Unraveling the Link between Olfactory Deficits and Neuropsychiatric Disorders

Symposium

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Kun Yang,[1] Carlos Ayala-Grosso,[2,3] Janardhan P. Bhattarai,[4] Andrew Sheriff,[5] Tsutomu Takahashi,[6] Alexandre S. Cristino,[7] Christina Zelano,[5] and Minghong Ma[4]

[1]Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, Maryland 21287, [2]Unit of Cellular Therapy, Centre of Experimental Medicine, Instituto Venezolano de Investigaciones Cientificas, Caracas, 1020-A, Venezuela, [3]Unit of Advanced Therapies, Instituto Distrital de Ciencia Biotecnología e Innovación en Salud, Bogotá, Colombia 111-611, [4]Department of Neuroscience, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania 19104, [5]Department of Neurology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois 60611, [6]Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, Toyama, 930-0194, Japan, and [7]Griffith Institute for Drug Discovery, Griffith University, Brisbane, Queensland 4111, Australia

Smell loss has caught public attention during the recent COVID-19 pandemic. Research on olfactory function in health and disease gains new momentum. Smell deficits have long been recognized as an early clinical sign associated with neuropsychiatric disorders. Here we review research on the associations between olfactory deficits and neuropathological conditions, focusing on recent progress in four areas: (1) human clinical studies of the correlations between smell deficits and neuropsychiatric disorders; (2) development of olfactory mucosa-derived tissue and cell models for studying the molecular pathologic mechanisms; (3) recent findings in brain imaging studies of structural and functional connectivity changes in olfactory pathways in neuropsychiatric disorders; and (4) application of preclinical animal models to validate and extend the findings from human subjects. Together, these studies have provided strong evidence of the link between the olfactory system and neuropsychiatric disorders, highlighting the relevance of deepening our understanding of the role of the olfactory system in pathophysiological processes. Following the lead of studies reviewed here, future research in this field may open the door to the early detection of neuropsychiatric disorders, personalized treatment approaches, and potential therapeutic interventions through nasal administration techniques, such as nasal brush or nasal spray.

Introduction

Often underappreciated, the sense of smell plays a vital role in our daily life, such as alerting us of potential air hazards and helping us to appreciate food flavors. The olfactory system is responsible for detecting and distinguishing numerous odors in our environment (Firestein, 2001; Mori and Sakano, 2021), and is likely to connect with emotion and cognition (Richardson and Zucco, 1989; Sohrabi et al., 2012; Stevenson, 2013). Comprising a complex network of sensory organs, neural pathways, and brain regions, the olfactory system allows us to experience the rich and diverse world of smells. The olfactory system's significance extends beyond its role in perceiving pleasant fragrances or avoiding unpleasant odors. The olfactory system also carries respiration-entrained rhythmic signals to widespread brain regions (Tort et al., 2018; Heck et al., 2022). Since respiration is highly dynamic because of metabolic needs and emotional states, the olfactory system thus influences brain activity in the absence of odors.

The peripheral olfactory system, located in the nasal cavity, is directly exposed to environmental stressors (e.g., viral infection and air pollution) (van Os et al., 2008; Wahbeh and Avramopoulos, 2021). Adolescent exposures to these environmental stressors have been identified as risk factors for neuropathological manifestations (Mortensen et al., 1999; Newbury et al., 2019; Antonsen et al., 2020). Exploring the molecular, structural, and functional alterations in the olfactory system during critical developmental periods may provide valuable insights into the potential risk factors and mechanisms involved in the onset of neuropsychiatric disorders. On the other hand, the olfactory system develops in conjunction with the early forebrain. Disruption in forebrain development may also affect the olfactory system and manifest olfactory dysfunction. Olfactory dysfunction could be a predictor of neuropsychiatric disorders (Corcoran et al., 2005; Atanasova et al., 2008; Fullard et al., 2016; He et al., 2020). These distinct characteristics of the olfactory system and its intricate connection to various physiological and psychological processes make it a valuable resource for translational research, offering potential breakthroughs in diagnostics, therapeutics, and understanding of the brain and behavior.

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Correspondence should be addressed to Kun Yang at kunyang@jhmi.edu or Minghong Ma at minghong@pennmedicine.upenn.edu.

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In this review, we delve into recent clinical and preclinical findings, aiming to bridge critical knowledge gaps between olfaction and neuropsychiatric disorders. We begin by reviewing the consistent observations between smell deficits and neurologic conditions reported in clinical/epidemiology studies. These smell deficits may serve as indicators of fundamental pathophysiology associated with neuropsychiatric disorders. Exploring molecular mechanisms underlying the associations between smell deficits and these disorders will not only enhance our understanding but also open doors to early detection and intervention. Olfactory mucosa (OM), the key component of the olfactory system located outside the cranium, offers noninvasive access to neuronal cells through nasal biopsies in living human subjects. In this regard, we review the recent progress and achievements in establishing OM-derived neuronal cell models. These cell models provide a unique platform for identifying molecular signatures of neuropsychiatric disorders, paving the way for further advancements in our understanding of these complex conditions. Moving forward, we review brain imaging studies that explore the structural alterations and impaired functional connectivity within and beyond the olfactory pathways, elucidating their associations with neuropsychiatric disorders. Finally, we delve into the realm of preclinical animal models, which are crucial in validating and expanding on the clinical findings. These animal models permit mechanistic manipulations to identify causal factors underlying the associations observed in clinical studies. Overall, this review aims to synthesize recent advancements in the field, address critical knowledge gaps, and foster a comprehensive understanding of the intricate relationship between olfaction and neuropathological manifestations.

Smell deficits in patients with neuropsychiatric disorders

There is ample evidence of smell deficits across neuropsychiatric disorders, such as Alzheimer's disease, Parkinson's disease, and schizophrenia (Moberg et al., 2014; Kotecha et al., 2018; Marin et al., 2018; Silva et al., 2018). Alzheimer's and Parkinson's patients display olfactory impairments in odor detection, discrimination, and identification (Marin et al., 2018; Jung et al., 2019), which occur several years before the neuropathological manifestation (Fullard et al., 2017; Adams et al., 2018; Kotecha et al., 2018). Olfactory impairments have also been extensively reported in patients with schizophrenia (Malaspina et al., 1994; Kopala et al., 1995; Turetsky and Moberg, 2009; Ishizuka et al., 2010; Cohen et al., 2012; Moberg et al., 2014; Kiparizoska and Ikuta, 2017), as well as in patients with first-episode psychosis (Kamath et al., 2014, 2018, 2019; Chen et al., 2018). Furthermore, smell deficits are found in people who are at high risk for psychosis and may predict their transition to psychosis (Brewer et al., 2003; Woodberry et al., 2010; Kotlicka-Antczak et al., 2017), as well as poor outcomes in those who have psychosis (Good et al., 2010; Lin et al., 2015).

Notably, significant correlations of smell deficits with negative symptoms (e.g., avolition and anhedonia) and social processes in psychotic patients have been reproducibly reported by many groups (Corcoran et al., 2005; Good et al., 2006; Ishizuka et al., 2010; Cieslak et al., 2015; de Nijs et al., 2018; Kamath et al., 2018; Takahashi et al., 2018; Lui et al., 2020; Etyemez et al., 2022). In contrast, such an association is not observed between smell deficits and positive symptoms (delusion, hallucination) (Brewer et al., 2001; Good et al., 2006, 2010; Ishizuka et al., 2010; Kamath et al., 2018; Takahashi et al., 2018). Meanwhile, reduced odor identification ability, which reflects olfactory processing in the CNS (Soudry et al., 2011), is associated with both state and trait anxiety ratings (Takahashi et al., 2015) in healthy controls. Together, these findings suggest that olfactory deficits and specific clinical conditions (e.g., negative symptoms, social cognitive deficits) may be driven by common factors, or they share common pathologic mechanisms in the olfactory system.

OM-derived tissue and cell models for studying the molecular mechanisms of neuropsychiatric disorders

The OM, composed of the olfactory epithelium and lamina propria (Fig. 1*A*), is a specialized tissue located in the superior portion of the nasal cavity. The olfactory epithelium is lined with millions of olfactory sensory neurons (OSNs), which possess unique receptor proteins capable of binding to specific odor molecules. When we inhale, the odor molecules interact with the receptors, triggering electrical signals that are transmitted to the brain for processing. One of the most intriguing aspects of the OM is the presence of stem cells, which are capable of self-renewal and generating neuronal precursors throughout the entire human lifetime. These precursors include neural stem cells known as basal cells. As expected for neural stem cells, basal cells are multipotent and allow the continuous replacement of neuronal and non-neuronal cells, such as OSNs and sustentacular cells (of astrocytic lineage) (Cascella et al., 2007; Leung et al., 2007). In addition, the lamina propria underneath the olfactory epithelium contains another less accessible population of multipotent stem cells, whose features meet common criteria of mesenchymal stromal cells following consensus from Tissue Stem Cell Committee of the International Society for Cellular Therapy (Mackay-Sim, 2010). While obtaining biopsied brain tissues from living subjects is extremely difficult, the OM has been considered as a useful biopsied sample for studying the molecular signatures and cellular traits underpinning neuropsychiatric disorders as early as the 1980s (Lovell et al., 1982; Graziadei and Monti Graziadei, 1985; Talamo et al., 1989).

The OM is located outside the cranium, which allows for obtaining cells in the neural lineage via noninvasive nasal biopsies from living human subjects. To selectively capture neural epithelium and minimize mucosal tissue contamination in the nasal biopsy, multiple groups have developed methods to enrich olfactory neuroepithelium-derived cells (ONCs) from biopsied tissues (Borgmann-Winter et al., 2009, 2015; Mackay-Sim, 2012; Narayan et al., 2014; Lavoie et al., 2017; Kumar et al., 2018; Rhie et al., 2018; Palominos et al., 2022). These ONCs have been shown to resemble molecular profiles of neurons in the human brain, especially immature neurons (Horiuchi et al., 2013; Doostparast Torshizi et al., 2019; Evgrafov et al., 2020; Yang et al., 2022). By using ONCs, important molecular signatures of neuropsychiatric disorders have been unveiled. For instance, multiple groups have recently reported alterations in molecular pathways, including cell cycle, immune/inflammatory and redox signaling, cytoskeletons, cell–cell interaction, cell adhesion and migration patterns, and calcium signaling, in olfactory neuronal tissue/cells from schizophrenia patients via nasal biopsy (Féron et al., 1999; Fan et al., 2012, 2013; Kano et al., 2013; Mor et al., 2013; Solís-Chagoyán et al., 2013; Brown et al., 2014; English et al., 2015; Borgmann-Winter et al., 2016; Horiuchi et al., 2016; Tee et al., 2017; Vitale et al., 2017; Rhie et al., 2018; Evgrafov et al., 2020; Tee and Mackay-Sim, 2021; Yang et al., 2021; Jaaro-Peled et al., 2022). Schizophrenia-patient-derived ONCs have also been investigated for their differences in transcriptomics, proteomics, and methylomics with common pathways emerging from genes differentially expressed associated with protein synthesis, cell cycle, cell adhesion, and

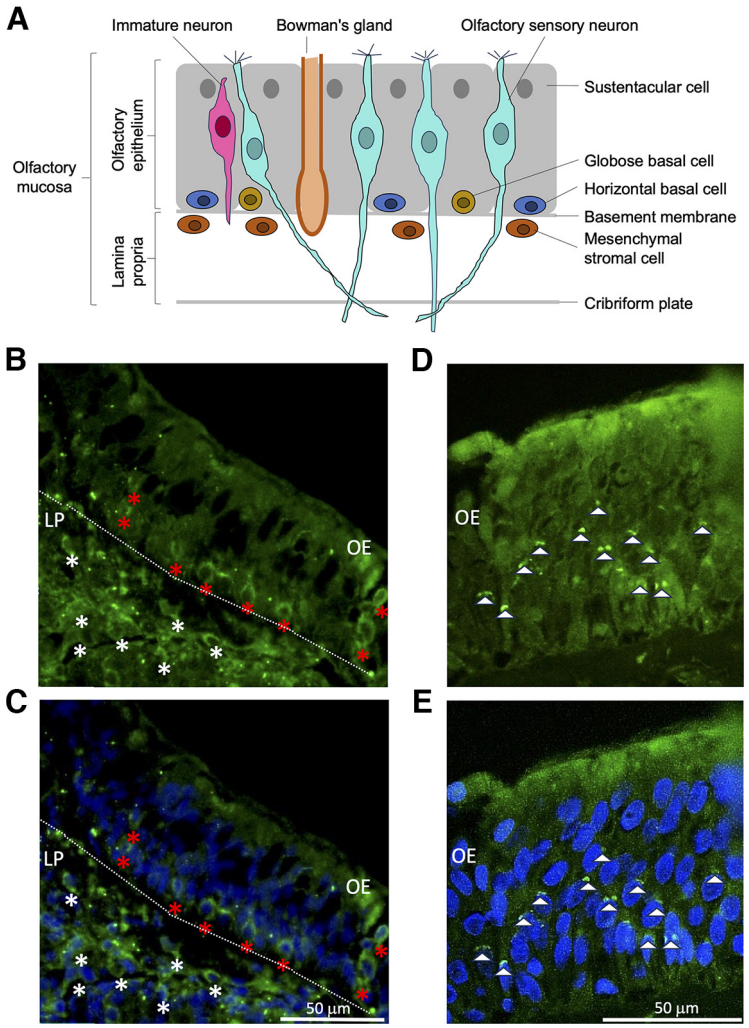

Figure 1. The expression of amyloid-β and α-synuclein in OM from patients with a median of 22 months of long-term precedent SARS-CoV-2 infection. ***A***, Scheme of human OM. ***B***, The OM tissue sections from post-SARS-CoV-2 infection subjects were immunolabeled with a monoclonal mouse anti-amyloid-β (6F3D-DAKO, green), followed by an FITC anti-mouse secondary antibody. Red asterisks indicate basal cells in the olfactory epithelium (OE). White asterisks underline olfactory parenchyma mesenchymal stromal cells in the lamina propria (LP). White dotted line separates OE and LP. ***C***, Overlap of anti-amyloid-β (green) and blue nuclei (stained by DAPI), highlighting the expression of cytoplasmic amyloid-β in these cell reservoirs. ***D***, OM tissue sections were immunolabeled with anti-α-synuclein (green), followed by an FITC anti-mouse secondary antibody. Arrowheads point to punctate immunofluorescence expression of α-synuclein. ***E***, Overlap of anti-α-synuclein (green) and blue nuclei (stained by DAPI).

migration (Matigian et al., 2010; English et al., 2015; Vitale et al., 2017). A recent study of human ONCs and animal models identified the involvement of the miR-124-AMPAR pathway in behavioral deficits shared between schizophrenia and bipolar disorder (Namkung et al., 2023). One advantage of having ONCs from living subjects is that we could directly study the associations between neuronal molecular changes and clinical outcomes. By integrating molecular data (gene expression and protein levels) from patient-derived ONCs and neurocognitive assessments from the same patients, a recent study examined the clinical potentials of drug targets suggested by genome-wide association studies and prioritized chloride channel protein 2 as one promising drug target for psychotic disorders (Mihaljevic et al., 2022). While most published studies currently focus on cross-sectional data, ONCs have unique advantages in longitudinal studies as they can be repeatedly biopsied from living subjects. Important molecular mechanisms underlying disease trajectory are expected to be unveiled by integrating longitudinal nasal biopsies with clinical and imaging data from the same subjects in the future.

In addition to their successful applications in studying the molecular mechanisms of neurodevelopmental disorders, ONCs have also been used to study neurodegenerative disorders. Patient-derived ONCs manifest abnormal amyloid components together with tau hyperphosphorylation, which has led to the proposal of these cells as a novel diagnostic tool for Alzheimer's disease (Féron et al., 1998; Ayala-Grosso et al., 2015; Lampinen et al., 2022; Rantanen et al., 2022). An endogenous deficit in mitochondrial complex I is observed in ONCs from patients with Parkinson's disease (Murtaza et al., 2016). Transplanted human ONCs are able to generate dopaminergic cells and reduce the behavioral asymmetry induced by the ablation of the dopaminergic neurons in the rat model of Parkinson's disease, suggesting the potential of ONCs in cell transplantation therapies (Murrell et al., 2008).

While continuous attention has been paid to OM in neurologic and psychiatric studies, OM is recently in the spotlight during the COVID pandemic. Recent meta-analysis studies showed that 5%-10% of COVID-19 patients had persistent smell deficits or other symptoms 6 months after the infection (Tan et al., 2022; Thaweethai et al., 2023). While the precise causes of post-

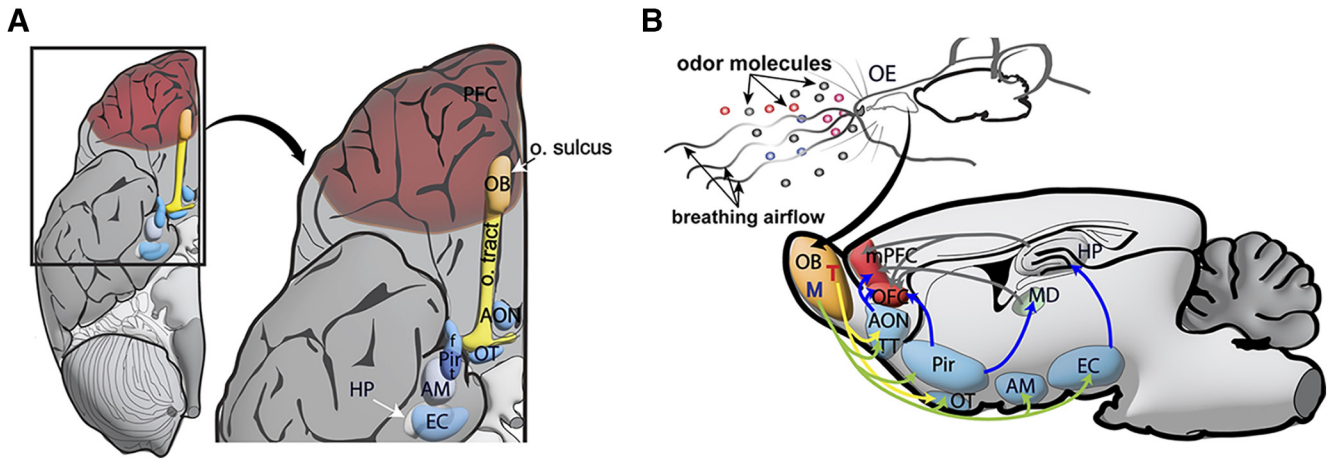

Figure 2. The olfactory system and its connections with other brain regions. ***A***, Ventral view of a schematic human brain (right hemisphere). ***B***, Sagittal view of a schematic mouse brain. o. sulcus, Olfactory sulcus; T, tufted cells; M, mitral cells; o. tract, olfactory tract; TT, tenia tecta; Pir, piriform cortex (f, frontal; t, temporal); AM, amygdala; EC, entorhinal cortex; MD, mediodorsal nucleus of thalamus; HP, hippocampus. Not all projections among these brain regions are shown. Many of the projections are reciprocal.

COVID-19 syndrome remain largely elusive, the prevalence of associated neurologic symptoms with an increased risk of anxiety and depression at 16 month follow-up suggests at least a brain origin (Guerrero et al., 2021; Leng et al., 2023). A classical view, as far as SARS-CoV-2 is concerned, is based on the extensive inflammatory processes occurring in the OM and olfactory circuits, but often with conflicting findings concerning SARS-CoV-2 neurotropism (Emmi et al., 2022). Systematic analyses of human OM tissue biopsies and cultured cells from COVID-19 patients with olfactory impairments and neurologic alterations are needed. Ongoing efforts have been invested in studying the prevalence of Alzheimer's disease pathology and other neurodegenerative proteinopathies in patients with precedent SARS-CoV-2 infection. Preliminary studies revealed the expression of amyloid-β in olfactory basal cells and mesenchymal stromal-like cells in the lamina propria, as well as the expression of α-synuclein in interstitial intermediate cells, in OM tissues from patients with a median of 22 months of long-term precedent SARS-CoV-2 infection (Fig. 1*B–E*).

Structural and functional connectivity impairments in the olfactory pathways in patients with neuropsychiatric disorders

The peripheral OM is connected with the central intracranial olfactory areas via the olfactory nerves. The olfactory bulb (OB) is the first relay station in the olfactory pathways (Fig. 2*A*). The OB collects the sensory afferents from OSNs located in the olfactory epithelium, ends with the olfactory tract, and is closely located to the olfactory sulcus of the frontal lobe (Rombaux et al., 2009). Olfactory information is then transmitted via the olfactory tract to the primary olfactory cortical and subcortical regions including the anterior olfactory nucleus (AON), piriform cortex, olfactory tubercle (OT), and amygdala, and subsequently to secondary olfactory cortices, including the orbitofrontal cortex (OFC). These olfactory pathways are responsible for odor detection, discrimination, and identification (Soudry et al., 2011). Despite a large number of studies demonstrating olfactory deficits in neuropsychiatric disorders, few neuroimaging studies have examined the relationship of olfactory deficits to structural and functional abnormalities of these cortical regions, and the results have been inconsistent (Good and Sullivan, 2015). On the other hand, accumulating evidence suggests a crucial role of the OB and the olfactory sulcus in the pathophysiology of neuropsychiatric disorders. A reduction in the OB volume has been reproducibly reported in patients with schizophrenia (Turetsky et al., 2000; Nguyen et al., 2011; Yang et al., 2021). Such reduction is also seen in youths at high risk for psychosis and first-degree family members of schizophrenia patients to a lesser extent (Turetsky et al., 2003, 2018), implying that the changes in the OB are not a secondary outcome of the medication. In addition, reduced OB volumes have also been reported in patients with Alzheimer's disease and Parkinson's disease (Li et al., 2016; Jobin et al., 2021).

A recent MRI study demonstrates that the olfactory sulcus depth, which possibly reflects embryonic development of the olfactory system (Chi et al., 1977), is positively correlated with odor identification performance in healthy individuals and patients with various stages of psychosis (Takahashi et al., 2019a). Because an abnormally shallow olfactory sulcus has been reported in psychotic disorders regardless of illness states (e.g., high-risk status, first-episode, and chronic stage) (Takahashi et al., 2013; Nishikawa et al., 2016), psychosis subgroups (i.e., schizophrenia, schizophreniform psychosis, affective psychosis, and other psychosis patients) (Takahashi et al., 2014b), and clinical subtype of schizophrenia (e.g., deficit vs nondeficit subtype) (Takahashi et al., 2017), the olfactory sulcus morphology could be a stable marker of vulnerability to psychosis. Further, it is suggested that the altered depth of the olfactory sulcus, which exists before psychosis onset, could be predictive of transition to psychosis in individuals at clinically high risk for developing psychosis (i.e., at-risk mental state) (Takahashi et al., 2014b). Since patients with other neuropsychiatric disorders, such as bipolar disorder (Takahashi et al., 2014a), major depression (Takahashi et al., 2016), and borderline personality disorder (Takahashi et al., 2019b), also exhibit a significantly shallower olfactory sulcus compared with healthy controls, it is possible that early neurodevelopmental abnormalities associated with the olfactory system contribute to the neurobiology of various neuropsychiatric disorders. Further multimodal (e.g., neurophysiological and functional neuroimaging) studies will be needed to examine the functional significance of these olfactory sulcus morphologic changes in neuropsychiatric disorders.

In addition to structural abnormalities, functional connectivity impairments associated with neurologic and mental conditions have also been studied. Recent research using

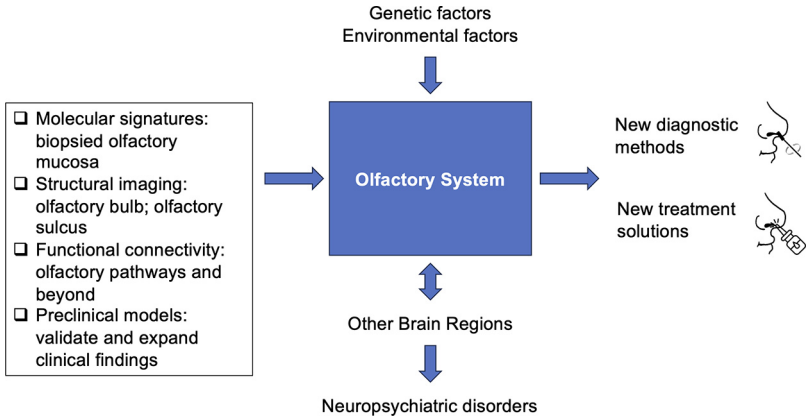

Figure 3. Olfactory system and neuropsychiatric disorders. The olfactory system, which is directly exposed to outside environments and linked to cortical regions regulating emotion and cognition, could play an important role in neuropathological manifestations. This notion is strongly supported by consistent clinical observations of olfactory deficits in patients with neuropsychiatric disorders. In addition, recent progresses in tissue and cell models derived from biopsied olfactory mucosa from living human subjects, brain imaging studies of structural and functional connectivity changes in olfactory pathways, and preclinical animal models have further deepened our knowledge about the olfactory system and its potential role in neurologic conditions. Future studies of the olfactory system may provide opportunities for developing novel diagnostic tools and therapeutic interventions through nasal administration techniques, such as nasal brush or nasal spray.

whole-brain functional connectivity showed primary olfactory subregions form parallel whole-brain networks (Zhou et al., 2019; Echevarria-Cooper et al., 2022). These networks are implicated in neurologic and mental conditions. For example, frontal piriform cortex exhibits strong bilateral functional connectivity to dorsal striatum in healthy individuals, and with cingulate cortex to some extent (Zhou et al., 2019), while it exhibits decreased functional connectivity with both the NAc and mPFC in patients with schizophrenia (Kiparizoska and Ikuta, 2017). Moreover, the OT exhibits the strongest functional connectivity with mPFC and also shows functional connectivity with the rest of the ventral striatum (Zhou et al., 2019). The ventral striatum is implicated in neuropsychiatric disorders by virtue of their roles in reward processing and reinforcement learning (McCutcheon et al., 2019; Cansler et al., 2020). Furthermore, AON exhibits strong functional connectivity with OFC (Zhou et al., 2019). Increased OFC volume and decreased resting-state activation are related to schizophrenia (Lacerda et al., 2007; Kanahara et al., 2013); hence, investigations of functional connectivity between AON and OFC should prove useful here. Similarly, AON exhibits strong functional connectivity with anterior insula in healthy populations (Zhou et al., 2019), while anterior insula exhibits regional abnormalities as well as aberrant functional connectivity in neuropsychiatric disorders (Namkung et al., 2017; Kulason et al., 2022). Decreased resting-state anterior insula activation is associated with the severity of negative symptoms in schizophrenia (Manoliu et al., 2013). Moreover, schizophrenia patients exhibit olfactory deficits related to negative symptoms (Ishizuka et al., 2010; Kamath et al., 2018) and decreased pleasantness ratings of odors (Zou et al., 2018), which is related to the role of anterior insula in hedonic judgment (Namkung et al., 2017). Together, these results motivate further investigation into functional connectivity between primary olfactory subregion networks as a covariate with disease severity and related olfactory deficits.

Quantification of coherence in neural oscillations measured with intracranial EEG has been used to further highlight the strong connection between human olfactory and hippocampal systems, and can measure functional connectivity with greater temporal resolution than fMRI. Human olfactory cortex and hippocampal systems measured at the level of intracranial EEG exhibit theta (3-8 Hz) phase-coupling related to inhalation, which is not seen between auditory cortex and hippocampus (Zhou et al., 2021). Rhythmic coupling between respiration and neural oscillations in several brain regions has increasingly been reported as a part of healthy human brain function (Zelano et al., 2016; Perl et al., 2019; Kluger and Gross, 2021; Watanabe et al., 2023). As both respiration and hippocampal networks exhibit dysfunction in patients with neuropsychiatric disorders, clinical studies should incorporate a focus on respiratory-hippocampal interactions. For instance, patients with schizophrenia exhibit faster and more variable respiratory rates positively correlated with positive symptoms, and shallower respiratory volume most pronounced during exhalation compared with controls (Paterson, 1935; Peupelmann et al., 2009; Bär et al., 2012). Thus, it is likely that aberrant respiration would disrupt normal respiratory-related piriform-hippocampal coupling, which may contribute to impaired hippocampal plasticity in schizophrenia (Pajonk et al., 2010). Similarly, structural deficits in hippocampus also could disrupt normal piriform-hippocampal coupling. Patients with schizophrenia exhibit bilateral reduced hippocampal and amygdalar volume, with smaller hippocampal volume associated with impaired olfactory discrimination performance (Rupp et al., 2005). Characterizing interactions between olfactory and hippocampal areas in relation to disease-related changes in respiration and hippocampal morphology will assist in targeted analysis and treatments.

Preclinical study of the olfactory system: a window to explore the cause and mechanisms underlying neuropsychiatric disorders

Despite the strong evidence from human clinical studies for the association between olfactory deficits and neuropsychiatric disorders, a conceptual framework for explaining the impact of olfactory processing on higher brain functions (cognition, motivation, memory, and emotion) remains obscure. Since the olfactory networks (e.g., the paleocortex) remain relatively unchanged for millions of years, and the neural basis of complex behaviors can be analyzed at the molecular, cellular, and circuit levels in rodents, they provide an invaluable preclinical model for probing the neural mechanisms underlying

olfactory and other clinical deficits in neuropsychiatric disorders. It is worth noting that profound neurobiological differences exist between the rodent and human olfactory systems. Rodents contain multiple olfactory sensory systems (e.g., the main olfactory system as detailed below and the vomeronasal organ/accessory olfactory system), each of which plays distinct roles in olfactory behaviors. Compared with rodents, humans express fewer G protein-coupled odorant receptors (~400 compared with ~1200 in mice). Caution should be exerted in translating findings from preclinical rodent models to humans.

The rodent main OM resembles the human OM in cellular composition, structure, and function. The rodent main OM harbors ~10 million OSNs, each of which expresses a single odorant receptor type from a large repertoire. The OSNs expressing the same odorant receptor type converge their axons onto a few discrete glomeruli in the OB, where they make monosynaptic connections with OB neurons, including two types of principal neurons: mitral and tufted cells. These two types of neurons project to a number of cortical and subcortical regions: mitral cells send elaborated axonal collaterals to most of these regions, including AON, tenia tecta, OT, piriform cortex, several amygdala areas, and lateral entorhinal cortex, whereas tufted cells predominantly target the anterior structures (e.g., AON/tenia tecta and OT; Fig. 2*B*) (Mori and Sakano, 2021; Bhattarai et al., 2022). The olfactory cortical regions subsequently project to the limbic system (e.g., hippocampus) and neocortex, including mPFC and OFC, via multiple pathways. Rodent mPFC spans the anterior cingulate, prelimbic, and infralimbic cortices, sharing homology with human ACC subregions: Brodmann area 24, 32, and 25, respectively (Bicks et al., 2015; van Heukelum et al., 2020; Bhattarai et al., 2022). These olfactory-prefrontal pathways are supported by anatomic and functional evidence (Gottfried and Zald, 2005; Hoover and Vertes, 2007; DeNardo et al., 2015; Biskamp et al., 2017; Moberly et al., 2018; Ährlund-Richter et al., 2019; Zhou et al., 2019). Consequently, it takes only three synapses for prefrontal neurons to receive sensory information originating in OSNs. In addition to sensing odors, OSNs also transmit nasal breathing signals into the brain (Grosmaitre et al., 2007; Iwata et al., 2017). Even in the absence of odors, respiration-entrained olfactory signals shape the neural activity in widespread brain regions (including mPFC and OFC), in both rodents and humans (Zelano et al., 2016; Biskamp et al., 2017; Herrero et al., 2018; Kőszeghy et al., 2018; Moberly et al., 2018; Bagur et al., 2021; Kluger et al., 2021; Karalis and Sirota, 2022).

Rodent mPFC (human ACC) and OFC are essential brain hubs involved in cognition, motivation, memory, and emotion. Abnormalities in these regions are implicated in a variety of neuropsychiatric disorders (Kringelbach, 2005; Der-Avakian and Markou, 2012; Strauss et al., 2014; Bicks et al., 2015; Ko, 2017; Chini and Hanganu-Opatz, 2021; Rolls, 2021; Bhattarai et al., 2022). The close network connection between the olfactory system and PFC provides a potential mechanistic link between smell deficits and clinical symptoms in neuropsychiatric disorders. Adolescence to young adulthood is a critical period for PFC maturation (Chini and Hanganu-Opatz, 2021; Benoit et al., 2022a), which depends on its excitatory inputs, revealed by manipulating the thalamocortical pathway (Benoit et al., 2022b). It is plausible that inputs from the olfactory system also contribute to normal PFC maturation and function during this period. Even in the adult brain, PFC neurons are constantly influenced by the olfactory inputs in the presence or absence of odors via spontaneous, respiration- and/or odor-induced activity. Disruption of the olfactory pathways leads to behavioral deficits beyond odor-guided tasks in rodents (Hasegawa et al., 2022). For example, inducible local olfactory epithelium inflammation dampened social cognition and consummatory drive, methimazole-induced olfactory epithelium ablation altered auditory cued fear responses, olfactory bulbectomy impaired learning, memory, and motivational behaviors accompanied with hyperactivity, and genetic deletion of a key olfactory signaling protein in OSNs led to anxiety-like behaviors as well as deficits in spatial memory and social behavior. These behavioral changes are often accompanied by molecular, structural, and functional changes in the olfactory system (OM, OB, and olfactory cortices) and other brain regions (e.g., hippocampus), although potential changes in the PFC circuitry remain little explored. Given the direct projection from the olfactory cortices to PFC, it is plausible that disruption of the olfactory system impairs PFC function and PFC-mediated behaviors, including those manifested in neuropsychiatric disorders.

In conclusion, in this review, we summarize the recent progress in studying the olfactory system to understand the origin and mechanisms of neuropsychiatric disorders. We focus on the strong clinical evidence of the association between smell deficits and neurologic conditions, development of biopsied human OM as a tissue/cell model for investigating the molecular pathologic signatures, the clinical findings of structural and functional connectivity alterations in olfactory pathways and their relationship with neuropsychiatric disorders, and the validity and potentials of using animal models to expand the clinical observations in human subjects. While previous clinical and preclinical studies have provided compelling evidence of the importance of the olfactory system in pathophysiology processes associated with neuropsychiatric disorders, the exact role of the olfactory system as a contributing factor or indicator for neurologic conditions is still unknown. Additionally, whether or how the observed neuronal molecular changes in the OM in patients with neuropsychiatric disorders are linked to the structural and functional impairments in olfactory pathways is still an open question. Multimodal and longitudinal clinical studies combined with animal models are promising approaches to deepen our understanding of the pathophysiological role of the olfactory system.

The olfactory system represents a captivating field of study that intertwines the realms of neuroscience, psychology, and clinical research. By unraveling the intricate relationship between the olfactory system and neurologic conditions, we may uncover the molecular and neural processes that contribute to neuropsychiatric disorders. Furthermore, the olfactory system presents a unique opportunity for developing diagnostic tools and therapeutic interventions. Biomarkers and drug targets identified through olfactory research hold promise for early detection, personalized treatment approaches, and potential interventions through nasal administration techniques, such as nasal brush or nasal spray (Fig. 3).

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