Chapter

Neurological and Neuropsychiatric Disorders in Relation to Olfactory Dysfunction

Naina Bhatia-Dey and Thomas Heinbockel

Abstract

Olfaction is an underestimated sensory modality in terms of its predictive value as an indicator of disorders. It is a well-known phenomenon that a significant percentage of people afflicted with certain prevalent disorders causing degenerative neuropathology, progressive loss of memory and communication function, normal age-based decline of physiological functions, intellectual challenges, depressive and anxiety disorders as well as post-traumatic stress disorders, present with a range of olfactory deficits. Here, we review our understanding of these deficits and their relation to various clinical manifestations such as neurological and neuropsychiatric diseases and disorders. At the outset, we will briefly describe the olfactory pathway from olfactory sensory neurons in the nasal epithelium to the olfactory bulb and on to olfactory cortical and subcortical structures involved in olfaction such as the amygdala.

Keywords: aging, Alzheimer's disease, amygdala, dementia, hippocampus, limbic system, mood disorders, olfactory bulb, olfactory cortex, olfactory sensory neuron, Parkinson's disease

1. Introduction

This chapter provides a cursory description of a well-known phenomenon, namely that a significant percentage of people afflicted with certain prevalent disorders causing degenerative neuropathology, depressive and anxiety disorders, progressive loss of memory and communication function such as Autism Spectrum Disorder (ASD), intellectual challenges, as well as post-traumatic stress disorders present with a range of olfactory deficits. Here, we review our understanding of these deficits and their relation to various clinical manifestations such as neurological and neuropsychiatric diseases and disorders, disorders affecting mood, cognition, communication and memory and finally, olfactory deficits as secondary outcome of therapeutic drugs. At the outset, we will briefly describe the olfactory pathway from olfactory sensory neurons in the nasal epithelium to the olfactory bulb and on to olfactory cortical structures and subcortical structures involved in olfaction such as the amygdala. Then, we shall discuss olfaction in the context of normal age-based decline of physiological functions relating olfactory deficits to the onset of neurodegenerative pathology, decline in cognition, memory, ability to communicate as well as with episodes of depression and anxiety.

2. The olfactory system

The main role of the olfactory system is the detection of odors. This function is critical for food selection by detecting olfactory and gustatory signals. Moreover, our sense of smell plays a role in reproductive and neuroendocrine regulation and is relevant for memory, aggression, emotion, social organization, and recognition of prey and predators [1]. Social chemical stimuli or semiochemical signals are processed by the olfactory system in most mammals. These chemicals differ from general odorants and mediate physiological aspects of mating and aggression. These chemical signals are processed in the accessory olfactory bulb in the brain which is part of the vomeronasal system [1].

The olfactory pathway starts deep in the nasal cavity with an olfactory epithelium that sits on the superior conchae (**Figure 1**). This pseudostratified ciliated columnar epithelium houses olfactory sensory neurons, supporting cells (sustentacular cells), and basal stem cells. In addition, Bowman's glands located in the connective tissue under the epithelium (lamina propria) send ducts to the surface of the epithelium and secrete a serous fluid that immerses the cilia of olfactory receptor neurons in a mucous layer to trap odorant molecules. Odorant molecules bind to olfactory receptor proteins in the cilia of olfactory sensory neuron dendrites. The number of cilia that emerges from the dendrite of an olfactory sensory neuron is relatively small, 20 to 30, compared to the ciliated cells that are found in the respiratory epithelium (~300 cilia). Air-borne odorant molecules in the air that we breathe in activate the olfactory receptor proteins in the olfactory cilia. Odorant molecules can find their way to the olfactory sensory neurons either through the

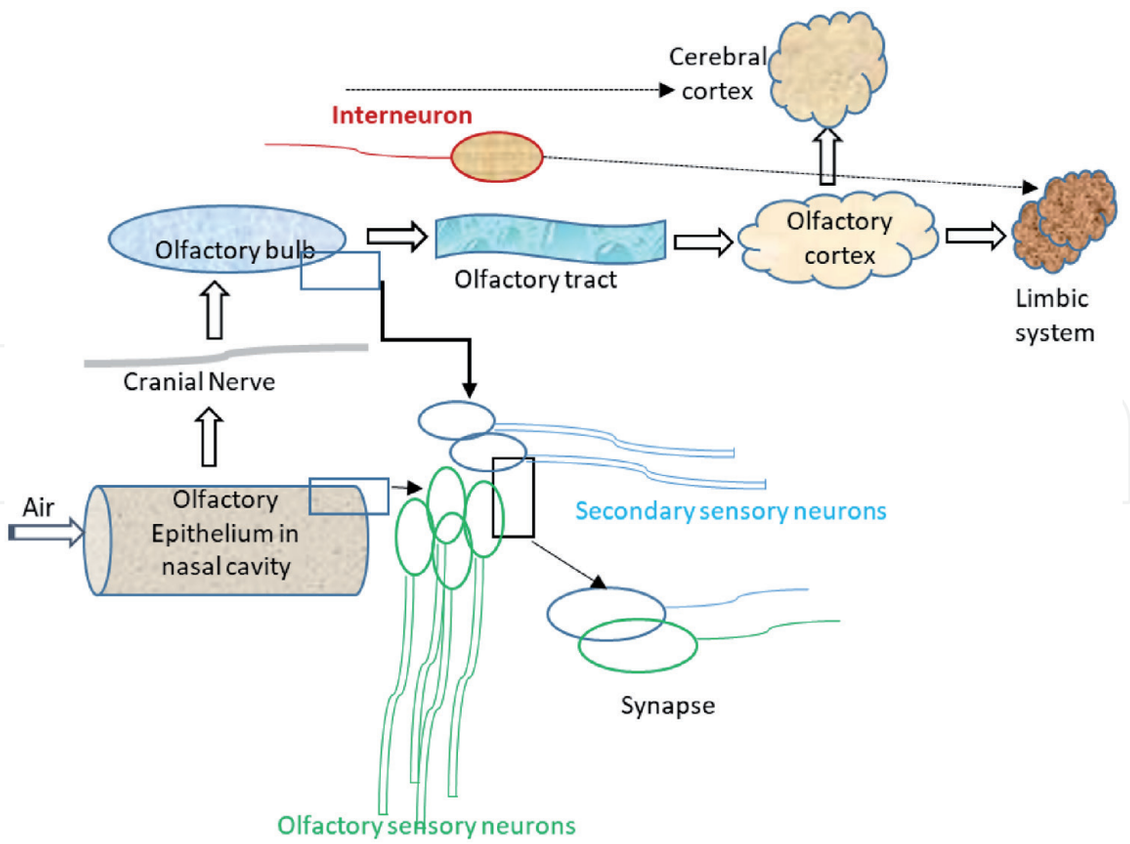

Figure 1.
Schematic representation of olfactory pathways. Olfactory sensory neurons in the olfactory epithelium of the nasal cavity send their axons to form synapses with secondary sensory neurons in the olfactory bulb. A small number of neurons from the olfactory bulb participate in olfactory processing as they exchange information with both limbic system components and cortical structures.

nose (orthonasal stimulation) or from the mouth to the nose (retronasal stimulation) [2]. Often this retronasal olfactory stimulation is confused with taste, which takes place in taste buds in the tongue and soft palate of the oral cavity. However, food odors and the consistency of the food ('crunchiness') together with tastants contribute to the flavor or aroma of food. The membrane of olfactory sensory neuron cilia houses odorant receptor proteins and thereby activates these neurons in the nasal epithelium. The olfactory receptor proteins form a large gene family (1000 genes in rodents, 350 in humans, [3, 4]). Each olfactory sensory neuron sends an axon through the cribriform plate of the ethmoid bone to the ipsilateral main olfactory bulb in the brain (**Figure 1**). The axons of olfactory sensory neurons coalesce to form the olfactory nerve (cranial nerve I) and olfactory nerve layer of the main olfactory bulb.

The main olfactory bulb is a cortical structure of the cerebrum. However, the main olfactory bulb is not part of the neocortex but part of the allocortex as shown by its fetal development and cytoarchitecture. Neocortical structures undergo a prenatal phase that results in six layers, whereas allocortical structures have three or four layers in the mature brain [5]. While the main olfactory bulb presents itself as a small extension of the brain in humans, in rodents, the main olfactory bulb is a large structure that fills roughly a quarter of the length of the cranial cavity [6] and is dedicated to the processing of odorant information [1, 2, 7].

Several million sensory neurons are present in the olfactory epithelium. A given olfactory receptor protein is expressed by several thousand of them. The olfactory sensory neurons that express the same olfactory receptor protein send their axon to the same one or two glomeruli in the main olfactory bulb to form synaptic contacts (**Figure 1**). The dendrites of interneurons (juxtaglomerular cells) and output neurons (mitral and tufted neurons) in the olfactory bulb synapse with olfactory sensory neurons. Compared to the large number of olfactory sensory neurons, only relatively few output neurons innervate each glomerulus. These output neurons send their axons to higher order brain centers for brain processing of olfactory signals [8]. The precise sending of olfactory sensory neuron axons to specific glomeruli is critical for the discrimination of odorants [2]. The axons of output neurons leave the main olfactory bulb through the lateral olfactory tract and terminate in various higher order olfactory centers such as the anterior olfactory nucleus (AON), piriform cortex, the anterior parahippocampal cortex (entorhinal cortex), and the cortico-medial amygdala, all of which belong to limbic system (**Figure 1**) and are on the ipsilateral brain side. In contrast to other sensory modalities, the olfactory pathway routes sensory information directly from the olfactory bulb to cortical centers and bypasses the thalamus [1, 2].

The amygdala is a collection of nuclei in the limbic system [9]. The basolateral nucleus is the largest one and receives input from sensory cortices (vision, hearing) as well as direct auditory signals through a subcortical structure, the medial geniculate nucleus which is part of the thalamus. The olfactory bulb and piriform cortex send sensory information to the cortical and medial nuclei of the amygdala, the cortico-medial nucleus [10, 11]. In addition, the amygdala receives input from other cortical and subcortical brain systems, such as the prefrontal cortex with the anterior cingulate and orbitofrontal cortices. In turn, both piriform cortex and amygdala project to the orbitofrontal cortex to regulate emotion and associative learning. The amygdala is also connected with the entorhinal and hippocampal system for long-term memory [12]. Furthermore, the amygdala is a target for fibers from the hippocampus and rhinal (olfactory) cortices [10, 11]. Functionally, it has been established that odors have the ability to evoke strong emotions and trigger the recall of emotional memories and modulate cognition [11].

Not only does the olfactory bulb send axons to higher order olfactory centers (afferent fibers), an even larger number of centrifugal axons originating in higher olfactory centers innervate the olfactory bulb glomeruli (efferent fibers) [6, 13, 14]. These centrifugal neurons have been shown to provide modulatory feedback to neurons in the different layers of the main olfactory bulb which is important for experience-dependent modulation [13]. The origin of the centrifugal fibers is in the locus coeruleus (noradrenergic), the horizontal limb of the diagonal band of Broca (cholinergic), and the raphe nucleus (serotonergic) [15–18]. The centrifugal fibers travel mainly through the anterior olfactory nucleus and the anterior commissure, and very little through the lateral olfactory tract [13].

3. Aging effects in the olfactory system

Age-associated impairment in the sense of olfaction has been well documented [19–23]. Akin to neurodegenerative pathology, a decline in olfactory acuity and olfactory dysfunction are common features of the normal aging process [24–27] detectable in over 50% individuals ranging in age from 65 to 80 years and almost in 75% of those above 80 years [24, 28–30]. This decline in olfactory function is detected using different kinds of tests such as psychophysical, psychophysiological and electrophysiological tests that determine odor detection, identification and discrimination, odor related physiological changes in cardiac and respiratory system as well as odor-event related potentials [29]. However, studies analyzing the mechanism of non-pathological, normal chronological age-related decline of olfactory acuity and impaired olfactory function are limited, despite the fact that deficits in the olfactory sense are considered as important symptom for early and differential diagnosis of neurodegenerative disorders [28]. At the anatomical level, the sense of olfaction is affected by age-associated ossification and closure of foramina of the cribriform plate [29, 31]. There is evidence of a quantitative reduction in the olfactory epithelium and its replacement by respiratory epithelium in normal subjects of the aging population which is evident in biopsies of the upper nasal septum [32]. It is now clearly evident that in the course of normal aging, suboptimal olfaction and olfactory dysfunction are associated with a number of anatomical and physiological features such as age-associated thinning of the olfactory neuroepithelium, altered cellular patterns and regional distribution of nuclei of olfactory sensory and sustentacular cells [29], reduction of mucosal metabolizing enzymes and sensory loss of olfactory sensory cells to various odorants along with a cumulative effect of environmental exposure to the olfactory epithelium [30]. An additional causative factor is the parallel loss of olfactory function in direct correlation with a clear age-associated decline in the volume of the olfactory bulb in adults of both genders [33–35]. Other than the olfactory bulb, a reduction in volume of AON, amygdala, hippocampus and piriform cortex in the limbic system contribute to a loss of olfaction due to their pivotal role in olfactory processing [36]. Testing the sensitivity and response of isolated sensory neurons to odorant mixtures indicates a loss of olfactory sensitivity and specificity in neurons derived from older subjects [37]. In older individuals, there is evidence of decreased beta-event related synchronization in response to certain pleasant odorants and, therefore, these individuals rated such odorants as less pleasant, thereby, denoting a decline in olfactory processing [38]. A change in olfactory perception represents subtle olfactory dysfunction that appears to precede a number neurodegenerative disorders and is presumed due to loss of synaptic function [39, 40]. Subsequent studies have shown that loss in olfactory sensitivity and perception is heterogeneous and appears to be more specific to heavier molecules [41]. Inherent allelic variations of brain

derived neurotrophic factor (BDNF) also affect and add to age-dependent olfactory decline [29, 42]. A comparative research study quantifying heritability of odor identification and cognition detected a role of common genes in both olfaction and cognition. However, heritability of odor identification was lower in contrast to that of cognition [43]. Quantitative analysis of olfaction using odor identification (OI) scale in community dwelling subjects of age group 70–79 years reveals association of higher risk of dementia with poor OI score [44] and reduction in OI has been linked to advanced physiological brain aging as well as with a number of neurodegenerative diseases [45]. An aging cortical synapse in limbic structures has been considered as a hallmark of age-associated decline in cognition [46]. However, such studies are still preliminary for the olfactory bulb, despite evidence of growth factor dependent induction of synaptic strength in olfactory bulb cell layers during odor-dependent social transmission of food preference [47]. Chronological age adds to the impact of environmental exposure through living and working conditions on all physiological systems and their functions [48]. Experimental analysis indicates age-dependent accumulation of somatic mutations using both proliferative and non-proliferative cell types from human brain tissue [49]. It further indicates the probability of mutation accumulation in neurons. Genome-wide single somatic nucleotide variant analysis on DNA of 159 single neurons of 15 normal individuals with a wide age range (4 months to 82 years) and 9 individuals diagnosed with early onset of neurodegeneration revealed linear increase in both sets, indicating age-dependent accumulation of somatic mutations as significant factor affecting neurodegeneration [50]. Research studies of classical neurodegenerative disorders have proposed that the observed variability of olfactory dysfunction in diverse neurological and neuropsychiatric diseases could aid in early differential diagnosis of Alzheimer's disease (AD), Parkinson's disease (PD), mild cognitive impairment (MCI), progressive supranuclear palsy (PSP) and frontotemporal lobar degeneration known as FTLD-TDP43 [51–54]. A cell biology oriented experimental approach to detect the presence of neurodegeneration-associated proteins used nasal brushing to collect olfactory neurons from olfactory mucosa of normal subjects and detected four different characteristic proteins involved in neurodegenerative pathology: α-synuclein, transactive response DNA-binding protein 43 (TDP-43), hyperphosphorylated tau and β-amyloid proteins [55]. These findings have prompted an analysis of the parallel progression of loss of olfaction with onset of neurodegenerative pathology and/or decline in cognitive abilities as initial symptoms of neurological and neuropsychiatric disorders.

4. Alzheimer's disease, dementia and olfactory deficits

Olfactory deficiencies are evident in a number of neurodegenerative disorders such as AD, dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), MCI, PD and Huntington disease [40, 51, 56–59]. In an extensive two year study with six-monthly follow up, all MCI patients with lower range of olfaction score but no subjective smelling loss detected by standard UPSIT (University of Pennsylvania Smell Identification Test) developed AD. In contrast, in a control group of higher olfaction score, AD occurrence was nil [60]. A similar association of lower olfaction score with development of AD pathology was evident in a multiethnic community cohort with UPSIT test [61]. In a comparative OI analysis of FTD and AD patients with normal age matched control individuals, OI score of FTD patients differed significantly with control group, however, there was a close resemblance in OI pattern of FTD patients with OI in AD patients [62]. An analysis using Pocket Small Test as indicator of OI performance in AD patients and healthy young and age matched control group of individuals detected reduced OI in an older control group

than in a younger control group, and AD patients had even reduced OI compared to their age matched control group [27]. At the cellular level, a characteristic neuropathological feature of AD is the appearance of neurofibrillary tangles consisting of hyperphosphorylated tau protein [63]. In relation to olfactory dysfunction, the two key hallmarks of AD neuropathology are the detection of amyloid-beta (Aβ) and hyperphosphorylated tau protein in the olfactory system; both have been detected together with impaired olfaction much before a clinical presentation of the disease [57]. An analysis assessing OI as indicator of presymptomatic AD pathogenesis in cognitively normal aged individuals shows an association of reduced OI with lower cognitive score and older age as well as increased ratio of total tau protein to phosphorylated tau protein in cerebrospinal fluid [64]. Therefore, at the behavioral level, diminished OI has emerged as a practical and affordable biomarker of AD pathology [64] as well as prodromal symptom of AD [65].

5. Parkinson's disease and olfactory impairment

A major factor leading to neurodegenerative PD pathology is the loss of dopaminergic neurons from the substantia nigra, resulting in slow but substantial loss of dopamine that eventually leads to many clinical motor symptoms such as bradykinesia, rigidity, tremor, instability of posture and decline of cognitive function [66]. The olfactory system is a severely affected non-motor system in PD patients with early appearance of olfactory dysfunction that remains independent of progressive PD symptoms, their duration and treatment [67]. Additional research studies have indicated association of olfactory dysfunction with PD for over three decades [25, 68]. Olfactory dysfunction, including hyposmia and decline in olfactory acuity, has been established as one of the earliest features of PD. These are detectable in approximately 90% of early stage PD patients, where they may precede the onset of the motor symptoms by a margin of years [69–73]. Hyposmia and progressive olfactory decline in PD patients have been attributed to central olfactory processing, since the olfactory epithelium biopsy samples of PD patients were normal [74]. Subsequent MRI studies indicate a varying degree of reduction in olfactory bulb volume and depth of olfactory sulcus in PD patients than in normal control individuals. These studies indicate an association of anatomical changes with altered olfaction in PD patients [75]. Lewy bodies and Lewy neurites comprised of α-synuclein are histological hallmarks of neurodegenerative pathology in PD [76]. The olfactory bulb and lower brainstem have been considered as the induction site for the onset of histopathological features comprising of both Lew bodies and Lewy neurites [73, 77]. Along with the peripheral nervous system, such histological aberrations also begin to appear in gut nerve plexa and the olfactory bulb, thereby indicating participation of olfactory bulb cell layers in the progression of neurodegenerative pathology of PD [78].

Dementia associated with PD, known as Parkinson's disease dementia (PDD), is one of the most debilitating symptoms of PD and is difficult to predict during early stages of the disease. A research study using OSIT-J (odor stick identification test for Japanese) shows over 18 fold increase in risk of dementia for PD patients with severe hyposmia [79]. Indeed OI has emerged as a reliable tool for providing excellent diagnostic accuracy for PD distinguishing it from PD mimics [80].

6. Mood and communication disorders

In addition to aging, neurodegenerative and psychiatric conditions, olfactory deficits including low OI appear as characteristic feature of mild to severe major

depressive disorders [81, 82]. As there is overlap in brain regions involved in AD, depression and olfactory processing, olfactory dysfunction could be the potential early biomarker of both AD and depressive disorders [83]. Similar to research studies using animal models that indicate a strong link between loss of olfaction and depressive behavior, a comparative analysis of age matched control individuals and patients diagnosed with depression showed loss of normal olfaction as marker of depression in humans [84]. Literature reviews of multiple research findings using specific parameters indicate a clear and consistent relation between depression and poor life quality in individuals from both clinical and community setting in age dependent manner [85]. Encoded olfactory stimuli activate emotional memory [86]; olfactory system and brain circuits participating in memory and cognition show a close anatomical link as well as frequent functional alteration in patients with depression [87–89]. Additional analysis clearly denotes a reciprocal relationship between olfaction and depression; patients with olfactory dysfunction show worsening depressive symptoms while olfactory performance is clearly reduced in depression patients in comparison to normal controls [90]. Moreover,

Declined olfactory acuity and olfactory dysfunction are also evident in individuals suffering with post-traumatic stress disorder (PTSD) and in patients diagnosed with major depressive disorder (MDD). PTSD leads to decreased olfactory bulb volume, thereby leading to decreased olfactory acuity, additional olfactory deficits and dysfunction [35]. MDD indicates decline in both primary and secondary olfactory processing [84, 91]. MDD patients denote lower score for olfactory threshold, odor discrimination in 40-point smell identification test in comparison to normal controls At the same time, patients with olfactory dysfunction show clear symptoms of depression that become acute in comparative analysis of hyposmic to anosmic subjects [90].

ASD adult patients show decline in odor identification ability [92]. Experimental evidence in two different mouse models of ASD indicates weaker and fewer synapses between olfactory sensory nerve terminals and olfactory bulb tufted cell layer; and weaker synapses between olfactory sensory nerve terminals and inhibitory periglomerular cells of the olfactory bulb [93]. Duplication of GABA receptor genes and deletion of TOP3B, topoisomerase involved in relaxation of supercoiled DNA contribute to autism susceptibility and have been assigned to gene families with specific contribution to neurodevelopmental disorders [94]. Out of 102 identified genes that contribute to ASD, most genes are expressed and enriched early in excitatory and inhibitory neuronal lineages and affect synapses [95].

7. Drugs

The regenerative ability of olfactory epithelium has made it an attractive target for exploring and evaluating therapeutic strategies to distinguish and treat drug induced olfactory disorders [96]. More than 86% of cancer patients of wide age range display smell and taste disorders that persist even after completion of chemotherapy for cancer [97]. However, not every therapeutic chemotherapy drugs has negative impact on olfactory acuity (personal communication). *Bacopa monnieri* extracts administration reverses bulbectomy induced neurochemical and histological alterations in mouse model of depression; cognition dysfunction is reversed through a mechanism that enhances synaptic plasticity related signaling, BDNF transcription and protection of cholinergic systems [98].

The flavonoid Naringenin functions as antidepressant by restoring serotonin and noradrenaline levels in brain tissue [99]. In bulbectomized mice, two weeks of Naringenin treatment ameliorated depression like behavioral alterations, decreased

elevated pro-inflammatory cytokines and increased levels of BDNF and serotonin in hippocampus and cortex [100].

Depression with psychomotor agitation (PMA) is a putative psychiatric disorder associated with substance dependence, specifically, opioids. It remains unaffected by drug induced major depressive episodes indicating complex interplay of therapeutic drugs in treating depression [101].

The AON, a key area of the olfactory system, shows accumulation of characteristic neuropathological markers such as hyperphosphorylated tau, α-synuclein and β-amyloid proteins at the earliest stages of AD in a Somatostatin (SST) expressing subpopulation of interneurons. In the limbic system, the same accumulation is evident in same subpopulation of interneurons [102]. However, SST is unequally involved in two predominant neurodegenerative disorders with a very strong involvement in AD pathology but quite weaker participation in PD. In early stages of AD, SST is reduced in olfactory areas whereas it is preserved in non-demented PD cases [102]. Further analysis of SST related olfactory deficiencies will pave the way of SST based therapeutic approaches.

Olfactory dysfunctions unrelated to blocked nasal passages are present in a significant percentage of Covid-19 patients [103–105]. Altered expression of SARS-CoV-2 entry genes in supporting cells of the olfactory epithelium has been proposed as a mechanism underlying COVID-19-associated anosmia [106, 107].

8. Discussion and conclusions

The mammalian olfactory bulb has been termed the "brain inside the brain", due to the presence of sensory inputs, neuronal lamination and contribution of new neural elements throughout the lifetime [108]. It plays a pivotal role in olfactory processing [8, 109]. In addition to AD, PD, MCI and depressive disorders, inadequate and/or improper olfactory function together with impaired olfactory processing exist in many other neurodegenerative and neuropsychiatric disorders. For instance, in the case of multiple sclerosis (MS), prevalence of olfactory dysfunction ranges from 20 to 45% of the MS population. However, the mechanism of loss of olfaction remains unknown, except for decreased olfactory bulb and brain volume [110, 111]. In patients with a diagnosis of a behavioral FTD variant, OI and odor discrimination did not show any difference from control cases, but there was a significant difference in the odor association test. It has been attributed to impaired olfactory processing [112]. Within the healthy population, impulsive tendencies exhibit some link to olfactory defects [113]. Narcolepsy is associated with hypocretin deficiency of the limbic system. Despite genetic predisposition, it has been postulated to increase by environmental substances that may access the olfactory bulb, triggering neuroinflammation and induce neurodegeneration [114].

Single cell transcriptome analysis during mouse olfactory neurogenesis in early development reveals that expression of olfactory receptor (OR) genes becomes progressively restricted to one gene per neuron in each mature neuron instead of several receptor genes that express in immature neurons [115, 116]. Expression of a single OR allele in olfactory sensory neurons is the outcome of coalescence of multiple intergenic enhancers to a multi-chromosomal hub that allows the expression of a single OR allele while the remaining OR genes converge into few heterochromatic compartments leading to effective transcriptional silencing [117]. Age associated chromosomal breakage and DNA damage lead to an increase in markers of genome instability [118] and requires many layers of regulatory functions such as inducing senescence [48], reducing accumulation of DNA damage and enhancing DNA repair pathways [119]. Genome protection from DNA damage to minimize

aging effects is also an effective strategy to minimize risk factor for neurodegeneration [119]. This is likely to retain olfactory acuity and ability based on the model proposed by Bashkirova and Lomvardas [117].

Single cell RNA sequencing reveals differentially regulated and expressed genes as neuronal markers specific to adult born interneurons that may serve as molecular markers for synapse formation, synapse maintenance, and neural plasticity of adult brain circuits [120]. Research studies analyzing functional mechanisms of these markers and their regulation are likely to facilitate the understanding of decreased OI, olfactory dysfunction and onset of neurodegenerative pathology.

Olfactory ensheathing glial cells help olfactory bulb neurons to connect with both the peripheral and central nervous system, and, therefore, they have been widely used as therapeutic tools for neural repair and olfactory/neural regeneration for injuries and neurodegenerative pathological conditions [121]. Indeed, the olfactory bulb has emerged as an attractive target for many novel therapeutic approaches [122].

Another fast growing research topic addresses the role of microRNAs in regulating genes that participate in cognition and neurodegeneration [123–125] and olfactory acuity. Such findings would also add to a better understanding of the relationship between olfactory dysfunction and neurodegenerative pathologies.

Targeting synaptic deficits in AD patients and aging individuals by improving synaptic plasticity though alteration of structural deficits in dendritic spines through microRNA mediated regulatory pathways could be an effective and novel therapeutic strategy for AD as well as other neurodegenerative disorders [126].

Acknowledgements

This work was supported in part by grants from the National Science Foundation (NSF IOS-1355034) and the **Charles and Mary** Latham Trust Fund.

Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this chapter.

Author details

Naina Bhatia-Dey and Thomas Heinbockel*
Department of Anatomy, Howard University College of Medicine, Washington, DC, USA

*Address all correspondence to: theinbockel@howard.edu

References

[1] Shipley, MT; Ennis, M. Functional organization of olfactory system. J. Neurobiol. 1996; 30: 123-176.

[2] Ennis M, Hamilton KA, Hayar A. Neurochemistry of the main olfactory system. In Handbook of Neurochemistry and Molecular Neurobiology: Sensory Neurochemistry; Springer: New York, NY, USA, 2007; 137-204.

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

[4] Young JM, Friedman C, Williams EM, Ross JA, Tonnes-Priddy L, Trask BJ. Different evolutionary processes shaped the mouse and human olfactory receptor gene families. Hum Mol Genet. 2002; 11:535-546. Doi. org/10.1093/hmg/11.5.535

[5] Schiebler TH, Schmidt W, Zilles K. Anatomie, 8 ed.; Springer Verlag, Berlin, Germany, 1999.

[6] Swanson LW. Brain Maps: Structure of the Rat Brain. A Laboratory Guide with Printed and Electronic Templates for Data, Models and Schematics, 3rd ed.; Elsevier: Amsterdam, the Netherland. 2004.

[7] Heinbockel T, Heyward PM. Glutamate synapses in olfactory neural circuits. In Amino Acid Receptor Research; Paley, B.F., Warfield, T.E., Eds.; Nova Science Publishers: New York, NY, USA, 2009; 16: 379-414

[8] Shepherd, G.M.; Chen, W.R.; Greer, C.A. Olfactory Bulb. In Synaptic Organization of the Brain, 5th ed.; Shepherd, G.M., Ed.; Oxford University Press: New York, NY, USA, 2004a; 165-216.

[9] Pape HC, Driesang RB, Heinbockel T, Laxmi TR, Meis S, Seidenbecher T, Szinyei C, Frey U, Stork O. Cellular processes in the amygdala: gates to emotional memory? Zoology, 2001; 104: 232-240. Doi. org/10.1078/0944-2006-00029

[10] Bernardi S, Salzman CD. The contribution of nonhuman primate research to the understanding of emotion and cognition and its clinical relevance. Proc Natl Acad Sci USA. 2019; 116: 26305-26312. Doi: 10.1073/ pnas.1902293116.

[11] Kadohisa M. Effects of odor on emotion, with implications. Front Syst Neurosci. 2013; 7:66. Doi: 10.3389/ fnsys.2013.00066.

[12] Seidenbecher T, Laxmi TR, Stork O, Pape HC. Amygdalar and hippocampal theta rhythm synchronization during fear memory retrieval. Science. 2003; 301:846-50. Doi: 10.1126/ science.1085818

[13] Kiselycznyk C, Zhang S, Linster C. Role of Centrifugal Projections to the Olfactory Bulb in Olfactory Processing. Learn. Mem. 2006, 13, 575-579. Doi:10.1101/lm.285706

[14] Laaris N, Puche, A, Ennis, M. Complementary postsynaptic activity patterns elicited in olfactory bulb by stimulation of mitral/tufted and centrifugal fiber inputs to granule cells. J. Neurophysiol. 2007; 97:296-306. Doi. org/10.1152/jn.00823.2006

[15] Macrides F, Davis BJ, Youngs WM, Nadi NS, Margolis, FL. Cholinergic and catecholaminergic afferents to the olfactory bulb in the hamster: A neuroanatomical, biochemical, and histochemical investigation. J. Comp. Neurol. 1981:203: 495-514.

[16] Halasz N. The Vertebrate Olfactory System; Akademia Kiado: Budapest, Hungary, 1990.

[17] Shipley MT. Olfactory System. In: The Rat Nervous System; Academic Press: Sydney, Australia, 1995; 899-928.

[18] Cleland TA, Linster C. Central Olfactory Structures. In Handbook of Olfaction and Gustation; Marcel Dekker: New York, NY, USA, 2003; 165-181.

[19] Murphy C, Schubert CR, Cruickshanks KJ, Klein BE, Klein R, Nondahl DM. Prevalence of olfactory impairment in older adults. JAMA. 2002; 288:2307-2312.Doi:10.1001/jama.288.18.2307

[20] Brämerson A, Johansson L, Ek L, Nordin S, Bende M. Prevalence of olfactory dysfunction: The Skövde population-based study. Laryngoscope 2004; 114: 733-737. Doi.org/10.1097/00005537-200404000-00026

[21] Vennemann MM, Hummel T, Berger K. The association between smoking and smell and taste impairment in the general population. J Neurol 2008; 255: 1121-6. Doi.org/10.1007/s00415-008-0807-9

[22] Schubert CR, Cruickshanks KJ, Fischer ME, Huang G-H, Klein BEK, Klein R. et al. Olfactory impairment in an adult population: the beaver dam offspring study. Chem. Senses. 2012; 37:325-334. Doi:10.1093/chemse/bjr102

[23] Masurkar AV, and Devanand DP. Olfactory dysfunction in the elderly: basic circuitry and alterations with normal aging and Alzheimer's disease. Curr. Geriatr. Rep. 2014; 3, 91-100. Doi.org/10.1007/s13670-014-0080-y

[24] Doty RL. The olfactory system and its disorders. Semin.Neurol. 2009; 29: 74-81. Doi 10.1055/s-0028-1124025. ISSN 0271-8235.

[25] Masaoka Y, Yoshimura N, Inoue M, Kawamura M, Homma I. Impairment of odor recognition in Parkinson's disease caused by weak activations of the orbitofrontal cortex. Neuroscience Letters. 2007; 412:45-50. Doi:10.1016/j.neulet.2006.10.055

[26] Huttenbrink KB, Hummel T, Berg D, Gasser T, Hähner A. Olfactory dysfunction: common in later life and early warning of neurodegenerative disease. Dtsch Arztebl Int. 2013; 110: 1-7. Doi: 10.3238/arztebl.2013.0001

[27] Makowska I, Kloszewska I, Grabowska A, Szatkowska I, Rymarczyk K. Olfactory deficits in normal aging and Alzheimer's disease in the polish elderly population. Arch Clin Neuropsychol 2011; 26:270-279. Doi:10.1093/arclin/acr011

[28] Mobley AS, Rodriguez-Gil DJ, Imamura F, Greer CA. Aging in the olfactory system. Trends Neurosci. 2013; 37:77-84. Doi.org/10.1016/j.tins.2013.11.004

[29] Doty RL, Kamath V. The influences of age on olfaction: a review. Front Psychol 2014; 5:20. Doi: 10.3389/fpsyg.2014.0020

[30] Attems J, Walker L, Jellinger KA. Olfaction and aging: a mini-review. Gerontology. 2015; 61:485-490. Doi: 10.1159/000381619

[31] Kalmey JK, Thewissen JG, Dluzen DE. Age-related size reduction of foramina in the cribriform plate. Anat Rec 1998;251:326-329

[32] Paik SI, Lehman MN, Seiden AM, Duncan HJ, Smith DV. Human Olfactory Biopsy: The Influence of Age and Receptor Distribution. *Arch Otolaryngol Head Neck Surg.* 1992; 118:731-738. Doi:10.1001/archotol.1992.01880070061012

[33] Buschhuter D, Smitka M, Puschmann S, Gerber JC, Witt M, Abolmaali ND, Hummel T. Correlation

between olfactory bulb volume and olfactory function. Neuroimage. 2008; 42:498-502. Doi 10.1016/j.neuroimage.2008.05.004

[34] Yousem DM, Geckle RJ, Bilker WB, McKeown DA, Doty RL. Posttraumatic olfactory dysfunction: MR and clinical evaluation. AJNR. 1996; 17:1171-1179. Doi 0195-6108/96/1706-117

[35] Yousem DM, Geckle RJ, Bilker WB, Kroger H, Doty RL. Posttraumatic smell loss: Relationship of psychophysical tests and volumes of the olfactory bulbs and tracts and the temporal lobes. Acad Radiol. 1999; 6:264-272. Doi: 10.1016/S1076-6332(99)80449-8

[36] Segura B, Baggio HC, Solana E, Palacios EM, Vendrell P, Bargallo N, Junque C. Neuroanatomical correlates of olfactory loss in normal aged subjects. Behav Brain Res. 2013; 246: 148-153. Doi.org/10.1016/j.bbr.2013.02.025

[37] Rawson NE, Gomez G, Cowart BJ, Kriete A, Pribitkin E, Restrepo D. Age-associated loss of selectivity in human olfactory sensory neurons. Neurobiol Aging. 2012; 33:1913-1919. Doi.org/10.1016/j.neurobiolaging.2011.09.036

[38] Joussain P, Thevenet M, Rouby C, Bensafi M. Effect of Aging on Hedonic Appreciation of Pleasant and Unpleasant Odors. PLoS ONE 2013; 8: e61376. Doi:10.1371/journal.pone.0061376

[39] Acebes A, Martín-Peña A, Chevalier V, Ferrús A. Synapse loss in olfactory local interneurons modifies perception. J Neurosci 2011; 31:2734-45. Doi.org/10.1523/JNEUROSCI.5046-10.2011

[40] Barresi M, Ciurleo R, Giacoppo S, Foti CV, Celi D, Bramanti P et al. Evaluation of olfactory dysfunction in neurodegenerative diseases. J. Neurol. Sci. 2012; 323, 16-24. Doi.org/10.1016/j.jns.2012.08.028

[41] Sinding C, Puschmann L, Hummel T: Is the age-related loss in olfactory sensitivity similar for light and heavy molecules? Chem Senses 2014; 39: 383-390. Doi:10.1093/chemse/bju004

[42] Hedner M, Nilsson LG, Olofsson JK, Bergman O, Eriksson E, Nyberg L et al. Age-related olfactory decline is associated with the BDNF Val66met polymorphism: evidence from a population-based study. Front. Aging Neurosci. 2010; 2:24. Doi. org/10.1080/13803391003683070.

[43] Doty RL, Petersen I, Mensah N, & Christensen, K (2011). Genetic and environmental influences on odor identification ability in the very old. Psychology and Aging, 26(4), 864-871. Doi.org/10.1037/a0023263

[44] Yaffe K, Freimer D, Chen H, et al. Olfaction and risk of dementia in a biracial cohort of older adults. Neurology 2017; 88: 456-462. Doi.org/10.1212/WNL.0000000000003558

[45] Van Regemorter V, Hummel T, Rosenzweig F, Mouraux A, Rombaux P and Huart C (2020) Mechanisms Linking Olfactory Impairment and Risk of Mortality. Front. Neurosci. 14:140. Doi: 10.3389/fnins.2020.00140

[46] Morrison JH and Baxter MG. The ageing cortical synapse: hallmarks and implications for cognitive decline. Nat. Rev. Neurosci. 2012; 13:240-250. Doi. org/10.1038/nrn3200

[47] Liu Z, Chen Z, Shang C, Yan F, Shi Y, Zhang J, Qu B, Han, H, Wang Y, Li D, Südhof TC, Cao P. IGF1-dependent synaptic plasticity of mitral cells in olfactory memory during social learning. Neuron. 2017; 95: 106-122. Doi.org/10.1016/j.neuron.2017.06.015

[48] Bhatia-Dey N, Kanherkar RR, Stair SE, Makarev EO and Csoka AB (2016) Cellular Senescence as the Causal

Nexus of Aging. Front. Genet. 7:13. doi: 10.3389/fgene.2016.00013

[49] Hoang ML, Kinde I, Tomasetti C, McMahon KW, Rosenquist TA, Grollman AP, et al. Genome-wide quantification of rare somatic mutations in normal human tissues using massively parallel sequencing. Proc Natl Acad Sci U S A. 2016; 113:9846-51. Doi:10.1073/pnas.1607794113/

[50] Lodato MA, Rodin RE, Bohrson CL, Coulter ME, Barton AR., Kwon M, ... Walsh, C. A. (2018). Aging and neurodegeneration are associated with increased mutations in single human neurons. Science, 359, 555-559. Doi. org/10.1126/science.aao4426

[51] Djordjevic J, Jones-Gotman M, De Sousa K, Chertkow H. Olfaction in patients with mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 2008; 29:693-706. Doi.org/10.1016/j. neurobiolaging.2006.11.014.

[52] Doty, RL Olfactory dysfunction in neurodegenerative diseases: is there a common pathological substrate? Lancet. Neurol. 2017, 16, 478-488. Doi. org/10.1016/S1474-4422(17)30123-0

[53] Marin C, Vilas D, Langdon C, Alobid I, López-Chacón M, Haehner A, Hummel T, Mullol J Olfactory dysfunction in neurodegenerative diseases. Curr Allergy Asthma Rep 2018; 18, 42. Doi.org/10.1007/ s11882-018-0796-4

[54] Doty RL and Hawkes CH. Chemosensory dysfunction in neurodegenerative diseases. Smell and Taste. 2019; 325-360. Doi:10.1016/ B978-0-444-63855-7.00020-4,

[55] Brozzetti L, Sacchetto L, Cecchini MP, Avesani A, Perra D, Bongianni M, Portioli C, Scupoli M, Ghetti B, Monaco S, Buffelli M and ZanussoGNeurodegeneration-Associated Proteins in Human Olfactory Neurons Collected by Nasal Brushing. Front. Neurosci. 2020; 14:145.Doi: 10.3389/ fnins.2020.00145

[56] Heyanka DJ, Golden CJ, McCue RB II, Scarisbrick DM, Linck JF, Zlatkin NI (2014). Olfactory deficits in frontotemporal dementia as measured by the Alberta smell test. Appl. Neuropsychol. Adult 21, 176-182. Doi:10.1080/ 09084282.2013.782031

[57] Franks KH, Chuah MI, King AE and Vickers JC. Connectivity of Pathology: The Olfactory System as a Model for Network-Driven Mechanisms of Alzheimer's Disease Pathogenesis. Front. Aging Neurosci. 2015; 7:234. Doi: 10.3389/fnagi.2015.00234

[58] Mesholam RI, Moberg PJ, Mahr RN, & Doty RL. Olfaction in neurodegenerative disease: A meta-analysis of olfactory functioning in Alzheimer's and Parkinson's diseases. Archives of Neurology. 1998; 55, 84-90. Doi:10.1001/archneur.55.1.84

[59] Luzzi S, Snowden JS, Neary D, Coccia M, Provinciali L, Ralph MAL. Distinct patterns of olfactory impairment in Alzheimer's disease, semantic dementia, frontotemporal dementia, and corticobasal degeneration. Neuropsychologia, 2007; 45:1823-1831. Doi:10.1016/j. neuropsychologia.2006.12.008

[60] Devanand DP, Michaels-Marston KS, Liu X, et al. Olfactory deficits in patients with mild cognitive impairment predict Alzheimer's disease at follow-up. Am J Psychiatry 2000; 157:1399-405. Doi.org/10.1176/appi. ajp.157.9.1399

[61] Devanand DP, Lee S, Manly J, et al. Olfactory deficits predict cognitive decline and Alzheimer dementia in an urban community. Neurology. 2015; 84: 182-189. Doi.org/10.1212/ WNL.0000000000001132

[62] McLaughlin NC, Westervelt HJ Odor identification deficits in frontotemporal dementia: a preliminary study. Arch Clin Neuropsychol. 2008; 23, 119-123. Doi:10.1016/j.acn.2007.07.008

[63] Spillantini MG and Goedert M. Tau pathology and neurodegeneration. Lancet Neurol 2013; 123, 609-622.

[64] Lafaille-Magnan ME, Poirier J, Etienne P, Tremblay-Mercier J, Frenette J, Rosa-Neto P, et al. PREVENT-AD Research Group. Odor identification as a biomarker of preclinical AD in older adults at risk. Neurology. 2017; 89:327-35. Doi 10.1212/WNL.0000000000004159

[65] Rey NL, Wesson DW, Brundin P. The olfactory bulb as the entry site for prion-like propagation in neurodegenerative diseases. Neurobiology of Disease, 2018: 109: 226-248. Doi.org/10.1016/j.nbd.2016.12.013

[66] Fujita KA, Ostaszewski M, Matsuoka Y, et al. Integrating pathways of Parkinson's disease in a molecular interaction map. Mol Neurobiol 2014; 49:88-102. Doi 10.1007/s12035-013-8489-4

[67] Wszolek ZK, Markopoulou K. Olfactory dysfunction in Parkinson's disease. Clin Neurosci 1998;5:94-101

[68] Doty RL, Deems DA, Stellar S. Olfactory dysfunction in Parkinsonism: a general deficit unrelated to neurologic signs, disease stage, or disease duration. Neurology. 1988; 38:1237-124.

[69] Doty RL, Stern, MB, Pfeiffer C, Gollomp, SM, Hurting HI. Bilateral olfactory dysfunction in early stage treated and untreated idiopathic Parkinson's disease. J. Neurol. Neurosurg. Psychiatry. 1992; 55, 138-142

[70] Ponsen MM, Stoffers D, Booij J, van Eck-Smit BLF, Wolters EC, Berendse HW. Idiopathic hyposmia as a preclinical sign of Parkinson's disease. Ann Neurol. 2004; 56:173-181. Doi: 10.1002/ana.20160

[71] Doty RL. Olfactory dysfunction in Parkinson disease. Nat.Rev.Neurol. 2012a; 8:329-339. Doi:10.1038/nrneurol.2012.80

[72] Doty RL. Olfaction in Parkinson's disease and related disorders. Neurobiol. Dis. 2012b; 46, 527-552. Doi.org/10.1016/j.nbd.2011.10.026

[73] Fullard ME, Morley JF, Duda JE. Olfactory dysfunction as an early biomarker in Parkinson's disease. Neurosci Bull. 2017; 33:515-25. Doi.org/10.1007/s12264-017-0170-x

[74] Witt M, Bormann K, Gudziol V. Biopsies of olfactory epithelium in patients with Parkinson's disease. Mov Disord. 2009; 24: 906-914. Doi: 10.1002/mds.22464

[75] Wang J, You H, Liu JF, Ni DF, Zhang ZX, Guan J. Association of olfactory bulb volume and olfactory sulcus depth with olfactory function in patients with Parkinson disease. AJNR Am J Neuroradiol. 2011; 32:677-681. Doi.org/10.3174/ajnr.A2350

[76] Luk KC, Lee VM. Modeling Lewy pathology propagation in Parkinson's disease. Parkinsonism Relat Disord. 2014; 20:S85–S87. Doi.org/10.1016/S1353-8020(13)70022-1

[77] Del Tredici K, Rub U, De Vos RA, Bohl JR, Braak H. Where does Parkinson disease pathology begin in the brain? J Neuropathol Exp Neurol. 2002; 61: 413-426. Doi.org/10.1093/jnen/61.5.413

[78] Espay AJ, Kalia LV, Gan-Or Z, et al. Disease modification and biomarker development in Parkinson disease: Revision or reconstruction? Neurology. 2020; 94:481-494. Doi:10.1212/WNL.0000000000009107

[79] Takeda A, Baba T, Kikuchi A., Hasegawa T, Sugeno N, Konno M., Miura E. & Mori E. Olfactory dysfunction and dementia in Parkinson's disease. J. Parkinsons Dis. 2014; 4: 181-187. Doi: 10.3233/JPD-130277

[80] Mahlknecht P, Pechlaner R, Boesveldt S, Volc D, Pinter B, Reiter E, et al. Optimizing odor identification testing as quick and accurate diagnostic tool for Parkinson's disease. Movement Disorders. 2016; 31:1408-1413. Doi: 10.1002/mds.26637

[81] Zucco, GM, Bollini F. Odour recognition memory and odour identification in patients with mild and severe major depressive disorders. Psychiatry Res. 2011; 190: 217-220. Doi:10.1016/j.psychres.2011.08.025

[82] Taalman H, Wallace C and Milev R. Olfactory Functioning and Depression: A Systematic Review. Front. Psychiatry. 2017; 8:190. Doi: 10.3389/fpsyt.2017.00190

[83] Naudin M, Atanasova B. Olfactory markers of depression and Alzheimer's disease. Neurosci. Biobehav. Rev. 2014; 45, 262-270. Doi: 10.1016/j.psychres.2014.08.050

[84] Croy I, Negoias S, Novakova L, Landis B, Hummel T. Learning about the functions of the olfactory system from people without a sense of smell. PLoS One 2012; 7, e33365.Doi: 10.1016/j.jad.2013.12.026

[85] Sivertsen H, Bjørkløf GH, Engedal K, Selbæk G, Helvik A-S. Depression and Quality of Life in Older Persons: A Review. Dement. Geriatr. Cogn. Disord. 2015; 40:311-339. Doi: 10.1159/000437299

[86] Rochet M, El-Hage W, Richa S, Kazour F, Atanasova B. Depression, olfaction, and quality of life: a mutual relationship. Brain Sci. 2018; 8: 80. Doi:10.3390/brainsci8050080

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

[88] Anderson AK, Christoff K, Stappen I, Panitz D, Ghahremani DG, Glover G, Gabrieli JDE, Sobel N. Dissociated neural representations of intensity and valence in human olfaction. Nat. Neurosci. 2003; 6:196-202. Doi.org/10.1038/nn1001

[89] Kiracanski K, Joormann J, Gotlib IH. Cognitive aspects of depression: Cognitive aspects of depression. Wiley Interdiscip. Rev. Cogn. Sci. 2012; 3:301-313. Doi: 10.1002/wcs.1177

[90] Kohli P, Soler ZM, Nguyen SA, Muus JS, Schlosser RJ. The association between olfaction and depression: a systematic review. Chem. Senses. 2016; 41: 479-86. Doi:10.1093/chemse/bjw061

[91] Negoias S, Hummel T, Symmank A, Schellong J, Joraschky P, & Croy I. Olfactory bulb volume predicts therapeutic outcome in major depression disorder. Brain imaging and behavior. 2015; Doi 10.1007/s11682-015-9400-x

[92] Wicker B, Monfardini E, & Royet J-P. Olfactory processing in adults with autism spectrum disorders. Molecular Autism. 2016; 7:1-11. Doi 10.1186/s13229-016-0070-3

[93] Geramita MA, Wen JA, Rannals, MD, Urban NN. Decreased amplitude and reliability of odor-evoked responses in two mouse models of autism Journal of Neurophysiology. 2020; 123: 1283-1294. Doi.org/10.1152/jn.00277.2019

[94] Riley JD, Delahunty, C, Alsadah A, Mazzola, S. Further evidence of GABRA4 and TOP3B as autism susceptibility genes European Journal of Medical Genetics. 2020; 63: Doi.org/10.1016/j.ejmg.2020.103876

[95] Satterstrom FK, Kosmicki JA, Wang J, Breen MS, De Rubeis S, An J-Y., Peng M, Collins, R., Grove, J., Klei L., Stevens C, Reichert J, Mulhern MS, Artomov M, Gerges S, Sheppard, B., Xu X, Bhaduri A, Norman U, Brand H, Schwartz G., Nguyen R, & Guerrero EE. Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism. Cell. 2020; 180:568-584. Doi. org/10.1016/j.cell.2019.12.036

[96] Hummel T, Landis BN, Hüttenbrink KB. Smell and taste disorders. GMS Curr Top Otorhinolaryngol Head Neck Surg. 2011; 10:Doc04. Doi: 10.3205/cto000077,

[97] Cohen J, Wakefield CE, Laing DG. Smell and taste disorders resulting from cancer and chemotherapy. Curr Pharm Des 2016; 22:2253-63.

[98] Le XTPham HTN, Do PT. et al. *Bacopa monnieri* Ameliorates Memory Deficits in Olfactory Bulbectomized Mice: Possible Involvement of Glutamatergic and Cholinergic Systems. Neurochem Res. 2013; 38:2201-2215. Doi 10.1007/s11064-013-1129-6

[99] Yi LT, Li J, Li HC, Su DX, Quan, XB, He XC, Wang XH. Antidepressant like behavioral, neurochemical and neuroendocrine effects of Naringenin in the mouse repeated tail suspension test. Prog. Neuro Psychopharmacol. Biol. Psychiatry. 2012; 39:175-181. Doi. org/10.1016/j.pnpbp.2012.06.009.

[100] Bansal Y, Singh R, Saroj P, Sodhi RK, Kuhad A. Naringenin protects against oxido-inflammatory aberrations and altered tryptophan metabolism in olfactory bulbectomized-mice model of depression. Toxicol. Appl. Pharmacol. 2018; 355: 257-268. Doi.org/10.1016/j.taap.2018.07.010

[101] Leventhal AM, Gelernter J, Oslin D, Anton RF, Farrer LA, Kranzler, HR. Agitated depression in substance dependence Drug and Alcohol Dependence. 2011; 116:163-169. Doi:10.1016/j.drugalcdep.2010.12.012

[102] Saiz-Sanchez D, Ubeda-Bañon I, Flores-Cuadrado A, Gonzalez-Rodriguez M, Villar-Conde S, Astillero-LopezV andMartinez-MarcosA. Somatostatin, Olfaction, and Neurodegeneration. Front. Neurosci. 2020; 14:96. Doi: 10.3389/ fnins.2020.00096

[103] Cooper KW, Brann DH, Farruggia MC, Bhutani S, Pellegrino R, Tsukahara T, Weinreb C, Joseph PV, Larson ED, Parma V, Albers MW, Barlow LA, Datta SR, and Di Pizio A. 2020 COVID-19 and the chemical senses: supporting players take center stage. Neuron, 2020; 107: 219-233 doi. org/10.1016/j.neuron.2020.06.032

[104] Parma V, Ohla K, Veldhuizen MG, Niv MY, Kelly CE, Bakke AJ, Cooper KW, Bouysset C, Pirastu N, DibattistaM,KaurR,LiuzzaMT,PepinoMY, Schopf V, Pereda-Loth V, Olsson SB, Gerkin RC, Domínguez PR, Albayay J, Farruggia MC, Bhutani S, Fjaeldstad AW, Kumar R, Menini A, Bensafi M, Sandell M, Konstantinidis I, Di Pizio A, Genovese F, Oztürk L, Thomas-Danguin T, Frasnelli J, Boesveldt S, Saatci Ö, Saraiva LR, Lin C, Golebiowski J, Hwang LD, Ozdener MH, Guàrdia MD, Laudamiel C, Ritchie M, HavlícekJ., PierronD, RouraE, NavarroM, Nolden AA, Lim J, Whitcroft KL, Colquitt LR, Ferdenzi C, Brindha EV, Altundag A, Macchi A., Nunez-Parra A, Patel ZM, Fiorucci S, Philpott CM, Smith BC, Lundström JN, Mucignat C, Parker JK, van den Brink M, Schmuker M, Fischmeister FPS, Heinbockel T, Shields VDC, Faraji F, Santamaría E, Fredborg WEA, Morini G., Olofsson JK, Jalessi M, Karni N, D'Errico A, Alizadeh R, Pellegrino R, Meyer P, Huart C, Chen B, SolerGM,AlwashahiMK,Welge-LüssenA, Freiherr J, De Groot JHB, Klein H, Okamoto M., Singh PB, Hsieh JW, GCCR

Group Author, Reed DR, Hummel T, Munger SD and Hayes JE More than smell - COVID-19 is associated with severe impairment of smell, taste, and chemesthesis. Chem Senses; 2020; bjaa041.

[105] Pellegrino R, Cooper KW, Di Pizio A, Joseph PV, Bhutani S, Parma V. Corona viruses and the chemical senses: Past, present, and future. Chem Senses. 2020. DOI: 10.1093/chemse/bjaa031

[106] Brann DH, Tsukahara T, Weinreb C, Lipovsek M, Van den Berge K, Gong B, Chance R, Macaulay IC, Chou HJ, Fletcher RB, Das D, Street K, Roux de Bezieux H, Choi YG, Risso D, Dudoit S, Purdom E, Mill J, Hachem RA, Matsunami H, Logan DW, Goldstein BJ, Grubb MS, Ngai J, Datta SR. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. Sci. Adv; 2020; 10.1126/sciadv.abc5801

[107] Bryche B, St Albin A, Murri S, Lacôte S, Pulido, C, Ar Gouilh M, Lesellier, S, Servat A, Wasniewski, M, Picard-Meyer E. Massive transient damage of the olfactory epithelium associated with infection of sustentacular cells by SARS-CoV-2 in golden Syrian hamsters. Brain. Behav. Immun. 2020. doi.org/10.1016/j.bbi.2020.06.032

[108] Diaz D, Gomez C, Munoz-Castaneda R, et al. The olfactory system as a puzzle: playing with its pieces. Anat Rec. (Hoboken) 2013; 296: 1383-1400. Doi 10.1002/ar.22748

[109] Heinbockel T. Introductory chapter: Mechanisms and function of synaptic plasticity. In: Synaptic Plasticity. Thomas Heinbockel (ed.), Rijeka, Croatia, InTech Publisher. 2017; 3-13, Doi.org/10.5772/67891

[110] Lucassen EB, Turel A, Knehans A, Huang X, Eslinger P. Olfactory dysfunction in multiple sclerosis: a scoping review of the literature. Mult. Scler. Relat. Disord. 2016; 6:1-9. Doi.org/10.1016/j.msard.2015.12.002.

[111] Baney J. A cause of olfactory dysfunction in MS? Neurol. Rev. 2011; 19: 7.

[112] Orasji SSS, Mulder JL, de Bruijn SFTM, Wirtz PW. Olfactory dysfunction in behavioral variant frontotemporal dementia. Clin Neurol Neurosurg. 2016; 141:106-110. Doi.org/10.1016/j.clineuro.2016.01.003 0303-8467

[113] Herman AM, Critchley, H, & Duka T. Decreased olfactory discrimination is associated with impulsivity in healthy volunteers. Scientific Reports. 2018; 8. Doi: 10.1038/s41598-018-34056-9

[114] Mori I. The olfactory bulb: A link between environmental agents and narcolepsy. Medical hypotheses. 2019; 126: 66-68. doi.org/10.1016/j.mehy.2019.03.017

[115] Tan L, Li Q, Xie XS. Olfactory sensory neurons transiently express multiple olfactory receptors during development. Mol. Syst. Biol., 2015; 11:844. Doi 10.15252/msb.20156639

[116] Hanchate NK, Kondoh K, Lu Z, Kuang D, Ye X, Qiu X, Pachter L, Trapnell C, Buck LB. Single-cell transcriptomics reveals receptor transformations during olfactory neurogenesis, Science. 2015; 350:1251-1255. Doi:10.1126/science.aad2456

[117] Bashkirova E & Lomvardas S. Olfactory receptor genes make the case for inter-chromosomal interactions. Curr Opin Genet Dev. 2019; 55:106-113. Doi.org/10.1016/j.gde.2019.07.004

[118] Sedelnikova OA, Horikawa I, Zimonjic DB, Popescu NC, Bonner WM, Barrett JC. Senescing human cells and ageing mice accumulate DNA lesions with unrepairable double-strand breaks. Nat. Cell Biol. 2004; 6:168-70. Doi: 10.1038/ncb1095

[119] Petr, MA, Tulika T, Carmona-Marin LM, Scheibye-Knudsen M. Protecting the Aging Genome. Trends Cell Biol. 2020; S0962-8924. Protecting the Aging Genome. Trends Cell Biol. 2020; S0962-8924. Doi. org/10.1016/j.tcb.2019.12.001

[120] Tepe B, Hill MC, Pekarek BT, Hunt PJ, Martin TJ, Martin JF, Arenkiel BR. Single-cell RNA-Seq of mouse olfactory bulb reveals cellular heterogeneity and activity-dependent molecular census of adult-born neurons. Cell Rep. 2018; 25: 2689-2703. Doi. org/10.1016/j.celrep.2018.11.034

[121] Chou RH, Lu CY, Fan JR, Yu YL, Shyu WC. The potential therapeutic applications of olfactory ensheathing cells in regenerative medicine. Cell Transplant. 2014; 23:567-71. Doi. org/10.3727/096368914X678508

[122] Bhatia-Dey N and Heinbockel T. Endocannabinoid-Mediated Neuromodulation in the Olfactory Bulb: Functional and Therapeutic Significance. Int. J. Mol. Sci. 2020, 21: 2850. Doi:10.3390/ ijms21082850

[123] Xu B, Karayiorgou M, Gogos JA. MicroRNAs in psychiatric and neurodevelopmental disorders. Brain Res. 2010; 1338:78-88. Doi.org/10.1016/j. brainres.2010.03.109

[124] Hernandez-Rapp J, Rainone S, Hébert SS. MicroRNAs underlying memory deficits in neurodegenerative disorders. Prog. Neuropsychopharmacol. Biol. Psychiatry 2017; 73:79-86. Doi. org/10.1016/j.pnpbp.2016.04.011

[125] Swarbrick S, Wragg, N, Ghosh S, and Stolzing A. Systematic review of miRNA as biomarkers in Alzheimer's disease. Mol. Neurobiol. 2019; 56: 6156-6167. Doi: 10.1007/s12035-019-1500-y

[126] Reza-Zaldivar EE, Hernández-Sápiens MA, Minjarez B, Gómez-Pinedo U, Sánchez-González VJ, Márquez-Aguirre AL and Canales-Aguirre AA. Dendritic Spine and Synaptic Plasticity in Alzheimer's disease: A Focus on MicroRNA. Front. Cell Dev. Biol. 2020; 8:255.Doi: 10.3389/ fcell.2020.00255