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Symposium: Chemical Senses and Mechanisms of Neurodegenerative Diseases

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Abstract

Olfactory function is significantly and early impaired in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Epigenetic regulation and adult neurogenesis are some of the major cutting edge research directions in studying the mechanisms underlying neurodegenerative diseases. Leading scientists in these research areas were invited to participate in this symposium to introduce to the chemical senses community their novel insights into the mechanisms underlying neurodegenerative diseases. Insight into the mechanisms underlying olfactory system impairment in neurodegenerative diseases may facilitate both the identification of individuals likely to develop cognitive impairment or dementia who will benefit most from interventions at the earliest incidence of impairment, and the identification of new treatments for neurodegenerative diseases.

Keywords

olfaction; dementia; olfactory impairment; Alzheimer's Disease; neurodegenerative diseases; smell; neurogenesis

The prevalence of olfactory impairment increases significantly with age^{1,2} and profoundly so in neurodegenerative diseases, including Alzheimer's disease (AD).^{3,4} In AD, neuropathological changes begin in entorhinal and transentorhinal areas,⁵ 6⁷ regions important for processing olfactory information, and, significantly, neuropathy in these areas appears before clinical symptoms. 6 Entorhinal cortex and perirhinal cortex, CA1/subicular area of hippocampus, amygdala and the association cortices show the most severe lesions as the disease progresses, 6 suggesting further involvement of areas key to higher order processing of olfactory information. Neurogenesis in the adult mammalian brain takes place in dentate gyrus and the subventricular zone, with neurons from the latter region migrating to the olfactory bulb, which also shows adult neurogenesis. Disruption of neurogenesis or disruption of the incorporation of daughter cells into the olfactory bulb may be an underlying mechanism for the effects of age on the olfactory system⁸ and disruption of olfactory neurogenesis is a potential contributing mechanism for AD. 9 Memory loss is a defining feature of AD and these patients show particular vulnerability of odor memory.¹⁰ 11¹²13 Olfactory memory dysfunction has also been observed in persons at risk for AD. 14.15¹⁶17¹⁸

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Olfactory impairment in those at risk for AD because of family history,¹² genetic risk from the apolipoprotein $\epsilon 4$ allele^{13,14,15,16,17} or from evidence of mild cognitive impairment^{18,19,20} suggests the potential for olfactory function in combination with other indices to signal prodromal AD. Odor identification impairment is associated with structural changes in olfactory areas of the brain in Alzheimer's disease, including left hippocampal volume loss²¹ and increasing numbers of neurofibrillary tangles.²² The mechanisms underlying neurodegenerative disease and dementia and their reflection in olfactory function are largely unknown. Mechanistic understanding of the relationship between the olfactory system and dementia at the molecular, cellular, neurophysiological and behavioral levels is critical and may facilitate the identification of individuals who will develop cognitive impairment or dementia, who will benefit most from pharmaceutical interventions at the earliest incidence of impairment and thus, the association of olfactory dysfunction with cognitive impairment is of keen interest.

Claire Murphy began the session, providing the context for the symposium by reviewing the state of the field in human olfactory function in aging and neurodegenerative diseases, particularly Alzheimer's disease. In addition, she highlighted findings that support the use of cross-modal odor recognition memory to discriminate between normal older adults, those at risk for AD and AD patients. She reported new findings that demonstrated that measures of brain response during a cross-modal odor recognition memory task discriminate between older adults with and without the apolipoprotein $\epsilon 4$ allele, a potent genetic risk factor for AD.²² Howard Eichenbaum discussed the utility of rodent models of odor recognition memory to characterize age-related memory impairment, and presented strong parallel evidence that in both rodents and humans, older individuals rely on familiarity-based processes rather than recollective processes in declarative memory tasks.²³ His presentation highlighted both the commonality of age effects in humans and rodents and the commonality in hippocampal-dependent olfactory and spatial memory, both of which are impaired in older individuals.

Hongjun Song's research seeks a better understanding of cellular and molecular mechanisms regulating adult neural stem cells and neurogenesis, in order to facilitate the development of novel strategies for functional neuronal replacement therapy after injury or neurodegenerative diseases. He presented studies that have identified signaling molecules that regulate aspects of adult neurogenesis in an activity-dependent fashion.²⁴ His research has identified essential intrinsic regulators of adult neurogenesis in vivo. Dr. Song addressed olfactory bulb neurogenesis and its potential association with specific olfactory functions such as discrimination and memory. Li-Huei Tsai discussed her work deciphering the process of chromatin remodeling in hippocampus dependent learning and memory. She presented results that suggest that increased dendritic sprouting and synapse number may contribute to improved learning and recovery of long-term memory resulting from chromatin remodeling. In her manuscript, she speculates on common underlying mechanisms which may trigger aberrant cell cycle activity and DNA damage, two events associated with a number of neurodegenerative conditions.²⁵

This symposium sought to address the following aims: 1) To bring together scientists at the forefront of research on neurogenesis in aging, neurodegenerative diseases, and the chemical senses, 2) To stimulate investigation into the mechanisms that underlie age-related impairment in the chemical senses and the dramatic changes in olfactory function in neurodegenerative diseases, 3) To facilitate the application of state of the art innovative technology, particularly genetic, molecular and cellular biological techniques, to research on aging and the chemical senses, and 4) To identify directions for future research in chemosensory science. To these ends, the speakers introduced novel approaches and

hypotheses that have the potential to stimulate research into the mechanisms of neurodegenerative disease and its relation to olfactory dysfunction.

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References

1. Murphy C, Schubert CR, Cruickshanks KJ, Klein BE, Klein R, Nondahl DM. Prevalence of olfactory impairment in older adults. *Journal of the American Medical Association*. 2002; 288(18): 2307–2312. [PubMed: 12425708]
2. Schiffman SS. Taste and smell losses in normal aging and disease. *Journal of the American Medical Association*. 1997; 278(16):1357–1362. [PubMed: 9343468]
3. Serby M. Olfaction and Alzheimer's disease. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 1986; 10:579–586. [PubMed: 3541051]
4. Murphy C, Gilmore MM, Seery CS, Salmon DP, Lasker BP. Olfactory thresholds are associated with degree of dementia in Alzheimer's disease. *Neurobiol. Aging*. 1990; 11:465–469. [PubMed: 2381506]
5. Price JL, Davis PB, Morris JC, White DL. The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease. *Neurobiol. Aging*. 1991; 12:295–312. [PubMed: 1961359]
6. Braak H, Braak E. Diagnostic criteria for neuropathologic assessment of Alzheimer's disease. *Neurobiol. Aging*. 1997; 18:585–588.
7. Hyman BT. The neuropathological diagnosis of Alzheimer's disease: clinical-pathological studies. *Neurobiol. Aging*. 1997; 18(4 Suppl):S27–S32. [PubMed: 9330982]
8. Enwere E, Shingo T, Gregg C, Fujikawa H, Ohta S, Weiss S. Aging results in reduced epidermal growth factor receptor signaling, diminished olfactory neurogenesis, and deficits in fine olfactory discrimination. *J. Neuroscience*. 2004; 24:8354–8365.
9. Curtis MA, Faull RL, Eriksson PS. The effect of neurodegenerative diseases on the subventricular zone. *Nature Rev Neurosci*. 2007; 8:712–723. [PubMed: 17704813]
10. Moberg PJ, Pearlson GD, Speedie LJ, Lipsey JR, Strauss ME, Folstein SE. Olfactory recognition: differential impairments in early and late Huntington's and Alzheimer's diseases. *J Clin Exp Neuropsychol*. 1987; 9:650–664. [PubMed: 2961789]
11. Nordin S, Murphy C. Impaired sensory and cognitive olfactory function in questionable Alzheimer's disease. *Neuropsychology*. 1996; 10:112–119.
12. Schiffman SS, Clark CM, Warwick ZS. Gustatory and olfactory dysfunction in dementia: not specific to Alzheimer's disease. *Neurobiology of Aging*. 1990; 11(6):597–600. [PubMed: 2280803]
13. Gilbert PE, Murphy C. The effect of the ApoE ϵ 4 allele on recognition memory for olfactory and visual stimuli in patients with pathologically confirmed Alzheimer's disease, probable Alzheimer's disease, and healthy elderly controls. *Journal of Clinical and Experimental Neuropsychology*. 2004; 26(6):779–794. [PubMed: 15370375]
14. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvensen GS, Roses AD. Apolipoprotein E: high avidity binding to β -amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proceedings of the National Academy of Sciences of the United States of America*. 1993; 90:1977–1981. [PubMed: 8446617]
15. Roses AD. Apolipoprotein E affects the rate of Alzheimer disease expression: beta-amyloid burden is a secondary consequence dependent on APOE genotype and duration of disease. *Journal of Neuropathology and Experimental Neurology*. 1994; 53(5):429–437. [PubMed: 8083686]
16. Murphy C, Bacon AW, Bondi MW, Salmon DP. Apolipoprotein E status is associated with odor identification deficits in nondemented older persons. *Ann New York Acad Sciences*. 1998; 855:744–750.

17. Graves AB, Bowen JD, Rajaram L, McCormick WC, McCurry SM, Schellenberg GD, Larson EB. Impaired olfaction as a marker for cognitive decline: Interaction with apolipoprotein E epsilon4 status. *Neurology*. 1999; 53(7):1480–1487. [PubMed: 10534255]
18. Devanand MD, Michaels-Marston KS, Lui SL, Pelton GH, Padilla M, Marder K, Bell K, Stern Y, Mayeux R. Olfactory deficits in patients with mild cognitive impairment predict Alzheimer's disease at follow-up. *Am. J. Psychiatry*. 2000; 157:1399–1405. [PubMed: 10964854]
19. Wilson RS, Arnold SE, Tang Y, et al. Odor identification and incidence of mild cognitive impairment in older age. *Arch Gen Psychiatry*. 2007; 64:802–808. [PubMed: 17606814]
20. Schubert CR, Carmichael LL, Murphy C, Klein BE, Klein R, Cruickshanks CJ. Olfaction and the 5-year incidence of cognitive impairment in an epidemiological study of older adults. *J. Amer. Geriatrics Soc.* 2008; 56:1517–1521.
21. Murphy C, Jernigan TL, Fennema-Notestine C. Left hippocampal volume loss in Alzheimer's disease is reflected in performance on odor identification: a structural MRI study. *Journal of the International Neuropsychological Society*. 2003; 9(3):459–471. [PubMed: 12666770]
22. Wilson RS, Arnold SE, Schneider JA, et al. The relationship between cerebral Alzheimer's disease pathology and odour identification in old age. *J. Neurol Neurosurg Psychiatry*. 2007; 78:30–35. [PubMed: 17012338]
23. Murphy C, Solomon E, Haase L, Wang M, Morgan C. Olfaction in aging and Alzheimer's disease: Event-related potentials to a cross-modal odor recognition memory task discriminate ApoE ε4+ and ApoE ε4− individuals. *Ann New York Acad Sciences*. in press (this volume).
24. Eichenbaum H, Robitsek RJ. Olfactory memory: A bridge between humans and animals in models of cognitive aging. *Ann New York Acad Sciences*. in press (this volume).
25. Ma DA, Kim WR, Ming G, Song H. Activity-dependent extrinsic regulation of adult hippocampal and olfactory bulb neurogenesis. *Ann New York Acad Sciences*. in press (this volume).
25. Kim D, Tsai L. Linking cell cycle reentry and DNA damage in neurodegeneration. *Ann New York Acad Sciences*. in press (this volume).