Olfactory Dysfunction: Its Early Temporal Relationship and Neural Correlates in the Pathogenesis of Alzheimer's disease

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Abstract

We interact with the physical world through our senses and these aid our behavioral performance and various activities of life. Sensory information is transmitted in neuronal networks and the brain optimally interprets the external and internal milieu/environment. This paper delineates the framework in which the pathogenesis of memory and cognitive dysfunction is underpinned by sensory olfactory dysfunction. ERC is the gateway for olfactory input to the hippocampus, and there is seamless synchronization between sensory function and hippocampal activity. Transmission of olfactory information to the hippocampus is sequential - it is projected from the olfactory receptors to olfactory bulb to the primary olfactory cortex (comprised of the anterior olfactory nucleus, the olfactory tubercle, the piriform cortex) to the entorhinal cortex (ERC). Through perforant pathway ERC enables olfactory inputs to effectively excite hippocampal neurons. One of the earliest pathological changes in Alzheimer's disease (AD) include the olfactory dysfunction and the atrophy in ERC and hippocampus (rate in ERC is higher than in the hippocampus). Olfactory dysfunction negatively impacts the ERC and the deafferenting of the hippocampus from olfactory inputs upregulates memory decline. Olfactory dysfunction, therefore, is an important and early correlate of AD pathology. A number of factors described here may cause olfactory dysfunction; this may lead to hypoperfusion, hypometabolism, impaired synaptic transmission, and variable atrophy in olfaction-related regions. Improvement in olfactory function, therefore, is an important goal in order to attenuate cognitive neuropathology in aging and AD. This article seeks to provide a comprehensive and balanced overview of olfactory neuropathology in incipient AD, and suggests strategies to enhance olfactory function and ameliorate cognitive decline.

1. Introduction

Late onset Alzheimer's disease (AD) is a neurodegenerative dementing disorder in those over the age of 65. AD is the most common cause of senile dementia and affects 7% of individuals over 65 years of age and 40% of individuals over 80. Despite research advances over the past three decades, we still have a gloomy picture today since no effective treatment is available to prevent, halt, or reverse AD. Armed with the available knowledge of its molecular, cellular, and neurophysiological mechanisms, investigative efforts need to appreciate and fully address the multifactoriality also of this complex disease. In this regard, many salient aspects of neuropathology of AD are well characterized and repeatedly confirmed. The diverse mechanisms encompass: 1. amyloid beta (A β) (Selkoe, 2001; Tanzi and Bertram, 2005), 2. tau-neurofibrillary tangles (NFT) (Braak H, Braak, 1991), 3. inflammation (Blalock et al., 2005; Wyss-Coray and Rogers, 2012), 4. apolipoprotein E (APOE) gene (Roses, 1994), hypoperfusion and hypometabolism (Román, 2004; Murray et al., 2011; Roher et al., 2012), 5. oxidative stress (Nunomura et al., 2001), and 6. synaptic dysfunction (Pozueta et al., 2013).

The available data on biology, biochemistry, and pathology of A β and the NFT are overwhelmingly excessive, and may have overshadowed a rational and incisive discussion of the fundamental and upstream process(s) of the neuronal cell death in AD – prior to generation of A β and NFT. Throughout the course of AD, multiple pathways become perturbed both pre- and post- A β and NFT generation. This point is important, since the great majority of papers refer to these two obvious pathologies as being “causative of AD”. It needs to be underscored that the generation of A β and NFT are in fact the downstream phenomena. So what constitutes the “Upstream” events— *i.e.* the very initial pathological perturbation(s) in the evolution of this disease that precede the hallmark A β and NFT deposition pathology? What are some of the very early disease-related processes? Therefore, the endeavor here is conceptually driven and hopes to provide insights in this regard, highlighting the mechanisms that may underlie the initial pre-plaque neuropathogenesis of AD.

Mouse models of AD are important in contributing to our knowledge of early neuropathology and disease progression; these models, therefore, are a useful tool to study AD pathophysiology and the resulting cognitive deficits. Transgenic Tg2576 mice are considered to model the very early stages of AD. These mice do not show extensive cell loss, and their pathological deficits encompass impairments in synaptic function, reductions in dendritic spine density, and disturbed mitochondrial function - occurring prior to A β plaque formation (Jacobsen et al., 2006; Lanz et al., 2003). The neuropathogenesis of AD begins before histopathological lesions of amyloid plaque (Hanzel et al., 2014; Murray et al., 2014); indeed, various studies have also shown that cognitive impairments in several mouse models begin prior to the appearance of overt plaque pathology (Moechars et al., 1999; Westerman et al., 2002; Kelly et al., 2003).

Our different senses provide information about the environment; their qualitative/quantitative interaction aids our behavioral performance and quality of life (Kayser and Logothetis, 2007). Somatosensory evoked potentials are generated in afferent pathways, subcortical structures, and various regions of cerebral cortex following stimulation of somatic sensory receptors. The brain processes this sensory information arriving in neuronal networks and optimally interprets the internal and external milieu/environment. Neuronal processing of incoming sensory information from sensory receptors/regions is indeed a function of changing synaptic transmission/inputs, and generation of corresponding action potentials (McCarthy et al., 1991; Keil and Müller, 2010). Neurobiological studies have provided evidence for this bottom-up processing from sensory receptors to primary sensory areas, and then into the higher association areas (Fuhrmann et al., 2008). There is evidence for the synchronization between sensory function and hippocampal activity, e.g. during encoding and retrieval of olfactory-associative memory (Igarashi et al., 2014). Transmission of sensory information to the hippocampus, obviously, entails sequential information processing in the sensory/olfactory regions. Fluctuations in sensory excitation accordingly induce modulation of cortico-hippocampal connections and synaptic plasticity. The knowledge of susceptibility of olfactory function in prodromal neurodegenerative disease has made the olfactory neural network in animals an important tool to study the early neurodegenerative disease mechanism(s) (Wesson et al., 2010; 2011). This article seeks to provide a comprehensive and balanced overview of this possible incipient neuropathology in AD.

Amongst the earliest symptoms of AD are impairments in olfactory discrimination and odor recognition memory (Ferreira-Moyano and Barragan, 1989; Gilbert et al., 2004). Olfactory dysfunction – i.e. raised olfactory thresholds and impaired odor identification, therefore, is a recognized risk factor in the pathogenesis of AD (Gray et al., 2001; Peters et al., 2003). Brain structures closely related to the olfactory system correspondingly demonstrate significant dysfunction. Not surprisingly, there is evidence that the brains of AD patients invariably exhibit neuropathology in the ERC (Gomez Isla et al., 1996; Du et al., 2004; Velayudhan et al., 2013) and the hippocampus (Stoub et al., 2006; Devanand et al., 2007). This further reflects a correlation between the psychophysical measures of olfactory function and volumetric loss of hippocampus (Murphy et al., 2003). Several recent studies have confirmed the above data, and have emphasized the potential utility of olfactory dysfunction test and the hippocampal volume loss for early detection of AD (Kjelvik et al., 2014; Marigliano et al., 2014).

2. Sensory System – Parietal Cortex

We interact with the physical world through our senses. Our brain seamlessly integrates signals from multiple sensory modalities. The sense of taste, smell, touch, sight, and hearing, all are based on a basic template. Corresponding dedicated external sensory organs detect environmental cues and conduct these sensory messages, and a related specific CNS region processes, interprets, and acts upon such cues, spatially and temporally. Olfactory information *e.g.* is projected from the olfactory bulb to the primary

olfactory cortex which is comprised of the anterior olfactory nucleus, the olfactory tubercle, the piriform cortex, the entorhinal cortex (ERC), and the parietal cortex. Neurological details of links between disparate sensory stimuli from the heterogeneous sensory modalities and their integration in central circuits of the CNS is beyond the scope of this paper.

In a recent study, volumetric analyses of changes were studied in a transgenic mouse model for AD; two time points were chosen for this analysis: 7 weeks after APP induction, just before the onset of amyloid formation, and 4 months after APP induction, when a moderate amyloid burden had accumulated (Badea et al., 2010). The most overt change in brain volume between the APP/TTA double-transgenic AD mice (DBL) and TTA single-transgenic controls (TTA) siblings was a decrease of $\sim 5\text{--}6\%$ overall brain volume. Importantly, this reduction was apparent prior to amyloid generation which persisted in the older animals (Badea et al., 2010). The overall brain volume decrease before the onset of amyloid plaques, suggests that the AD pathogenesis begins prior to onset of plaques – the visible histopathological lesions. The early volumetric changes correlate with functional alterations (Moechars et al., 1999; Westerman et al., 2002; Kelly et al., 2003). Further, early pre-plaque alterations in cortical regions of transgenic AD mice are indicative of predisposition of these regions to later A β pathology (Grand'maison et al., 2013).

There is a global principle in that chemosensory processing shares the general subdivision into a ventral and a dorsal stream for tactile, visual, auditory, and olfactory information processing. Specifically, the left intraparietal sulcus and the right superior frontal sulcus are more activated when odorants were localized. For the same task, independent component analysis identified a significant cluster in the left parietal lobe (paracentral lobule) as well as in the right hippocampus (Frasnelli et al., 2012). Functional magnetic resonance imaging (fMRI) has demonstrated olfactory activity in the olfactory bulb (OB), entorhinal cortex (4%), and temporo-parietal cortex (Toledano et al., 2012). Indeed, primary olfactory cortex projects olfactory stimuli to secondary olfactory regions including the hippocampus, thalamus, orbitofrontal cortex, and cingulate gyrus (Weismann et al., 2001).

Studying transgenic mice is instructive, since they reproduce many features of the human disease and provide a rational model/basis for examining pathological (pre- and post-amyloid) alterations in the brain (Badea et al., 2010). By the time sporadic AD present with symptoms, these patients have already developed amyloid pathology (Kemppainen et al., 2007; Forsberg et al., 2008). However, the pre-plaque stage of DBL mice is similar to early AD. Not all areas in the brain of DBL transgenic mice are affected equally; the somatosensory cortex suffers the highest damage (Badea et al., 2010). In healthy elderly, gray and white matter atrophy also involves parietal lobe (Teipel et al., 2010). Interestingly, longitudinal assessment (by MRI) of brain volume in inherited AD revealed significant atrophy in the ERC and hippocampus (Fox et al., 2001, Fox et al., 1996; Schott et al., 2003), and significantly greater PiB A β load in the parietal cortex and sensorimotor cortex (Honea et al., 2012). In amnesic MCI patients who were followed longitudinally, the only region that showed significant increase in NFTs in the neocortex was the parietal lobe (Markesbery et al., 2006). Prodromal AD patients could be distinguished on the basis of

decreased perfusion in the parietal lobe (Habert et al., 2011). The FDG- positron emission tomography (PET) data provided independent validation by demonstrating hypometabolism in bilateral parietal/parietotemporal, and bilateral posterior cingulate in non-demented/amnesic MCI subjects (Ercoli et al., 2012). Interestingly, increased amyloid burden together with metabolic dysfunction has been demonstrated in the parietal lobe of younger AD patients (age 56 ± 4 years) also (Ossenkoppele et al., 2012). In a relatively large (167 patients) clinically based study, patients with MCI who subsequently developed AD (compared both to stable MCI patients and healthy elderly controls) showed significantly lower regional cerebral blood flow (rCBF)-values in parietal area. Further, the rCBF in the left parietal cortex showed the best diagnostic prediction (with 77.2% accuracy), while analysis of the bilateral parietal rCBF decrease could predict AD with 78.1% accuracy (Hansson et al., 2009). Several studies have corroborated this and have shown that functional abnormalities in the parietal cortex have the highest predictive value for the future development of AD, compared to other brain regions (Arnaiz et al., 2001; Borroni et al., 2006; Hirao et al., 2005; Huang et al., 2003; 2007; Mosconi et al., 2004).

The posterior cingulate and the medial parietal cortices together are referred to as the posteromedial cortex. Indeed, the posterior cingulate is interconnected with the parahippocampal regions (Parvizi et al. 2006). In addition to involvement in sensory function, parietal cortex also participates in episodic memory retrieval (Wagner et al., 2005; Vincent et al., 2006). Specific regions within parietal cortex that participate in this function include precuneus, posterior cingulate, and the inferior parietal lobule, (Cavanna and Trimble, 2006; Bonni et al., 2014; Qi et al., 2015; Scheff et al., 2015). In addition to hippocampus, parietal regions are also associated with retrieval of autobiographical memories (i.e., episodic recall, remembering, or recollection) (Andreasen et al. 1995; Maguire and Mummery 1999). Indeed, the inferior parietal lobule has direct projections to the hippocampus (Rockland and Van Hoesen 1999) and reciprocal connections with parahippocampal cortex (Cavada and Goldman-Rakic 1989; Kobayashi and Amaral, 2003; Lavenex et al. 2002; Suzuki and Amaral 1994). Further, the CA1 region of the hippocampus sends reciprocal projections showing a significant influence on activity in the inferior parietal lobule (Cavada and Goldman-Rakic 1989; Clower et al. 2001; Vincent et, 2006).

3. Entorhinal cortex (ERC)

The entorhinal cortex (ERC) receives input from the piriform cortex and mediates the flow of sensory information between these sites and the hippocampal formation. Long-term cognitive memory - declarative memory is dependent on the the hippocampus and the ERC, among other regions (Zola-Morgan et al., 1989; 1994). The olfactory structures are the only primary sensory system components that have direct projections to the ERC (Insausti et al. 2002). Anterograde tracing experiments found that all regions of the ERC project to the dentate gyrus and to the hippocampal CA3 and CA2 regions (Witter and Amaral, 1991). Layer II of the ERC gives rise to the perforant pathway, the major source of the sensory information and excitatory input to the hippocampus. Consequently, the integration of the afferent input to ERC plays

an important role in spatial memory and episodic memory functions. The lateral ERC receives direct input from OB mitral cells and piriform cortical pyramidal cells and is the gateway for olfactory input to the hippocampus (see above). Activity in the ERC is modulated by input from the hippocampus as well (Chapuis et al., 2013). Indeed, the ERC also projects back to the piriform cortex and OB. Given the pivotal function of ERC in working memory and multisensory integration, it may serve as a powerful bottom-up and top-down modulator and contributes to olfactory function (Chapuis et al., 2013).

Stimulation of the perforant path via population spike generated gamma wave (30-80 Hz) activity stimulates the hippocampus (the dentate gyrus) (Vanderwolf, 2001). Bursts of gamma waves were elicited in the dentate gyrus when a rat sniffed at a variety of odors (Vanderwolf, 2001). Similarly, odorized air blown into a nostril enhanced a gamma wave response bilaterally in the dentate gyrus. Learning of an olfactory discrimination task is accompanied by increased spine density along the apical dendrites of pyramidal neurons in the piriform cortex. When rats were trained to discriminate positive cues in pairs, the mean spine density on apical dendrites in neurons from trained rats increased by 20.5% (relative to neurons from pseudo-trained or naive animals) (Knafo et al., 2004). Thus, olfactory stimulation in rats results in a net increase in the number of excitatory synapses in the hippocampus following olfactory learning (Knafo et al., 2004). Various studies have repeatedly documented a substantial olfactory input to the hippocampus, via the ERC (Habets et al., 1980; Overmann et al., 1980; Room and Groenewegen, 1986; Bartesaghi and Gessi, 2003). Indeed, the existence of a direct monosynaptic olfactory input into the ERC has been demonstrated (Biella and de Curtis, 2000; Liebetanz et al., 2002). In other words, the olfactory primary sensory system structures have direct projections to the ERC. Therefore, the pathway from the piriform cortex to hippocampus, via ERC, enables olfactory inputs to effectively excite hippocampal neurons (Room and Groenewegen, 1986; Bartesaghi and Gessi, 2003; Biella and de Curtis, 2000; Gnatkovsky et al., 2004).

Rodent studies have demonstrated that the perforant path input from the ERC to the DG is compromised both structurally and functionally in memory defects (Jacobsen et al., 2006). Quantitative imaging techniques have assessed the integrity of white matter and demonstrated alterations in the parahippocampal white matter that includes the perforant path; thus the dentate gyrus and other hippocampal subfields may be disconnected from incoming sensory information (Stoub et al., 2006). Such disconnection and degradation in transmission of sensory information, leading to dysfunctional ERC and hippocampal formation, could contribute to memory dysfunction in incipient AD (deToledo-Morrell et al., 2007). Accordingly, the earliest pathological changes in AD have been described in the ERC and hippocampus (Braak and Braak, 1991; Gomez-Isla et al., 1996). In incipient AD, i.e. before the onset of overt dementia, MCI converters to AD are best differentiated from non-converters on the basis of ERC volume (de Toledo-Morrell et al., 2000; Pennanen et al., 2004; Di Paola et al., 2007).

In 2- to 4-month-old Tg2576 transgenic mice, the ERC dysfunction occurs prior to A β deposition and behavioral impairments. The important work of Jacobsen et al. (2006) in DG of Tg2576 mice demonstrated decreased dendritic spine density, impaired long-term potentiation (LTP), and behavioral deficits occurring at age 4 months, i.e. long before amyloid plaque deposition. The latter did not significantly increase until approximately 18 months of age. Importantly, soluble human A β -40 and A β -42 were detectable in the ERC of 2-month-old Tg2576 mice – *i.e.* before plaque deposition (Duffy et al., 2015). At this early pre-plaque stage, these mice are impaired in ERC-dependent cognitive task and possess altered excitability (Duffy et al., 2015). Importantly, the very early emergence of olfactory system hyper-excitability corresponded not to detectable A β plaque deposition in the olfactory system, but rather to high levels of soluble A β in the anterior piriform cortex - a major afferent input to the LEC (Xu et al., 2014). In A β PP/PS1 transgenic mice also, soluble A β appeared in the olfactory epithelium at 1-2 months (mo); expanded to the olfactory bulb at 3-4 mo; encroached to the anterior olfactory nucleus, piriform cortex, ERC, and hippocampus at 6-7 mo; it increased in aged animals (9-10 mo) in several central cortices (Wesson et al., 2010; Wu et al., 2013).

The ERC is one of the brain regions to first display neuropathology in AD. Indeed, the atrophy rate in the ERC is higher than in the hippocampus of the AD patients; this is consistent with the view that AD pathology begins in the ERC (Du et al., 2004). There is a decrease in the neuronal number of the ERC in AD (Gomez Isla et al. 1996); this loss is quite dramatic, in that the number of neurons in layer II has been shown to decrease by 60% and in layer IV by 40% (compared with controls) even in very mild AD (Gomez Isla et al. 1996). The impact of ERC lesions on the hippocampal function has been well studied (Deller and Frotscher, 1997). AD subjects with thinner ERC had lower cognitive scores, higher disease severity, and predicted greater subsequent cognitive decline at one year follow up. Since ERC is affected early in AD, its rate of atrophy is higher during ongoing neurodegeneration (Velayudhan et al., 2013). Olfactory dysfunction-related damage to the ERC and deafferenting the hippocampus interferes with episodic memory consolidation in AD patients.

4. Retrosplenial Cortex (RSCx)

Retrosplenial cortex (RSCx) is another important region that is vital for memory. Neurons in layer V of the ERC provide projections to the RSCx (Insausti et al., 1997). RSCx has dense reciprocal projections with both the parahippocampal gyrus and the ERC (Insausti et al. 1987; Kobayashi and Amaral, 2003; Lavenex et al. 2002; Suzuki and Amaral, 1994). Further, strong connections also exist among the presubiculum, subiculum, and parahippocampal gyrus and the RSCx (Morris et al. 1999). The medial temporal lobe (MTL) cortical structures including the hippocampus show direct coding/interpretation for spatial and episodic information (Bird and Burgess, 2008); the RSCx is implicated as a putative convergent region that is essential to constructing such coherent representations, and for retrieving and navigating previously experienced events and environments (Epstein, 2008; Vann et al., 2009; Ranganath and Ritchey, 2012).

The RSCx (a component of posterior cingulate region) is one of the first regions to show metabolic hypoactivity in AD (Minoshima et al., 1997; Nestor et al., 2003). The RSCx has dense reciprocal interconnections with the hippocampal formation and with the anterior thalamic nuclei (van Groen et al., 1993; Vogt et al., 1987; Wyss and van Groen, 1992). Indeed, the latter themselves are closely linked to amnesia (Aggleton, 2008) and early pathology in AD (Braak et al., 1993; Thal et al., 2002). Thus, retrosplenial changes noted in early AD (Fox et al., 2001; Pengas et al., 2010) accompany pathology in interconnected regions (Buckner et al., 2008), and perturbations in its afferents (Aggleton, 2008; Fennema-Notestine et al., 2009).

The development of episodic memory deficits occurs during the early stages of AD when there is development of pathology in entorhinal-hippocampal regions (Braak and Braak, 1991; van Hoesen et al., 1991). In addition to the atrophy in these medial temporal lobe structures, their inter-connected region “RSCx” also shows evidence of functional abnormalities during the early stages of AD (Iaria et al., 2007; Maguire, 2001; Vann et al., 2009). Voxel-based analysis showed decreased [(11)C]-flumazenil binding in RSCx; this decrease precisely correlated with the RSCx region’s greatest degree of neuronal loss in early episodic memory decline/AD (Pascual et al., 2012).

There is dense reciprocal connection between the anterior thalamic nuclei and RSCx. Lesions in the thalamus and the hippocampus induce reductions in energy function, immediate-early gene deficits, and widespread transcriptome alterations in the RSCx - all of these are accompanied by cell loss or atrophy (Albasser et al., 2007; Jenkins et al., 2004; Poirier et al., 2008). Further, thalamic lesions cause a negative impact upregulating the loss of retrosplenial synaptic plasticity (Garden et al., 2009). Conceivably, dysregulated synaptic plasticity contributes to functional decline and eventual atrophy. Finally, any dysfunctionality in pathways that project to the RSCx will have a pathological impact in RSCx (Fellgiebel et al., 2008; Xie et al., 2006; Zhang et al., 2007; Zhou et al., 2008).

5. Olfactory Dysfunction in Aging

Olfaction is one of our basic senses and it is affected by aging (Wilson et al., 2007; Doty and Kamath, 2014). By far the most frequent cause of special sensory dysfunction, however, is disturbance related to the olfactory system (Mott and Leopold, 1991; Spielman, 1998). Association of smell identification function with cognition is well recognized (Vyhnalek et al., 2015). Chronic olfactory disorders, including the complete loss of the sense of smell (anosmia), are common; prevalence of the latter has been estimated to be about 19% (Nordin and Bramerson, 2008). Persisting cortical gray matter (GM) volume changes occur after anosmia; the absence of olfactory afferent input resulted in a decrease of the OB volume (Abolmaali et al. 2008). In the triple transgenic mouse, age-dependent alterations of the axonal transport rate have been shown to occur in the olfactory system (Kim et al., 2011; Wang et al., 2012).

Importantly, the olfactory axonal transport impairment was found to be a very early event in AD pathology in these transgenic mice - preceding deposition of A β plaques and Tau fibrils formation (Kim et al., 2011; Wang et al., 2012). The above studies underscore that olfactory dysfunction is associated with dysfunction in episodic memory, semantic memory, perceptual speed, and lower global cognition (Wilson et al., 2007).

6. Olfactory Dysfunction in Alzheimer's disease

Olfactory impairment is a well-known phenomenon in neurological diseases including AD (Murphy, 1999; Murphy et al. 2003). Anosmic patients possess atrophy in the medial prefrontal cortex (MPC), the anterior cingulate cortex (ACC), and the middle cingulate cortex (MCC) (Bitter et al., 2010). Volume decreases occur also in the dorsolateral prefrontal cortex (dlPFC), cerebellum, and the superior occipital gyrus (SOG). In addition, atrophy has been reported in the piriform cortex, the insular cortex, the orbitofrontal cortex (OFC), the supramarginal gyrus (SMG), the precuneus (Prec), the hippocampus, and in the parahippocampal region (Bitter et al., 2010). Importantly, atrophy noted above was a function of anosmia duration; its duration longer than 2 years had a deleterious impact in causing the above mentioned atrophy, compared with patients whose anosmic duration was less than 2 years (Bitter et al., 2010).

Olfactory dysfunction in amnesic mild cognitive impairment (aMCI) patients is well documented and considered to be an important early correlate of underlying AD pathology (Vyhnalek et al., 2015). Impaired smell identification is considered to be a diagnostic parameter of cognitive decline/aMCI, and a marker of conversion to AD. This is in keeping with olfactory dysfunction being a recognized risk factor in the pathogenesis of AD (Gray et al., 2001; Peters et al., 2003). Indeed, AD raises olfactory thresholds and impaired odor identification. Brain structures closely related to the olfactory system demonstrate significant early histopathology in MCI (Cross et al., 2013) and AD (Thompson et al., 1998), and the brains of AD patients invariably exhibit neuropathology in the ERC (Devanand et al., 2007). Worth noting is a correlation between the psychophysical measures of olfactory function and volumetric loss of hippocampus also (Murphy et al., 2003). Several recent studies have confirmed the above data, and have emphasized the potential utility of olfactory test and hippocampal volume loss for early detection of AD (Kjelvik et al., 2014; Marigliano et al., 2014). Although the two clinical predictors *i.e.* olfactory decline and hippocampal volume loss showed the same sensitivity of 92.3%, tests of the olfactory loss showed a higher specificity than the hippocampal volume loss – *i.e.* 75% vs. 60% (Marigliano et al., 2014). The [18 F]fluorodeoxyglucose (FDG)–PET showed lower metabolic rates in the anterior portion of the medial-temporal cortex in AD patients relative to controls (Buchsbaum et al., 1991).

7. Olfactory Dysfunction: Contributing Factors

7.1 Pollution

Air pollution is a complex mixture of gases (e.g., ozone), particulate matter, and organic compounds present in the air. Upregulation of cyclooxygenase-2 (COX-2), interleukin 1beta (IL-1 β), and

CD14 has been documented in olfactory bulb of healthy children and young adults residing in a city where air pollution is a serious environmental problem (Calderón-Garcidueñas et al., 2008). Inhabitants exposed to air pollution develop histopathologic changes in their nasal mucosa including loss of normal respiratory epithelium, prominent basal cell hyperplasia, squamous metaplasia/dysplasia, and submucosal vascular proliferation (Calderón-Garcidueñas et al., 1992). Increased COX-2 expression and A β -42 accumulation were found in the OB in autopsied brain tissue of cognitively and neurologically intact lifelong residents of the air polluted cities (Calderón-Garcidueñas et al., 2004). Residents exposed to severe air pollution exhibit OB inflammation, OB endothelial hyperplasia, and immunoreactivity to A β -42, and alpha-synuclein in neurons, glial cells and/or blood vessels (Calderón-Garcidueñas et al., 2010). Exposure to urban air pollution has been shown to enhance neuroinflammation in humans (Calderón-Garcidueñas et al., 2008; 2010; 2012a; 2012b; 2015a) and sustained inflammation in the rodent OB (Villarreal-Calderon et al., 2010). Similarly, nasal respiratory and olfactory epithelia have been shown to be early targets in healthy dogs naturally exposed to urban air pollution in Mexico City (Calderon-Garcidueñas et al., 2003). These dogs exhibited brain inflammation and Alzheimer's-like pathology (Calderón-Garcidueñas et al., 2007). Recently, APOE4 (see below) has been shown to modulate responses to air pollution, and showed olfactory decline, perturbations in white matter, and decreases in attention and short-term memory (Calderón-Garcidueñas et al., 2015a; 2015b). The above data show the influences of air pollution on olfaction and its potential contribution to neurodegeneration and Alzheimer's like pathology.

7.2 Aging

Widespread changes occur in the aging brain, including reductions in gray and white matter volume (Good et al. 2001; Salat et al. 2009), alterations in neurotransmitter systems (Muir, 1997; Backman et al. 2006), and regional hypoperfusion (Martin et al. 1991; Bertsch et al. 2009). Detection and discrimination of odors declines in humans with advancing age. Over half of individuals between ages of 65 and 80 years possess decreased olfactory function (Murphy et al., 2002; Doty and Kamath, 2014). Among older individuals without manifest cognitive impairment, olfactory dysfunction predicts subsequent development of MCI (Wilson et al., 2007). OB is the first and important relay station in odor processing, and significant correlation exists between OB volumes and olfactory function (Buschhüter et al., 2008). OB volume has been shown to decrease with age (Buschhüter et al., 2008) as well as with duration of olfactory loss (Rombaux et al., 2006). OB volume changes are sensitive and correlate with the degree of sinonasal inflammation also (Rombaux et al., 2008). Further, the human OB volume increases with an increase in olfactory function (Gudziol et al., 2009).

Impairments in the sense of smell are common in aged rodents as well (LaSarge et al., 2007; Patel and Larson, 2009; Young et al., 2009). The decrease in odor sensitivity is ascribed to degenerative changes in the olfactory epithelium. In both humans and rodents (Hinds and McNelly, 1981; Menco and Morrison, 2003), the number of olfactory sensory neurons declines with age, partly due to decreased

regeneration, owing to impairment in OB neurogenesis (Deckner et al., 1997; Weiler and Farbman, 1997; Kondo et al., 2010; Rey et al., 2012; Bianchi et al., 2014). In addition, there are inherent pathological alterations in aged olfactory epithelium (Kim et al., 2005; Kwon et al., 2005; Watanabe et al., 2007; Tillmann et al., 2009).

7.3 APOE4 Allele

Olfactory dysfunction is an early feature of AD that may precede cognitive signs. Persons with the APOE4 allele showed significantly poorer odor identification than those without this allele (Murphy et al., 1998). APOE4 individuals underwent odor identification decline more rapidly than the normal elderly (Calhoun-Haney and Murphy, 2005). In these persons, decline in odor identification occurred before declines in other measures of dementia. Subjects with one ApoE4 allele have an approximate 5-fold increased risk of AD (Hawkes, 2003). Indeed, a five-year follow-up study showed that poor odor identification ability in combination with older age and the APOE4 allele is predictive of global cognitive decline (Olofsson et al., 2009). AD cases were studied for tau pathology in the anterior olfactory nucleus (AON) (Tsuboi et al., 2003). Multiple linear regression analysis demonstrated that tau pathology in the AON correlated with Braak stage and with APOE4. This suggests a possible synergistic effect between aging, olfactory dysfunction, tau, and APOE4 in promoting AD neuropathology (Tsuboi et al., 2003). An age-dependent mutual reinforcement of the tau pathology and mitochondrial dysfunction has been shown (Kulic et al., 2011).

7.4 Rhinosinusitis

There are multiple sources of sinonasal inflammation; these include: infection, alcohol abuse, and OSA – all upregulate proinflammatory cytokines. The increased production of various cytokines that occurs in inflammation has been shown to have detrimental effects on the sensory and cognitive functions. In a transgenic mouse model of rhinosinusitis-associated olfactory inflammation, TNF- α causes olfactory neuron loss and reduced expression of growth-associated protein (GAP) 43 (a neuronal marker protein associated with the growth and development of immature neurons) (Lane et al., 2010; Turner et al., 2010a). Furthermore, TNF- α expression inhibits olfactory neuron regeneration (Suzuki et al., 2000; Turner et al., 2010b). Several reports document that chronic sinusitis is a common cause of olfactory dysfunction; however, its treatment is transient and incomplete (Raviv and Kern, 2006; Kern, 2000; Ozaki et al., 2010). The olfactory deficits in these patients are due to inflammatory changes within the olfactory mucosa. Topical or systemic corticosteroids can often partially or fully reverse the olfactory loss in rhinosinusitis (Rombaux et al., 2008).

7.5 Chemicals and Infection: Transmission Through Olfactory Nerve

Nerves may serve as a Portal to transmit infection and chemicals to the Brain. The uptake of Hg²⁺ occurs in the OB when given intranasally (Henriksson and Tjälve, 1998). However, even when given intraperitoneally, uptake of Hg²⁺ occurs in the OB glomerular layer and in the olfactory epithelium of rats.

Similarly, there is uptake of cobalt (Persson et al., 2003), manganese (Tjälve et al., 1996), and nickel (Tallkvist et al., 1998) also from the nasal mucosa into the brain via olfactory pathway.

Viruses may gain access via the olfactory nerve (ON, cranial nerve I) (Barnett and Perlman, 1993; Baker and Genter, 2003; Leyva-Grado et al., 2009; 2010). The ON pathway is an important route for viruses to enter the brain owing to its direct contact with the environment (Mori et al., 2001; Urbanska et al., 1997; Leyva-Grado et al., 2010), and its continuity with olfactory structures including piriform cortex in the brain. When influenza virus is intranasally introduced, signals from the ON triggers the acute phase response (APR); however, the ON transection prior to influenza viral infection reduced the number of viral antigen, TNF α , and IL1- β immunoreactive cells in the OB and its interconnected brain regions (Honjo et al., 2009). Importantly, as early as 15 hours post-infection, the number of cells expressing TNF- α and IL1- β mRNAs and proteins increased in the OB (Majde et al., 2007). *Corynebacterium diphtheria* is often found in the nasopharynx, hence diphtheria toxin may ascend to the brain; thus, this may be involved in sporadic AD - a disease with progression from the ERC to the hippocampus and other neocortical areas (Shibuya et al., 2013).

7. 6 Diabetes Mellitus

Diabetes is complicated by several serious medical conditions including the development of olfactory dysfunction. The presence of macrovascular disease, but not the presence of neuropathy, retinopathy, nephropathy, or hypertension was found to be associated with olfactory dysfunction (Weinstock et al., 1993). Indeed, odorant identification performance in diabetics decreased with increasing age, and smoking had an additive deleterious effect (Weinstock et al., 1993). This suggests that macrovascular - related ischemia in diverse olfactory regions, may have a negative impact on olfactory function. Interestingly, aged 3xTg-AD transgenic mice suffer from severe systemic autoimmune/inflammatory disease, as evidenced by splenomegaly, hepatomegaly, elevated serum levels of anti-nuclear/anti-dsDNA antibodies, low hematocrit, and increased number of splenocytes (Marchese et al., 2014). Importantly, these AD mice show sensory and cognitive deficits in the first 6 months of life, *i.e.* prior to significant amyloid- β or tau pathology (Marchese et al., 2014).

7.7 Obstructive Sleep Apnea

A recent study (78 volunteers, mean age - 46 ys) has demonstrated that OSA has significant negative effects on all orthonasal olfactory tasks, including threshold and discrimination (Salihoğlu et al., 2014). There was a significant negative correlation between apnea-hypopnea index and odor identification score. MRI revealed atrophy and loss of OB volumes in both right and left OB (Salihoğlu et al., 2014).

7. 8 Alcohol Abuse

Ethanol consumption in excess (even for four days) has been shown to induce significant damage in the piriform cortex, perirhinal cortex, ERC, and the dentate gyrus (Obernier et al., 2002).

Microglial activation, inflammatory cytokine production, and neurodegeneration occur in the parietal cortex, ERC, and the hippocampus following ethanol abuse (Zhao et al., 2013).

8. Olfactory Stimulation Increases Regional Cerebral Blood Flow

Tactile stimulation activates a spatially distributed neural network including the primary and secondary somatosensory cortex (Dressel et al., 2008; Jang et al., 2013). High spatial concurrent blood-oxygen-level-dependent (BOLD) and regional cerebral blood flow (rCBF) responses occur with sensory signals in contralateral sensorimotor cortex, highlighting a hemodynamic signature of distinct temporal phase of neuronal activity (Mullinger et al., 2013). In the wider context, stimulation of somatosensory as well as other sensory modalities including visual, taste and olfactory stimuli have been shown to activate disparate brain regions and enhance their rCBF and metabolism (Matsuura and Kanno, 2001; Kringelbach et al., 2003; Rolls et al., 2003a; 2003b; Kringelbach and Rolls, 2004; de Araujo et al., 2005; McCabe et al., 2008; Jin and Kim, 2008; Maihöfner et al., 2011).

The olfactory stimulation has been shown to activate several brain regions, including the OFC, piriform cortex, occipital cortex, amygdala, and insula (Qureshy et al., 2000; Bengtsson et al., 2001; Kobayashi et al., 2002; Djordjevic et al., 2005). Odor-evoked activation patterns have been studied recently in rats using functional ultrasound (fUS) imaging (Osmanski et al., 2014). Stimulation with two different odors (hexanal and pentylacetate) induced the activation of odor-specific regions including the OB and the piriform cortex (Osmanski et al., 2014). Indeed, PET and near-infrared spectroscopic (NIRS) imaging studies have documented significant rCBF increases during olfactory stimulation (Dade et al., 1998; Azuma et al., 2013). An odor inhalation-time of 20 min was sufficient to increase global CBF (Nasel et al., 1994).

Sensory stimulation causes neuronal activation and triggers an increase in rCBF in the brain. In different brain regions rCBF is spatially and temporally adjusted to neuronal functional activation, energy needs, and upregulated homeostasis (Paradiso et al., 1999; Royet et al., 2000; Vaidya et al., 2007). Utilizing two-photon imaging of CBF, neuronal calcium dynamics, and intracellular-extracellular recordings, it was shown that odor activates OB glomeruli in rodents (Chaigneau et al., 2007). Further, activation of postsynaptic glutamate receptors and rises in dendritic calcium underpin neurovascular coupling in the OB (Chaigneau et al., 2007). Healthy subjects were exposed to aversive olfactory stimuli and their rCBF was measured with PET. Stimulation with odor produced strong rCBF increases in amygdala and in the OFC reflecting strong functional interaction between these brain regions (Zald and Pardo, 1997). Indeed, measurement of the rCBF is used as an important parameter in the evaluation of cerebral function in neuropsychiatric conditions also (Kim and Watanuki, 2003; Law, 2007).

9. Olfactory Deficit Upregulates Memory Defect and Cognitive Impairment

Hyposmia (occurs in one out of four people) and anosmia (occurs in one out of 200 people) are common world wide in the elderly populations. Reduced rCBF in several areas of the brain in olfactory dysfunction/anosmia may lead to a functional decline and may cause cognitive decline (Imamura et al., 2009). Cortical perfusion has been shown to be significantly reduced in young transgenic AD mice (compared with wild-type mice) across most brain regions (Hébert et al., 2013). Metabolic impairment following hypoperfusion has been shown to affect neuronal and glial functions and thus cause functional damage (Cechetti et al., 2012). The transition from normal cognition to AD is associated with decreases in rCBF in crucial brain regions. Since hypoperfusion in parietal cortex is associated with prominent structural and functional changes, it can be used as a putative biomarker in identifying prodromal AD, and be used to observe the disease progression.

Given that there are age-related alterations in olfactory and multisensory processing (Cabeza et al., 2004; Grady, 2008), it is understandable that sensory/olfactory dysfunction has a major and early role in contributing deleterious impact, and upregulating cognitive and memory impairment. The FDG–PET scans of AD patients has clearly demonstrated reduced glucose metabolism in the parietal and superior/posterior temporal regions. Indeed, very early metabolic deficits occur in MCI and AD in the medial parietal cortex, and in the posterior cingulate and retrosplenial region (Small et al., 2008). Other studies have documented volume losses in the ERC, hippocampus, parietal cortex, and the cingulate gyrus in AD (compared with controls) (Tartaglia et al., 2011).

10. Role of Soluble A β oligomers in Olfactory Dysfunction: Impaired Synaptic Transmission

Many studies have shown that A β oligomers are a more important cause of synaptic and cognitive dysfunction than plaques. Excitotoxicity is a major contributor to cell death owing to glutamate rise and cytotoxic Ca²⁺ influx.

There is olfactory decline in normal aging; however, impairment of olfaction is much higher in AD (Nordin and Murphy, 1998). It was hypothesized, therefore, that AD would reduce olfactory-evoked perfusion in ERC and olfactory piriform cortex, where neuropathology begins. Right piriform cortex activation correlated with odor identification in elderly controls; however olfactory-evoked rCBF was impaired in AD patients (Kareken et al., 2001). The presence of underlying neuropathology involves areas critical to processing olfactory information (Murphy, 1999; Murphy et al., 2003). It is worth recapitulating that direct robust relationship exists between hippocampal volume and olfactory functional measures (Murphy et al., 2003; Kjelvik et al., 2014).

Disparate sensory modalities are progressively affected in AD (Djordjevic et al., 2008; Mesholam et al., 1998; Devanand et al., 2000; Bublak et al., 2011; Cronin-Golomb et al., 1991; Trick and Silverman,

1991; Fernandez et al., 2007). Further, local field potential recordings of oscillatory activity in the OB and the piriform cortex have revealed abnormal spontaneous and odour-related activity in the Tg2576 mouse model of AD (Wesson et al., 2011). Generalized spontaneous aberrant excitatory activity becomes apparent in the cortex and the hippocampus of AD mouse model (Palop et al., 2007), owing to dysfunctional synaptic integration (Stern et al., 2004).

The A β has been identified as a key molecule in the pathogenesis of AD. It accumulates in various forms in AD brains, including early soluble oligomeric oligomers and insoluble A β -plaques (Glabe, 2008). Several studies have documented different mechanisms of action for soluble A β ; these include changes in ion-channel properties (Hartley et al., 1999; Hsieh et al., 2006; Shankar et al., 2007), impairments of synaptic transmission and synaptic plasticity (Kamenetz et al., 2003; Chapman et al., 1999; Wei et al., 2010; Li et al., 2009; Shankar et al., 2008), and effects on the neural network (Palop et al., 2010). Initially, a reduced circuit of neurons may be capable of sustaining physiological activities, with the help of compensatory mechanisms (Palop et al., 2006; 2010). The reduced neuronal circuits in humans may sustain normal cognitive function, despite the presence of smoldering underlying neuropathology and disturbed sensory projection/central sensory processing (Price et al., 1999; Ashe and Zahs, 2010; Grienberger et al., 2012).

There is a parallel progression in the change of A β -load, sensory deficits, inhibition in the impaired network activity, and cortical dysfunction, as shown in the APP23 $\times$ PS45 mouse model of AD (Grienberger et al., 2012). Despite an ongoing generation of soluble A β oligomers during the first three months in these mice, the sensory neuronal function (orientation tuning of visual cortex neurons) was found to be normal. However, after the age of 4 months, an increase in both soluble A β and A β -plaques was associated with the progressive impairment of cortical neuronal function (Grienberger et al., 2012). It has been shown that soluble A β triggers axonal dysfunction in the olfactory epithelium in the absence of amyloid plaques *in vivo* in Tg2576 mice; overexpression of human APP in these mice perturbs the structural connectivity of the peripheral olfactory neural circuit (Cao et al., 2012). Indeed, soluble A β , by itself, is responsible for OB dysfunction both at electrophysiological and behavioral levels and directly affects OB network activity (Alvarado-Martínez et al., 2013). A β has been shown to decrease OB network activity, in a concentration- and time-dependent manner at clinically relevant concentrations (low nM) and in a reversible manner. Further, two weeks after intrabulbar injection, A β decreased the olfactory function in rodents (Alvarado-Martínez et al., 2013).

In the 5XFAD mice, interestingly, deficits in learning and memory start at four months of age when soluble A β is present (Grienberger et al., 2012) with its ongoing effect on olfactory function (Girard et al., 2014). In these 6-month-old mice, reduced glomerular area is found relative to non-transgenic controls (Cai et al., 2012). The olfactory nerve terminals in glomeruli showed age-related dystrophic and degenerative changes; these were associated with increased labeling for amyloidogenic proteins without any extracellular A β deposition (Cai et al., 2012). The axonal terminal pathology noted may affect neuronal

signal transmission and integration at the first olfactory synaptic relay (Cai et al., 2012) causing a cascading effect. Finally, the axonal dysfunction in the olfactory epithelium, glomeruli, and olfactory neural circuit (Cao et al., 2012) would cause hippocampal dysfunction (Girard et al., 2014) and an early impairment in memory and cognition.

11. Inflammation – Deleterious Impact on Olfactory Function

Inflammatory conditions involve activation of innate and adaptive immune mechanisms. These are composed of a complex network of cell types and signals and this poses a difficult therapeutic problem. Inflammatory signaling is carried out by several mediators that range from relatively large proteins to small peptides, gases, and protons. Thus, in order to adequately suppress pathological inflammation, treatment strategies need to target these diverse inflammatory mediators.

Neurodegenerative condition persists in chronic inflammatory pathology. There is gray matter atrophy during the inflammatory disease progression (Lisak, 2009), and correlates not only with motor, sensory and visual dysfunction, but cognitive deficits as well (Rao, 2001; Amato et al., 2004; Magnano et al., 2006). Hippocampal pathology begins early in inflammatory states (Sicotte et al., 2008; Ziehn et al., 2010). In a transgenic AD model, there is a marked upregulation of several inflammatory markers such as COX-2, TNF- α , IL-1 β , and fractalkine (CX3CL1) in both cerebral cortex and hippocampus (Hanzel et al., 2014). These markers are also expressed in A β -burdened neurons showing the occurrence of a proinflammatory process preceding amyloid plaque deposition, and further enhancing inflammation in AD (Hanzel et al., 2014). In AD, there is hippocampal CA1 degeneration and volume decrease; these are however associated with hippocampal-dependent dysfunction in learning and memory (Ziehn et al., 2010). Several data provide evidence that experimental autoimmune condition also correlates with deficits in hippocampal-dependent learning and memory, and is associated with microglial activation, synaptopathy/synaptic loss, and neurodegeneration (Mandolesi et al., 2010; Girard et al., 2014). Systemic LPS administration in adult mice resulted in rapid increase of brain TNF- α which remained elevated for 10 months. Indeed, inflammatory cytokines are released from infiltrating lymphocytes and/or activated microglia (Qin et al., 2007). Conversely, systemic TNF- α administration activated microglia and increased expression of pro-inflammatory factors including TNF- α , IL-1beta, MCP-1, and NF-kappaB p65 in the brain; all these are able to alter synaptic transmission (Qin et al., 2007). TNF- α has been shown to play a key role as a mediator of synaptic instability in the primary somatosensory cortex, and thus contribute to sensory and cognitive deficits (Yang et al., 2013). Pro-inflammatory cytokines are correlated with the disruption of synaptic networks, and thus contribute to impaired cortical function (Yang et al., 2013). Further, inflammation confers many pathological features including sensory deficits. In a transgenic mouse model of olfactory inflammation, loss of olfactory sensory neurons was present in the olfactory epithelium, where significant sub-epithelial inflammation was present (Sultan et al., 2011). Furthermore, inflammation has been shown to inhibit neuronal progenitor cell proliferation and prevent olfactory epithelium regeneration (Turner et al., 2010).

On the basis of a 13-year cause-specific multivariate mortality research, a recent study linked neuroinflammation independently to early death in AD (Nägga et al., 2014). One of the earliest detectable lesions in neurodegenerative conditions including AD is breakdown of the blood-brain barrier in association with neuroinflammation. Behavioral, memory, and cognitive declines in AD and AD mice develop owing to neuroinflammation (Daulatzai, 2012a; 2012b; 2012c; 2013a; 2013b; 2014a; 2014b). These above mentioned early changes that precede AD-like neuropathology are said to provide a causal link between inflammation and memory/cognitive decline (Marchese et al., 2014). Soluble A β generation is implicated in early AD-like pathology (Cai et al., 2012; Grienberger et al., 2012; Girard et al., 2014). Soluble A β directly affects OB network activity *in vitro* in slices obtained from mice and rats. A β decreases (in a concentration- and time-dependent manner) the network activity of OB slices at clinically relevant concentrations (low nM) and in a reversible manner (Alvarado-Martínez et al., 2013). These results indicate that soluble A β not only disrupts the network activity of the OB *in vitro* but can also trigger olfactory disruption. A β may increase the proportion of abnormally hypoactive or hyperactive/excitotoxic neurons in Olfactory-ERC-hippocampal circuits (Busche et al., 2008). Further, the above mentioned could be concurrent to other early hallmark pathologies of AD *viz.* tau accumulation in the ERC (Nelson et al., 2012), in the background of aging. It is likely that nascent A β further promotes the tau spread both within and beyond the ERC (de Calignon et al., 2012; Liu et al., 2012; Ahmed et al., 2014). The above described may trigger lower performance on memory tests in clinically normal older individuals who may be asymptomatic at-risk for future cognitive decline.

12. Cholinergic Deficit – Deleterious Impact on Olfactory Function

The ERC receives prominent cholinergic innervation from the basal forebrain (medial septum and the vertical limb of the diagonal band of Broca), and the specific cellular mechanisms in ERC are modulated through cholinergic activity (Heys et al., 2012). A low dose of nicotine enhances synaptic transmission and its plasticity, by acting through the non- $\alpha 7$ subtype of ACh receptor (nAChRs) (Tu et al., 2009). MCI subjects (who were not different from normal controls) were characterized with increased hippocampal choline acetyltransferase (ChAT) activity (DeKosky et al., 2002; Ikonomic et al., 2003). In contrast, the hippocampal ChAT levels showed marked decrease in AD cases; moreover, the hippocampal ChAT activity level correlated with the extent of AD lesions (Davies and Maloney, 1976; Perry et al., 1978a ; Perry et al., 1978b). However, a significant elevation of hippocampal ChAT was found in ERC-hippocampus in the MCI subjects classified as III/IV Braak stages. This was ascribed to a compensatory response to the progressive denervation of the hippocampus by depleted input from the ERC. The above findings demonstrate that memory loss observed in amnesic MCI (aMCI) is primarily a function of disrupted entorhinal-hippocampal connectivity, and not necessarily caused by cholinergic deficits (Ikonomic et al., 2003). However, a significant correlation does exist between aMCI patients with reduced cortical ACh activity and those who later convert to AD (Herholz et al., 2005). Consequently, memory dysfunction and cognitive impairment in AD patients is a function of cholinergic dysfunction also (Davies and Maloney, 1976; Perry et al., 1978a ; Perry et al., 1978b). In contrast, there is little correlation between the severity of the cognitive deficits manifested and A β deposition in AD patients (DeKosky et al., 1992, DeKosky and Scheff, 1990, Samuel et al., 1994; Terry et al., 1991; Giannakopoulos et al., 2003).

Cholinergic abnormalities in Tg2576 AD mice occur quite early, i.e. at approximately 4 months of age (Apelt et al., 2002; Fodero et al., 2002); subtle olfactory working memory deficit in Tg2576 mice also occurs at about 4 months of age. Indeed, the olfactory memory deficit in these Tg mice occur prior to A β deposition (Young et al., 2009; Hsiao et al., 1996; Kawarabayashi et al., 2001). Importantly, the olfactory memory deficits found in Tg2576 mice (at 4 months of age) coincides with the onset of altered glycolization of acetylcholinesterase in these mice at this age (Fodero et al., 2002). Furthermore, both olfactory memory deficit and cholinergic dysfunction occur several months prior to A β plaque deposition (Kawarabayashi et al., 2001).

ACh has been shown to increase the strength of afferent input, enhance theta rhythm oscillations, activate intrinsic mechanisms for persistent spiking, and increase the synaptic plasticity (Hasselmo, 2006). Extensive physiological research has demonstrated a number of common effects of ACh on the hippocampus, piriform cortex, and neocortex (Hasselmo, 1995, 1999). One such physiological effect of ACh serves to enhance the feed-forward afferent input within cortical circuits. Thus, ACh enhances sensory stimuli, response to sensory input, and encoding of memory for specific sensory stimuli (Hasselmo

and Giocomo, 2006). Conversely, lower levels of ACh are expected to have a negative impact, and alter the above mentioned specific functional properties in the cortices and upregulate dysfunction. Thus, a failure (or paucity) to produce a critical level of ACh by BFB and neurotrophic factors by dysfunctional OB, olfactory cortex, ERC and the hippocampus would adversely affect survival of the inter-connected chains of neurons and enhance neuronal dysfunction and degeneration (Wenk et al., 1984; Clarke et al., 1986; 1990; Morse et al., 1993; Burke et al., 1994; Venero et al., 1994; Leanza et al., 1996a; 1996b; Winters and Bussey, 2005).

13. Improving Olfactory Function: Therapeutic Strategies

Olfactory dysfunction is one of the key factors in aging and AD and as such warrants our serious consideration. In the mammalian OB, neural activity driven by olfactory stimuli can lead to experience-dependent changes in its structures and functions. The adult sensory system is capable of extensive functional plasticity. Therapy should aim at the restoration of axonal function, resolution of inflammation, and the restoration of normal impulse conduction – thus recover sensory dysfunction. Improvement in olfactory function therefore is identified as an important goal since it enhances rCBF, connectivity in olfactory regions, and cognitive gains. There is evidence that neural plasticity exists in OB; this can be harnessed utilizing the following disparate methods in order to mitigate olfactory dysfunction, cognitive decline in hyposmic and anosmic seniors, and enhance memory/cognition.

13.1 Applications of Chemosensory Trigeminal Stimulation

The anatomy of the olfactory neuroepithelium and the distribution of the trigeminal sensory/tactile receptors which occupy the nasal mucosa, is now reasonably well understood (Wrobel and Leopold, 2005). In the nose, the capacity to detect and react to volatile chemicals is mediated by two separate but interrelated sensory pathways, the olfactory and the trigeminal systems. However, most chemosensory stimulants, at sufficient concentration, produce both olfactory and trigeminal sensations. Olfactory neurons (ON) which are located in the olfactory epithelium are responsible for detection of odors. Loss of trigeminal function may affect the sense of smell (Husner et al., 2006). An increased excitation of the somatosensory system, e.g. with CO₂ results in reduced latencies and enhanced amplitudes of the evoked potentials (Kassab et al., 2009). In 1993, Livermore et al. performed an interesting experiment; they investigated the effects of trigeminal cutaneous stimulation on intensity estimates of intranasal chemical stimuli. While the left nostril was stimulated with chemical olfactory and trigeminal stimulants, four regions of the face were stimulated electrically. They found that the intensity estimates of the intranasal chemical stimulation increased after cutaneous electrical stimulation. These data indicate that the trigeminal nerve that enhances nasal chemoreception can be exploited to stimulate olfactory function and attenuate its dysfunction in aging and AD.

13.2 Exploiting Olfactory Learning

The OB is a highly plastic structure that responds to changes in olfactory status. OB volume correlates with olfactory function (Buschhüter et al., 2008; Rombaux et al., 2008). During olfactory associative training in the rat, synaptic efficiency was observed in the piriform cortex and the dentate gyrus; this suggest that when olfactory cues are reinforced the hippocampal processing reactivation takes place (Truchet et al., 2002; Knafo et al., 2004; Barkai, 2005; Restivo et al., 2006; Zelcer et al., 2006; Machado and Genaro, 2014). In another study, rats were trained to discriminate odors; after training completion, the mean spine density along the apical dendrites of the hippocampal neurons was significantly higher (20.5%) than the controls (Knafo et al., 2004; Restivo et al., 2006). Research in mice has further confirmed that the olfactory learning enhances dendritic spine growth in the hippocampus (Zelcer et al., 2006). Human studies also indicate that the olfactory input may generate different odor percepts depending on odor learning and experience. The olfactory learning induces intrinsic modifications in pyramidal neurons that create favorable Hebbian conditions for activity-dependent enhancement of synaptic connections between simultaneously activated neurons. Olfactory learning changes the intrinsic properties of the pyramidal neurons and enhances their excitability (Barkai, 2005). Ongoing olfactory learning is expected to keep the cortical system in a 'learning mode' in which memories for specific odors are acquired rapidly and efficiently (Barkai, 2005; Zelcer et al., 2006). It has been suggested that the enhanced excitability of CA1 neurons may serve as a mechanism for enhancement of hippocampus function. Recent studies have demonstrated that olfactory training may prevent olfactory deterioration in older people (Schriever et al., 2014). Other work has repeatedly emphasized that olfactory function increases significantly with a combined treatment regimen of topical nasal corticosteroid and a concurrent program of olfactory training (Fleiner et al., 2012; Konstantinidis et al., 2013; Enriquez et al., 2014).

The integration and survival of adult-born neurons are strongly influenced by olfactory learning; the latter strengthens the excitatory inputs onto adult-born granule cells (Lepousez et al., 2014). Survival of adult-born neurons during olfactory learning is a function of the OB plasticity. Indeed, enhanced sensory experience promotes remodeling of OB microcircuits and the synaptic integration of new neurons into cell type-specific olfactory circuits (Kerman et al., 2010; Arenkiel et al., 2011; Cleland, 2014). Odor stimulation-induced plasticity of OB function and its structural-physiological reorganization has been reconfirmed recently based on quantitative proteomics (Zeng et al., 2014). Interestingly, olfactory stimulation of neuronal circuits in the OB can actively prolong the odor-induced spike activity of bulbar output neurons; this therefore, transform a brief odor input into longer-lasting activity in the central olfactory system (Matsumoto et al., 2009; Lenk et al., 2014). Finally, administration of non-invasive physiologically-relevant olfactory stimulation in conjunction with Pharmacological treatment (see below) should be seriously considered for therapeutic benefit.

13. 3 Pharmacological Treatment

Olfactory dysfunction may be associated with increased apoptotic death of olfactory sensory neurons. Valproic acid (VPA), a histone deacetylase inhibitor, has neuro-regenerative effects. Oral VPA

in mice promoted regeneration of olfactory neurons in damaged neuroepithelium, increased epithelial thickness and number of olfactory marker protein (OMP) positive cells in the olfactory epithelium during recovery from methimazole-induced degeneration (Ogawa et al., 2014). Dysfunction of the sensory mucosa of the OB resulting from local inflammation can be treated by corticosteroids. Although both nasal and systemic corticosteroids have a beneficial effect on olfactory dysfunction, systemic treatment is the most powerful (Hellings and Rombaux, 2009). Minocycline has been shown to inhibit apoptosis apart from its anti-infective properties (Kern et al., 2004). Theophylline has shown to be an effective therapeutic agent to attenuate hyposmia in patients with smell loss. fMRI showed increased activation in olfactory regions, OFC, cingulate gyri, temporal lobe gyri, and the hippocampus (Levy et al., 1998). Uptake of theophylline into the rodent olfactory epithelium correlated with an increase in the olfactory signal transduction, measured via changes in the electro-olfactogram (EOG) (Gudziol et al., 2010). Since cholinergic dysfunction occurs with aging, non-selective muscarinic receptor agonist pilocarpine has been shown to prevent age-related spatial learning impairments in rats. Olfactory discrimination and short-term social memory of 3 and 24 month-old rats improved when treated with pilocarpine (Prediger et al., 2006). Interestingly, acute treatment with caffeine reversed age-related olfactory deficits reflecting the participation of adenosine receptors in the control of olfactory functions (Prediger et al., 2005).

14. Conclusions

A large number of hypotheses on the pathogenesis of AD underscore the inherent complexity of AD. There is copious evidence that olfactory dysfunction is also involved in the early pathogenesis of AD. This risk factor persists in old age, between ongoing late aging with no cognitive impairment and memory/cognitive dysfunction in dementia. This is an upstream pathology, as compared to downstream pathological characteristics of AD, *viz.* oxidative stress, impaired Ca^{2+} homeostasis, deposition of tau proteins and amyloid- β peptides, and ER stress in neurons that aggravate AD pathology. The cortico-cortical input to the hippocampus is provided via the perforant pathway, which contains axons originating in neurons of the ERC and terminating in the outer two-thirds of the molecular layer of the dentate gyrus. The ERC and hippocampus are the first cortical regions to be affected in AD, and their degenerative cellular process/atrophy leads to cognitive decline. Excessive and/or prolonged hyposmia/anosmia can be detrimental to neurons owing to its effect on axonal degeneration and synaptic dysfunction in interconnected regions. Subjects with olfactory activity deficit show a more extensive pattern of pathology (*i.e.* hypoperfusion, rCBF decrease, and volume atrophy), *i.e.* injury course, in olfactory regions encompassing nasal neuroepithelium, OB, piriform cortex, ERC, and indeed hippocampus. Progressive neuropathology results from a combination of both primary sensory/olfactory dysfunction, and secondary injury mechanisms including hypoperfusion, metabolic alterations, reactive oxygen injury, inflammation, mitochondrial dysfunction, excitotoxicity, and synaptic injury. The current paper highlights the vital need for rigorous investigation of olfactory decline to keep it in check. It is prudent to exploit the treatment strategy suggested here - comprised of trigeminal sensory stimulation in conjunction with olfactory

learning and pharmacological compounds (shown to be efficacious). This combination has an inherent potential to stimulate olfactory-related structures, enhance cholinergic and neurotrophic transport, prevent/delay neuronal atrophy/degeneration, abrogate volume loss, and ameliorate memory and cognitive decline. This therefore provides an opportunity for early neuroprotection and possible AD prevention.

(See References Below)

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