al., 1999). Also in rodents, acetylcholine activates muscarinergic acetylcholine receptors, coexpressed with odorant receptors on the cilia of ORNs (Hall, 2011), and changes the odorant sensitivity of ORNs (Li and Matsunami, 2011). The presence of cholinergic receptors on ORNs has also been demonstrated in a frog (*Rana ridibunda*) and a salamander species (*Ambystoma tigrinum*; Bouvet et al., 1987; Hedlund and Shepherd, 1983). The activity of the frog ORNs can be modified by acetylcholine and cholinergic antagonists, strongly suggesting that odorant-induced responses can also be affected by acetylcholine (Bouvet et al., 1987). In the OE of rodents, the activation of dopamine receptors on ORNs (Lucero, 2013, and references therein) has been shown to reduce their excitability and their odorant-induced responses (Hegg and Lucero, 2004). Trigeminal nerve fibers of the olfactory mucosa and the nasal nonsensory epithelium are involved in the detection of irritants and noxious stimuli and the initiation of protective reflexes (Silver and Finger, 2009). Stimulated trigeminal nerve endings also release neuropeptides and ATP that, in turn, activate their receptors on ORNs and modulate their sensitivity to odorants (Lucero, 2013, and references therein). In a frog species (*R. ridibunda*), it has been shown that the release of substance P from trigeminal fibers influences the activity and odorant-responsiveness of ORNs (Bouvet et al., 1987, 1988). In rodents, irritative substances induce the release of calcitonin gene-related peptide from trigeminal fibers. The subsequent activation of calcitonin gene-related peptide receptors on ORNs decreases the olfactory responses (Daiber et al., 2013). It is known that most irritants also activate odorant receptors, and the large majority of odorants, to some degree, also act as irritants. This means that the olfactory system and the epithelial trigeminal system are often activated simultaneously and influence each other (Brand, 2006). A cross talk between these two systems has also been reported in humans. The simultaneous presentation of an odorant and a trigeminal stimulus increased the detection threshold for the odorant, i.e., impaired the smelling ability (Daiber et al., 2013). Also, there is some evidence that ATP, released from trigeminal nerve fibers, initiates intraepithelial pathways that signal damage and initiate protective and regenerative processes in the OE (Lucero, 2013, and references therein). Also, the terminal nerve is involved in the modulation of peripheral odorant sensing. In hungry but not in sated axolotl (*Ambystoma mexicanum*), neuropeptide Y, probably released from the terminal nerve, has been shown to boost odorant responses. This mechanism is thought to facilitate foraging (Mousley et al., 2006). During the mating season of axolotls and mudpuppies (*Necturus maculosus*), another amphibian species, ORNs become more sensitive to gonadotropin-releasing hormone, which in turn decreases the sensitivity of ORNs to food odorants (Park and Eisthen, 2003; Zhang and Delay, 2007). In addition, in axolotls and mice, there is some evidence that FMRFamide is released from terminal nerve fibers and impacts the detection of odorant-induced signals in ORNs (Ni et al., 2008; Park et al., 2003).

Several modulatory substances are directly synthesized and released in the OE or diffuse into the OE from the lamina propria. Several receptors for these substances have been detected in the OE. These substances include ATP, endocannabinoids, nitric oxide, gonadotropin-releasing hormone, neuropeptide Y, insulin, orexin, leptin, substance P, calcitonin gene-related peptide, endothelin, and pituitary adenylate cyclase-activating polypeptide (Bryche et al., 2021; Hall, 2011; Lucero, 2013; Palouzier-Paulignan et al., 2012; Figure 3). In addition to the supporting cells, ORNs, gland cells, and basal cells, in the OE of rodents, there are so-called microvillar cells (Manzini et al., 2022). Several subtypes of microvillar cells have been described, all of which seem to be not directly connected to the olfactory bulb, i.e., they are not ORNs (Hansen and Finger, 2008; for reviews, see: Bryche et al., 2021; Lucero, 2013). The physiological functions of these cells have still not conclusively been determined, but there is growing evidence that the microvillar cells are critically involved in various modulatory pathways in the OE (see below).

The above-mentioned modulatory substances trigger a myriad of autocrine and paracrine effects on the different cell types of the OE. They signal epithelial damage, promote regenerative processes, and some of them are directly involved in the processing of olfactory signals (Bryche et al., 2021; Lucero, 2013). In the OE of mice, it has been shown that extracellular ATP, probably released from damaged cells, activates purinergic receptors on various epithelial cell types (Hegg et al., 2003). The overall effect is a suppression of odorant-induced responses of ORNs and

an initiation of neuroprotective and regenerative signaling pathways within the OE (Hegg et al., 2003; Lucero, 2013, and references therein). Similarly, in larval amphibians (*X. laevis*), extracellular ATP has been shown to mainly activate the supporting cells and basal cells (Hassenklöver et al., 2008, 2009) but also some ORNs and initiate a signaling pathway that supports cell turnover within the OE (Hassenklöver et al., 2008, 2009). For a summary of the current knowledge about purinergic signaling in the vertebrate OE and the cross talk of the purinergic system with other modulatory systems, I refer the readers to a recent review (Rotermund et al., 2019).

The presence of an endocannabinoid system has been reported in the OE of larval amphibians (*X. laevis*; Breunig et al., 2010; Czesnik et al., 2007) and mice (Hutch et al., 2015). In *Xenopus*, endocannabinoids that are locally released from ORNs and supporting cells increase the odorant-induced responses of ORNs by lowering their response threshold (Breunig et al., 2010; Czesnik et al., 2007). Thereby, the release of endocannabinoids depends on the hunger state of the larvae. The supporting cells of hungry larvae produce more epithelial endocannabinoids, which in turn increase the odorant sensitivity of ORNs (Breunig et al., 2010). This signaling pathway could support foraging. In mice, the epithelial endocannabinoid system appears not to be involved in the modulation of olfaction, but is rather involved in the regulation of basal cell proliferation (Hutch et al., 2015).

In rodents, it has been shown that odorants and other substances, and cold temperature, activate the microvillar cells, which in turn release acetylcoline that modulates the activity of the supporting cells and ORNs (Jiang et al., 2015; Lucero, 2013). The microvillar cells also release neuropeptide Y upon stimulation by ATP (Lucero, 2013). The application of neuropeptide Y to the OE of rats has been shown to increase the odorant-induced responses of ORNs, but only in hungry rats (Negroni et al., 2012). The gaseous messenger nitric oxide is produced by ORNs and has been shown to be involved in the adaptation of odorant-induced responses of ORNs (autocrine effect; Brunert et al., 2009). Possibly, nitric oxide also has some paracrine functions in the OE (Brunert et al., 2009). For further effects of modulatory substances within the OE, I refer the reader to some very informative reviews (Bryche et al., 2021; Lucero, 2013; Rotermund et al., 2019) and references therein.

The fact that vertebrate epithelial cells also express receptors for circulating hormones, such as ghrelin, adiponectin, arginine-vasopressin, endothelin, leptin, and insulin, in turn, suggests that endocrine mechanisms might also be involved in peripheral modulation of olfactory information and other epithelial signaling pathways (Bryche et al., 2021; Loch et al., 2013, 2015; Lucero, 2013; Figure 3). These hormones are probably transported to the lamina propria by the circulatory system and diffuse into the OE, but some of these hormones are also locally produced by cells within the OE (Bryche et al., 2021; Lucero, 2013). Thus, they can also exert some autocrine and/or paracrine effects in the OE. Ghrelin and adiponectin, known as starvation-related hormones, have been shown to increase the responses of ORNs to odorants (Loch et al., 2013, 2015). Insulin (Lacroix et al., 2008) and leptin, known as anorexigenic hormones, have been shown to decrease the odorant-induced activity of ORNs (Savigner et al., 2009). The receptors for orexin, an orexigenic peptide, have also been localized in the OE of rodents. Thus, orexin could also have direct modulatory effects on odor-induced responses of ORNs (Gorojankina et al., 2007).

Conclusions

Over the past decades, convincing evidence has been accumulated that already in the perireceptor space in the ML and the OE critical modulation and processing of odorant-induced signals take place. In addition, several intraepithelial signaling pathways that signal epithelial damage and initiate regeneration processes have been described. Despite the now established knowledge, most descriptions of the olfactory system still assume that the ORNs in the OE transmit the detected odorant signals to the olfactory bulb unchanged, i.e., without preprocessing. To fully understand the functioning of the olfactory system, we need to deepen our understanding of the peripheral processes that occur in the perireceptor space and the OE. Also, to properly interpret research findings from studies that focus on the higher olfactory centers, i.e., the olfactory bulb and the higher olfactory processing areas, the researcher must take into account that some critical processing of odor signals occurs before the signals reach the olfactory bulb.

With this review article, I would like to draw attention to the very important but often unconsidered modulatory mechanisms that occur in the olfactory periphery. It provides a concise overview of this interesting topic. Hopefully, this review will be beneficial to researchers that work in the field of olfaction and especially to students that are currently beginning to learn about this beautiful sense.

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Bionote

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Review article

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Mammalian social memory relies on neuromodulation in the olfactory bulb

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Abstract: In this review, we aim to integrate our recent findings on the vasopressin system and its role in social discrimination with other known neuromodulatory mechanisms in the olfactory bulb that are involved in different experimental models of social memory. Behavioral paradigms commonly used to investigate odor-related social memory are individual social memory in rodents, lamb recognition in sheep, and the Bruce effect in female mice. All three cases involve neuromodulation in the main and/or the accessory olfactory bulb, the first centers for olfactory processing. As a large diversity of neuromodulators participate in social memory formation, here, we focus primarily on shared neuromodulatory systems and their physiological effects, in particular, the social neuropeptides, vasopressin and oxytocin, and the arousal-related modulators, acetylcholine and noradrenaline.

Keywords: bruce effect; noradrenaline; olfactory bulb; social memory; vasopressin.

Zusammenfassung: In dieser Übersicht wollen wir unsere Erkenntnisse zum Vasopressin-System und seine Rolle bei der sozialen Diskriminierung mit anderen neuromodulatorischen Mechanismen im Bulbus olfaktorius verbinden, die an verschiedenen experimentellen Modellen des sozialen Gedächtnisses beteiligt sind. Paradigmen für geruchsbezogenes soziales Gedächtnis sind die soziale Diskriminierung bei Nagern, die Lammerkennung bei Schafen und der Bruce-Effekt bei weiblichen Mäusen. In allen drei Fällen ist eine Neuromodulation im Haupt- und/oder im akzessorischen Bulbus olfaktorius beteiligt. Da viele verschiedene Neuromodulatoren an der Bildung des sozialen Gedächtnisses beteiligt sind, konzentrieren wir uns hier auf gemeinsame neuromodulatorische Systeme, wie die sozialen Neuropeptide Vasopressin, Oxytocin und die erregungsabhängigen Modulatoren Acetylcholin und Noradrenalin.

Schlüsselwörter: Vasopressin; Soziales Gedächtnis; Bruce Effekt; Olfaktorischer Bulbus; Noradrenalin.

Introduction

Both individual survival and successful reproduction in mammals require proper behavioral responses toward conspecifics depending on their individual characteristics, such as, age, sex, and also familiarity. These responses may range from flight to peaceful cooperation, mating, or territorial aggression (Lukas and de Jong, 2015). Therefore, it is vital to investigate and assess conspecific identities prior to the initiation of social behavior. In various mammals, olfaction is an essential sensory modality to identify environmental stimuli, including conspecific individuals. In this review, we highlight examples of social odor memory, i.e., individual social memory in rodents, lamb recognition in ewes, and the memory formation for the Bruce effect in female mice, as well as the neuromodulatory mechanisms underlying the formation of those memories within the olfactory bulb. The olfactory bulb is the first relay station of olfactory processing, and a disruption of the memory trace there prevents the formation of social olfactory memory downstream, e.g., within the lateral septum, the hippocampus, and the amygdala (e.g. Dantzer et al., 1988, 1990; Terranova et al., 1994).

Paradigms for quantification of social memory in rodents

The term “social memory” is commonly used to describe the ability of animals to recognize a known conspecific or to discriminate known and novel conspecifics. In many

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publications, the terms "social memory", "social recognition", and "social discrimination" are used interchangeably and/or to specify a certain experimental paradigm; here, we refer to "social memory".

Traditionally, researchers quantify social memory abilities of rodents with the so-called habituation-dishabituation test, which can also be used for nonsocial stimuli. The test is carried out by letting subjects investigate the same stimulus several times, until the subjects lose their motivation to investigate the stimulus due to its successful recognition. This effect is called habituation. Again, the subjects show high motivation to investigate a novel stimulus (Thor and Holloway, 1982). Engelmann et al. (1995) introduced an alternative way to quantify recognition ability, the social discrimination paradigm. In the first session, i.e., the sampling phase, a stimulus is briefly introduced (4 min) to a subject for social interaction. After a certain interexposure interval, usually 30 or 60 min for rats and 120 min to 24 h for mice, a known and novel stimulus is simultaneously introduced to the subject. This second exposure is called the discrimination phase. The increased duration of investigation of the novel stimulus relative to the known stimulus serves as a measure of social memory (Engelmann et al., 2011). In this paradigm, the relative comparison between two stimuli allows to exclude the effects of general habituation to the exposure to social stimuli.

Role of the main olfactory bulb and the neuromodulatory mechanisms in social memory

Olfactory bulbectomy in rodents results in massive impairment of social memory, suggesting that olfaction is the primary sensory modality for discriminating individuals (Dantzer et al., 1990). Recent findings imply that social recognition in rodents requires somatosensory as well as auditory cues in addition (preprint, Haskal de la Zerda et al., 2020), thus social memory is likely based on multisensory integration.

The vasopressin and oxytocin neuropeptide systems in the main olfactory bulb have been identified as a major player in modulating social memory because it is shown that vasopressin 1a receptor or oxytocin receptor antagonists injected into the main olfactory bulb impair social memory (Dluzen et al., 1998a; Tobin et al., 2010). The vasopressin involved in social memory modulation in the olfactory bulb originates from intrinsic bulbar vasopressin-expressing cells (Suyama et al., 2021; Tobin et al., 2010). Morphologically, vasopressin cells are a subpopulation of superficial tufted cells (Lukas et al., 2019) and thus a subtype of the principal neurons of the olfactory bulb, i.e., the glutamatergic mitral and tufted cells. These neurons receive sensory information from the nose via excitatory inputs from the olfactory sensory neuron axons that terminate on their apical dendritic tuft (Halász, 1990). However, stimulation of the olfactory nerve causes fast inhibition of vasopressin cells, even though the same stimulation excites the neighboring mitral cells (Lukas et al., 2019). Thus, there is a substantial functional difference between vasopressin cells and mitral cells and other tufted cell subtypes. Moreover, the question arises how vasopressin cells can possibly become activated during social input.

Further investigations have revealed a mechanism that allows to unlock vasopressin cell activity upon coincident neuromodulatory input. The above-mentioned GABAergic inhibition is diminished in amplitude by different modulatory substances, e.g., noradrenaline and acetylcholine (Suyama et al., 2021). Acetylcholine modulation was found to overturn inhibition and enable action potential firing upon olfactory nerve stimulation in the majority of investigated vasopressin cells. The precise mechanism underlying this switchable excitability is not yet known. As to the origin of acetylcholine in the context of social memory, exposure to a conspecific increases the number of activated cholinergic neurons in the horizontal limb of the diagonal band of Broca, the main source of cholinergic neuromodulation in the olfactory bulb (Ojima et al., 1988), indicating that acetylcholine is released from centrifugal projections in the olfactory bulb, presumably during interaction with novel social stimuli (Suyama et al., 2021). Finally, injection of a cholinergic receptor antagonist in the olfactory bulb impairs social memory, but subsequent local injection of vasopressin rescues this effect. Thus, during social stimulation, cholinergic modulation of the olfactory bulb network is likely to stimulate vasopressin release in the olfactory bulb, which thereby enables social memory (Suyama et al., 2021). These findings are supported by experiments in mice (preprint, Müller et al., 2021), in which silencing of cholinergic projections from the horizontal diagonal band of Broca to the olfactory bulb impaired social memory.

Both vasopressin 1a receptors and vasopressin 1b receptors are expressed in various cell types in the main olfactory bulb. Vasopressin 1a receptors are found in the glomerular layer, the mitral cell layer, and the superficial granule cell layer (Tobin et al., 2010). Vasopressin 1b receptors are expressed in the mitral cell layer and the external plexiform layer, as well as on vasopressin cells,

indicating an autocrine pathway (Tobin et al., 2010); indeed, we found vasopressin to reduce the above-mentioned olfactory nerve-evoked inhibition of vasopressin cells (Lukas et al., 2019). Vasopressin application reduces the firing frequency of mitral cells responding to odor stimulation in anesthetized rats *in-vivo* (Tobin et al., 2010) and reduces olfactory nerve-evoked excitation in external tufted cells *in-vitro* (Lukas et al., 2019). These data suggest that vasopressin modulates the excitation–inhibition balance within the local circuits of inhibitory interneurons and projection neurons, probably to increase social odor perception and enable the associated memory formation.

Oxytocin receptors in the olfactory bulb can be found in some periglomerular cells, and the mitral cell and granule cell layers (Sun et al., 2021). Intrabulbar oxytocin administration enhances social memory in mice (Sun et al., 2021). Further, bulbar oxytocin application reduces basal activity and increases responses of principal neurons to odor presentation in awake animals, improving the signal-to-noise ratio, and thereby enhancing the discriminability of conspecific body odors (Sun et al., 2021). Aside from the modulatory effects of oxytocin that acts directly in the olfactory bulb, it was shown in mice that the oxytocin signaling in the anterior olfactory nucleus is also required for social memory (Oettl et al., 2016). Thus, oxytocin originating from the hypothalamus increases the activity of glutamatergic projections from the anterior olfactory nucleus, which in turn excite granule cells in the olfactory bulb, resulting in the increased tonic inhibition of mitral cells. However, mitral cell responses are still increased during odor presentation (Oettl et al., 2016), consistent with the results from Sun et al. (2021). Thus, the effects reported in Sun et al. (2021) might be partly due to the oxytocinergic modulation of these centrifugal inputs.

Intriguingly, vasopressin or oxytocin injection into the main olfactory bulb prolongs social memory in rats, i.e., from 30 min up to a 120 min interval. Further, oxytocin reliably induces an increase in bulbar noradrenaline release. However, oxytocin injection cannot prolong social memory, if bulbar noradrenaline release is disrupted. Thus, social memory prolongation is mediated by oxytocin modulation of noradrenaline release (Dluzen et al., 2000, 1998b).

In summary, social memory in rodents is enabled by a concerted action of various neuromodulatory mechanisms from within the olfactory bulb (Figure 1), but also from projections to the olfactory bulb. While the described mechanisms implement a short-term social memory (hours), we now turn to two examples for long-term maintenance of social memory (days–weeks), highlighting shared features.

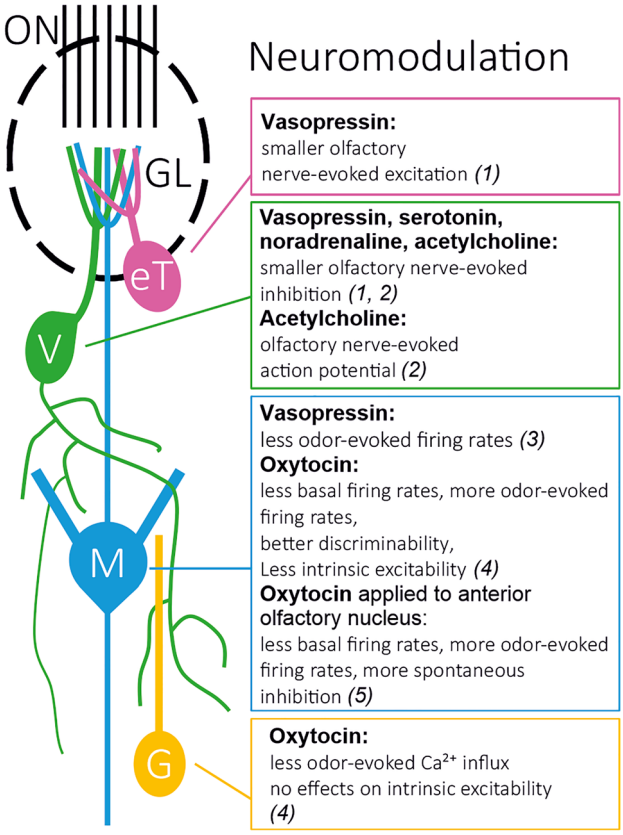

Figure 1: Neuromodulation in the main olfactory bulb related to social memory in rodents. Scheme: overview of cell types in the olfactory bulb network. Abbreviations: eT, external tufted cell; G, granule cell; GL, glomerulus; M, mitral cell; ON, olfactory nerve; and V, vasopressin cell. Boxes: known effects of respective neuromodulators on the electrophysiological activity of cell types in the olfactory bulb network, indicated by color coding and connecting lines. For a detailed description of neuromodulatory effects, please refer to the main text. (1) (Lukas et al., 2019), (2) (Suyama et al., 2021), (3) (Tobin et al., 2010), (4) (Sun et al., 2021), (5) (Oettl et al., 2016).

Lamb recognition in ewes and Bruce effect in female mice

Mammalian mothers, including ewes and mouse dams, must invest massively in the raising of their offspring. The individual memory formed for both, the recognition of their own offspring during lamb recognition and the recognition of a former mating partner during the Bruce effect help to prevent the waste of energy resources and time by the mothers. Thus, lamb recognition that results in aggression toward alien lambs ensures the availability of resources for

the own lamb. Similarly, when highly territorial male mice tend to kill unrelated pups, mouse dams terminate their pregnancy in case they meet a new dominant male, so they can mate directly with the new male.

Lamb recognition is based on the olfactory cues from lambs during or shortly after parturition, is functional already one day after birth, and is maintained until the end of the nursing period (Tschanz, 1962). This specific individual social memory was thoroughly investigated for several decades (review, e.g., Sanchez-Andrade and Kendrick, 2009). Interestingly, vaginocervical inputs and oxytocin, noradrenaline, and acetylcholine signaling in the olfactory bulb of ewes are prerequisites for the establishment of lamb memory (Kendrick et al., 1997a; Lévy et al., 1990, 1997). Accordingly, following birth or artificial vaginocervical stimulation, the concentration of various neurotransmitters and modulators in the olfactory bulb of ewes is increased, including glutamate, GABA, dopamine, oxytocin, noradrenaline, and acetylcholine (Kendrick et al., 1988; Lévy et al., 1993, 1995). Mitral cell responses to own lamb odors are increased after parturition, whereas the same cells respond less to alien lamb odors (Kendrick et al., 1992). Accordingly, it was proposed that noradrenaline release in the olfactory bulb caused by vaginocervical stimulation acts via reduction of GABA release, possibly triggering synaptic plasticity via AMPA and NMDA receptor-mediated mechanisms. Thus, the coincidence of vaginocervical stimulation and lamb-odor stimulation could enhance the synaptic connectivity between lamb-specific mitral cells and local inhibitory neurons, enabling the recognition of own-lamb odor signatures in the long term (Kendrick et al., 1992, 1997b).

Another famous example of social odor-related memory can be observed during the Bruce effect (Bruce, 1959). In female mice, a memory of the pheromonal signature of their mating partner is formed within 3–6 h after copulation (Kaba, 2010), probably via synaptic plasticity at the mitral cell–granule cell reciprocal synapses that enhances recurrent inhibition of mitral cells responsive to the pheromones of the mating partner, thereby suppressing transmission to the medial amygdala (Binns and Brennan, 2005; Kaba, 2010). However, pheromonal signals from other males encountered within five days after mating result in a failure of embryo implantation, i.e., pregnancy block, via inhibition of prolactin release in the periphery, which is essential to maintain corpora lutea function in mice (Bruce, 1959; Kaba, 2010).

Interestingly, noradrenaline levels in the accessory olfactory bulb are elevated following mating, which involves vaginocervical stimulation (Brennan et al., 1995), and noradrenaline signaling in the accessory olfactory bulb is needed for the formation of pheromonal memory retrieved during the Bruce effect (Kaba and Keverne, 1988; Rosser and Keverne, 1985). Moreover, noradrenaline facilitates long-term potentiation at reciprocal mitral cell–granule cell synapses in the accessory olfactory bulb (Huang et al., 2018), providing a potential mechanism for the abovementioned synaptic plasticity.

Also, social behavior-related neuropeptides, such as vasopressin and oxytocin, participate in the formation of this pheromonal memory at the synaptic level in the olfactory bulb (Fang et al., 2008; Wersinger et al., 2008).

Interestingly, pregnancy block phenomena are also found in other mammalian species, e.g., gelada baboons (Roberts et al., 2012), but the contribution of olfaction has not been established so far. However, inexplicable repeated pregnancy loss in women was observed to correlate with altered perception and brain activity in response to male body odor (Rozenkrantz et al., 2020). It remains to be elucidated whether this finding is indeed related to the Bruce effect.

Conclusions

Despite the involvement of many different neuromodulators and their receptors in social memory processes in the olfactory bulb, one shared mechanism is the modulation of the inhibition of projection neurons. Increased inhibition of projection neurons can result in better discriminability of similar odors including individual body odors, e.g., via eliminating potentially distracting weak odor components and/or via decorrelation of similar odor representations (Abraham et al., 2010; Devore and Linster, 2012; Oettl et al., 2016).

Another common mechanism is the involvement of centrifugal modulation via oxytocin, acetylcholine, or noradrenaline. Therefore, both olfactory inputs and different types of neuromodulatory top-down inputs to the olfactory bulb are required for the formation of social memory. These inputs may be triggered by social encounters, including reproduction-related interaction. For example, acetylcholine is thought to be released related to attention and arousal due to the presence of unfamiliar conspecifics (Suyama et al., 2021). During both, i.e., memory formation for lamb recognition during parturition and memory formation for the mate's odor during copulation preceding the Bruce effect, vaginocervical stimulation is the obvious additional input provided by a social partner that could facilitate memory formation via noradrenaline release. The sources of acetylcholine and noradrenaline release in the olfactory bulb, the diagonal band of Broca and the locus coeruleus, respectively, share

inputs from the somatosensory cortex and the social behavior network (e.g., amygdala, hypothalamus; Goodson, 2005). Thus, we speculate that these brain areas might transmit the social context to the olfactory bulb. There are even clues that the respective input to the neuromodulatory projection centers is segregated according to their output (Breton-Provencher et al., 2021; Gielow and Zaborszky, 2017). At this point, the neuroanatomical and functional correlates of social context transmission require substantial further investigation.

Oxytocin-mediated prolonged social memory in rats (Dluzen et al., 1998a), lamb recognition (Lévy et al., 1990), and the Bruce effect (Kaba and Keverne, 1988) are all dependent on noradrenaline signaling, whereas short-term social memory in rats is not (60 min exposure intervals, Dluzen et al., 2000). The involvement of noradrenaline in long-term memory formation is known from other limbic and cortical structures (Hansen, 2017; Kobayashi and Yasoshima, 2001). Intriguingly, noradrenaline modifies mitral cell–granule cell dendrodendritic synaptic transmission, implying a possible mechanism for long-term plasticity, i.e., odor memory (Mandairon and Linster, 2009; Matsutani and Yamamoto, 2008; Okutani et al., 1998). In the rat social discrimination paradigm described above, the initial interaction is restricted to 4 min, much shorter than interactions needed for lamb recognition (<2 h after birth; Poindron and Neindre, 1980) and the Bruce effect (within 3–6 h after copulation; Kaba, 2010). Indeed, longer interaction enables longer social memory in rats, for at least 24 h (Dantzer et al., 1987; Moura et al., 2010). Thus, it is tempting to speculate that in group-housing or colonies, noradrenaline-mediated long-term memory can also be formed.

The modulation of social sensory processing is known from other sensory modalities as well. For instance, excitability of pyramidal neurons in virgin female mouse auditory cortex during pups' ultrasonic vocalization is increased via oxytocin (Marlin et al., 2015), and rat barrel cortex pyramidal neurons are more excitable during whisker-based investigation of conspecifics versus inanimate objects (Lenschow and Brecht, 2015). However, top-down neuromodulation might be particularly strong in olfactory processing of social stimuli, possibly related to the overall strong presence of neuromodulatory projections to the olfactory bulb (Matsutani, 2010; Matsutani and Yamamoto, 2008; Shipley and Ennis, 1996) and to the high demands of the social memory tasks in terms of olfactory perceptual acuity. Social olfactory stimuli are complex mixtures of odors with only small quantitative differences between compared samples (e.g., Singer et al., 1997). Previously, we suggested that neuromodulation in social memory operates via mechanisms that are shared with olfactory perceptual learning (Wilson et al., 2004), i.e., involvement of acetylcholine and improvement of sensory acuity (Suyama et al., 2021). Therefore, it makes sense that the neuromodulators involved in olfactory perceptual learning, i.e., acetylcholine and/or noradrenaline (Devore and Linster, 2012; Vinera et al., 2015; Wilson et al., 2004), also contribute to social odor memory, as discussed here. In conclusion, we suggest that the role of neuromodulation within the olfactory bulb is to improve the perceptibility of olfactory signatures of conspecifics above a certain threshold to enable the proper behavioral response (social discrimination/lamb recognition) or the blockade of certain olfactory signatures to prevent or induce physiological responses (the Bruce effect).

We expect that this enhancement of perception comes at a certain cost, as these modulatory systems are not active per se. An obvious explanation would be that by default the olfactory system is broadly tuned to sample as many different odors as possible, also ones that are obscured by the strong background of a natural environment, to identify interesting odor sources. However, a task that requires to focus on a specific odor, e.g., social stimuli or food, may benefit from a transiently enhanced representation of the involved odors that improves their perception and the subsequent decision-making that leads to a behavioral response. This consideration is generalized from Oettl et al. (2016), who suggest that oxytocin modulation in the olfactory system promotes stimulus selection and information extraction in a social context and thereby facilitates memory formation. On a wider perspective, top-down neuromodulation in the olfactory bulb is heavily involved in the processing of other, nonsocial stimuli as well, e.g., during food search (Brunert and Rothermel, 2021).

In this review we focused on findings in mammalian species whose social cognition relies strongly on olfactory processing, whereas humans are considered to be more dependent on visual input. Nevertheless, patients with autism spectrum disorder were shown to suffer from impaired olfactory modulation, resulting in impaired social cognition-related behavioral responses (Endevelt-Shapira et al., 2018). However, it remains to be elucidated whether these observations are indeed linked to the very same neurobiological underpinnings as the findings in laboratory animals reviewed here.

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Bionotes

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Hajime Suyama is a postdoctoral fellow in Prof. Veronica Egger's lab in Regensburg. He is interested in vasopressinergic actions in the rat olfactory bulb in the context of social memory. During his research, he carries out *in vitro* patch-clamp recordings and Ca^{2+} imaging as well as *in vivo* behavioral analysis and immunohistochemical assays of neural activation. He joined the lab of Prof. Dr. Veronica Egger as a Ph.D. student and finished his doctoral study in 2021 under the supervision of Dr. Michael Lukas at the University of Regensburg, after he finished his veterinary medicine (D.V.M.) study in 2017 at the Azabu University in Japan.

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Michael Lukas is a senior postdoc in Professor Veronica Egger's lab in Regensburg. He is interested in the actions of social neuropeptides like vasopressin and oxytocin on neuronal networks involved in social communication, including olfaction. During his research, he carries out *in vitro* patch-clamp recordings and Ca^{2+} imaging as well as *in vivo* behavioral analysis and immunohistochemical assays of neural activation. He performed his Ph.D. thesis in the behavioral pharmacology lab of Prof. Inga Neumann, investigating the effects of vasopressin and oxytocin on social memory and anxiety, and finishing in 2011. He graduated as a biologist from the University of Regensburg in 2008.

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Toward the end of her studies of physics at TU Munich, Veronica Egger was enthralled by the neurosciences. After obtaining her Ph.D. thesis on the representation of whiskers in the rodent somatosensory cortex in Heidelberg (with Bert Sakmann, 1999), she started to work on synaptic processing in the olfactory bulb, with a focus on the reciprocal synapse between mitral cells and granule cells, as a postdoc at the Cold Spring Harbor Laboratory (with Zach Mainen and Karel Svoboda). In 2011, she became a junior research group leader (BMBF), and in 2013, she was appointed full professor at Regensburg University. By now, her lab could achieve experimental proof of the concept of the reciprocal spine operating as a "mini-neuron".

Review article

Annika Cichy*

How the body rules the nose

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Abstract: In order to survive, an organism has to adapt its behavioral actions to the current context by carefully balancing sensory input with physiological state and need. This challenge becomes particularly apparent for olfactory stimuli (volatile chemicals), which can signal not only food sources, mating partners, and offspring, but also pathogens, competitors, and predators. To achieve this difficult task, information processing in the olfactory system is strongly modulated by internal state (for example, metabolic or endocrine), environmental context, and previous experience. This article provides an overview how different internal states impact olfactory processing and discusses potential underlying mechanisms. It starts with a brief excurse on a leading model to study olfaction—*Mus musculus*—and concludes with implications for human health and disease.

Keywords: endocrine; metabolism; modulation; olfaction; social.

Zusammenfassung: Um zu überleben, muss ein Organismus sein Verhalten an den Umgebungskontext anpassen. Hierzu müssen eingehende sensorische Reize mit dem aktuellen physiologischen Zustand abgeglichen werden. Besonders deutlich wird diese Herausforderung bei olfaktorischen Reizen, die Nahrung, Sexualpartner und Nachkommen, aber auch Krankheitserreger, Konkurrenten und Fressfeinde signalisieren können. Um diese schwierige Aufgabe zu bewältigen, wird die Informationsverarbeitung im Geruchssystem stark durch den inneren Zustand (z. B. Stoffwechsel- oder Hormonstatus), den Umweltkontext und frühere Erfahrungen moduliert. In diesem Artikel gebe ich einen Überblick über den Einfluss verschiedener physiologischer Zustände auf die Geruchswahrnehmung, und erörtere mögliche zugrunde liegende Mechanismen. Ich stelle zunächst einen führenden Modelorganismus zur Untersuchung des Geruchsinns vor - *Mus musculus* - und diskutiere abschließend die Bedeutung für Gesundheit und Krankheit des menschlichen Organismus.

Schlüsselwörter: endokrin; Metabolismus; Modulation; Olfaktorik; sozial.

Introduction

A sudden change in or loss of our sense of smell has become one of the most concerning physiological signs for people around the globe in the last 2 years with COVID-19. The unfolding of this pandemic has placed an unprecedented focus on a sensory ability that—prior to the beginning of 2020—had received relatively little attention from most people. Although anosmia (the loss of the sense of smell) or hyposmia (a reduced ability to smell) have an underlying medical cause such as a viral infection, non-pathological modulation of our olfactory perception occurs constantly. These changes in perception result from an integration of environmental cues (odors) with our physiological state, previous experience, and the current context. Imagine the smell of fresh baked bread. Your immediate reaction will probably fall in between an urgent craving for food to "I couldn't care less" depending on whether you are on your way to work without eating breakfast or right after lunch. There is even a chance that you might react with a sudden aversion to the thought of food, for example, after an unpleasant experience with this odor in the past.

Although modulation of olfactory perception by hunger or experience is a prominent example, odor-guided behaviors can be modulated by a variety of internal states: A tired and stressed male will react differently than a sexually receptive female that is paying attention to a stimulus. This modulation can be essential for survival. A starved animal that is simultaneously exposed to food and predator odors must balance its metabolic needs with the potential danger and will more likely forage than a satiated animal.

In humans, modulation of olfactory perception has been reported since decades. Studies in humans have mainly focused on the overarching areas of metabolic state (for example, hunger or obesity) (Han et al., 2021; Ramaekers et al., 2016; Thompson et al., 1977) and

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modulation by sex and/or endocrine state (Cameron, 2014; Doty et al., 1985; Hummel et al., 1991; Koelega and Koster, 1974). Although these studies have found interesting correlations between physiological states and olfactory perception, it is rather difficult to causally link these two aspects in humans. Thus, this article mainly focuses on research in an animal model that is ideally suited to study modulation of olfactory processing—mice. For detailed information on these aspects in humans, the interested readers are referred to a series of excellent reviews (Boesveldt and de Graaf, 2017; Brand and Millot, 2001; Doty and Cameron, 2009; Peng et al., 2019; Sorokowski et al., 2019).

Modulation of olfactory processing: what we can learn from mice

Over the past century, the mouse (*Mus musculus*) has evolved as the leading mammalian model across disciplines in biomedical research. It shares many genetic and physiological similarities with humans, and provides several technical and economic advantages including a rich arsenal of genetic tools and an accelerated life span. The mouse model is especially suited to study olfactory processing. Mice are nocturnal and are born blind and deaf. Thus, they heavily rely on the olfactory system for sensory processing and numerous essential behaviors including the location of food sources, mating, the care of offspring, and avoidance of predators critically depend on olfactory input.

In the periphery, the main olfactory system of a mouse consists of the olfactory epithelium that lines the nasal cavity and harbors the olfactory sensory neurons (OSNs). These sensory neurons express olfactory receptors that detect odors (environmental chemicals) (Buck and Axel, 1991). In mice, there are ~1200 different olfactory receptors. Importantly, however, each sensory neuron only expresses one receptor type (Imai and Sakano, 2009; Mombaerts, 2004; Monahan and Lomvardas, 2015). This principle does not only determine the range of chemical molecules each neuron responds to, but is also critical for axonal wiring during development: the axons of neurons that express the same receptor type converge to spherical structures (glomeruli) in the olfactory bulb (Mombaerts et al., 1996; Ressler et al., 1994; Vassar et al., 1994). Here, they synapse onto projection neurons (mitral and tufted cells), which transmit information to higher olfactory brain centers (Miyamichi et al., 2011; Sosulski et al., 2011) (Figure 1). However, this information is not simply relayed, but rather undergoes complex processing by numerous interneurons and microcircuits (Egger and Kuner, 2021; Nagayama et al., 2014). In addition, sensory input can be modulated by centrifugal projections and circulating hormones, making the olfactory system an ideal model to study modulation of sensory perception (Brunert and Rothermel, 2021; Palouzier-Paulignan et al., 2012). On a behavioral level, this modulation is crucial to adapt the reaction of an individual mouse to a given olfactory stimulus based on its physiological state, environmental context, and experience.

Different internal states and their impacts on olfactory processing are discussed below.

Modulation by metabolic state

Anecdotally, the modulation of food odor perception by hunger state has been known for centuries. However, only more recently, studies have begun to shine light on the molecular mechanisms and neural circuits underlying the modulation of olfactory processing by metabolic state—which refers not only to the most often cited, transient state of hunger, but also to longer-lasting adaptations by prolonged changes in diet. Endocrine hormones and metabolic molecules that govern our nutritional state are traditionally classified as orexigenic (stimulating food intake; such as orexin, endocannabinoids, and neuropeptide-Y [NPY]) or anorexigenic (inhibiting food intake; such as insulin, leptin, and glucagon-like peptide-1). Although these factors are produced in several different tissues ranging from the intestinal tract to the brain, the olfactory system expresses receptors for all the aforementioned (Palouzier-Paulignan et al., 2012), sometimes at the highest levels compared to other brain regions as in the case of insulin (Hill et al., 1986). To causally link this receptor expression to physiological function and behavior, several elegant studies used a combination of genetics, physiological recordings in awake mice, and behavioral paradigms. For example, Soria-Gomez and colleagues revealed that cannabinoid type-1 receptors expressed on centrifugal feedback projections to the olfactory bulb promote food intake in fasted mice by increasing odor detection (Soria-Gomez et al., 2014). More recently, the group of Stephen Liberles addressed a long-standing question in the field: How does hunger specifically enhance the attraction to food odors, but not to nonfood related odors? Using optogenetic manipulation of freely behaving mice, they uncovered the molecular underpinnings of hunger-induced food odor attraction involving NPY signaling in a specialized subcircuit (Horio and Liberles, 2021). Interestingly, in flies (*Drosophila melanogaster*), short

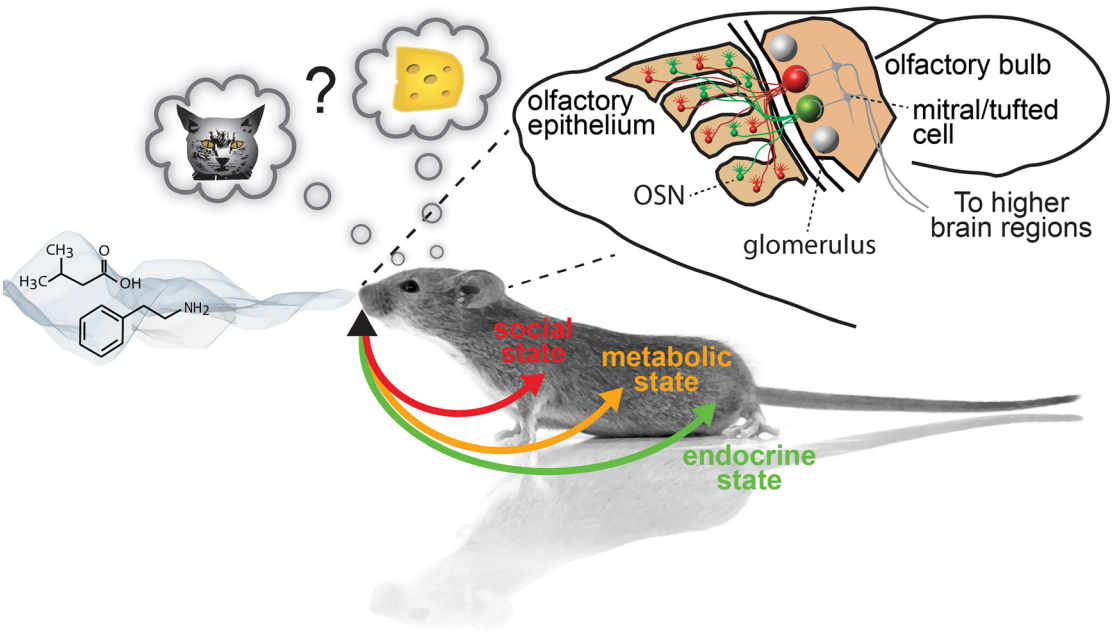

Figure 1: Processing of olfactory cues is modulated by internal state and *vice versa*.
Odors (indicated by chemical structures) are detected by OSNs in the olfactory epithelium that lines the nasal cavity. The physiological state (for example, social, metabolic, or endocrine) of the organism can modulate odor perception and *vice versa*, olfaction can influence the internal state (depicted by colored reciprocal arrows). Thus, the internal state affects decision-making upon odor detection, for example, if the mouse should explore an area to find food or retreat to avoid predators (indicated by cheese and cat symbol, respectively). Magnification: Organization of the mouse olfactory systems. OSNs that express the same olfactory receptor (represented by either red or green neurons) project to the same glomerulus in the olfactory bulb. There, they synapse onto projection neurons (mitral and tufted cells) that project to higher olfactory brain areas. OSN, olfactory sensory neuron. The chemical structures represent isovaleric acid (a "cheesy" odorant) and 2-phenylethylamine (a volatile chemical found in carnivore urine).

neuropeptide F (a mammalian NPY homolog) modulates the activity of food-odor responsive glomeruli and mediates odor-driven food search (Root et al., 2011), indicating a conserved mechanism across phylae.

Another study in mice unraveled a complex connection between the olfactory system and metabolic energy homeostasis involving signaling via the insulin-like growth factor-1. Remarkably, the loss of this molecule in OSNs improves olfactory performance and increases adiposity as well as insulin resistance (Riera et al., 2017). Thus, the sense of smell seems to have a profound impact on obesity and metabolic health. This study once more emphasizes the long-known bidirectional link between metabolic state and olfaction: The olfactory system can impact food intake and, oppositely, metabolic state can impact olfactory performance. Adding to this complexity, a very recent study, that uncoupled excess fat consumption and obesity, indicates that olfactory impairments previously attributed to the development of obesity are rather a consequence and not the cause of the consumption of excess fat (without developing obesity) (Chelette et al., 2022).

This topic is particularly important, considering the concerning increase in obesity worldwide. In humans, several recent studies found a correlation between increased bodyweight and impaired olfactory performance, when comparing obese patients with lean controls (Peng et al., 2019; Richardson et al., 2004; Velluzzi et al., 2022). In addition, Sun and colleagues found that overweight, but not healthy weight, individuals perceive odors as more intense when hungry than when satiated (Sun et al., 2016).

Future work is required to pinpoint the exact contribution of diet-induced changes versus overall metabolic state on olfactory processing and *vice versa*.

Modulation by sex and endocrine state

In humans, males and females appear to exhibit different olfactory abilities, which could be partly related to differences in endocrine status. The powerful impact of sex hormones on olfactory processing becomes most evident during pregnancy: Previously well-liked odors induce sudden aversion or even nausea. Although studies in

patients undergoing hormone replacement therapy or other manipulations of hormonal levels have provided some insights (Doty et al., 2015; Hughes et al., 2009; Kirgezen et al., 2021), it is hard to disentangle these complex regulatory circuits in humans. Even in the mouse model, we know little about the molecular and cellular mechanisms underlying sex-specific differences in olfactory detection and perception, since, as in most fields, studies preferably have used male mice for decades to avoid potential variability stemming from hormonal fluctuations. Most studies investigating sex-specific social cues have focused on the vomeronasal system (Tan and Stowers, 2020), a specialized pheromone-sensing olfactory subsystem, whose presence in humans is controversially discussed (D'Aniello et al., 2017; McGann, 2017). The Stowers lab uncovered a striking progesterone-dependent "off-switch" for a subset of vomeronasal sensory neurons that detect male-emitted pheromones, rendering females in diestrus (nonreceptive period) blind to these cues (Dey et al., 2015). Another study uncovered that the expression of a specific ion channel (called TRPM4) in female vomero-nasal neurons undergoes a cyclic regulation that is driven by ovarian sex hormones (Eckstein et al., 2020). Interestingly, a related mechanism was discovered in flies. Hussain and colleagues revealed that the attraction to polyamines (compounds that are essential for reproduction and embryonic development in all animals) in female flies is modulated at the level of the OSNs through the sex peptide receptor and its neuropeptide ligands depending on the females' reproductive state (Hussain et al., 2016). These findings indicate a potentially conserved mechanism across phylae.

Although it has become evident that the main olfactory system detects gender-specific social cues (Baum and Cherry, 2015; Dewan et al., 2018; Li et al., 2013; Lin et al., 2005), only one study has systematically compared odor-evoked responses in the main olfactory bulb between males and females (Kass et al., 2017). Here, the authors used calcium imaging to record the neuronal activity of olfactory glomeruli and found a significant difference in response kinetics and the number of responsive glomeruli that could contribute to contrast enhancement, which, in turn, could facilitate discrimination of closely related odors in females. Hormonal modulation of the peripheral olfactory system could potentially underlie these observations because gonadectomized mice (removing testes or ovaries, respectively) display changes in odor-evoked responses in olfactory glomeruli. The exact molecular and cellular mechanisms of this observation remain unknown. However, it has been reported that progesterone and estrogen receptors are expressed on all levels of the olfactory system from the peripheral sensory neurons to the olfactory bulb and higher brain regions (Dillon et al., 2013; Hoyk et al., 2014; Kanageswaran et al., 2015; Meffre et al., 2013), presenting a prominent target for the modulation of olfactory processing by the endocrine state.

Modulation by social state

Losing a sensory ability is devastating. However, most people are not particularly concerned about the impact of anosmia (the loss of the sense of smell) in their daily life. This may be because olfactory cues contribute in a more unconscious way to our overall well-being than, for example, visual stimuli. Thus, "we don't miss it, until it's gone". However, patients with anosmia severely suffer from an aspect that is often not considered when thinking about the loss of olfaction: social interactions (Blomkvist and Hofer, 2021; Philpott and Boak, 2014). Moreover, even in people with no obvious pathological changes, olfactory ability seems to be correlated with social life, for example, the number of social interactions (Boesveldt et al., 2017; Zou et al., 2016).

In turn, social status can impact olfactory processing. Although difficult to assess in humans, in mice, several methods exist to determine dominance status and hierarchy in group-housed mice (Desjardins et al., 1973; Fan et al., 2019). As described for the states above, the relationship between social state and olfaction is bidirectional. First, the excretion of several volatile and nonvolatile olfactory cues can be modulated by social status. Decades ago, Harvey and colleagues reported significant differences in the concentration of 16 urinary compounds between dominant and subordinate mice (Harvey et al., 1989). This phenomenon has been repeatedly observed over the years and expanded to include additional compounds (Li et al., 2013; Nelson et al., 2015; Thoss et al., 2019). On a behavioral level, this difference in olfactory cues most likely accounts for the enhanced attraction of females to dominant versus subordinate male urine (Jones and Nowell, 1974a; Mossman and Drickamer, 1996). The underlying molecular and cellular mechanisms are controversially discussed: Although some olfactory cues are produced in a testosterone-dependent manner and are (almost) absent in castrates, juveniles, and females (Harvey et al., 1989; Jones and Nowell, 1974b; Li et al., 2013), the relationship between hormonal status and rank is complex and depends on several factors including dominance hierarchy type (despotic vs. transitive) (Williamson et al., 2017). On the

other hand, much less is known about the influence of social status on olfactory perception. Although several studies have shown that social status affects the behavioral response to urine (for example, subordinate males display a significantly greater avoidance response to dominant male urine than dominant males (Hurst, 1993; Jones and Nowell, 1974a), much less is known about the individual components that elicit these differential responses. In collaboration, we recently discovered that the valence response of male mice to trimethylamine (a compound in adult male mouse urine [Li et al., 2013]) depends on the social status of male mice. Although dominant males show mild attraction, subordinate males avoid this cue. Moreover, a specific olfactory receptor (TAAR5) is required for these valence responses as well as aggression-related behaviors (Cichy et al., 2021). Further work is required to unravel the underlying neural circuits which remain largely elusive.

Additional states

In addition to the states discussed above, several other internal states can modulate olfactory processing.

It is now well-established that in an anesthetized state, multiple response parameters (for example, the number of responsive neurons in the olfactory bulb) significantly differ from response properties in the awake animal (Kato et al., 2012; Kollo et al., 2014; Rinberg et al., 2006), making it indispensable to study modulation of sensory processing in awake subjects. In addition, circadian rhythm also affects odor perception in animals and humans (Granados-Fuentes et al., 2006; Herz et al., 2017; Liu et al., 2018), which in turn has important implications for food anticipation and choices (Bhutani et al., 2019; Nolasco et al., 2021). The olfactory system and brain regions responsible for emotional processing are highly intertwined. Moreover, some odors (for example, predator cues) induce an immediate stress response (for example, fear) in animals and humans. Thus, it may not be surprising that neural circuits for olfactory processing and the internal state of stress have strong reciprocal connections (Bombail, 2019; Kondoh et al., 2016). The same is true for attention, expectation, and satisfaction/reward anticipation. A number of excellent recent reviews and articles discussing these states can be found here (Carlson et al., 2018; D'Souza and Vijayaraghavan, 2014; Gadziola et al., 2020; Keller, 2011; McGann, 2015).

Summary and conclusions

The olfactory system is ideally suited to integrate environmental odors that signal food, danger, and social relations with an organisms' current physiological state and needs. Several studies in humans have revealed interesting correlations between metabolic, endocrine, or sleep state and olfactory processing. However, findings are often conflicting. For example, although odor exposure seems to induce appetite, the effect of olfactory cues on food choices and intake are controversially discussed (Boesveldt and de Graaf, 2017). Numerous studies that benefit from the advantages of model organisms, such as genetic manipulations, have begun to uncover the underlying cellular and molecular mechanisms involved in the modulation of olfactory processing. However, intense further work is required to address several still unknown aspects. For example, work in insects indicates that a given form of modulation can target specific classes or types of olfactory receptors—an interesting concept that is still unknown in mammals. Moreover, future work is required to gain a better understanding of how different diseases affect olfactory perception and reciprocally how perturbing olfactory processing impacts the physiological state in these cases. This is particularly pressing with the rising cases of obesity, COVID-19-induced long-term perturbations of olfaction, and impairments of olfactory functions during aging and in several neurodegenerative diseases.

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Review article

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Information about space from time: how mammals navigate the odour landscape

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Abstract: Sensory input across modalities is highly dynamic, continuously confronting the brain with the task of making sense of the external world. Olfaction is a key sense that many species depend on for survival, for example to locate food sources and mating partners or to avoid encountering predators. In the absence of visual cues, olfactory cues are especially useful, as they provide information over a large range of distances. Natural odours form temporally complex plumes that show rapid fluctuations in odour concentration carrying information about the location of an odour source. This review focuses on how primarily mammals use this spatial information from olfactory cues to navigate their environment. I highlight progress made on the physical description of dynamically fluctuating odours, behavioural paradigms to investigate odour-guided navigation and review initial findings on the underlying neural mechanisms that allow mammals to extract spatial information from the dynamic odour landscape.

Keywords: active sampling; navigation; odour plume; olfaction; temporally complex structure.

Zusammenfassung: Sensorische Eindrücke aller Sinnesmodalitäten sind hoch dynamisch und stellen das Gehirn ununterbrochen vor die Aufgabe, die Außenwelt in ihrer Gesamtheit zu erfassen. Der Geruchssinn spielt für viele Spezies eine überlebenswichtige Rolle, zum Beispiel um Nahrungsquellen und Artgenossen zu finden, oder Begegnungen mit Raubtieren zu vermeiden. Olfaktorische Signale liefern sensorische Information über kurze und lange Entfernungen, auch wenn optische Eindrücke fehlen. Natürliche Gerüche bilden komplexe Duftwolken mit rapide fluktuierender Konzentration, die Informationen über den Ort einer Geruchsquelle tragen. Dieser Artikel gibt einen Überblick darüber wie vor allem Säugetiere räumliche Information aus Geruchssignalen ziehen können, um ihre Umwelt zu navigieren. Beleuchtet werden Fortschritte in der physikalischen Beschreibung dynamischer Gerüche, Verhaltensparadigmen zur Untersuchung olfaktorischer Navigation, sowie erste Erkenntisse über potentielle zu Grunde liegende neuronale Mechanismen, die es Säugern erlauben, räumliche Information aus der dynamischen Geruchswelt zu erlangen.

Schlüsselwörter: aktives Samplen; Duftwolke; Geruchssinn; Navigation; zeitlich komplexe Struktur.

Introduction and objectives

Organisms across phyla use olfactory information to orient themselves within their environment, for example to find food sources and mating partners. Odours carry information over a large range of distances, thus allowing behaviours that range from simple object detection and recognition, to trail tracking and navigation using odour plumes from afar. Recently, the temporal dynamics of odours have come into focus, introducing a shift from viewing olfaction as a static and slow modality. While the significance of temporal dynamics for invertebrates has been recognised some time ago (reviewed in Baker et al., 2018; Cardé and Willis, 2008; Reddy et al., 2022a; Vickers, 2000), it only recently started to gain interest in mammalian olfaction research (Ackels et al., 2021; Crimaldi et al., 2022; Marin et al., 2021; Reddy et al., 2022a), with the latter being the focus of this review.

Here, I first introduce what spatiotemporal information is inherent to odour signals, how to measure it, and which physical features can be used to characterise the complex distribution of olfactory cues in the odour environment. I next describe active sampling strategies that mammals, in particular laboratory rodents, use to gather olfactory information. I then give an overview of the computational capabilities of the olfactory system, with a focus on the olfactory bulb (OB), to process fine temporal information from dynamic odours. I next set out various experimental paradigms that have been designed to

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investigate olfactory-guided spatial behaviours, specifically the tracking of odour trails and navigation using airborne olfactory cues. This review aims to highlight how recent advances in understanding odour plume dynamics and the design of more naturalistic behavioural paradigms provide a promising gateway to gain mechanistic understanding of mammalian odour-guided navigation.

Spatiotemporal information in dynamic odour signals

Odour-guided animals are faced with two vital challenges: (1) separating out relevant odour sources from a complex olfactory landscape and (2) deducing the location of such odour sources, for example food sources or mating partners, when navigating their environment.

A prerequisite to investigate odour-dependent behaviours is a clear description of the sensory stimulus space. The perceptual space of colour vision is low-dimensional and is fundamentally defined by the wavelength spectrum of the light source. Such a clear-cut definition does not exist in olfaction as thousands of volatile odorous chemicals exist in nature. A quantitative understanding of odour space therefore remains a major point of discussion in olfaction research (Meister, 2015). In addition to the plethora of different chemicals, in a natural olfactory scene, odours rarely occur in isolation. Instead they most often compose complex mixtures consisting of many different molecules that vary in their composition and the concentration of their components (Mori et al., 1999). Moreover, environmental conditions generate complex air movements that lead to the formation of turbulent plumes that consist of odour filaments often fluctuating at high frequencies interrupted by odourless space (Figure 1). Odours in a natural environment are thus dynamic in both space and time (Celani et al., 2014; Moore and Crimaldi, 2004; Murlis et al., 1992; Mylne and Mason, 1991; Shraiman et al., 2000).

There are ways to faithfully measure spatial and temporal information of odour signals in order to characterise their physical features. A widespread method to detect odours at a single location is using a photoionisation detector (Justus et al., 2002) that ionises odour molecules with high temporal resolution with ultraviolet light and generates a concentration dependent voltage signal. It is furthermore feasible, albeit technically more challenging, to visualize odour plumes using planar laser-induced fluorescence (PLIF) and thereby perform measurements of plume dynamics with high temporal and spatial precision

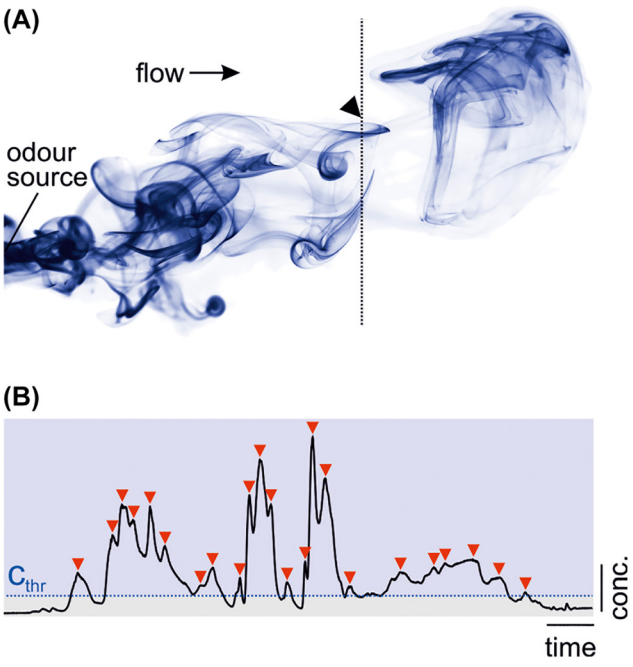

Figure 1: Structure and time course of a complex odour plume. (A) Two-dimensional section of a turbulent smoke plume highlighting its chaotic distribution in airflow direction. (B) Example recording of an odour plume reproduced using a high-speed odour delivery device (Ackels et al., 2021). Red triangles: odour concentration peaks above threshold (C_{thr}, dotted blue line). Plume in (A) adapted from (http://creativity103.com/collections/Smoke/smoke_plume.jpg).

(Connor et al., 2018; Crimaldi and Koseff, 2001). To predict how odours are transported in a turbulent environment is a computationally challenging problem. Computational fluid dynamics simulations (Celani et al., 2014) and information-theoretic approaches (Boie et al., 2018), however, can shed light onto odour plume statistics and the spatial information they carry.

As a plume emanates from its source, it widens in space, resulting in a change of the statistics of concentration fluctuations (Ackels et al., 2021; Moore and Atema, 1991; Murlis et al., 1992; Weissburg et al., 2002). Several features have been identified to vary reliably with distance to the source. These include the height and onset slope of a peak (Moore and Atema, 1991), intermittency, which is defined as the fraction of time the local concentration is above a certain threshold (Riffell et al., 2014) and average bout count, defined as events of large, consistent changes in the measured signal (Schmuker et al., 2016) (Figure 1B). Importantly, it has been suggested that the spatiotemporal patterns of odour plumes hold information about the location, distance and composition of odour sources (Celani et al., 2014; Hopfield, 1991; Murlis et al., 2000): Odours from the same or close by sources show a high

degree of correlation in their concentration fluctuations, whereas odours from distant sources fluctuate in an uncorrelated manner, allowing mice to perform source separation (Ackels et al., 2021).

Understanding how odour signal features and animal sampling strategies are linked to neural correlates and behaviour has attracted considerable interest over the past years and has become an active field of research in mammalian neuroscience (Ackels et al., 2021; Findley et al., 2021; Gumaste et al., 2020; Jordan et al., 2018; Lewis et al., 2021; Tariq et al., 2021).

Active sampling of odour information

Animals continuously gather olfactory sensory information – a crucial precondition to successfully localize and identify an odour source. Additionally, odour-guided animals are usually not stationary but instead continuously sample olfactory cues while navigating the environment. Active exploration thus changes the odour signal dynamics and reformats it to ultimately allow for more efficient search strategies. Examples of active sensing in invertebrates manifest as movement of the entire body or its appendages, including wing flapping (Chapman et al., 2018; Li et al., 2018) or antennae flicking (Devine and Atema, 1982; Reeder and Ache, 1980), imposing additional intermittency onto the odour stimulus (Huston et al., 2015).

These behaviours can be considered as the functional equivalent of vertebrate sniffing – active sampling of olfactory information through the intermittent inhalation of odour molecules into the nasal cavity. The frequency of sniffing in rodents covers a wide range of 2–12 Hz (Welker, 1964) and changes with both stimulus and contextual features such as odour novelty (Esquivelzeta Rabell et al., 2017; Verhagen et al., 2007), and attentiveness of the animal (Jordan et al., 2018; Kepecs et al., 2006; Wachowiak, 2011; Wesson et al., 2008). Importantly, active sensing strongly impacts on how a stimulus is represented in the brain, for example by modulating the frequency content of the signal even before its initial transduction by olfactory sensory neurons (OSNs) in the nasal epithelium.

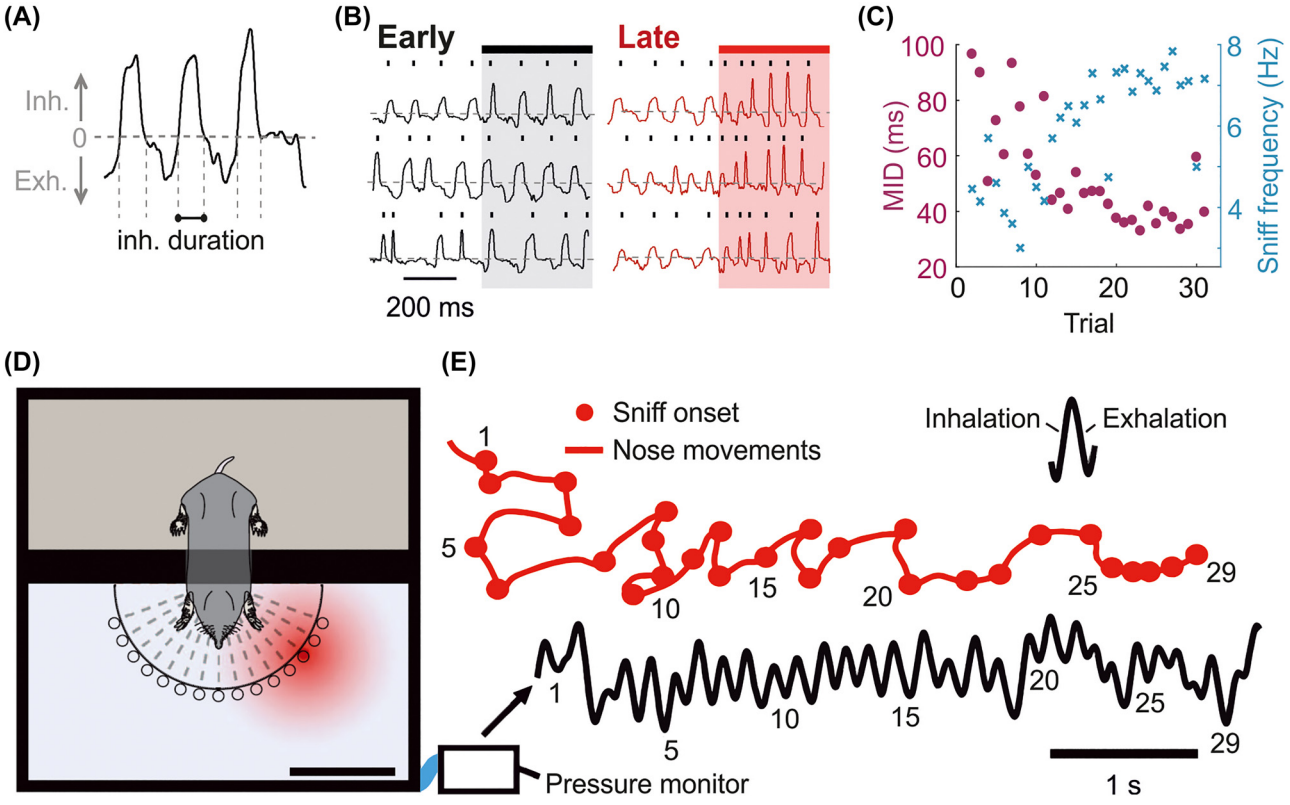

Figure 2: Active sampling behaviour.
(A) Diagram to show the extraction of inhalation duration from an example nasal flow trace. (B) Example nasal flow traces showing the emergence of rapid sniffing between early and late trials. (C) Mean inhalation duration (MID) for the example in (B) calculated for each trial (first 500 ms of stimulus) in purple dots. Blue crosses show corresponding sniff frequency for each trial (from Jordan et al., 2018).
(D) Experimental chamber to investigate serial and stereo olfactory sampling using an Eastern mole. (E) An air-pressure monitor recorded respiration. Sniffs (red dots) were correlated to nose movements (red lines) acquired by high-speed videorecordings (from Catania, 2013).

Modulation of sniff frequency and intensity affects odour representation in the brain (Parabucki et al., 2019; Verhagen et al., 2007; Wachowiak, 2011). Acceleration of sniff frequency and shorter inhalation duration, for example, evolve over the course of learning an odour discrimination task (Figure 2A–C) and enhance odour representation during learning (Jordan et al., 2018).

So far, an individual sniff has generally been considered to be the unit of information for olfactory processing, forming a 'snapshot' of the olfactory surroundings (Kepecs et al., 2006). According to this view, fast fluctuations in odour concentration at sub-sniff resolution would be rendered inaccessible to the mammalian olfactory system. An increasing number of studies, however, indicate that fine temporal information – faster than the respiration frequency – is accessible to mammals (Ackels et al., 2021; Cury and Uchida, 2010; Shusterman et al., 2011; Smear et al., 2011, 2013).

In addition to the active modulation of serial sniffing, the bilateral organization of the mammalian olfactory system allows for signal comparison across nostrils, analogous to depth perception and sound localization in the visual and auditory system, respectively. Mice and rats use binaral cues for inter-naris odour information comparison (Esquivelzeta Rabell et al., 2017; Rajan et al., 2006) and stereo-smelling has been shown to be used for navigation across species including snakes (Schwenk, 1994) and even humans (Bekesy, 1964; Porter et al., 2007; Wu et al., 2020). Eastern moles can readily locate a food source in a radial search paradigm, relying on information sampled through both nostrils (Catania, 2013) (Figure 2D, E). In accordance with this, occluding one naris reduced odour trail-tracking ability in rats (Khan et al., 2012) and mice (Jones and Urban, 2018) and impaired odour direction sensitivity in moles (Catania, 2013). The utility of stereo-olfaction is likely highest when sampling occurs in close proximity to an odour source, as with increasing distance the difference in signal across the two nares might become indistinguishable from fluctuations in turbulent mixing (Reddy et al., 2022). Another form of active sampling observed during trail tracking in rats, moles, dogs and humans is head-scanning (Catania, 2013; Khan et al., 2012; Porter et al., 2007) which often goes together with changes in sniff frequency.

Sniffing behaviour governs the way odour information reaches the olfactory system, making respiration activity a crucial parameter that needs to be monitored when studying olfactory physiology and behaviour. Based on the experimental conditions, a number of methods with varying precision, reliability and invasiveness have been developed over the past decades. These are reviewed in detail by Grimaud and Murthy (2018) and I will introduce only the most common techniques here.

An established way to measure respiration is using air movement through the nose, which provides a more direct readout compared to neural or muscular activity (Feldman et al., 2013). In stationary, head-restrained animals, a face mask combined with a flow meter can be positioned in front of the animal's snout to establish precise, non-invasive respiration recordings that can directly be paired with the delivery of odour stimuli (Bolding and Franks, 2017). Another method that has been extended to freely moving animals is to detect changes in pressure (Li et al., 2014; Reisert et al., 2014; Verhagen et al., 2007) or temperature (Jones and Urban, 2018; Khan et al., 2012; McAfee et al., 2016; Uchida and Mainen, 2003) using an intranasally implanted sensor. While intranasal sensors open up the possibility to study social or navigation behaviour, these implants can potentially disrupt airflow through the nasal cavity and thus affect odour perception. A less disruptive surgical procedure was established in recent studies, however, where a temperature probe is implanted between the nasal bone and inner epithelium of mice, and is thereby not protruding into the nasal cavity, leaving the nasal epithelium intact (Findley et al., 2021; McAfee et al., 2016).

Active sampling behaviour plays a major role in odour processing. To understand, how animals extract spatial information from natural odour plumes, therefore requires reliable, non-disruptive and precise recording of sniffing behaviour across experimental paradigms.

Temporal precision of olfactory signal processing

Natural odours often get transported via turbulent air flow which creates spatiotemporally complex plumes. Under these conditions, fluctuations in odour concentration can reach frequencies that far exceed the respiration rate of mammals. The mammalian sense of smell is generally considered to be a 'slow sense', with its temporal bandwidth governed by the respiration rate (Kepecs et al., 2006; Wachowiak, 2011). A number of recent studies, however, show that mammals can access sub-sniff odour information, providing them with the ability to encode temporal information from dynamic odour signals with astonishing precision.

It has been demonstrated that insects use the temporal structure of odour plumes to deduce information about the location (Demir et al., 2020; Mafra-Neto and Cardé, 1994;

Murlis et al., 1992; Vergassola et al., 2007; Vickers, 2000) and composition (Riffell et al., 2014; Szyszka et al., 2012, 2014) of an odour source. Insects can follow fast odour concentration changes (Brown et al., 2005; Geffen et al., 2009; Kim et al., 2011) due to their extremely fast olfactory signal transduction cascade that results in a response latency of approximately 2 ms as recorded from OSNs (Szyszka et al., 2014). Odour asynchronies as short as 6 ms suffice to segregate learned odour components within a mixture and are encoded differently from their synchronous counterparts in the antennal lobe (Stierle et al., 2013). The sensitivity to temporal odour dynamics therefore enables insects to perform odour-background segregation and source separation.

Much less is known for the mammalian olfactory system when it comes to sensitivity towards spatial and temporal patterns of odours. Mice can detect and discriminate odours within a few 100 ms (Abraham et al., 2004; Uchida and Mainen, 2003) and the olfactory bulb (OB) neural circuitry is, in principle, equipped to resolve fine odour dynamics on a millisecond timescale (Cury and Uchida, 2010; Shusterman et al., 2011). Light-evoked 'virtual odour' signals coupled to the respiration cycle can be discriminated by mice at the sub-sniff level when OSNs are stimulated optogenetically at only 10–20 ms intervals (Li et al., 2014; Smear et al., 2011, 2013). Patterned optogenetic stimulation of OB projection neurons, so called mitral/tufted cells (MTCs), revealed that stimulus delays of as little as 13 ms are distinguishable by mice (Rebello et al., 2014). Shifting stimulus timing of optogenetically targeted MTCs within the sniff cycle, in particular towards the beginning of the cycle, changes behavioural performance in mice when discriminating neuronal activation patterns (Chong et al., 2020). Synthetic odours created via optogenetic stimulation can thus be represented with high temporal precision at frequencies far exceeding that of the animal's respiration.

Artificial stimulation using optogenetics provides a well-controlled and precise way to probe the olfactory system. It should, however, not be seen as a substitute that is equivalent to presenting actual odours. A long-standing challenge in olfaction research is the precise control of the odour stimulus, owing to the high volatility of many odorous chemicals. Recent developmental advances in high-speed odour delivery devices (Ackels et al., 2021; Raiser et al., 2017) now allow to reproduce the complex temporal structure of natural odours with minimal stimulus onset delay. Presenting odours fluctuating at frequencies exceeding the respiration rate allows to test experimentally whether these dynamics are accessible to the mammalian olfactory system at the sub-sniff level. Recent work shows that mice can extract spatial information from high-frequency temporal odour dynamics carried by natural plumes. The correlation structure of odours fluctuating at 20 Hz is encoded in MTCs and thus, in principle, provides a neural correlate to perform odour-source separation (Ackels et al., 2021; Dasgupta et al., 2022). Presenting natural plumes from within a wind tunnel to head-fixed mice reveals that rapid odour concentration fluctuations structure the activity of glomerular MTC populations (Lewis et al., 2021).

Taken together, there is substantial evidence that the OB neural circuitry harbours the computational bandwidth to encode temporal information from dynamic sensory input at fast time scales – both created artificially using light pulses and from actual odour stimuli. This introduces the exciting prospect to further investigate the mechanisms underlying natural odour processing to better understand olfactory-guided behaviours.

Spatial behaviours based on olfaction

Some mammals are well-known to exploit their sense of smell for navigation. The complexity of natural odour landscapes and the difficulty to recreate these conditions in a laboratory setting, however, have constrained our understanding of how spatial information carried by natural odours aids navigation through complex environments. Assessing behavioural performance is further complicated by the fact that animals, for example trained to follow an odour track or to localise an odour source, will revert to a variety of strategies to solve this particular task, depending on a number of behavioural parameters such as experimental conditions and training level.

Promising new developments now allow to perform neurophysiological recordings, monitor respiration (Findley et al., 2021; Liu et al., 2020) and record odour information using head-mounted odour sensors (Tariq et al., 2021) in freely moving animals. This created the opportunity to directly link the sampling strategy and odour concentration profile to neural activity patterns during complex behaviours. New odour delivery devices that are capable of reliably reproducing the temporal dynamics of natural odour plumes (Ackels et al., 2021) give precise control over the odour stimulus and create the possibility to probe the olfactory system systematically using dynamic stimuli in a controlled laboratory setting, in particular during head-fixed physiology and/or behaviour experiments.

In the following sections, I will highlight what is currently known about how mammals can extract spatial information for navigation from surface-borne odour cues during trail tracking and from airborne olfactory cues.

Tracking surface-borne odours

Animals deposit and follow surface-borne scent trails in the context of several different behaviours. Tracking the trail of a specific odour and distinguishing it from the plethora of olfactory cues in a natural landscape can become vital to either find an odour source, in the case of food or mating partners, or to avoid approaching it, for example in the case of a predator animal. A prominent behaviour found in many species is placing urine scent marks within the home territory (Arakawa et al., 2008). This can serve multiple purposes: for example, to guide the depositor through its habitat by establishing navigation routes (Benhamou, 1989) but also to alert other animals about crossing into foreign territory (Hurst and Beynon, 2004).

Several experimental paradigms have been established to study odour trail tracking in the laboratory, including trails printed on paper spools in a treadmill (Khan et al., 2012; Mathis et al., 2018) or drawn on a surface in an open field (Jones and Urban, 2018; Porter et al., 2007). Rats (Khan et al., 2012; Wallace et al., 2002), mice (Jones and Urban, 2018) and even humans (Porter et al., 2007) can track odours using the concentration gradient formed around the trail. When tracking an odour trial, rats scan their nose across the trail and widen the scan path when the nose diverges too far from it (Figure 3A), reminiscent of casting movements seen in insects. Mice trained to follow an odour trail, and to ignore a distractor trail (Figure 3B), show increased cumulative distance from the trail when left with only one nostril available to sample information (Figure 3C). Both an increased sniff rate to compare sensory information between sniffs, and stereo-olfaction to gather directional information by comparing sensory input between both nares (Catania, 2013; Jones and Urban, 2018; Khan et al., 2012; Porter et al., 2007) maximise the sampling efficiency and result in improved odour trail tracking.

Tracking odour trails in the wild adds an additional layer of complexity: The animal needs to detect the direction from which an odour originates, for example when hunting for prey or avoiding to become preyed upon. To locate an odour source, tracking dogs follow a 3-step strategy: a searching phase, a deciding phase and a tracking phase (Thesen et al., 1993). It has been proposed that dogs base their decision on the direction of an odour trail by comparing the concentration of odour cues

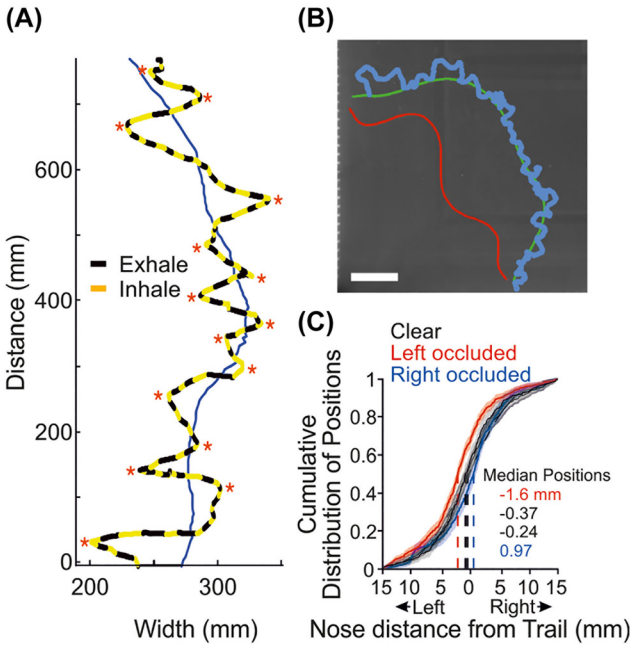

Figure 3: Surface-borne odour tracking.
(A) An example stretch of odour trail tracking showing each sniff overlaid on the nose trajectory. Black indicates inhalation and yellow exhalation. Multiple sniffs are taken during each nose oscillation (from Khan et al., 2012). (B) Nose positions (blue) of a trained mouse, tracking the rewarded (green) trail. Distractor trail is shown in red. (C) Cumulative distribution of nose position relative to the trail for one animal during clear/un-occluded (black), left nostril occluded (red), and right nostril occluded (blue), conditions. Dashed lines indicate position of the median of each distribution (B and C from Jones and Urban, 2018).

between a small number of footsteps (Hepper and Wells, 2005). Recent theoretical work shows that animals form an estimate of where the trail is headed by performing a sector search strategy and using past contacts with the help of an intrinsic, geometric notion of trail continuity (Reddy et al., 2022b).

The ability to follow surface-borne scent marks or food trails can be vital for the survival of an animal. When orienting in relation to more distant odour sources, however, the animal has to rely on tracking airborne odours that travel in the form of odour plumes.

Tracking airborne odours

Airborne odours show higher spatiotemporal complexity compared to surface-borne odours in several respects: Concentration gradients between the inside and the outside of an odour plume are less steep and the concentration profile of an odour plume often fluctuates at

high-frequencies imposed by air turbulence (Figure 1). Wind speed and direction are additional parameters that the animal needs to factor in when localising the source of a plume. Navigating through airborne odours, therefore, likely imposes a significantly greater challenge than localising the source of an odour trail.

To investigate what spatial information animals are able to extract from odour plumes in a laboratory setting requires reproducing key features of a complex olfactory environment under controlled conditions. In recent years, significant advances have been made in the experimental design of tasks that reflect, at least in part, natural conditions. Examples include behavioural arenas in which mice are tasked to localise the source of odour plumes under turbulent airflow conditions (Findley et al., 2021; Gire et al., 2016; Gumaste et al., 2020; Liu et al., 2020) or probing mice with temporally complex odour stimuli and reproduced odour plumes in an automated behavioural setup (Ackels et al., 2021). Further, olfactory virtual realities (VR) have been proven to serve as a promising framework to investigate airborne odour tracking under turbulent conditions in stationary animals (Baker et al., 2018; Fischler-Ruiz et al., 2021; Radvansky and Dombeck, 2018; Radvansky et al., 2021).

To date, only a few studies have investigated mammalian plume-tracking navigation (Bhattacharyya and Singh Bhalla, 2015; Findley et al., 2021; Gire et al., 2016; Gumaste et al., 2020; Jackson et al., 2020; Liu et al., 2020). Mice efficiently locate the source of an airborne odour plume in a behavioural arena using a gradient-based algorithm (Gire et al., 2016). After memorising the port locations, however, the limited number of possible rewarded spots leads to a systematic serial-sampling foraging strategy. Consistent with this, rats move straight to one target port in a multichoice olfactory arena under near-laminar flow conditions and sample through potential targets until they reach the rewarded port (Bhattacharyya and Singh Bhalla, 2015). A serial-sampling strategy does not necessarily argue for navigation entirely based on olfactory information. It suggests, however, that animals make direct associations between the odour stimulus and target locations. Olfactory information is thereby integrated into their cognitive spatial map that they use to navigate. Even humans are capable of returning to a defined location in space using odours alone, corroborating the use of odour-informed spatial maps of the environment (Jacobs et al., 2015).

In an odour source localization task mice shift their search strategy with increasingly complex environmental conditions caused by turbulent airflow (Gumaste et al., 2020; Jackson et al., 2020) and with distance to the source, as measured by speed and orientation towards the source (Liu et al., 2020). To ensure that animals rely solely on odour information and to discourage serial sampling, trials were terminated when the animal reached an unrewarded port (Gumaste et al., 2020). In a study where mice were tasked to navigate towards an odour source, sniffing and head movements were highly synchronized (Findley et al., 2021). Here, task performance was not impacted by naris occlusion, suggesting that mice rely primarily on temporal comparisons across sniffs and not stereo-olfaction during airborne odour navigation.

Olfactory VR setups provide an experimental tool that allows for controlled stimulus presentation and recording neural activity in behaving, albeit head-fixed, animals. It has been shown that odour cues serve as landmarks to guide virtual navigation in the absence of visual stimuli and promote place cell representation in the hippocampus, thereby improving navigation performance over time (Fischler-Ruiz et al., 2021). This finding was supported by another study where different proportions of hippocampal CA1 neurons were activated during navigation, depending on whether mice were pursuing a visual landmark or tracking an odour gradient (Radvansky et al., 2021).

Where is the neural information underlying odour-guided navigation generated and processed? Mechanistic understanding of these behaviours remains sparse. Van Rijzingen et al. have shown that removal of the OBs in rats severely impairs spatial orientation in the Morris water maze, despite the presence of visual cues, thus illustrating the olfactory system's significance for navigation (van Rijzingen et al., 1995). Olfactory bulb cell populations recorded in head-fixed mice can follow the temporal patterns of odour plumes that were recorded in real-time with a head-mounted odour sensor (Lewis et al., 2021). Piriform cortex neurons recorded in freely moving rats performing an odour-cued navigation task form a spatial map of the environment by associating spatial and olfactory information (Poo et al., 2021).

In summary, progress made in recent years in terms of behavioural task designs and recording methods offers great opportunities to gain deeper understanding of how spatial information carried by odour plumes aides navigation.

Conclusions

The temporal dynamics of odours carry spatial information about an odour landscape. This can be of vital importance when navigating an environment, in particular for nocturnal animals such as mice or rats. In a recent paradigm shift, the sense of smell is increasingly

acknowledged to be a high-bandwidth modality. In this review, I highlighted how this has led to major advances in describing dynamic odour statistics, designing behavioural tasks and presenting spatiotemporally complex odours. While this research has just started to gain traction in mammals, it has the potential to promote our understanding of how dynamic odours allow to infer information about space from time.

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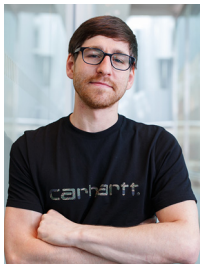

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Review article

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Functional role of the anterior olfactory nucleus in sensory information processing

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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

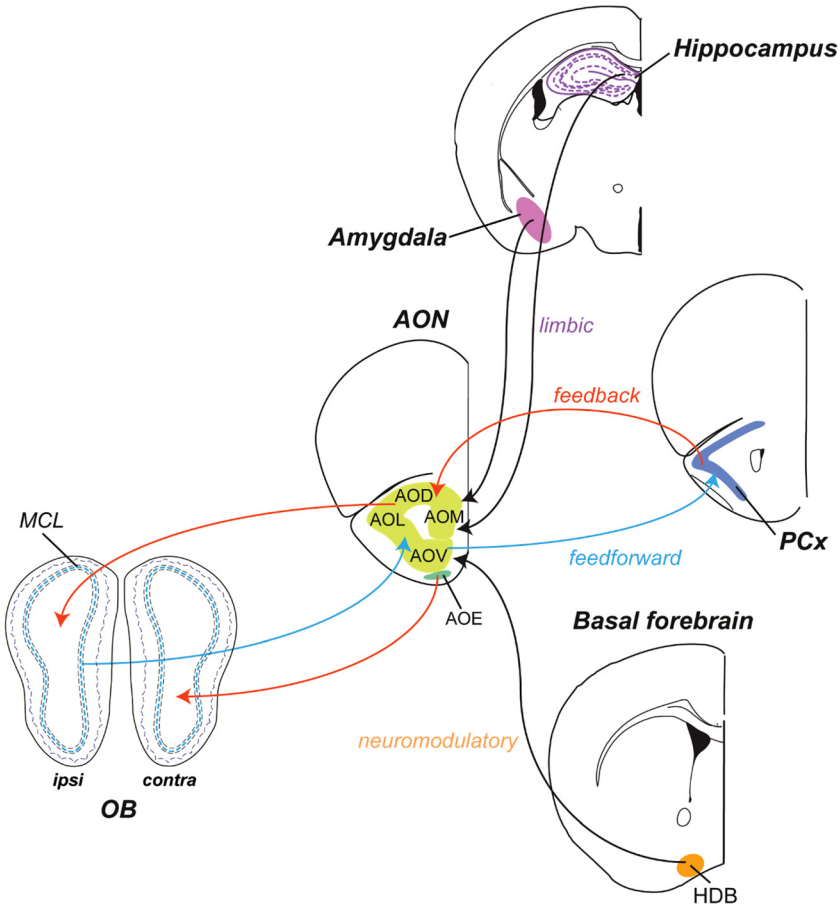

Figure 1: AON input-output connections. As part of the olfactory cortex, the AON is directly innervated by mitral and tufted cells, the principal neurons of the OB. The AON projects in a top-down fashion back to the OB. The AON is the only area sending projections to both the ipsi- and contralateral 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

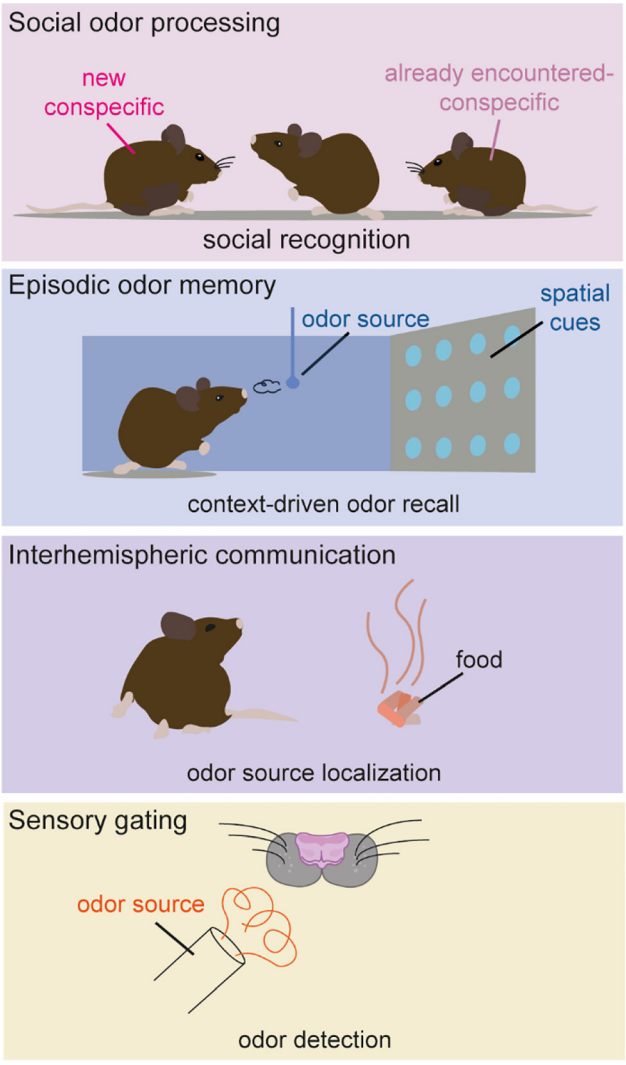

Figure 2: AON modulation of olfactory behaviors. The AON has been implicated in different functions, including regulation of social interactions, recollection of context-dependent odor memories, interhemispheric communication to support odor source localization, and influencing olfactory detection by 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 neurodevelopmental disorders (Hartig et al., 2021; Tonacci et al., 2017), mental health conditions (Daniels and Vermetten, 2016; Vermetten et al., 2007), and early stages of neurodegenerative 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 neurodevelopmental 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 neurodegenerative diseases or neurodevelopmental disorders.

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Markus Rothermel studied biology at the Ruhr University Bochum. His doctoral thesis with Hanns Hatt focused on "trigeminal perception" and was funded by scholarships from the research training group GRK 736. For his postdoctoral time, he joined the laboratory of Matt Wachowiak in the US, focusing on information processing in the rodent olfactory system, a project for which he was awarded a DFG research fellowship. In October 2014, he returned to Germany to establish an Emmy Noether research group at the RWTH Aachen University. In 2018, he became a part of the DFG Research Training Group (GRK 2416), followed by an IZKF (Interdisciplinary Center for Clinical Research) joint research project in 2020. In 2021, he accepted a Professorship position for Cellular Biology at the University of Veterinary Medicine Hanover. His main interests are sensory systems in health and disease.

Review article

Johanna K. Kostka* and Sebastian H. Bitzenhofer*

How the sense of smell influences cognition throughout life

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Abstract: Although mostly unaware, we constantly navigate a complex landscape of airborne molecules. The perception of these molecules helps us navigate, shapes our social life, and can trigger emotionally charged memories transporting us back to the past within a split second. While the processing of olfactory information in early sensory areas is well understood, how the sense of smell affects cognition only recently gained attention in the field of neuroscience. Here, we review links between olfaction and cognition and explore the idea that the activity in olfactory areas may be critical for coordinating cognitive networks. Further, we discuss how olfactory activity may shape the development of cognitive networks and associations between the decline of olfactory and cognitive abilities in aging. Olfaction provides a great tool to study large-scale networks underlying cognitive abilities and bears the potential for a better understanding of cognitive symptoms associated with many mental disorders.

Keywords: networks; odor; olfaction; oscillations; respiration.

Zusammenfassung: Obwohl meist nicht bewusst, navigieren wir ständig durch eine komplexe Landschaft von Duftstoffen. Die Wahrnehmung dieser Duftstoffe hilft uns bei der Orientierung, prägt unser soziales Leben und kann emotionale Erinnerungen auslösen, die uns innerhalb von Sekundenbruchteilen in die Vergangenheit zurückversetzen. Während die Verarbeitung olfaktorischer Informationen in frühen sensorischen Arealen gut verstanden ist, ist die Frage wie der Geruchssinn die Kognition beeinflusst erst vor kurzem in das Blickfeld der neurowissenschaftlichen Forschung gerückt. Wir diskutieren hier das Zusammenspiel zwischen Geruchssinn und Kognition und untersuchen die Idee, dass die Aktivität in olfaktorischen Arealen entscheidend zur Koordination kognitiver Netzwerkaktivität beiträgt. Darüber hinaus diskutieren wir, wie olfaktorische Aktivität die Entwicklung kognitiver Netzwerke beeinflussen kann, sowie Assoziationen zwischen dem Rückgang olfaktorischer und kognitiver Fähigkeiten im Alter. Der Geruchssinn bietet ein großartiges Werkzeug zur Untersuchung weitläufiger Netzwerke, die kognitiven Fähigkeiten zugrunde liegen, und birgt das Potenzial für ein besseres Verständnis kognitiver Symptome, die mit vielen psychischen Störungen einhergehen.

Schlüsselwörter: Atmung; Geruch; Netzwerke; Olfaktorik; Oszillationen.

Introduction

Most people are familiar with the phenomenon that a particular smell can trigger strong memories. However, due to the dominance of vision and hearing in our day-to-day life, olfaction has long been overlooked in the field of cognition. The term cognition refers to mental processes as diverse as perception, memory, working memory, decision making, and more. Despite substantial differences, all these tasks require coordinated activity in distributed brain areas centered around a core network consisting of the hippocampal formation and frontal cortical areas (Uhlhaas and Singer, 2006). In this article, we will refer to this network with the term ‘cognitive system’.

Only recently, olfaction gained attention in studying behaviors in the context of cognition. In rodents, cognitive functions are strongly influenced by the sense of smell as they use odor cues for memory, decision making, and navigation (Fischler-Ruiz et al., 2021; Igarashi et al., 2014; Symanski et al., 2021). Human behavior, even though we are not always consciously aware of it, is also influenced by odor cues, and the performance in olfactory and cognitive tests correlates in healthy adults (Yahiaoui-Doktor et al.,

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2019) and elderly (Uchida et al., 2020). The strong influence of olfaction on cognitive functions can be explained by a tight anatomical and functional coupling between the olfactory and the cognitive system.

In mammals, rhythmic inhalations evoke temporally structured activity in the olfactory bulb, which is termed as respiration rhythm. This prominent rhythm spreads not only within the olfactory system but also organizes activity in the cognitive system (Heck et al., 2019; Karalis and Sirota, 2022; Mori et al., 2013; Tort et al., 2018). The coordination of activity across spatially distributed areas facilitates communication within large-scale brain networks (Uhlhaas and Singer, 2006). Impaired coordination of activity in distributed brain networks centered on the hippocampal formation and the frontal cortex is thought to be the central network dysfunction underlying cognitive symptoms in mental disorders (Uhlhaas and Singer, 2006). Of note, the respiration rhythm coordinates activity in the cognitive system during early development (Gretenkord et al., 2019). Impaired synchronization of activity in the hippocampal-prefrontal networks in mental disorders manifests during neonatal ages when mice rely on olfaction as their main source of sensory input (Chini et al., 2020; Richter et al., 2019). At an older age, the decline in cognitive performance associated with mental disorders is accompanied by a decline in olfactory performance, and deficits in olfaction have been proposed as an early biomarker for disorders such as Alzheimer's disease and Parkinson's disease (Murphy, 2019).

With this review, we aim to link the concept of olfactory-driven coordination of widespread network activity with the correlation between olfactory and cognitive performance and discuss potential implications for mental disorders from the beginning until the end of life.

Lateral entorhinal cortex links the olfactory and cognitive system

The olfactory sensory neurons in the nasal cavity detect odor molecules and relay the information to the olfactory bulb; this is the initial processing stage of the olfactory information in the central nervous system. Mitral and tufted cells are the output neurons of the olfactory bulb and project to a range of brain areas considering the olfactory system, including the piriform cortex, lateral entorhinal cortex, and many more (Igarashi et al., 2012). The cognitive system consists of higher associative areas centered around the hippocampal formation and the frontal cortical networks, particularly the prefrontal cortex (Uhlhaas and Singer, 2006). The entorhinal cortex provides the main input to the hippocampus and is considered the gateway to the hippocampal-prefrontal network (Witter et al., 2017).

In contrast to all other senses, the olfactory system lacks a first-order thalamic relay resulting in a short pathway to the hippocampal formation, critical for cognitive functions (Figure 1). The lateral entorhinal cortex plays a prominent role in the interaction between the olfactory and the cognitive system. In addition to the direct input from the olfactory bulb, the lateral entorhinal cortex receives indirect olfactory input through the piriform cortex and sends outputs to a range of hippocampal subdivisions, as well as direct projections to the prefrontal cortex. Inputs from the olfactory bulb and piriform cortex arrive in superficial layers of the lateral entorhinal cortex and preferentially target reelin-expressing fan cells in layer 2a (Bitzenhofer et al., 2022). Nonoverlapping populations of fan cells project to the dentate gyrus and the medial prefrontal cortex, whereas pyramidal cells in layers 2b and 3 project to the hippocampal subdivision CA1 (Bitzenhofer et al., 2022; Leitner et al., 2016; Li et al., 2017; Xu et al., 2021). Projection neurons in the hippocampus project to deep layers of the lateral entorhinal cortex and the medial prefrontal cortex, among other areas (Witter et al., 2017). Further, the lateral entorhinal cortex is reciprocally connected with the orbitofrontal cortex that also receives input from the piriform cortex and is associated with the learning of odor value (Wang et al., 2020). Projections to the amygdala are thought to be involved in triggering emotional memory aspects. This information is also mediated to the hippocampus via the lateral entorhinal cortex which acts as

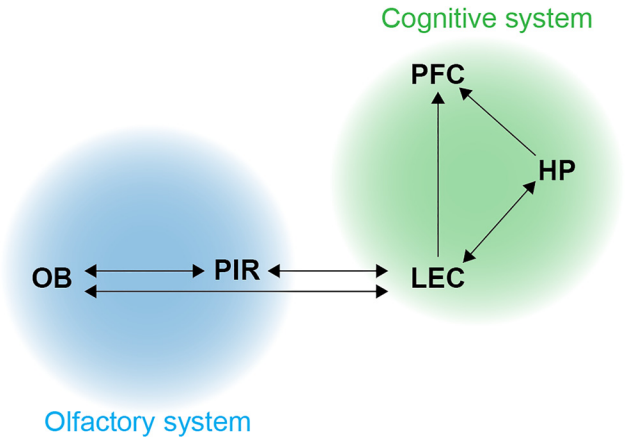

Figure 1: Simplified schematic showing the main connectivity between the olfactory system and the cognitive system. The lateral entorhinal cortex acts as a gateway between the two systems. (HP–hippocampus, LEC–lateral entorhinal cortex, OB–olfactory bulb, PFC–prefrontal cortex, and PIR–piriform cortex).

a gateway for amygdala influences on memory consolidation (Roesler and McGaugh, 2022).

The strong connectivity between the olfactory and the cognitive system has also been observed functionally. Odor exposure triggers a transient increase in firing rate in the olfactory system, but also in the lateral entorhinal cortex and the hippocampus (Bitzenhofer et al., 2022; Leitner et al., 2016), and learned odor value representations have been described in the prefrontal cortex (Wang et al., 2020). Further, direct projections from lateral entorhinal cortex pyramidal neurons to CA1 were shown to be important for associative odor memories (Li et al., 2017), and lateral entorhinal cortex lesions impair odor-associative memory (Persson et al., 2022; Wilson et al., 2013), object-place-context memory (Vandrey et al., 2020), and social memory (Lopez-Rojas et al., 2022). This emphasizes the important role of the lateral entorhinal cortex for the interaction between the olfactory and the cognitive system.

The communication between the olfactory and the cognitive system is not merely a unidirectional transfer of sensory information to higher associative areas. In addition to the bottom-up projections, there is a range of top-down projections within and between the two systems with the potential to modulate activity in early olfactory areas (Boyd et al., 2012; Chen and Padmanabhan, 2022). In fact, most areas that receive input from the olfactory bulb send direct feedback projections, including the piriform cortex and the lateral entorhinal cortex (Padmanabhan et al., 2019). While projections from the hippocampus to the olfactory bulb and piriform cortex do exist, they are sparse and their functions are not clear. However, the olfactory system receives a strong feedback from the cognitive system through the lateral entorhinal cortex, recently proposed to underlie the formation of spatial maps in the posterior piriform cortex during navigation (Poo et al., 2022) and to enable flexible coding strategies (Chen and Padmanabhan, 2022).

Olfactory activity synchronizes cognitive networks

In mammals, respiration results in the rhythmic sampling of olfactory information. Evoked activity in the olfactory sensory neurons during this repetitive sampling induces an oscillatory rhythm in the olfactory bulb, which is termed as respiration rhythm (Ackels et al., 2020). In rodents, this rhythm is typically in the range of 2–4 Hz, but can increase up to 12 Hz during sniffing and running (Kay et al., 2009). In humans, respiration is typically in the range of 0.16–0.33 Hz (Zelano et al., 2016). In rodents, nasal respiration modulates local field potentials and membrane oscillations in several cortical and subcortical brain areas including the piriform cortex, the lateral entorhinal cortex, the hippocampus, and the prefrontal cortex (Figure 2) (Biskamp et al., 2017; Lockmann et al., 2018; Tort et al., 2018).

The respiration rhythm is not the only rhythm associated with olfaction, but each inhalation induces a temporal sequence of rhythmic network activity on a faster timescale. Initially, odor inhalation induces activity in the gamma frequency range, followed by slower oscillations in the beta frequency range. Although brief gamma activity mainly reflects the coordination of odor-evoked activity in local networks, sustained activity in beta frequency synchronizes across the olfactory system and spreads into the cognitive system (Mori et al., 2013). Interestingly, the olfactory bulb gamma activity persists when the olfactory bulb output via the lateral olfactory tract is lesioned, but the odor-induced beta activity is disrupted, indicating that it depends on the feedback from downstream areas (Neville and Haberly, 2003). These rhythms are not only prominent in the olfactory system during odor sampling but also occur

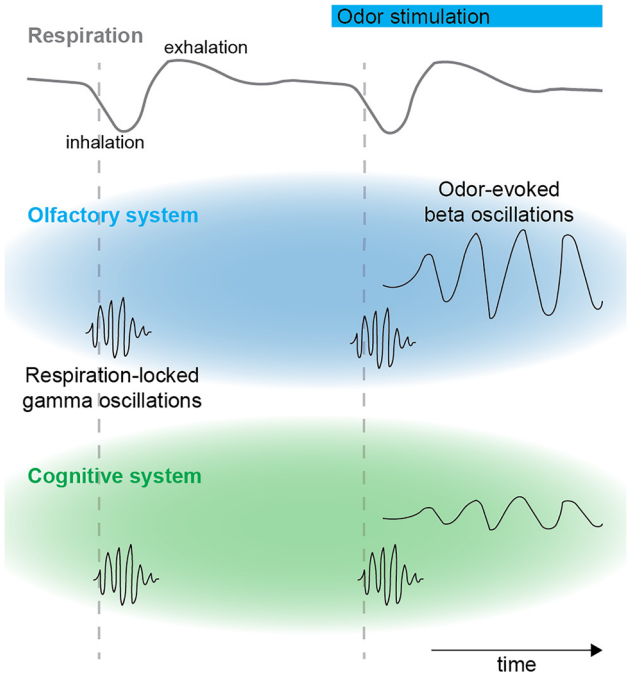

Figure 2: Olfactory activity synchronizes the olfactory system and the cognitive system in oscillatory rhythms. Respiration-related activity temporally organizes periods of high and low excitability that spread from the olfactory to the cognitive system and results in synchronized activity in the gamma frequency range. Odor stimulation induces synchronous activity in the beta frequency range in both systems.

in the cognitive system during odor-guided memory and decision-making tasks.

During working memory and decision-making tasks, the phase of the respiration rhythm modulates the local neuronal firing as well as the gamma and beta oscillations in several areas of the cognitive system, such as the hippocampus, the lateral entorhinal cortex, and the prefrontal cortex (Biskamp et al., 2017; Karalis and Sirota, 2022; Lockmann et al., 2018). The synchronization of remote brain areas is a hallmark of cognitive functions (Uhlhaas and Singer, 2006). Similar to the coordination of fast gamma activity by slower oscillations in the theta frequency range which is important for several cognitive functions such as working memory, the respiratory rhythm was suggested to coordinate the interactions between distant networks during cognitive processing (Heck et al., 2019; Karalis and Sirota, 2022).

Although studies causally testing the importance of this synchronization for cognitive performance are missing so far, first correlative studies in humans suggest that olfactory-driven synchronization of the cortical systems is important during memory processes and decision-making. In line with the rodent literature, recent studies in humans found a nasal breathing-induced respiratory rhythm in brain areas such as the piriform cortex, the hippocampus, and the amygdala. They show that the respiratory rhythm drops when participants switch to oral breathing and that the respiration rhythm modulates memory recall and task performance, indicating that nasal breathing directly influences cognitive performance (Nakamura et al., 2018; Zelano et al., 2016). In line with this, Arshamian and colleagues showed that memory consolidation is improved during nasal breathing compared to oral breathing in humans (Arshamian et al., 2018). Similar correlations of perception and cognition have been reported for other physiological rhythms, such as the heartbeat. How these other rhythms interact with the respiratory rhythm and its influence on cognition is not clear.

In addition to the respiratory rhythm, beta and gamma oscillations in brain areas such as the piriform cortex, the lateral entorhinal cortex, the hippocampus, and the prefrontal cortex have been implicated in the processing of olfactory information related to cognitive functions. Oscillations in the beta frequency range in the piriform cortex, the lateral entorhinal cortex, and the hippocampus arise during odor sensation and odor-guided learning tasks (Gourévitch et al., 2010; Igarashi et al., 2014). The lateral entorhinal cortex synchronizes fast oscillatory activity in distributed cortical areas critical for memory encoding in a hippocampus-dependent manner (Luo et al., 2022). Furthermore, oscillations in beta frequency synchronize across olfactory and cognitive networks during olfactory learning tasks and within hippocampus-prefrontal cortex networks during memory-guided decision-making tasks (Igarashi et al., 2014; Symanski et al., 2021). Of note, the firing of beta-entrained interneurons in hippocampal CA1 is linked to accurate performance during associative odor memory and decision-making tasks, suggesting that beta oscillations enable the recruitment and coordination of neurons that are involved in the processing of task-relevant odor information (Rangel et al., 2016; Symanski et al., 2021). Intracranial recordings in the human piriform cortex revealed similar odor-induced beta and gamma oscillations, and their presence was shown to correlate with accurate odor perception (Yang et al., 2022).

Thus, during olfactory-guided cognitive processing, the respiratory rhythm entrains the widely distributed brain areas of the olfactory and the cognitive system in beta and gamma oscillations.

Early entrainment of olfactory-cognitive networks

Rodents are born with limited sensory abilities. While their eyes and ears remain closed until the end of the second postnatal week (Martini et al., 2021), newborn rodents smell from birth, and their ability to survive depends strongly on the functionality of the sense of olfaction (Logan et al., 2012). Besides using olfaction for early cue-directed behaviors such as finding the nipple of the dam, newborn mice are also able to perform easy odor discriminations and form associative odor memories (Armstrong et al., 2006; Logan et al., 2012). In line with the early functionality of olfaction, mitral and tufted cells, the sole output neurons of the olfactory bulb, develop prenatally between embryonic day 11 and 16, and their afferent connectivity is largely established at birth (Hirata et al., 2019; Walz et al., 2006). By contrast, glutamatergic feedback connections to the olfactory bulb develop postnatally in an area-specific manner (Kostka and Bitzenhofer, 2022). Moreover, interneurons in the olfactory bulb are generated only during late embryonic to neonatal ages (Batista-Brito et al., 2008), and the biophysical properties of mitral cells are still maturing postnatally (Yu et al., 2015). Therefore, even though functional from birth, the olfactory bulb microcircuitry is still undergoing developmental changes during the first postnatal weeks. In line with this, the neonatal network activity in the developing olfactory bulb lacks the characteristic fast gamma oscillations

observed in adults during odor stimulation (Fletcher et al., 2005). An activity in the neonatal olfactory bulb is instead characterized by the respiratory rhythm as well as discontinuous oscillatory events in the theta/beta frequency range during passive sniffing and increased oscillatory activity in the beta frequency range during odor sampling (Gretenkord et al., 2019).

Axons of olfactory bulb mitral cells reach the lateral entorhinal cortex as well as the other regions of the olfactory cortex around embryonic day 16 (Walz et al., 2006). At neonatal ages, calbindin-expressing pyramidal neurons in layers 2b and 3 of the lateral entorhinal cortex project to the CA1 region of the hippocampus, which in turn projects to the prefrontal cortex (Hartung et al., 2016; Xu et al., 2021). Moreover, reelin-positive fan cells of layer 2a project to the dentate gyrus and prefrontal cortex at the neonatal age (Xu et al., 2021). Thus, the anatomical bottom-up connectivity between the olfactory and the cognitive system is established in neonatal mice. Besides the anatomical connectivity, the functional interaction between the olfactory system and the cognitive system is established early in life. Mitral cells in the developing olfactory bulb mediate the entrainment of lateral entorhinal cortex oscillations in the respiration rhythm as well as in theta/beta oscillations during passive sniffing (Gretenkord et al., 2019). Further, the activation of mitral cells by olfactory or optogenetic stimulation entrains the hippocampal-prefrontal network in beta oscillations by the end of the first postnatal week in mice (Gretenkord et al., 2019; Kostka and Hanganu-Opatz, 2021). Thus, olfactory inputs can influence coordinated activity patterns in developing cognitive networks.

Whether early synchronization of the olfactory and the cognitive system in oscillatory rhythms influences the maturation of these networks is unknown. However, considering the importance of oscillatory coupling in beta frequency between the hippocampus and the prefrontal cortex during neonatal development for the emergence of later cognitive abilities (Bitzenhofer et al., 2021; Chini et al., 2020; Richter et al., 2019; Xu et al., 2021), it is tempting to speculate that the olfactory experience during neonatal age may contribute to the functional development of these networks.

Correlated decline of olfaction and cognition in aging

Although many questions remain to be answered about the role of olfaction in the development of cognitive networks, a clearer picture starts to emerge at the other end of the life span. A decline in both olfactory sensation and cognitive abilities is common in old age (Attems et al., 2015; Murman, 2015). Although the performance in olfactory and cognitive tests correlates during adulthood, particularly strong associations can be found for the elderly (Uchida et al., 2020; Yahiaoui-Doktor et al., 2019). This association is not only present in healthy individuals, but a reduction in olfactory performance also correlates with cognitive impairments in Alzheimer's disease, Parkinson's disease, mild cognitive impairment, and others (Attems et al., 2015). Therefore, the olfactory function has been suggested as an early biomarker for cognitive decline in neurological disorders, particularly promising for Alzheimer's disease.

Impaired olfaction is among the most common non-motor dysfunction in Parkinson's disease and often appears before movement deficits (Doty, 2012). Pathological changes related to Parkinson's disease appear early in the olfactory bulb, but the mechanisms of olfactory dysfunction remain unclear. Interestingly, the olfactory dysfunction correlates with cognitive impairment and has been suggested as a biomarker for disease progression for Parkinson's disease (Cecchini et al., 2019). However, it is still unclear to what extent the olfactory dysfunction, and a potentially resulting lack of coordination in cognitive networks, contributes to cognitive symptoms in Parkinson's disease.

Structural and functional changes in the entorhinal cortex and hippocampus underlie cognitive impairment in dementia (Murphy, 2019). A functional disconnection between the hippocampus and the prefrontal cortex has been reported in patients with Alzheimer's disease (Grady et al., 2001). This dysfunction may underlie reduced olfactory working memory capacity reported in a mouse model for Alzheimer's disease (Huang et al., 2020). The hippocampal atrophy is correlated with olfactory impairment in patients with Alzheimer's disease (Murphy et al., 2003), and the disrupted connectivity in the olfactory bulb–lateral entorhinal cortex–hippocampus network is associated with deficits in recognition memory in a rat model for Alzheimer's disease (Salimi et al., 2022).

Due to its prominent position in the connection between the olfactory and the cognitive system, the lateral entorhinal cortex is the most likely candidate to link olfactory and cognitive deficits. The lateral entorhinal cortex is one of the first areas to show morphological abnormalities in Alzheimer's disease (Khan et al., 2014; Murphy, 2019; Stranahan and Mattson, 2010). Further, the selective vulnerability of neurons in layer 2 of the entorhinal cortex, the layer that

receives most olfactory input and sends strong projections to the hippocampus, has been reported during aging and Alzheimer's disease (Stranahan and Mattson, 2010).

Of interest, the loss of olfaction (anosmia) and cognitive impairments are associated with SARS-CoV2 infections. A recent study on patients with SARS-CoV2 infections found tissue damage in the primary olfactory cortex, a reduction of gray matter thickness in the parahippocampal gyrus, including the entorhinal cortex, as well as cognitive impairments (Douaud et al., 2022). Further studies are required to clarify how these alterations relate to each other.

Conclusions

Growing evidence points toward a powerful link between olfaction and cognition. Odor-evoked activity spreads across the entire olfactory and cognitive system, resulting in the modulation of neuronal activity by respiration and the synchronization of network activity in the beta frequency range in several brain areas. Thus, breathing provides a temporal framework of alternating activity levels that are able to synchronize distant brain areas. Strong connectivity between olfactory areas and the cognitive network underlies this phenomenon, with the lateral entorhinal cortex representing the major area linking the two systems. Only recently, the link between olfaction and cognition gained more attention in the field of neuroscience, and several findings point toward tight coupling of both systems across life. However, several open questions remain about the role of olfaction in cognition and its diagnostic potential (Box 1).

Due to the early functionality of olfaction compared to hearing and seeing and the early drive of the cognitive system, we hypothesize that the olfactory experience at the neonatal age might influence the development of the cognitive network. It remains to be investigated whether the olfactory input at a young age has a causal influence on the development of the hippocampal-cortical network and thus the emergence of cognitive abilities later in life. How the sense of smell influences network synchronization in the cognitive systems during development is also interesting in the light of the early manifestation of disrupted network synchronization in mental disorders such as schizophrenia long before symptoms emerge (Chini et al., 2020). If a causal link between olfactory dysfunction and impaired maturation of the cognitive network exists, then an impaired sense of smell during development could act as a possible biomarker for the presymptomatic diagnosis of mental disorders.

The influence of sensory systems on cognitive systems is not unique to olfaction. Other sensory systems are associated with cognitive abilities and mental disorders; however, the influence of olfaction seems to be particularly strong and shows the greatest promise as an early biomarker for Alzheimer's disease and Parkinson's disease (Doty, 2012; Murphy, 2019). The strong and direct connectivity between the olfactory and cognitive system, as well as the rhythmic sampling during respiration coordinating activity in widespread networks, could be the reason for the crucial role of olfaction. However, it is unclear whether the olfactory dysfunction is specific enough to dissociate between diseases and whether the link between the association of olfactory and cognitive dysfunctions is causal or merely correlational. Nevertheless, including olfactory dysfunction as a biomarker for Alzheimer's disease and Parkinson's disease bears great potential for the detection and prediction of disease progression at early stages, critical for therapeutic intervention. Whether the diagnostic potential transfers to cognitive symptoms in other disease types needs further investigation.

Box 1: Open questions.

Does olfactory experience during early development influence the functional maturation of the cognitive system and the development of cognitive abilities?

Is the coordination of activity in the cognitive system by the respiration rhythm necessary for cognitive processing?

Is olfactory dysfunction specific enough as a biomarker for Alzheimer's disease and Parkinson's disease? Does olfactory dysfunction and the lack of coordination in olfactory rhythms contribute to cognitive dysfunctions?

Does olfactory dysfunction contribute to cognitive symptoms in other mental and neurodevelopmental disorders?

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Bionotes

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Presentation of scientific institutions

Kristina Endres*, Bernd Bufe and Alexey Tarasov

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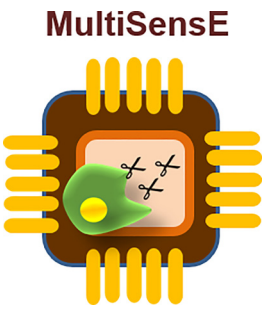

“Multiparametric sensors for real-time analysis of inflammatory processes”

In 2018, the German state of Rhineland-Palatinate introduced a new funding program, called “Forschungskolleg Rheinland-Pfalz”. The goal is to foster collaborations and joint doctoral programs between Universities and Universities of Applied Sciences (UAS). It should also encourage UAS graduates to pursue a PhD degree.

In 2021, a new interdisciplinary consortium was positively evaluated by the Ministry of Science and Health: MultiSensE. The consortium is led by Hochschule Kaiserslautern (a UAS) with three principal investigators (PIs) participating: Bernd Bufe, Monika Saumer, and Alexey Tarasov (project coordinator). The university partners are JGU Mainz, represented by three PIs: Kristina Endres, Tanja Schirmeister, Christian Kersten, and TU Kaiserslautern with PI Christiane Ziegler. The partners cover a broad range of expertise from physics and chemistry to biology and pharmacy. Together with five doctoral students, the PIs develop new tools for real-time analysis of inflammatory processes.

The project is focused on proteases, a class of enzymes that help the body to cleave protein molecules. Proteases are crucial for activation and invasion of immune cells and support physiological function that protects the organism against infections and other threats. Malfunctions in this diverse family of enzymes promote chronic inflammatory processes, which may worsen or even lead to the onset of many disorders such as Alzheimer’s disease, multiple sclerosis and inflammatory bowel disease. Due to their central role in disease progression, proteases are also considered as targets for novel therapies. However, the exact mechanisms of protease malfunction are so far only insufficiently understood, in part due to a lack of appropriate tools. Therefore, there is a large need for new time- and space-resolved assay methods and technology platforms that allow highly parallel non-invasive analysis of protease activity at the cellular and subcellular level. A simultaneous recording of further parameters such as morphology, electrical activity or oxidative stress in real time would be helpful to open up new fields of application in diagnostics and therapy through a more precise understanding of cell type specific reactions. Requirements for such a system are optical transparency, nanomaterial-driven selective attachment of cells, and appropriate signal-to-noise ratios for accurate measurements. Finally, the array should be adapted to small-scale multi-well formats and made available for long-term measurements.

The MultiSensE project develops a new type of biosensor technology that combines rapid measurement of protease activity with multiple disease-related cell parameters. Among available technologies, potentiometric biosensors have an attractive set of properties that can fulfil the requirements stated above. Potentiometric biosensors are easy to miniaturize, non-invasive, and have been used successfully for the detection of pH changes, small metal ions, and proteins with high sensitivity and selectivity.

Electrodes are modified with synthetic designer peptides, carrying a charged group (Figure 1). Target proteases can cleave the peptide at a specific site underneath the charged group. As a result, the charged group is removed and the sensor signal decreases.

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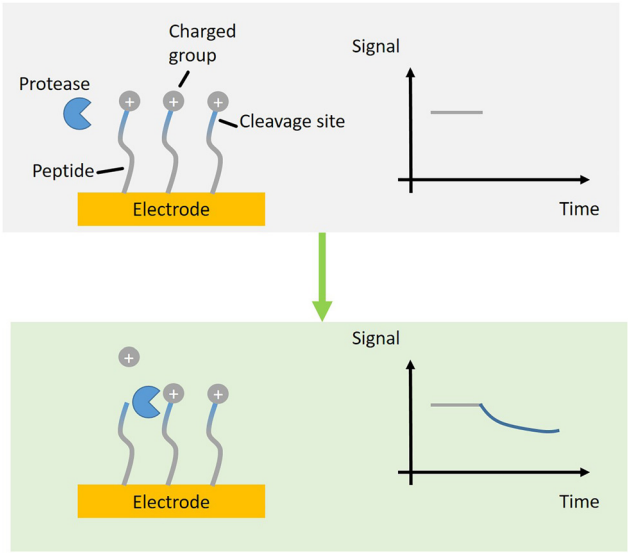

Figure 1: Principle of the protease biosensor. Upper panel: Charged peptides with high specificity for model proteases are tethered to the electrode surface. This yields a stable baseline of the electrical signal. Lower panel: Upon cleavage by released proteases, charge on the electrode is diminished, reducing the sensor signal.

The cells are placed on adherent layers next to the electrodes (Figure 2). The activity of proteases released from cells will be directly measured by the adjacent biosensor. The use of new transparent materials will also allow additional microscopic observation of various cell parameters, including pH, calcium concentration, oxidative stress, cell cycle or apoptosis.

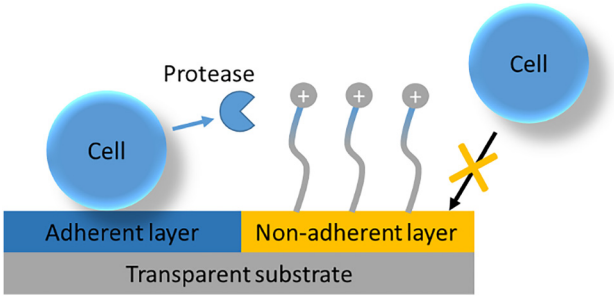

Figure 2: Measurement scheme for proteases released from cells.

In addition to its scientific goals, the consortium offers a structured doctoral program to train the PhD students. Each PhD student is supervised by a Thesis Advisory Board, consisting of one professor from a university and one from UAS. The PhD program includes a bundle of measures to provide excellent training for the PhD students, to reach the European[1] and German[2] profile descriptors for first-stage researchers, and in line with the vision “Talented Researchers for Society” set out by the League of European Research Universities.[3]

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Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

1 https://euraxess.ec.europa.eu/europe/career-development/training-researchers/research-profiles-descriptors.
2 https://www.kmk.org/fileadmin/Dateien/veroeffentlichungen_beschluesse/2017/2017_02_16-Qualifikationsrahmen.pdf.
3 https://www.leru.org/publications/doctoral-degrees-beyond-2010-training-talented-researchers-for-society.

Nachrichten aus der Gesellschaft

https://doi.org/10.1515/nf-2022-0015

Protokoll der Mitgliederversammlung, Sonntag, 10. Juli 2022
(Paris, Expo Porte de Versailles, im Rahmen des FENS Forum 2022)

Versammlungsleiter ist der Vize-Präsident der Neurowissenschaftlichen Gesellschaft, Prof. Dr. Frank Kirchhoff

Protokollführerin ist die Sektionssprecherin Prof. Dr. Veronica Egger in Vertretung des entschuldigten Generalsekretärs der Neurowissenschaftlichen Gesellschaft.

Die Anzahl der teilnehmenden Mitglieder beträgt 16.
Die Versammlung wurde satzungsgemäß einberufen, die Tagesordnung war den Mitgliedern bei der Einberufung mitgeteilt worden.

Beginn: 18:45 Uhr
Ende: 20:00 Uhr

Tagesordnung

(1) Begrüßung durch den Vize-Präsidenten
(2) Bestätigung des Protokolls der letzten Mitgliederversammlung
(3) Bericht des Schatzmeisters/Bericht der Kassenprüfer
(4) Mitteilungen
(5) Bericht zur Göttinger Jahrestagung 2023
(6) Vorstandswahlen 2023
(7) Aktivitäten der Gesellschaft
(8) Verschiedenes

1 Begrüßung durch den Vize-Präsidenten

Frank Kirchhoff begrüßt die Anwesenden und eröffnet die Sitzung. Ergänzungen zur Tagesordnung werden nicht gewünscht.

2 Bestätigung des Protokolls der letzten Mitgliederversammlung

Das Protokoll der letzten Mitgliederversammlung vom 22. März 2021 ist in der Ausgabe 2/2021 von Neuroforum erschienen. Ergänzungen werden nicht gewünscht. Es wird mit 16 Ja-Stimmen, 0 Enthaltung und 0 Nein-Stimmen angenommen.

3 Bericht des Schatzmeisters / Bericht der Kassenprüfer

Frank Kirchhoff erläutert in Vertretung für den Schatzmeister Ansgar Büschges die Jahresabrechnung der NWG zum Ende 2021 im Vergleich zu den Vorjahren und kommentiert einige Posten. Wie immer zeigt die Jahresabrechnung der NWG die zweijährigen, durch die Göttinger Tagung bedingten Schwankungen, d.h. in den geraden Jahren fließen die Teilnehmergebühren auf das NWG-Konto, und in den ungeraden Jahren wird das Geld

für die Göttinger Tagung wieder ausgegeben. Durch die Online-Tagung in 2021 zeigen sich Kosten und Ausgaben zwar auf einem geringeren Level, aber es ergibt keine gravierende Änderung in der Gesamtdarstellung.

Seitdem die Klaus Tschira Stiftung die Finanzierung von dasGehirn.info übernommen hat, gehen auch diese Einnahmen und Ausgaben direkt über die NWG und nicht mehr über den Sponsor, wie zu Zeiten der Hertie-Finanzierung. Zudem ist auffällig, dass aufgrund der Corona-Situation kaum Reisekosten angefallen sind und die Beitragserhöhung sowie Neuaufgliederung der Mitglieder eine leichte Erhöhung der Beitragseinnahmen mit sich geführt hat. Frank Kirchhoff weist zudem darauf hin, dass trotz des guten Jahresendergebnisses die Vermögensentwicklung weiterhin eine Tendenz nach unten aufweist.

Die Einnahmen und Ausgaben der NWG im Jahr 2021 wurden am 21. und 22. Februar 2022 von den Kassenprüfern Helmut Kettenmann und Christian Rosenmund geprüft. Die Kassenprüfer bestätigen eine korrekte Kontenführung und empfehlen der Mitgliederversammlung, den Schatzmeister zu entlasten.

Die Mitgliederversammlung entlastet den Schatzmeister auf der Grundlage des Berichts der Kassenprüfer mit 16 Ja-Stimmen, 0 Enthaltung und 0 Nein-Stimmen.

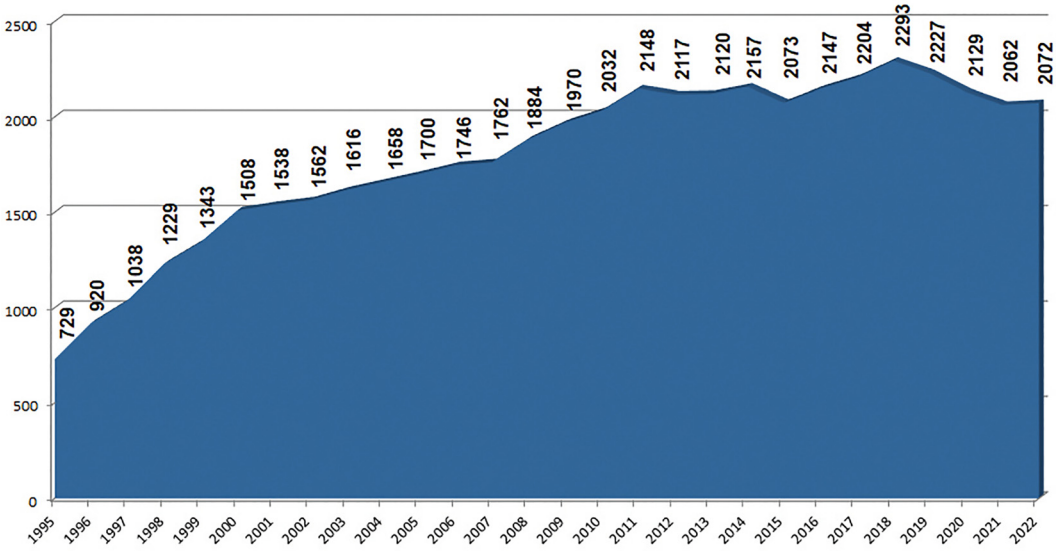
Helmut Kettenmann und Christian Rosenmund sind bereit, die Kassenprüfung 2023 nochmals zu übernehmen. Die Mitgliederversammlung bestätigt die Kassenprüfer Helmut Kettenmann und Christian Rosenmund für die Kassenprüfung 2022 mit 16 Ja-Stimmen, 0 Enthaltung und 0 Nein-Stimmen.

Die Mitgliederversammlung entlastet den Vorstand mit 16 Ja-Stimmen, 0 Enthaltung und 0 Nein-Stimmen.

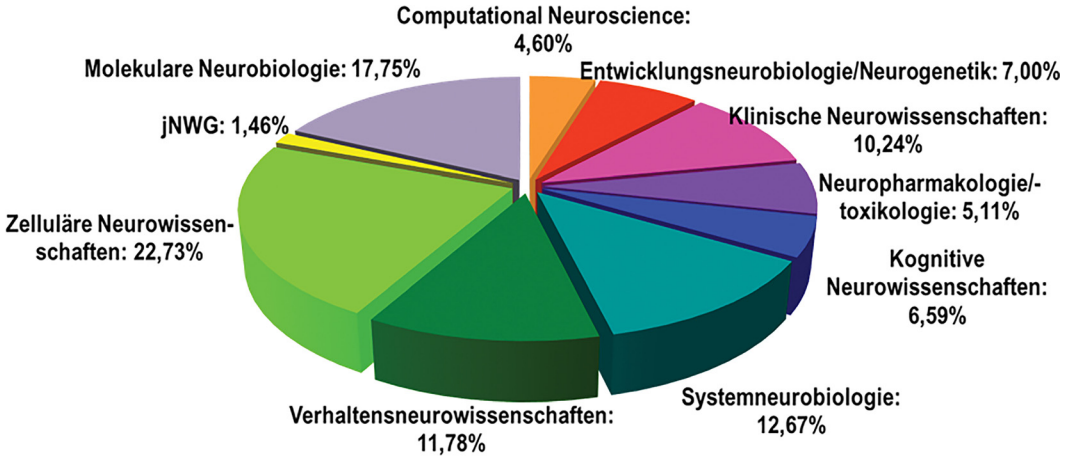
4 Mitteilungen

4.1 Mitgliederzahlen und Sektionsverteilung

Die Mitgliederzahlen stagnieren, liegen aber seit 2010 konstant über 2.000. Dennoch gibt es weiterhin Potential und Frank Kirchhoff ruft die Principal Investigators auf, die NWG als Networking-Organisation weiter zu stärken und in den eigenen Gruppen Mitarbeiter zur Mitgliedschaft zu ermuntern.



Entwicklung der Mitgliederzahlen 1995 – 2022



Die Sektionsstärken haben sich seit Jahren kaum verändert.

Die Verteilung der Mitglieder auf die Sektionen ist weiterhin unverändert. Frank Kirchhoff weist darauf hin, dass es bis zu 18 weitere Gesellschaften mit dem Titel „Neuro“ im Namen gibt und äußert den Wunsch mehr klinische Kollegen für die NWG zu gewinnen.

Anhand einer Übersicht erläutert Frank Kirchhoff noch einmal die neue und gerechtere Eingruppierung der Mitglieder seit 2020, welche sich mit Stand 1.1.2022 folgendermaßen aufteilen: Studierende ca. 22%, Postdocs ca. 33% und Seniors ca. 45%.

4.2 FENS

Die NWG hat die Teilnahme am FENS Forum 2022 mit 10 Stipendien in Höhe von 500€ an engagierte Nachwuchsforscher unterstützt. Diese wurden von dem Komitee Ansgar Büschges und Frank Kirchhoff ausgewählt und schließlich am 10. Juli 2022 am FENS-Stand an die Stipendiaten verteilt.

Bezugnehmend auf das FENS Forum selbst weist Frank Kirchhoff darauf hin, dass im Programmkomitee für das FENS Forum keine deutschen Mitglieder vertreten sind und dass es auch keine deutschen Sprecher in den Plenary und Special Lectures gibt. Das letzte FENS Council Meeting war vom 30.11. bis 1.12.2021 und die NWG wurde durch Christine Rose vertreten. Die Wahl für das FENS Executive Committee und weitere Committees für die Amtsperiode 2022 – 2024 erfolgte beim FENS Council Meeting am Vortag. Leider wurden die von der NWG vorgeschlagenen Kandidaten nicht gewählt. Die Wahl zum Programmkomitee für das FENS Forum 2024 wird beim Council Meeting im November 2022 erfolgen. Vor diesem Hintergrund ruft Frank Kirchhoff auf, aktiver zu werden, um besser vertreten zu sein und die deutsche Forschung präsenter zu machen.

4.3 German Brain Council

Frank Kirchhoff informiert, dass Christine Rose als Beisitzerin im German Brain Council (GBC) die Grundlagenwissenschaften seit 1.1.2020 in Nachfolge von Hans-Joachim Pflüger vertritt. Ziel des GBC ist es, die Interessen von Neurowissenschaftlern ins Bewusstsein von Parlamentariern zu rücken. Frank Kirchhoff benennt die weiteren Beisitzer sowie den aktuellen GBS Vorstand.

4.4 Leopoldina

Die NWG wird nun für das siebte Deutsch-Israelische Neuroscience Inter-Academy Symposium die zur Verfügung gestellten Stipendien (in Höhe von insg. maximal 2.500€) auszahlen können. Das bisher durch die Corona-Situation verschobene Meeting konnte jetzt vom 28. - 29. Juni 2022 stattfinden.

4.5 DFG Fachkollegienwahl

Die NWG ist bei der Fachkollegienwahl 2022 in 14 Fachkollegien vorschlagsberechtigt. Frank Kirchhoff führt aus, dass dies einerseits die Kerngebiete der Neurowissenschaften sind (2.23-01 bis 2.23-11), sowie bei den Grundlagen der Biologie und Medizin auch die Bioinformatik und Theoretischen Biologie (2.21-07). Hinzu kommen diesmal bei der Psychologie die Biologische Psychologie und Kognitive Neurowissenschaften (1.22-02) sowie im Bereich der Zoologie die Biologie des Verhaltens und der Sinne (2.13-04). Die NWG darf insgesamt 86 Kandidierende vorschlagen (doppelte Anzahl der zu

Wählenden). Dies erfolgt meist in Abstimmung mit anderen Fachgesellschaften, um den Vorschlägen mehr Nachdruck zu verleihen. Frank Kirchhoff macht darauf aufmerksam, dass es eine einzigartige Situation ist, dass Wissenschaftler für Wissenschaftler in diesem Rahmen eine Wahl treffen und fordert auf, vielzählige Vorschläge zu machen.

5 Bericht zur Göttinger Tagung

Die Göttinger Tagung 2023 ist bereits in Vorbereitung und sowohl die Auswahl der Symposien als auch die der Hauptredner ist getroffen und bestätigt. Frank Kirchhoff führt aus, dass sich die kommende Tagung wie gewohnt aus 34 Symposien (aus 54 Vorschlägen), 7 Hauptrednern und der Schilling-Preis-Lecture, 2 Breaking News Symposien, dem Schram-Satellite-Symposium und verschiedenen Workshops zusammensetzen wird. Die Deadline für Early Registration, Abstract Submission und Stipendienbewerbungen ist der 12. Oktober 2022. Anhand der Übersicht der ausgewählten Symposien und Benennung einzelner zeigt Frank Kirchhoff die Bandbreite der kommenden Tagung auf.

6 Vorstandswahlen 2023 – 2025

6.1 Vorschläge für Kandidierende

Frank Kirchhoff weist auf die Neuwahlen für den Vorstand 2023-2025 hin und macht darauf aufmerksam, welche der bisherigen Mitglieder nicht mehr kandidieren möchten oder können. Einerseits stellt er die Vorschläge des Vorstandes für neue Kandidaten vor, andererseits bittet er dringend um Vorschläge aus den Reihen der Mitglieder. Beim Kandidaten Gary Lewin als möglichen künftigen Generalsekretär führt er aus, dass dieser als wissenschaftlicher Repräsentant gleichzeitig gut den Standort der Geschäftsstelle und die Gesellschaft verknüpfen könnte. Vorschläge für die Neuwahlen sind bis zum 1. September 2022 an die Geschäftsstelle zu richten.

6.2 Wahlmodus

Frank Kirchhoff erläutert, dass die bisherige Briefwahl aus unterschiedlichen Gründen nicht mehr zeitgemäß ist und stellt diese und die elektronische Wahl gegenüber. Er weist darauf hin, dass es keine Mischform von Briefwahl und elektronischer Wahl geben wird. Für die Umstellung auf die elektronische Wahl ist eine Satzungsänderung notwendig, die entsprechend folgenden Wortlaut hätte: „Die Mitglieder des Vorstands werden auf Vorschlag des Vorstandes durch Briefwahl ***oder durch vergleichbare sichere elektronische Wahlformen*** von den Mitgliedern der Gesellschaft gewählt."

Die Mitgliederversammlung stimmt der Satzungsänderung mit 15 Ja-Stimmen, 0 Enthaltung und 1 Nein-Stimme zu.

7 Aktivitäten der Gesellschaft

7.1 Lehrerfortbildung

Die Veranstaltungen der Lehrerfortbildung bringen neueste Erkenntnisse in die Schulen und sorgen für Transparenz der Wissenschaft und Forschung. In der Hoffnung, dass die Corona-Situation nicht erneut verschiedenste Aktivitäten ausbremst, bittet Frank Kirchhoff um weitere Vorschläge für das kommende Schuljahr.

7.2 Methodenkurse

Die angebotenen Methodenkurse sind coronabedingt leider sehr zurückgegangen. Hier wäre es wünschenswert, wenn sie die Anzahl wieder verdoppelt und Frank Kirchhoff bittet wie bei der Lehrerfortbildung die Mitglieder umgehend noch aktiv zu werden und Vorschläge für Veranstaltungen einzureichen.

7.3 dasGehirn.info

Frank Kirchhoff betont, dass dasGehirn.info der Outreach der NWG ist und die Website nach wie vor erfreuliche Aufmerksamkeit generiert. Um diese zu erhalten bzw. zu verbessern, werden einige Veränderungen auf der Website angestrebt. Hierzu gehört, dass folgende 5 Bereiche neu entstehen werden: Forschung in Instituten und Programmen, in Organisationen, in Verbänden, in Patientenvereinigungen und in Forschende Pharma. Diese Aufgliederung bietet Verbänden und Organisationen die Möglichkeit, sich klarer darzustellen und Schwerpunkte herauszuarbeiten.

Frank Kirchhoff weist in diesem Zusammenhang auf mehrere Kooperationen mit DFG-Projekten und weiteren Themenpartnerschaften hin, die derzeit in Vorbereitung sind. Er informiert außerdem, dass die kostenneutrale Projektlaufzeitverlängerung durch die Klaus-Tschira-Stiftung zum 31.12.2023 endet und von der Heinz und Chica Schaller-Stiftung eine Zusage über eine Förderung von 150.000€ für drei Jahre vorliegt.

7.4 Neuroforum

Das Neuroforum als Organ der Gesellschaft wird aus Kostengründen zum Ende des Jahres als Printversion eingestellt und in einem digitalen Format zur Verfügung stehen.

7.5 Junge NWG (jNWG)

Frank Kirchhoff gibt kurz einen Überblick zu den Aktivitäten der jNWG wie den Virtual Career Pitch, die eigenverantwortliche Durchführung der erfolgreichen NeuroCon und dem Beitrag an der Göttinger Tagung mit einem eigenen Symposium. Er stellt heraus, dass die Zusammenarbeit und Synchronisation mit anderen Gesellschaften sehr wichtig ist und sieht die jNWG hier vorneweg. Sie strebt mehr Zusammenarbeit mit den Nachwuchsorganisationen in Deutschland (Junge Physiologen, Junge Neurologen) und der EU an.

7.6 NWG-Preise

Im Zusammenhang mit der Göttinger Tagung wird auch wieder der Schilling-Forschungspreis ausgeschrieben. Frank Kirchhoff bittet für diesen gut dotierten Preis um zahlreiche Bewerbungen und die Motivierung potentieller Kandidaten im jeweiligen Umfeld.

Zudem kündigt er an, dass auch der Breaking News Preis im Rahmen der Göttinger Tagung 2023 auf der Grundlage der beiden dort stattfindenden Breaking News Symposien wieder verliehen werden wird.

7.7 Stipendien

Frank Kirchhoff gibt einen Überblick zur Vergabe der Stipendien von 2019 bis 2023 im Rahmen der Veranstaltungen Göttinger Tagung, FENS Forum und Deutsch-Israelisches Inter-Academy Neuroscience Symposium der Leopoldina. Er weist darauf hin, dass die in 2022 vergebenen Stipendien nach aktualisierten Kriterien ausgewählt wurden, die im Vorstand zuvor diskutiert und beschlossen worden waren. Wichtigste Neuerungen sind, dass pro Labor nur eine Bewerbung akzeptiert wird, dass bei Studierenden oder Postdocs aus Verbundprojekten und gut finanzierten Instituten eine Begründung gefordert wird, warum die Reise mit einem Stipendium finanziert werden soll, und dass die Promotion nicht länger als 4 Jahre zurückliegen soll.

8 Verschiedenes

Es werden keine weiteren Diskussionspunkte gewünscht.

Ende der Sitzung: 20:00 Uhr

Prof. Dr. Frank Kirchhoff
(Vize-Präsident)

Protokollführer
Prof. Dr. Veronica Egger
(Sektionssprecherin Zelluläre Neurobiologie)

Kandidatenvorschläge erbeten: Vorstandswahl für die Amtsperiode 2023–2025

Liebe NWG-Mitglieder,

laut Satzung ist im Januar 2023 die Wahl des NWG-Vorstandes für die Amtsperiode 2023–2025, die mit dem Ende der Göttinger Tagung am 25. März 2023 beginnen wird, fällig.

Alle Mitglieder sind aufgefordert, Vorschläge für die Positionen der Sektionssprecher*, des Schatzmeisters, des Generalsekretärs und des Vizepräsidenten bei der Geschäftsstelle einzureichen.

Das Amt des Präsidenten steht nicht zur Wahl, laut Satzung wird der Vizepräsident der vorangegangenen Amtsperiode automatisch Präsident der nächsten Amtsperiode.

Es können nur Vorschläge berücksichtigt werden, die die komplette postalische Adresse, die Telefonnummer und die Email-Adresse des Kandidaten enthalten.

Der Stichtag für die Einsendung von Vorschlägen ist der **1. September 2022**.

Bitte schicken Sie diese per Email an Meino Alexandra Gibson (gibson@mdc-berlin.de)

Die Vorschläge werden von der Wahlkommission der NWG für die endgültige Wahlliste gesichtet und bei Bedarf ergänzt werden.

*für alle Personen-und Amtsbezeichnungen gilt selbstverständlich m/w/d.

Stipendien für die Teilnahme am 15th Göttingen Meeting of the German Neuroscience Society (Göttingen, 22. – 25. März 2023)

Auch in diesem Jahr stellt die Neurowissenschaftliche Gesellschaft wieder Stipendien für die Teilnahme am 15th Göttingen Meeting of the German Neuroscience Society zur Verfügung stellen. Wird das Meeting physisch stattfinden, beträgt die Höhe des Stipendiums pauschal 300 €. Sollte es ein virtuelles Meeting werden, übernimmt die NWG die Registrierungsgebühr und die Abstract Handling Fee bis max. 300 €. Wenn es als Hybrid-Meeting stattfindet, wird je nach Art der Teilnahme das eine oder das andere bezahlt.

Die Auswahl aus den Bewerbungen trifft ein Komitee aus NWG-Vorstandsmitgliedern.

Für eine Bewerbung sind folgende Kriterien zu erfüllen:

- Bewerben können sich Promovierende und junge Postdocs, deren Promotion zum Zeitpunkt der Bewerbung nicht weiter als 4 Jahre zurück liegt, und
- die mit einem eigenen Beitrag teilnehmen und davon Erstautor sind,
- und die NWG-Mitglied sind, egal ob sie im In- oder Ausland leben und arbeiten.

Die Bewerbung muss über die Homepage der NWG (https://nwg-info.de/de/karriere/stipendien/jahrestagung/application) eingereicht werden.

Folgende Unterlagen sind auf Deutsch oder auf Englisch einzureichen:

- Bewerbungsschreiben (max. 3.000 Zeichen inkl. Leerstellen)
- Lebenslauf (max. 3.000 Zeichen inkl. Leerstellen)
- Publikationsliste (falls vorhanden)
- Kopie des beim Göttingen Meeting 2023 präsentierten Abstracts (max. 3.000 Zeichen inkl. Leerstellen)
- Ein kurzes Unterstützerschreiben, wobei jeder Arbeitsgruppen-Leiter nur einen Antrag unterstützen darf.
- Anträge aus Verbundprojekten (SFB, FOR, GRK) oder Blaue Liste Instituten (MPI, etc.) müssen eine Begründung beinhalten, warum auf die begrenzten Mittel der NWG zurückgegriffen wird

Unvollständige Anträge werden nicht gewertet und gleich abschlägig beschieden.

Die Bewerbung um ein Stipendium ersetzt NICHT die Registrierung für das Göttingen Meeting. Diese muss unabhängig von der Stipendienbewerbung durchgeführt werden.

Bewerbungsschluss ist der 12. Oktober 2022.

NEU auf dasGehirn.info

Im Juni ist dasGehirn.info mit dem Thema **Gehirntrauma** online gegangen, das mit den folgenden Beiträgen erarbeitet wurde:

Lädierte Sportlerhirne - Der Kopf von Boxern, American-Football-, Eishockey- oder Fußballspielern ist immer wieder Stößen ausgesetzt. Auf lange Sicht kann dies Krankheiten auslösen, darunter verschiedene Formen der Demenz.

Traumatische Folgen fürs Gehirn - Das Schädel-Hirn-Trauma ist die „große" Gehirnerschütterung. Groß und vielfältig sind die Erschütterungen für die Nervenzellen in der Tat.

Erschütternde Folgen - Gehirnerschütterung? Halb so wild, denken viele. Und so machen Sportler nach einem Rumms gegen den Schädel häufig einfach weiter. Doch er kann Anstoß zu einer Kettenreaktion sein, die noch über Jahre Spuren hinterlässt.

110 Hirne - Die chronisch traumatische Enzephalopathie (CET) war lange Zeit ein Waisenkind unter den Erkrankungen des Gehirns. Erst die Arbeit einer Pathologin zeigte, wie groß das Problem wirklich ist.

Unter dem Titel **Hirnschäden durch Sport?** führte Arvid Leyh 2017 ein Videointerview mit Prof. Michael Fröhlich und Prof. Eckhard Friauf: Gehirnerschütterung ist eine triviale Angelegenheit. Denken wir, kennen wir ja. Doch so einfach ist es nicht: Es mehren sich die Hinweise, dass eine Häufung – im American Football, im Boxen – zu echten Hirnschäden führen kann. Auch im Fußball?

2019 entstand am Rande der NWG-Tagung das Videointerview: **Ann McKee on CTE**: Ihre Erkenntnisse über Chronic traumatic encephalopathy #CTE haben es bis in die New York Times geschafft. Wer mit Fußball (soccer) oder American Football zu tun hat, sollte sich das vermutlich ansehen, denn selbst Gehirnerschütterungen sind nicht harmlos.

In der Mediathek ist ein neuer Beitrag hinzugekommen:
#BerlinBrains2022: "Let's take a cold hard look at how the brain represents temperature": It feels very natural to touch an object and immediately identify whether it is warm or cold. But how does this actually work? As natural as sensing temperature may seem to us, we still don't know how and where the brain makes sense of temperature information. Jean-Sébastien Jouhanneau and Clarissa Whitmire explain in their talk how the brain processes sensory information to generate a perception of the outside world and what their results mean for all of us.

Es heißt, Menschen sind Augentiere. Dabei ist der Tastsinn nicht weniger wichtig, um eine Wahrnehmung unserer Umwelt zu erzeugen. Dass sich unsere Farbwahrnehmung aus drei Farben zusammensetzt, ist bekannt. Schon Hermann von Helmholtz erkannte, dass es in der Netzhaut drei Rezeptoren für die drei Grundfarben Rot, Grün und Blau gibt. Doch wie nehmen wir Temperatur wahr? Gibt es da auch getrennte Empfänger für kalt und warm? Und wie entsteht die Wahrnehmung im Gehirn? Jean-Sébastien Jouhanneau und Clarissa Whitmire vom Max-Delbrück-Centrum für molekulare Medizin nehmen Sie mit auf eine Reise in die Welt aus Temperatur und Tastsinn bis Ihnen kalt und heiß wird, wenn Sie die Welt wahrnehmen wie nie zuvor...

In dem Format **Frage an das Gehirn** beantworten Experten regelmäßig Fragen unserer Leser. Zuletzt ging es um die folgenden Fragen:

Hat sich das Gehirn in den letzten 500 Jahren verändert? - Hat sich das menschliche Gehirn in den letzten 500 Jahren angepasst, um sich an die Informationsflut anzupassen?

Warum machen Schokoriegel gute Laune? – Ist eigentlich bekannt, wie Schokolade im Gehirn bewirkt, dass wir gute Laune bekommen?

Was passiert beim Grübeln im Gehirn? - Manchmal komme ich ins Grübeln und kann gar nicht wieder aufhören. Warum ist das so und was passiert dabei im Gehirn?

In der Rubrik **Neues aus der Wissenschaft** macht dasGehirn.info Ende Mai / Anfang Juni 2022 auf die folgenden Pressemeldungen aus den Instituten aufmerksam:

Kein Hirntumorrisiko durch Handystrahlung | Deutsche Gesellschaft für Neurologie e.V. (31.05.2022)

Gesunde Entwicklung dank älterer Geschwister | Max-Planck-Institut für evolutionäre Anthropologie (31.05.2022)

Neuer antidepressiver Wirkmechanismus von Ketamin entdeckt | Max-Planck-Institut für Psychiatrie (01.06.2022)

Primaten und Nichtprimaten unterscheiden sich im Bau der Nervenzellen | Ruhr-Universität Bochum (03.06.2022)

Eiweißveränderungen im Nervenwasser zeigen Entzündungsprozesse im Gehirn an | Deutsches Zentrum für Neurodegenerative Erkrankungen e. V. (DZNE), Eberhard-Karls-Universität Tübingen, Hertie Institute für klinische Hirnforschung (15.06.2022)

Schädel-Hirn-Verletzungen erhöhen das Risiko für schwere Folgeerkrankungen | Deutsche Gesellschaft für Neurologie e.V. (16.06.2022)

Beruhigen, um zu denken: neue Netzwerke im menschlichen Gehirn | Max-Planck-Institut für Hirnforschung (23.06.2022)

Möchten Sie eine Pressemeldung an **dasGehirn.info** weitergeben oder Ihr Institut vorstellen, wenden Sie sich bitte an Arvid Leyh (a.leyh@dasgehirn.info).

Neueintritte

Folgende Kolleginnen und Kollegen dürfen wir als Mitglieder der Neurowissenschaftlichen Gesellschaft begrüßen:

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Der Mitgliedsstand zum 15. Juli 2022 beträgt 2.072 Mitglieder.