

## Invited Mini Review

## Olfactory neuropathology in Alzheimer's disease: a sign of ongoing neurodegeneration

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**Olfactory neuropathology is a cause of olfactory loss in Alzheimer's disease (AD). Olfactory dysfunction is also associated with memory and cognitive dysfunction and is an incidental finding of AD dementia. Here we review neuropathological research on the olfactory system in AD, considering both structural and functional evidence. Experimental and clinical findings identify olfactory dysfunction as an early indicator of AD. In keeping with this, amyloid- $\beta$  production and neuro-inflammation are related to underlying causes of impaired olfaction. Notably, physiological features of the spatial map in the olfactory system suggest the evidence of ongoing neurodegeneration. Our aim in this review is to examine olfactory pathology findings essential to identifying mechanisms of olfactory dysfunction in the development of AD in hopes of supporting investigations leading towards revealing potential diagnostic methods and causes of early pathogenesis in the olfactory system. [BMB Reports 2021; 54(6): 295-304]**

## INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and one of the most prevalent forms of dementia (1). Major symptoms include memory loss and cognitive dysfunction. Several comorbidities in AD often coexist or are prominent, such as depression, circadian rhythm or sleep disturbances,

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and sensory-perceptual problems (2-4). Among other AD symptoms, olfactory dysfunction is not only a highly prevalent symptom in AD (5) but also an early diagnostic biomarker (6). That is, olfactory dysfunction is present in the early stages of AD and in probable AD patients who have mild cognitive impairment (MCI) (7). Therefore, olfactory deficits in AD have received increasing attention over the past few years in fundamental to clinical research. Because the representative pathologic hallmarks of AD are amyloid plaques and neurofibrillary tangles as well as brain atrophy (8), characterization of such pathological alterations in the olfactory system have been explored in an attempt to identify early stages of AD.

The olfactory system transmits chemical signals from the sensory epithelium and bulb to the olfactory cortex, following a serial synaptic interface (9-11). The olfactory bulb is the convergence of the peripheral olfactory system and the central subcortical systems that interconnect the olfactory sensory neuronal axons and the mitral cell dendrites. When studying olfactory dysfunction in AD, recent research efforts have implicated cortical olfactory regions (12, 13). However, several studies have reported clear pathogenesis in the olfactory sensory neurons (OSN) as well as in the olfactory bulbs (OB) in both rodent and human subjects (14, 15), little is known about the roles of the olfactory epithelium (OE) and the OB in AD progression.

Herein, we review the literature on olfactory dysfunction in AD in order to examine how anatomical and physiological characteristics are disrupted in OSNs and OB and how that contributes to olfactory dysfunction in AD. In agreement with a recent review (16), we suggest a mechanism of olfactory impairment involving OE and OB neurodegeneration. Pathophysiological findings are mainly from human studies, whereas cellular, molecular, and mechanistic evidence come mostly from rodent research. We then discuss the significance of the peripheral olfactory (including the OE and a part of OB) degeneration in smell dysfunction in AD.

## METHODS

We conducted a systematic search using PubMed for pathophysiological findings underlying olfactory dysfunction in AD as described in rodent and human studies. We conducted the search within English literature published up to March 2021 using the following search terms: "Alzheimer's disease", "olfactory dysfunction", "Alzheimer's pathology", "olfactory system". We used keywords independently and in various combinations. Research articles and reviews obtained were mainly published within the previous five years. We added additional articles following a cross-reference search within review and original articles.

## THE NEUROPATHOLOGY OF ALZHEIMER'S DISEASE

AD is a progressive and incurable neurodegenerative disease

that can be characterized neuropathologically by protein accumulation, including amyloid plaques and neurofibrillary tangles (17). Amyloid plaques are composed of misfolded amyloid- $\beta$  ( $A\beta$ ) proteins and are first found in the basal temporal cortex and orbitofrontal cortex, then progress to the neocortex, basal ganglia, hippocampal formation, and the amygdala as AD progresses (17). Neurofibrillary tangles made of tau inclusions appear in the locus coeruleus and entorhinal cortex, then spread to the neocortex and hippocampal formation throughout the brain (18). Because of the increasing distribution of the protein aggregates, AD patients show brain atrophy as a pathological feature with severe memory and cognitive impairment as clinical symptoms (19).

Current clinical trials are assessing the ability of various interventions to reduce cognitive deficits and progressive neural impairment of patients with AD (20). Because neuronal injury is currently irreversible, identifying appropriate diagnostics,

**Table 1.** Pathological alterations in the olfactory system of patients with Alzheimer's disease (AD)

Findings	Methods	Clinical stage	Measured AD pathology	Refs.
Reduced OB volume and white matter of the olfactory tract	MRI, DTI 3T-MRI	aMCI	n/a	(74)
$\beta_{1-42}$ , p-tau, and astrogliosis in the glomerular layer, anterior olfactory nucleus, olfactory tubercle	IHC	MCI, moderate-AD, severe-AD	$\beta_{1-42}$ , p-tau, astrogliosis	(13)
$\beta$ -amyloid aggregates, PHF-tau, and $\alpha$ -synuclein in the anterior olfactory nucleus	IHC	n/a	$\beta$ -amyloid, PHF-tau, $\alpha$ -synuclein	(12)
$\beta$ -amyloid, tau in the piriform cortex	IHC	AD	$\beta$ -amyloid, tau	(38)
Deficit in olfactory identification	Olfactory identification test, DTI 3T-MRI	aMCI, AD, MCI-DLB, MCI-AD	Lewy body	(6, 74-76)
Deficit in olfactory identification differentiated AD from aging	Olfactory identification test	aMCI, AD, healthy aging	n/a	(23)
Reduced ability to identify a specific subset of smell	Olfactory identification test	AD	n/a	(71, 72)
Impaired olfactory identification (proportional to cognitive impairment in aMCI)	Olfactory identification test	aMCI, non-aMCI	n/a	(22)
Implication: damaged OSNs and olfactory malfunction following exposure to air-pollutants	Statistics, epidemiology	n/a	n/a	(77)
One-fifth of allergic and chronic rhinitis patients develop AD	Medical examination, IgE assay	Allergic diseases with AD	Inflammation	(48)
$\beta$ -amyloid aggregates, PHF-tau, and $\alpha$ -synuclein in the OE	IHC	AD, OND	$\beta$ -amyloid, PHF-tau, $\alpha$ -synuclein	(14)
$\beta$ -amyloid in nasal secretions	WB IME biosensor	AD, OND	$\beta$ -amyloid	(37)
$\beta$ -amyloid in nasal discharge (correlated with cognitive decline)	LC/MS WB IME biosensor	Probable AD (mild, moderate AD)	$\beta$ -amyloid ( $A\beta^{*56}$ , $A\beta O$ )	(73)
apoE4 correlated with odor identification deficits	Odor threshold test, olfactory identification test	n/a	apoE4	(39)

OB: olfactory bulb, MRI: magnetic resonance imaging, DTI-3T: 3.0 Tesla diffusion tensor imaging, aMCI: amnesic mild cognitive impairment, AD: Alzheimer's disease, n/a: non-applicable, IHC: immunohistochemistry, DLB: dementia with Lewy body, OSN: olfactory sensory neuron, OE: olfactory epithelium, OND: other neurodegenerative disease, PHF: paired helical filament.

interventions, and treatment methods for AD is essential. Epidemiological studies indicate that olfactory dysfunction can predict cognitive decline (21). Murphy (2019) reported that olfactory impairment might serve as an early indicator of AD.

## OLFACTORY DYSFUNCTION IN ALZHEIMER'S DISEASE

Anatomical and physiological alterations of the olfactory system in AD have been studied using various approaches (Tables 1 and 2). In AD patients, olfactory dysfunction usually appears as a reduced smelling ability known as hyposmia (22). Unlike congenital anosmia, olfactory deficits in AD patients appear during preclinical stages of the disease before the manifestation of cardinal AD symptoms. Specifically, decreased olfactory abilities have been shown in MCI and are proportional to cognitive impairment in amnesic MCI (aMCI) (6). Dysfunction of odor discrimination has therefore been suggested as a predictive behavioral measure for AD (22). For this reason, a particular "Odorant Item Specific Olfactory Identification" test

has been proposed, where certain odors can differentiate AD from general aging (23).

Because deficits in olfactory performance are associated with impaired memory and cognitive function, deficits in olfaction in AD can be interpreted as a consequence of a decline in perceptual processing and episodic memory (24). However, olfactory impairment also predicted cognitive deficits in the non-demented adult population (25). Nonetheless, the AD pathogenesis in the olfactory system (see details "Neuropathology of the olfactory system in AD") supports the premise that olfactory deficits occur and progress prior to severe cognitive and memory decline in AD progression. Thus, attempts to characterize the early stages of AD have highlighted the interest in the olfactory system as revealing olfactory dysfunction pathophysiology in AD.

**Table 2.** Pathological alterations in the olfactory system in mouse models of Alzheimer's disease (AD)

Findings	Methods	Strain (age)	Refs.
- Decreased OE thickness - Increased populations of TUNEL (+) cell - Decreased in number and length of dendritic spines - Deficit in olfactory behavior and $\beta$ -amyloid deposition - Increased latency in finding buried food, reduced peanut butter preference	IHC, TUNEL assay, EM	Tg2576 (6, 12 M) APP/PS1 (9M)	(40, 43)
- Distorted ultrastructure and subcellular components in the OE - Decreased mature OSNs	ELISA, IHC, PCR, EM, BrdU assay	hAPP (3 w)	(44, 78)
- Earlier $\beta$ -amyloid deposition in the olfactory system than brain region	IHC, Thio-S staining	Tg2576 (3, 6, 16, 21M)	(41)
- Region specific APP processing - Restricted expression of $\beta$ -secretase only in the olfactory glomerulus in the OB	WB, IHC, ISH	Tg2576 (10M), BACE null	(40, 42)
- Reduced response to odorants (only specific odorant) - Region specific calcium inactivation of OSN correlated with region specific $\beta$ -amyloid deposition - Deficits of turnover ratio of OE	Odor detection test, calcium imaging, IHC, TUNEL assay	Tg6799 (3M)	(62)
- Damaged OSNs and olfactory malfunction following exposure to air-pollutant nanoparticles	IHC, PCR, WB, nitrite assay	C57BL6 (3M), Fischer 344 rats (12w)	(46)
- Aberrant OSNs projection to the glomeruli	IHC, ISH, AAV modulation,	Tg2576 (13, 24M)	(15)
- Higher expressions levels and activity of $\gamma$ -secretase in the OE - $\beta$ -amyloid ( $A\beta^{*56}$ ) accumulates more quickly in the OE	IHC, TUNEL assay, EM	Tg2576 (10M),	(45)
- Correlation between deficit of olfactory habituation and spatial-temporal $\beta$ -amyloid deposition - Deficit in odor investigation and habituation	Odor cross-habituation test	Tg2576 (3, 6, 16, 21M)	(41)
- Altered the OSN connectivity by inducing human $\beta$ -amyloid - Decreased response to aversive odor in induced human $\beta$ -amyloid condition	IHC, TMT assay, hidden food assay	CORMAP mouse, Tg2576 (13, 24M)	(15)
- Injected $\beta$ -amyloid in the OB transferring to other brain region	$\beta$ -amyloid injection, IHC, TUNEL, WB	C57BL6 (7-8w)	(53)

OE: olfactory epithelium, TUNEL (+): terminal deoxynucleotidyl transferase dUTP nick end labeling-positive, IHC: immunohistochemistry, EM: electric microscopy, Tg: transgenic mouse, M: months, OSN: olfactory sensory neuron, ELISA: enzyme-linked immunosorbent assay, PCR: polymerase chain reaction, BrdU: 5-bromodeoxy-2-deoxyuridine, hAPP: human amyloid precursor protein, w: weeks, OB: olfactory bulb, WB: western blot, ISH: in situ hybridization, BACE:  $\beta$ -site amyloid cleavage enzyme, AAV: Adeno-associated virus, TMT: 2,3,5-Trimethyl-3-thiazoline, CORMAP: Conditional, Olfactory Sensory Neuron-Restricted Mosaic expression of APPsw and PLAP.

## ORGANIZATION OF THE OLFACTORY SYSTEM

### Peripheral olfactory system

The processing of odor signals in mammals is initiated in the OE, with OSNs being the primary neuron in the OE (Fig. 1). The somata of OSNs are organized in orderly layers based on maturity, ranging from basal cells to matured neurons (26). Once an odorant, i.e., a gaseous molecule or any airborne substances, reaches the OE and binds to the odorant receptors located in the OSNs, the OSNs transduce the odor information into electrical signals that trigger neurotransmitter release in the OBs (10). Subsequently, those neuronal signals are transmitted to the olfactory cortex through the olfactory tract and tubercles (10). Mucus secreted by Bowman's glands and sustentacular cells protect the OE's structure and maintain its homeostasis (27).

### Synaptic interface between peripheral and central components

Synaptic connectivity between the OSNs and central olfactory neurons in the OB glomeruli is essential for the initial detection, identification, and discrimination of the odors (28). Thus, early synaptic dysfunction in the OSNs could lead to greater impairment of olfactory information processing, thereby causing olfactory deficits. The structure of the OB shows a conserved laminar organization across species (29). Basically, the glomerulus, a neuropil structure of intertwining axons of OSNs, dendrites of periglomerular cells, and dendrites of mitral/tufted cells, is the focus of initial processing of olfactory information (30). The glomeruli are the first recipient of sensory inputs,

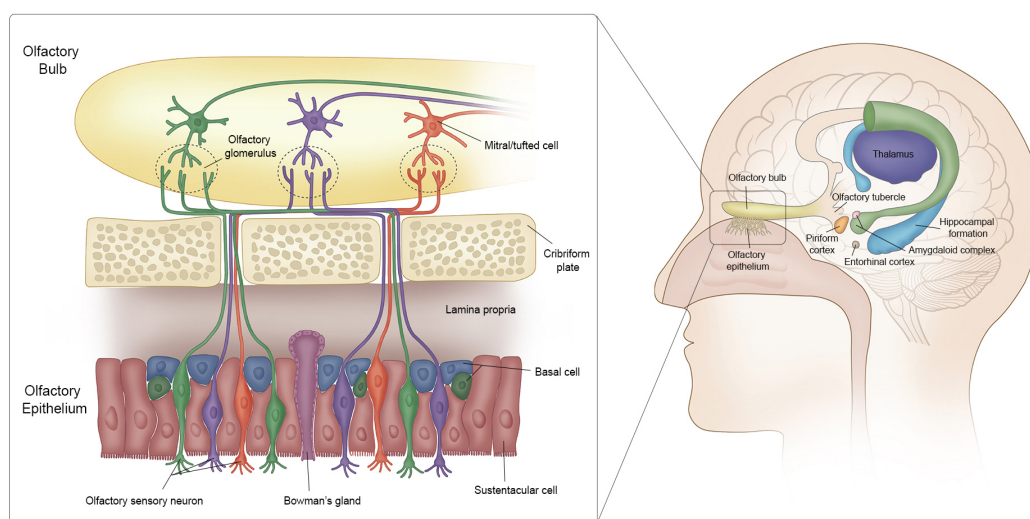
because they host the first synapse in the olfactory system. In the glomerular network, which is well described in rodents, axons from OSNs expressing the same odorant receptor converge into approximately two of the 1,800 glomeruli in each OB (31, 32). The periglomerular cells are dopaminergic/GABAergic neurons that form an inhibitory feedback loop with the OSNs (33).

### Central olfactory system

The olfactory system is anatomically distinctive, and the projections are highly organized. The primary olfactory cortex includes the anterior olfactory nucleus, the olfactory tubercle, the piriform cortex, the entorhinal cortex, and the amygdala, including the orbitofrontal regions and the neural signals projecting to the secondary olfactory cortex in the orbitofrontal cortex (Fig. 1) (34). The afferent input from the OB is transmitted to the primary olfactory cortex through the olfactory tubercles composed of axons of mitral/tuft cells and GABAergic interneurons (35). These cells are differentiated from progenitor cells that have migrated from the subventricular zone (35). This track forms the first cranial nerve in the central nervous system (36).

## NEUROPATHOLOGY OF THE OLFACTORY SYSTEM IN AD

Olfaction can be compromised not only by a severe memory and cognitive disruption, but also by olfactory pathways damaged by injury or chronic exposure to toxic substances triggering AD pathogenesis. In this context, the olfactory system



**Fig. 1.** Scheme of the olfactory system. (Left) Scheme of olfactory sensory neuron projections. Olfactory sensory neurons transduce odor information via electrical signals that trigger neurotransmitter release in the olfactory bulb. Mucus secreted by Bowman's glands and sustentacular cells protect the olfactory epithelium's structure and maintain homeostasis. (Right) Scheme of the olfactory system according to the process of olfaction.

can be seen as a distinctly damaged site independent of the limbic system in terms of both AD pathologies and diagnostic opportunities. Clinical studies have reported forms of proteinopathy in the peripheral olfactory system in AD patients. For instance, A $\beta$  and p-tau-immunoreactivity have been found in the OE of AD patients (14). Interestingly, the degree of immunoreactivity in the OE correlated with semiquantitative ratings of cortical amyloid and tau-lesion ratings (14). Large amounts of A $\beta$  detected in nasal secretions may indicate that such proteins originate from the epithelium and peripheral olfactory neurons (37). In the glomeruli of the OB, A $\beta$  and hyperphosphorylated tau have been detected, exhibiting progressive expression as Braak stages of AD pathology increased (17), but no significant changes were observed within the olfactory tract (13). Given these findings, the peripheral olfactory system could be behind the generation of the toxic misfolded proteins that affect OSNs.

Moreover, both A $\beta$  and tau have been observed in the cortical olfactory areas in AD patients, including the olfactory peduncle, the anterior olfactory nucleus (12, 13), and the piriform cortex (38). A more recent study suggests that the olfactory system can be a hub to spread misfolded proteins to interconnected cortical areas and could seed the misfoldings of native proteins (12). In line with proteinopathy, patients with the apolipoprotein E4 (apoE4) allele, a well-known genetic factor linked with AD onset and an A $\beta$  accumulation-triggering factor, are highly associated with olfactory deficits (39).

## MECHANISMS OF THE OLFACTORY PATHOPHYSIOLOGY IN AD

### Amyloid precursor protein (APP) processing

In a transgenic mouse model for AD, the enzyme expression involved in AD pathogenesis indicates a mechanism that may underly olfactory pathology. Positive A $\beta$  immunoreactivity was found within the glomerular layer in young mice (40) and increased across the inner OB cell layers as the disease progressed (41). Expression of  $\beta$ -secretase, a major enzyme involved in amyloidosis, was observed only in the glomerular layer of the OB even in C57BL/6 mice, a common inbred strain of laboratory mice, showing that the glomerulus layer is likely the main region in A $\beta$  production among the OB layers (42).

A correlation between olfactory dysfunction and amyloid deposition was reported in APP/PS1 mice (43). Transgenic mice with selective overexpressing humanized APP (hAPP) in either mature or immature OSNs exhibited widespread cell-autonomous apoptosis in OSNs, exhibiting that A $\beta$  pathology is involved in olfactory neurodegeneration (44). Electron microscopy showed a decreased glomerular connectivity along with subcellular structural deficits (44). Furthermore, OSNs may play a role in independent APP processing. In one of the most well-characterized and widely used transgenic mouse models, the Tg2576 mouse model that conventionally overexpresses hAPP, the OE exhibits a higher expression level and activity of

$\gamma$ -secretase than that of other brain regions (45). Increased  $\beta$ -secretase levels in the olfactory glomerular layer have also been observed in Tg2576 (40).

### Neuroinflammation

Apart from direct AD pathology, several environmental toxic factors can affect olfaction by damaging the OE, indicating that local toxicity is sufficient to impair smell. For instance, air dust and nanoparticles damage OSNs directly, causing oxidative stress and neuroinflammation similar to amyloid deposition (46). A variety of air pollutants trigger oxidative stress in the OE, resulting in protein misfolding, mitochondrial dysfunction, and neuronal apoptosis. Furthermore, such factors recruit reactive microglia that can exacerbate inflammation by releasing pro-inflammatory cytokines such as TNF- $\alpha$ , IL- $\beta$ , or IFN $\gamma$  (47). Interestingly, clinical studies have shown that one fifth of diagnosed patients with AD have a history of allergies and chronic rhinitis that had required some sort of treatment (48). Such toxic factors not only cause neuronal damage directly but could also exacerbate ongoing pathological processes such as neuroinflammation (49) leading to further olfactory disturbances.

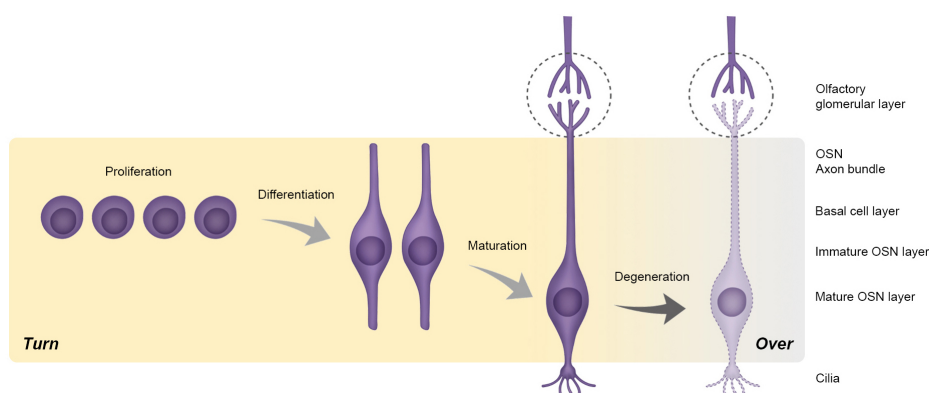
### Spreading pathology along the neural circuit

The OB receives serotonergic projections from brainstem raphe nuclei that could form a reciprocal pathway that receives down-top signals through the olfactory cortex and modulates OSNs' synaptic activity (50). Given theories that emphasize the brainstem's role in AD pathology, raphe-OB connections could play a key function in AD pathology (51), because raphe pathology happens at early AD stages (52), implying that the OB is also involved in an early stage from both anterograde and retrograde influences. According to several other studies, the OB could deliver misfolded proteins into the brain. As evidence, A $\beta$  that was injected into the OB of C57BL/6 mice was also found in other brain regions, such as the frontal cortex (53). A prion-like spreading of toxic molecules that could cause olfactory abnormalities might occur in the non-cortical olfactory structures (54).

### Physiology of spatially conserved map

Physiological functions are closely related to progressive pathological alterations in the olfactory system and can induce smell dysfunction in the onset of AD. The spatially conserved map in the olfactory system (55) may play a critical role in the manifestation and progression of olfactory impairment in AD.

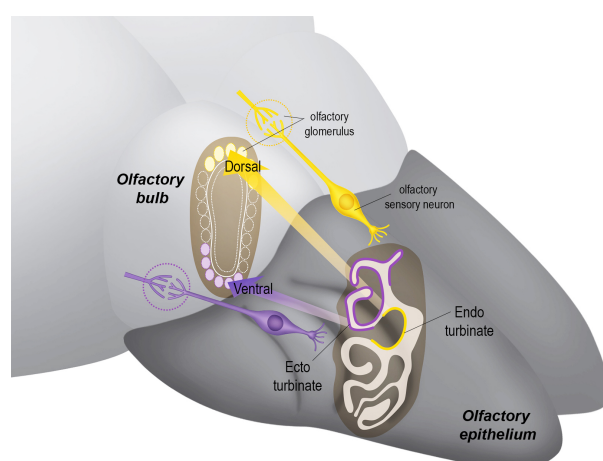
According to rodent studies, a physiologically conserved axis between the OE and OB can affect decreasing or increasing AD pathogenesis and olfactory dysfunction. Naturally, the mammalian main olfactory system has a spatially organized neuroregeneration and projection of OSNs, which originate from progenitor cells located in the basal layer that proliferate (56) and mature by sending their axons to reach the OB. After development, OSNs can degenerate because of physical injury, cellular stress, aging, and AD-related pathology. To



**Fig. 2.** Scheme of the turnover of olfactory sensory neurons. Once the olfactory sensory neurons (OSNs) degenerate in the lifetime, new OSNs originate from progenitor cells located in the basal layer that proliferate and send their axons to the olfactory bulb.

maintain the structure of the OE, basal cells proliferate and differentiate into immature OSNs, then into mature OSNs, by rendering a synaptic interface with the mitral cellular dendrite in the OB (Fig. 2). This process occurs throughout life and is called the replacement or turnover of OSNs (57). Odorant receptor genes in the OSNs determine axonal projections to dorsal and ventral (ectoturbinates and endoturbinates in the OE's coronal plain) glomeruli in the OB (55) that show the topographic projection and subzonal organization (Fig. 3) (58, 59). OSN replacement is also regulated by a variety of physiological factors such as retinoic acid, a well-known cell differentiation promoter (60, 61). The two domains (endoturbinate-dorsal and ectoturbinate-ventral) summarize the zonal organization in the olfactory system and have different physiologies (Fig. 3). For example, when progenitor cells harvested from the dorsal OE were transplanted into the ventral region in mice, the transplant-derived neurons expressed a selective immunoreactive ventral marker OCAM (olfactory cell adhesion molecule) and lost a dorsal marker NQO1 (NADPH dehydrogenase) to match their new location (61). Additionally, Liberia *et al.* (26) and Son *et al.* (62) showed that OSNs in the ventral OE have a faster ratio of turnover (regeneration and degeneration) than do those in the dorsal part, suggesting that repetitive OSN turnover triggers neuronal death of mature OSNs by driving excessive apoptosis, metabolic wastes, and neuroinflammation. Together, these events could cause more olfactory neuropathology to promote pathological processes, such as APP expression and neuroinflammation.

Overexpression of  $\beta$ -secretase may impair olfactory function by causing cell death in ventrally projecting OSNs (40). In line with this, the mRNA of  $\beta$ -secretase protein 1 (BACE1) was expressed in the ectoturbinate of OE in C57BL/6 (42). In addition, oligomeric A $\beta$ s and  $\beta$ -secretase proteins were robustly expressed in the ventral parts of the glomeruli in Tg2576 (40). Calcium activity was decreased in the OSNs in ventral regions where oligomeric A $\beta$  is highly overexpressed and significantly



**Fig. 3.** Scheme of the spatially conserved map in the mouse olfactory system. The zonal organization, endoturbinates-dorsal glomerulus axis (yellow), and ectoturbinates-ventral glomerulus axis (purple). The two drawings in yellow and purple are representations of two olfactory sensory neurons, with the colors emphasizing the regional topography of sensory inputs to the olfactory bulb.

damaged OSN turnover in the ectoturbinate OE more than in the endoturbinate OE in 5xFAD with mutated human APP and presenilin 1 gene, a transgenic mouse model that can recapitulate AD-related early and aggressive phenotypes (62). Regarding neuroinflammation, Hasegawa-Ishii *et al.* (63) reported that intranasal administration of lipopolysaccharide induced an inflammatory response and synaptic loss in OSNs by triggering both microglia and astrocyte activation in the OB. Intriguingly, inflammatory monocyte immunoreactivity (Ly-6) was highly indicated in the ectoturbinate of the OE.

Extrinsic stimulation can affect different physiologies of the spatially conserved map of the olfactory system. OSNs are

exposed to inhaled air and are therefore vulnerable to environmental factors such as air pollutants that cause DNA damage and cellular stress (64) whereas the ectoturbinate in the OE have a curved structure that increases contact with inhaled air (65). OSNs are also sensitive to changes in air pressure and air flow (26, 66). Structural and functional changes of the spatially conserved map can affect neuronal stability in the olfactory system and initiate a vicious cycle that could cause further damage. Further studies are required to define neuronal damage and excessive immune responses involved in the ectoturbinate and the endoturbinate.

The conserved map is strongly preserved across species (67, 68). Intriguingly, in a human postmortem study, the volume of ventral glomeruli was reduced in Parkinson's disease patients' OBs (69). However, many aspects remain to be explored in AD patients.

### CLINICAL IMPLICATIONS OF OLFACTORY PATHOPHYSIOLOGY IN AD

The olfactory system has received much interest in recent years as a novel tool for drug delivery and diagnosis in AD. Despite the advances in AD biomarker research, knowledge about the applicability and accuracy of markers remains incomplete. An olfactory test for AD was developed by Richard L. Doty in 1984 (70) and has been applied in clinical research and diagnosis over the last 30 years. Olfactory dysfunction in AD exhibits specific features, with clinical studies showing patients have difficulties identifying a specific subset of odorants (71). In particular, the peanut-butter smell, which has been suggested as a reference test for AD patients, must be closer in order for AD patients to detect the smell than is needed for healthy controls (72). Partial hyposmia or specific anosmia is when one has an otherwise normal sense of smell but cannot perceive one or more specific odors. A recent study using 5xFAD suggested that the features and mechanism of the partial olfactory dysfunction demonstrating regionally specific A $\beta$  accumulation influences partial olfactory dysfunction during early AD pathogenesis (62). These results suggest that continued research on mechanisms within olfactory-system pathophysiology can provide new light in early AD diagnoses.

Olfactory neuropathology allows us to speculate that the impaired OE includes altered cellular and molecular components. Hence nasal fluid from the OE may feasibly contain high-throughput biological material information which mirrors AD pathological changes in the olfactory system (37) that could be linked to the OE. The composition of oligomerized A $\beta$  proteins in nasal discharge is also closely correlated with cognitive function during AD progression (73). Thus, nasal-fluid biomarkers could prove to be a candidate sourcing tool in AD similar to cerebrospinal fluid and plasma biomarkers. Correspondingly, the olfactory system may provide a new platform for conducting preclinical and clinical studies to improve diagnostics in AD and better understand the mechanisms behind

neurodegeneration in AD.

### CONCLUSION

This review highlights the significance of olfactory pathophysiology and olfactory dysfunction in AD progression. The olfactory function can be impaired by the AD pathologies derived by amyloidogenic APP processing and neuroinflammation in the olfactory system. In particular, the physiological features of the spatially conserved map in the OE and OB play a complex role in ongoing olfactory neurodegeneration that induces abnormal olfaction within AD. This review suggests that olfactory neuropathology and neurodegeneration itself can be seen as the main underlying cause of olfactory dysfunction rather than it being derived from higher cortical area deficits seen throughout AD. Taken together, AD is an incurable and irreversible disease, but AD-related olfactory dysfunction provides clues towards diagnostic methods and gives insight into onset mechanisms in AD pathogenesis.

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### AUTHOR CONTRIBUTIONS

Gowoon Son: Conceptualization, Methodology, Investigation, Drawing figures, Writing-original draft preparation. Ali Jahanshahi: Conceptualization, Writing-reviewing and editing, Supervision. Seung-Jun Yoo: Conceptualization, Writing-reviewing and editing. Jackson T. Boonstra: Writing-reviewing and editing. David A. Hopkins: Writing-reviewing and editing, Harry W. M. Steinbusch: Writing-reviewing and editing, Supervision, Project administration. Cheil Moon: Writing-reviewing and editing, Supervision, Project administration, Funding acquisition.

### AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### CONFLICTS OF INTEREST

The authors have no conflicting interests.



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