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Neural correlates of olfactory dysfunction: A systematic review

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ABSTRACT

Olfactory dysfunction affects over 20% of the population. Despite progress in understanding its neural pathophysiology, research remains fragmented. This systematic review synthesizes evidence of brain structural and functional measures, and their association with clinical characteristics (e.g., etiology, duration) in patients with olfactory dysfunction. This may help to identify neural correlates and potential neuroimaging biomarkers of olfactory dysfunction's severity and progression. Following PRISMA guidelines, we screened 2374 papers and included 164 studies. Structural MRI studies consistently reported reduced olfactory bulb volume and/or sulcus depth, alongside gray matter reduction in the orbitofrontal cortex, hippocampus, insula, and amygdala in acquired olfactory dysfunction and paradoxical increases in congenital anosmia. Diffusion tensor imaging studies showed widespread white matter abnormalities, with prominent fractional anisotropy reductions. Resting-state and task-based fMRI studies showed heterogeneous, global alterations in connectivity and/or reactivity. PET/SPECT studies generally reported reduced perfusion or hypometabolism in frontal regions, especially in the orbitofrontal regions. Dopamine transporter imaging showed more frequent dopaminergic deficits in Parkinson's and prodromal individuals with hyposmia. Electroencephalography studies, despite methodological heterogeneity, generally found prolonged latencies and reduced amplitudes in olfactory event-related potentials. Across techniques, these brain alterations often showed low-to-moderate correlations with olfactory function. Although etiological and methodological heterogeneity currently obstructs the identification of robust neuroimaging biomarkers of olfactory dysfunction's severity and progression, current evidence indicates that olfactory dysfunction involves widespread structural and functional alterations, mainly in olfaction-related areas, with the orbitofrontal cortex as a key area emerging across techniques. Large-scale, standardized studies are needed to enable stratified diagnosis and personalized prognosis.

1. Introduction

The olfactory system is essential for human survival and quality of life. Olfaction serves as an early warning system against environmental hazards (e.g., toxic gases, fire, spoiled food), and contributes to flavor perception and dietary behaviors. Furthermore, olfactory cues help assess hygiene in personal and shared environments and support social interactions (McGann, 2017; Oleszkiewicz et al., 2025; Stevenson, 2010). This vital system is engaged when odor molecules first enter the nasal cavity and bind to olfactory receptor neurons in the olfactory epithelium. Subsequently, signals travel via the olfactory nerve to the olfactory bulb (OB), the brain's primary relay station for odor processing. From there, information is routed to primary olfactory regions, including the piriform cortex, the entorhinal cortex and parts of the amygdala. Finally, signals reach secondary olfactory regions, including the hippocampus, parahippocampal gyrus, orbitofrontal cortex, anterior cingulate cortex and anterior insular cortex/frontal operculum, where affective coding of odors and integration with other sensory inputs takes place (Branigan and Tadi, 2025; Duchamp-Viret et al., 2023; Lundstrom et al., 2011).

The intricate architecture of this pathway renders it vulnerable to disruption. An estimated 20% of the general population experiences olfactory dysfunction (OD) (Whitcroft and Hummel, 2019). This dysfunction is broadly categorized into quantitative and qualitative domains. Quantitative OD include anosmia (complete smell loss) and hyposmia (reduction in the sense of smell). Conversely, qualitative OD involves aberrant odor perception, notably parosmia (distorted smell in the presence of an odorant) and phantosmia (smell in the absence of a stimulus) (Whitcroft et al., 2023), that are typically unpleasant. Qualitative disorders such as parosmia are more prevalent in post-viral conditions than in other conditions and can substantially impair quality of life (Eo et al., 2023). There are various etiologies that lead to OD. The

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most prevalent causes are sinonasal disease (e.g., chronic rhinosinusitis), which obstructs airflow and cause inflammation in the olfactory epithelium, impairing olfactory function (Lin and Yeh, 2022). Post-viral OD represents another major category. Viral infections often cause inflammation in the nasal passages, which impairs olfactory perception (Hummel et al., 2016; Whitcroft et al., 2023). Emerging research indicates that viruses such as SARS-CoV-2 may extend beyond mucosal inflammation, potentially causing direct central olfactory damage by viral invasion (Doty, 2022; Parma et al., 2020). Traumatic brain injury is a major cause of permanent OD, as it can induce shearing of olfactory fibers at the cribriform plate, and central nervous system damage such as contusions or gliosis. Moreover, the severity of OD has been shown to correlate with severity and localization of olfactory regions' lesions (Hsieh et al., 2024). In addition, OD has been increasingly linked to neurological disorders. While frequently cited as a prodromal feature of neurodegenerative diseases like Parkinson's and Alzheimer's (Bhatia-Dey and Heinbockel, 2021; Kovacs, 2004), olfactory impairment is also observed across a broader spectrum of central nervous system conditions, such as epilepsy, multiple sclerosis (Hummel et al., 2016; Whitcroft et al., 2023). Studies consistently demonstrate an age-related decline in olfactory function, paralleling alterations in the olfactory epithelium, olfactory bulbs, and central processing regions (Kondo et al., 2020). Congenital dysfunction, which is characterized by lifelong anosmia or severe hyposmia, often link to hypoplastic or aplastic olfactory bulbs, and immature or absent olfactory sensory neurons (Karstensen and Tommerup, 2012). Other associated etiologies include exposure to drugs or toxins, psychiatric disorders, metabolic conditions (e.g., diabetes, vitamin B12 deficiency), and iatrogenic injury from surgery (Hummel et al., 2016; Whitcroft et al., 2023). When no identifiable cause is found, cases are classified as idiopathic OD. Ultimately, these diverse etiologies involve distinct pathological mechanisms that may be peripheral, central, or combined. Furthermore, the duration of dysfunction plays a significant role; prolonged olfactory loss stemming from initial peripheral damage can eventually trigger central neuroplastic reorganization as the brain adapts to reduced sensory input (Frasnelli et al., 2011; Kollndorfer et al., 2015).

Across the etiologies, OD directly or indirectly contributes to structural and functional brain alterations. Structural alterations are changes in brain anatomy, such as atrophy or damage to specific regions or neural pathways. Functional alterations involve changes in how the brain processes information, including altered neural reactivity, connectivity, metabolism, neurochemical transmission, and electrophysiological activity. These neural alterations of OD affect both the olfactory pathway and broader brain networks (Pellegrino et al., 2021). Over the past decades, advances in neuroimaging and electrophysiological techniques have led to an increasing number of studies investigating the structural and functional brain alterations underlying OD. The most commonly used brain measures and their (dis)advantages are described in Table 1.

Despite significant progress in understanding OD, current research remains fragmented, with studies often focusing on isolated aspects of neural alterations or on separate etiologies. Some reviews have attempted to synthesize findings on brain alterations, often focusing exclusively on either structural or functional changes, or certain techniques. For example, Manan et al. (2022) conducted a systematic review on structural brain alterations in OD measured with MRI. Han et al. (2019) and Hura et al. (2022) focused exclusively on studies employing structural and functional MRI. Although some reviews have attempted to bridge structural and functional domains, their scope was limited to certain populations. Bothwell et al. (2023), for example, examined both brain structure and function but restricted their analysis to aging populations. Likewise, Keshavarz et al. (2021) and Abdul Manan et al. (2025) focused specifically on Covid-19-related OD, and Torres-Pasillas et al. (2023) provided a comprehensive review of brain alteration of OD but limited to Parkinson's disease. These studies and systematic reviews, while valuable, offer only a partial view of the neural correlates of OD.

Table 1
Neuroimaging and other techniques for olfactory dysfunction research.

Technology	Main outcomes	Advantages	Limitations
Structural MRI (sMRI)	Olfactory bulb volume (OBV), olfactory sulcus depth (OSD), cortical thickness, regional gray matter volume	Excellent soft tissue contrast; high spatial resolution (<1 mm); non-invasive.	Expensive; static measure (cannot assess function); sensitive to motion.
Diffusion MRI	Structural connectivity integrity, microstructural integrity (e.g., Fractional Anisotropy).	Maps white matter pathways in vivo; non-invasive.	Indirect measure of microstructure; lower spatial resolution than sMRI; complex modeling.
Task-based functional MRI (fMRI)	Odor-evoked activity, task-based functional connectivity	High spatial resolution (~2–3 mm); Whole-brain coverage.	Indirect measure of neural activity; Poor temporal resolution (seconds); Expensive; Sensitive to motion.
Resting-state fMRI	functional connectivity, network organization, regional measures (e.g., regional homogeneity (ReHo), amplitude of low-frequency fluctuations (ALFF/fALFF))	No task required; reveals baseline network organization.	"Resting" state is not controlled; complex interpretation.
fNIRS	Cortical hemodynamic changes (oxygenated/deoxygenated blood) during olfactory tasks.	Portable; low-cost; tolerant of motion; good temporal resolution (~100 ms).	Limited to cortical surface; poor spatial resolution (~1–3 cm); Cannot image subcortical areas.
PET / SPECT/ MRI	Regional cerebral blood flow, glucose metabolism, specific receptor binding (e.g., dopamine).	Provides molecular and metabolic information; specific tracer options.	Ionizing radiation (invasive); low temporal resolution (minutes); very expensive.
EEG	Event-Related Potentials (ERPs), oscillatory power (e.g., gamma band).	Excellent temporal resolution (<1 ms); direct measure of neuronal activity; non-invasive; low-cost.	Very poor spatial resolution; sensitive to artifacts (eye, muscle, heart).
MEG	Odor-evoked magnetic signals, oscillatory activity.	Excellent temporal resolution (<1 ms); direct measure of neuronal activity; better spatial resolution than EEG.	Expensive; technically complex; poorer spatial resolution than fMRI.

fNIRS: functional near-infrared spectroscopy; PET: positron emission tomography; SPECT: single photon emission computed tomography; EEG: electroencephalography; MEG: magnetoencephalography.

Therefore, our systematic review aimed to consolidate the brain research on the neural correlates of OD and provide a comprehensive understanding of the relationship between OD, brain structure and function. It addresses three core questions: 1) What are the neural correlates of OD? 2) What are the associations between olfactory function and brain measures in individuals with OD? And 3) How do clinical characteristics (etiology, pathophysiology) relate to brain measures?

2. Method

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. An overview of the screening process is provided in Fig. 1. The study protocol was prospectively registered in PROSPERO and is available at https://www.crd.york.ac.uk/PROSPERO/view/CRD42024559585.

2.1. Search strategy

A systematic search was conducted in four electronic databases—PubMed (which includes MEDLINE-indexed records), Cochrane Library CENTRAL, Scopus, and Web of Science for original English-language articles published from January 1, 1994 through July 30, 2024. A search update was performed on October 30, 2025, but no additional eligible studies were identified. A targeted search strategy

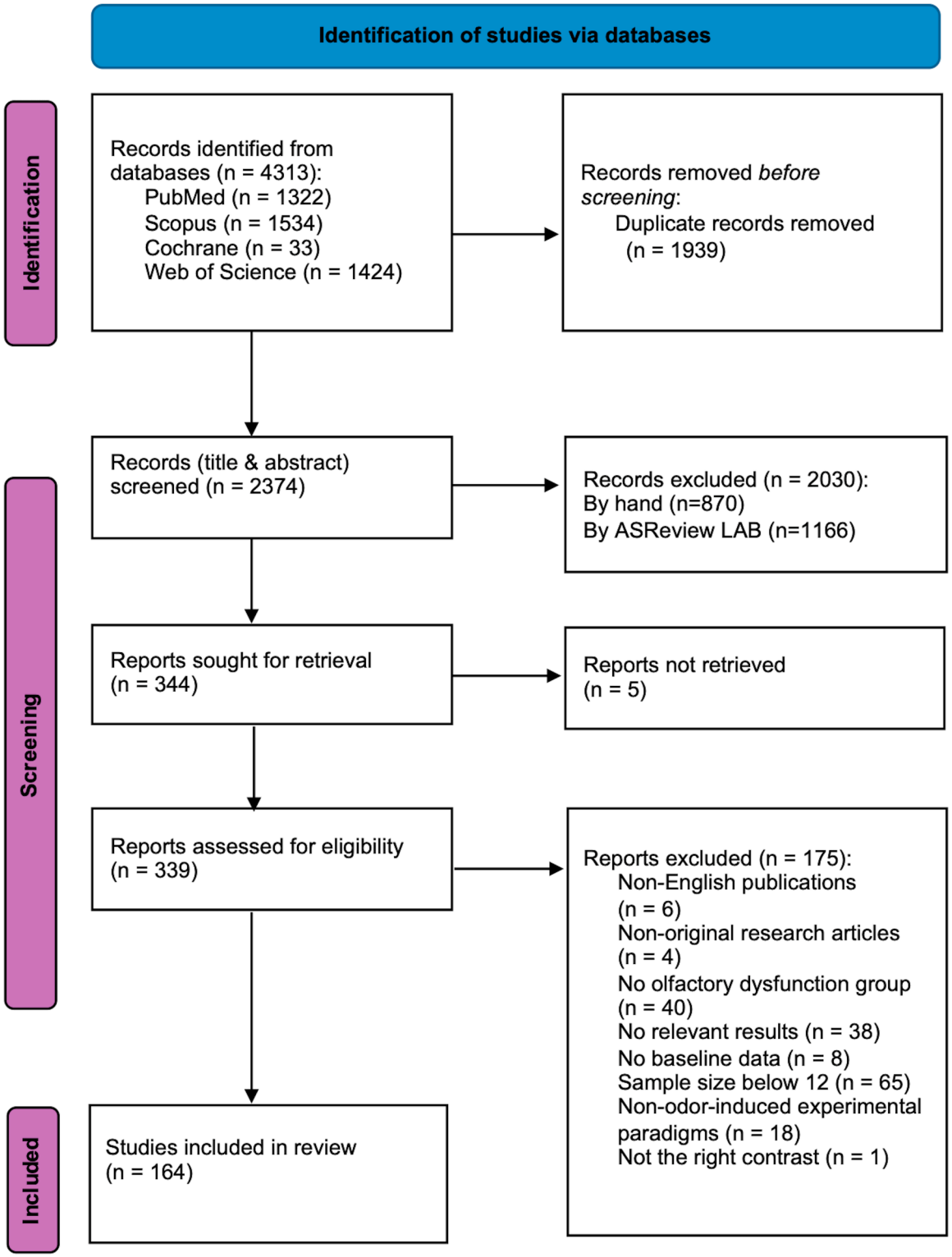

Fig. 1. PRISMA flow diagram.

was developed by using keywords and Medical Subject Headings (MeSH) terms related to OD (e.g., "anosmia", "hyposmia", "parosmia", "phantosmia", "olfactory dysfunction", "smell loss") combined with terms related to brain measurements (e.g., "magnetic resonance imaging" [MRI], "diffusion tensor imaging" [DTI], "positron emission tomography" [PET], "electroencephalography" [EEG], "single-photon emission computed tomography" [SPECT], "Dopamine transporter" [DAT]) or brain-related outcomes (e.g., "olfactory bulb volume" [OBV], "olfactory sulcus depth" [OSD], "cortical thickness"). The search terms were iteratively refined in collaboration with two domain experts (PS, SB) and finalized with guidance from an experienced research librarian. Detailed search strategies and terms for each database are provided in Supplementary Material **A**.

2.2. Eligibility criteria

All articles included in this systematic review met the following predefined eligibility criteria.

Participants: Patients with OD (anosmia or hyposmia, parosmia and phantosmia) as defined in the article.

Study designs: Eligible designs included cross-sectional, cohort, case-control, and intervention studies. For longitudinal studies, to avoid confounding by recovery, we only included brain findings at baseline to confirm the presence of OD in participants.

Outcomes**:** Outcomes included measure of olfactory function, and neural correlates of OD, encompassing structural and/or functional brain metrics. Structural outcomes included OB morphology and volume, OSD, regional gray matter volumes, DTI parameters. Functional outcomes focused on resting-state functional connectivity, task-based functional connectivity and neural activation during olfactory stimulation, and metabolic/neurochemical markers (e.g., PET/SPECT measures). Additionally, associations between olfactory function (e.g., clinical smell test scores) and these structural/functional brain measures were evaluated.

Exclusion Criteria: Case reports, animal studies, non-peer-reviewed literature, studies unrelated to OD. Small neuroimaging samples are known to result in low reproducibility (Button et al., 2013; Poldrack et al., 2017), therefore we excluded studies with fewer than 12 participants per group. Investigations measuring brain activation induced by non-olfactory stimuli (e.g., trigeminal odorants, sniffing or imagination tasks without odors) were also excluded.

2.3. Study selection

Two independent reviewers (YH and MB) conducted the literature search up to July 30, 2024, which was updated on October 30, 2025 by YH and SB. Records were imported into EndNote™ X9 for deduplication and organization. Title/abstract screening was performed using the ASReview (ASReview LAB developers, 2023). which employs active learning algorithms to prioritize relevant studies. Following this, the full texts of all candidate articles underwent dual independent evaluation by two reviewers to determine final inclusion or exclusion based on the eligibility criteria. Any discrepancies were resolved via discussion, with input from a third expert reviewer when necessary. A list of excluded studies during full-text review is available in Supplementary Material **B.**

2.4. Data extraction

Two independent reviewers (YH and SS) conducted the literature data extraction. Any discrepancies were resolved via discussion, with input from a third expert reviewer when necessary. The data extracted from the included studies encompassed key demographic information (e.g., age, sex, and sample size) for both the patient and control groups, alongside clinical characteristics specific to the patients, such as the etiology and duration of the olfactory dysfunction. Furthermore, we systematically recorded the methodologies employed for olfactory assessment and the resulting olfactory function scores of the participant population. Finally, all reported brain measurements and neural outcomes, which included identified brain regions, hemodynamic responses, changes in gray matter volume, and event-related components, were extracted.

2.5. Risk of bias assessment

Study quality was evaluated with the use of the adapted version of Newcastle-Ottawa Scale (NOS) (Peterson et al., 2011) for cross-sectional studies (Supplementary Material **C**) by two independent reviewers (YH and SS). The NOS criteria included: 1) Selection: representativeness of participants and diagnostic validity; 2) Comparability: adjustment for confounders (e.g., age, sex); 3) Outcome: reliability of brain assessments.

Results of the bias assessment are summarized in Supplementary Material **C**. Eleven studies were deemed to have a high risk of bias (score <7).

3. Results and discussion

A total of 4313 publications were retrieved. After removal of duplicates, 2374 studies were screened for eligibility based on their titles and abstracts. This resulted in 339 studies for full-text review. Ultimately, we identified 164 original articles meeting our inclusion criteria, covering multiple treatment techniques and diverse populations (Fig. 1). Comprehensive details of the included studies are summarized in Table 2.

3.1. Findings on structural brain alterations in olfactory dysfunction (OD)

3.1.1. Olfactory bulb (OB) and olfactory sulcus (OS) studies

63 studies encompassing 3832 patients measured morphological features of OB and/or OS, examining various etiologies of OD. The age of participants ranged from 7 to 83 years across included studies. The lowest reported mean age was 18.0 (Levy et al., 2013) and the highest was 67.1 years (Chen et al., 2018). The distribution of etiologies was as follows: Covid-19 related OD (n = 15), congenital OD (n = 11), post-viral OD (n = 11), post-traumatic OD (n = 11), neurological diseases (n = 7), idiopathic OD (n = 5), rhinosinusitis-related OD (n = 2), other etiologies (n = 2; e.g., diabetes- or laryngectomy-related), and mixed etiologies (n = 8). Some studies investigated multiple etiologies. The review focused on three primary aspects: 1) frequencies of OB or OS abnormalities (n = 25); 2) differences in OBV/OSD measurements compared to control groups (n = 50); and 3) associations between OBV/OSD metrics and psychophysical olfactory test performance (n = 23). The detailed findings of included studies are summarized in Supplementary Material **D.**

3.1.1.1. Prevalence of morphological abnormalities. A total of 25 studies reported the frequencies of OB or OS abnormalities. Structural abnormalities within the OB and OS, defined as any deviation from normal morphology including aplasia, hypoplasia, signal alterations, or shape anomalies, showed distinct patterns across etiologies. In congenital OD, OB abnormalities were nearly universal, reported in ~100% of patients (Bortolotto Felippe Trentin et al., 2023; Braun et al., 2016; Hacquart et al., 2017; Levy et al., 2013; Yan et al., 2024); OS abnormalities commonly coexist with OB abnormalities, though with lower frequencies, ranging from 56% to 93% (Bortolotto Felippe Trentin et al., 2023; Hacquart et al., 2017; Koenigkam-Santos et al., 2011; Yousem et al., 1999) Among patients with Covid-19 related OD, the reported frequency of OB abnormalities varied widely, from 7% (Abdou et al., 2023) to 91% (Kandemirli et al., 2021). Data on OS abnormalities in this group were limited; only one study reported a rate of 55% (Fjaeldstad

Table 2
Comprehensive details of the included studies.

First Author (Year)	OD N (Female)	OD age (mean ± SD / Range)	OD duration (months)	OD etiologies	OD categories	Olfactory test(s)	Olfactory score(s)	Non-olfactory groups characteristics
Bonanni et al. (2006)	25 (13)	46.16 ± 18	not specified	posttraumatic	anosmia	self-complained and clinical testing (odorous substances detection)	not specified	no control group(s)
Brämerson (2008)	23 (10)	50 (18–74)	not specified	mixed	mixed	butanol threshold test and Scandinavian Odor Identification Test (SOIT)	mean butanol threshold (95% confidence interval): 1.6 (0.8–2.3); mean SOIT(95% confidence interval): 7.3 (5.4–9.2)	24(19 F) healthy controls, age = 46; mean butanol threshold (95% confidence interval): 7.3 (6.6–8.0); mean SOIT(95% confidence interval): 14.6 (14.1–15.1)
Çelik (2022)	98 (30)	male: 36.01 ± 12.68; female: 36.46 ± 14.82	not specified	posttraumatic	mixed	self-complained	not specified	no control group(s)
Guan et al. (2009)	12 (8)	42.9 (27–59)	not specified	post-viral (non Covid-19)	mixed	Toyota and Takagi olfactometer test (T&T) for detection and recognition thresholds	not specified	no control group(s)
Güdücü (2019)	56 (25)	46.8 ± 20.0	not specified	mixed	anosmia	Sniffin' Sticks Test	TDI = 12.4 ± 5.2	46 (23 F) normosmic controls, age = 33.2 ± 13.8, TDI = 36.7 ± 4.5
Guo (2021)	61 (39)	47.50 ± 11.04	2–7.5	post-viral (non Covid-19)	not specified	Sniffin' Sticks Test	responder group = 15.34 ± 4.14, Non-responder group = 11.10 ± 3.71	20 (10 F) normosmic controls, age = 47.50 ± 11.04, TDI = 34.60 ± 3.05
Hu et al. (2010)	92 (33)	19–58	> 3	sinonasal disease (rhinosinusitis)	not specified	Toyota and Takagi olfactometer test (T&T) (detection and recognition thresholds)	preoperative T&T: nonpolyp group = 1.9 ± 1.8, Polyp group1: TDImin = 19.0 ± 6.5,	no control group(s)
Huart et al. (2015)	group1:13 (5); group2: 13 (10); in total: 26 (15)	group1: 70.46 ± 5.97; group2: 52.00 ± 9.78	not specified	group1: mild cognitive impairment; group2: post-viral (non Covid-19)	not specified	Sniffin' Sticks Test	TDImax = 23.9 ± 7.7; group2: TDImin = 19.1 ± 6.5, TDImax = 21.8 ± 6.9	13 (7 F) healthy controls, age = 69.69 ± 8.35, TDImax = 27.0 ± 3.7, TDImin = 24.6 ± 4.1,
Iannilli (2017)	hyposmia: 20; anosmia: 13; in total: 33 (-)	hyposmia: 65.6 ± 7.8; anosmia: 63.1 ± 9.7	not specified	mixed	group1: anosmia; group 2: hyposmia	Sniffin' Sticks Test	hyposmia group: TDI = 22.1 ± 1.4; anosmia group: TDI = 11.3 ± 1.5 Parkinson's disease group: TDI = 21.8 ± 1.5	21 normosmic controls, age = 60.5 ± 7.1 years, TDI = 34.6 ± 1.3; 17 Parkinson's disease patients, age = 65.5 ± 7.5, TDI = 21.8 ± 1.5
Landis et al. (2005)	19 (13)	47 ± 3.8	> 48	mixed	mixed	Sniffin' Sticks Test, orthonasal and retronasal identification (the percentage of correctly identified items)	TDI: mean score 12.5 ± 1.8; orthonasal identification: 36.1% ± 5.4%; retronasal identification: 54.7% ± 5.7%	no control group(s)
Li (2023)a	34 (21)	59 ± 16	8.89 ± 11.67	mixed	mixed	Sniffin' Sticks Test	total patients: TDI = 21.74 ± 6.77,	17 (10 F) healthy controls, age = 50 ± 14 years, TDI = 34.62 ± 2.7
Li (2024)a	group1: 23 (16); group2: 21 (14); in total: 44 (30)	group1: 48 ± 14; group2: 52 ± 12; in total: 50 ± 13	group1: 25.4 ± 3.89; group2: 27.8 ± 18.88; in total: 23.05 ± 30.86	mixed	group1: hyposmia with parosmia; group2: hyposmia without parosmia	Sniffin' Sticks test and Odor threshold for furfural mercaptan and 2,6-nona-dienal and Sniffin' Sticks parosmia test	group1: TDI = 25.57 ± 5.16, group2: TDI= 23.82 ± 4.30	21 (15 F) normosmic controls, age = 45 ± 14, TDI = 32.98 ± 2.68

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Table 2 (*continued*)

First Author (Year)	OD N (Female)	OD age (mean ± SD / Range)	OD duration (months)	OD etiologies	OD categories	Olfactory test(s)	Olfactory score(s)	Non-olfactory groups characteristics
Limphaibool et al. (2020)	38 (16)	45 ± 16.1	not specified	posttraumatic	mixed	subjective blast (Elsberg-Levy) olfactory testing (perception and identification thresholds)	no odor perception n = 27, no odor identification n = 36 N = 11: perception thresholds, mint = 18 cm3 ± 14, anise = 22 cm3 ± 16;	31 (14 F) normosmic controls, age = 51 ± 14.6; olfactory test (cm3): odor perception _anise = 8 ± 3; odor perception _mint = 5 ± 3; odor identification _anise = 12 ± 7; odor identification _mint = 10 ± 6;
Rombaux (2007)	65 (34)	51 ± 16	not specified	mixed	mixed	clinical psychophysical testing (orthonasal and retronasal test)	Orthonasal = 16.9 ± 7.2; retronasal = 12.7 ± 3.6	no control group(s)
Rombaux et al. (2010a)	27 (17)	54.8 (22–74)	not specified	post-viral (non Covid-19)	mixed	Sniffin' Sticks Test	TDI = 16.7 ± 5.76 (baseline); retronasal score = 10.4 ± 3.49 (baseline)	no control group(s)
Schaub and Damm (2012)	20 (11)	57.8 ± 7.66	not specified	aging	hyposmia	Sniffin' Sticks Test	TDI = 22.86 ± 4.03	(13 F) normosmic controls, age = 26.55 ± 6.61; TDI = 38.18 ± 1.79
Schriever (2017)	18 (12)	46.6 ± 6.3	not specified	mixed	mixed	Sniffin' Sticks test battery	not specified	20 (11 F) normosmic controls, age = 23.8 ± 2.8; TDI = 36.5 ± 2.9
Whitcroft (2017)	anosmics: 40 (17); hyposmics: 20 (11); in total: 60 (28)	anosmics: 55 ± 25; hyposmics: 49 ± 17	not specified	mixed	mixed	Sniffin' Sticks Test	anosmic group: TDI = 11.0 ± 2.95; hyposmic group: TDI = 25.9 ± 3.4	41 (22 F) normosmic controls, age = 32 ± 12; TDI scores = 36.0 ± 3.6
Yang (2012)	anosmics: 88 (45); hyposmics: 86 (41); in total: 174 (86)	anosmics: 42 ± 11; hyposmics: 41 ± 15	not specified	mixed	mixed	T&T olfactometer	functional anosmia: T&T = 5.59 ± 0.49; hyposmia: T&T = 2.04 ± 2.21	98 (48 F) healthy control, age = 40 ± 13, T&T = -1.21 ± 0.86)
Chen (2021)	group1: 31 (16); group2: 64 (45); in total: 95 (61)	group1: 69.6 ± 5.8; group2: 68.5 ± 7.4	not specified	group1: non-depression; group2: late-life depression	Identification impaired	Sniffin' Sticks identification test	group1: TDI = 7.9 ± 1.9 group2: TDI = 7.1 ± 1.7	70(45 F) normosmic controls, age = 66.5 ± 6.3; identification scores = 12.1 ± 1.3; 93(74 F) late-life depression with intact identification, age = 66.6 ± 7.1, identification scores = 11.8 ± 1.1
Iravani (2021)	20 (11)	56 ± 10.38	14 ± 9.86	mixed	anosmia	Sniffin' Sticks Test	TDI = 13.35 ± 0.5	23(12 F) healthy controls, age = 55 ± 7.89; TDI = 35.21 ± 0.65
Ma (2023)	28 (9)	42.25 ± 13.99	not specified	sinonasal disease (rhinosinusitis)	not specified	2020 European Position Paper on Rhinosinusitis and Nasal Polyps	TDI = 13.84 ± 34.67	29 (12 F) patients with chronic rhinosinusitis without olfactory dysfunction, age = 36.33 ± 11.49, TDI scores = 36.23 ± 2.79
Manara et al. (2018)	44 (0)	31.52 ± 10.53	not specified	congenital (Kallmann syndrome)	mixed	clinical profile	not specified	26 age-matched healthy controls
Muccioli (2023)	23 (12)	37 ± 14	11 ± 5	post-viral Covid-19	hyposmia	Sniffin' Sticks test	TDI = 23.63 ± 5.32	26(13 F) healthy controls, age = 38.5 ± 13.7
Park (2019)	16 (5)	43.2 ± 10.2	not specified	posttraumatic	anosmia	Korean Version of Sniffin' Stick II (KVSS-II) test	KVSS-II = 9.44 ± 3.7	12(4 F) healthy controls, age = 26.8 ± 8.4

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Table 2 (*continued*)

First Author (Year)	OD N (Female)	OD age (mean ± SD / Range)	OD duration (months)	OD etiologies	OD categories	Olfactory test(s)	Olfactory score(s)	Non-olfactory groups characteristics
Siva (2024)	15 (8)	70.7 ± 4.8	not specified	neurological disease (Parkinson's disease)	hyposmia	OSIT-J (Odor Stick Identification Test for the Japanese)	OSIT-*J* = 1.7 ± 1.1	group1: 15(9 F) PD patients with normal cognitive ability, age: 64.4 ± 7.2, OSIT-J score: 7.5 ± 1.5 group2: 15(8 F) healthy controls, age: 63.3 ± 5.2, OSIT-J score 10.4 ± 1.3
Su (2015)	38 (13)	61.0 ± 8.86	not specified	neurological disease (Parkinson's disease)	hyposmia	"Five Odors for Olfactory Detection Arrays" for olfactory detection threshold (TOD)	TOD = 0.44 ± 1.15	group1: 16 (7 F) Parkinson's disease patients without hyposmia, age: 57.25 ± 7.58, TOD score: −1.74 ± 0.16) group2: 22(7 F) healthy controls, age: 58.23 ± 6.82, TOD score: −1.76 ± 0.22)
Thaploo et al. (2023)	group1: 49 (30); group2: 45 (25); group3: 51 (35); in total: 145 (90)	group1: 41.2 ± 16.2; group2: 42.7 ± 14.6; group3: 42.5 ± 13.5	hyposmia: 9.7 ± 6 (group1); 10.5 ± 4.3 (group2); 11.2 ± 5(group3); parosmia: 0 (group1); 2.1 ± 0.35 (group2); 2.0 ± 0.21 (group3)	post-viral Covid-19	group1: no parosmia; group2: mild parosmia; group3: sever parosmia	Sniffin' Sticks threshold test and parosmia scoring questionnaire	threshold scores: 4.4 ± 1.8 (group1), 4.3 ± 2 (group2), 4.0 ± 1.9 (group3)	no control group(s)
Tremblay (2020)a	group1: 15 (7); group2: 15 (6); in total: 30 (13)	group1: 66.8 ± 7.3; group2: 62.8 ± 9.2	not specified	group1: neurological disease (Parkinson's disease); group2: mixed (non Parkinson's disease)	hyposmia	Sniffin' Sticks threshold test	group1: TDI = 17.5 ± 6.9; group2: TDI = 17.3 ± 7.7	15 (7 F) healthy controls, age = 66.3 ± 6.3, TDI = 38.0 ± 3.0
Wang (2022)	15 (8)	70.7 ± 4.8	not specified	neurological disease (Parkinson's disease)	hyposmia	Japanese Odor Stick Identification Test (OSIT-J)	OSIT-*J* = 1.7 ± 1.1	group1: 15(8 F) healthy controls, age = 63.3 ± 5.2, OSIT-*J* = 10.4 ± 1.3 group2: 15 (9 F) Parkinson's disease with normal olfaction or mild hyposmia, age = 64.4 ± 7.2, OSIT-*J* = 7.5 ± 1.5
Yoneyama (2018)	15 (8)	70.7 ± 4.8	not specified	neurological disease (Parkinson's disease)	hyposmia	Japanese Odor Stick Identification Test (OSIT-J)	OSIT-*J* = 1.7 ± 1.1	group1: 15(8 F) healthy controls, age = 63.3 ± 5.2, OSIT-*J* = 10.4 ± 1.3 group2: 15 (9 F) Parkinson's disease with normal olfaction or mild hyposmia, age = 64.4 ± 7.2, OSIT-*J* = 7.5 ± 1.5
Zhang (2022)	24 (10)	43.6 ± 14.0	≥ 3	post-viral Covid-19	not specified	Butanol threshold test (BTT) and UPSIT	BTT= 2.25 ± 1.09; UPSIT = 23.6 ± 7.4	13 (7 F) healthy controls, age = 45.0 ± 13.2
Zhang (2023)	28 (11)	38.37 ± 15.63	not specified	sinonasal disease (rhinosinusitis)	hyposmia	Sniffin' Sticks threshold test	TDI = 13.84 ± 3.67	25 (12 F) healthy controls, age = 45.94 ± 11.69, TDI = 35.86 ± 2.44 24(10 F) rhinosinusitis without OD, age = 37.56

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Table 2 (*continued*)

First Author (Year)	OD N (Female)	OD age (mean ± SD / Range)	OD duration (months)	OD etiologies	OD categories	Olfactory test(s)	Olfactory score(s)	Non-olfactory groups characteristics
								± 13.49, TDI = 34.23 ± 2.79
Fan (2022)	group1: PD mild/ moderate: 17 (6); group2: PD severe microsmia: 18 (6); group3: PD anosmia: 21 (7); in total: 56 (19)	group1: 59.12 ± 10.18; group2: 62.61 ± 10.06; group3: 57.14 ± 10.18	not specified	neurological disease (Parkinson's disease)	group1: hyposmia; group2: hyposmia; group3: anosmia	UPSIT	group1: UPSIT = 30.18 ± 1.78 group2: UPSIT = 22.06 ± 1.96 group3: UPSIT = 14.67 ± 2.60	26 (8 F) Parkinson's disease with normal olfaction, age= 62.57 ± 10.45, UPSIT= 36.38 ± 1.60
Peter (2021)	33 (21)	34.2 ± 12.9	life long	congenital (isolated)	anosmia	self reported and Sniffin' Sticks Test	TDI = 10.9 ± 2.3	33 (21 F) healthy controls, age: 34.1 ± 12.2, TDI: 35.3 ± 3.8
Jiramongkolchai (2021)	16 (11)	60.0 ± 10.5	12 (range 3–240)	post-viral (non Covid-19)	mixed	clinical history, UPSIT, Sniffin' Sticks test, visual analog scale (VAS, scores 0–50)	median UPSIT (range): 21 (10−33); median TDI (range): 19.0 (8–27.25); median VAS (range): 12.0 (0−50);	20 (15 F) healthy controls, age = 55.0 ± 9.2 years, median UPSIT (range) = 37 (34–39)
Georgiopoulos (2024)	group1: Parkinson's disease: 14 (5); group2: post-viral hyposmia (PV): 15 (8); in total: 29 (13)	group1: 63–73 (70); group2: 63–73 (63)	not specified	group1: neurological disease (Parkinson's disease) group2: post-viral (including covid-19)	mixed	Sniffin' Sticks test	group1: TDI scores = 21.75 ± 5.25; group2: TDI scores = 16.25 ± 6	15 (6 F) healthy controls, age = 66 (64−77), TDI scores = 31.25 ± 3.75
Han (2018)a	group1: posttraumatic hyposmia: 19 (11); group2: posttraumatic anosmia: 21 (7); in total: 40 (18)	group1: 51.7 (11.7); group2: 51.0 (12.4)	not specified	posttraumatic	mixed	Sniffin' Sticks test	group1: 22.3 ± 4.1; group2: 11.0 ± 2.7	19(4 F) healthy controls, age = 44.7 ± 13.1, TDI scores = 34.0 ± 3.2
Iannilli (2011)	17 (11)	48 ± 4	not specified	mixed	anosmia	Sniffin' Sticks test	not specified	17 (11 F) normosmic controls, mean age = 41 ± 4
Kaheni (2024)	42 (13)	28.59 ± 4.72	not specified	posttraumatic	mixed	Sniffin' Sticks test	TDI = 12.12 ± 4.22	40 (21 F) healthy controls, mean age = 26 ± 3.56 years, TDI = 36.59 ± 1.61
Kohanpour (2023)	16 (-)	36.3 (22–50)	≥ 24	posttraumatic	anosmia	Sniffin' Sticks test	TDI scores < 16	15 (4 F) healthy controls, mean age (range): 30.1 (20–39) years, TDI scores > 30
Pellegrino (2021)	functional anosmia: 25 (6); hyposmic patients: 16 (10); in total: 41 (16)	anosmia: 54.4 ± 13.2; hyposmia: 51.5 ± 11.38	hyposmia: 39.5 ± 52.42; anosmia: 32.34 ± 37.88	posttraumatic	not specified	Sniffin' Sticks test	anosmia: TDI = 11.49 ± 2.83; hyposmia: TDI = 22.06 ± 3.73	22 (10 F) normosmic controls, age = 45.68 ± 13.12; TDI = 33.77 ± 3.08
Reichert (2018)	anosmics: 29 (19); hyposmics: 19 (11); in total: 48 (30)	anosmia: 60.3 ± 14.53; hyposmia: 57.9 ± 11.34	not specified	mixed	mixed	Sniffin' Sticks test	TDI = 16.33 ± 6.4	no control group(s)
Yunpeng (2021)	22 (11)	44.32 ± 18.63	14 congenital anosmia: lifelong; 8 idiopathic: 55.13 ± 37.33	mixed	not specified	Sniffin' Sticks test	TDI = 11.86 ± 4.07	16 (10 F) normosmic controls
Yousem (1996)b	25 (11)	29.8 (11−68)	not specified	congenital	mixed	self-reported and UPSIT	not specified	no control group(s)
Abdou (2023)	110 (86)	31.82 ± 10.15	not specified	post-viral Covid-19	mixed	self-reported and smell diskettes test	smell diskettes test (mean scores: 1–3 for OD	50 (33 F) healthy controls, age = 35.14 ± 12.37 years, smell diskettes test scores range: 7–8

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Table 2 (*continued*)

First Author (Year)	OD N (Female)	OD age (mean ± SD / Range)	OD duration (months)	OD etiologies	OD categories	Olfactory test(s)	Olfactory score(s)	Non-olfactory groups characteristics
Abolmaali et al. (2002)	16 (14)	27 (12–51)	life long	congenital	anosmia	self-reported, Sniffin' Sticks test, electrophysiologic testing with chemosensory evoked potentials	TDI ≤ 15; no Oerps	8 (4 F) healthy controls, mean age (range): 24 (21−27) years
Akkaya et al. (2021)	59 (26)	54.5 (21–71)	not specified	post-viral Covid-19	anosmia	self-reported	not specified	64 (31 F) Covid-19 normosmia, mean age (range): 55 (19–80) years
Altundag et al. (2021)	group1: Covid-19 anosmia: 24 (14); group2: post-viral anosmia: 38 (21); in total: 62 (35)	group1: 35 ± 11.5; group2: 43.7 ± 11.8	group1: 0.72; group2: 4	group1: post-viral Covid-19; group2: post-viral (non Covid-19)	anosmia	Sniffin' Sticks olfactory test	group1: TDI = 3.6 ± 3.3; group1: TDI = 5.5 ± 5.1;	29 (13 F) normosmic controls, age = 36.9 ± 11 years; TDI = 35 ± 2.3
Altunisik (2021)	36 (19)	37.33 ± 7.38	not specified	post-viral Covid-19	anosmia	self-reported	not specified	80 (44 F) normosmic controls, age = 35.74 ± 8.38 years
Bortolotto Felippe Trentin et al. (2023)	17 (4)	19–57	life long	congenital (Kallmann's syndrome)	mixed	self-reported and Sniffin' Sticks test	not specified	34 healthy patients matched for age and sex
Braun (2016)	20 (7)	28.1 (17–44)	not specified	congenital (Bardet–Biedl syndrome)	mixed	UPSIT	not specified	12 (8 F) healthy controls, mean age (range): 35.6 (26–51) years
Brudasca (2023)	67 (52)	44 ± 13	> 2	post-viral Covid-19	mixed	European Test of Olfactory Capabilities (ETOC)	not specified	no control group(s)
Capelli et al. (2023)	196 (116)	53 (42–60)	not specified	mixed	not specified	self-reported	not specified	39 (19 F) normosmic controls without Covid-19 symtoms or history, mean age (range): 55 (46 – 66)
Chen (2018)	53 (38);	67.1 ± 6.6	not specified	depression	not specified	Sniffin' Sticks test	OI (olfactory identification) = 7.3 ± 1.8; OT (olfactory threshold) = 7.9 ± 2.4	50 (28 F) Alzheimer's disease patients, age = 71.9 ± 9.9, OI = 5.8 ± 1.8, OT = 4.6 ± 1.8; 60 (36 F) healthy controls, age = 65.4 ± 7.3, OI = 11.8 ± 1.7, OT = 7.6 ± 2.5
Chung (2018)	subjective OD: 34 (19); normosmia: 10; hyposmia/anosmia: 24; in total: 34 (19)	51.4 (9–72)	59.2 (range 2–552)	mixed	mixed	Korean Version of the Sniffin' Sticks II test; QOD; VAS;	hyposmia/anosmia group (n = 24): mean TDI (range): 15.3 (6–27); normosmia group (n = 10): mean TDI (range): 35.5 (27.25–43).	10 normosmic controls, mean TDI (range): 35.5 (27.25–43)
Desser (2021)	79(-)	not specified	not specified	mixed	mixed	Sniffin sticks test	TDI = 18 ± 6.72	91 normosmic controls, TDI = 36.39 ± 2.10
Eliezer et al. (2020)	20 (10)	34.6 ± 8.8	0.2 ± 0.1	post-viral Covid-19	mixed	visual olfactory score(VOS, score 0–10)	VOS = 1.6 ± 1.9 (baseline)	20 (8 F) healthy controls, mean age = 33.9 ± 7.8, VOS = 9.4 ± 0.7
Genetzaki et al. (2024)	group1: 18; group2: 20; in total: 38 (-)	43.4 ± 4.3	6–13.5	post-viral (non Covid-19)	not specified	Sniffin' Sticks test	group1: TDI scores = 16.8 group2: TDI scores = 17.1	no control group(s)
Goektas (2009)	24 (13)	52.4 ± 14.4	74.6 ± 149	mixed	mixed	Objective olfactometry using chemosensory evoked potentials; subjective olfactometry with Sniffin' Sticks TDI test	TDI = 10.7 ± 9.3	no control group(s)

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Table 2 (*continued*)

First Author (Year)	OD N (Female)	OD age (mean ± SD / Range)	OD duration (months)	OD etiologies	OD categories	Olfactory test(s)	Olfactory score(s)	Non-olfactory groups characteristics
Gurbuz et al. (2021)	12(2)	54.25 ± 3.96	not specified	diabetic olfactopathy	not specified	CCCRC orthonasal olfaction test	CCCRC= 4.27 ± 0.67	13 (3 F) healthy controls, age = 55.23 ± 4.23, CCCRC = 6.42 ± 0.37
Hacquart (2017)	19 (4)	26 ± 11	life long	congenital (Kallmann syndrome)	mixed	self-reported (questionnaire)	not specified	19 (4 F) healthy controls, age = 27 ± 10 years
Haehner et al. (2008)	post-viral: 14; posttraumatic: 4; in total: 18 (12)	post-viral: 65 (50–76); posttraumatic: 59 (23–72)	15 (range 3–72)	mixed	mixed	Sniffin' Sticks test	TDI = 17.6 ± 6.8 (baseline)	no control group(s)
Han (2018)b	posttraumatic hyposmia: 22 (12); posttraumatic anosmia: 24 (9); in total: 46 (21)	posttraumatic hyposmia: 52.5 ± 13.4; posttraumatic anosmia: 53.7 ± 13.7; total posttraumatic: 53.0 ± 13.3	not specified	posttraumatic	mixed	Sniffin' Sticks test	hyposmia group: TDI = = 22.0 ± 4.0; anosmia group: TDI = 11.3 ± 2.7.	22 (5 F) healthy controls, age = 45.0 ± 13.9 years, TDI = 33.8 ± 3.1
Hu (2023)	46 (27)	45.4 ± 14.6	10.2 ± 14.8	post-viral (non Covid-19)	not specified	Sniffin' Sticks test	TDI = 12.32 ± 6.53	no control group(s)
Huart et al. (2011)	36 (24)	38 (7–79)	life long	congenital	anosmia	questionnaire and Sniffin' Sticks test and OERPs	not specified	70 (36 F) controls, mean age (range): 36.5 (7–72) years
Hummel (2015)	group1: 201; group2: 99; group3: 78; in total: 378 (185)	49 ± 14	not specified	group1: posttraumatic; group2: chronic rhinosinusitis; group3: post-viral (non Covid-19)	not specified	Sniffin' Sticks test and retronasal test	TDI mean ± standard error of the mean: group1: 15.5 ± 0.5; group2: 19.1 ± 0.9; group3: 20.7 ± 0.9. retronasal test mean ± SEM: group1: 0.4 ± 0.0; group2:0.5 ± 0.0; group3:= 0.7 ± 0.1.	no control group(s)
Jiang (2009)	54 (22)	39.0 (17–60)	not specified	posttraumatic	anosmia	Phenyl Ethyl Alcohol (PEA) threshold test	threshold test: −1	30 (6 F) posttraumatic normosmia, mean age (range): 43.4 (20−90)
Kandemirli et al. (2021)	23 (14)	29 (22–41)	1–4	post-viral Covid-19	anosmia	Sniffin' Sticks test	mean TDI (range): 4 (1–8.5)	no control group(s)
Li et al. (2018)	group1: 19 (15); group2: 15 (9); in total: 34 (24)	group1: 47.4 ± 9.7; group2: 46.5 ± 11.1	not specified	neurological disease group1: neuromyelitis optica: group2: multiple sclerosis	not specified	T&T olfactometer test (Japanese standard)	median (range): group1: detection threshold = -1.8 (-2.0, −1.0); group2: detection threshold = -1.9 (-1.0, 1.3) group1: recognition threshold = 0.9 (-1.6, 6.0); group2: recognition threshold = 0.7 (-1.2, 4.0)	no control group(s)
Li (2023)b	604 (323)	62.3 ± 14.9	not specified	mixed	not specified	Sniffin' Sticks-12 items	olfactory function score = 8.79 ± 1.56.	493 (261 F) normosmic controls, age = 49.7 ± 17.8; olfactory function score = 11.36 ± 0.48
Mahmut et al. (2020)	27 (26)	66.1 ± 10.1	54 ± 55	idiopathic	mixed	Sniffin' Sticks test	TDI = 16.23 ± 6.32	27(15 F) healthy controls, age = 65.3 ± 10.1, TDI = 34.36 ± 3.59
Mueller et al. (2005)	group1: 22 (13); group2: 9 (2); in total: 31 (15)	group1: 57 (30–74); group2: 52 (21–70)	3–108	group1: post-viral: group2: posttraumatic; in total: mixed	mixed	Sniffin' Sticks test	group1: TDI = 18.4 (8.0–31.5); group2: TDI = 11.3 (5.0–17.3)	17 (13 F) healthy controls, mean age (range): 49 (28–62) years, TDI = 31.6 (20.5–40.0).

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Table 2 (*continued*)

First Author (Year)	OD N (Female)	OD age (mean ± SD / Range)	OD duration (months)	OD etiologies	OD categories	Olfactory test(s)	Olfactory score(s)	Non-olfactory groups characteristics
Nehara et al. (2019)	20 (4)	22.4 ± 5.04	life long	congenital (Kallmann syndrome)	not specified	Indian smell identification test	not specified	20 (2 F) normosmic idiopathic hypogonadotropic hypogonadism, age = 20.6 ± 2.48
Parlak (2024)	31 (17)	54 ± 13.8	not specified	post-viral Covid-19	mixed	visual analog scale (score 1–10)	not specified	35 (18 F) age-matched healthy controls, mean age = 59.9 ± 17.4
Petersen (2024)	224 (99)	55.79 ± 7.25	not specified	post-viral Covid-19	not specified	visual analog scale (score 1–10)and Sniffin' Sticks-12 items (olfactometry scores)	at acute stage, OD (n = 96): olfactometry scores = 10.04 ± 1.97; at baseline stage (~8 month after Covid-19 infection), OD (n = 30): olfactometry scores = 8.67 ± 2.62; at follow-up stage (~22 month after Covid-19 infection), OD (n = 25): olfactometry scores = 8.40 ± 2.74	at acute stage, normosmia patients: olfactometry scores = 10.46 ± 1.31; at baseline stage (~8 month after Covid-19 infection), normosmia patients: olfactometry scores = 10.58 ± 1.22; at follow-up stage (~22 month after Covid-19 infection) OD: normosmia patients = 10.56 ± 1.22
Rashed et al. (2020)	32 (13)	57.7 ± 3.5	not specified	neurological disease (Parkinson's disease)	anosmia	Sniffin' Sticks test, questionnaires	TDI = 16.22 ± 5.34	24 healthy age, sex matched controls subjects, TDI = 32.75 ± 3.72
Rombaux et al. (2010b)	22 (13)	53.7 (31–78)	8.4 (range 3–19)	idiopathic	not specified	Sniffin' Sticks test	TDI mean (95% confidence interval) = 14.5 (95% 12.5–16.6); retronasal scores mean (95% confidence interval) = 9.1 (4–11)	22 (13 F) healthy controls; mean age = 52 years (range: 28–77 years) TDI mean (95% confidence interval) = 30.4 (28.3–32.5); retronasal scores mean (95% confidence interval) = 17.4 (15–18)
Rombaux et al. (2012)	group1: 28 (19); group2: 32 (20); in total: 60 (39)	group1: 59.7 (27–79); group2: 41.6 (24–74)	group1: 15.9; group2: 14.8	group1: post-viral (non-Covid-19); group2: posttraumatic	not specified	Sniffin' Sticks test	TDI mean (95% 95% confidence interval): group1: 16.7 (14.6–18.8) group2: 13.0 (11.2–14.7)	no control group(s)
Rombaux (2006)a	26 (21)	46 (30–68)	6 (1–15)	post-viral (non Covid-19)	mixed	Sniffin' Sticks test	17.5 ± 5.2	no control group(s)
Rombaux (2006)b	25 (13)	43.9 (20–70)	not specified	posttraumatic	mixed	Sniffin' Sticks test	TDI = 12 ± 5.8; retronasal odor identification mean score: 9.5 ± 3.1	no control group(s)
Salihoglu (2018)	group1: 14 (0); group2: 12 (0); in total: 26 (0)	23.64 ± 3.46	life long	congenital (hypogonadotrophic hypogonadism)	group1: anosmia; group2: hyposmia	Sniffin' Sticks test	anosmia: TDI = 11.21 ± 2.46; retronasal score = 8.50 ± 3.01 hyposmia: TDI = 23.96 ± 1.62; retronasal score = 16.33 ± 1.72	group1: 31 (0 F) healthy controls, age = 24.19 ± 3.89, TDI = 35.66 ± 2.09; retronasal score = 16.84 ± 2.18; group2: normosmic IHH (n = 19), age not specified, TDI = 34.24 ± 1.41, retronasal score = 16.47 ± 2.44
Tremblay (2020)b	group1: 15 (7); group2: 15 (6); in total: 30 (13)	group1: 66.8 ± 7.3; group2: 62.8 ± 9.2	not specified	group1:Parkinson's disease group2: non-Parkinsonian (mixed)	not specified	Sniffin' Sticks test	group1: TDI = 17.5 ± 6.9 group2:TDI = 17.3 ± 7.7	15 (7 F), healthy controls age = 66.3 ± 6.3; TDI = 38.0 ± 3.0
Türk (2020)	29 (14)	34.1 ± 7.8	not specified	neurological disease (Mesial Temporal Lobe Epilepsy, MTLE)	hyposmia	Sniffin' Sticks test	TDI = 21.4 ± 2.1	group1: 19 normosmia with MTLE, age = 31.9 ± 9.1, TDI = 36.7 ± 2.9

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First Author (Year)	OD N (Female)	OD age (mean ± SD / Range)	OD duration (months)	OD etiologies	OD categories	Olfactory test(s)	Olfactory score(s)	Non-olfactory groups characteristics
								group2: 20 (12 F) age and sex matched healthy controls, age = 27.5 ± 3.5 group3: 30 (17) age and sex matched healthy controls, age = 28.3 ± 11.4, TDI = 38.40
Veyseller et al. (2012)	15 (0)	57.3 ± 6.32	not specified	laryngectomy	not specified	Connecticut Chemosensory Clinical Research Center (CCCRC)	CCCRC = 2.4 ± 1.12	no control group(s)
Yan (2024)	31 (21)	48.7 ± 16.8	life long	congenital (isolated, non-Kallmann)	anosmia	Sniffin' Sticks test	TDI = 11.7 ± 3.0	62 (42 F) healthy controls (42 F), age = 48.1 ± 17.3; TDI = 34.4 ± 4.1
Yan et al. (2022)	77 (38)	51 ± 15.2	not specified	mixed	not specified	Sniffin' Sticks test	TDI = 18.6 ± 8.5	77(38 F) healthy controls, age = 51 ± 15.5 years, TDI = 33.5 ± 4.2
Yousem (1996)a	25 (11)	36 ± 9.8	not specified	posttraumatic	not specified	self-reported and UPSIT	UPSIT = 12 patients scored < 18 (anosmic), 8 scored 18–25 (severely impaired), 4 scores 27–34 (mildly impaired), 1 scored 35 (normal)	8 (6 F) healthy controls, age ranged from 43 to 70 years
Postma (2023)	dataset 1: 66 (38); dataset 2: 42 (25); dataset 3: 181 (107) – post-viral: 68 (51); chronic rhinosinusitis: 61 (24); posttraumatic: 52 (32); in total: 289 (170)	dataset 1: 59 ± 16.3; dataset 2: 54 ± 15.4; dataset 3: post-viral 60 ± 10.7; chronic rhinosinusitis 59 ± 12.7; posttraumatic 49 ± 16.7	0–24: 60 patients; 24–60: 66; 60–120: 47; > 120: 57	mixed for database 1 and 2; for database 3: post- viral group (non-covid); sinonasal group; posttraumatic	mixed	Sniffin' Sticks test	dataset 1: TDI = 16.1 ± 7.6; dataset 2: TDI = 17.0 ± 7.0; dataset 3:post-viral: TDI = 18.4 ± 6.7; chronic rhinosinusitis: TDI = 15.5 ± 6.6; posttraumatic: TDI = 14.8 ± 6.6	no control group(s)
Yildirim (2020)	post-viral OD: 41 (24); posttraumatic OD: 13 (7); idiopathic OD: 28 (14); obstructive OD: 17 (12); in total: 99 (67)	44.0 ± 13.6; post-viral OD: 47.0 ± 14.4; posttraumatic OD: 44.0 ± 11.0; idiopathic OD: 43.0 ± 13.9; obstructive OD: 43.0 ± 12.2	not specified	group1: post-viral; group2: posttraumatic; group3: idiopathic; group4: sinonasal	not specified	Sniffin' Sticks test	not specified	17 healthy controls, age = 38 ± 13.3
Yousem (1999)	36 (15)	35 ± 11.4	not specified	mixed	group1: anosmia; group2: hyposmia	clinical history, UPSIT, odor memory test, phenylethyl alcohol detection threshold	UPSIT total: 21.9 ± 10.5; left: 10.5 ± 5.2; right: 11.4 ± 5.6 Odor memory test left: 5.3 ± 3.1; right: 5.1 ± 3.0 phenylethyl alcohol detection threshold left: −4.0 ± 2.9; right: −3.9 ± 2.7	24 (12 F) healthy controls, age = 39 ± 11.5 years, UPSIT total = 36.6 ± 2.6, odor memory test left: 9.0 ± 2.7; right: 9.4 ± 1.8; phenylethyl alcohol detection threshold left: −6.9 ± 2.3; right: −7.0 ± 2.1
Fjaeldstad (2022)	group1: 51 (30); group2: 37 (22); in total: 88 (52)	group1: 57.6 (53.7, 61.4); group2: 56.3 (51.8, 60.7); in total: 57.0 (54.2, 59.9)	life long	group1: idiopathic; group2: mixed	not specified	Sniffin' Sticks test	14.1 (13.0, 15.2): idiopathic: 14.1 (12.6, 15,6); others: 14.1 (12.5, 15.8)	no control group(s)
Levy (2013)	40 (25)	18 ± 3	not specified	congenital	mixed	olfactometry for detection thresholds, recognition	not specified	22 (14 F) normosmia; age = 52 ± 5

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First Author (Year)	OD N (Female)	OD age (mean ± SD / Range)	OD duration (months)	OD etiologies	OD categories	Olfactory test(s)	Olfactory score(s)	Non-olfactory groups characteristics
						thresholds, and magnitude estimation		
Baba (2011)	Parkinson's disease with severe hyposmia: 33; Parkinson's disease with moderate hyposmia:19; in total: 52 (not specified)	66 ± 6.3	not specified	neurological disease (Parkinson's disease)	hyposmia	Odor Stick Identification Test for Japanese (OSIT-J)	OSIT-J score: 2.3 ± 1.4	17 Parkinson's disease with normal smell, age = 62.5 ± 7.7, OSIT-J score: 8.8 ± 0.9;
Berendse (2001)	25 (not specified)	59 ± 6	not specified	neurological disease (prodromal Parkinson's disease)	hyposmia	odor detection, discrimination, and identification tests	not specified	23 normosmic relatives, age = 58 ± 6 years; 16 early-stage untreated Parkinson's disease patients, age = 58 ± 6 years
Donegani et al. (2021)	14 (7)	64.4 ± 10.9	not specified	post-viral Covid-19	hyposmia	smell diskettes olfaction test	not specified	61 subjects (48 healthy controls, 13 smoldering myeloma), age: 61.1 ± 11.1
Eftekhari (2006)	16 (-)	32.1 ± 10.9	not specified	posttraumatic	anosmia	Cain's test (olfactory identification)	not specified	18 posttraumatic controls with normal smell; 13 age-matched healthy controls (no trauma or olfactory dysfunction)
Gerami (2011)	19 (9)	37.5 ± 8	not specified	posttraumatic	not specified	UPSIT	UPSIT = 11.2 ± 2.7	13 (6 F) normosmia, age = 34.46 ± 7.12, UPSIT = 36.7 ± 3.2
Jennings (2017)	185 (85)	64.5 ± 7.9	not specified	neurological disease (prodromal Parkinson's disease)	hyposmia	UPSIT	not specified	95 (55 F) normosmic controls, age = 62.3 ± 9.9
Lee (2015)	96 (44)	68.7 ± 9.3	not specified	neurological disease (Parkinson's disease)	hyposmia	Cross Cultural Smell Identification Test (CCSIT)	not specified	53 (30 F) normosmic PD, age = 62.4 ± 10.5; mean CCSIT scores ≥ 9
Marrero-González (2020)	25 (16)	66.8 ± 7.4	46.8	idiopathic (Prodromal Parkinson's disease)	hyposmia	Barcelona Smell Test 24 (BAST-24)	BAST-24 identification: 19.62 ± 15.99 BAST-24 detection: 49.23 ± 35.19 BAST-24 Recognition/ Memory: 27.31 ± 20.41	18 (5 F) healthy controls, age = 69.5 ± 6.8
Morbelli (2022)	group1: 21 (12); group2: 82 (34); in total: 103 (46)	group1: 62.1 ± 11.6; group2: 71.8 ± 7.4	not specified	group1: post-viral Covid-19; group2: neurological disease (Parkinson's disease)	hyposmia	Covid-19 olfactory dysfunction: self-reported, confirmed by Sniffin' Sticks test; PD patients with hyposmia (either 8-item smell diskettes olfactory test or Sniffin' Sticks test)	not specified	23 (14 F) Covid-19 without hyposmia, age = 59.9 ± 12.9; 16 (9 F) PD patients without hyposmia, age = 73.1 ± 7.2
Oh (2018)	50 (19)	66.6 ± 7.3	not specified	neurological disease (Parkinson's disease)	hyposmia	Cross-Cultural Smell Identification Test (CCSIT)	CCSIT score = 4.7 ± 1.8	37 (24 F) normosmic Parkinson's disease, age = 62.4 ± 10.5; CCSIT score = 8.9 ± 1.0
Ponsen (2010)	40 (21)	59.2 ± 5.8	not specified	neurological disease (prodromal Parkinson's disease)	hyposmia	odor detection, discrimination, and identification tests	hyposmic relatives: odor detection = 10.8 ± 1.9 odor discrimination= 15.5 ± 3.6 odor identification = 7.3 ± 2.1	38 (21 F) normosmic relatives, age = 58.5 ± 6.6 odor detection = 14.8 ± 1.3 odor discrimination = 25.7 ± 2.0

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Table 2 (*continued*)

First Author (Year)	OD N (Female)	OD age (mean ± SD / Range)	OD duration (months)	OD etiologies	OD categories	Olfactory test(s)	Olfactory score(s)	Non-olfactory groups characteristics
								odor identification = 10.9 ± 0.9
Ponsen (2004)	40 (21)	59.2 ± 5.8	not specified	neurological disease (prodromal Parkinson's disease)	hyposmia	odor detection, discrimination, and identification tasks	hyposmic relatives: odor detection = 10.8 ± 1.9 odor discrimination= 15.5 ± 3.6 odor identification = 7.3 ± 2.1	38 (21 F) normosmic relatives, age = 58.5 ± 6.6 odor detection = 14.8 ± 1.3 odor discrimination = 25.7 ± 2.0 odor identification = 10.9 ± 0.9
Savic (2009)	12 (0)	21–42	56.4 (18–120)	sinonasal disease (nasal polyps)	anosmia	n-butyl alcohol test and phenyl ethyl alcohol test	cannot detect any odors	12 (0 F) normosmic controls, age ranged from 21 to 36 years
Siderowf (2020)	203 (106)	64.7 ± 8.1	not specified	neurological disease (prodromal Parkinson's disease)	hyposmia	self-reported and UPSIT	not specified	100 normosmic individuals
Yoo (2020)	hyposmia: 136 (83); anosmia: 48 (16); in total: 184 (99)	hyposmia: 64.9 ± 7.8; anosmia: 69.7 ± 6.8	not specified	neurological disease (Parkinson's disease)	mixed	Cross-Cultural Smell Identification Test (CCSIT)	not specified	44 (25 F) normosmic Parkinson's disease patients, age = 62.7 ± 8.4
Yoo (2024)	140 (52)	69.9 ± 8.8	not specified	neurological disease (Parkinson's disease)	hyposmia	Cross-Cultural Smell Identification Test (CCSIT)	CCSIT: median (interquartile range) = 5.0 (2.0)	29 (18 F) normosmic Parkinson's disease, age = 64.7 ± 7.7, CCSIT median (interquartile range) = 9.0 (1.0)
Arrigoni (2024)	35 (25)	40 (31–53)	not specified	post-viral Covid-19	anosmia	self-reported	not specified	14 (8 F) Covid-19 with predominant cognitive symptoms, mean age (range): 62(45–70) 16(11 F) healthy controls: mean age (range): 56(51–61)
Chen (2020)	20 (10)	42.2 ± 18.2	not specified	mixed	anosmia	Sniffin' Sticks; retronasal Tests-20 items	TDI = 11.9 ± 4.3; retronasal olfaction = 10.8 ± 2.5	16(6 F) healthy controls, age = 49.2 ± 12.2; TDI = 34.0 ± 5.9; retronasal test = 15.8 ± 2.4
Felix (2021)	57 (24)	75.0 ± 3.1	not specified	aging	hyposmia	Brief Smell Identification Test (BSIT)	BSIT = 6.6 (1.6)	208 (127 F) older people without hyposmia, age = 74.8 ± 2.6; BSIT = 10.6 ± 1.0
Sherif (2022)	62 (48)	37 (16−83)	2 (0.5–6.5)	post-viral Covid-19	anosmia	smell diskettes	not specified	23 (17 F) normosmia, mean age (range): 36 (17−61)
Wen (2017)	70 (27)	59.69 ± 7.84	not specified	neurological disease (Parkinson's disease)	hyposmia	UPSIT	UPSIT = 17.53 ± 5.85	group1: 33 (20 F) health control, age = 57.93 ± 11.30, UPSIT = 36.39 ± 1.60; group2: 18 (11 F) normosmic Parkinson's disease, age = 57.66 ± 9.26, UPSIT = 35.94 ± 1.39
Campabadal (2023)	23 (20)	51.96 ± 7.92	not specified	post-viral Covid-19	not specified	Spanish version of UPSIT	UPSIT= 25.83 ± 3.35	25 (18 F) Covid-19 with normal olfaction, age = 48.04 ± 7.59; UPSIT scores = 32.92 ± 1.53
Avnioglu (2023)	16 (6)	42.62 ± 16.57	not specified	idiopathic	anosmia	visual analog scale and 96% ethyl alcohol detection test	not specified	16 (9 F) healthy controls, age = 43.37 ± 18.98 years

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Table 2 (*continued*)

First Author (Year)	OD N (Female)	OD age (mean ± SD / Range)	OD duration (months)	OD etiologies	OD categories	Olfactory test(s)	Olfactory score(s)	Non-olfactory groups characteristics
Bitter (2010)a	24 (10)	43.0 ± 11.4	> 10	mixed	hyposmia	Sniffin' Sticks test	TDI = 20.6 ± 2.6	43 (18 F) healthy controls, age = 43.0 ± 13.8 years, TDI = 34.1 ± 2.5
Bitter et al. (2011)	22 (10)	53.6 ± 9.3	29.0 ± 19.9	mixed	not specified	Sniffin' Sticks test	TDI = 22.2 ± 5.9	no normosmic control
Braun et al. (2014)	20 (7)	28.1 (17–44)	life long	congenital (Bardet-Biedl syndrome)	mixed	UPSIT & Suprathreshold olfaction evaluation (identification of odors like vanillin, thymol, eucalyptol)	not specified	14 (9 F) healthy normosmia, mean age (range): 35.9 (28–51)
Capelli (2024)	84 (50)	49 (35–57)	not specified	Covid-19	mixed	self-reported	not specified	17 (7 F) healthy controls, mean age (range): 51 (41–52); 61(38 F) Covid-19 patients with cognitive disorders, mean age (range): 57(52–63)
Dintica et al. (2019)	group1: 213 (119); group2: 29 (14); in total: 242 (133)	group1:79.0 ± 7.1; group2: 81.5 ± 6.4	not specified	aging	group1: hyposmia; group2: anosmia	Brief Smell Identification Test (BSIT)	group1: BSIT = 9.0 ± 1.1 group2: BSIT= 5.3 ± 1.1	138 (114 F) normosmic controls, age = 77.0 ± 6.5 years, BSIT = 11.3 ± 0.5
Frasnelli (2013)	17 (11)	40.3 ± 17.6	life long	congenital	anosmia	Sniffin' Sticks test, olfactory event-related potentials (no response to olfactory stimulation), MRI confirmation (no detectable olfactory bulb)	not specified	17 (12 F) normosmic controls; age = 39.2 ± 14.4 years
Gao (2022)	22 (13)	40.91 ± 11.06	not specified	posttraumatic	anosmia	Sniffin' Sticks test	TDI = 11.67 ± 3.35	18 (8 F) healthy controls age = 34.78 ± 13.69 years TDI = 35.28 ± 1.81
Gellrich (2018)	30 (16)	60.7 ± 10.3	33.6 ± 61.2	post-viral (non Covid-19)	hyposmia	Sniffin' Sticks test	TDI = 16.4 ± 3.6	31 (17 F) healthy controls, age = 53.5 ± 6.7
Gezegen (2024)	36 (21)	34.4 ± 11.01	2.0 ± 2.5	Covid-19	hyposmia	Sniffin' Sticks test	TDI = 31.98 ± 0.67	21 (16 F) normosmic Covid-19,age = 32.9 ± 9.03 years; TDI = 35.47 ± 0.88 25 (11 F) healthy controls, age = 31.8 ± 7.93 years, TDI = 35.28 ± 0.79
Han (2017)	21 (10)	49.6 ± 14.1	not specified	sinonasal disease (rhinosinusitis)	not specified	Sniffin' Sticks test	TDI = 13.3 ± 8.3	31 (22 F) healthy controls: age = 43.9 ± 19.8 years, TDI = 24.4 ± 2.3
Hwang et al. (2019)	62 (28)	65.7 ± 7.85	not specified	neurological disease (Parkinson's disease)	hyposmia	retronasal test	retronasal scores = 5.2 ± 1.6	40 (26 F) normosmic Parkinson's disease patients, age = 65.7 ± 10.4 years CCSIT score: 8.9 ± 1.0
Kamath et al. (2022)	group1: 101 (55); group2: 103 (48); in total: 204 (103)	group1: 76.9 ± 5.1; group2: 77.8 ± 5.3	not specified	aging and neurological disease (group1: older adults with normal cognition; group2: mild cognitive impairment)	not specified	Sniffin' Sticks-12 items	group1: olfactory scores = 5.1 ± 1.2; group2: olfactory scores = 4.5 ± 1.7	935 (597 F) normosmic controls with normal cognition, age = 75.8 ± 5.3 years, olfactory scores: 10.0 ± 1.4; 461 (263 F) normosmic with mild cognitive impairment, age = 76.3 ± 5.2 years, olfactory scores = 9.6 ± 1.5
Karstensen (2018)	17 (11)	49.1 ± 13.8	life long	congenital (genetic)	mixed	Sniffin' Sticks test	TDI = 15.43 ± 4.99	16 (9 F) normosmic controls, age = 47.2 ± 16.1 years

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Table 2 (*continued*)

First Author (Year)	OD N (Female)	OD age (mean ± SD / Range)	OD duration (months)	OD etiologies	OD categories	Olfactory test(s)	Olfactory score(s)	Non-olfactory groups characteristics
								TDI = 31.59 ± 4.80 threshold scores = 8.09 ± 2.36 discrimination scores = 12.38 ± 2.23 identification scores = 11.13 ± 2.13
Koenigkam-Santos et al. (2010)	21 (0)	38 (11–60)	life long	congenital (Kallmann syndrome)	not specified	UPSIT	14 anosmic patients: UPSIT = 11 ± 3; 6 hyposmic patients: UPSIT= 27 ± 1	16 (0 F) healthy controls, mean age (range): 34(22–50)
Koenigkam-Santos (2011)	21 (0)	38 (11–60)	life long	congenital (Kallmann syndrome)	not specified	UPSIT	14 anosmic patients: UPSIT = 11 ± 3; 6 hyposmic patients: UPSIT= 27 ± 1	16 (0 F) healthy controls, mean age (range): 34(22–50)
Lee et al. (2020)	64 (35)	57.8 ± 11.9	75.6 ± 152.4	mixed	not specified	Korean version of Sniffin sticks (KVSS)	KVSS < 28	34 (20 F) normosmic controls, age = 47.1 ± 12.2
Lee et al. (2022)	22 (9)	51.7 ± 8.7	68.4 ± 61.2	mixed	not specified	Butanol threshold test (BTT)	BTT ranged 0–1	30 (9 F) healthy controls, age = 48.5 ± 10.3 years
Li et al. (2024)	36 (17)	67.1 ± 4.1	not specified	neurological disease (Parkinson's disease)	hyposmia	visual analogue scale (VAS)	VAS = 8.4 ± 1.1.	40 (21 F) healthy controls, age = 65.0 ± 4.2 years. VAS = 0.3 ± 0.5
Lian et al. (2019)	30 (20)	66.43 ± 11.71	not specified	neurological disease (Alzheimer's disease)	not specified	Sniffin' Sticks test	TDI = 15.17 ± 5.55	30 (17 F) normosmic controls, age = 65.33 ± 9.99 years, TDI = 28.00 ± 4.80
Ottaviano (2015)	38 (0)	29.2 ± 10.8	life long	congenital (Kallmann syndrome)	mixed	Sniffin' Sticks test for Kallmann syndrome; Sniffin' Sticks-12 items for controls	TDI = 10.56 ± 4.13	17 (0 F) normosmic controls, age = 31.0 ± 14.4, Screening 12 test score = 10.90 ± 1.02
Peng (2013)	19 (14)	45.3 ± 10.2	37.4 (2–240)	mixed	anosmia	T&T olfactometer	T&T scores > 5.5	20 (14 F) normosmic controls,age = 43.6 ± 14.8 years, T&T scores = -1.0–1.2
Perlaki et al. (2024)	38 (24)	26.6 ± 5.0	not specified	post-viral Covid-19	anosmia	Covid-19 related questionnaires	median score = 10 (IQR: 7.5–10).	37 (23 F) normosmic controls, age = 25.9 ± 2.8 years.
Peter (2023)	group1: 30 (17); group2: 49 (29); in total: 79 (46)	group1: 35.8 ± 9.7; group2: 36.3 ± 11.7	not specified	congenital	anosmia	Sniffin' Sticks test	group1: TDI: 9.5 ± 2.4 group2: TDI: 10.3 ± 2.4	group1: 30 (17 F) normosmic controls, age = 35.4 ± 10.0 years, TDI = 35.9 ± 3.3 group2: 49 (29 F) healthy controls, age = 36.1 ± 11.5 years, TDI: 35.5 ± 3.5
Peter (2020)	33 (21)	34.2 ± 12.9	life long	congenital	anosmia	Sniffin' Sticks test	TDI = 10.9 ± 2.3	34 (22 F) normosmic controls, age = 34.0 ± 12.1 years, TDI = 35.4 ± 3.8
Postma et al. (2021)	group1: 87 (61); group2: 63 (24); group3: 80 (42); group4: 27 (15); in total: 257 (142)	group1: 61 ± 11.6; group2: 59 ± 11.9; group3: 62 ± 13.5; group4: 33 ± 16.4	0–24: 60 patients; 24–60: 66; 60–120: 47; > 120: 57	group1: post-viral, group2: chronic inflammation, group3: idiopathic, group4: congenital anosmia	mixed	Sniffin' Sticks test	group1: TDI = 18.6 ± 6.23 group2: TDI = 14.8 ± 6.46 group3: TDI = 14.3 ± 5.48 group4: TDI = 10.1 ± 2.94	no control group(s)
Rezaeyan (2023)	39 (16)	29.79 ± 8.12	8.6 ± 5.7	posttraumatic	anosmia	Sniffin' Sticks test	TDI: 12.69 ± 4.92	39 (18 F) healthy controls, age = 30.51 ± 11.1 years, TDI = 36.31 ± 2.62
Roh et al. (2021)	18 (9)	60.50 ± 9.90	not specified	neurological disease (Parkinson's disease)	hyposmia	Cross-Cultural Smell Identification Test (CCSIT)	CCSIT = 5.56 ± 1.46	18 (9 F) normosmic Parkinson's disease patients,

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Table 2 (*continued*)

First Author (Year)	OD N (Female)	OD age (mean ± SD / Range)	OD duration (months)	OD etiologies	OD categories	Olfactory test(s)	Olfactory score(s)	Non-olfactory groups characteristics
								age = 60.17 ± 10.07 years, CCSIT = 8.67 ± 1.0
Thaploo (2022)	13 (not specified)	30.6 ± 12.4	life long	congenital	anosmia	Sniffin' Sticks test	TDI = 12.69 ± 2.9	15 healthy controls, age = 38.6 ± 11.3 years, TDI = 34.1 ± 3.0
Wu (2011)	12 (7)	60.5 ± 10.0	not specified	neurological disease (Parkinson's disease)	hyposmia	"Five odors olfactory detection arrays" method (detection threshold (DT) and identification threshold (IT))	DT = 1.39 ± 0.42; IT = 2.78 ± 0.45	26 (12 F) healthy controls, age = 59 ± 10 years, DT = -0.6 ± 0.83, IT = 1.09 ± 0.54 14 (5 F) normosmic Parkinson's disease patients, age = 57.6 ± 10.1 years, DT: 0.14 ± 0.47, IT: 2.18 ± 0.81
Yao et al. (2014)	16(7)	48.6 ± 9.9	42 months (6–120)	idiopathic	not specified	T&T olfactometer test and Sniffin' Sticks test	T&T = 5.8 ± 0.2; TDI = 9.4 ± 3.6	16 (7 F) healthy controls, age = 52.5 ± 8.7 years, T&T = 0.6 ± 0.4, TDI = 29.9 ± 1.3
Langdon (2018)	42 (13)	34.4 ± 12.1	not specified	posttraumatic	not specified	Brief Assessment of Smell Identification Test – 24 items (detection, recognition, identification), n-Butanol threshold Test (n-BTt) and visual analog scale (VAS, scores 0–100)	n-BTt = 1.8 ± 1.9, detection = 51.8 ± 41.9, recognition= 22.7 ± 28.2, identification = 23.2 ± 23.6, VAS = 77.6 ± 24.8	20 (7 F) healthy controls, age = 38.6 ± 7.4
Yao et al. (2018)	19 (14)	37.7 ± 8.4	49.2 ± 31.2	post-viral (non Covid-19)	not specified	Sniffin' Sticks and T&T olfactometer test	TDI = 4.8 ± 2.4; T&T = 5.8 ± 0.2	19(14 F) healthy controls, age = 35.4 ± 7.9, T&T = = − 0.4 ± 0.8, TDI = 32.1 ± 3.3
Zhang et al. (2015)	26 (23)	50.5 ± 10.8	not specified	neurological disease (neuromyelitis optica spectrum disorder)	mixed	T&T olfactometer (detection and recognition thresholds)	mean detection threshold (range): −1.9 (-2.0, −1.2) mean recognition threshold (range): 1.6 (0.4, 6.0)	26 (18 F) healthy controls, age = 45.3 ± 11.1 years, mean detection threshold (range): −2.0 (-2.0, −1.4) mean recognition threshold (range): −0.2 (-0.8, 0.7)
Baek et al. (2020)	89 (55)	group1: 75.4 ± 8.7 group2: 76.9 ± 8.0	not specified	neurological disease (Alzheimer's disease)	hyposmia	Cross-Cultural Smell Identification Test (CCSIT)	group1: 4.9 ± 2.1; group2: 4.3 ± 2.2	group1: 72 (51 F) normosmia, age = 67.2 ± 9.0, CCSIT = 9.6 ± 1.2 group2: 25 (17 F) normosmia, age = 9.3 ± 1.1, CCSIT = 9.3 ± 1.1
Liu et al. (2016)	group1: 143 (101); group2: 117 (50); in total: 260 (151)	group1: 46.74 ± 13.66; group2: 43.51 ± 12.86	group1:: 7.4 ± 6.6; group1: 21.9 ± 19.6	group1: post-viral (non Covid-19); group2: mixed (non post-viral)	mixed	Sniffin' Sticks test	not specified	no control group(s)
Liu (2018)	20 (12)	44 ± 12	26.4 (3.6–96)	idiopathic	mixed	T&T olfactometry and Sniffin' Sticks test	TDI = 14.16 ± 5.42, T&T = 5.28 ± 0.74	20 (12 F) healthy controls, age = 44 ± 12, TDI = 32.08 ± 3.13, T&T = −1.10 ± 1.06
Rombaux et al. (2009)	122 (86)	53.9 (95% confidence interval: 51.6–56.1)	not specified	post-viral (non Covid-19)	mixed	Sniffin' Sticks and retronasal test	retronasal score = 10.5 ± 4.1; TDI = 18.5 ± 6.8	no control group(s)
Miao (2015)	26 (11)	40.08 ± 10.70	11.5 (0.3–108)	posttraumatic	anosmia	T&T olfactometry and Sniffin' Sticks test	T&T = 5.92 ± 0.13; TDI = 5.38 ± 2.826	21 (9 F) healthy control, age = 42.52 ± 11.64, T&T = -

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Table 2 (*continued*)

First Author (Year)	OD N (Female)	OD age (mean ± SD / Range)	OD duration (months)	OD etiologies	OD categories	Olfactory test(s)	Olfactory score(s)	Non-olfactory groups characteristics
								0.99 ± 0.97, TDI = 32.05 ± 2.89
Bitter (2010)b	17 (11)	49.6 ± 13.8	49.8 (12–252)	mixed	anosmia	Sniffin' Sticks test	TDI = 10.2 ± 2.7	17 normosmic control, OI = 14.9 ± 1.3
Atighechi (2009)	21 (2)	27.6 ± 11.39	not specified	posttraumatic	anosmia	Cain's identification test (threshold and identification test)	not specified	19 age and sex matched nontraumatic healthy individuals for SPECT comparison; 10 age and sex matched traumatic normosmic for MRI comparison
Baba et al. (2012)	24 (7)	65.0 ± 6.2	not specified	neurological disease (Parkinson's disease)	hyposmia	Japanese Odor Stick Identification Test (OSIT-J)	OSIT-*J* = 2.3 ± 1.4	20 (14 F) Parkinson's disease without severe hyposmia, age = 65.5 ± 6.1, OSIT-*J* = 7.1 ± 1.3; 11 (6 F) healthy controls, age = 63.3 ± 4.7 for PET comparison; 14 (7 F) healthy controls, age = 63.1 ± 4.4 for MRI comparison;
Niesen (2021)	12 (10)	42.6 (23–60)	0.5 ± 0.3	Covid-19	mixed	Sniffin' Sticks test-identification	identification scores = 8 ± 1.4	26 (5 F) healthy subjects; mean age (range): 35 years (22−52)
Porcu (2024)	15 (7)	70.7 ± 4.8	not specified	neurological disease (Parkinson's disease)	hyposmia	Japanese Odor Stick Identification Test (OSIT-J)	OSIT-*J* = 1.7 ± 1.1	15 (8 F) healthy controls, age = 63.3 ± 5.2, OSIT-*J* = 10.4 ± 1.3; 15 (6 F) Parkinson's disease with normosmia / mild hyposmia, age = 64.4 ± 7.2, OSIT-*J* = 7.5 ± 1.5
Xie (2024)	group1: 45 (29); group2: 35 (25); in total: 80 (54)	group1: 66 (61–74); group2: 64 (61–71)	not specified	group1: neurological disease (Alzheimer's disease); group2: dementia-free (mixed)	anosmia	UPSIT	group1: mean UPSIT (range):12(10–16) group2: mean UPSIT (range):16(13–18)	156(99 F) normosmic controls, mean age (range): 60(55.25–66), mean UPSIT (range): 25(22–27)
Yildirim (2022)	group1: 31 (21); group2:97 (59); in total: 128 (80)	group1:32.5 ± 10.8; group2:45.9 ± 13.5	group1: 1.5; group2: 6	group1: Covid-19; group2: post-viral (non Covid-19)	mixed	Sniffin' Sticks test	group1: TDI = 9.31 ± 2.89; group2: TDI = 12.71 ± 4.33	no control group(s)
Moon (2018)	16 (5)	42.2 ± 10.4	not specified	posttraumatic	anosmia	Korean version of Sniffin' Sticks (KVSS II)	KVSS II score = 3.2 ± 2.9	19 (8 F) healthy controls, age = 29.3 ± 8.5 years, KVSS II score > 27.25
Haehner (2018)	19 (not specified)	56.9 ± 14.4	129.6 ± 153.6	idiopathic	not specified	Sniffin' Sticks Test	TDI = 14.5 ± 4.6	17 (not specified sex) healthy controls, age = 51.7 ± 12.5, TDI = 34.2 ± 3.0; 12(not specified sex) Parkinson's disease patients, age = 62.8 ± 7.1, TDI = 17.2 ± 6.5
Nigro et al. (2021)	23 (8)	63.6 ± 9.3	not specified	neurological disease (Parkinson's disease)	hyposmia	Italian Olfactory Identification Test (IOIT)	IOIT = 13.7 ± 4.9	18 (6 F) healthy controls, age= 56.3 ± 13.7 years

F:female; Covid-19: Coronavirus disease 2019; TDI: threshold, Discrimination, Identification score (Sniffin' Sticks); UPSIT =University of Pennsylvania Smell Identification Test.

et al., 2022). For post-traumatic OD, findings showed considerable heterogeneity in OB or olfactory tract injury, with reported rates spanning from 15% to 89% (Atighechi et al., 2009; Jiang et al., 2009; Miao et al., 2015; Yousem et al., 1996). Studies including OD with mixed etiologies reported abnormalities from 67% to 89% (Chung et al., 2018; Goektas et al., 2009; Yousem et al., 1999), while only one study reported a rate of 64% for non-Covid-19 post-viral OD (Yildirim et al., 2020).

3.1.1.2. Quantitative measurements of OB volume and OS depth. A total of 53 studies measured the OBV and OSD. An overview of included studies are shown in Fig. 2 (for OBV) and Fig. 3 (for OSD). Normative benchmarks define healthy OBV as $\geq 58\ mm^3$ (<45 years) and $\geq 46\ mm^3$ (>45 years) (Buschhüter et al., 2008), while normative OSD ranges from 7.55 to 8.78 mm in young adults down to 5.28–6.19 mm in those over 55 (Li et al., 2023). Compared to other etiologies, patients with congenital OD shows the smallest OB volumes and lowest OSD, while patients with Covid-19 related OD had biggest OB volumes. Across etiologies, smaller OBV was coupled with lower OSD, except in patients with idiopathic OD. This finding is consistent with a study that reported a strong correlation between OBV and OSD, with a correlation coefficient exceeding 0.71 (Ottaviano et al., 2015). Across hemispheres, volumetry patterns were generally symmetric, except in patients with congenital OD, who exhibited greater olfactory sulcus depth on the right compared to the left.

A total of 50 studies examined alterations in olfactory bulb volume (OBV) and OSD in OD patients compared to normosmic control groups (including disease-related or healthy control groups). There was strong consensus: 45 studies (90%) reported significant reductions in OBV, OSD, or both, when comparing patients with OD (e.g., post-viral, post-traumatic, neurological) to individuals in normosmic control groups. Among these, 11 studies specifically investigated Covid-19 related OD. While the majority aligned with the overall trend of reduced OBV/OSD, five studies deviated, reporting either no significant difference or paradoxical OBV enlargement. Specifically, Akkaya et al. (2021) observed no OBV/OSD differences in a group of 59 patients with Covid-19-induced anosmia relative to normosmic controls but did report altered bulb shape. Similarly, Eliezer et al. (2020) observed no volumetric OBV differences in 20 patients with acute Covid-19 related OD (duration <15 days) compared with individuals without OD. Muccioli et al. (2023), studying 23 patients with persistent Covid-19 related OD (duration: 11 ± 5 months), also found no volumetric changes. By contrast, two studies employing the Box-frame method reported paradoxical increases in OBV, interpreted as edema or inflammation. The Box-frame technique is a manual, two-dimensional method that calculates the OBV by defining a standardized rectangular volume based on external anatomical landmarks. Because it measures the volume of the entire space where the OB resides, including surrounding fluid and pathological changes, the resulting measurement may reflect edema or inflammation rather than true neural tissue volume. Sherif et al. (2022) found a significantly larger OBV in 62 patients with Covid-19 related OD (duration: 0.5–6.5 months) compared to control groups (83.6 mm^3 vs. 30.5 mm^3). Abdou et al. (2023) replicated this finding of enlarged OBV in a larger group of 110 patients (81.3 mm^3 vs. 31.8 mm^3 in controls).

3.1.1.3. Association with olfactory function. A total of 23 studies further examined the association between OBV and olfactory function, overall demonstrating a robust positive relationship. Twenty studies (86.9%) reported significant positive correlations, while three found no association (Goektas et al., 2009; Hu et al., 2023; Langdon et al., 2018). In nearly all studies, olfactory function was assessed with validated psychophysical measures (e.g., University of Pennsylvania Smell Identification Test, Sniffin' Sticks). Across studies, a lower OBV was consistently associated with worse olfactory function, with reported correlation coefficients ranging widely from 0.15 to 0.93. The only study employing a self-reported measure of olfactory dysfunction, using a visual analogue scale, found no correlation with OBV (Langdon et al., 2018). This underscores that subjective assessments do not reliably capture olfactory function, consistent with evidence showing poor agreement between patient-reported outcomes and psychophysical testing (Whitcroft et al., 2023). Compared to other etiologies, patients with congenital OD demonstrated the strongest association between OBV and olfactory function ($r = 0.40–0.93$). Results from studies including patients with other etiologies or mixed etiologies ($r = 0.13–0.66$) displayed substantial variability, with some reporting non-significant results (Goektas et al., 2009; Hu et al., 2023; Langdon et al., 2018; Postma et al., 2023). In studies that analyzed hemispheres separately, all reported a symmetrical correlation pattern (Chen et al., 2018; Hummel et al., 2015; Rombaux et al., 2006; Salihoglu et al., 2018; Yousem et al., 1999).

3.1.1.4. Discussions of OB and OS findings. Evidence for the relationship between OSD and olfactory function was limited ($n = 7$) and less consistent. Only four of the seven studies reported a significant relationship (Hummel et al., 2015; Kandemirli et al., 2021; Ottaviano et al., 2015; Rezaeyan et al., 2023), while the others found no association (Langdon et al., 2018; Liu et al., 2018; Rombaux et al., 2006). Correlation coefficients linking olfactory function to OSD varied substantially. Three of the four studies (Hummel et al., 2015; Kandemirli et al., 2021; Ottaviano et al., 2015; Rezaeyan et al., 2023) consistently reported that patients with worse olfactory function had lower OSD ($r = 0.15–0.34$). By contrast, one study (Kandemirli et al., 2021) reported a negative correlation ($r = -0.57$) in Covid-19 related anosmia. In studies that examined the hemispheres separately, right OSD consistently showed a significant correlation with olfactory function, whereas left OSD showed no correlation (Hummel et al., 2015; Rezaeyan et al., 2023).

Our review demonstrates that patients with OD generally show alterations of the OB and/or OS across etiologies. In most contexts, the smaller OBV and lower OSD are associated with worse olfactory function, supporting their role as reliable structural brain markers. Across hemispheres, OB volumetry and correlation patterns were generally symmetric, suggesting that OD represents a generalized rather than a lateralized neuroplastic response. In contrast, OSD appears to exhibit some degree of asymmetry. Although a synthesis of 63 studies confirms that alterations in OB and OS structure are a consistent feature of OD, studies including various etiologies exhibit significant heterogeneity. This is reflected in widely varying OB/OS abnormality rates, OBV/OSD values, and correlation coefficients, which underscores the heterogeneous pathologies underlying OD.

When looking into specific etiologies, we found that patients with congenital OD had the most severe and consistent alterations, with nearly universal OB and OS abnormalities, markedly reduced OBV and OSD, and the strongest associations with olfactory function. Neurological, post-traumatic OD and post-viral OD showed moderate-to-severe reductions in OBV and OSD with consistent correlations to olfactory function. By contrast, Covid-19 related OD emerged as the most heterogeneous etiology: studies reported reduced, normal, or paradoxically enlarged OBV, and inconsistent OSD findings. The heterogeneity in olfactory bulb volume findings among Covid-19 related OD studies likely stems from methodological limitations and temporal dynamics. For instance, the Box-frame technique's inherent assumption of regular OB morphology can lead to inaccurate OBV measurements. Studies have reported a higher prevalence of abnormally shaped OBs in patients with Covid-19 related OD compared to control groups (Parlak et al., 2024; Yildirim et al., 2020). Using the Box-frame technique, Abdou et al. (2023) and Sherif et al. (2022) found that Covid-19 related OD patients had nearly twice the OBV of controls, whereas other studies employing manual segmentation reported decreased OBV compared to control groups (Altunisik et al., 2021; Brudasca et al., 2023; Gezegen et al., 2024). Temporal dynamics may also account for the conflicting results of these studies, as early inflammatory swelling could precede subsequent atrophy. Indeed, several studies indicate that the morphology and

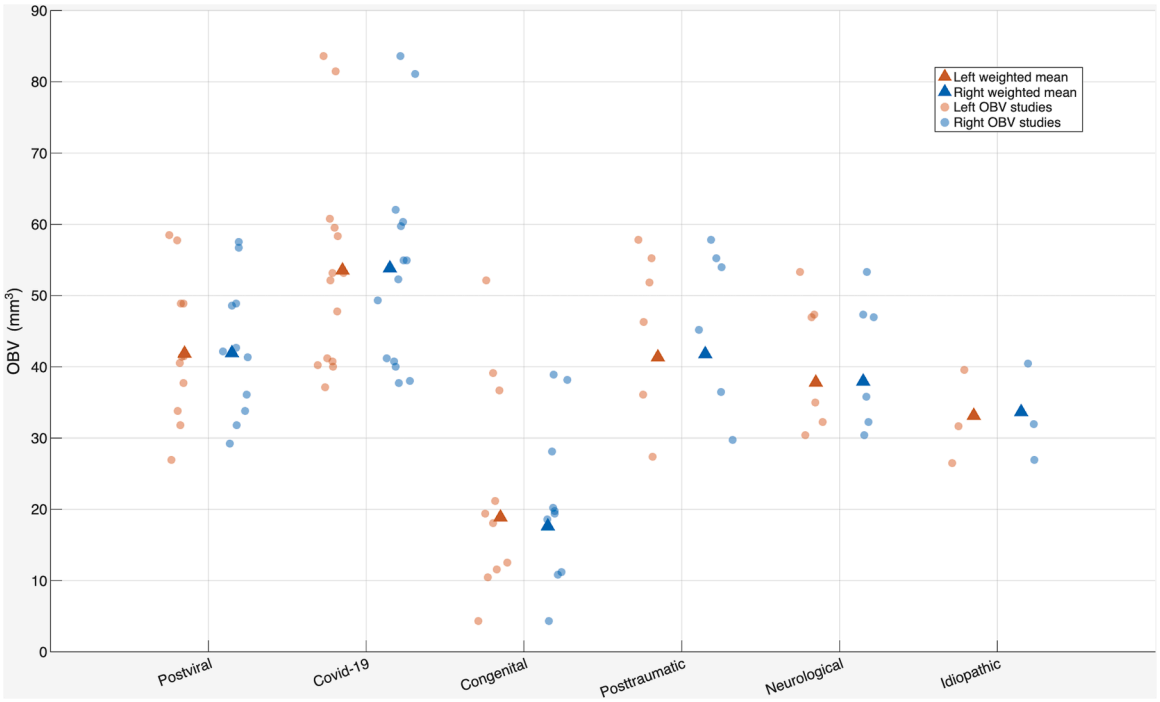

Fig. 2. Summary of olfactory bulb volume (OBV) findings across included studies. For visualization purposes, studies that reported only a single mean OBV value were plotted with identical left and right OBV values. For studies reporting only total OBV half the volume was plotted for each side. Weighted mean OBV values were calculated as $(OBV_1 \cdot n_1 + OBV_2 \cdot n_2 + \ldots) / \text{Total n}$.

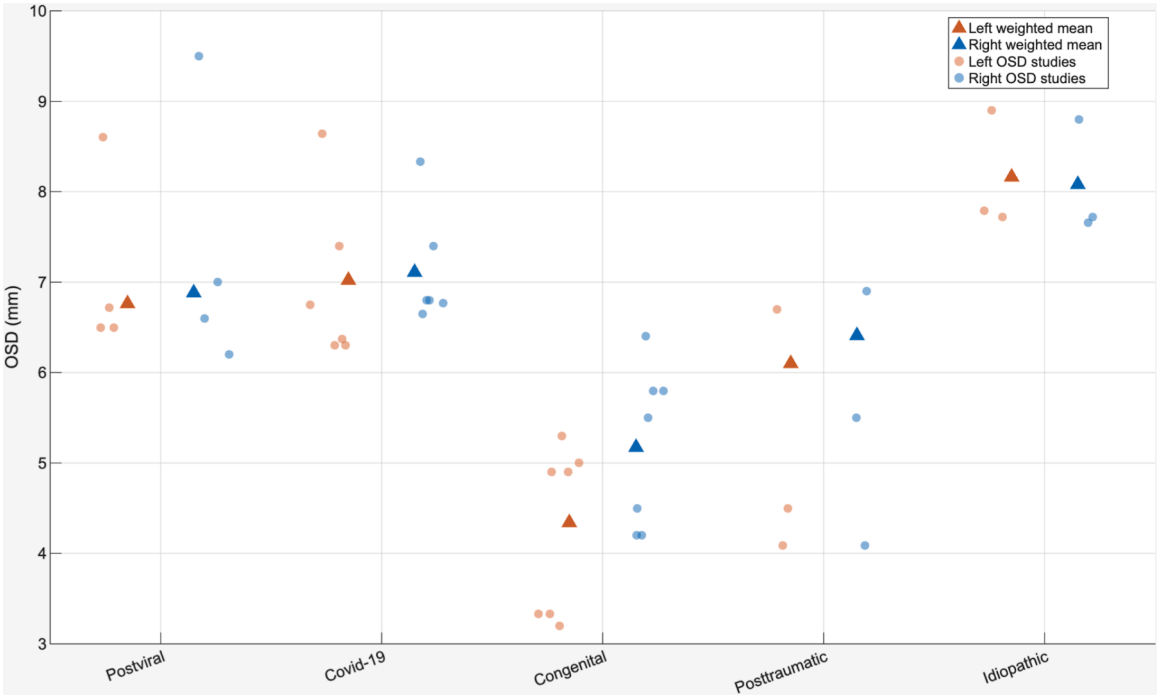

Fig. 3. Summary of olfactory sulcus depth (OSD) findings across included studies. For visualization purposes, studies that reported only a single mean OSD value were plotted with identical left and right OSD values. For studies reporting only total OSD half the volume was plotted for each side. Weighted mean OSD values were calculated using: $(OSD_1 \cdot n_1 + OSD_2 \cdot n_2 + \ldots) / \text{Total n}$.

volumetric structure of the OB may change over time in patients with Covid-19 related OD (Morra et al., 2024; Petersen et al., 2024). Similar transient increases have been documented in other neurological conditions. For example, Yau et al. (2015) reported a temporary rise in hippocampal gray matter volume in individuals with familial Alzheimer's disease before subsequent atrophy occurred. Although OB/OS enlargement appears unique to Covid-19 related OD in the current studies, its underlying mechanism remains unclear. Covid-19 offers a rare opportunity to study OD from the acute phase onward, unlike most clinical population, which typically include only patients with long-standing

OD. This model could also inform future studies of early inflammatory changes in other etiologies of OD. Longitudinal cohorts are essential to clarify the relationship between OB/OS volumetry and recovery or progression to chronic dysfunction. For example, Sherif et al. (2022) did not observe a difference in OBV between patients with OD and individuals without OD but did identify microstructural disruptions in the olfactory tracts. This confirms that multimodal imaging is critical for a comprehensive assessment of the neurological OB/OS changes underlying OD.

Although OBV and OSD are currently the most widely applied parameters, they capture only part of the underlying pathophysiology. A key priority for future research is the adoption of standardized definitions of olfactory abnormalities. In this systematic review, studies varied in whether they classified abnormalities based on volume thresholds, sulcus depth, morphology, or signal changes, making comparisons across populations difficult. Clearer criteria would improve reproducibility and help to draw reliable conclusions across different studies. Second, OBV measurement methods include manual segmentation, automatic segmentation, and the Box-frame method. Among these, Box-frame method assumes a regular OB shape, may provide inaccurate outcomes, particularly in cases with abnormal OB morphology. Additionally, inter-individual variability, such as total intracranial volume, can influence OBV and OSD, with larger brains generally associated with higher gray matter volume and gyrification (Luders et al., 2002). Moving the field forward, the automation of these structural measures is critical. Automation removes observer subjectivity, improves measurement reliability, saves significant time, and enables easy incorporation into large-scale research studies and clinical practice (Desser et al., 2021; Postma et al., 2023).

OBV has robust correlations with psychophysical olfactory test performance. More than 85% of the included studies (n = 20) reported significant correlations between OBV and psychophysical olfactory test scores, with 8 studies showing correlation coefficients exceeding 0.5, supporting OBV as a robust and meaningful biomarker of olfactory function. In contrast, self-report measures, such as visual analog scales failed to show correlation with OBV or OSD. This discrepancy likely arises from the low sensitivity and poor reliability of self reported olfactory function compared to objective tests (Patel et al., 2025; Valls-Mateus et al., 2022). Although smaller OBV was coupled with lower OSD across etiologies, except in patients with idiopathic OD, evidence linking OSD to olfactory function is limited and inconsistent. Given these uncertainties, future research should further explore whether OSD can serve as a reliable biomarker for olfactory function.

3.1.2. Regional brain volumetry studies

A total of 42 studies, encompassing 2081 patients, were included in the analysis of regional brain volumetric alterations in individuals with OD. The etiologies were as follows: neurological disease (n = 15), congenital (n = 8), Covid-19 (n = 4), post-traumatic (n = 3), post-viral (n = 2), idiopathic (n = 2), rhinosinusitis disease (n = 1), aging (n = 1), and mixed etiologies (n = 8). Some studies investigated multiple etiologies. The detailed findings of included studies are summarized in Supplementary Material **E.**

3.1.2.1. Regional gray matter volume differences. A summary of volumetric differences between individuals without OD and participants with OD in each region is provided in Table 2. We found a core olfactory atrophy signature across studies: half of all studies (n = 20) showed primary cortex (e.g., piriform, entorhinal cortices, amygdala) atrophy and most (n = 35) showed secondary olfactory cortex atrophy (e.g., OFC, insula, cingulate, hippocampus); Additionally, non-olfactory key areas including the cerebellum (Avnioglu et al., 2023; Bitter et al., 2010a, 2010b; Gao et al., 2022; Han et al., 2018a; Peng et al., 2013) and precuneus (Bitter et al., 2010a, 2010b; Li et al., 2024; Peng et al., 2013; Yoneyama et al., 2018) also showed volumetric differences. Specifically, we found gray matter volume differences in the OFC (21 studies; 18 reporting volume decreases, 3 reporting increases), hippocampus (decreased volume in 17 studies; half of these (n = 8) occurred within neurological disease related OD), insula (15 studies; 14 reporting volume decreases, 1 reporting an increase), amygdala (11 studies reporting volume decreases) and piriform cortex (10 studies; 8 reporting decreases, 2 increases). Six studies reported differences in white matter volume, revealing a mixed pattern of both atrophy and hypertrophy in the white matter tracts connecting the orbitofrontal cortex and related temporal/limbic structures (insula, hippocampus) (Avnioglu et al., 2023; Bitter et al., 2010a; Frasnelli et al., 2013; Gao et al., 2022; Peng et al., 2013; Wu et al., 2011).

3.1.2.2. Etiology-specific volumetric patterns. When examining volumetric changes for different etiologies, the patterns vary slightly. For congenital OD (n = 8), most studies showed increased volume of olfaction-related areas, including the piriform cortex (Frasnelli et al., 2013; Karstensen et al., 2018), and medial OFC (Ottaviano et al., 2015; Peter et al., 2023, 2020). Ottaviano et al. (2015) further reported negative correlations between the cortical thickness close to the OS, which is within the medial OFC, and TDI scores ($r = -0.5$, $p = 0.001$). However, some studies also showed that patients with congenital OD had smaller gray matter volume in the OS than control groups (Karstensen et al., 2018) (Peter et al., 2023, 2020). For neurological OD, 14 studies showed widespread brain volume decrease comparing with normosmic control groups, with particularly pronounced atrophy in the hippocampal/ parahippocampal cortex (n = 8), and amygdala volume reduction (n = 6). For Covid-19 related OD (n = 4), three studies reported decreased volume in the olfactory regions in patients comparing with control groups, while one study did not detect any volume differences (Muccioli et al., 2023). These studies also reported additional volume decreases in the putamen and caudate (Campabadal et al., 2023; Capelli et al., 2024), highlighting that olfactory impairment in Covid-19 may extend beyond classical olfactory regions. In posttraumatic OD (n = 3), both primary and secondary olfactory cortex volumes were consistently reduced, with two studies additionally observing thalamus volume decreases (Han et al., 2018a; Rezaeyan et al., 2023). Other OD etiologies (e.g., idiopathic and post viral, rhinosinusitis, aging) were studied less extensively, but findings generally pointed toward volume reductions in olfaction-related regions, with occasional involvement of other areas such as the thalamus (Gellrich et al., 2018; Han et al., 2017). In cases of mixed-cause OD, decreases in gray matter volume extended beyond olfaction-related areas, including the precuneus (Bitter et al., 2010a, 2010b; Peng et al., 2013), widespread frontal and temporal cortex regions (Bitter et al., 2010a, 2010b; Iravani et al., 2021; Peng et al., 2013), and cerebellar regions (Bitter et al., 2010a, 2010b; Peng et al., 2013).

3.1.2.3. Discussions of volumetric findings. Our systematic analysis indicates that OD is associated with widespread volume reductions in olfaction-related areas, most markedly within the OFC, hippocampus, insula, amygdala, piriform cortex, and additionally in the precuneus and cerebellum. In contrast, the few studies reporting volume increases in the OFC (n = 3) and piriform cortex (n = 2) were confined to patients with congenital OD. Notably, the piriform cortex (PC), typically considered as the primary olfactory cortex, did not rank among the most frequently affected regions. Volumetric outcomes varied substantially with the etiology of OD. In patients with mixed etiologies, studies reported a wide range of gray matter reductions. However, distinct volumetric patterns have been found across specific etiologies. In neurological disorders, volume loss is most prominently observed in the hippocampus and amygdala likely related to cognitive problems in those populations. Post-traumatic OD consistently shows decreased volume in both primary and secondary olfactory cortices, with additional reductions in the thalamus. Covid-19 related OD has been associated with

volume loss in olfaction-related areas as well as subcortical structures such as the putamen and caudate nucleus. In contrast, congenital OD is characterized by predominant volume increases in the olfactory cortex, with mixed alterations in the OFC and piriform cortex.

Interestingly, most studies focusing on congenital OD showed increased volume of olfaction-related areas (Frasnelli et al., 2013; Karstensen et al., 2018; Ottaviano et al., 2015; Peter et al., 2023, 2020). This robust pattern of structural expansion in congenital OD strongly suggests a process of neural compensatory reorganization in response to the chronic absence of sensory input during disease development. In contrast, findings of volume increase in acquired OD are scarce and heterogeneous. Volume increases have been reported in isolated cases of idiopathic OD (e.g., cerebellar enlargement, (Avnioglu et al., 2023), neurological OD (e.g., insula, (Yoneyama et al., 2018), and post-traumatic OD (paracentral lobule, precentral gyrus, and superior parietal lobule, (Gao et al., 2022). While these isolated observations may tentatively suggest limited compensatory mechanisms in acquired OD, they must be interpreted with caution. Alternatively, and particularly in acute phases of acquired OD (such as post-traumatic cases), these volume increases may reflect transient edema or inflammatory processes rather than stable compensatory changes. This distinction is further supported by our results of OBV enlargement in Covid-19 related OD, which may represent a transient inflammatory response, aligning more closely with the interpretation of edema than permanent reorganization.

However, these conclusions should be interpreted with caution. Our synthesis relied on frequency counts of reported regional brain volume changes across studies, an approach that may overemphasize some findings while underestimating effect sizes or statistical robustness. Another limitation lies in the heterogeneity of control groups: many studies compared patients with OD to individuals without OD, while others contrasted them with disease-matched controls. For instance, Gezegen et al. (2024) reported a decrease in cortical thickness in the left orbital sulci in patients with Covid-19 related hyposmia relative to individuals without OD, yet found no significant differences when comparing hyposmic to normosmic individuals with post-Covid-19. Additionally, since few studies reported the duration of olfactory loss, we were not able to systematically examine its effects.

3.1.3. *Diffusion tensor imaging (DTI) studies*

A total of 9 DTI papers were included, involving 322 patients with OD, with diverse etiologies: Covid-19 (n = 3), neurological disease (n = 2), idiopathic (n = 1), congenital (n = 1), aging (n = 1), and mixed etiologies (n = 1). Some studies investigated multiple etiologies. The detailed findings of included studies are summarized in Supplementary Material **F**.

3.1.3.1. Regional microstructural findings. DTI studies in OD commonly employ metrics such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) to assess microstructural brain alterations. FA is the most frequently reported measure (n = 8). It reflects the directional coherence of water diffusion and serves as an indirect marker of white matter integrity. Reductions in FA are interpreted as signs of disrupted axonal organization or myelination. Half of the studies reported significant reductions, reflecting microstructural alterations in acquired OD. These alterations were identified in the olfactory bulb (Sherif et al., 2022), olfactory tract (Nigro et al., 2021), and substantia nigra (Haehner et al., 2018), as well as in broader white matter tracts including the right uncinate fasciculus and cerebellar peduncle (Arrigoni et al., 2024). Conversely, one study on congenital OD reported an increase in FA (Thaploo et al., 2022). However, three studies also reported no FA differences (Campabadal et al., 2023; Chen et al., 2020; Wen et al., 2017). MD quantifies the overall magnitude of water diffusion and is sensitive to cellular density and tissue degeneration, with increases in MD suggesting microstructural disorganization or neuronal loss. 4 of 7 studies reported increased MD in patients with OD, particularly in the OFC (Campabadal et al., 2023; Felix et al., 2021); However, the remaining three studies did not find MD differences between patients with OD and individuals in normosmic control groups (Haehner et al., 2018; Nigro et al., 2021; Wen et al., 2017). RD elevations are often associated with demyelination, whereas changes in AD are more closely linked to axonal damage, however, only three studies report these parameters. However, only three studies analyzed these specific diffusivity metrics. Regarding AD, none of the three studies found significant differences between patients with OD and controls (Campabadal et al., 2023; Haehner et al., 2018; Nigro et al., 2021). In terms of RD, findings were largely non-significant, with the exception of Campabadal et al. (2023), who reported increased RD in the anterior corona radiata, genu of the corpus callosum, and the uncinate fasciculus.

3.1.3.2. Network-level and graph-theoretical findings. Next to these regional analyses, three studies employed graph theoretical approaches or network-based statistics to investigate network-level brain alterations in OD (Arrigoni et al., 2024; Chen et al., 2020; Wen et al., 2017). These studies consistently reported alterations in global network organization, although the specific metrics varied. Findings included reduced modularity (Arrigoni et al., 2024), decreased global efficiency (Wen et al., 2017), and increased shortest path length (Chen et al., 2020). Despite these methodological differences, the results converge to reflect impaired global segregation and reduced global integration. At the regional level, however, findings were more heterogeneous, with mixed patterns of alteration in specific olfaction-related regions. Furthermore, of the four studies that examined the relationship between diffusion-derived properties and olfactory function, three found moderate correlations ($r = 0.31–0.52$), whereas one study found no association (Wen et al., 2017). More specifically, these studies consistently indicated that poorer olfactory function was associated with greater disruption of network efficiency (Chen et al., 2020) or reduced regional microstructural integrity (Campabadal et al., 2023; Haehner et al., 2018).

3.1.3.3. Discussions of DTI findings. Collectively, DTI studies show that acquired OD is consistently associated with microstructural alterations in olfaction-related regions, most prominently reflected in FA reductions and MD increases. In contrast, congenital OD shows a different pattern, with FA increases reported in the OFC (Thaploo et al., 2022). At the network level, OD has been linked to alterations in global topological organization, including decreased global efficiency (Wen et al., 2017), modularity (Arrigoni et al., 2024) or increased shortest path length (Chen et al., 2020), reflecting impaired global segregation and reduced global integration. The findings for regional olfactory networks remain heterogeneous, with some studies suggesting disrupted connectivity in key olfactory areas, including the insula (Arrigoni et al., 2024), OFC (Arrigoni et al., 2024; Wen et al., 2017), and amygdala (Chen et al., 2020) and or compensatory mechanisms (Arrigoni et al., 2024; Chen et al., 2020). Taken together, DTI findings support that that impaired white matter microstructural integrity is a common feature of OD. However, it remains challenging to identify consistent alterations in specific tracts or connections, given the combination of etiology-specific factors, disease stage, and methodological heterogeneity across studies such as variation in outcome measures, regions of interest, and imaging coverage. In addition, the moderate correlations between DTI metrics and olfactory function underscore its limited diagnostic value. Nevertheless DTI has potential to provide complementary measures of OD severity and progression. These findings also show partial convergence with volumetric studies. For instance, both volumetric and diffusion

studies consistently implicate the OFC as a key affected region, with four out of seven DTI studies reporting OFC involvement. This underscores its potential role as a central hub in the pathophysiology of OD. In addition, paradoxical FA increases in the bilateral OFC in congenital OD align with evidence of increased OFC gray matter volume in this group. Future studies should incorporate multimodal imaging (structural and functional) to triangulate the conflicting results with regard to the OFC.

3.2. Findings on functional brain alterations in OD

3.2.1. Resting-state fMRI studies

A total of 17 studies involving 591 patients with resting-state fMRI data were included, examining various etiologies of OD and comparing individuals with OD to individuals in normosmic control groups: neurological diseases (n = 8), Covid-19 (n = 2), post-viral non-Covid-19 (n = 1), rhinosinusitis (n = 2), congenital (n = 1), post-traumatic (n = 1) and mixed OD etiologies (n = 3). Some studies investigated multiple etiologies. One study investigated two separate categories, These studies employed diverse analytical approaches to examine both regional brain activity and large-scale functional network organization. These included regional activity metrics, such as fractional amplitude of low-frequency fluctuations (fALFF) and regional homogeneity (ReHo), functional connectivity (FC) analyses (e.g., seed-based FC, independent component analysis, voxel-mirrored homotopic connectivity, and functional covariance strength), and graph-theoretical measures (e.g., clustering coefficient, modularity, small-worldness) of network topology. The detailed findings of the included studies are summarized in Supplementary Material **G**.

3.2.1.1. Regional resting-state functional findings. At the regional level, three studies reported alterations in key olfaction-related areas, particularly the OFC and parahippocampal gyrus, across diverse etiologies including late-life depression with olfactory impairment, Parkinson's hyposmia, and chronic rhinosinusitis (Chen et al., 2021; Su et al., 2015; Zhang et al., 2023). Notably, these studies demonstrated both increases and decreases in local activity measures such as ReHo and fALFF. These bidirectional alterations may reflect both neural deficiency and compensatory neuroplastic adaptation of baseline activity. In addition, correlations between regional activity measures and olfactory function were observed (Chen et al., 2021; Su et al., 2015).

3.2.1.2. Network-level and graph-theoretical findings. At the network level, FC and independent component analysis studies yielded heterogeneous functional connectivity patterns. Out of 14 studies, four reported decreased connectivity (Ma et al., 2023; Porcu et al., 2024; Wang et al., 2022; Xie et al., 2024), four reported increased connectivity (Fan et al., 2022; Jiramongkolchai et al., 2021; Porcu et al., 2024; Zhang et al., 2022), two reported null findings (Peter et al., 2021; Siva et al., 2024), and four described mixed alterations (Iravani et al., 2021; Park et al., 2019; Su et al., 2015; Yoneyama et al., 2018). Among studies identifying decreased FC, alterations were localized within the olfactory network (ON), defined here as the functional circuits connecting key anatomical regions such as the piriform cortex, amygdala, insula, and orbitofrontal cortex, or between the ON and other regions (Iravani et al., 2021; Ma et al., 2023; Wang et al., 2022; Xie et al., 2024; Yoneyama et al., 2018). Some studies showed that reduced connectivity in key olfactory nodes was associated with worse olfactory function. Specifically, Xie et al. (2024) reported that mean functional connectivity strength across the olfactory network positively predicted UPSIT scores ($\beta = 2.03$). Regarding specific nodes, Yoneyama et al. (2018) found that reduced amygdala connectivity significantly correlated with hyposmia severity, while Iravani et al. (2021) identified a significant correlation between TDI scores and functional connectivity of the posterior piriform cortex ($r = -0.33$) Among the studies reporting increased FC, there were consistent alterations involving the ON, either within the ON (Fan et al., 2022; Park et al., 2019; Tremblay et al., 2020) or between the ON and other regions (Su et al., 2015; Zhang et al., 2022). Some studies reported moderate negative correlations (coefficient values: −0.33 to −0.50) between FC values and olfactory function (Fan et al., 2022; Iravani et al., 2021; Zhang et al., 2022). Increased FC was not restricted to the ON, extending into the visual network and default mode network (Jiramongkolchai et al., 2021; Yoneyama et al., 2018; Zhang et al., 2022).

Four studies using graph-theoretical network analysis studies provided further insight into global network organization. Three of these demonstrated reductions in global modularity and local efficiency, affecting either whole-brain networks (Park et al., 2019; Siva et al., 2024) or the ON (Muccioli et al., 2023), whereas Tremblay et al. (2020) reported no difference in modularity between patients with OD and normosmic controls. These results indicate a general trend toward less specialized and less efficiently segregated brain networks. Moreover, reductions in network segregation were associated with reduced olfactory function in several studies (Muccioli et al., 2023; Park et al., 2019). In contrast, network integration (e.g., global efficiency) appeared largely preserved across most etiologies (Muccioli et al., 2023; Siva et al., 2024), with the exception of Park et al. (2019), who reported increased efficiency specifically in patients with posttraumatic anosmia. These mixed results likely reflect differences in analytic methods (e.g., whole-brain vs. network-specific) and disease heterogeneity (e.g., varied etiologies and severity of OD).

3.2.1.3. Discussions of resting-state fMRI findings. Taken together, our review shows current functional connectivity studies reported a complex and inconsistent pattern. Regional activity in olfactory structures is increased or decreased, while functional connectivity within the ON shows instances of both decline and strengthening. Furthermore, large-scale network topology frequently exhibits a shift towards reduced segregation at the whole brain or ON level, with inconsistent alterations in network integration. These findings collectively suggest the coexistence of ON deficiency and global reorganization in OD. Some studies interpret the significantly increased FC within and between ON nodes as a possible compensation mechanism (Fan et al., 2022; Iravani et al., 2021; Zhang et al., 2022). Differences in statistical thresholds, analytic approaches (ReHo, fALFF, FC, graph theory), and olfactory assessment tools drive considerable heterogeneity across studies, thereby hindering cross-study comparisons. Furthermore, etiological confounders complicate interpretation. Control group selection adds further variability, with some studies recruiting healthy individuals and others including disease-matched individuals. Finally, given that some studies found moderate correlations between connectivity measures and olfactory function, future work could explore whether resting-state fMRI can complement behavioral testing in clinical practice.

3.2.2. Task-based fMRI studies

Ten papers including 301 patients with olfactory task-based fMRI data, covering various OD etiologies were included: post-traumatic (n = 5), neurological disease (Parkinson's disease; n = 2), post-viral (n = 1), and mixed (n = 4). Some studies investigated multiple etiologies. The experimental paradigms used were diverse. Stimuli presented ranged from purely olfactory and pleasant odors such as peach, coffee, and chocolate (Georgiopoulos et al., 2024; Han et al., 2018b; Reichert et al., 2018) (Georgiopoulos, 2024; Han, 2018; Reichert, 2018), to unpleasant or neutral trigeminal–olfactory compounds such as fish sauce, β-mercaptoethanol, and n-butanol (Moon et al., 2018; Yildirim et al., 2022). Stimulus durations varied considerably, from brief exposures of 0.25 s (Iannilli et al., 2011) to prolonged presentation of up to 120 s (Yildirim et al., 2022). Stimuli also differed in concentration, number of repetitions and interstimulus interval. These studies reported

odor-induced regional activation in patients with OD, as well as activation differences relative to normosmic controls. Notably, several studies also assessed task-based functional connectivity, such as seed-based correlation and co-activation pattern. The detailed findings of included studies are summarized in Supplementary Material **H.**

3.2.2.1. Odor-evoked activation differences. Task-based fMRI studies in patients with OD indicate that odor stimulation can still elicit activation in several key olfaction-related regions, regardless of whether patients experience hyposmia (Han et al., 2018b; Kaheni et al., 2024; Moon et al., 2018; Pellegrino et al., 2021; Reichert et al., 2018; Yunpeng et al., 2021) or anosmia (Iannilli et al., 2011; Moon et al., 2018; Yildirim et al., 2022). Activation has been reported in the piriform cortex (Kaheni et al., 2024; Moon et al., 2018,; Pellegrino et al., 2021; Reichert et al., 2018), OFC (Han et al., 2018b; Kaheni et al., 2024; Moon et al., 2018, for the citral odor condition), parahippocampal gyrus (Han et al., 2018b; Iannilli et al., 2011), and insula (Moon et al., 2018, for the citral odor condition; Yunpeng et al., 2021). At the same time, several studies have documented the absence of primary olfactory cortex activation in OD groups (Han et al., 2018b; Iannilli et al., 2011; Kohanpour et al., 2023; Moon et al., 2018, for the 2-mercaptoethanol odor condition; Yunpeng et al., 2021).

When compared directly with individuals with normal olfactory function, individuals with OD frequently show reduced activation in primary and secondary olfactory regions (Han et al., 2018b; Kohanpour et al., 2023; Moon et al., 2018; Yunpeng et al., 2021). In contrast, Iannilli et al. (2011) reported greater responses in the dorsolateral prefrontal cortex and anterior cingulate cortex in individuals with OD compared with healthy individuals, whereas the latter showed stronger activation in the cerebellum. Only two studies assessed task-based FC differences between patients with OD and normosmic controls. Both reported altered FC between the piriform and anterior cingulate cortices, but showed divergent patterns: Georgiopoulos et al. (2024) found reduced recruitment of this network in PD patients (using co-activation analysis), whereas Tremblay et al. (2020) observed increased connectivity (seed-based analysis) in non-PD hyposmia (mixed etiologies). However, not all studies showed significant group differences: both Kaheni et al. (2024) and Pellegrino et al. (2021) found no differences between patients with post-traumatic OD and control groups in either olfactory-induced activation.

3.2.2.2. Correlations with olfactory function. Beyond group-level comparisons, four studies have further examined correlations between neural responses and olfactory function. All of these studies found positive moderate correlations ($r = 0.3–0.4$) between brain responses and olfactory function, in various sensory and associated regions (Georgiopoulos et al., 2024; Moon et al., 2018; Pellegrino et al., 2021; Reichert et al., 2018). Interestingly, Pellegrino et al. (2021) found bidirectional correlations, with stronger neural responses in the mediodorsal thalamus, ventromedial prefrontal cortex, and posterior cingulate cortex associated with greater olfactory impairment, whereas better olfactory function was linked to greater activation in the frontal operculum and anterior insula.

3.2.2.3. Discussions of task-based fMRI findings. Taken together, studies employing various olfactory task paradigms support a general pattern in which OD is characterized by hypoactivation and decreased FC in olfactory regions, accompanied in some cases by paradoxical responses in prefrontal and limbic areas, such as hyperactivation (Iannilli et al., 2011) or activation that scales positively with OD severity (Pellegrino et al., 2021). Changes in task-based functional connectivity, particularly in the piriform cortex, were consistent with these activation patterns. Interestingly, even in patients with functional anosmia, olfaction-related brain regions (e.g., piriform cortex, OFC, anterior insula) can still show some activation upon olfactory stimulation (Iannilli et al., 2011; Moon et al., 2018; Yildirim et al., 2022). This provides evidence that the central olfactory system in these patients is not fully compromised. This functional preservation aligns with evidence that patients with anosmia can improve their olfactory function following olfactory training (Delgado-Lima et al., 2024). However, the methodological heterogeneity (e.g., population, experiment parameters, analysis methods) limited the further synthesis of the currently available studies. Moreover, hyperactivation in prefrontal and limbic areas aligns with the increased FC findings in resting state-fMRI studies. Future research could use multimodal neuroimaging to validate these findings. Given that odor-induced brain activation shows moderate correlations with behavioral olfactory function, task-based fMRI measures may hold potential as prognostic biomarkers for recovery and the effectiveness of treatment with olfactory training. Finally, it remains important to investigate whether distinct OD etiologies are associated with specific neural activation signatures. Establishing these neural phenotypes could help stratify patients based on their neurobiological status and guide prognosis and personalized therapy.

3.2.3. Glucose metabolism and reginal cerebral blood flow studies

3.2.3.1. Glucose metabolism findings. Four [^{18}F]-FDG PET studies examined brain glucose metabolism in individuals with OD compared with individuals with normal olfactory function. These studies, encompassing 181 individuals with Covid-19 related OD or Parkinson's disease related OD. Of these, three studies consistently reported frontal hypometabolism (Baba et al., 2011; Morbelli et al., 2022; Niesen et al., 2021). In addition, Morbelli et al. (2022) provided direct comparative evidence for etiology-specific metabolic patterns: Parkinson's disease related OD featured more pronounced occipital reductions, whereas Covid-19 related OD was associated with limbic hypometabolism. Notably, individuals with Covid-19-related OD also exhibited hypermetabolism in the OFC, posterior cingulate cortex, and thalamus (Niesen et al., 2021). Correlational analyses further underscored the clinical relevance of FDG-PET measures, with regional metabolic alterations linked to olfactory function: Niesen et al. (2021) reported strong associations between identification scores and metabolism in OFC and piriform cortices ($r \approx -0.94$), while Morbelli et al. (2022) found etiology-specific correlations involving the gyrus rectus/ACC in Covid-19 and occipital regions in PD. The detailed findings of included studies are summarized in Supplementary Material **I.**

3.2.3.2. Regional cerebral blood flow findings. Four studies using Tc-99m-ECD SPECT or ^{15}O-H_2O PET examined regional cerebral blood flow (rCBF) alterations in individuals with anosmia, including a total of 68 individuals with posttraumatic anosmia (Atighechi et al., 2009; Eftekhari et al., 2006; Gerami et al., 2011) or anosmia associated with chronic rhinosinusitis (Savic et al., 2009). Regarding resting-state rCBF, reduced frontal perfusion was consistently reported in patients with posttraumatic anosmia, particularly within the frontal areas (Atighechi et al., 2009; Eftekhari et al., 2006). In contrast, Gerami et al. (2011) did not observe baseline perfusion differences between patients with anosmia and normosmic controls. However, when assessing odor-induced rCBF changes, they found that both groups showed decreased OFC perfusion relative to baseline, with a more pronounced reduction in patients with anosmia. Savic et al. (2009) also investigated regional cerebral blood flow during olfactory stimulation in patients with anosmia secondary to chronic rhinosinusitis and observed decreased activation in key olfactory regions, including the amygdala, piriform cortex, and anterior insula, relative to normosmic controls. The detailed findings of included studies are summarized in Supplementary Material **J.**

3.2.3.3. Discussions of metabolic and perfusion findings. Overall, SPECT studies converge on reduced regional cerebral blood flow, particularly in the OFC, while PET studies consistently demonstrate frontal hypometabolism, with the notable exception of OFC hypermetabolism in patients with Covid-19 (Niesen et al., 2021). This pattern of divergent OFC alterations across studies is not isolated but mirrors findings across other structural modalities. While the majority of olfactory regions follow a predictable trajectory of functional and structural disruption (i.e., hypometabolism, reduced FA, and atrophy) consistent with OD, the OFC exhibits a uniquely complex profile. For instance, DTI studies show that acquired OD is consistently associated with microstructural degradation (reduced FA, increased MD), whereas the OFC is the only region to exhibit FA increase in patients with congenital OD. A similar dissociation is observed in structural MRI: while our review showed that patients with OD had uniform gray matter volume reductions in olfactory regions, most markedly within the OFC (18 studies), a subset of studies reported either exclusive volume increases (1 study) or mixed patterns of regional increases and decreases (2 studies) within the OFC in congenital populations. Collectively, these findings identify the OFC as a distinct outlier within the olfactory regions for its bidirectional plasticity in OD.

3.2.4. Dopamine transporter imaging (DAT) studies

DAT imaging, performed with PET or SPECT radiotracers such as [^{1} ^{23}I] β-CIT, [^{1} ^{31}I] FP-CIT, or [^{1} ^{8}F] FP-CIT, enables assessment of striatal dopaminergic integrity. Ten DAT imaging studies involving 988 patients with OD were identified, including two study pairs that reported overlapping population (Jennings et al., 2017; Siderowf et al., 2020) / (Ponsen et al., 2004, 2010). In Parkinson's disease population, [^{1} ^{8}F]-FP-CIT PET was consistently used, whereas prodromal Parkinson's disease studies relied on [^{1} ^{23}I] β-CIT SPECT or [^{1} ^{31}I] FP-CIT SPECT. The detailed findings of included studies are summarized in Supplementary Material **K**.

3.2.4.1. DAT findings. Across Parkinson's disease patients with OD, converging evidence indicated regionally specific DAT reductions, most consistently in the caudate and ventral striatum (Lee et al., 2015; Yoo et al., 2024), whereas no significant differences with healthy individuals were observed at the whole-striatum level (Lee et al., 2015) or in the putamen (Oh et al., 2018; Yoo et al., 2020). In prodromal Parkinson's disease population with hyposmia, all studies reported a higher prevalence of dopaminergic deficits relative to normosmic individuals (Berendse et al., 2001; Jennings et al., 2017; Marrero-González et al., 2020; Ponsen et al., 2004, 2010; Siderowf et al., 2020).

3.2.4.2. Discussions of dopaminergic findings. Taken together, Parkinson's disease patients with OD exhibit dopaminergic deficits in specific striatal subregions, particularly the caudate and ventral striatum, with no consistent involvement of the putamen or the whole striatum. In prodromal Parkinson's disease population with hyposmia, all studies reported higher rates of DAT deficits compared to normosmic control groups. However, the included studies exhibited methodological heterogeneity in terms of tracer selection and quantitative outcome measures (standardized uptake value ratio or specific binding ratio), which limits direct comparisons and synthesis across studies. Additionally, in studies on prodromal Parkinson's disease, longitudinal findings demonstrated that hyposmic individuals with baseline DAT alterations are more likely to progress to clinical Parkinson's disease (Berendse et al., 2001; Jennings et al., 2017; Ponsen et al., 2004, 2010; Siderowf et al., 2020). These results support that combining olfactory testing with DAT imaging may provide a strategy for early Parkinson's disease detection (Borghammer et al., 2014; Deeb et al., 2010). Finally, specific binding ratios of the dopamine transporter in the striatum have been positively associated with olfactory function, also in healthy subjects (Pak et al., 2018). Covid-19 cases have also demonstrated striatal DAT reduction (Cavallieri et al., 2022). This evidence indicates that dopaminergic vulnerability may not be exclusive to the Parkinson's disease spectrum. While current research is primarily focused on Parkinson's disease and its prodromal stages, future studies should include other etiologies of OD to provide a more comprehensive understanding of the role of dopamine signaling in olfactory function.

3.2.5. EEG studies

24 EEG studies comprising 1577 patients with OD of various etiologies were included: traumatic brain injury (n = 8), post-viral etiologies including Covid-19 (n = 7), and mixed etiologies (n = 10). Some studies investigated multiple etiologies. The studies primarily evaluated three outcomes: olfactory event-related potentials (OERPs) detection rates (n = 17 studies), ERP latency and amplitude differences (n = 12), and correlations between EEG measures and olfactory function test (n = 6). Odor stimuli varied across studies, with the majority using pure olfactory compounds (e.g., phenyl ethyl alcohol, amyl acetate; n = 20) and a smaller subset employing olfactory-trigeminal stimuli (e.g., mint, benzaldehyde; n = 4). Stimuli also differed in concentration, number of repetitions and interstimulus interval. The detailed findings of included studies are summarized in Supplementary Material **L.**

3.2.5.1. Olfactory event-related potentials (OERPs) and EEG oscillations findings. OERP detection rates varied substantially across individuals, ranging from 0% (Rombaux et al., 2007) to 89% (Li et al., 2024) in individuals with anosmia. Across studies, individuals with OD generally exhibited prolonged N1 and P2 latencies indicating delayed central processing of olfactory inputs, and reduced amplitudes, reflecting diminished cortical recruitment, compared with healthy control groups (Fig. 4). Specifically, mean N1 latencies ranged from 390 to 556 ms in individuals with OD, whereas they ranged from 348 to 451 ms in healthy individuals. Mean P2 latencies ranged from 566 to 690 ms in individuals with OD and from 521 to 660 ms in healthy individuals. Mean N1 amplitudes ranged from −2.65 to −5.82 μV in individuals with OD and from −3.25 to −6.02 μV in healthy individuals. Mean P2 amplitudes ranged from + 2.6 to + 10.4 μV in individuals with OD and from + 2.9 to + 8.5 μV in healthy individuals. One exception was reported in a study using very short interstimulus intervals, in which individuals with OD demonstrated shorter latencies and higher amplitudes relative to healthy individuals (Whitcroft et al., 2017).

Compared to OERPs, the assessment of olfactory event-related oscillations in the frequency domain remains relatively underexplored (Bonanni et al., 2006; Schriever et al., 2017). Heterogeneity in olfactory event-related oscillations analysis, including selection of frequency bands, time windows, and metrics such as power, coherence, or entropy, limits comparability across studies. Source localization, critical for interpreting neural sources of the electrical activity detected at the scalp, was performed in only one study (Iannilli et al., 2017; Güdücü et al., 2019) which revealed distinct olfactory processing patterns in patients with Parkinson's disease-related olfactory loss within the right angular gyrus, right parahippocampal gyrus, and right anterior cingulate cortex compared to controls.

3.2.5.2. Correlations with olfactory function. Six studies reported correlations between EEG parameters (e.g., latencies, amplitudes, odor-evoked EEG power changes) and olfactory function (e.g., identification scores, threshold scores, retronasal scores). Shorter OERPs latencies, indicative of faster neural responses, were consistently associated with better olfactory function, with absolute Pearson correlation coefficients (|r|) ranging from 0.35 to 0.82 for N1 or P2 latencies (Guo et al., 2021; Yang et al., 2012). Smaller OERP amplitudes were associated with worse olfaction, with correlations ranging from |r| = 0.22–0.82 (Guo et al., 2021; Liu et al., 2018; Yang et al., 2012). Only

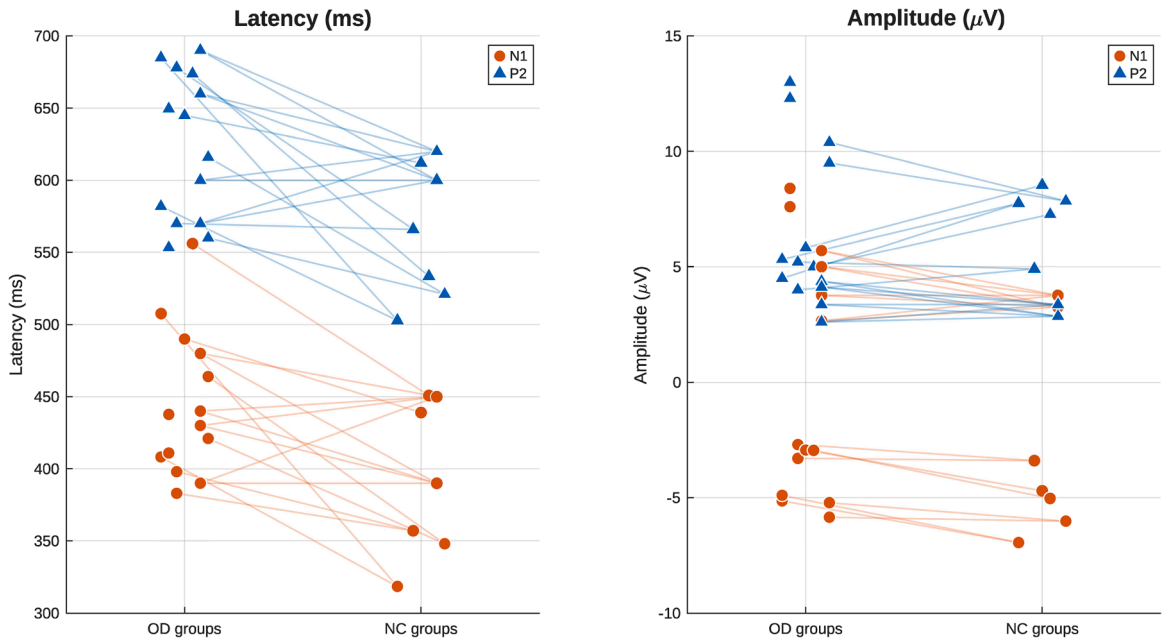

Fig. 4. Summary of olfactory event-related potential (OERP) N1 and P2 components. Comparison of N1 (orange circles) and P2 (blue triangles) between olfactory dysfunction (OD) groups and normosmic control (NC) groups. The left panel displays mean latency, and the right panel displays mean amplitude. Lines connect paired data points from the same study; isolated points represent studies without an internal control group.

one study reported a moderate positive correlation (r = 0.42) between time-frequency EEG power changes and olfactory function (Schriever et al., 2017).

3.2.5.3. Discussions of EEG findings. In summary, EEG studies showed substantial variability in several aspects, including patient characteristics (e.g., severity and etiology), stimulus type (e.g., pure odors versus trigeminal stimuli), and methodological approaches (e.g., short versus long interstimulus intervals), as well as outcome measures. While this diversity offers insights from multiple perspectives, it also contributes to inconsistent findings across studies. For example, OERP detection rates varied substantially across individuals, ranging from 0% (Rombaux et al., 2007) to 89% (Li et al., 2024) in individuals with anosmia. Also the finding of inconsistent latency/amplitude outcomes under different interstimulus intervals (Whitcroft et al., 2017) shows how experimental design choices may strongly influence results. Similarly, correlations between EEG parameters and olfactory function, although statistically significant, exhibited wide variation in strength (r = 0.22–0.82) (Guo et al., 2021; Liu et al., 2018; Yang et al., 2012). This suggests that factors, such as OD etiologies, experiments' design, or olfactory tests, may affect these relationships. These findings emphasize the need for standardized protocols in olfactory EEG research. Key areas for standardization include the use of uniform odorants, stimulus timing, transparent data processing, and rigorous participant characterization based on olfactory function and etiology. Research on olfactory event-related oscillations in patients with OD promising but underutilized avenue for future investigation. Given that spatial and spectral EEG properties are closely linked to olfactory processing in healthy populations (Li et al., 2025; Ninenko et al., 2023), extending this work to OD populations could find novel biomarkers of dysfunction. Also, the mechanistic interpretation of such data is currently limited by the inherent difficulty of precise source localization when using EEG alone. Future research would benefit from integration with or validation by complementary neuroimaging techniques, such as MRI with excellent spatial resolution. Advanced analytical approaches, such as representational similarity analysis (Cichy and Oliva, 2020), allow researchers to resolve brain responses simultaneously in space and time. By mathematically linking multivariate response patterns from fMRI and EEG based on their representational similarity, this framework facilitates cross-modal comparisons of neural activity alterations and improves the mechanistic understanding of OD.

4. Conclusion

This systematic review synthesized evidence from 164 moderate-to-high quality studies investigating the neural correlates of OD across more than 10,000 individuals.

OD is associated with widespread structural and functional brain alterations. Structural MRI studies consistently report reduced OBV and OSD, alongside gray matter reductions in key olfactory regions such as the OFC, hippocampus, anterior insula, and amygdala. Diffusion MRI highlights white matter abnormalities, with reduced FA in acquired OD and unexpected increases in congenital OD. Functional neuroimaging (resting state-fMRI, task-based fMRI, PET, SPECT) showed heterogenous findings within olfactory networks. EEG studies show prolonged latencies and reduced amplitudes in olfactory event-related potentials. While the majority of olfactory regions follow a predictable trajectory of structural and functional disruption (i.e., reduced FA, and atrophy, hypoactive, hypometabolism) consistent with acquired OD, the congenital OD and Covid-19 related OD showed a different pattern. Notably, the OFC appeared distinct from these trajectories, acting as a key area of bidirectional alteration.

Across techniques, better olfactory function is generally associated with larger OB/OS measures and more preserved structural integrity in olfaction-related regions. Resting-state functional connectivity patterns and metabolic and brain activity also correlate with olfactory function. Our review suggests that olfaction-related neuroimaging features hold translational value, and could serve as potential biomarkers to enhance clinical practice by improving diagnostic accuracy, forecasting patient outcomes, and informing personalized treatment strategies.

Etiology-specific patterns emerged across studies. All kinds of OD, except Covid-19 related OD, consistently show a reduction in OBV/OSD. Acquired OD typically shows structural and functional deterioration,

while congenital OD presents unexpected increases in several brain metrics. Although duration of OD also appears to influence brain measures (Abdul Manan et al., 2025), systematic synthesis of these effects requires that future research consistently report the duration, strictly distinguishing between general disease duration and the specific duration of smell loss.

In conclusion, although there is substantial evidence of central structural and functional alterations in OD, the methodological heterogeneity, such as varying techniques, diverse etiologies and different experimental paradigms and outcome measures complicate the synthesis of robust neural correlates and impede clinical translation. Based on the available evidence, central neuroimaging markers cannot yet be recommended as reliable diagnostic tools for routine clinical assessment of OD. However, we do recommend their use as supplementary objective measures to complement psychophysical testing. At the same time, this review's findings consistently highlight the multifaceted and etiology-dependent nature of OD-related structural and functional brain alterations. To address the current limitations, future research should adopt standardized, large-scale, and etiology-specific and multimodal protocols. This will help to unlock the translational potential of central olfactory biomarkers for refining diagnostics, predicting prognosis, and guiding the choice of and development of therapeutic strategies.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT-4.0 and GPT-5 to assist with language editing. All content generated using these tools was subsequently reviewed, revised, and approved by the authors, who take full responsibility for the final manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2026.106665.

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