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At the interface of sensory and motor dysfunctions and Alzheimer's disease

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Abstract Recent evidence indicates that sensory and motor changes may precede the cognitive symptoms of Alzheimer's disease (AD) by several years and may signify increased risk of developing AD. Traditionally, sensory and motor dysfunctions in aging and AD have been studied separately. To ascertain the evidence supporting the relationship between age-related changes in sensory and motor systems and the development of AD and to facilitate communication between several disciplines, the National Institute on Aging held an exploratory workshop titled "Sensory and Motor Dysfunctions in Aging and AD." The scientific sessions of the workshop focused on age-related and neuropathologic changes in the olfactory, visual, auditory, and motor systems, followed by extensive discussion and hypothesis generation related to the possible links among sensory, cognitive, and motor domains

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in aging and AD. Based on the data presented and discussed at this workshop, it is clear that sensory and motor regions of the central nervous system are affected by AD pathology and that interventions targeting amelioration of sensory-motor deficits in AD may enhance patient function as AD progresses.

Keywords: Sensory; Motor; Olfaction; Vision; Auditory function; Alzheimer's disease; Aging

1. Introduction

With advancing age, we may notice ourselves walking a little more slowly or having a bit of difficulty navigating our environment; hearing less well; or not sensing the ambient aroma as acutely. Often, we think of these sensory or motor changes as signs of aging; rarely do we think of them as early signs of Alzheimer's disease (AD). For AD research, the defining phenotypic impairment is progressive loss of cognitive function, which we often consider as the first function to be lost in patients. However, clinical research has led to the recognition that changes in sensory and motor systems are present in many people at the early stages of AD. In particular, several longitudinal studies indicate that changes in olfaction, hearing, and even walking speed may precede the onset of cognitive impairments and dementia by 5 to 15 years and are strong risk factors for AD dementia [1–5].

These clinical findings, together with the recognition that AD pathology develops over many years, raise the exciting possibility that specific sensory or motor changes may be early noninvasive biomarkers for AD or, even more provocatively, that treating these sensory or motor symptoms may help to prevent or treat AD dementia. Although attempts have been made to explore these possibilities, it has quickly become obvious that current clinical measures of sensory or motor changes are not specific to AD. For instance, people may develop these sensory or motor impairments in association with other types of neurologic disorders, such as Parkinson's disease (PD) [6] or distinct non-AD types of dementia [7], or they may be caused by nonneurologic impairments of the nose, eye, ear, or muscles [8]. In fact, most older adults with sensory or motor impairments do not seem to exhibit progression to the cognitive symptoms of AD. Neither do all AD patients begin with some or any of these sensory or motor changes. Consequently, the significance of these sensory or motor dysfunctions for the pathogenesis and diagnosis of AD has remained largely elusive, if not often controversial. To unravel the relationships between age-related sensory and motor dysfunctions and AD and harness their potential, new ideas, perspectives, and investigations are in order.

A number of recent advances in AD research necessitate a reconsideration of the role for sensory and motor dysfunction in aging and AD. First, the recently revised diagnostic criteria and guidelines for AD have expanded the conceptual framework of the disease to include a "preclinical" stage, which occurs years before the onset of the noticeable cognitive symptoms with the appearance of the underlying AD pathophysiological disease process, in particular the accumulation of the amyloid-β (Aβ) protein [9]. The specific markers, in particular functional markers, of this "preclinical" stage, have yet to be defined. Thus, it is timely to consider that the existence of noncognitive functional changes, such as sensory or motor changes, may exemplify this "preclinical" stage and help to identify people 10 or 15 years before they are clinically diagnosed with AD. Second, findings reported from neuropathologic assessments of patients diagnosed with AD seem to corroborate this possibility. For instance, the deposition of the Aβ peptide, one of the key hallmarks of AD pathology, may first appear in sensory association areas, well before its appearance in regions involving memory, such as entorhinal and hippocampal areas, and also before the cognitive clinical symptoms of AD [10]. It may therefore be worth investigating whether combining AD pathology with specific sensory/motor changes would improve predictions of the emergence of the cognitive impairments and progression to AD dementia. Third, genome-wide association studies have now established multiple susceptibility genes for non-Mendelian forms of AD, many of which have proposed molecular effects on the production, aggregation, or clearance of Aβ [11] and other AD-related molecules such as ApoE [12]. Although these genes were identified based on diagnosis by cognitive symptoms of AD, it will be interesting to examine whether people with the AD susceptibility genes also develop the sensory or motor changes well before they progress to cognitive impairments and dementia [13]. More importantly, will a combination of the presence of AD susceptibility genes with the sensory and motor changes increase the sensitivity and specificity to predict the emergence of cognitive impairments and progression to dementia?

To advance our comprehensive understanding of the pathology and clinical manifestations of AD and to explore the relevance of sensory and motor impairments in aging to AD, the National Institute on Aging convened a 2-day workshop titled "Sensory and Motor Dysfunctions in Aging and AD" in the summer of 2010. The invited participants included many individuals who have contributed in leading ways to AD research and investigators in the fields of sensory and motor neuroscience and behavior who have been interested in but may not have been most directly involved with AD research. To recapture the spirit and presentations at this workshop as well as to highlight the potential new directions of research related to sensory/motor systems and