Chapter 4

Olfaction, among the First Senses to Develop and Decline

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Additional information is available at the end of the chapter

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Abstract

Olfaction is one of the most conserved senses across species. It plays a crucial role in animals' and humans' life by influencing food intake, reproduction and social behavior. The olfactory system is composed of a peripheral neuroepithelium and a central olfactory nerve and is one of the few central nervous system (CNS) structures with direct access to the external environment without passage through the Blood Brain Barrier (BBB). This makes this nerve system of importance for understanding how exogenous stimuli may contribute to neuronal damage as well as for diagnostic and therapeutic purposes. Interestingly, olfactory activity physiologically declines with aging, but its alteration can be further impaired by various neurological conditions. For example, in progressive neurodegenerative disorders, such as Alzheimer's disease (AD), olfaction is the first sense to be impaired before the onset of cognitive symptoms, suggesting that olfactory transmission may characterize early neural network imbalances. In this work, we will explore the main olfactory anatomical structures, the cytoarchitecture, the neurogenesis, several pathological conditions characterized by olfactory deficit and the potential use of this sense to diagnose and treat CNS pathologies.

Keywords: olfaction, olfactory system, olfactory dysfunction, Alzheimer's disease, chronic inflammation, cancer, traumatic brain injury, neurological disorders, olfactory tests, nasal biopsies, diagnosis, therapeutic target

1. Introduction

Olfaction is among the most preserved senses across species based on its fundamental role for survival. In fact, this sense influences vital activities such as feeding, reproductive and social behavior.

The variety of functions modulated by olfaction relies on the direct connectivity of the olfactory tract to the piriform cortex, entorhinal cortex, hippocampus and amygdala regulating innate and acquired olfactory perception, memory, fear and alertness (**Figure 1**). In mammals, the major components of the olfactory system consist of the olfactory neuroepithelium (OE), the primary olfactory area, the olfactory bulb (OB) and its cortical projections, considered as secondary olfactory network areas (**Figure 1**) [1]. The olfactory network is, besides the visual system, the only nerve tract with direct access to the external environment without passage through the BBB and represents a viable and non-invasive source of CNS-derived biomarkers. Furthermore, chemosensory transduction manifests itself through the sense of smell, which is readily testable [2]. The olfactory system starts developing at mid gestation [3–5] and is mainly unchanged in all vertebrates [6, 7]. After birth, olfaction is essential in assisting the development of locomotor activities and spatial orientation as demonstrated in both rodents and humans [8–11]. These evidences underlie how the onset of olfactory deficits may induce a wide range of (reversible or irreversible) impairments with potential life-threatening consequences. The most common alterations consist in either an exaggerated sense of smell "hyperosmia," a reduced sense of smell "hyposmia" or the absence of smell "anosmia". Hyperosmia is often co-symptomatic to schizophrenia and manic disorders [12, 13], whereas hyposmia occurs naturally with aging [14] and is exacerbated in progressive neurodegenerative disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD) [14–17]. In addition, olfaction can be also completely

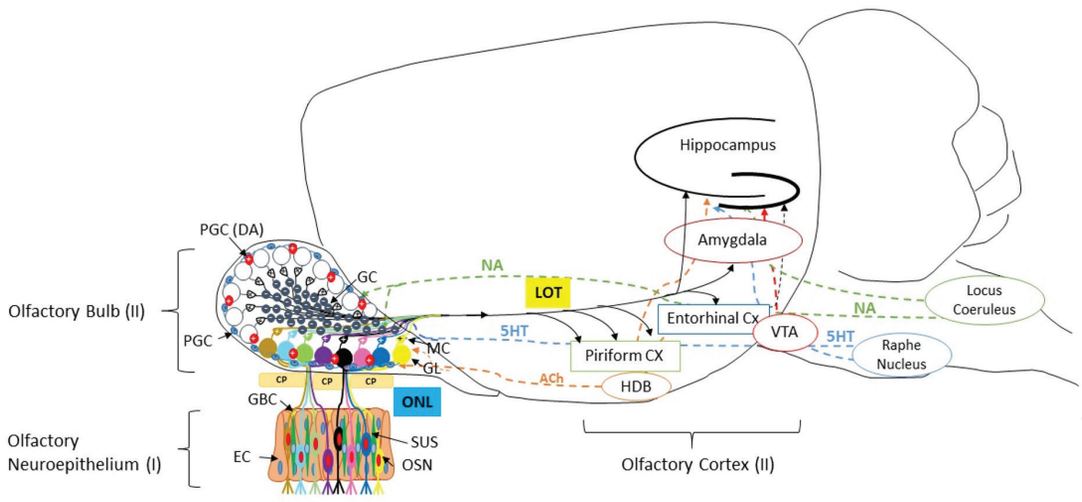

Figure 1. Olfactory system anatomy in the mammalian brain. Drawing of the primary (I) and secondary (II) network areas of the olfactory system and its corticofugal (continuous lines) and centrifugal (dotted lines) connections. The pseudostratified neuroepithelium located in the upper olfactory mucosa is displayed with its major cell types, epithelial cells (EC), globose basal cells (GBC), sustentacular cells (SUS), olfactory sensory neurons (OSNs). The OSNs project their apical dendritic cilia in the nasal cavity and their axons towards the brain to form the olfactory nerve layer (ONL, blue highlight), by passing through small foramina in the cribriform plate (CP). In the olfactory bulb, the ONL terminals synapse with excitatory mitral cells (MC; positive charge) and tufted cells (TC, not represented) in the glomerular layer (GL). Inhibitory periglomerular cells (PGCs; negative charge), dopaminergic PGCs (DA, positive charge) and inhibitory granular cells (GC, negative charge) modulate the activity of MC and TC through dendrodendritic synapses. MC axonal projections assemble to form the lateral olfactory tract (LOT, yellow highlight) projecting to the piriform cortex, entorhinal cortex, amygdala and hippocampus, representing the olfactory cortex (II). Cholinergic terminals (ACh, orange) from the horizontal limb of the diagonal band of Broca (HDB), serotoninergic efferents (5-HT, light blue) from the raphe nuclei, and noradrenergic fibers (NA, green) from the locus coeruleus innervate the olfactory bulb and olfactory cortex. Dopaminergic neurons of the ventral tegmental area (VTA, red) modulate the activity of the olfactory cortex. Cx: cortex.

lost after trauma [16, 18, 19] or certain types of cancer [20–23]. Furthermore, the early olfactory deficit in AD [24] has been shown to be a strong predictor of the progression of dementia [25–28]. Diagnosis of this sense remains underlooked and there is no consensus on the use of olfactory tests to assess/categorize neurological dysfunctions [29]. Interestingly, the studies testing olfaction in Tau and APP mouse models of AD, or α-synuclein models have shown that this sense is significantly altered [30–32]. Moreover, recent studies raise the possibility that endogenous [33–37] (PrP, Aβ, Tau, α-synuclein) and microbial [38, 39] amyloid-like peptides are accumulated in the nasal neuroepithelium and may propagate via retrograde transport to higher brain structures [40]. This might explain why Aβ, Tau, α-synuclein depositions are first observable in the olfactory bulb and olfactory tract, as their accumulation is associated to fibrillary tangle dysgenesis [41] and correlate with Braak staging progression [42].

Despite the strong evidence indicating that olfactory transmission deficit is an early predictor of neurodegenerative processes, the poor understanding of the molecular and cellular mechanisms underlying olfactory activity in the primary as well as secondary olfactory network areas has marred the use of olfaction and olfactory testing as bona fide targets in clinical setting. In this chapter, we elaborate on the anatomical and physiological properties of the olfactory system, its development by sampling the vast literature of olfaction in mammals. We then expand on the role of olfaction in humans and smell deficits as readout of neurological diseases as well as other pathologies. With this work we aim to provide further support for considering the olfactory system as source of physiological and biological biomarker(s) based on its direct connection with the brain and emphasize the use of this easily accessible sensory system as an ideally suited functio-anatomical window for monitoring brain health as well as for therapeutic targeting.

2. Olfactory system anatomy

In vertebrates the olfactory network is activated when an odorant, inhaled through the airways, binds to a specific receptor expressed on specialized neurons, known as olfactory sensory neurons (OSNs) or olfactory receptor neurons (ORNs), embedded in the upper olfactory mucosa. Every OSN expresses a specific odorant receptor (OR), which is activated only when a unique ligand (odor molecule) binds to it [43]. In 1991, Buck and Axel identified 18 genes encoding ORs [44] and for such discovery they were awarded the Nobel Prize in 2004. Few years later, more than 1000 OR genes were discovered in rodents [45] but only 378 OR were found in humans [46]. The OSN are characterized by their unique and exclusive ORs expression. The sorted olfactory signal is then transmitted from the OSNs' axons, bundling as the olfactory nerve layer (ONL) in direction of specific glomeruli located in the OB [47]. Furthermore, innervation of the OB by the OSN axons is spatially segregated along the dorsomedial and lateroventral axis (zone I, II, III, and IV) respecting the spatial positioning of these neurons in the neuroepithelium. This "glomerular convergence" allows OSN projections to be widely dispersed across the bulb, while maintaining specificity for classes of odorant chemicals. For example, the dorsomedial zone I has convergence of OSN axons detecting n-fatty acids or n-aliphatic aldehydes but not alkanes [47–49]. The chemical and anatomical organization of ONL inputs defines the discrete odorant map of the OB, which is further relayed to the connecting mitral (MC) and tufted cells (TC) via axodendritic synapses [48]. Mitral and tufted principal neurons, constituting the output from

the OB to the cortex, are finely tuned through dendrodendritic synapses mostly from periglomerular (PGC) and granular (GC) interneurons. These GABAergic and dopaminergic (DA) neurons are continuously replaced at least in rodents [50–52] and are essential for modulating mitral and tufted cells' firing rates and increasing/decreasing their synchronous firing activity in presence/absence of an odorant [53–55]. Further, cholinergic, serotoninergic and noradrenergic afferents, originating respectively from the horizontal limb of the diagonal band of Broca (HDB) [56], raphe nuclei [57] and locus coeruleus [58], modulate the response of the PGC, MC and GC (**Figure 1**). These centrifugal afferents innervate the bulb in its integrity and appear to be involved in the early deficit observed in AD and PD [59]. From the bulb, axonal projections of the relay MC, form the lateral olfactory tract (LOT) and innervate higher brain areas (**Figure 1**). Neuroimaging studies reveal that the higher olfactory areas encompasse different cerebral structures, which are mainly divided in primary and secondary olfactory regions [60, 61]. The first network area comprises the piriform and entorhinal cortices, the amygdala and hippocampus, whereas the second neuronal hub includes the thalamus, the orbitofrontal cortex, cingulate and insula [60, 62, 63]. In these higher brain areas, the signal is integrated and loses spatial resolution [64]. This decomposition effect has been explained by the combinatorial cortical network ideally suited for decoding of incoming spatially segregated signals [65]. Overall, based on the heterogeneity of brain structures implicated in the modulation and processing of olfactory stimuli, the olfactory deficit phenotype and the degree of severity of olfactory impairment may vary substantially.

3. Adult neurogenesis in the olfactory system

In all mammals, including humans, neurogenesis is maintained in the neuroepithelium through the presence of neural stem cells located close to the basal lamina. In adult rodents two type of cells populate the stem cell niche, globose basal cells (GBC), representing the neural stem cells population and horizontal basal cells (HBC), with ependymal cell characteristics functioning as supporting neurogenic cells. Conversely, in humans there is no distinction between GBC and HBC, with the first appearing as the only population occupying the niche [66]. GBCs comprise transit amplifying *Mash1* positive progenitors and *Ngn-1* expressing Intermediate Neural Progenitors (INPs), ultimately differentiating into OSN [67, 68]. Besides the neurogenic lineage, GBC give also rise to SUS, a glial-like cell type intercalated between OSNs in the epithelium [69, 70] (**Figure 1**). The sustained regenerative capacity of the neuroepithelium can compensate for the vulnerability of the OSNs and SUSs, which are in direct contact with the airways of the nasal cavity exposed to exogenous species, such as microorganisms and possible neurotoxic particles. The interaction between potentially dangerous sources and the cells of the neuroepithelium requires a continuous cell turnover in order to maintain the network functionality. Furthermore, the stem cells of the neuroepithelium represent a source of human neuronal precursors that may be employed for *in-vitro* pharmacology studies, diagnostic and regenerative therapies [71, 72].

In rodents, neurogenesis takes also place in the OB, where both GC and PGC are constantly replaced via the migration of neuronal precursors from the lateral ventricles walls to the rostral migratory stream (RMS), to reach their final destination areas: the periglomerular cell layer

and granule cell layer [73]. It has been long debated whether OB neurogenesis occurs also in humans. Despite the presence of glia cells in the adult human SVZ, potentially representing a quiescent stem cells' population, doublecortin positive migrating neurons are observed in the RMS only until the 6th month of age postnatally [74]. Overall, the events promoting the renewal and replacement of the OB interneurons support the cellular turnover of the OB and its evoked odorant activity. This may have an essential role in the regulation of physiological functions in rodents, such as recognition of pheromones and food intake, or in favoring the distribution of infectious substances, entering into the brain via the nostrils and reaching the OE/OB compartment. On the other hand, the lack of OB neurogenesis in humans might be explained on one side by the reduction of olfactory diversity, since they present less turnover in the CNS networks compared to rodents, and by the compensatory use through other senses (vision, hearing, somatosensation, gustation) requiring less adaptive integration from the renewing interneurons.

4. Signaling transduction in olfaction

Olfactory transduction begins at the level of the cilia of the OSN protruding in the nasal cavity and through cascading amplification mechanisms reducing the threshold for odorant molecules detection. Each olfactory sensory neuron has about 12 ciliary branches, which increase the binding probability of the odorant molecules to the receptors compensating for the sequestration of the molecules in the nasal mucous covering the nasal neuroepithelium. Discrete odorants interact with specific olfactory receptors and activate a sequence of intracellular events leading to ionotropic channel activation and excitatory transmission through the ONL to the brain. In rodents, there are about 1000 genes encoding for different ORs. Each olfactory sensory neuron expresses only one type of OR through a monoallelic stochastic gene selection process occurring during the maturation of the OSN [43]. The ORs are G-protein coupled transmembrane receptors characterized by seven hydrophobic domains, whose diversity determines the heterogeneity and specificity of the response [75]. Upon binding to the odor molecule, a Gα olf protein, associated to the OR, is activated and converts guanosine 5′-diphosphate (GDP) to guanosine 5′-triphosphate (GTP). Further, by detachment of the beta/gamma subunits it activates the adenylate cyclase (AC) transmembrane protein converting ATP into a c-AMP [76]. This secondary messenger, c-AMP, has a high diffusion speed (20 μm/s) [77] and is rapidly sensed by the surrounding ionotropic Ca^{2+}/Na^{+} gated channels (CNG) allowing Ca^{2+}/Na^{+} inflow [78]. The rise in Ca^{2+} activates the Cl(Ca) channels, which extrude Cl-ions, potentiating by about 90% the depolarizing inward current [79, 80]. Intracellular ciliary Ca^{2+} influences the sensitivity of the CGN to c-AMP determining its desensitization or adaptation when exposure to an odor is prolonged or when the interval between exposures is short [81]. This mechanism needs to be taken into account when planning an olfactory testing paradigm in rodent and humans. Finally, unrelated odorants switch off CNG channels in a phenomenon called masking, which preserves the specificity of signal transduction to the OB [82]. These cascading events expand the signal transduction time from 1 millisecond to the order of 100 millisecond [83] producing a molar non-linear amplification of the signal and contributing to the signal persistence. The excitatory signal from the ONL axons is then transferred to the apical dendrites of MC through glutamatergic synapses [84] and modulated through presynaptic and postsynaptic inputs of DAergic and GABAergic afferents of PGC and juxtaglomerular

interneurons spanning one or more glomeruli and regulating the spatiodynamic resolution of the odors evoked responses [85, 86]. Further, firing synchronization and signal amplification is achieved by dendrodendritic inhibitory synapses between GC and MC located in the external plexiform layer [87, 88]. The fine-tuned excitatory signal is relayed through the LOT to the cortical and neocortical structures, where an odor-evoked depression, by presynaptic metabotropic glutamate receptor (mGluR) II/III activation, contributes to signal adaptation and attenuation, typical of the cortical sensory responsiveness [89, 90]. Despite the physiology of olfactory transmission has been well characterized in rodents, much less is known about the physiology of this system in humans.

5. Olfaction in early life, adulthood, aging and mortality

Olfaction is among the most preserved senses throughout species and plays a vital role in daily life, being fundamental for feeding, reproductive and social behavior. Several studies described that in mammals, including humans, the sense of smell is developed during the first weeks of fetal life [9, 22, 91, 92]. Both in rats and humans, it has been shown that the odor of the amniotic fluid and the milk from the mother are perceived and memorized by the fetus, which, after birth, is capable to recognize and distinguish them from those of a surrogate mother [8, 10]. Moreover, experiments of olfactory stimulation in rat pups just after birth (0, 1, 2 hours) show an increase in locomotor activity compared to the unexposed pups [9].

In humans, clinical observations conducted on infants revealed their capability in locating the mother's breast without assistance [93, 94], suggesting that the maternal breast odor is the driving force guiding their orientation and providing a sense of protection [9]. For instance, during hospitalization, the maternal contact and odor have a beneficial effect on relaxing the neonate when crying. These aspects constitute the "non-verbal communication", which plays a fundamental role during the early neonatal phase to build and reinforce the mum-infant bonds [10]. Infants familiarize with odorants during pregnancy through mum's diet, through a chemosensory transmission mother-infant [92]. Thus, in the critical period of early postnatal development, when vision is still poor, olfaction is employed as one of the first senses besides touch to make contact with the external world. Even if with adulthood, olfaction becomes less relevant for survival, particularly in modern humans, it underlies strong odor-cued memories and emotions. These associative processes triggered by odor perception depend on the output of the LOT to the hippocampus and amygdala and have been essential for animals to locate food [95], for the selection of mating candidates [96] and to identify predators [97, 98]. One of the most striking examples of olfactory sensitivity for foraging is the ability of the brown bear to sniff odors from more than 10 miles away, therefore representing a significant threat to campers and hikers carrying food in natural reserves. Studies indicate that the acuity and high sensitivity to odors of larger canid depends on the extended olfactory surface areas of the turbinates rather than the relative size of the olfactory system to the brain [99]. Furthermore, the smell-based mate selection is most prominent in females and appear to be dependent on the HLA variants inherited by the father [100, 101], triggering an emotional and behavioral response aimed at reproductive activity and species' preservation. Finally, the "smell of danger" has been employed in odor-based fear conditioning to test amygdala's function as well

as hippocampal plasticity [102, 103]. Interestingly, fox or cat urine is widely used in testing passive olfactory avoidance in rodents despite these laboratory animals never encountered a predator [104]. This suggests that odor-cued memories are ingrained in the DNA and research demonstrated that are the result of heritable epigenetic modifications [105]. Furthermore, studies in humans showed that most odor-cued memories are formed in the first decade of life [106] and appear stronger than the ones evoked by words or visual cues reflecting accurately one's autobiography throughout life [107, 108]. Finally, olfactory acuity is particularly developed in occupational workers such as sommelier, perfumers and chefs, which can perceive hedonic odors among a mix to deliver unique pleasant and palatable combinations [109, 110]. It remains unclear whether odor protheticity depends on the plasticity of the neuroepithelium or the distribution of the olfactory receptive elements. With aging, humans of both genders progressively lose their olfactory acuity and the ability to identify an odor: more than 50% of individuals aged 65–82 suffer from olfactory deficit [14, 111, 112]. Several factors account for the dysfunction including chronic damage to the neuroepithelium by neurotoxins and misfolded proteins [113], depletion of ciliary ORs, neuroinflammation and reduced vascularization [114]. As a result of the OSN damage with age, bulbar atrophy [115] and glomerular degeneration are associated to neurofibrillary tangle (NFT) depositions and olfactory processing and perception deficits [117]. Olfactory dysfunction (OD) in the elderly represents a source of discomfort and can pose a serious risk to safety [118]. Last, olfactory deficit has been shown to be an early predictor of mortality in old age [119]. This body of data indicates that olfaction is one of the primary form of environmental communication in mammals [120].

6. Olfactory dysfunctions

The olfactory activity is mainly composed of two hierarchical independent processes, where the first, defined as "peripheral", is based on the acuity or capability to perceive an odorant, while the second, named as "central", is involved on the memory or ability to identify an odor [61, 121]. Alteration in peripheral processes is linked to deficits occurring at the olfactory neuroepithelium, specifically at the levels of the OSN. On the other hand, damages to central processes can be attributed to deficits in the OB compartment and in higher cerebral regions, such as cortical and limbic system structures. This observation is supported by studies showing impaired odor identification with unaffected threshold activity in subjects presenting injures in the orbitofrontal cortex or the dorsomedial thalamic nucleus [122]. The integrity of olfactory perception, normosmia, can be impaired by alterations which can be divided in two main categories indicating a (1) quantitative or (2) qualitative impairment of the sense of smell. The first category is composed by anosmia, hyposmia or microsmia and hyperosmia, whereas the second one is represented by dysosmia, subdivided in parosmia and phantosmia or olfactory hallucination. These categories and their definition are summarized in **Table 1**. Apart from normosmia, which represents the physiological condition of the sense of smell, all the other cases can be determined by a wide spectrum of causes. In order to assess olfaction in humans, several tests are nowadays available to monitor the sensitivity of the olfactory system aiming to detect at an early stage the presence of different disorders. A test, which is commonly adopted to evaluate the olfactory responsiveness, is the University of Pennsylvania Smell Identification Test (UPSIT), developed by Doty and colleagues in 1984 [29]. This scratch

Physiological olfactory condition
Normosmia: normal olfactory function
Quantitative olfactory dysfunctions
Anosmia: total loss of smell
Hyposmia: decreased sense of smell
Hyperosmia: increased sense of smell
Qualitative olfactory dysfunctions
Dysosmia: qualitative alteration of the sense of smell. It includes:
(1) Parosmia: odor distortion
(2) Phantosmia: odor perception without the presence of the source

Table 1. Classification of the olfactory conditions.

and smell test enables the evaluation of the general smell function, e.g. odor identification and odor detection, assigning a final score which reflects the individual ability to recognize by exclusion several odors. The original tests includes 40 booklets with 4 odor per booklet, although shorter mini-UPSIT (Brief Smell Identification Test – BSIT) of 12, 15 and 16 odors

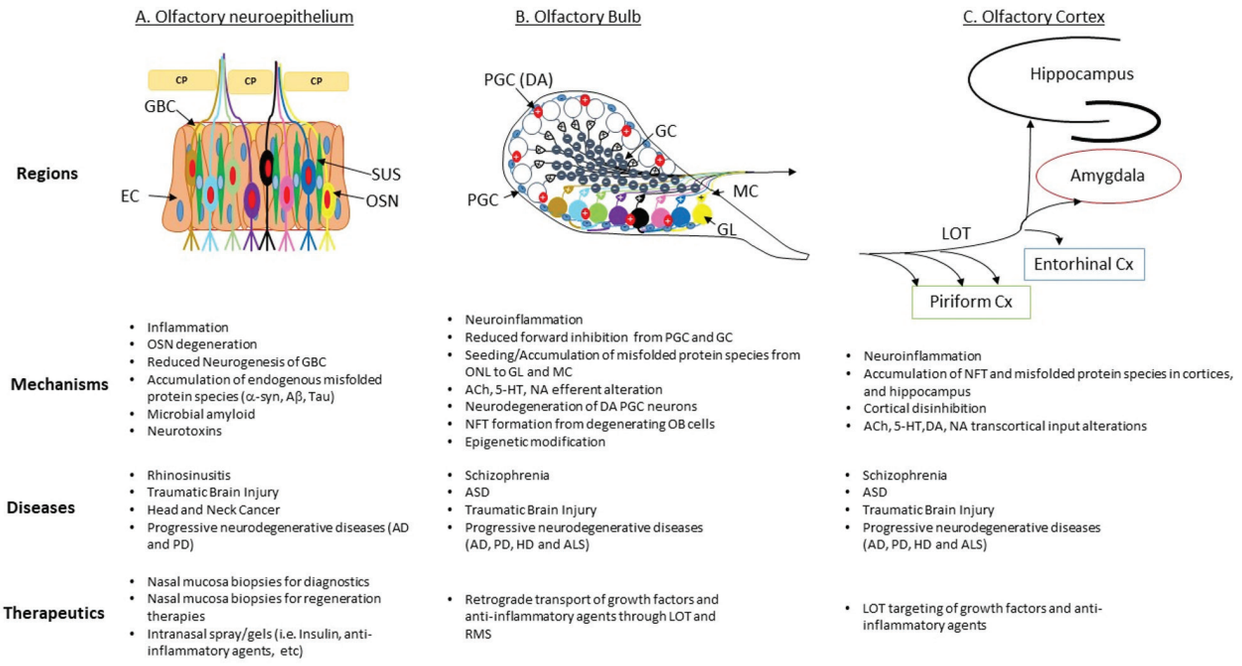

Figure 2. Breakdown of affected regions and potential mechanisms in olfactory deficiencies and window for diagnostic/treatment. Related processes, diseases and possible therapeutic approaches centered on the olfactory neuroepithelium (A), olfactory bulb (B) and olfactory cortex (C). Abbreviations: EC, epithelial cells; GBC, globose basal cells; SUS, sustentacular cells; OSN, olfactory sensory neuron; GC, granule cell; PGC, periglomerular cell; PGC (DA), periglomerular dopaminergic cells; ONL, olfactory nerve layer; CP, cribriform plate; GL, glomerular layer; MC, mitral cell; LOT, lateral olfactory tract; ACh, acetylcholine; DA, dopamine; 5-HT, 5-hydroxytryptamine; NA, noradrenaline; NFT, neurofibrillary tangles; AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease; ALS, Amyotropic lateral sclerosis; ASD, autistic spectrum disorders.

have been used before [123–125] and they seem to be a viable solution for testing olfaction on human subjects limiting desensitization mechanisms intrinsic to olfactory transduction. On the other hand, a "forced-choice phenyl ethyl alcohol odor detection threshold test" [26], also called as the Snap and Sniff® Threshold Test, allows for rapid and reliable determinations of olfactory detection thresholds. Subjects are exposed to concentrations of phenyl ethyl alcohol, ranging from 10^{-2} to 10^{-9} log vol/vol in half-log concentration steps, along with blanks for forced-choice testing [126]. This test controls for a subject's response bias or criterion for responding independently of the subject's actual sensory sensitivity. Both tests can be self-administered and are equipped with a score card making olfactory testing accessible and convenient for both clinical and personal use.

Hereafter, we describe some human pathologies which can lead to olfactory dysfunctions (**Figure 2**).

7. Systemic diseases

7.1. Chronic inflammation

Many pathological events are characterized by a persistent inflammatory response, as observed in patients suffering from sinonasal diseases, such as acute or chronic rhinosinusitis, allergic or non-allergic rhinitis [127–129] (**Table 2**). In addition to nasal congestion and altered mucus secretion, these conditions represent a common cause of olfactory impairment [127, 128, 130–132]. For instance, it has been reported that between 14 and 30% of the patients affected by chronic rhinosinusitis (CRS) show olfactory dysfunction [129, 132–134]. The inflammatory event underlying sinonasal pathologies can be divided in two processes: the inflammatory mechanism itself and the conductive (or transport) component [127–129, 135], which compromises the proper diffusion of odorants towards the olfactory neuroepithelium [136–138]. The functionality of the nasal epithelium is affected since the topical inflammation reduces the airflow and subsequently the binding of the odor molecules to the ORs expressed on their cilia. The synthesis of pro-inflammatory factors can induce the loss or impairment of the ORs, which are then unable of signal transmission due to a reduced detection threshold [129, 135]. Several studies suggest that

Pathology	Olfactory impairment	References
Chronic inflammation (Chronic Rhinosinusitis)	Anosmia, hyposmia	127–129, 133, 134
Cancer (Head–neck cancer)	Hyposmia, dysosmia	20, 146, 156, 157
Traumatic brain injury	Reversible anosmia, reversible hyposmia, reversible parosmia	19, 176–179, 184, 185
Neuropsychiatric disorders (Schizophrenia and ASD)	Hyposmia, hyperosmia, dysosmia	60, 61, 189–193, 196–198, 219, 220
Neurodegenerative diseases (Alzheimer's, Parkinson's and Huntington's disease)	Hyposmia	17, 24–26, 226–228, 236–240

Table 2. Summary of the diseases described in this chapter and their observed olfactory alterations.

the relation between CRS and olfactory dysfunction could be multifactorial, since several events can trigger olfactory disbalance in chronic rhinosinusitis cases, such as the different degree of the inflammatory response [131, 132, 137] or the medical or surgical intervention in patients suffering from this pathology [129, 132]. Moreover, it has been described that CRS patients with anosmia present an altered mucus composition, which affects olfactory epithelium neurogenesis [139]. To evaluate and monitor the entity of olfactory loss in CRS subjects various tests can be carried out [140, 141] and also the detection of biomarkers, such as neuron-specific enolase [142] could provide further support in predicting the development of such disorder. All together, these evidence indicate that a constant inflammatory status of the nasal mucosa, in presence of rhinitis, sinusitis and rhinosinusitis can lead to a variable spectrum of olfactory dysfunctions whose severity depends from the inflammatory degree itself. The chronic inflammation in CRS and the absence of the BBB between the primary and secondary olfactory areas poses a serious risk for the propagation of neuroinflammatory species leading to neurodegenerative events. Indeed, a recent report indicates that patients with a history of chronic sinusitis are more prone to develop dementia [143] or stroke [144, 145]. This supports the notion that peripheral sinus inflammation should be promptly treated with pharmacological and surgical approaches, to contain the symptoms of nasal obstruction and prevent the neuroinflammatory spread.

7.2. Cancer

Studies on head and neck cancer (HNC) reported that different symptoms associated to the treatment, such as radiotherapy and chemotherapy, can include smell and taste dysfunction [20] (**Table 2**). The impairment in these senses can appear early in HNC patients and progressively become more severe in the long-term period [146]. Laryngeal cancer patients which are best treated by total laryngectomy, based on removal of the nasal neuroepithelium, suffer from hyposmia and gustatory alteration [21, 147]. In normal conditions the olfactory receptors are not considered as potential contributors in cancerogenesis, but their physiological capability in binding to organic compounds and the subsequent signal transduction essential for survival or migratory events could support their involvement in fostering cancer cells [148–150]. Interestingly, it has been described that some ORs are present in other tissues and organs not related to the "olfactory circuit", such as muscle [151], kidney [152] and lung [22]. Former studies demonstrated that one OR is implicated in the pathobiology of prostate cancer cell migration and proliferation, making this protein a possible parameter to monitor the patient's clinical condition [150, 153, 154]. Recently, Ranzani and colleagues investigated the characteristics of olfactory receptors in cancer cell lineage and tumors. Interestingly, they found that several ORs are expressed in different tumorigenic cell lines and tumors, e.g. the OR2C3 has been observed both in diverse cancer lines and melanomas, suggesting that this receptor might participate to the development of this tumor [23, 155]. Numerous studies showed that more than 70% of cancer cases show taste and smell dysfunctions [156]. Most of these alterations are reported after cancer treatment [157], whereas changes in these senses in pre-treatment phase are not clarified. The reasons could be attributed to multiple events, like (1) mechanical interference, due to tumor obstruction of the chemoreceptor sites; (2) neurological origin, where cancer affects signal transmission; and (3) metabolic, related to a higher urea concentration in the saliva associated to tissue catabolism [23, 158].

Another fundamental aspect which connects cancer and olfaction is the employment of this sense in early detection of this pathology. In particular, canine olfaction and lately electronic

noses (e-noses) represent a promising, non-invasive manner to screen tumors [159–161]. The high sensitivity of dogs in odorants perception render them suitable for this clinical purpose, in fact they are used to distinguish healthy controls and cancer subjects upon exposure of biological samples, whereas the electronic noses present chemo-sensory components able to identify specific biomarkers in exhaled breath [161]. Both canines and e-noses can detect volatile organic compounds (VOCs) in biological specimens. It is well recognized that dogs can perceive specific VOCs in several samples, such as urine, expired breath, blood and stool [162–166]. For instance, diverse VOCs have been identified in the breath of individuals affected by lung, ovarian, prostate, bladder and colorectal tumor [167–170]. The use of electronic noses is increasing as differently from dogs, do not require training and maintenance, are relatively inexpensive and easy to handle. These new devices can analyze volatile molecules present in expired air via gas chromatography and chemosensory apparatus [171–175]. Notably, both canine olfaction and e-noses represent two powerful systems in detecting several kinds of tumors during their asymptomatic stages allowing an earlier and potentially more effective therapy. Overall, it appears that olfactory deficits are involved in the clinical phase of cancer progression, and atypical odor identification can be employed to diagnose mutagenic processes early on.

8. Central nervous system disorders

8.1. Trauma

Traumatic brain injury (TBI) constitutes one of most frequent causes of olfactory dysfunction, affecting both genders [19, 176–178] (**Table 2**). One of the first medical reports about OD, in 1864, described a post-traumatic total loss of smell and a more dated description of anosmia was reported in 1837 after head trauma (HT) from a horse riding accident [179]. Depending on the severity of the trauma, the degree of olfactory impairment can show a quite diverse clinical outcome ranging from microsmia to anosmia [178, 180–182], which can be in both cases partially recovered [181, 182]. Subjects affected by parosmia show a gradual recovery of olfactory ability following a medium-long term period after the accident [178, 181]. The severity of the trauma depends also from the cranial region interested, i.e. frontal injury is associated with a lower olfactory disability compared to the temporal and occipital lobes [181], although there is contradictory evidence on the latter [179]. After head injury, MRI analysis revealed a reduction in olfactory bulb volume as compared to control subjects [178, 181]. The reason why after HT the sense of smell is often permanently lost is due to the failed regeneration of the olfactory neuroepithelium, which directly impacts the signal transmission to the OB. In particular, the axonal re-growth of the OSNs is influenced by the injury degree [183], since it can severely compromise the ONL over its whole length [181]. A crucial aspect, which is widely debated, is the olfactory function recovery after a traumatic brain injury (TBI), which distinguishes the post-TBI hyposmia as mild, medium and severe [178]. Several studies indicate a proportional cause–effect event between trauma severity and olfactory impairment [184, 185], whereas other works suggest that the TBI entity is not directly correlated with the degree of olfactory dysfunction [179, 180]. The trauma can also have indirect consequences on the olfactory system performance, affecting cortical and subcortical areas, which are involved in the physiological olfactory responsiveness. In clinical trials, it has been observed that administration

of therapeutics, such as steroids, might improve the olfactory activity in trauma subjects [186–188]. By favoring the re-absorption of the edema or removal of the hematoma in the affected area, steroids can increase or restore the sense of smell [188]. Overall, these observations indicate that hyposmia is one of the subtlest sensory changes after trauma, which may phenotypically signal regenerative processes in these patients.

8.2. Schizophrenia and autism

A substantial number of studies indicates a correlation between schizophrenia and olfactory impairment (**Table 2**). There are several aspects of olfaction that can be assessed to characterize the schizophrenia-spectrum disorders (SSD). In particular, subjects affected by this neuropsychiatric disease present alterations in performing correctly diverse olfactory tasks, such as odor sensitivity, identification and discrimination, when exposed to different odorants [60, 61, 189–192]. Due to the disbalance in olfactory activity, it has been suggested to consider this deficit as a parameter to identify SSD. Moreover, the negative symptoms which characterize this illness have been related to the dysfunction in olfactory accuracy [193]. Nevertheless, there are controversial reports describing an alteration in the sense of smell in schizophrenia-associated disorders [190, 194] and others showing the absence of olfactory changes between psychotic patients and healthy controls [193, 195, 196]. Starting from this discrepancy, Auster and colleagues addressed whether the presence of olfactory deficits could represent a reliable marker for subjects potentially susceptible to develop schizophrenia. They investigated this aspect comparing the smell functionality in four different groups: (1) schizophrenic individuals, (2) persons with different mental disorders than schizophrenia, (3) subjects affected by schizotypy and (4) healthy controls [193]. To achieve their goal, they modified a common olfaction test, the "Sniffin' Sticks" [193, 197], in order to expand its efficiency for free recall tests in addition to olfaction ability and discrimination. They observed that schizophrenic people appear to have a reduced assortment of pleasant odors compared to healthy subjects and they report smells as less good over the controls [193, 196, 198], being in line with other reports [66, 193, 196, 198, 199]. Functional and structural alterations of the olfactory circuitry have been observed in schizophrenic patients using fMRI analysis [200] and electro olfactogram (EOG) measuring olfactory evoked potentials (EP) [194, 201]. At the biomarker level, cell culture preparations from nasal epithelium showed an alteration in G protein-coupled receptors (GPCRs) cascade, likely affecting the olfactory processing observed in this psychiatric disorder [202]. Another study reported that schizophrenic subjects are characterized by aberrant neuronal differentiation in the nasal neuroepithelium [203] suggesting that neurodevelopmental deficits may underlie the olfactory dysfunction. Indeed, prenatal or perinatal inflammation [204, 205] affect brain development and may cause the excitatory/inhibitory (E/I) disbalance characteristic of schizophrenia. Works in mice have demonstrated that NMDA hypofunction has a characteristic temporal and spatial resolution that explains the onset of schizophrenia: in early postnatal life, NMDA dysfunction occurs first in GABAergic interneurons, leading to excitatory derepression. As a compensatory mechanism, a progressive homeostatic downregulation of glutamatergic of NMDA transmission, results in NMDA hypofunction of cortical excitatory networks in the adult [206]. Based on the composition of the olfactory bulb, with a major inhibitory component and mitral cells representing the only

excitatory neurons, it is conceivable that olfactory transmission defect can arise early on due to the interference of feedforward inhibition of PGC and GC onto mitral cells, necessary for olfactory signal sorting/scaling [207–209]. The connection between neurodevelopmental deficits, E/I imbalance and olfactory deficits in adult life is captured by the numerous studies indicating that the developmental molecule Reelin [210], regulating synaptic plasticity, behavior [211–213] and olfaction [30], is reduced in a subset of interneurons in the prefrontal cortex of schizophrenic patients [214]. Interestingly, Reelin deficiency has also been reported in AD [215–217], suggesting common mechanisms between schizophrenia and progressive neurodegeneration. E/I imbalance also alters dopaminergic transmission. In the setting of local and corticofugal dopaminergic innervation to the bulb, it is expected that olfactory signal transmission may be also affected, as previously demonstrated in rats treated with inhibitors of D2 receptor [218]. This body of studies supports the notion that olfactory impairment may be an early indicator of E/I imbalance.

Only recently the attention has been pointed on the possibility of olfactory deterioration in autism spectrum disorders (ASD), comprising autism (stricto sensu) and Asperger syndrome [219, 220] (**Table 2**). ASD individuals reported an unpleasant strong perception of odors and Galle and colleagues demonstrated that depending on the olfactory tasks performed, a difference in autistic, Asperger and control subjects could be recognized. In particular, the olfactory identification was affected in autistic individuals compared to the other groups [219]. Furthermore, studies using rodent models indicate the olfactory bulb among the brain regions critical for ASD pathogenesis [221–223]. Moreover, the OR2L13G-protein locus, initializing neuronal response to odorants, was shown to be differentially methylated in ASDs suggesting a possible rationale for olfactory dysfunction in these pathologies.

Developmental NMDA hypofunction is also reported in ASD [224, 225]. In both schizophrenia and ASD, E/I imbalances at bulbar and cortical level likely underlie the olfactory transmission alterations.

8.3. Progressive neurodegenerative disorders

Olfactory activity progressively decreases with aging [14] and its decline is even accelerated with chronic neurodegenerative disorders, such as Alzheimer's disease (AD) [25, 26], Parkinson's disease (PD) [17, 24] and Huntington's disease (HD) [226, 227] (**Table 2**). Olfactory dysfunction in PD is very prominent (90% of the cases) [228] and the extent of the impairment is comparable to the one observed in early onset AD and other progressive neurodegenerative disorders. Indeed, in the initial stages of AD the olfactory function is the first to be affected [24], so this sense could represent an early predictor of the disease. Olfactory dysfunction observed in progressive neurodegenerative diseases could underlie impairments in either the olfactory neuroepithelium, OBs, LOT or olfactory cortices [42]. Interestingly, it has been reported that proteinaceous aggregates, like Amyloid-β [33], phosphorylated Tau [34, 35, 229], α-synuclein [230, 231], which are characteristic of AD, PD and HD, are deposited in first instance in the olfactory mucosa where they are thought to exert a bactericidal action [232]. The aberrant accumulation of misfolded proteins can trigger several side effects, causing a transduction deficit and inflammatory responses attempting to reduce/avoid the microbial diffusion into the brain. Based on the absence of the BBB in

the olfactory tract, cells and misfolded proteins can be easily propagated within the brain and subsequently affect other olfactory system components, as olfactory cortices and connected areas (hippocampus and amygdala) [233]. All these cerebral structures and their related functions are damaged in AD, and to a lesser extent in normal aging [42]. Interestingly, OB and olfactory tract axonal atrophy has been already detected in MCI which might progressively evolve in AD [234]. In the initial Braak stages, the OB undergoes axonal atrophy [235] and in the majority of definite AD cases the olfactory impairment correlate with cortical AD pathology [236–240]. These observations implicate an early critical involvement of the olfactory system in neurodegenerative disorders.

Several molecular mechanisms contributing to AD pathobiology have been demonstrated to interfere with olfaction:

1. Amyloid-β, which is overexpressed in AD and contributes to the amyloidogenic pathway, has physiological functions, ranging from metal ion sequestration, synaptic plasticity modulation, and antimicrobial activity [33]. The amyloid peptide shares some aspects with a highly conserved antimicrobial proteins (AMPs) family [232]. Based on their ability to form oligomers and fibrils to surround harmful microbial agents, toxic substances and even aberrant cells, the AMPs produced by the OSNs represent the first and only defensive barrier of the CNS against pathogens. Furthermore, beside its endogenous production, Aβ may also have a microbial origin, aggravating the neurodegenerative process [39, 241]. The gastrointestinal (GI) compartment represents the principal source of the human microbiome and is tightly connected with the CNS through the GI tract-CNS axis, which interconnects these structures via immune system molecules, cytokines, hormones and nervous signals [39, 242–244]. Interestingly, the microorganisms residing in the GI tract can synthesize several peptides including lipopolysaccharides (LPS) and amyloids [241, 242, 245, 246]. These evidence indicate that a mutual benefit host-microbiome is also related to the production of these amyloid exudates within a "homeostatic range", that, when disbalanced, could likely contribute to the etiology of chronic neurodegenerative diseases [247–250]. Therefore, the impairment observed in amyloid turnover and clearance during neurodegenerative pathologies could be attributed to the combination of "human Aβ burden" and the additional microbial Aβ peptides. This growing amyloid load in the OE and GI tract, can cause chronic inflammation which on the long run may affect BBB integrity and functionality [38, 39, 247, 251–253]. Overall, the deposition of insoluble Amyloid-β causes several side effects as (i) olfactory transduction deficit due to interference with OSN surface receptors, (ii) inflammatory responses attempting to reduce/prevent the microbial diffusion and (iii) seeding activity into the brain.

2. ApoE4 carriers have a higher incidence of olfactory deficit and are at risk for developing AD [254]. Moreover, ApoE4 blocks OE cultures neurite outgrowth in contrast to the trophic role of ApoE2 and ApoE3 [255].

3. Reports show SOD upregulation in OE and OB in AD patients compared to healthy controls [256] as well as an increase in oxidative response in AD neuroepithelium [255].

4. Along with network hyperactivity in the early stages of dementia, a reduction of calcium binding proteins has been observed in OSNs [257].

5. Imbalances in Acetylcholine (ACh) [258, 259], Dopamine (DA) [260–262], Serotonin (5-HT) [57, 263], and Norepinephrine (NA) [264] of the centrifugal afferents to the bulb or olfactory cortex affect olfactory transmission but can also influence microglia activation and neuro-inflammatory processes [265, 266].
6. Transient overexpression of hAPP impacts the glomeruli structure and axonal projections towards the corresponding target [267], which is partially rescued by switching off the synthesis of hAPP.
7. Dystrophic axon terminals favor amyloid deposition in AD and other disorders [116].
8. Progressive reduction in neuronal signaling components such as Reelin [268, 269] and Notch [270, 271] in AD may influence olfactory transmission as shown in rodent models [30, 272].

Despite the non-specificity of olfactory dysfunction in neurodegenerative diseases, this deficit is apparent in the pre-symptomatic phase [273, 274]. The underlying mechanisms are still poorly understood and only few studies have analyzed olfactory behavior in animal models of AD (Tg2576 [36], hTau [36]) and PD (*Pink*KO [275], α-Syn [276, 277], Bac Tg [278], VMAT2 [279]). Taken the susceptibility of the olfactory system to early molecular changes occurring in dementia, olfactory functions could be employed to predict/monitor the onset of the cognitive symptoms in AD as well its progression.

9. Olfactory route for diagnostic and therapeutics

The advantage of nasal biopsies in investigating specific olfactory disorders and also related neurodegenerative pathologies is still debated. Several studies suggest that this surgical procedure might not be specific enough to be routinely adopted in identifying primary events which anticipate neurodegenerative diseases [280]. Nevertheless, both the accessibility and heterogeneous cytoarchitecture of the olfactory neuroepithelium, make this specimen valuable for molecular diagnosis of neurological diseases [281]. Furthermore, the increasing precision and accuracy in obtaining nasal biopsies through laser surgery render this procedure safe, fast and with no major consequences, due to the constant neurogenesis occurring in the OE [282]. Nasal biopsies can be employed to detect aberrant misfolded proteins (Aβ, p-Tau, α-Syn, PrP, etc.,), produced by the OSNs, reflecting early neural network imbalances in the asymptomatic phase of different neurological pathologies. Furthermore, the stem cells population residing in the olfactory mucosa is a relevant source of biological material for diagnosing genetic modification related to neurological diseases, performing *in-vitro* pharmacology assays and possibly regenerative therapies after trauma. Thus, nasal mucosa biopsies constitute a useful tool in recognizing susceptible subjects with early subclinical neurodegenerative processes and introduce them well in advance to therapeutics or new medical trials. Sampling of the mucosa has been previously employed in the diagnosis of genetic variants in schizophrenia [71] and as experimental tool to investigate mechanisms underlying a variety of neurological disorders (ranging from schizophrenia, ASD, Rett syndrome, bipolar disorders to

Alzheimer's disease) [71]. Finally, nasal secretions may be also a valuable liquid biopsy to perform longitudinal monitoring of pathological profiles in the progression of AD [283, 284]. Besides the accessibility of the olfactory system for diagnosing brain health, intranasal (IN) drug delivery offers great potential for brain targeting through by-passing the BBB [285]. IN delivery is currently approved for systemic drugs for a wide range of indications, including hormone replacement therapy, osteoporosis, migraine, prostate cancer, and influenza vaccine [286]. Approved CNS applications include IN administration of opioids for chronic cancer pain (fentanyl, buprenorphine and morphine) [287] based on their small molecular weight (200–400 Daltons) and their rapid onset. Repurposing of IN insulin, approved for Diabetes I, is being investigated for the treatment of Insulin hypometabolism in dementia [288]. So far, the clinical studies have demonstrated that IN insulin can revert the cognitive symptoms and reduce the amyloid load in both MCI [289] and early stage AD [290, 291] (https://clinicaltrials.gov/). Nevertheless, the little understanding of the absorbance mechanisms through the nasal route and the biodistribution variability based on nasal secretion and local inflammatory processes are slowing down the development of intranasal CNS drug. Recent preclinical studies in rodents have underlined the potential of IN administration for CNS diseases, as this route shows superior pharmacodynamics [292], allows up to 20 folds higher drug bioavailability [293] and rapid transport through the rostral migratory stream to limbic structures [294]. Nevertheless, more clinical studies are needed to develop IN applications that have prognostic and diagnostic value.

10. Conclusions

Olfaction is one of the most essential senses in mammals throughout life and appears to be a relevant readout for both peripheral and central neural processes. The research in the past 30 years has used mouse models to cast light on important cellular and molecular mechanisms governing odor specification in the olfactory neuroepithelium and olfactory bulb and signal encoding in the cerebral cortex. During the same period, a bulk of clinical studies reported a strong association between many neurological diseases and olfactory deficits, suggesting that olfactory activity can sentinel subtle changes in key brain areas connected to the olfactory system. Nevertheless, the processes underlying this quite ubiquitous phenotypical dysfunction are poorly understood. Indeed, despite the clinical evidence from patients, relevant clinical models of neurological diseases have been rarely tested to unravel the basis of olfactory alteration. We believe that this field needs to close the gap between bench-side and bed-side research to devise better diagnostic and therapeutic strategies, which can exploit the accessibility and non-invasiveness of this cranial nerve.

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Conflict of interests

The authors declare no conflict of interests.

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References

[1] Wilson DA, Kadohisa M, Fletcher ML. Cortical contributions to olfaction: Plasticity and perception. Seminars in Cell & Developmental Biology. 2006;**17**:462-470

[2] Laing DG, Doty RL, Breipohl W. The Human Sense of Smell. Springer Science & Business Media; 2012

[3] Murray RC, Navi D, Fesenko J, Lander AD, Calof AL. Widespread defects in the primary olfactory pathway caused by loss of Mash1 function. The Journal of Neuroscience. 2003;**23**:1769-1780

[4] Treloar H, Miller A Ray A, Greer C. Development of the olfactory system. In: Menini A, editor. The Neurobiology of Olfaction. Vol. 20092457. CRC Press; 2009. pp. 131-155

[5] de Castro F. Wiring olfaction: The cellular and molecular mechanisms that guide the development of synaptic connections from the nose to the cortex. Frontiers in Neuroscience. 2009;**3**:52

[6] Sarnat HB, Yu W. Maturation and dysgenesis of the human olfactory bulb. Brain Pathology. 2016;**26**:301-318

[7] Walker WF, Liem KF. Functional Anatomy of the Vertebrates: An Evolutionary Perspective. Saunders College Pub.; 1994

[8] Miller SS, Spear NE. Mere odor exposure learning in the rat neonate immediately after birth and 1 day later. Developmental Psychobiology. 2010;**52**:343-351

[9] Miller SS, Spear NE. Olfactory learning in the rat neonate soon after birth. Developmental Psychobiology. 2008;**50**:554-565

[10] Hugill K. The senses of touch and olfaction in early mother–infant interaction. British Journal of Midwifery. 2015;**23**:238-243

[11] Miller SS, Spear NE. Olfactory learning in the rat immediately after birth: Unique salience of first odors. Developmental Psychobiology. 2009;**51**:488-504

[12] Moberg PJ et al. Meta-analysis of olfactory function in schizophrenia, first-degree family members, and youths at-risk for psychosis. Schizophrenia Bulletin. 2014;**40**:50-59

[13] Turetsky BI, Hahn C-G, Borgmann-Winter K, Moberg PJ. Scents and nonsense: Olfactory dysfunction in schizophrenia. Schizophrenia Bulletin. 2009;**35**:1117-1131

[14] Doty RL, Kamath V. The influences of age on olfaction: A review. Frontiers in Psychology. 2014;**5**:20

[15] Devanand DP et al. Olfactory deficits in patients with mild cognitive impairment predict Alzheimer's disease at follow-up. The American Journal of Psychiatry. 2000;**157**:1399-1405

[16] Conti MZ et al. Odor identification deficit predicts clinical conversion from mild cognitive impairment to dementia due to Alzheimer's disease. Archives of Clinical Neuropsychology. 2013;**28**:391-399

[17] Doty RL. Olfaction in Parkinson's disease and related disorders. Neurobiology of Disease. 2012;**46**:527-552

[18] Bakker K, Catroppa C, Anderson V. Anosmia and olfactory outcomes following paediatric traumatic brain injury. Brain Injury. 2016;**30**:191-198

[19] Schofield PW, Moore TM, Gardner A. Traumatic brain injury and olfaction: A systematic review. Frontiers in Neurology. 2014 Jan 22;**5**:5

[20] Álvarez-Camacho M, Gonella S, Campbell S, Scrimger RA, Wismer WV. A systematic review of smell alterations after radiotherapy for head and neck cancer. Cancer Treatment Reviews. 2017;**54**:110-121

[21] Riva G, Sensini M, Corvino A, Pecorari G, Garzaro M. Smell and taste impairment after total laryngectomy. The Annals of Otology, Rhinology, and Laryngology. 2017;**126**:548-554

[22] Gu X et al. Chemosensory functions for pulmonary neuroendocrine cells. American Journal of Respiratory Cell and Molecular Biology. 2014;**50**:637-646

[23] Spotten LE et al. Subjective and objective taste and smell changes in cancer. Annals of Oncology. 2017;**28**:969-984

[24] Rahayel S, Frasnelli J, Joubert S. The effect of Alzheimer's disease and Parkinson's disease on olfaction: A meta-analysis. Behavioural Brain Research. 2012;**231**:60-74

[25] Knupfer L, Spiegel R. Differences in olfactory test performance between normal aged, Alzheimer and vascular type dementia individuals. International Journal of Geriatric Psychiatry. 1986;**1**:3-14

[26] Doty RL, Reyes PF, Gregor T. Presence of both odor identification and detection deficits in Alzheimer's disease. Brain Research Bulletin. 1987;**18**:597-600

[27] Doty RL. The olfactory vector hypothesis of neurodegenerative disease: Is it viable? Annals of Neurology. 2008;**63**:7-15

[28] Mesholam RI, Moberg PJ, Mahr RN, Doty RL. Olfaction in neurodegenerative disease. Archives of Neurology. 1998;**55**:84

[29] Doty RL, Shaman P, Kimmelman CP, Dann MS. University of pennsylvania smell identification test: A rapid quantitative olfactory function test for the clinic. Laryngoscope. 1984;**94**:176-178

[30] Larson J, Hoffman JS, Guidotti A, Costa E. Olfactory discrimination learning deficit in heterozygous reeler mice. Brain Research. 2003;**971**:40-46

[31] Lehmkuhl AM, Dirr ER, Fleming SM. Olfactory assays for mouse models of neurodegenerative disease. Journal of Visualized Experiments. 2014 Aug 25;(90):e51804

[32] Witt RM, Galligan MM, Despinoy JR, Segal R. Olfactory behavioral testing in the adult mouse. Journal of Visualized Experiments. 2009 Jan 28;(23):pii: 949. DOI: 10.3791/949

[33] Kumar DKV et al. Amyloid-peptide protects against microbial infection in mouse and worm models of Alzheimers disease. Science Translational Medicine. 2016;**8**:340ra72-340ra72

[34] Arnold SE et al. Olfactory epithelium amyloid-beta and paired helical filament-tau pathology in Alzheimer disease. Annals of Neurology. 2010;**67**:462-469

[35] Crino PB et al. Beta-amyloid peptide and amyloid precursor proteins in olfactory mucosa of patients with Alzheimer's disease, Parkinson's disease, and Down syndrome. The Annals of Otology, Rhinology, and Laryngology. 1995;**104**:655-661

[36] Wesson DW, Levy E, Nixon RA, Wilson DA. Olfactory dysfunction correlates with amyloid- burden in an Alzheimer's disease mouse model. Journal of Neuroscience. 2010;**30**:505-514

[37] Zanusso G et al. Detection of pathologic prion protein in the olfactory epithelium in sporadic Creutzfeldt–Jakob disease. The New England Journal of Medicine. 2003;**348**:711-719

[38] Blanco LP, Evans ML, Smith DR, Badtke MP, Chapman MR. Diversity, biogenesis and function of microbial amyloids. Trends in Microbiology. 2012;**20**:66-73

[39] Hill JM, Lukiw WJ. Microbial-generated amyloids and Alzheimer's disease (AD). Frontiers in Aging Neuroscience. 2015;**7**:9

[40] Rey NL, Wesson DW, Brundin P. The olfactory bulb as the entry site for prion-like propagation in neurodegenerative diseases. Neurobiology of Disease. 2018 Jan;**109**(Pt B): 226-248. DOI: 10.1016/j.nbd.2016.12.013

[41] Arriagada PV, Louis DN, Hedley-Whyte ET, Hyman BT. Neurofibrillary tangles and olfactory dysgenesis. Lancet. 1991;**337**:559

[42] Attems J, Walker L, Jellinger KA. Olfactory bulb involvement in neurodegenerative diseases. Acta Neuropathologica. 2014;**127**:459-475

[43] Serizawa S, Miyamichi K, Sakano H. One neuron-one receptor rule in the mouse olfactory system. Trends in Genetics. 2004;**20**:648-653

[44] Buck L, Axel R. A novel multigene family may encode odorant receptors: A molecular basis for odor recognition. Cell. 1991;**65**:175-187

[45] Zhang X, Zhang X, Firestein S. Comparative genomics of odorant and pheromone receptor genes in rodents. Genomics. 2007;**89**:441-450

[46] Fleischer J, Breer H, Strotmann J. Mammalian olfactory receptors. Frontiers in Cellular Neuroscience. 2009;**3**:9

[47] Mori K, Nagao H, Yoshihara Y. The olfactory bulb: Coding and processing of odor molecule information. Science. 1999;**286**:711-715

[48] Mori K, Yoshihara Y. Molecular recognition and olfactory processing in the mammalian olfactory system. Progress in Neurobiology. 1995;**45**:585-619

[49] Mori K. Maps of odorant molecular features in the mammalian olfactory bulb. Physiological Reviews. 2006;**86**:409-433

[50] Lledo P-M, Saghatelyan A, Lemasson M. Inhibitory interneurons in the olfactory bulb: From development to function. The Neuroscientist. 2004;**10**:292-303

[51] Yoshihara S-I, Takahashi H, Tsuboi A. Molecular mechanisms regulating the dendritic development of Newborn olfactory bulb interneurons in a sensory experience-dependent manner. Frontiers in Neuroscience. 2016 Jan 12;**9**:514

[52] Lledo P-M, Merkle FT, Alvarez-Buylla A. Origin and function of olfactory bulb interneuron diversity. Trends in Neurosciences. 2008;**31**:392-400

[53] Angelo K, Margrie TW. Population diversity and function of hyperpolarization-activated current in olfactory bulb mitral cells. Scientific Reports. 2011;**1**:50

[54] Burton SD. Inhibitory circuits of the mammalian main olfactory bulb. Journal of Neurophysiology. 2017;**118**:2034-2051

[55] Rapid feedforward inhibition and asynchronous excitation regulate granule cell activity in the mammalian main olfactory bulb. The Journal of Neuroscience. 2015 Oct 21;**35**(42):14103-14122. DOI: 10.1523/JNEUROSCI.0746-15.2015

[56] Záborszky L, Carlsen J, Brashear HR, Heimer L. Cholinergic and GABAergic afferents to the olfactory bulb in the rat with special emphasis on the projection neurons in the nucleus of the horizontal limb of the diagonal band. The Journal of Comparative Neurology. 1986;**243**:488-509

[57] Petzold GC, Hagiwara A, Murthy VN. Serotonergic modulation of odor input to the mammalian olfactory bulb. Nature Neuroscience. 2009;**12**:784-791

[58] Shipley MT, Halloran FJ, de la Torre J. Surprisingly rich projection from locus coeruleus to the olfactory bulb in the rat. Brain Research. 1985;**329**:294-299

[59] Kratskin I, Belluzzi O. Anatomy and neurochemistry of the olfactory bulb. In: Handbook of Olfaction and Gustation. New York, NY: Marcel Dekker. 2003. pp. 139-164

[60] Good KP, Sullivan RL. Olfactory function in psychotic disorders: Insights from neuroimaging studies. World Journal of Psychiatry. 2015;**5**:210-221

[61] Atanasova B et al. Olfaction: A potential cognitive marker of psychiatric disorders. Neuroscience and Biobehavioral Reviews. 2008;**32**:1315-1325

[62] Zatorre RJ, Jones-Gotman M, Evans AC, Meyer E. Functional localization and lateralization of human olfactory cortex. Nature. 1992;**360**:339-340

[63] Savic I, Gulyas B, Larsson M, Roland P. Olfactory functions are mediated by parallel and hierarchical processing. Neuron. 2000;**26**:735-745

[64] Buonviso N, Revial MF, Jourdan F. The projections of mitral cells from small local regions of the olfactory bulb: An anterograde tracing study using PHA-L (*Phaseolus vulgaris* Leucoagglutinin). The European Journal of Neuroscience. 1991;**3**:493-500

[65] Haberly LB. Parallel-distributed processing in olfactory cortex: New insights from morphological and physiological analysis of neuronal circuitry. Chemical Senses. 2001; **26**:551-576

[66] Hahn C-G et al. In vivo and in vitro neurogenesis in human olfactory epithelium. The Journal of Comparative Neurology. 2005;**483**:154-163

[67] DeHamer MK, Guevara JL, Hannon K, Olwin BB, Calof AL. Genesis of olfactory receptor neurons in vitro: Regulation of progenitor cell divisions by fibroblast growth factors. Neuron. 1994;**13**:1083-1097

[68] Doetsch F. The glial identity of neural stem cells. Nature Neuroscience. 2003;**6**:1127-1134

[69] Beites CL, Kawauchi S, Crocker CE, Calof AL. Identification and molecular regulation of neural stem cells in the olfactory epithelium. Experimental Cell Research. 2005; **306**:309-316

[70] Goldstein BJ, Schwob JE. Analysis of the globose basal cell compartment in rat olfactory epithelium using GBC-1, a new monoclonal antibody against globose basal cells. The Journal of Neuroscience. 1996;**16**:4005-4016

[71] Lavoie J, Sawa A, Ishizuka K. Application of olfactory tissue and its neural progenitors to schizophrenia and psychiatric research. Current Opinion in Psychiatry. 2017;**30**:176-183

[72] Costanzo RM, Yagi S. Olfactory epithelial transplantation: Possible mechanism for restoration of smell. Current Opinion in Otolaryngology & Head and Neck Surgery. 2011;**19**:54-57

[73] Lim DA, Alvarez-Buylla A. The adult ventricular-subventricular zone (V-SVZ) and olfactory bulb (OB) neurogenesis. Cold Spring Harbor Perspectives in Biology. 2016;**8**:a018820

[74] Sanai N et al. Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration. Nature. 2004;**427**:740-744

[75] Jones DT, Reed RR. Golf: An olfactory neuron specific-G protein involved in odorant signal transduction. Science. 1989;**244**:790-795

[76] Bakalyar HA, Reed RR. Identification of a specialized adenylyl cyclase that may mediate odorant detection. Science. 1990;**250**:1403-1406

[77] Chen C, Nakamura T, Koutalos Y. Cyclic AMP diffusion coefficient in frog olfactory cilia. Biophysical Journal. 1999;**76**:2861-2867

[78] Dhallan RS, Yau KW, Schrader KA, Reed RR. Primary structure and functional expression of a cyclic nucleotide-activated channel from olfactory neurons. Nature. 1990;**347**:184-187

[79] Gonzalez-Silva C et al. Ca^{2-} activated Cl− channels of the ClCa family express in the cilia of a subset of rat olfactory sensory neurons. PLoS One. 2013;**8**:e69295

[80] Mura CV, Delgado R, Delgado MG, Restrepo D, Bacigalupo J. A CLCA regulatory protein present in the chemosensory cilia of olfactory sensory neurons induces a Ca^{2-} activated Cl^{-} current when transfected into HEK293. BMC Neuroscience. 2017 Aug 11;**18**(1):61

[81] Kurahashi T, Menini A. Mechanism of odorant adaptation in the olfactory receptor cell. Nature. 1997;**385**:725-729

[82] Chen T-Y, Takeuchi H, Kurahashi T. Odorant inhibition of the olfactory cyclic nucleotide-gated channel with a native molecular assembly. The Journal of General Physiology. 2006;**128**:365-371

[83] Takeuchi H, Kurahashi T. Identification of second messenger mediating signal transduction in the olfactory receptor cell. The Journal of General Physiology. 2003;**122**:557-567

[84] Dudley CA, Moss RL. Electrophysiological evidence for glutamate as a vomeronasal receptor cell neurotransmitter. Brain Research. 1995;**675**:208-214

[85] Aroniadou-Anderjaska V, Zhou FM, Priest CA, Ennis M, Shipley MT. Tonic and synaptically evoked presynaptic inhibition of sensory input to the rat olfactory bulb via GABA(B) heteroreceptors. Journal of Neurophysiology. 2000;**84**:1194-1203

[86] Pírez N, Wachowiak M. In vivo modulation of sensory input to the olfactory bulb by tonic and activity-dependent presynaptic inhibition of receptor neurons. The Journal of Neuroscience. 2008;**28**:6360-6371

[87] Huang L, Garcia I, Jen H-I, Arenkiel BR. Reciprocal connectivity between mitral cells and external plexiform layer interneurons in the mouse olfactory bulb. Frontiers in Neural Circuits. 2013;**7**:32

[88] Isaacson JS, Strowbridge BW. Olfactory reciprocal synapses: Dendritic signaling in the CNS. Neuron. 1998;**20**:749-761

[89] Best AR, Wilson DA. Coordinate synaptic mechanisms contributing to olfactory cortical adaptation. The Journal of Neuroscience. 2004;**24**:652-660

[90] Chung S, Li X, Nelson SB. Short-term depression at thalamocortical synapses contributes to rapid adaptation of cortical sensory responses in vivo. Neuron. 2002;**34**:437-446

[91] Schaal B. Olfaction in infants and children: Developmental and functional perspectives. Chemical Senses. 1988;**13**:145-190

[92] Schaal B, Marlier L, Soussignan R. Human foetuses learn odours from their pregnant mother's diet. Chemical Senses. 2000;**25**:729-737

[93] Varendi H, Porter RH. Breast odour as the only maternal stimulus elicits crawling towards the odour source. Acta Paediatrica. 2001;**90**:372-375

[94] Varendi H, Porter RH, Winberg J. Does the newborn baby find the nipple by smell? Lancet. 1994;**344**:989-990

[95] Stoddart DM, Michael Stoddart D. Detection of food. In The Ecology of Vertebrate Olfaction. Springer Verlag. 1980. pp. 63-84

[96] Brennan PA, Keverne EB. Neural mechanisms of mammalian olfactory learning. Progress in Neurobiology. 1997;**51**:457-481

[97] Takahashi LK, Nakashima BR, Hong H, Watanabe K. The smell of danger: A behavioral and neural analysis of predator odor-induced fear. Neuroscience and Biobehavioral Reviews. 2005;**29**:1157-1167

[98] Dielenberg RA, McGregor IS. Defensive behavior in rats towards predatory odors: A review. Neuroscience and Biobehavioral Reviews. 2001;**25**:597-609

[99] Green PA et al. Respiratory and olfactory turbinal size in canid and arctoid carnivorans. Journal of Anatomy. 2012;**221**:609-621

[100] Jacob S, McClintock MK, Zelano B, Ober C. Paternally inherited HLA alleles are associated with women's choice of male odor. Nature Genetics. 2002;**30**:175-179

[101] Penn DJ, Potts WK. The evolution of mating preferences and major histocompatibility complex genes. The American Naturalist. 1999;**153**:145-164

[102] Otto T, Cousens G, Herzog C. Behavioral and neuropsychological foundations of olfactory fear conditioning. Behavioural Brain Research. 2000;**110**:119-128

[103] Paschall GY, Davis M. Olfactory-mediated fear-potentiated startle. Behavioral Neuroscience. 2002;**116**:4-12

[104] Blozovski D, Cudennec A. Passive avoidance learning in the young rat. Developmental Psychobiology. 1980;**13**:513-518

[105] Parsons RG, Ressler KJ. Implications of memory modulation for post-traumatic stress and fear disorders. Nature Neuroscience. 2013;**16**:146-153

[106] Van Toller S, Kendal-Reed M. A possible protocognitive role for odor in human infant development. Brain and Cognition. 1995;**29**:275-293

[107] Chu S, Downes JJ. Odour-evoked autobiographical memories: Psychological investigations of proustian phenomena. Chemical Senses. 2000;**25**:111-116

[108] Willander J, Larsson M. Smell your way back to childhood: Autobiographical odor memory. Psychonomic Bulletin & Review. 2006;**13**:240-244

[109] Doty RL. On the protheticity of olfactory pleasantness and intensity. Perceptual and Motor Skills. 1997;**85**:1439-1449

[110] Nakano S, Ayabe-Kanamura S. The influence of olfactory contexts on the sequential rating of odor pleasantness. Perception. 2016;**46**:393-405

[111] Attems J, Walker L, Jellinger KA. Olfaction and aging: A mini-review. Gerontology. 2015; **61**:485-490

[112] Choudhury ES, Moberg P, Doty RL. Influences of age and sex on a microencapsulated odor memory test. Chemical Senses. 2003;**28**:799-805

[113] Loo AT, Youngentob SL, Kent PF, Schwob JE. The aging olfactory epithelium: Neurogenesis, response to damage, and odorant-induced activity. International Journal of Developmental Neuroscience. 1996;**14**:881-900

[114] Naessen R. An enquiry on the morphological characteristics and possible changes with age in the olfactory region of man. Acta Oto-Laryngologica. 1971;**71**:49-62

[115] Hummel T et al. Correlation between olfactory bulb volume and olfactory function in children and adolescents. Experimental Brain Research. 2011;**214**:285-291

[116] Cai Y et al. An age-related axon terminal pathology around the first olfactory relay that involves amyloidogenic protein overexpression without plaque formation. Neuroscience. 2012;**215**:160-173

[117] Wilson RS, Arnold SE, Schneider JA, Tang Y, Bennett DA. The relationship between cerebral Alzheimer's disease pathology and odour identification in old age. Journal of Neurology, Neurosurgery, and Psychiatry. 2007;**78**:30-35

[118] Gopinath B, Sue CM, Kifley A, Mitchell P. The association between olfactory impairment and total mortality in older adults. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2012;**67**:204-209

[119] Wilson RS, Yu L, Bennett DA. Odor identification and mortality in old age. Chemical Senses. 2011;**36**:63-67

[120] Muller-Schwarze, D. Chemical Ecology of Vertebrates. Cambridge University Press; 2006

[121] Martzke JS, Kopala LC, Good KP. Olfactory dysfunction in neuropsychiatric disorders: Review and methodological considerations. Biological Psychiatry. 1997;**42**:721-732

[122] Jones-Gotman M, Zatorre RJ. Olfactory identification deficits in patients with focal cerebral excision. Neuropsychologia. 1988;**26**:387-400

[123] Lawton M et al. Equating scores of the University of Pennsylvania Smell Identification Test and Sniffin' sticks test in patients with Parkinson's disease. Parkinsonism & Related Disorders. 2016;**33**:96-101

[124] Weierstall R, Pause BM. Development of a 15-item odour discrimination test (Düsseldorf odour discrimination test). Perception. 2012;**41**:193-203

[125] Wilson RS, Arnold SE, Tang Y, Bennett DA. Odor identification and decline in different cognitive domains in old age. Neuroepidemiology. 2006;**26**:61-67

[126] Doty RL. Olfactory dysfunction and its measurement in the clinic. World Journal of Otorhinolaryngology-Head and Neck Surgery. 2015;**1**:28-33

[127] Ciofalo A et al. Olfactory dysfunction in acute rhinosinusitis: Intranasal sodium hyaluronate as adjuvant treatment. European Archives of Oto-Rhino-Laryngology. 2017; **274**:803-808

[128] Klimek L, Eggers G. Olfactory dysfunction in allergic rhinitis is related to nasal eosinophilic inflammation. The Journal of Allergy and Clinical Immunology. 1997;**100**:158-164

[129] Raviv JR, Kern RC. Chronic rhinosinusitis and olfactory dysfunction. In: Hummel T, Welge-Lüssen A, editors. Taste and Smell. Vol. 63. Karger; 2006. pp. 108-124

[130] Kohli P et al. The prevalence of olfactory dysfunction in chronic rhinosinusitis. Laryngoscope. 2017;**127**:309-320

[131] Rombaux P, Huart C, Levie P, Cingi C, Hummel T. Olfaction in chronic rhinosinusitis. Current Allergy and Asthma Reports. 2016;**16**

[132] Sánchez-Vallecillo MV, Fraire ME, Baena-Cagnani C, Zernotti ME. Olfactory dysfunction in patients with chronic rhinosinusitis. International Journal of Otolaryngology. 2012;**2012**:1-5

[133] Holbrook EH, Leopold DA. An updated review of clinical olfaction. Current Opinion in Otolaryngology & Head and Neck Surgery. 2006;**14**:23-28

[134] Seiden AM, Duncan HJ. The diagnosis of a conductive olfactory loss. Laryngoscope. 2001;**111**:9-14

[135] Mott AE, Leopold DA. Disorders in taste and smell. The Medical Clinics of North America. 1991;**75**:1321-1353

[136] Jafek BW, Moran DT, Eller PM, Rowley 3rd JC, Jafek TB. Steroid-dependent anosmia. Archives of Otolaryngology – Head & Neck Surgery. 1987;**113**:547-549

[137] Kern RC. Chronic sinusitis and anosmia: Pathologic changes in the olfactory mucosa. Laryngoscope. 2000;**110**:1071-1077

[138] Stevens MH. Steroid-dependent anosmia. Laryngoscope. 2001;**111**:200-203

[139] Robinson AM, Conley DB, Shinners MJ, Kern RC. Apoptosis in the aging olfactory epithelium. Laryngoscope. 2002;**112**:1431-1435

[140] El Rassi E et al. Sensitivity analysis and diagnostic accuracy of the brief smell identification test in patients with chronic rhinosinusitis. International Forum of Allergy Rhinology. 2016;**6**:287-292

[141] Soler ZM, Kohli P, Storck KA, Schlosser RJ. Olfactory impairment in chronic Rhinosinusitis using threshold, discrimination, and identification scores. Chemical Senses. 2016 Jul 28. pii: bjw080. DOI: 10.1093/chemse/bjw080

[142] Tsybikov NN, Egorova EV, Kuznik BI, Fefelova EV, Magen E. Neuron-specific enolase in nasal secretions as a novel biomarker of olfactory dysfunction in chronic rhinosinusitis. American Journal of Rhinology & Allergy. 2016;**30**:65-69

[143] Yasue M et al. Prevalence of sinusitis detected by magnetic resonance imaging in subjects with dementia or Alzheimer's disease. Current Alzheimer Research. 2015;**12**:1006-1011

[144] Kang J-H, Wu C-S, Keller JJ, Lin H-C. Chronic rhinosinusitis increased the risk of stroke: A 5-year follow-up study. Laryngoscope. 2013;**123**:835-840

[145] Wu C-W, Chao P-Z, Hao W-R, Liou T-H, Lin H-W. Risk of stroke among patients with rhinosinusitis: A population-based study in Taiwan. American Journal of Rhinology & Allergy. 2012;**26**:278-282

[146] Bansal M et al. Radiation related morbidities and their impact on quality of life in head and neck cancer patients receiving radical radiotherapy. Quality of Life Research. 2004;**13**:481-488

[147] Caldas ASC et al. Gustatory and olfactory dysfunction in laryngectomized patients. Brazilian Journal of Otorhinolaryngology. 2013;**79**:546-554

[148] Kalbe B et al. Helional-induced activation of human olfactory receptor 2J3 promotes apoptosis and inhibits proliferation in a non-small-cell lung cancer cell line. European Journal of Cell Biology. 2017;**96**:34-46

[149] Maßberg D et al. The activation of OR51E1 causes growth suppression of human prostate cancer cells. Oncotarget. 2016;**7**:48231-48249

[150] Sanz G et al. Promotion of cancer cell invasiveness and metastasis emergence caused by olfactory receptor stimulation. PLoS One. 2014;**9**:e85110

[151] Griffin CA, Kafadar KA, Pavlath GK. MOR23 promotes muscle regeneration and regulates cell adhesion and migration. Developmental Cell. 2009;**17**:649-661

[152] Pluznick JL et al. Olfactory receptor responding to gut microbiota-derived signals plays a role in renin secretion and blood pressure regulation. Proceedings of the National Academy of Sciences of the United States of America. 2013;**110**:4410-4415

[153] Neuhaus EM et al. Activation of an olfactory receptor inhibits proliferation of prostate cancer cells. The Journal of Biological Chemistry. 2009;**284**:16218-16225

[154] Rodriguez M et al. PSGR promotes prostatic intraepithelial neoplasia and prostate cancer xenograft growth through NF-κB. Oncogene. 2014;**3**:e114

[155] Ranzani M et al. Revisiting olfactory receptors as putative drivers of cancer. Wellcome Open Research. 2017;**2**:9

[156] Bernhardson B-M, Tishelman C, Rutqvist LE. Self-reported taste and smell changes during cancer chemotherapy. Supportive Care in Cancer. 2008;**16**:275-283

[157] Hong JH et al. Taste and odor abnormalities in cancer patients. The Journal of Supportive Oncology. 2009;**7**:58-65

[158] Kamath S, Booth P, Lad TE, Kohrs MB, McGuire WP. Taste thresholds of patients with cancer of the esophagus. Cancer. 1983;**52**:386-389

[159] Bijland LR, Bomers MK, Smulders YM. Smelling the diagnosis: A review on the use of scent in diagnosing disease. The Netherlands Journal of Medicine. 2013;**71**:300-307

[160] Jezierski T, Walczak M, Ligor T, Rudnicka J, Buszewski B. Study of the art: Canine olfaction used for cancer detection on the basis of breath odour. Perspectives and limitations. Journal of Breath Research. 2015;**9**:027001

[161] Brooks SW, Moore DR, Marzouk EB, Glenn FR, Hallock RM. Canine olfaction and electronic nose detection of volatile organic compounds in the detection of cancer: A review. Cancer Investigation. 2015;**33**:411-419

[162] Amundsen T, Sundstrøm S, Buvik T, Gederaas OA, Haaverstad R. Can dogs smell lung cancer? First study using exhaled breath and urine screening in unselected patients with suspected lung cancer. Acta Oncologica. 2014;**53**:307-315

[163] Horvath G, Andersson H, Nemes S. Cancer odor in the blood of ovarian cancer patients: A retrospective study of detection by dogs during treatment, 3 and 6 months afterward. BMC Cancer. 2013;**13**:396

[164] McCulloch M et al. Diagnostic accuracy of canine scent detection in early- and late-stage lung and breast cancers. Integrative Cancer Therapies. 2006;**5**:30-39

[165] Sonoda H et al. Colorectal cancer screening with odour material by canine scent detection. Gut. 2011;**60**:814-819

[166] Taverna G et al. Olfactory system of highly trained dogs detects prostate cancer in urine samples. The Journal of Urology. 2015;**193**:1382-1387

[167] Banks R, Selby P. Clinical proteomics—Insights into pathologies and benefits for patients. Lancet. 2003;**362**:415-416

[168] Carpagnano GE, Foschino-Barbaro MP, Resta O, Gramiccioni E, Carpagnano F. Endothelin-1 is increased in the breath condensate of patients with non-small-cell lung cancer. Oncology. 2004;**66**:180-184

[169] Okano T et al. Plasma proteomics of lung cancer by a linkage of multi-dimensional liquid chromatography and two-dimensional difference gel electrophoresis. Proteomics. 2006;**6**:3938-3948

[170] Phillips M et al. Volatile organic compounds in breath as markers of lung cancer: A cross-sectional study. Lancet. 1999;**353**:1930-1933

[171] Asimakopoulos AD et al. Prostate cancer diagnosis through electronic nose in the urine headspace setting: A pilot study. Prostate Cancer and Prostatic Diseases. 2014;**17**:206-211

[172] Di Natale C et al. Lung cancer identification by the analysis of breath by means of an array of non-selective gas sensors. Biosensors & Bioelectronics. 2003;**18**:1209-1218

[173] Krilaviciute A et al. Detection of cancer through exhaled breath: A systematic review. Oncotarget. 2015;**6**:38643-38657

[174] Peled N et al. Use of a nanoparticle-based artificial olfactory system, NaNose, to distinguish malignant from benign pulmonary nodules. Journal of Clinical Orthodontics. 2010;**28**:10521-10521

[175] Peng G et al. Detection of lung, breast, colorectal, and prostate cancers from exhaled breath using a single array of nanosensors. British Journal of Cancer. 2010;**103**:542-551

[176] Doty RL. Studies of human olfaction from the University of Pennsylvania Smell and Taste Center. Chemical Senses. 1997;**22**:565-586

[177] Hummel T, Landis BN and Hüttenbrink K-B. Smell and taste disorders. GMS Current Topics in Otorhinolaryngology, Head and Neck Surgery. 2011;**10**:Doc04

[178] Proskynitopoulos PJ, Stippler M, Kasper EM. Post-traumatic anosmia in patients with mild traumatic brain injury (mTBI): A systematic and illustrated review. Surgical Neurology International. 2016;**7**:S263-S275

[179] Sumner D. Post-traumatic anosmia. Brain. 1964;**87**:107-120

[180] Haxel BR, Grant L, Mackay-Sim A. Olfactory dysfunction after head injury. The Journal of Head Trauma Rehabilitation. 2008;**23**:407-413

[181] Doty RL et al. Olfactory dysfunction in patients with head trauma. Archives of Neurology. 1997;**54**:1131-1140

[182] Reden J et al. Recovery of olfactory function following closed head injury or infections of the upper respiratory tract. Archives of Otolaryngology – Head & Neck Surgery. 2006; **132**:265-269

[183] Costanzo RM. Regeneration and rewiring the olfactory bulb. Chemical Senses. 2005; **30**(Suppl 1):i133-i134

[184] Levin HS, High WM, Eisenberg HM. Impairment of olfactory recognition after closed head injury. Brain. 1985;**108**(Pt 3):579-591

[185] van Damme PA, Freihofer HP. Disturbances of smell and taste after high central midface fractures. Journal of Cranio-Maxillo-Facial Surgery. 1992;**20**:248-250

[186] Fujii M, Fukazawa K, Takayasu S, Sakagami M. Olfactory dysfunction in patients with head trauma. Auris Nasus Larynx. 2002;**29**:35-40

[187] Jiang R-S et al. Steroid treatment of posttraumatic anosmia. European Archives of Oto-Rhino-Laryngology. 2010;**267**:1563-1567

[188] Ikeda K, Sakurada T, Takasaka T, Okitsu T, Yoshida S. Anosmia following head trauma: Preliminary study of steroid treatment. The Tohoku Journal of Experimental Medicine. 1995;**177**:343-351

[189] Pełka-Wysiecka J et al. Odors identification differences in deficit and nondeficit schizophrenia. Pharmacological Reports. 2016;**68**:390-395

[190] Turetsky BI, Moberg PJ. An odor-specific threshold deficit implicates abnormal intracellular cyclic AMP signaling in schizophrenia. The American Journal of Psychiatry. 2009;**166**:226-233

[191] Brewer WJ, Pantelis C. Olfactory sensitivity: Functioning in schizophrenia and implications for understanding the nature and progression of psychosis. Vitamins and Hormones. 2010;**83**:305-329

[192] Robabeh S, Mohammad JM, Reza A, Mahan B. The evaluation of olfactory function in patients with schizophrenia. Global Journal of Health Science. 2015;**7**:319-330

[193] Auster TL, Cohen AS, Callaway DA, Brown LA. Objective and subjective olfaction across the schizophrenia spectrum. Psychiatry. 2014;**77**:57-66

[194] Turetsky BI et al. Physiologic impairment of olfactory stimulus processing in schizophrenia. Biological Psychiatry. 2003;**53**:403-411

[195] Compton MT, Chien VH. No association between psychometrically-determined schizotypy and olfactory identification ability in first-degree relatives of patients with schizophrenia and non-psychiatric controls. Schizophrenia Research. 2008;**100**:216-223

[196] Kamath V, Bedwell JS. Olfactory identification performance in individuals with psychometrically-defined schizotypy. Schizophrenia Research. 2008;**100**:212-215

[197] Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. 'Sniffin' sticks': Olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chemical Senses. 1997;**22**:39-52

[198] Moberg PJ et al. Impairment of odor hedonics in men with schizophrenia. The American Journal of Psychiatry. 2003;**160**:1784-1789

[199] Doop ML, Park S. On knowing and judging smells: Identification and hedonic judgment of odors in schizophrenia. Schizophrenia Research. 2006;**81**:317-319

[200] Kiparizoska S, Ikuta T. Disrupted olfactory integration in schizophrenia: Functional connectivity study. The International Journal of Neuropsychopharmacology. 2017; **20**:740-746

[201] Turetsky BI, Hahn C-G, Arnold SE, Moberg PJ. Olfactory receptor neuron dysfunction in schizophrenia. Neuropsychopharmacology. 2009;**34**:767-774

[202] Borgmann-Winter KE et al. Altered G protein coupling in olfactory neuroepithelial cells from patients with schizophrenia. Schizophrenia Bulletin. 2016;**42**:377-385

[203] Arnold SE et al. Dysregulation of olfactory receptor neuron lineage in schizophrenia. Archives of General Psychiatry. 2001;**58**:829-835

[204] Watkins CC, Andrews SR. Clinical studies of neuroinflammatory mechanisms in schizophrenia. Schizophrenia Research. 2016;**176**:14-22

[205] Brown AS, Derkits EJ. Prenatal infection and schizophrenia: A review of epidemiologic and translational studies. The American Journal of Psychiatry. 2010;**167**:261-280

[206] Nakazawa K, Jeevakumar V, Nakao K. Spatial and temporal boundaries of NMDA receptor hypofunction leading to schizophrenia. NPJ Schizophrenia. 2017;**3**:7

[207] Lagier S et al. GABAergic inhibition at dendrodendritic synapses tunes gamma oscillations in the olfactory bulb. Proceedings of the National Academy of Sciences of the United States of America. 2007;**104**:7259-7264

[208] Egger V, Urban NN. Dynamic connectivity in the mitral cell-granule cell microcircuit. Seminars in Cell & Developmental Biology. 2006;**17**:424-432

[209] Gire DH, Schoppa NE. Control of on/off glomerular signaling by a local GABAergic microcircuit in the olfactory bulb. Journal of Neuroscience. 2009;**29**:13454-13464

[210] Hong SE et al. Autosomal recessive lissencephaly with cerebellar hypoplasia is associated with human RELN mutations. Nature Genetics. 2000;**26**:93-96

[211] Brosda J, Dietz F, Koch M. Impairment of cognitive performance after reelin knockdown in the medial prefrontal cortex of pubertal or adult rats. Neurobiology of Disease. 2011;**44**:239-247

[212] Sui L, Wang Y, Ju L-H, Chen M. Epigenetic regulation of reelin and brain-derived neurotrophic factor genes in long-term potentiation in rat medial prefrontal cortex. Neurobiology of Learning and Memory. 2012;**97**:425-440

[213] Imai H et al. Dorsal forebrain-specific deficiency of Reelin-Dab1 signal causes Behavioral abnormalities related to psychiatric disorders. Cerebral Cortex. 2017;**27**:3485-3501

[214] Guidotti A et al. Decrease in reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder: A postmortem brain study. Archives of General Psychiatry. 2000;**57**:1061-1069

[215] Botella-López A et al. Reelin expression and glycosylation patterns are altered in Alzheimer's disease. Proceedings of the National Academy of Sciences of the United States of America. 2006;**103**:5573-5578

[216] Fehér Á, Juhász A, Pákáski M, Kálmán J, Janka Z. Genetic analysis of the RELN gene: Gender specific association with Alzheimer's disease. Psychiatry Research. 2015; **230**:716-718

[217] Seripa D et al. The RELN locus in Alzheimer's disease. Journal of Alzheimer's Disease. 2008;**14**:335-344

[218] Escanilla O, Yuhas C, Marzan D, Linster C. Dopaminergic modulation of olfactory bulb processing affects odor discrimination learning in rats. Behavioral Neuroscience. 2009;**123**:828-833

[219] Galle SA, Courchesne V, Mottron L, Frasnelli J. Olfaction in the autism spectrum. Perception. 2013;**42**:341-355

[220] Tonacci A et al. Olfaction in autism spectrum disorders: A systematic review. Child Neuropsychology. 2015;**23**:1-25

[221] Katayama Y et al. CHD8 haploinsufficiency results in autistic-like phenotypes in mice. Nature. 2016;**537**:675-679

[222] Cho H et al. Changes in brain metabolic connectivity underlie autistic-like social deficits in a rat model of autism spectrum disorder. Scientific Reports. 2017;**7**

[223] Huang T-N, Hsueh Y-P. Brain-specific transcriptional regulator T-brain-1 controls brain wiring and neuronal activity in autism spectrum disorders. Frontiers in Neuroscience. 2015;**9**:406

[224] Canitano R, Pallagrosi M. Autism spectrum disorders and schizophrenia spectrum disorders: Excitation/inhibition imbalance and developmental trajectories. Frontiers in Psychiatry. 2017;**8**:69

[225] Gao R, Penzes P. Common mechanisms of excitatory and inhibitory imbalance in schizophrenia and autism spectrum disorders. Current Molecular Medicine. 2015;**15**:146-167

[226] Moberg PJ, Doty RL. Olfactory function in Huntington's disease patients and at-risk offspring. The International Journal of Neuroscience. 1997;**89**:133-139

[227] Lemiere J. Huntington's Disease: Early Detection and Progression of Cognitive Changes in Patients and Asymptomatic Mutation Carriers. Leuven: University Press; 2004

[228] Hawkes CH, Doty RL. The Neurology of Olfaction. Cambridge University Press. 2009

[229] Kovács T, Cairns NJ, Lantos PL. Beta-amyloid deposition and neurofibrillary tangle formation in the olfactory bulb in ageing and Alzheimer's disease. Neuropathology and Applied Neurobiology. 1999;**25**:481-491

[230] Ubeda-Bañon I et al. Alpha-synucleinopathy in the human olfactory system in Parkinson's disease: Involvement of calcium-binding protein- and substance P-positive cells. Acta Neuropathologica. 2010;**119**:723-735

[231] Rey NL, Petit GH, Bousset L, Melki R, Brundin P. Transfer of human α-synuclein from the olfactory bulb to interconnected brain regions in mice. Acta Neuropathologica. 2013;**126**:555-573

[232] Kagan BL et al. Antimicrobial properties of amyloid peptides. Molecular Pharmaceutics. 2011;**9**:708-717

[233] Kovács T. The olfactory system in Alzheimer's disease: Pathology, pathophysiology and pathway for therapy. Translational Neuroscience. 2012 Sep;**237**(1):1-7

[234] Davies DC, Brooks JW, Lewis DA. Axonal loss from the olfactory tracts in Alzheimer's disease. Neurobiology of Aging. 1993;**14**:353-357

[235] Kovács T, Cairns NJ, Lantos PL. Olfactory centres in Alzheimer's disease: Olfactory bulb is involved in early Braak's stages. Neuroreport. 2001;**12**:285-288

[236] Ohm TG, Braak H. Olfactory bulb changes in Alzheimer's disease. Acta Neuropathologica. 1987;**73**:365-369

[237] Struble RG, Clark HB. Olfactory bulb lesions in Alzheimer's disease. Neurobiology of Aging. 1992;**13**:469-473

[238] Attems J, Lintner F, Jellinger KA. Olfactory involvement in aging and Alzheimer's disease: An autopsy study. Journal of Alzheimer's Disease. 2005;**7**:149-157 (discussion 173-80)

[239] Attems J, Jellinger KA. Olfactory tau pathology in Alzheimer disease and mild cognitive impairment. Clinical Neuropathology. 2006;**25**:265-271

[240] Talamo BR et al. Pathological changes in olfactory neurons in patients with Alzheimer's disease. Nature. 1989;**337**:736-739

[241] Dua P, Y Z. Microbial sources of amyloid and relevance to Amyloidogenesis and Alzheimer's disease (AD). Journal of Alzheimer's, Parkinsonism and Dementia. 2015 Mar;**5**(1):177

[242] Bhattacharjee S, Lukiw WJ. Alzheimer's disease and the microbiome. Frontiers in Cellular Neuroscience. 2013;**7**:153

[243] Catanzaro R et al. The gut microbiota and its correlations with the central nervous system disorders. Panminerva Medica. 2015;**57**:127-143

[244] Friedland RP. Mechanisms of molecular mimicry involving the microbiota in neurodegeneration. Journal of Alzheimer's Disease. 2015;**45**:349-362

[245] Syed AK, Boles BR. Fold modulating function: Bacterial toxins to functional amyloids. Frontiers in Microbiology. 2014;**5**:401

[246] Rhee SH. Lipopolysaccharide: Basic biochemistry, intracellular signaling, and physiological impacts in the gut. Intestinal Research. 2014;**12**:90-95

[247] Marques F, Sousa JC, Sousa N, Palha JA. Blood-brain-barriers in aging and in Alzheimer's disease. Molecular Neurodegeneration. 2013;**8**:38

[248] Shoemark DK, Allen SJ. The microbiome and disease: Reviewing the links between the oral microbiome, aging, and Alzheimer's disease. Journal of Alzheimer's Disease. 2015;**43**:725-738

[249] Tran L, Greenwood-Van Meerveld B. Age-associated remodeling of the intestinal epithelial barrier. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2013;**68**:1045-1056

[250] Oakley R, Tharakan B. Vascular hyperpermeability and aging. Aging and Disease. 2014; **5**:114-125

[251] Hammer ND, Wang X, McGuffie BA, Chapman MR. Amyloids: Friend or foe? Journal of Alzheimer's Disease. 2008;**13**:407-419

[252] Higaki S, Gebhardt BM, Lukiw WJ, Thompson HW, Hill JM. Effect of immunosuppression on gene expression in the HSV-1 latently infected mouse trigeminal ganglion. Investigative Ophthalmology & Visual Science. 2002;**43**:1862-1869

[253] Stilling RM, Dinan TG, Cryan JF. Microbial genes, brain & behaviour – epigenetic regulation of the gut-brain axis. Genes, Brain, and Behavior. 2013;**13**:69-86

[254] Sliger M, Lander T, Murphy C. Effects of the ApoE epsilon4 allele on olfactory function in Down syndrome. Journal of Alzheimer's Disease. 2004;**6**:397-402 (discussion 443-9)

[255] Hussain A, Luong M, Pooley A, Nathan BP. Isoform-specific effects of apoE on neurite outgrowth in olfactory epithelium culture. Journal of Biomedical Science. 2013;**20**:49

[256] Kulkarni-Narla A, Getchell TV, Schmitt FA, Getchell ML. Manganese and copper-zinc superoxide dismutases in the human olfactory mucosa: Increased immunoreactivity in Alzheimer's disease. Experimental Neurology. 1996;**140**:115-125

[257] Yamagishi M, Takami S, Getchell TV. Ontogenetic expression of spot 35 protein (Calbindin-D28K) in human olfactory receptor neurons and its decrease in Alzheimer's disease patients. Annals of Otology, Rhinology & Laryngology. 1996;**105**:132-139

[258] Pignatelli A, Belluzzi O. Cholinergic modulation of dopaminergic neurons in the mouse olfactory bulb. Chemical Senses. 2008;**33**:331-338

[259] Arendt T, Bigl V, Arendt A, Tennstedt A. Loss of neurons in the nucleus basalis of Meynert in Alzheimer's disease, paralysis agitans and Korsakoff's disease. Acta Neuropathologica. 1983;**61**:101-108

[260] Huisman E, Uylings HBM, Hoogland PV. A 100% increase of dopaminergic cells in the olfactory bulb may explain hyposmia in Parkinson's disease. Movement Disorders. 2004;**19**:687-692

[261] Mundiñano I-C et al. Increased dopaminergic cells and protein aggregates in the olfactory bulb of patients with neurodegenerative disorders. Acta Neuropathologica. 2011;**122**:61-74

[262] Loopuijt LD, Sebens JB. Loss of dopamine receptors in the olfactory bulb of patients with Alzheimer's disease. Brain Research. 1990;**529**:239-244

[263] Kovacs GG et al. Nucleus-specific alteration of raphe neurons in human neurodegenerative disorders. Neuroreport. 2003;**14**:73-76

[264] Zarow C, Lyness SA, Mortimer JA, Chui HC. Neuronal loss is greater in the locus coeruleus than nucleus basalis and substantia nigra in Alzheimer and Parkinson diseases. Archives of Neurology. 2003;**60**:337-341

[265] Feinstein DL et al. Noradrenergic regulation of inflammatory gene expression in brain. Neurochemistry International. 2002;**41**:357-365

[266] De Simone R, Ajmone-Cat MA, Carnevale D, Minghetti L. Activation of alpha7 nicotinic acetylcholine receptor by nicotine selectively up-regulates cyclooxygenase-2 and prostaglandin E2 in rat microglial cultures. Journal of Neuroinflammation. 2005;**2**:4

[267] Cheng N, Bai L, Steuer E, Belluscio L. Olfactory functions scale with circuit restoration in a rapidly reversible Alzheimer's disease model. Journal of Neuroscience. 2013; **33**:12208-12217

[268] Knuesel I et al. Age-related accumulation of Reelin in amyloid-like deposits. Neurobiology of Aging. 2009;**30**:697-716

[269] Cuchillo-Ibañez I, Balmaceda V, Mata-Balaguer T, Lopez-Font I, Sáez-Valero J. Reelin in Alzheimer's disease, increased levels but impaired signaling: When more is less. Journal of Alzheimer's Disease. 2016;**52**:403-416

[270] Brai E, Alina Raio N, Alberi L. Notch1 hallmarks fibrillary depositions in sporadic Alzheimer's disease. Acta Neuropathologica Communications. 2016;**4**:64

[271] Marathe S, Jaquet M, Annoni J-M, Alberi L. Jagged1 is altered in Alzheimer's disease and regulates spatial memory processing. Frontiers in Cellular Neuroscience. 2017;**11**:220

[272] Brai E et al. Notch1 activity in the olfactory bulb is odour-dependent and contributes to olfactory behaviour. The European Journal of Neuroscience. 2014;**40**:3436-3449

[273] Albers MW, Tabert MH, Devanand DP. Olfactory dysfunction as a predictor of neurodegenerative disease. Current Neurology and Neuroscience Reports. 2006;**6**:379-386

[274] Markopoulou K et al. Assessment of olfactory function in MAPT-associated neurodegenerative disease reveals odor-identification irreproducibility as a non-disease-specific, general characteristic of olfactory dysfunction. PLoS One. 2016;**11**:e0165112

[275] Glasl L et al. Pink1-deficiency in mice impairs gait, olfaction and serotonergic innervation of the olfactory bulb. Experimental Neurology. 2012;**235**:214-227

[276] Kim YH, Lussier S, Rane A, Choi SW, Andersen JK. Inducible dopaminergic glutathione depletion in an alpha-synuclein transgenic mouse model results in age-related olfactory dysfunction. Neuroscience. 2011;**172**:379-386

[277] Fleming SM et al. Olfactory deficits in mice overexpressing human wildtype alpha-synuclein. The European Journal of Neuroscience. 2008;**28**:247-256

[278] Nuber S et al. A progressive dopaminergic phenotype associated with neurotoxic conversion of α-synuclein in BAC-transgenic rats. Brain. 2013;**136**:412-432

[279] Taylor TN, Caudle WM, Miller GW. VMAT2-deficient mice display Nigral and Extranigral pathology and motor and nonmotor symptoms of Parkinson's disease. Parkinsons Disease. 2011;**2011**:124165

[280] Jellinger KA. Olfactory bulb alpha-synucleinopathy has high specificity and sensitivity for Lewy body disorders. Acta Neuropathologica. 2009;**117**:215-216 (author reply 217-8)

[281] Lavoie J et al. The olfactory neural epithelium as a tool in neuroscience. Trends in Molecular Medicine. 2017;**23**:100-103

[282] Narayan S et al. Olfactory neurons obtained through nasal biopsy combined with laser-capture microdissection: A potential approach to study treatment response in mental disorders. Journal of Visualized Experiments. 2014 Dec 4;(94). DOI: 10.3791/51853

[283] Henkin RI, Velicu I. cAMP and cGMP in nasal mucus: Relationships to taste and smell dysfunction, gender and age. Clinical & Investigative Medicine. 2008;**31**:71

[284] Henkin RI, Velicu I. 30 Insulin receptors as well as insulin are present in saliva and nasal mucus. Journal of Investigative Medicine. 2006;**54**:S378

[285] Illum L. Is nose-to-brain transport of drugs in man a reality? The Journal of Pharmacy and Pharmacology. 2004;**56**:3-17

[286] Pires A, Fortuna A, Alves G, Falcão A. Intranasal drug delivery: How, why and what for? Journal of Pharmacy & Pharmaceutical Sciences. 2009;**12**:288-311

[287] Grassin-Delyle S et al. Intranasal drug delivery: An efficient and non-invasive route for systemic administration: Focus on opioids. Pharmacology & Therapeutics. 2012; **134**:366-379

[288] Willette AA, Modanlo N, Kapogiannis D, Alzheimer's Disease Neuroimaging Initiative. Insulin resistance predicts medial temporal hypermetabolism in mild cognitive impairment conversion to Alzheimer disease. Diabetes. 2015;**64**:1933-1940

[289] Craft S et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: A pilot clinical trial. Archives of Neurology. 2012;**69**:29-38

[290] Claxton A et al. Long-acting intranasal insulin detemir improves cognition for adults with mild cognitive impairment or early-stage Alzheimer's disease dementia. Journal of Alzheimer's Disease. 2015;**44**:897-906

[291] Reger MA et al. Intranasal insulin improves cognition and modulates beta-amyloid in early AD. Neurology. 2008;**70**:440-448

[292] Wong YC, Zuo Z. Brain disposition and catalepsy after intranasal delivery of loxapine: Role of metabolism in PK/PD of intranasal CNS drugs. Pharmaceutical Research. 2013;**30**:2368-2384

[293] Hanson LR et al. Intranasal deferoxamine provides increased brain exposure and significant protection in rat ischemic stroke. The Journal of Pharmacology and Experimental Therapeutics. 2009;**330**:679-686

[294] Scranton RA, Fletcher L, Sprague S, Jimenez DF, Digicaylioglu M. The rostral migratory stream plays a key role in intranasal delivery of drugs into the CNS. PLoS One. 2011;**6**:e18711

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