Published in final edited form as:
Curr Geriatr Rep. 2014 June 1; 3(2): 91–100. doi:10.1007/s13670-014-0080-y.

Olfactory Dysfunction in the Elderly: Basic Circuitry and Alterations with Normal Aging and Alzheimer's Disease

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Abstract

Preclinical detection of Alzheimer disease is critical to determining at-risk individuals in order to improve patient and caregiver planning for their futures and to identify individuals likely to benefit from treatment as advances in therapeutics develop over time. Identification of olfactory dysfunction at the preclinical and early stages of the disease is a potentially useful method to accomplish these goals. We first review basic olfactory circuitry. We then evaluate the evidence of pathophysiological change in the olfactory processing pathways during aging and Alzheimer disease in both human and animal models. We also review olfactory behavioral studies during these processes in both types of models. In doing so, we suggest hypotheses about the localization and mechanisms of olfactory dysfunction and identify important avenues for future work.

Keywords

Olfaction; Alzheimer disease; mild cognitive impairment; aging; early detection; amyloid plaque; tau; neurofibrillary tangle; olfactory epithelium; olfactory bulb; piriform cortex; orbitofrontal cortex; entorhinal cortex; hippocampus

Introduction

The predicted exponential rise in the aging population and Alzheimer disease (AD) prevalence has emboldened efforts to develop better therapies. It is therefore critical to elucidate the pathological mechanism in AD itself as well as its relationship to aging, its biggest demographic risk factor. In addition, it has become imperative to develop strategies for pre-clinical detection, given the possibility that future therapies may be used to prevent rather than reverse the disease. Evidence of age-dependent decline in olfactory ability, and anatomical involvement of olfactory pathways and olfactory behavioral deficits early in AD have led to the idea that this sensory system may provide an interesting avenue by which to tackle these issues. Additionally, olfactory dysfunction is also implicated in Parkinson

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Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

disease, reviewed recently (Doty 2012), suggesting that olfactory pathways may be particularly vulnerable to neurodegenerative conditions. Here, we review the pathophysiological changes in olfactory circuits as well as deficits in olfactory-related behaviors during normal aging and AD, both in humans and in rodent models. In this manner, we provide a background by which to better understand the localization and pathological basis of olfactory deficits found in these interrelated processes, and to cite critical areas for future research.

Brief overview of the olfactory system

The olfactory pathway is summarized in Figure 1 (reproduced with permission from Wolters Kluwer Health). For further detail see extensive reviews (ex. Shepherd et al 2004). Odors enter the nasal cavity, dissolve in the olfactory mucosa, and interact with olfactory receptor neurons (ORNs) in the epithelium via transmembrane G-protein coupled olfactory receptor (OR) proteins. Each ORN expresses one OR type, and ORNs expressing the like ORs project to the same glomeruli on the olfactory bulb (OB). Glomeruli are spherical structures in which ORN axons synapse onto apical dendrites of OB output neurons, mitral and tufted cells. This is modulated by periglomerular (PG) interneuron subtypes expressing GABA, dopamine, and other neurotransmitters. In the external plexiform layer of the OB, output is further modulated by granule cell (GC) inhibition delivered to lateral dendrites. Deeper layers of the OB include the mitral cell layer, internal plexiform layer, and granule cell layer. In rodent, PG and GCs are replenished by adult neurogenesis in the subventricular zone (SVZ). OB principal neurons subsequently project to higher structures via the lateral olfactory tract that include the anterior olfactory nucleus (AON), olfactory tubercle, amygdala, piriform cortex (PC), and entorhinal cortex (EC). From here, information flows to neocortical regions including the orbital or orbitofrontal region of prefrontal cortex (PFC) that occurs directly or via the mediodorsal thalamus. The EC provides the primary input to the hippocampus. There are also recurrent pathways between these regions, and even back to the OB. Modulation by noradrenergic, serotoninergic, and cholinergic input from locus coeruleus, raphe nuclei, and nucleus basalis, respectively, occurs across all levels of the system.

Brief overview of olfactory behavioral assessment

Olfaction is tested in many ways in both humans and laboratory animals. Odor identification tests assess the ability to correctly name an odor, describe its quality, or choose descriptive words from a list. Examples include the University of Pennsylvania Smell Identification Test and the Brief Smell Identification Test. Details regardings these and other aspects of human olfactory testing have been reviewed (Doty, 2007). Odor threshold is the minimum concentration for reliable detection, and sensitivity is inversely proportional to this. Discrimination is the ability to differentiate two or more odors. Social odor memory, tested in rodents, represents reduced exploration of an unfamiliar rodent with repeated exposure. Similarly, habituation is decreased responsiveness to a non-social odor upon repeated presentations, and dishabituation represents responsiveness to a habituated odor as if it were again novel. In olfactory reversal testing of animals, positive and negative rewards for discriminating between two odors are switched to assess cognitive flexibility. Olfactory

working memory can be tested if a task requires the subject to actively remember a particular sequence of odors.

Pathophysiological changes in the olfactory areas with normal aging and Alzheimer disease in humans

Few studies have examined human olfactory pathology with respect to normal aging. During senescence, the ORN population declines as olfactory epithelium is gradually replaced with respiratory epithelium (Paik et al 1992). ORNs from older versus young live donors show reduced response specificity rather than decreased thresholds (Rawson et al 2012). In the olfactory bulb, there are reports of either no decline in glomerular number (Maresh et al 2008), or reduction in glomeruli and mitral cells with age (Meisami et al 1998). At the network level, late components of the olfactory event related potential show increased latency with age, suggesting that central structures are involved (Morgan et al 1999). Similarly, functional MRI during olfactory stimulation, identification, and discrimination tests in young and old patients has revealed abnormal blood-oxygen-level dependent (BOLD) responses in the piriform cortex, frontal and temporal lobes of older subjects (Yousem et al 1999, Suzuki et al 2001, Kareken et al 2003, Cerf-Ducastel and Murphy 2003, Wang et al 2005). Therefore, olfactory decline with normal aging in humans appears to localize to the olfactory epithelium and higher cortical areas.

In AD, the human OB shows minimal mature amyloid plaque (Mann et al 1988, Reyes et al 1993, ter Laak et al 1994, Mundinano et al 2011, Cai et al 2012, Esiri and Wilcock 1984, Ohm and Braak 1987, Loopujit and Sebens 1990, Hyman et al 1991, Struble and Clark 1992). Neurofibrillary tangle (NFT) burden in the OB is typically higher (Ohm and Braak 1987, Mann et al 1988, Hyman et al 1991, Reyes et al 1993, Mundinano et al 2011), though sometimes also negligible (Loopujit and Sebens 1990, Struble and Clark 1992, ter Laak et al 1994, Esiri and Wilcock 1984). With disease progression, there is consistently more tau than beta amyloid-related pathology in the OB, but the likelihood and extent of both increase with Braak stage (Attems et al 2005). In a study of brain tissue derived from AD patients and controls, pathology was reported in the OB at Braak stage 0 and 1, including in some controls (Kovacs et al 2001). This suggests that OB involvement can occur at early stages. It is unclear if controls represented pre-clinical AD or normal aging, as such changes have not been reported in studies of pure senescence discussed above.

The OB of patients with Alzheimer disease may show reduced volume compared to agematched controls (Mundinano et al 2011, ter Laak et al 1994). All layers can be affected by NFTs and plaque, some noting a preponderence in the superficial layer (Ohm and Braak 1987, Loopujit and Sebens 1990, Kovacs et al 1999). Morphological changes have also been noted in the superficial strata. Specifically, there the olfactory epithelium shows plaque (Struble and Clark 1992, Kovacs et al 1999) and glomeruli may be hyperplastic (Struble and Clark 1992) or reduced in area (Cai et al 2012). Processing may be further affected by an increase in dopaminergic interneurons (Mundinano et al 2011) or loss of D2 dopamine receptors (Loopujit and Sebens 1990). Mitral cell loss is evident in some studies but not others (Struble and Clark 1992, Loopujit and Sebens 1990, ter Laak et al 1994, Hyman et al 1991). These studies suggest that, similar to normal aging, the first layers of the peripheral

olfactory system are particularly vulnerable to Alzheimer change compared to the rest of the OB.

Compared to the OB, higher order regions display more extensive plaque and tangles (Reyes et al 1993). Functional MRI and SPECT of AD patients have been useful to detail region-specific physiological implications, demonstrating abnormal BOLD responses and hypoperfusion, respectively, in the piriform cortex during various olfactory tests (Li et al 2010, Wang et al 2010, Kareken et al 2001). FDG-PET during an olfactory memory task in AD patients showed hypometabolism in the anterior medial temporal cortex (Buchsbaum et al 1991). Reduced odor identification, discrimination, and detection threshold in patients with early Alzheimer disease correlated with hypometabolism in a broad network involving parietal and frontal cortex, thalamus, and cerebellum (Forster et al 2010). In sum, these studies suggest that olfactory deficits in AD can correlate with dysfunction in higher cortical areas, in addition to or despite pathologic change in the OB and epithelium.

Pathophysiological changes in the olfactory areas in aged animals and animal models of Alzheimer disease

Age-related changes in the olfactory system of rodents have been studied in animals greater than 2 years of age, at which age-related cognitive impairment is most apparent. At this point, there is a decline in ORN density (Meisami et al 1989, Hinds and McNelly 1981, Lee et al 2009) but maintenance of individual ORN sensitivity (Lee et al 2009). Consequently, within the glomeruli, there is a reduction of synaptic interactions (Hinds and McNelly 1981, Richard et al 2010). In some mouse strains there is age-related proliferation of dopaminergic interneurons (Mirich et al 2002), despite decreased neurogenesis (Tropepe et al 1997, Enwere et al 2004, Mobley et al 2013). This could suggest age-related alteration in interneuron turnover. There are inconsistent findings regarding mitral cell stability and synapses with granule cells (Hinds and McNelly 1979, Forbes 1984, Richard et al 2010). Overall, changes in the rodent appear similar to those in the human.

The aging piriform cortex shows a loss of AMPA receptors (Gocel and Larson 2013). Research on the aging frontal and temporal lobe has been extensive and is beyond the scope of this review, though the prefrontal cortex and dentate gyrus have been implicated in age-related cognitive decline (Samson and Barnes 2013). Few studies have approached these areas in relation to olfaction. Dysfunction of the cholinergic septohippocampal pathway leads to a deficit in social odor memory (Terranova et al 1994). In vivo neuronal recordings from orbitofrontal cortex in older rats show abnormal rigidity of their responses to odors during reversal tasks (Schoenbaum et al 2006). The implication of rodent frontal and temporal lobe dysfunction with olfactory dysfunction is consistent with human studies.

There exist multiple mouse models of AD based on overexpression of one or amyloidogenic human genes, and these include the Tg2576, APP/PS1, and 5xFAD mice. The 3xTg mouse is unique because it also includes tau. We review features of these models, beginning peripherally and progressing centrally.

Dysmorphic ORN axon terminals can be seen in multiple models prior to the appearance of Aβ plaque in the epithelium (Cai et al 2012), which does not form until 18 months in the Tg2576 mouse (Guerin et al 2009, Kameshima et al 2012). Nonspecific immunoreactivity to Aβ can occur in the epithelium as early as 1–2 months, preceding insoluble plaque formation (Wu et al 2013). This suggests a role for ORN axonal dysfunction, via actions of soluble Aβ, in activity-dependent pathophysiology of OB function. Indeed, glomerular area is reduced in the 5xFAD model prior to plaque appearance (Cai et al 2012). Additionally, mice in which APP is overexpressed only in ORNs demonstrate pre-plaque apoptosis in the epithelium and disruption of axonal targeting and circuitry in the glomerulus (Cheng et al 2011, Cao et al 2012, Cheng et al 2013).

In contrast to the epithelium, the OB shows plaque formation as early as 3–4 months (Rockenstein et al 2001, Lehman et al 2003, Smith et al 2007, Kameshima et al 2012, Cai et al 2012, Wu et al 2013, but see Cassano et al 2011). Despite earlier onset of amyloidogenesis in the glomerular layer, the granule cell layer is particularly susceptible to volume reduction and both soluble and insoluble Aβ (Guerin et al 2009, Wesson et al 2010, Cai et al 2012, Saiz-Sanchez et al 2013). Interneuron markers are also reduced, with calretinin (CR) and somatostatin (SOM) affected prior to parvalbumin (PV) (Saiz-Sanchez et al 2013). Regarding interneurons, neurogenesis has also been reported to be disrupted early, evidenced by hypoactivity, hyperactivity, or plaque in the SVZ (Cai et al 2012, Guerin et al 2009, Haughey et al 2002, Demars et al 2010, Sotthibundhu et al 2009, but see Zhang et al 2007). A role for non-plaque related pathology is suggested by abnormal spontaneous electrical activity in the Tg2576 mouse at 3–4 months, prior to granule cell layer plaque deposition, which corresponds instead to abnormal odor-evoked activity at 6–7 months (Wesson et al 2010). Lastly, the OB does not show tau immunoreactivity in the 3xTg mouse (Cassano et al 2011).

The piriform cortex displays both signs of general amyloidogenesis, insoluble Aβ plaque, and also neurofibrillary tangles (Lewis et al 2001, Wesson et al 2010, Cassano et al 2011, Kim et al 2012, Wu et al 2013). In general, the progression of changes is temporally delayed when compared to the olfactory bulb and epithelium, beginning as early as 6–7 months, and layer III is particularly vulnerable (Wesson et al 2010, Wu et al 2013). Similar to the OB, SOM- and CR-expression in interneurons declines first, followed by PV and calbindin (CB), prior to diffuse amyloidosis (Saiz-Sanchez et al 2012). Also analogous to the OB, in the Tg2576 mouse there is aberrant spontaneous electrical activity in the piriform cortex at an early stage, followed by abnormal odor-evoked activity and hypoactivity at late stages that largely precedes insoluble plaque formation (Wesson et al 2011).

Few studies have studied hippocampal and frontal cortical changes in reference to olfactory system pathology. In the Tg2576 and APP/PS1 model, changes occur later in hippocampus and entorhinal cortex than in the OB and epithelium, typically matching the time course of changes in the piriform cortex, and with frontal cortex involved similarly or later (Wesson et al 2010, Wu et al 2013). A reverse or alternative time course is suggested in the double APP mutation mouse and the 5xFAD model (Rockenstein et al 2001, Cai et al 2012, Girard et al 2013). At 18 months, amyloid and tau-related changes are found in orbitofrontal and entorhinal cortex, as well as hippocampus in the 3xTg model (Cassano et al 2011).

In summary, mouse models of AD have been useful to study the effects of amyloid plaque and soluble Aβ on olfactory brain circuits. However, there are several limitations. First, AD models develop deficits before age-related dysfunction commences. Secondly, the temporal progression of pathology does not correlate well with human AD. Lastly, there has been minimal work on the role of tau, despite more NFTs than plaque in the olfactory system in humans. Regarding this, the lack of OB tau immunoreactivity in the 3xTg mouse may diminish its utility.

Olfactory behavioral testing in humans with normal aging and Alzheimer disease

A summary of some key findings is provided in Table 1. We focus on recent studies with at least 50 total participants, and, if included, total longitudinal follow-up of no less than 1 year, typically with age matched controls. These primarily focus on Alzheimer disease and mild cognitive impairment (MCI) restricted to the memory domain, amnestic MCI , with odor detection identification as the primary test. Common to nearly all the studies is a correlation between baseline olfactory test scores and cognitive status, either quantitatively defined or qualitatively defined as MCI or dementia. Although this could be due to change in ther peripheral olfactory system detailed above, this has also been specifically associated with signs of functional and structural impairment related to the temporal lobe, including recall and hippocampal volume (Royall et al 2002, Devanand et al 2010, Murphy et al 2003). It should be noted that a general decline in odor identification with aging, especially above age 70, has long been documented (Doty et al 1984). Indeed, an inverse correlation with age and olfactory test scores is corroborated in some of these studies (Wilson et al 2007a, Devanand et al 2010). However, contributions of true normal aging are difficult to ascertain in human subjects because it is unclear whether “controls” harbor preclinical Alzheimer changes and because the likelihood of such changes increases with age. This is evident with findings in the longitudinal studies that lower performance on odor identification or odor sensitivity tests predicts cognitive decline, specifically conversion from normal to MCI or from MCI to dementia (Bacon et al 1998, Graves et al 1999, Devanand et al 2000, Royall et al 2002, Tabert et al 2005, Wilson et al 2007a, Devanand et al 2008, Schubert et al, 2008, Conti et al 2013). Therefore, early olfactory impairment may signify early Alzheimer pathology and may be useful as part of a preclinical detection strategy. Olfactory identification deficits are associated with a 4–5 fold increased risk of conversion from MCI to AD, and appear to contribute unique variance in the prediction of conversion from MCI to AD, and reinforce the view that multiple biomarkers and clinical markers may need to be assessed to improve diagnostic and predictive accuracy (Devanand et al, 2008).

Amyloid imaging with Pittsburgh compound B (PiB) found that presence of amyloid did not distinguish olfactory identification scores within the amnestic MCI group, despite lower performance compared to control (Bahar-Fuchs et al 2010). This may indicate that neocortical amyloid plaque burden itself is not related to olfactory identification deficits, at least at this early stage, and the findings are consistent with the neuropathological findings of predominantly tau and not amyloid pathology in the olfactory bulb and other olfactory

regions in the early stages of AD (Hyman et al, 1991). A neuropathological study also found that entorhinal cortex and CA1/subiculum tau burden predicted olfactory test scores better than plaque, though testing was done on average over 2 years prior to death (Wilson et al 2007b). Such findings would also further limit the utility of the predominantly amyloid-based mouse models.

Lastly, because other variants of MCI may signify neurodegenerative diseases other than Alzheimer disease or higher rates of conversion to dementia, MCI subtypes have also been examined. MCI can be amnestic, defined above, or non-amnestic, in which one cognitive domain other than memory is affected. Multidomain amnestic MCI involves memory and at least one other cognitive area, whereas multidomain non-amnestic MCI involves at least two domains other than memory. The results have been conflicting, either finding no difference in olfactory performance between MCI subtypes (Westervelt et al 2008), distinct differences between them (Devanand et al 2010), or significant difference from control only in multidomain amnestic MCI (Lehrner et al 2009).

However, overall there is a clear increase in olfactory deficits from normal to MCI to AD (Tabert et al, 2010; Devanand et al, 2010). In humans, these deficits occur initially in odor identification and progress to odor discrimination and odor sensitivity (Bacon Moore et al, 1999; Djordjevic et al, 2008). This suggests that the early olfactory deficit in AD incorporates not only damage in the olfactory bulb but also in higher order olfactory pathways (e.g., piriform, hippocampal, entorhinal, orbitofrontal cortex) that subserve olfactory memory and interpretation of odors. More correlation with Braak stage is needed, though OB changes can indeed occur with early entorhinal and hippocampal changes (Kovacs et al 2001).

Olfactory behavioral testing in senescent animals and models of Alzheimer disease

We first review the findings in studies of normal aging, in progression of cognitive complexity of the task. Overall, behavioral deficits in animals with normal aging occur at older ages than the earliest deficits in Alzheimer disease mice. As mentioned above, this should be interpreted in light of age-related pathology also occurring much later than Alzheimer changes. We first review studies in normal aging, and then studies with Alzheimer disease mice.

Odor sensitivity has been reported by some groups to decline with pure aging in rodents (Kraemer and Apfelbach 2004, Patel and Larson 2009, but see Enwere et al 2004, LaSarge et al 2007). Odor discrimination, which involves processing in the OB and higher, is less consistently affected by age (Enwere et al 2004, Prediger et al 2006, Patel and Larson 2009, Kramer and Apfelbach 2004, Luu et al 2008). Odor habituation and dishabituation, which depend on piriform cortex function, were examined in one study of rats, which found intact habituation but impaired dishabituation at 22 months (Guan and Dluzen 1994). Olfactory-specific learning deficits have been reported in 2 year old rodents (Roman et al 1996, LaSarge et al 2007) and odor long term memory, which may be cortical-dependent, was impaired in 2 year old rats (Roman et al 1996). Performance on the olfactory reversal task,

which is orbitofrontal cortex-dependent, declines with age as well (Schoenbaum et al 2006). Finally, social memory, which is highly olfactoryrelated in rodents, has been found be impaired with senescence (Terranova et al 1994, Prediger et al 2006). Lesion studies implicated a role of hippocampal CA1 and the septohippocampal projection (Terranova et al 1994).

Regarding animal models of Alzheimer disease, a summary of some key studies is provided in Table 2. Overall, such studies have demonstrated behavioral deficits roughly correlating with temporal progression of pathology. Despite epithelial changes, general olfactory sensitivity is typically not affected (Guerin et al 2009, Cassano et al 2011, Montgomery et al 2011, Phillips et al 2011, but see Rey et al 2012, Wu et al 2013). This may be because animals are tested prior to age-dependent decline in epithelial function. Nonetheless, the AD mouse model findings are consistent with human data showing early odor identification deficits in AD while odor sensitivity remains largely preserved (Djordjevic et al, 2008). Because each type of mouse displays slightly different Alzheimer pathology, we briefly review by model in the context of pathology reviewed more extensively above.

The 5xFAD mouse shows decreased performance on frontal-dependent tasks as early as 4 months, corresponding to early neocortical plaque burden in this model (Girard et al 2012, Cai et al 2012). The 3xTg mouse, with minimal OB changes but extensive amyloid and tau pathology in the limbic system and cortex, demonstrates impaired social transmission of odor above 12 months (Cassano et al 2011). The APP/PS1 model provides conflicting results. Some have found impairment in odor sensitivity at 3–4 months, spatial memory at 9–10 months, and odor habituation above 12 months, which roughly correlate with progression of pathology from epithelium and OB to the hippocampus and piriform cortex (Rey et al 2012, Wu et al 2013). However, others have found intact odor sensitivity, odor discrimination, and spatial memory, but learning impairments (Montgomery et al 2011, Phillips et al 2011). The Tg2576 model demonstrates deficits in atypical odor habituation at 3 months, short-term odor memory at 6.5–8 months, odor discrimination at 6–7 months, short-term odor habituation at 12–16 months, and social odor memory at 23 months (Young et al 2009, Deacon et al 2009, Guerin et al 2009, Wesson et al 2010, Wesson et al 2011). This also maps to the progression of pathology from early nonfibrillar Ab in superficial layers of the OB to later onset pathology in higher cortical regions (Wesson et al 2010). There is also a report of an early deficit in olfactory working memory at 4 months, despite unclear evidence of classical neocortical pathology at this age (Young et al 2009).

Conclusions

In summary, examination of structural and physiological decline in the olfactory pathways during normal aging has revealed some commonality between human and mouse. This is critical because this may indicate brain regions or specific circuits that may in addition be susceptible to the Alzheimer disease process. The olfactory sensory neurons within epithelium, and therefore glomerular level processing, appear to be particularly affected by aging. This may explain changes in odor sensitivity in advanced age. In addition, there is pathophysiological evidence in both species that piriform cortex, frontal cortex and temporal lobe regions are also predisposed to dysfunction during senescence. Further work is needed

to elucidate the precise mechanisms by which aging induces altered olfactory processing within these regions, notably the oribitofrontal region of prefrontal cortex and the dentate gyrus of the hippocampus. Additionally, little is known regarding age-dependent perturbation of the piriform cortex and other primary olfactory cortices, for example at the level of circuit anatomy and physiology in mouse and fMRI in human.

In AD, human and animal behavioral studies provide evidence that olfactory dysfunction can occur early in the disease process, even at a preclinical stage. In mouse, a temporal sequence of olfactory deficits can sometimes correlate with disease spread. However, the this spread does not correlate well to the human Braak stages. Human studies have shown progression from odor identification deficits to odor discrimination and odor sensitivity deficits as the disease process in AD leads to clinical manifestations, as well as strong predictive utility for conversion from normal to MCI and from MCI to AD. The relationship between olfactory deficits and another predictive risk factor, the 4 allele of the apolipoprotein E gene (*APO*-ε4), is unclear and warrants further research. Some studies find that *APO*-ε4 carriers perform worse on olfactory identification at baseline (Murphy et al 1998, Graves et al 1999, Olofsson et al 2010) whereas another study did not (Doty et al 2011). *APO*-ε4 status appears to have an additive effect to olfactory dysfunction alone for predicting cognitive decline (Graves et al 1999), though it has also been associated with low scores independent of dementia conversion (Olofsson et al 2010). This may suggest an additional role for apolipoprotein E in normal olfactory processing. Additionally, though there is evidence for preclinical utility in sporadic AD, in a small clinical sample of family members of AD patients with the autosomal dominant presenelin-1 mutation, smell testing was not predictive for conversion to dementia (Nee and Lippa 2001). Further validation is needed with larger populations, but this could suggest that olfactory involvement can be different in AD variants. This may also partly explain inconsistencies within mouse models that utilize different human amyloidogenic genes.

Furthermore, regional brain specificity, neurophysiology, and correlation to Braak stage are not as well defined in human AD studies. Further exploration is needed regarding the role of various kinds of pathology and which brain region most contributes to deficits at these different stages. At an early stage, the behavioral effects of olfactory bulb and sensory neuron dysfunction, given early Alzheimer changes and age-related susceptibility in both species, seems plausible from animal studies but is not clear from human work. However, a major discrepancy is that tau pathology in the OB, prominent in the human, has not been demonstrated in the mouse models. In humans, evidence currently supports a role for piriform cortex and medial temporal lobe, apart from the OB. More studies coupling amyloid imaging with olfactory testing at the preclinical stage, with longitudinal followup, would be helpful to more clearly define the role of amyloid plaque in perturbing neocortical odor processing. Additionally, other forms pathology, especially tau, soluble Aβ, and subtle circuit perturbations, have been studied to various extents in animal work but their contribution to olfactory behavioral deficits in human remain elusive, though this may change as tau PET ligands are developed. Further experiments regarding these issues are needed in the mouse model while technical hurdles to examine them in human need to be addressed.

Acknowledgments

Arjun V. Masurkar has received financial support through grants from the National Institute of Mental Health (T32) and the Charles and Lee Brown Fellowship.

D. P. Devanand has received financial support through grants from the National Institute on Aging and Eli Lilly (investigator-initated research grant), and has served as an advisory board member for AbbVie.

Annotated References

* of importance

** of major importance

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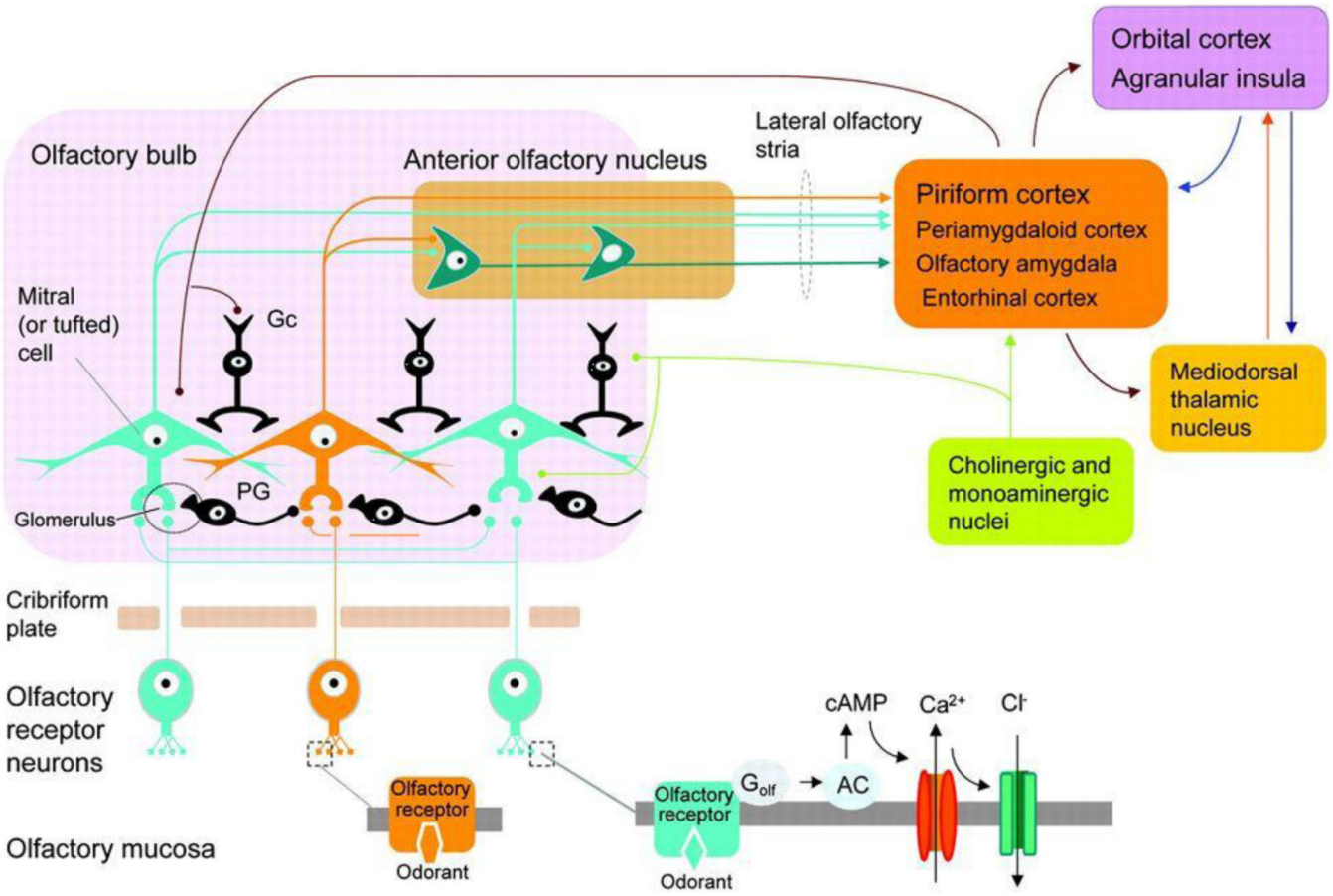

Figure 1.

Diagram of the Olfactory Pathway. From Benarroch EE, "Olfactory system: Functional organization and involvement in neurodegenerative disease," *Neurology*, Volume 75(12): 1104–1109, with permission from Wolters Kluwer Health.

Table 1

Human Olfactory Behavioral Studies

Study	Study subjects and design	Test	Results
Eibenstein et al 2005	29 aMCI, 29 controls	Odor ID	Amnestic MCI worse than controls
Djordjevic et al 2008	51 MCI, 27 AD, 33 control	Odor threshold, odor ID, odor discrimination	MCI with impaired identification; discrimination & identification predict cognitive baseline better more than sensitivity; AD worse than MCI in all 3 tests
Laakso et al 2009	486 control, 72 MCI	Odor ID, delayed odor recall, Boston Naming	MCI worse than control in all 3 but odor scores are better than Boston naming performance
Bahar-Fuchs et al 2010	19 control, 24aMCI, 20 AD	Odor ID, amyloid (PiB) imaging	aMCI worse than controls, PiB uptake inversely correlated with scores; PiB positivity did not distinguish scores within aMCI
Velayudhan et al 2013	57 mild-mod AD, 24 nondemented controls	Odor ID	scores lower in AD than controls and correlate with baseline MMSE
Westervelt et al 2008	17 aMCI, 46 multidomain aMCI, 25 non-aMCI, 44 AD, 21 control	Odor ID	MCI worse than control, AD worse than MCI, no difference between MCI subgroups
Lehrner et al 2009	11 aMCI, 19 multidomain aMCI, 21 non-aMCI, 13 multidomain non-aMCI, 40 controls	Odor ID	Scores related to cognitive baseline but difference only between multidomain aMCI and control
Devanand et al 2010	802 control, 170 aMCI, 120 non-aMCI	Odor ID	scores are inversely correlated with age, positively correlated with tests of recall, fluency, naming, hippocampal volume, differ with MCI type
Bacon et al 1998	70 amnestic MCI, longitudinal over 1 year	Odor threshold	8 aMCI who converted to AD had lower sensitivity
Graves et al 1999	1604 nondemented, longitudinal over 2 years	Odor ID	higher baseline olfactory impairment associated with higher odds ratio for cognitive decline
Devanand et al 2000	90 MCI, 45 controls, longitudinal at 6 mo intervals	Odor ID	lower scores in MCI; 18 MCI who converted to AD had lower baseline scores
Royall et al 2002	173 controls, longitudinal over 3 years	Odor ID	Baseline anosmia associated with poor baseline cognitive performance (short-term verbal memory) and greater decline
Tabert et al 2005	147 MCI, 100 AD, 63 control, longitudinal over 3 years	Odor ID	Performance on 10-item test mapped to baseline severity and predicted conversion
Wilson et al 2007a	589 controls, longitudinal up to 5 years	Odor ID	177 developed MCI; lower odor ID score predicted conversion and was associated with lower cognitive baseline and rate of decline
Devanand et al 2008	126 MCI, longitudinal at 6 mo intervals	Odor ID	33 converted to AD; odor score + 4 other measures showed 85.2% sensitivity 90% specificity for conversion prediction
Schubert et al 2008	1920 nondemented, longitudinal over 5 years	Odor ID	Impairment associated with cognitive decline on the MMSE
Conti et al 2013	88 MCI, 46 control, longitudinal over 2 years	Odor ID	impairment associated with higher likelihood of conversion to dementia, independent of MMSE

AD: Alzheimer disease; Odor ID: odor identification; MCI: mild cognitive impairment; aMCI: amnestic MCI; non-aMCI: non-aMCI: non-amnestic MCI; MMSE: Mini-mental state examination; PiB: Pittsburgh compound B

Table 2

Animal olfactory behavioral studies

Study	AD Model	Age	Task	Result
Cassano et al. 2011	3xTg	18 months	Odor discrimination, social behavior	Intact discrimination, impaired social transmission
Girard et al. 2013	5xFAD	2-,4-,6-months	Olfactory delayed alternation and reversal	Deficits at 4 months
Phillips et al. 2011	APP/PS1	6–8 months	Odor versus visuospatial sensitivity and discrimination	Intact olfaction, impaired visuospatial
Montgomery et al. 2011	APP/PS1	12 months	Odor sensitivity, learning, spatial memory	Intact odor sensitivity, deficient learning, intact spatial memory
Wu et al. 2013	APP/PS1	1–10 months	Odor sensitivity, spatial memory	Decreased sensitivity at 3–4 months and deficient spatial memory at 9–10 months
Young et al. 2009	Tg2576	4–12 months	Olfactory working memory	Deficits as early as 4 months, worse with age
Deacon et al. 2009	Tg2576	Up to 23months	Odor sensitivity, social memory	Normal sensitivity, deficits in social memory
Guerin et al. 2009	Tg2576	6.5–8 months	Odor detection, habituation, associative learning	Normal detection and associative learning, impaired habituation due to short-term memory deficit
Wesson et al. 2010	Tg2576	3–29 months	Odor habituation	Habituation deficit at 3–4 months, increased investigation time at 16 months
Wesson et al. 2011	Tg2576	3 months+	Odor habituation	Deficit at 6–7 months