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Peer reviewed

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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.

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

AD, the workshop organizers and participants worked together to generate this synthesized review.

The review is composed of four similarly structured sections that present an analysis of the current evidence related to age-related changes in the olfactory, visual, auditory, and motor systems in the context of AD. Each section evaluates the relationship of the sensory or motor modality to AD at the clinical and epidemiologic, neuroanatomic and pathophysiological, genetic, neuroimaging and neurophysiology, and cellular and molecular levels. Each section begins with a summary of key findings and ends with suggestions for future research directions. More detailed meta-articles for each modality are included in the accompanying Appendix, which include a summary of the normal physiology of each sensory or motor modality. In Section 6, a conceptual framework is presented regarding the interface of sensory and motor dysfunctions of aging and AD, followed by a discussion of several testable hypotheses to evaluate the etiologic significance and clinical utility of the diagnostic precision and therapeutic efficacy offered by sensory and motor systems in preclinical and clinical AD.

2. Olfactory system in aging and AD

2.1. Summary of key findings

1. Olfactory impairment is prevalent in AD patients and presents in some cognitively normal older adults.
2. Olfactory dysfunction alone may predict progression toward AD dementia in a clinical setting and toward prodromal AD in preclinical subjects at a population level.
3. AD pathology is present in the peripheral and central olfactory neural networks in most AD patients and some cognitively normal older adults, and the pathology is related to impaired odor identification.
4. Cognitively normal older adults who are genetically at risk for AD may have worse olfactory function than noncarriers.
5. Olfactory impairment is associated with reduced hippocampal volume by structural magnetic resonance imaging (MRI).
6. Both odor-evoked functional MRI (fMRI) and event-related potentials (ERPs) are preferentially affected in AD patients and individuals genetically at risk for AD.
7. In transgenic mice overexpressing Aβ or tau, the presence of AD pathology in the olfactory system strongly correlates with olfactory perceptual impairments.

2.2. Epidemiologic and clinical studies

Studies have shown that olfactory function declines significantly with age [8,14]. Although only about 6% of people between the ages of 50 to 59 years show impairments in odor identification, the percentage of individuals aged 60 to 69 years triples. By the age of 80 years or above, more than 60% of individuals show impairment in odor identification. Moreover, three-quarters of the people with impairments of odor identification did not report that their sense of smell was compromised [15]. Although initially interpreted as a consequence of aging, subsequent studies support the notion that preclinical or prodromal AD or PD may contribute to this olfactory decline [16–18].

The connection between olfactory impairment and AD, initially reported in 1987 [19], has been confirmed in numerous studies that assessed odor identification, detection threshold, and odor recognition memory in patients diagnosed with the dementia phase of AD [6,20,21]. More importantly, many studies have shown that olfactory impairment is more prevalent in individuals who go on to develop the dementia phase of AD and may precede the onset of cognitive impairment by several years [22–26]. In particular, in patients with mild cognitive impairment (MCI), olfactory impairment was a strong predictor for conversion to AD dementia in a clinical setting [23]. Among older adults with no cognitive impairment in the Rush Memory and Aging cohort, difficulty in odor identification was also predictive of subsequent development of MCI [26]. Moreover, older individuals with odor identification score within the normal range were highly unlikely to go on to develop AD in a 5-year period.

However, olfactory impairment alone is not adequate to predict which individuals will decline cognitively, especially in the general population [24]. Other factors may contribute to olfactory impairment in older adults, including peripheral, for example, conductive nasal disease, sinus diseases, allergies, and central, for example, head trauma and incipient PD, etiologies [6,15,27,28]. Although current methods of assessing olfactory function cannot satisfactorily differentiate olfactory impairments due to AD from other causes, new olfactory measures designed from insights about the neuropathology, genetics, neuroimaging, neurophysiology, and cellular and molecular mechanisms of AD may improve their sensitivity and specificity. Additionally, combining olfactory assessments with other biomarkers for AD may enhance their diagnostic accuracy [1]. Because olfactory testing is not expensive and is noninvasive and appears to capture a unique proportion of the variance in the preclinical and prodromal stages of AD [1], it remains an important component of the battery of genetic, molecular, and clinical biomarkers that comprise an AD risk profile to detect and, perhaps, follow the trajectory of AD, in its preclinical and prodromal phases.

2.3. Neuropathologic studies

The canonical AD pathology of neuronal loss in the setting of amyloid plaques and neurofibrillary tangles (NFTs) afflicts many components of the olfactory neural system [29]. Accumulation of NFTs in the entorhinal cortex

(EC) is an early site of AD pathology and correlates best with the initial appearance of the cognitive symptoms in AD [30,31]. The olfactory pathway is the most direct path between the entorhinal/hippocampal region and the external environment, that is, olfactory epithelium (OE). Although the entorhinal areas receive direct connections from the olfactory bulb (OB), relatively little is known about the mechanisms underlying the entorhinal-mediated olfactory processing and whether the presence of AD pathology in entorhinal regions directly affects olfactory function [32]. However, a significant relationship has been demonstrated between odor identification and a composite measure of plaques and tangles in multiple brain areas implicated in AD, including the EC, in a cohort of individuals who died without cognitive impairment, and between odor identification and volume loss on quantitative MRI in the right amygdala and bilateral EC and perirhinal cortex [33]. Together, these results suggest that olfactory function may reflect incipient pathology before individuals show clinical evidence of AD [29,34,35].

Accumulations of neuropil threads (NPTs) and NFTs have been found in the OBs of patients diagnosed with definite AD, many patients diagnosed with probable AD or MCI, and some cognitively normal older adults [36]. In addition, the frequencies of tau deposits in the OB and EC were highly correlated [29,36], indicating that both NPTs and NFTs appear in the olfactory system as early as they do in the EC. Although a recent animal model study reported the correlation of olfactory dysfunction with Aβ burden in the OB and piriform cortex [37], further research is needed to establish the relationship between the appearance of AD pathology in the olfactory neural network and olfactory function in humans. As we gain more insight into the physiology of the processing olfactory input from the OB to cortical regions, it will be important to investigate the mechanisms by which AD pathology may influence the structure and function of the olfactory neural network, in particular, during the preclinical stages of AD.

In the OE, both Aβ and tauopathies have been shown to be highly enriched in postmortem tissues of individuals diagnosed with AD compared with cognitively normal older adults or young subjects, and the presence of OE AD pathology correlates with the presence of AD brain pathology [38–40]. Like the EC and OB, AD pathology can also be found in the OE of a small fraction of the cognitively normal older adults [34,38,41]. Until the advent of amyloid imaging and the unmasking of amyloid plaques in up to 30% of individuals with normal cognition [42], this lack of complete correlation between the presence of AD pathologies in the OE and clinical diagnosis of AD dementia had diminished the interest and effort of further diagnostic and mechanistic research in the past two decades. In light of the introduction of the "preclinical" stage for AD, future research is warranted to assess whether AD pathologies in the OE in cognitively normal older adults are also indicative of the preclinical stage of AD and whether pathologic

expression of Aβ may contribute to olfactory neuron loss and olfactory impairment. The accessibility of the OE for biopsy [40], despite its recognized limitation [43], has potential value for pathologic and mechanistic studies. Further studies are needed to determine whether molecular markers that can specifically differentiate AD from PD or other types of pathologic processes among individuals with olfactory dysfunction will be of particular value.

In summary, AD pathology can be found at every level of the neural pathway processing olfactory information, and AD pathology is associated with impaired odor identification. Moreover, AD pathology is found in the olfactory neural network of cognitively normal older adults. However, little is known about the impact of AD pathology on the function of cells in the olfactory pathway. Further research to define the relationships between AD pathology and olfactory function in cognitively normal subjects will determine whether olfactory dysfunction may be a functional marker of the preclinical stage of AD and will facilitate the development of the next generation of olfactory tests to increase the sensitivity and specificity of olfactory testing for predicting the progression of AD.

2.4. Genetics

Although olfactory impairments are highly prevalent in older adults, in particular among adults aged 80 years or older, whether age-related olfactory dysfunction is hereditary and whether alterations in genes or the epigenetic landscape is associated with these olfactory impairments remain rich areas for investigation. Several studies demonstrate that olfactory impairment is more prevalent in individuals genetically at risk for AD. Olfactory function in first-degree relatives of patients with AD [44] or in individuals with a family history of dementia [45] is considerably lower than their age-matched cognitively normal controls. Cognitively normal older adults carrying the *APOE* ε4 allele, the most robust genetic risk allele for the late-onset AD [11], also may have much worse performance on a number of olfactory functions, including odor identification [46], odor threshold [47], and odor memory [48], than the age-matched noncarriers.

Genetic risk factors for AD may significantly enhance the power of olfactory tests to predict the progression to cognitive impairment and dementia. In a community-based longitudinal study of memory and aging in King County, Washington, the presence of both olfactory impairment and at least one *APOE* ε4 allele substantially increased the odds ratio (OR) for predicting cognitive decline compared with considering either olfactory impairment or carrying at least one *APOE* ε4 allele alone [22]. With the identification of new AD susceptibility genes [11], it will be important to ascertain whether and how combining olfactory testing with AD genetic risk alleles in cognitively normal older adults may enhance the prediction of future progression to AD

cognitive symptoms. Likewise, such combinations of genetic markers with olfactory functional markers may help identify older individuals at risk of developing AD and increase the specificity of potential therapeutic treatments.

2.5. Neuroimaging and neurophysiology

Although it is not yet known whether the volumes of the olfactory pathway as measured by structural MRI are altered in patients with olfactory impairment, it has been shown that odor identification can predict left hippocampal volume in AD patients measured by structural MRI [49]. In a clinical study, combining olfactory testing with structural MRI measures of hippocampus and EC led to strong predictive accuracy of conversion from MCI to AD dementia, which was appreciably higher than either measure alone [1]. fMRI studies reveal that in AD patients, activation of several olfactory central processing areas, including piriform cortex, EC, and hippocampus, is altered in response to odor stimuli or odor-dependent tasks [50–52]. A recent fMRI investigation of brain response during recognition memory for odor stimuli showed significant disruption in functional connectivity in nondemented *APOE* ε4 carriers compared with individuals without the ε4 allele [53]. However, the utility of these olfactory-dependent fMRI measures, especially when combined with genetic risk factors, in predicting the clinical and pathologic trajectory of AD remains to be investigated.

Although neuroimaging studies are best suited to reveal neuroanatomic regions associated with olfactory impairment and AD, neurophysiological approaches, such as ERP, are exquisitely sensitive to temporal changes in the response of the brain to external stimuli. Sensory or perceptual elicited responses tend to be represented by early components of the ERP waveform, whereas cognitive and memory-dependent responses are typically indicated by later components. Early odor-evoked ERPs distinguish patients with AD dementia from cognitively normal controls [54]. In cognitively normal older adults, longer latencies for the cognitive component of odor-evoked ERPs can differentiate *APOE* ε4 carrying individuals from noncarriers [55]. Further studies are needed to determine whether odor-evoked ERPs predict the clinical and pathologic progression of AD, at least to the similar degree as cognitive task–dependent ERPs [54].

2.6. Cellular mechanisms and model systems

Much of the efforts to elucidate the cellular and molecular underpinnings of AD pathogenesis using cellular and animal models have focused on the memory and cognitive systems involving the hippocampus and EC, and few have examined the olfactory system. Extant studies of the olfactory system are correlational analyses of (1) transgenic models overexpressing AD-linked genes broadly throughout the brain,

(2) characterization of engineered lines that express AD genes specifically in neuronal subtypes within the neural network that processes olfactory information, and (3) investigation of the regenerative capacity of the adult olfactory neurons.

In transgenic mice overexpressing either Aβ or tau throughout the brain, sensory impairments of olfactory habituation or discrimination have been observed [37,56–58]. Importantly, these deficits appear at a very young age (3–6 months old), well before the onset of memory or other cognitive deficits. The deposition of AD pathology in the OB in these transgenic animals is consistent with the observations that AD pathology can be observed in human OB from cognitively normal older adults and individuals diagnosed with AD [29]. At a structural level, a recent study demonstrated that overexpression of a pathogenic allele of APP, Aβ$_{40}$ alone or Aβ$_{42}$ alone, but not the wild type or synthetic mutant isoform of APP, disrupted the structural connectivity of the peripheral olfactory neural circuit in mice in the absence of amyloid plaques [56], resulting in olfactory deficits. More recently, a line with overexpression of a synthetic chimeric mouse-human APP, which results in accelerated olfactory sensory neuron death, was found to have structural connectivity and behavioral anomalies [58].

Recent findings suggest that pathology resulting from the overexpression of tau [59–61] or Aβ [62] specifically in EC neurons can propagate to synaptically connected downstream neurons. Future studies using olfactory neuron–specific transgenes may help to test the possibility of propagation from the OB to the piriform cortex or to EC neurons. Recent work demonstrates that treatments which promote Aβ degradation can rescue both olfactory system physiology and odor perception in transgenic mice overexpressing Aβ [37,63,64]. It will be important to determine whether reversing the olfactory impairments may prevent the occurrence of cognitive impairments emanating from downstream circuits in these transgenic models.

Another unique property of the olfactory system is that both the OE and the OB have regenerative capacity that persists throughout adulthood, even in old age [65]. In mice that are genetically deficient of *APOE*, the rate of olfactory nerve regeneration in the OE is significantly delayed, along with multiple measures of olfactory function [66–68]. Although the synaptic integrity of the OB is also compromised in the *APOE*-deficient mice [69], it is not yet known whether its regenerative capacity is also decreased or delayed. Interestingly, estrogen treatment has been shown to stimulate the regeneration of OE and synaptogenesis of OB in an *APOE*-dependent manner [70].

2.7. Key research directions

1. Olfactory dysfunction is a promising biomarker of early pathophysiological events of AD. Prospective studies of olfactory tests designed purposefully for

detection of preclinical AD based on insights summarized previously are needed in both the clinical setting and at the population level to determine their sensitivity and specificity for predicting the progression of cognitive impairments in AD, either alone or in combination with olfactory epithelial biopsy, genetic, neuroimaging, molecular, and other biomarkers. Further analysis is needed to determine whether an olfactory outcome can be used as an intermediate outcome in a clinical trial of preclinical and prodromal AD.

2. Mechanistic studies leveraging the many advantages of the olfactory neural circuit as a model system for early AD pathogenesis will ascertain whether neural system failure in general and olfactory functional impairment specifically is caused by reversible neuronal dysfunction or irreversible neurodegenerative changes. Moreover, mouse genetic engineering to introduce AD pathogenetic features to different levels of the olfactory system will determine the relative contributions of changes in the epithelium, OB, and piriform, entorhinal, and perirhinal cortices to olfactory dysfunction. This knowledge can be translated to design clinical screening instruments with improved sensitivity and specificity.

3. Visual system in aging and AD

3.1. Summary of key findings

1. Subpopulations of patients with AD have concomitant eye diseases, and particular visual functions are selectively impaired in subgroups of AD patients.
2. Improvement of visual environment or stimulus may augment some cognitive functions in AD patients.
3. AD pathology is present in the peripheral and central pathways of the visual neural system and is present in visual association cortical areas in some cognitively normal older adults.
4. Genetic factors, such as ApoE and complement factor H, have been implicated in both AD and age-related macular degeneration (AMD) share genetic risk factors based on genetic/genomic association studies, although their effects may not be the same.
5. Structural and functional changes of the retina and peripheral nerve fibers can be detected in patients with AD.
6. Impairments of electrophysiological and psychophysical measures of central visual function are present in subpopulations of AD patients.
7. In transgenic mice overexpressing Aβ or APP, the presence of AD pathology in the retina is associated structural and functional disturbances.
8. Anti-Aβ treatment in mouse models of AMD or glaucoma ameliorates the underlying structural or functional changes associated with retina and retinal ganglion cells (RGCs).

3.2. Epidemiologic and clinical studies

Cataracts, AMD, glaucoma, and diabetic retinopathy (DR) have significant impact on visual function in aging [71]. Cataracts are the leading cause of low vision, and AMD is the leading cause of irreversible vision loss in older adults worldwide [72]. Multiple lines of evidence suggest that cataracts are associated with AD [73], and specific subtypes of age-related cataract (ARC) and AD are related genetically and etiologically [74,75].

In the mammalian lens, APP, Aβ, and components of the Aβ biogenesis pathway are expressed and processed in equatorial epithelia and cortical fiber cells [76,77]. Cytosolic Aβ deposition has also been described to be present in lens fiber cells in AD patients and may contribute to the pathogenesis of supranuclear cataract and age-related lens degeneration [73]. Aβ binds αB-crystallin and promotes lens protein aggregation [73]. Supporting this, Tg2576 transgenic mice expressing a pathogenic human APP isoform [78] have a significantly increased rate of cataracts. In Down syndrome (DS; trisomy 21), an additional *APP* allele results in cerebral accumulation of Aβ, early-onset neuropathology, and age-dependent cognitive defects [79,80]. DS patients develop supranuclear opacification accompanied by accelerated supranuclear Aβ accumulation, amyloid pathology, and fiber cell cytoplasmic Aβ aggregates, which is identical to lens pathology in AD patients, suggesting Aβ accu-mulation is the key pathologic determinant in supranuclear cataract in both DS and AD [74]. Consistently, mice carrying the DS critical region including a complete copy of human *APP* have increased expression of human and mouse endogenous APP and develop age-related lens degeneration [81]. A recent study provided further genetic evidence that ARC and AD are related etiologically. It has been shown that δ-catenin is genetically and biologically associated with cortical cataract and future AD-related structural and functional brain changes [75]. However, conflicting evidence argued that Aβ has no contribution to cortical cataract in donors with or without AD [82], suggesting that further study is needed to delineate the nature of the relationship between AD and cataract.

Type I and type II diabetes have also been shown to be associated with AD [83–86], and diabetes is the direct cause of DR. Nearly all individuals who have had type I diabetes for more than 15 years develop DR. Approximately 50% to 80% of type II diabetic patients also develop retinopathy after 20 years of diabetes [87]. Therefore, it is conceivable that DR may also be clinically associated with AD. In fact, it has been reported that, like what is reported in CSF of AD patients [88], there is a significant decrease in the $Aβ_{42}$ level and a significant increase in the tau level in patients with DR [89], suggesting potential roles of Aβ and tau in DR.

Both AMD and AD are neurodegenerative diseases in which aging is the principal risk factor [90]. There is a significant association between the late stages of AMD and cognitive impairment [91–93]. In one study, individuals with advanced AMD had an increased 2-year

risk of developing AD compared with those with better vision, although the risk was relatively small [91,93]. Interestingly, persons with severe cognitive impairment as measured by word fluency were also more likely to have early AMD than people with better test performance, although no association with other measures of cognitive impairment was reported [94]. However, a recent study with a large cohort constructed from English National Health Service showed that the risk for AD or dementia after AMD was not elevated. The likelihood of being admitted for AMD after AD or dementia was very low, suggesting that although AD and AMD may share environmental risk factors and histopathologic features, their coexistence at the individual level is no different from that expected by chance [95].

Glaucoma was also observed at a higher incidence rate in AD patients than in cognitively normal controls [96]. Patients clinically diagnosed with both dementia and glaucoma had faster and more aggressive progression of glaucomatous optic neuropathy than patients with glaucoma alone; the optic nerve appeared to be less resistant to elevated intraocular pressure (IOP) levels in glaucoma patients with AD than glaucoma alone patients [97]. However, an epidemiologic study from Denmark showed that there was no increased risk of developing AD in patients with glaucoma [98], suggesting that glaucoma per se may not be a risk factor for AD. Conversely, intracranial pressure is lower in patients with normal-tension glaucoma compared with patients with primary open-angle glaucoma and nonglaucomatous control subjects. Decreased CSF production and turnover in AD patients may contribute to higher risk of developing glaucoma in AD patients [99]. Further study is needed to confirm this hypothesis.

Acetylcholinesterase inhibitors (AChEIs), which delay the cognitive decline of AD [100], may have a protective effect on the development of glaucoma. Topical rivastigmine lowered IOP in rabbits [101]. Oral administration of donepezil in normotensive AD patients resulted in decreased IOP and pupil diameter [102]. A pilot study in normotensive glaucoma patients showed that donepezil improved visual field, optic nerve layer blood flow, and regional cerebral blood flow, although IOP was not significantly changed. No deterioration of normotensive glaucoma morbidity was found in any of the measured parameters after 12 months of treatment [103]. These studies suggest that cholinergic dysfunction may be a common pathologic change in AD and glaucoma, and AChEIs may have dual benefit for treatment of both AD and glaucoma.

In addition to eye diseases, many visual system functions have been shown to decline with age, including visual acuity [104], color discrimination [105], contrast sensitivity at high spatial frequencies [106], depth perceptions [107], motion perception [108,109], visually guided body motion [110], visual processing speed [104], and prolonged dark adaptation [111]. Certain aspects of these visual functions have been reported to be more selectively impaired in subgroups of AD patients than the age-matched cognitively normal controls. For instance, in one study, more than 50% of AD patients failed to discriminate blue color correctly, whereas less than 25% of cognitively normal controls would make the same mistake; there was little difference between AD patients and controls in discriminating red or green colors [112]. Wijk et al. [113] also reported more specific difficulty by AD patients in discriminating blue and green colors. However, other investigators have reported general color vision deficits in AD patients [114]. Similarly, performance on monocular and binocular depth perception tests was significantly poorer in AD patients than in cognitively normal controls [115]. AD patients also showed impaired contrast sensitivity to both high and low spatial frequencies, whereas cognitively normal older adults only had reduced contrast sensitivity at high spatial frequencies [116]. It has been demonstrated in a longitudinal study that AD patients show changes in sensitivity to abruptly changing low spatial frequencies in as little as 6 months, suggesting a selective change in the large cell (magnocellular) neural system responsible for detecting large moving objects [117]. Consistent with this finding are reports of visual motion sensitivity also showing pronounced threshold elevations in a subpopulation of older adults and in AD patients [109,118,119]. In addition, the ability to distinguish the shape of a set of moving dots in a three-dimensional structure and the self-movement direction simulated in radial dot motion was significantly impaired in at least a subpopulation of AD patients, demonstrating the potential functional impact of AD on visual motion perception [120,121]. Nevertheless, whether these visual functional impairments occur before or after the onset of cognitive impairment in AD patients will require further longitudinal studies.

In considering the evidence supporting the associations between visual dysfunctions and cognition, it is conceivable that diminished visual information, either caused by AD pathology or other pathologies, may directly impact vision-dependent cognitive outcomes. Deficits in the visual cognition of AD patients have been widely reported [122–132]. Recent work by Toner et al. [133] has provided some evidence that the performance of AD patients in tasks such as letter identification, word reading, picture naming, face discrimination, and digit cancellation can be improved, sometimes to normal levels, simply by increasing the contrast of stimuli to compensate for their contrast sensitivity deficit [134–136]. In addition, enhancing the contrast or strength of visual stimuli may improve advanced AD patients' activities of daily living (ADL), such as pill finding [137], playing Bingo [138], and eating [139]. The positive impact of stimulus enhancement has been shown in patients who had been screened for visual acuity and major age-related vision problems, such as cataracts, glaucoma, and macular degeneration [133–138]. It is likely that the stimulus enhancement would not help patients with severe vision pathology. Although we do not know whether enhancing the visual environment may have any impact on

the underlying pathologic events of AD, this line of studies suggests that aspects of the functional impairments experienced by some AD patients may be at least partially corrected by nonpharmacologic approaches such as enhancing relevant visual signals. The line of research also suggests that cognitive evaluation of AD patients with tests that require vision may underestimate the competence of the patients unless vision-fair tests are used that compensate for vision deficits.

3.3. Neuropathologic studies

Aβ pathology has been shown to be present in most, if not all, segments of the visual pathway. In the frontal eye structures, Aβ deposition can be found inside the lens fiber cells and primary aqueous humor and vitreous bodies of AD patients. The molecular chaperone alpha B-crystallin, important for maintaining the transparency of the lens, can bind with Aβ, which may promote lens protein aggregation, thus contributing to the pathogenesis of supranuclear cataract and age-related lens degeneration [73]. The levels of the soluble derivative of APP are particularly high in the vitreous and low in the aqueous humor. Both $A\beta_{40}$ and $A\beta_{42}$ levels are approximately twofold greater in the vitreous than in the aqueous body [140]. In fact, Aβ peptide is found in 40% of the aqueous humor of patients with glaucoma [141] at a concentration comparable with that in the cerebrospinal fluid [73]. However, the normal levels of Aβ40 and Aβ42 and the pathogenic significance of the presence of AD-related pathologies in the frontal eye structure remain to be elucidated. Whether the pathogeneses of AD and glaucoma or cataract shares common features in biochemistry and etiology requires further investigations.

The peripheral nerve components of the visual pathway, in particular the RGCs and the optic nerve fiber layer (NFL), develop cell death and axon degeneration in patients with AD. More than 25 years ago, Hinton et al. [142] reported widespread axonal degeneration in optic nerves of 8 of 10 AD patients, as well as a reduction of the number of RGCs, and thinning of optic NFLs in 3 of the 4 AD patients examined, relative to age-matched controls. With regard to RGC loss in AD, both macular and peripheral retinas are dominantly affected in the fovea and the superior and inferior quadrants, and the overall neuronal loss amounts to 36.4% [143,144]. In the early postmortem histologic studies, it was suggested that this pattern of RGC loss in AD is quite distinct from the RGC loss in glaucoma, which selectively affects the midperipheral retina with no or little involvement of the macula [145–147]. However, growing evidence using new imaging technologies, for example, frequency-domain optical coherence tomography and spectral-domain optical coherence tomography, demonstrate early glaucomatous damage to the macula [148–153]. Studies on the similarity and difference between macular changes in AD and glaucoma by these advanced imaging technologies are required to further

delineate the connection of pathologic course of AD-related retinal changes and glaucoma. In addition, AD patients exhibit a thinning of the optic disc rim with increased cup volume and a reduction in the rim area to disc area ratio, whereas glaucoma patients endure a more pronounced pallor and focal loss of the neural rim [154].

With regard to changes in the NFL in AD, significant axonal degeneration has been found in retrobulbar optic nerves, and the axonal degeneration was more dominant in the posterior segment of the nerve, raising the possibility of retrograde axonal degeneration and subsequent RGC loss elicited by pathologic events in subcortical and cortical visual areas [155]. Together, these findings suggest that RGC loss and NFL changes in AD may be unique and not the result of advanced undiagnosed glaucoma [147]. However, it is important to point out that the presence of AD pathologies in the precortical visual pathways is not uniform for all AD patients as some histologic studies with small sample sizes failed to see statistically significant reductions in the RGC number or NFL changes [156,157]. Moreover, AD pathology, such as Aβ deposition, has been found in the drusen, extracellular deposits beneath the retinal pigment epithelium or within the optic nerve head, in patients with AMD but with no AD dementia [90,158–161]. Thus, further investigations are required to ascertain whether these controversial findings reflect the underlying heterogeneity of AD and the general relevance of these visual components in the pathogenesis of AD dementia.

The presence of AD pathologies in subcortical visual center, primary visual cortex, visual association cortex, and high-order visual association cortex of the inferior temporal gyrus has been extensively reported [162–165]. However, the temporal sequence of AD pathologic deposition in these visual areas and the associated clinical significance have been debated. The current canonical view states that the neuropathology of AD is typically first seen in the limbic and perilimbic cortices with subsequent extension to the higher order posterior association areas, and then to successively lower order association areas, and finally primary sensory and motor regions [166–168]. Yet, several histology studies indicate that the posterior cortical visual areas can be substantially affected with AD pathologies in the early stages of AD or before the onset of dementia [164,169]. One possible factor that may help to reconcile these findings is that the conventional clinical diagnostic criteria of AD used for neuropathologic analyses rely heavily on verbal amnestic criteria, which may tend to promote findings of sentinel histopathologic markers in hippocampal, subicular, and entorhinal areas. In contrast, when visuospatial criteria [170] are used as the basis for neuropathologic analyses, the earliest AD histopathologic markers are found at the transition zone between striate and prestriate visual cortex [171]. In fact, posterior cortical atrophy (PCA), a syndrome with an insidious onset of visual dysfunction, is now commonly considered as a variant of AD [172–174].

3.4. Genetics

APOE polymorphisms differentially modify risk for AMD and AD [92,175–180]. In sporadic AD, the *APOE* ε4 allele is the strongest risk factor [175–177,180,181], whereas the *APOE* ε2 allele confers a reduced risk [175,181]. In contrast, the *APOE* ε2 allele is linked to an elevated risk for AMD, and the *APOE* ε4 allele appears to have lower risk for the disease [92,178,179,182]. In addition, inflammatory processes seem to be involved in both AMD and AD. Polymorphism of CFH is the major genetic risk factor for AMD [183–186] and has been associated with an increased risk for AD [180]. CFH has been detected in amyloid plaques in the brains of AD patients [187], and increased levels of CFH have been detected in the plasma of AD patients [188]. However, a recent study of the relationship between complement factor–related AMD genetic risk factors and AD [189] revealed modestly significant associations between CFH, the age-related maculopathy susceptibility protein 2, and the complement component 3 single-nucleotide polymorphisms (SNPs) with AD, but these relationships were in different direction to that observed in AMD. In addition, the multilocus genetic model that predicts around a half of the sibling risk for AMD does not predict risk for AD. These results suggest that although activation of the alternative complement pathway is central to AMD pathogenesis, it is less involved in AD [189]. Future efforts may identify other discrete risk factors and biomarkers that could be combined with these genetic risk factors to enhance the predictive value and specificity of the onset and progression of AD and AMD. Recently, a genome-wide association study of the Framingham Eye Study cohort showed that δ-catenin, a protein that interacts with the presenilins, is genetically and biologically associated with ARC and future AD-related structural and functional brain changes [75], offering another possible genetic link between age-related eye disorders and AD.

3.5. Neuroimaging and neurophysiology

Structural and functional changes of the peripheral and central visual systems in aging have been reported (as assessed by methods discussed in the Appendix [visual systems]). In patients with mild-to-moderate probable AD, there is a significant reduction of two retinal hemodynamic parameters compared with age-matched controls [190]. In addition, significant thinning of NFL thickness has been reported in AD patients, as well as patients with MCI [190–194]. Moreover, the morphologic changes of NFL thickness in AD patients significantly correlated with the delay of implicit times of pattern electroretinogram [194]. The mean total macular volume was also significantly reduced in AD patients, and the reduction correlated with the severity of cognitive impairment measured by Mini-Mental State Examination [191]. However, whether any of these structural or functional changes in the retina would serve as potential diagnostic biomarkers for early diagnosis

of AD may require longitudinal studies of older adults transitioning from normal aging to AD or older adults genetically at risk for AD.

The most extensively studied central visual function in AD is motion processing, in particular as determined by radial optic flow. Psychophysical analysis has revealed that AD patients exhibit exquisite deficits in differentiating movement directions inferred from optic flow [195–197]. Further neurophysiological studies suggest that both the sensory/perceptual components and the cognitive components involved in motion perception under optic flow are affected in early AD patients as both the earlier and later components of ERP signals are diminished under a variety of experimental paradigms [198–201]. In addition, these neurophysiological deficits highly correlate with navigational impairments in AD patients [202]. AD patients with severe cognitive impairments but less navigational impairments show nearly normal early ERP signals [203], suggesting that the visual perceptual components of these patients may remain intact and supporting the existence of functional heterogeneity in the AD patient population. Conversely, a small proportion of cognitively normal older adults also exhibit navigational impairments and the associated changes in the early components of ERP signals [202]. Whether the navigational impairments in these cognitive normal older adults may be a preclinical sign of AD may require further longitudinal assessments, possibly in combination with genetic risk factors. In addition, further studies are required to delineate the relationship between motion processing impairments in AD and what may be a fundamental insensitivity to the temporal dynamics of visual stimuli [204,205], possibly linked to underlying retinal pathology [192,206], and genetic risk factors for AD.

A variety of neuroimaging studies support the conclusion that central visual dysfunction is an important part of functional impairment in AD. Positron emission tomography (PET) measurement of regional cerebral blood flow suggests great involvement of dorsal stream visual motion areas than of ventral object-oriented areas [207,208]. Studies have shown that hypoactivation in the posterior visual association areas measured by fMRI is strongly associated with the navigational impairments or visuospatial disorientation in patients with AD [168,209–211]. Whether the hypoactivation in the visual association cortex directly relates to the presence of AD pathologies in this area, or is a consequence of system-wide disturbances that may precede pathologic changes, may best be determined by coupling with metabolic and ligand-specific imaging modalities.

3.6. Cellular mechanisms and model systems

Mechanistic studies of the visual system using model organisms have thus far primarily focused on three questions in transgenic mice overexpressing APP, Aβ, or tau: Can AD-like pathology be detected in visual pathways? If so, is

the AD pathology associated with specific visual impairments? If so, would removal of this AD pathology reverse visual impairments?

The lenses harvested from AD- and DS-related mouse models show characteristic patterns of supranuclear opacification accompanied by accelerated supranuclear Aβ accumulation [81], similar to the pathologic events observed in DS patients and the lens pathology in AD patients [74]. Individuals with DS develop AD neuropathology in their third and fourth decades, and they have a significantly elevated risk for dementia later in life [212]. The postmortem retinas of various AD mouse models also contain Aβ plaques, revealed by the plaque-labeling fluorochrome, curcumin [213]. The plaques are associated with functional defects [214–217], consistent with clinical observations. Systemic administration of curcumin to APPswe/PS1Δ9 transgenic mice allows in vivo detection of Aβ plaques in the retina using noninvasive optic imaging, earlier than the appearance of Aβ plaques in the brain [213], suggesting that retinal Aβ plaques may also be an early noninvasive diagnostic biomarker for AD. Recently, the presence of pathogenic APP and/or amyloid plaques in a mouse model of AD was shown to alter cortical plasticity in the primary visual and association areas [218,219].

Anti-Aβ treatment in an AMD mouse model reduced the amount of Aβ in the retina, and the electroretinogram deficit was abrogated [220,221], suggesting that Aβ may be a therapeutic target for visual defects in both AD [222] and AMD. Investigations of glaucoma mouse models support the link between AD and glaucoma pathologies [223–225]. Targeting Aβ formation and aggregation pathways effectively reduced glaucomatous RGC apoptosis in vivo, suggesting that although RGC loss in AD has its unique characteristics and may not be the result of advanced undiagnosed glaucoma [147], the Aβ pathway may contribute to glaucoma-induced RGC apoptosis [224]. Further investigations into the impact of targeting Aβ on visual dysfunction in glaucoma-related animal models may provide important insights into the molecular link between glaucoma and AD.

3.7. Key research directions

1. Longitudinal studies of cognitively normal subjects who are followed until conversion to symptomatic AD in both clinical settings and at a population level are needed to characterize the temporal relationships between visual dysfunctions and cognitive impairments in AD. These studies will test the clinical utility of following visual dysfunction, by determining its sensitivity and specificity for predicting the progression of cognitive impairments in AD, either alone or in combination with genetic, noninvasive retinal imaging, neuroimaging, or other biomarkers.
2. Mechanistic studies in model organisms and humans are needed to ascertain whether functional visual impairment in AD is caused by neurodegenerative or

disordered structural plasticity changes in the visual system and to determine the relative contributions of these changes in the lens, retina, retinal nerve fiber, primary visual cortex, and visual association cortex as a consequence of AD pathogenesis with its associated brain dysfunction.

4. Auditory system in aging and AD

4.1. Summary of key findings

1. Hearing loss is highly prevalent in older adults, and it is the most prevalent sensory loss in older adults.
2. Impairments in speech perception in noise, often an indication of central auditory dysfunction, are also quite common in older adults.
3. Both hearing loss and central auditory dysfunction are associated with a high risk of conversion to dementia 5 to 10 years later.
4. AD pathology is found in the central areas of the auditory neural pathway in most AD patients but not in the peripheral ear and cochlear structures.
5. Combining CSF Aβ levels with auditory evoked responses may enhance the predictive accuracy of conversion to AD dementia.
6. Greater peripheral hearing loss is associated with poorer performance on both verbal and nonverbal cognitive tests.
7. In older adults, the frontal and temporoparietal cortices are recruited to facilitate auditory speech processing as revealed by fMRI studies.
8. In transgenic mice overexpressing APP, the presence of AD pathology in primary auditory cortex is associated with changes in auditory evoked responses.

4.2. Epidemiologic and clinical studies

The prevalence of age-related hearing loss in older adults, referred to as presbycusis, doubles with each increasing age decade [226]. About 40% to 45% of adults aged 65 years and older show some degree of hearing impairment, with this figure rising to 83% in the population over the age of 70 years [227]. These data make hearing loss the third most prevalent chronic medical condition among older adults, exceeded only by arthritis and hypertension [228]. The most common complaint among older adults with regard to their hearing is difficulty in understanding speech, with such complaints doubling with each decade over the age of 60 years [229]. This problem is especially exacerbated in the presence of background noise. Indeed, one of the hallmarks of age-related central hearing impairment is a difficulty in speech recognition in a noisy background, even when speech recognition is relatively good in a quiet background [230,231]. Older adults are especially susceptible to interference from the presence of competing speakers (cocktail party effect), due in part to poor frequency

resolution and encoding of sounds by the impaired cochlea and in part to higher level cognitive factors [232–234].

Some small longitudinal studies have shown that deficits in central auditory processing in the absence of severe peripheral hearing loss, as assessed by measures discussed in the Appendix (auditory system), were associated with high incidences of cognitive decline and AD dementia [2,235–237]. These studies have demonstrated that individuals with central auditory dysfunction were at a significantly increased risk for incident dementia with hazard ratios ranging from 9.9 (95% confidence interval [CI], 3.6–26.7) to 23.3 (95% CI, 6.6–82.7) [236,237]. Because behavioral measures of central auditory processing include an individual's ability to understand speech embedded in noise, competing speech, or under dichotic listening conditions, central processing within the primary auditory cortex and higher order association areas is required for the participant to identify and understand the presented signal. Further research examining the basis of this association has demonstrated that measures of central auditory function are strongly associated with measures of executive function [237], which in turn has been implicated as an early marker for dementia [238–242]. There are likely shared cognitive processes underlying both central auditory function and executive functioning given that both tasks require participants to selectively attend to one stream of information while inhibiting nonrelevant information [243]. Further studies may be required to ascertain the relationship between central auditory function and executive functions, in particular testing whether deficits in central auditory processing and executive functions may result from the same neurodegenerative processes that precede dementia [237].

Recently, a prospective study using data from the Baltimore Longitudinal Study of Aging has demonstrated that peripheral hearing loss as measured with pure-tone audiometry is independently associated with incident dementia. In this study [3], a cohort of 639 adults without prevalent dementia or MCI at baseline was followed for a median of 11.9 years. Hearing loss at baseline was associated with the risk of incident all-cause dementia after adjustment for known confounders (1.27× increased risk/10 dB of hearing loss; 95% CI, 1.06–1.50). In another prospective study of 1984 community-dwelling older adults, findings were similar with hearing loss being independently associated with accelerated rates of cognitive decline on both verbal and nonverbal measures of cognition over 6 years [244]. Most recently, a study of the 1057 surviving men of the Caerphilly cohort also confirmed the association of pure-tone average threshold with dementia and cognitive decline over a 17-year period [245]. These findings have profound implications for the relationship between hearing loss and cognitive impairments in AD and dementia. A shared neuropathologic etiology is a possibility [246]. Alternatively, hearing loss may be associated with dementia through a causal pathway mediated by social isolation and/or cognitive load. Communication impairments caused by hearing loss can lead to social isolation in older adults [247], and epidemiologic [248] and neuroanatomic studies [249] have demonstrated associations between social isolation and dementia. As indicated previously, the negative effect of hearing loss on cognitive performance is suggested by studies demonstrating that under conditions in which auditory perception is difficult (i.e., hearing loss), greater cognitive resources are dedicated to auditory perceptual processing to the detriment of other cognitive processes such as working memory [250–252]. Further mechanistic and interventional studies will be required to test these possible relationships between hearing loss and AD.

4.3. Neuropathologic studies

The presence of AD pathologies in the auditory system has not been extensively studied. In the few reported studies, the peripheral auditory structures (including the cochlea and associated hair cells), unlike the counterparts in the peripheral olfactory and visual pathways, do not contain plaques and tangles in patients with AD, although mild degeneration of hair cells, neural processes, and spiral ganglion cells in the basal membrane of the cochlea has been reported [253,254]. However, both plaques and tangles have been found in many major components of the central auditory pathways. Specifically, Ohm and Braak first reported in 1989 that considerable plaque formation can be found in the central nucleus and dorsomedial nucleus of the inferior colliculus and, to a lesser degree, in the deep layers of the dorsal cortex of the inferior colliculus in the midbrain among all the confirmed AD patients. In addition, NFTs were occasionally found in the dorsal cochlear nucleus, periolivary region, ventral nucleus of the lateral lemniscus of the brainstem, and central nucleus of the inferior colliculus in the midbrain [162]. The presence of plaques and tangles in the inferior colliculus was later confirmed [254]. It is important to note that these pathologic changes were detected in advanced AD patients. In addition, senile plaques and NFTs were found in the medial geniculate nucleus in the thalamus as well as the primary auditory and auditory association cortices for all the AD patients examined [254]. Although sensorineural hearing loss and central hearing deficits have been reported in AD patients, it remains to be studied whether the presence of AD pathologies in the central auditory pathways are related to hearing loss in those adults. Moreover, whether the pathologies may be present in presymptomatic AD patients with hearing loss and thus contributing to their hearing impairment has not yet been investigated.

4.4. Genetics

Genetic influences have been considered to play an important role in the development of age-related hearing loss [255]. For example, data from a comparative study of

hearing acuity for 179 monozygotic and 150 dizygotic adult twin pairs ranging in age from 52 to 60 years submitted to biometric modeling showed that 65% to 70% of the variance in the middle and high frequency ranges could be accounted for by genetic factors [256]. However, only a few studies have examined the gene risk factors for age-related hearing loss, or presbycusis. Thus far, only three genes, *KCNQ4* (encoding a voltage-gated potassium channel), *NAT2* (N-acetyltransferase), and *GRM7* (glutamate metabotropic receptor 7), are considered susceptibility genes for presbycusis that have been verified by studies in at least two different populations [257–260]. Whether people carrying risk alleles of these genes for presbycusis would be more susceptible to the development of AD has not yet been investigated. Nevertheless, one recent population-based study of older adults (85 years or older) found that six subjects with the *APOE* ε4/4 genotype had the highest levels of hearing loss, those with the *APOE* ε3/4 or ε2/4 genotype had intermediate levels of hearing loss, and those without the *APOE* ε4 allele had the lowest levels of hearing loss [261]. In addition, in this study, the *APOE* ε4 allele was associated with a twofold increased risk of hearing impairment compared with those without the *APOE* ε4 allele, suggesting that the *APOE* ε4 allele contributes to the development of age-related hearing loss. As the *APOE* ε4 allele is also the strongest genetic risk factor for developing AD, it will be important to examine whether a combination of hearing loss and *APOE* ε4 would predict conversion to AD for older adults with normal cognition but some level of hearing loss at the baseline.

4.5. Neuroimaging and neurophysiology

Auditory evoked potentials (AEPs) are commonly used to assess neurophysiological integrity of the ascending auditory pathway and primary auditory cortex. AEPs include auditory brainstem responses (ABRs), which consist of five waves (I–V) generated by the peripheral portion of cranial nerve VIII, central portion of cranial nerve VIII, cochlear nucleus, superior olivary complex/lateral lemniscus, and inferior colliculus, respectively. AEPs also include middle latency responses, which are the earliest auditory cortical responses and typically occur at 30 to 50 ms after the stimulus onset with P30 and P50 indicating the two major evoked potential peaks. The third type of AEPs typically occurs in the late latency range, thus called late latency responses (LLRs), and they also measure functions of the auditory cortex and the associated cortices. The P1 peak occurs at 100 ms after the onset of stimulus; other LLRs include P2, P3, and N1, which occurs between P1 and P2.

In older adults, the amplitude and latency of these AEPs are highly influenced by the complexity of the sound signals and the degree of hearing loss that each individual has. For older adults with or without hearing loss, the P1 and N1 latencies are delayed compared with young adults with normal hearing [262]. Moreover, the N1 latency delay was absent when a simpler sound signal was used, and the latency delays for both P1 and N1 were absent at a slower rate of sound presentation but magnified at a faster rate of sound presentation [262], demonstrating the intricate interrelationships between the function of the central auditory system and the degree of sound complexity. The effects of aging and hearing loss on ABRs have been largely inconsistent [263], possibly due to the variations in the choice of sound stimuli and the definition of hearing loss. Nevertheless, age-related hearing loss is associated with decreases in the amplitude and delays in the latency of all waves in ABRs [264]. Few studies thus far looked into how the AERs are affected in people with both AD and hearing loss or people with hearing loss and genetically at risk for AD. One recent clinical study of 53 MCI patients showed that an index combining delayed latencies and reduced amplitudes of AERs with CSF Aβ levels achieved higher values of sensitivity and specificity in the discrimination between AD converters and MCI stable patients, relative to the separate use of CSF Aβ levels and AERs [265]. More systematic studies of AERs in AD patients or patients at risk for AD in combination with other AD-related biomarkers, similar to the ones discussed in the olfactory and visual sections, may be helpful to evaluate the relationships among hearing loss, AERs, and AD.

Functional and structural neuroimaging studies have offered some important insights about hearing loss and cognitive function in older adults. For instance, the degree of hearing loss has been associated with decreases in fMRI signals across all major neural components along the auditory ascending pathway, including the primary auditory cortex and the decrease in gray matter volume of the primary auditory cortex [266]. Further neuroimaging studies have demonstrated a compensatory recruitment of regions in the frontal and temporoparietal cortex to maintain auditory speech processing in older adults [267], and this pattern of neural compensation may explain the general preservation of language comprehension that is seen even in individuals with advanced dementia [268]. The cognitive load induced by hearing loss could, therefore, result in a smaller pool of resources being available for other cognitive tasks [269] with a consequent depletion of cognitive reserve and earlier expression of dementia symptomatology. Such a hypothesis is generally consistent with cross-sectional and longitudinal studies demonstrating that greater hearing loss is primarily associated with poorer performance on those cognitive tests (verbal and nonverbal) that would be expected to overwhelm available resources (e.g., tests of memory and executive function) rather than cognitive tests focused on less complex speeded tasks [244,270,271]. Although we do not know yet whether this proposed mechanism may underlie the connection between hearing loss and future development of cognitive impairments in patients at risk for AD, further studies to ascertain the impact of rehabilitating auditory function in older adults with hearing loss on their long-term prospect of cognitive function may provide important

insight about the significance of restoring or maintaining auditory function on delaying AD dementia. Moreover, it may be of great value to study how the auditory pathways and the associated higher level cortical areas are affected in AD patients or older adults genetically at risk for AD, using fMRI, structural MRI, and PET imaging technologies specifically designed for AD studies.

4.6. Cellular mechanisms and model systems

Thus far, only one study has examined changes in AEPs in mice carrying mutated human amyloid precursor protein and presenilin 1 transgenes [272]. Interestingly, the AEPs in the middle latency range, which are indicative of primary auditory cortical function, are most affected in these transgenic mice, and these changes are associated with the appearance of Aβ pathology in the primary auditory cortex. However, the effects on hearing in these transgenic mice were not examined in this study. Future systematic analysis of the structure and function of the auditory system in AD-relevant transgenic models may be helpful to decipher the relevance of AD pathologies in age-related hearing loss in older adults.

4.7. Key research directions

1. The prevalence of hearing loss in patients with AD is unknown. Whether peripheral and central auditory dysfunctions are promising biomarkers of early pathophysiological events of AD remains to be tested. Prospective studies, starting with cognitively normal subjects who are then followed until conversion to symptomatic AD in both clinical settings and at a population level, are needed to characterize and demonstrate the clinical utility of peripheral and central auditory dysfunction, including its sensitivity and specificity for predicting the progression of cognitive impairments in AD, either alone or in combination with genetic, neurophysiological, neuroimaging, or other biomarkers.

2. Interventional studies of hearing rehabilitative treatment on cognition and dementia are needed to definitively assess the relationship between hearing loss and AD.

3. Mechanistic studies in humans and model organisms are needed to ascertain whether some of the auditory dysfunctions in cognitively normal older adults may be caused by neurodegenerative and neuroplastic processes related to AD pathology.

5. Motor systems in aging and AD

5.1. Summary of key findings

1. Motor impairment is highly prevalent in older adults.
2. Many pyramidal and extrapyramidal (or parkinsonian) motor impairments affect a substantial portion of AD patients, even at an early stage of the disease, and progressively worsen along with cognitive impairment. Motor impairment may precede the onset of cognitive impairment for AD by a decade and longer.
3. AD pathology can be found in motor neurons of the pyramidal motor pathways and in extrapyramidal motor pathways in AD patients, as well as in some cognitively intact older adults; the presence of AD pathology in monoaminergic nuclei, including the locus coeruleus (LC) and substantia nigra (SN), correlates with the presence of some motor signs.
4. A number of genes (*p16*, interleukin-18 [IL-18], and *COMT*) have been associated with alterations in motor function in nondemented older adults, and the AD risk genes, *PS1* and *APOE* ε4, have been associated with several motor symptoms in AD.
5. In healthy older adults, the primary motor cortex exhibits hypoexcitability, whereas in AD patients, the primary motor cortex exhibits hyperexcitability.
6. Many cellular and molecular pathways involved in aging and longevity have been implicated in both AD and PD, suggesting a convergence of pathways for therapeutic targeting.
7. In transgenic models of AD, overexpression of genes involved in AD pathology (*PS1*, *APP*, Aβ, tau, and *APOE*) is associated with significant motor neuron impairments at the cellular and behavioral levels.

5.2. Epidemiologic and clinical studies

It has been estimated that by the age of 80 years, up to 50% of older adults may have some element of motor impairment [273]. Although the relationships between many of these motor functions and AD have not been fully investigated, a recent study suggests that both the level and the rate of declining grip strength in older adults are associated with an increased risk for developing AD, similar to parkinsonian signs [4,274]. In addition, studies reported that older adults with amnestic MCI showed worse performance on factors reflecting rhythmicity and variability of gait compared with older adults with nonamnestic MCI or healthy older controls [275–277]. Furthermore, prominent and distinct abnormalities of both simple and complex eye movements have been reported in patients with AD [278,279] and can be used to differentiate the clinical syndrome in AD from other types of dementia and predict the underlying pathology [280]. Finger-tapping speed has also been shown to decline after the onset of dementia [281,282]. Whether such motoric declines could be a valuable early marker for AD requires further study.

Because of their relevance to PD, extrapyramidal motor functions have been extensively studied. In a community population of older adults, the prevalence of parkinsonian-type motor dysfunction is fairly high, estimated to be about 15% for people aged 65 to 74 years, 30% for those aged 75 to

84 years, and 50% for those aged 85 years and older [283] and are associated with the risk for disability [284]. Although many of these motor syndromes and signs have been described in various AD populations, for this review, we will focus on those that are the most commonly of interest in clinical practice and management of AD, as well as being of potential value for what they may tell us about the biology of AD itself. For example, in a population-based study [282], seven motor measures (present or absent) were assessed: bradykinesia, rest tremor, limb rigidity, tone increase, axial tone, deviation of gait and posture from normal, and an aggregate measure called "parkinsonism" (defined as the presence of 2 of 3 signs among rest tremor, limb rigidity, or bradykinesia). Using this approach, gait and postural changes of any kind were present in nearly 50% among those with dementia (all types combined), and the classical parkinsonism was present in about 12% of dementia patients. Furthermore, among community-dwelling persons with AD, parkinsonian signs are an important predictor of mortality [285]. Because motor signs, in particular gait impairment, may be common in non-AD dementias (vascular, dementia with Lewy bodies, and PD with dementia) compared with AD [5,7,286], these results may be used to frame the upper prevalence bounds for identifying motor signs in dementia patients in general practice. More specific estimates for motor signs in AD have been reported in a population-based sample of older adults living in New York City. Motor signs, assessed using a modified United Parkinson's Disease Rating Scale [287], were present in 18.5% of octogenarian AD patients at first diagnosis. The predominant signs were in the domains of posture/gait (combined in the study; 11%), bradykinesia (6%), speech/facial expression (5%), and rigidity (5%). Of note, this was a prospective study beginning with non–cognitively impaired participants. About 12% of these normal volunteers were noted to have motor signs. Furthermore, after a follow-up period of 3.6 years, the motor signs increase overall (22%) in the AD patients. The relative proportion of these signs remained the same across the longitudinal study suggesting that these signs are present or develop before AD begins and are progressive. Others have shown in prospective studies of initially cognitively intact older volunteers that motor signs, and in particular gait speed, are likely changing years before manifestation of AD symptoms [4,281,282,288,289]. A recent longitudinal study examining motor signs in initially cognitively healthy adults observed the emergence of accelerated rates of motor decline (gait speed slowing) 12 years preceding the emergence of MCI and slowing of manual tapping speed at or near the time when cognitive impairment was observed [281]. Although other parkinsonian signs such as tremor [290,291], myoclonus [292], and muscle weakness [293] also have been associated with AD, the timing of these motor changes in relation to cognitive impairment has not been widely studied.

Dementia itself may indirectly influence motor function. During cognitive-motor "dual tasking" paradigms, which require the participants to walk and perform a secondary interference task [294], motor performance may be compromised. The advantage of using the dual-task approach is that attentional demands are experimentally manipulated. It has been reported that allocation of attention to concurrent and competing tasks depends on executive processes that are responsible for cortical control of locomotion, and the frontal subcortical regions are especially vulnerable to effects of vascular disease in aging [295,296]. Hence, it is possible to make inferences about the causal effect of attention resources on gait and mobility performance [295]. Whether cognitive training may also enhance motor function remains to be an important area for additional research.

5.3. Neuropathologic studies

Aβ deposition and neurofibrillary tangles have been widely reported to be found in many cortical areas, including the primary motor cortex and supplementary motor areas [273], in not only AD patients [166] but also cognitively intact older adults [297]. However, the degree to which these pathologic markers directly affect the function and associated motor behaviors mediated through the motor neurons in these brain regions is unclear. It is also worth noting that for a number of motor neuron degenerative diseases, such as amyotrophic lateral sclerosis, progressive supranuclear palsy, corticobasal degeneration, and Lewy body dementia, burden of AD pathologies is fairly common in cortical motor areas [297], further supporting the possibility that the presence of AD pathology in cortical motor areas could contribute to motor neuron degeneration.

For the extrapyramidal motor pathway, the presence of AD pathology appears to be predominantly in the midbrain SN area, although progressive and early degeneration is also present in other monamine neurons, such as the LC [298]. An early study examined sections of basal ganglia, subthalamic nucleus, and SN for NFTs and NPTs and in the SN for neuronal numbers in patients with AD [299]. Although NFTs and NPTs were present in all these regions in AD patients, they were more prevalent and in higher densities in the SN region. In addition, the numbers of NFTs and NPTs in the SN were positively correlated with rigidity, tremor, and bradykinesia in these AD patients without the concomitant presence of Lewy bodies. There were no correlations between NFTs and NPTs in the basal ganglia or subthalamic nucleus and extrapyramidal signs in AD. More recently, a study of 86 cases from the Religious Orders Study also reported that overall 78% of the older adults with or without dementia had NFT pathologies in the SN regardless of the status of dementia [300], and the SN pathologies were specifically correlated with motor signs related to a cluster of gait, balance, and posture signs (arising from a chair, shuffling gait, body bradykinesia, turning, posture, and postural stability). But none of the motor signs were associated with measures of amyloid burden, infarcts, or Lewy bodies. The presence of AD pathologies in both the medial and

lateral SN suggests that the dopaminergic afferent pathway to the putamen and caudate nucleus of the basal ganglia/striatum may be affected. However, the significance of this clinicopathologic association may be confounded by the presence of multiple pathologies in AD patients. The presence of SN α-synuclein aggregates and SN neuronal loss may interfere with the correlation between AD NFT pathology and extrapyramidal motor impairments because the SN synucleinopathy and neuronal loss also strongly correlate with these motor signs [301]. Several recent studies suggest that a number of common neuropathologies, including nigral synuclein and neuronal loss, cerebrovascular pathologies, and AD pathology, may make separate contributions to the severity of parkinsonism in older adults with and without dementia [273,302]. Further research may thus be necessary to dissect the differences in the contributions of these common neuropathologies to late-life motor and cognitive impairments.

Although AD/NFT pathology in other extrapyramidal brain regions is not strongly associated with the extrapyramidal motor impairments, other types of neuropathologic changes in non-SN motor regions have been implicated in the extrapyramidal motor signs in AD. Early studies of the neurochemistry of motor signs in AD suggested that there were deficits in monoaminergic systems as assessed by CSF in AD patients who developed extrapyramidal signs [303] or myoclonus [304]. In addition, common white matter pathologies may play an important role in motor signs with AD. White matter pathologies commonly include myelin pallor, decreased axons, blood-brain barrier breakdown, spongiosis, and dilated perivascular spaces [305]. Although these changes are not considered part of the classic AD pathology spectrum, they are nevertheless very common with aging [306] and have not been accounted for in most postmortem studies of AD. Nevertheless, these white matter changes are commonly found in regions through which the corticospinal tract traverses and have been consistently associated with motor change and thus likely play a significant role in older AD patients with gait or generalized slowing [307–309].

5.4. Genetics

Two studies in 2007 offered initial evidence to suggest genetic factors affecting physical function, in particular gait speed, in older adults. One of the studies examined 938 older adults and found that an SNP of the genetic region encoding the p16[INK4a], a protein important for regulating cell senescence, aging, and tumor suppression, was associated with reduced gait speed and physical function [310]. Another study, on the other hand, identified that an SNP in the proinflammatory cytokine interleukin-18 gene was associated with improved walking speed after examining 1671 older adults from two studies [311]. More recently, the Met[158]/Val[158] allele in the *COMT* gene, which has been implicated in regulating cognitive processes and regulating

tonic dopamine release in the striatum, was also shown to be associated with faster gait speed based on a study of 278 nondemented older adults [312]. However, whether any of these genetic factors may relate to the gait speed changes associated with AD has not been investigated.

The discovery of genetic variants of AD has further shaped the recognition and understanding of motor signs associated with AD [313]. A recent review of the clinical phenotype of nine kindreds with early-onset AD caused by different presenilin 1 point mutations showed that some of these cases were frequently linked to several motor syndromes including spastic paraparesis, parkinsonism, and myoclonus [314]. The clear genetic link to AD in these early-onset autosomal dominant variants presents one of the strongest arguments that motor signs can be a part of the fundamental clinical phenotype of AD, rather than a secondary phenomenon simply associated with common aging of the nervous system. In another study of community-dwelling older adults, an increased rate of motor decline was associated with the presence of at least one copy of the *APOE* ε4 allele, and this association appeared to increase with age [13]. As more genetic risk factors have been associated with AD, it will be important to ascertain whether any of these newly identified AD risk genes may be associated with motor impairment in AD. Furthermore, although most of the genetic studies have been predominantly focused on gait speed, further analysis on the association of these genetic risk factors with other types of motor impairment in aging and AD may be required to gain a more complete understanding of the genetic associations among motor dysfunction, aging, and AD.

5.5. Neuroimaging and neurophysiology

Transcranial magnetic stimulation is a powerful noninvasive tool to disrupt neural activity in focal brain regions, even repetitively, thus allowing the assessment of brain activity in the form of evoked potentials on a millisecond scale [315]. In healthy older adults, the primary motor cortex exhibits reduced amplitudes of evoked potentials at a resting state but preserved excitation threshold compared with younger adults [316]. For AD patients, the primary motor cortex became hyperexcitable as the threshold for excitation was significantly lower than that in healthy older adults, whereas the amplitude and the latency remained largely comparable [317]. However, this hyperexcitability was unlikely due to dysfunction of inhibitory intracortical cholinergic circuits because the cholinesterase inhibitor rivastigmine failed to reverse the hyperexcitability [317]. Future studies will determine whether preclinical AD, MCI patients, and people genetically at risk for AD have hyperexcitability in primary motor cortex as a candidate biomarker for AD pathogenesis.

Neuroimaging studies, both structural and functional, have been shown to be useful in assessing brain changes associated with specific oculomotor abnormalities in aging and neurodegenerative conditions [318,319]. However,

because most of the current neuroimaging instruments are not portable and movement-related artifacts degrade the resolution of these imaging techniques, functional neuroimaging cannot be performed when subjects are walking or have abnormal involuntary movements. Several neuroimaging studies find that white matter change may be a reflection of both vascular injury and secondary degeneration from cortical AD pathology [320–322], complementing population-based autopsy series that have shown that the coexistence of AD and vascular disease to be the rule, rather than the exception [323,324]. However, how these neuroimaging signatures may change in people at risk for AD or AD patients remains largely unknown. There is a clear relationship between white matter hyperintensity change on MRI usually attributed to small-vessel ischemic disease and the rate of cognitive and motor slowing over time [308]. Further studies using imaging may be helpful to identify widespread vascular disease and its concomitant role in motor change in AD as well.

5.6. Cellular mechanisms and model systems

Aging of the motor system in model organisms has primarily focused on the SN in the context of the relevance to PD. As with AD, aging is the greatest risk factor for the development and progression of PD [325]. Many cellular mechanisms commonly implicated in the aging process, including mitochondrial dysfunction, age-related declines in the activity of proteasomes, dysregulation of the cell cycle by histone deacetylases such as sirtuins, reduced efficiency of chaperones, imbalanced autophagic recycling, changes in inflammation, altered complement and microglia activation, impaired response to neurotrophic factors, progressive accumulation of iron in brain with age, dysregulation of the longevity-affecting insulin signaling pathway, and age-related deposition of α-synuclein, have been linked to the pathogenesis of PD [325]. Some of these aging pathways have also been associated with the pathogenesis of AD, suggesting the existence of several common cellular mechanisms underlying AD and PD for the aged.

Interestingly, the effects of AD pathologies on motor neuron function have been reported for AD transgenic models by a number of studies. Transgenic mice expressing mutant *PS1* variants showed significant motor deficits as assessed by muscle action potentials and rotarod running tests [326]. In transgenic mice overexpressing either human four-repeat tau, diverse mutant human tau isoforms that cause frontotemporal dementia, or various human APP or Aβ mutants, significant axonopathy and impairments in motor performance, such as beam walking, inverted grip hanging, or hindlimb clasping, have been reported across many studies [327]. Moreover, in mice overexpressing the human *APOE* ε4 protein in the brain and spinal cord, neurons developed an age-dependent axonopathy and severe sensorimotor defects, such as reduced locomotor activity and swimming inability [327]. Together, these findings support the possibil-

ity that motor impairments observed in AD patients or people genetically at risk for AD may be attributable to underlying AD pathology and also that systems other than the cholinergic one may partake in these degenerative dysfunctions. Future studies will be needed to assess whether treatments that are developed to prevent or lower levels of AD pathology would improve or prevent further declines of motor function and delay cognitive impairment.

5.7. Key research directions

1. The relative contributions from motor systems, in particular AD pathology in cortical motor regions, to neuropsychological tests that probe both cognitive and pyramidal motor functions and that comprise part of the clinical diagnosis of AD remain to be addressed.
2. Prospective studies, starting with cognitively normal subjects followed until conversion to AD dementia and autopsy in both clinical settings and at a population level, are needed to characterize and demonstrate the clinical utility of combining motor functional changes with genetic, neurophysiological, neuroimaging, or other biomarkers for identifying individuals at risk and characterizing the progress of cognitive and motor impairment in AD.
3. Mechanistic studies, in both humans and model organisms, are necessary to understand the etiologic relationship between cognitive and motor impairment in AD.
4. Interventional studies may be helpful to address whether improving motor functions in preclinical AD population will delay or reverse cognitive declines.

6. Discussion

In this section, we present a conceptual framework to connect dysfunctions in sensory and motor systems with AD (see Fig. 1), including a brief summary of the supporting evidence. Then, we address three major concerns regarding the diagnostic and etiologic value of sensory and motor dysfunctions for the pathogenesis of AD and propose a number of testable hypotheses for future research. With the current emphasis of AD research on the preclinical disease phase and cost-effectiveness, we argue that a deeper understanding of the sensory and motor changes that occur in the context of AD offers a viable road forward toward early detection of AD and toward therapeutic interventions to improve the quality of life of AD patients.

The cognitive and behavioral manifestations of AD define the natural history of the clinical disease. The natural history of the molecular and cellular alterations caused by AD, such as the accumulation and aggregation of proteins and changes in the synaptic number and plasticity, remains under intense investigation [196,328]. These efforts have
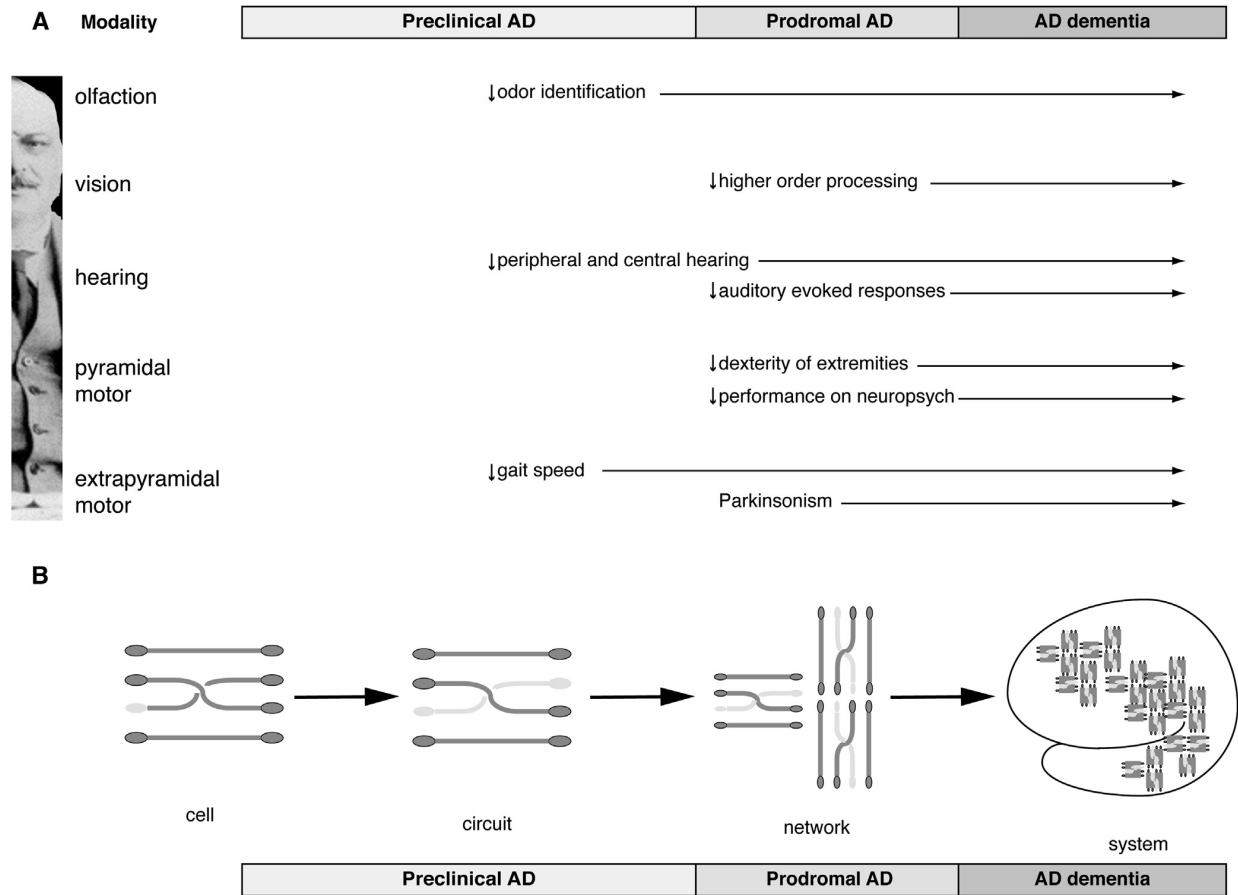
Fig. 1. Models of the relationship between sensory/motor dysfunction and AD. (A) A clinical model. Seminal observations of dysfunction of each sensory/motor modality are documented at the earliest reported stage during the clinical course of AD based on the studies referenced in this review. Parallel progression of these initial sensory or motor dysfunctions to advanced AD dementia raises the question of whether AD may be a heterogeneous disease in origin or a disease with heterogeneous clinical courses. A comprehensive assessment of all relevant sensory and motor measures from the preclinical stage of AD to the advanced dementia stage may help to test this possibility. Future research may also aim to extend these findings to earlier periods of the preclinical AD stage with better sensitivity and specificity by either improving the measurement methodology for detecting sensory and motor changes or by combining sensory/motor measures with other biomarkers, such as cerebrospinal fluid, neuroimaging, and genetic risk factors for AD. (B) A cellular model. A schematic framework of disease progression in which the light gray neurons represent dysfunctional neurons. In this model, dysfunction arises sporadically and then propagates in a pattern that is instructed by the connectivity of the involved neurons, circuits, networks, and systems. Because we speculate that disease initiation is sporadic, the involved circuits and networks at the earliest stages will likely differ between individual patients. This model may be tested by further research with AD-related model organisms to assess the mechanisms of disease progression from a sensory or motor domain to the cognitive domain and to investigate the effects of early intervention on early sensory or motor dysfunction and on prevention of progression to cognitive impairment. AD, Alzheimer's disease.

tremendously increased our understanding of the pathologic and clinical events of AD. However, disappointing results from recent therapeutic trials in the dementia stage indicate that a deeper understanding is required to reduce the burden of AD. Recent revisions of the clinical criteria and proposed revisions of the pathologic criteria for the diagnosis of AD reflect an appreciation that AD develops over decades and that its various clinical manifestations are a later stage, representing only a fraction of the total disease duration [9,329,330]. Currently, disentangling changes due to the aging process and the pathogenesis of preclinical AD are very challenging.

As summarized in the preceding sections, a wide range of sensory and motor systems are commonly impaired in old age. Moreover, many deficits in olfactory, auditory, visual, and motor systems presage or appear concurrently with the cognitive symptoms that currently define the clinical picture of AD. In particular, for most neural systems examined, a case-control design revealed significant differences between young and old individuals or patients with AD relative to controls. In longitudinal studies cited earlier, significant differences in olfactory and auditory performance separated individuals who converted to the dementia phase of AD from individuals

who did not. These findings raise a tantalizing possibility that certain sensory and motor deficits occur early in the course of AD pathogenesis—preceding cognitive impairments—and thus might serve as a means for early detection and therapeutic intervention to forestall further functional deterioration and cognitive impairment.

From a neural system perspective, integrated sensory, motor, and cognitive systems provide the means for the organism to perceive and respond to its environment, that is, deficits in any of these components can lead to impaired function at the clinical/behavioral level. Processing sensory input and generating motor output are among the most fundamental functions of the mammalian neural system. Organisms experience their environment through their sensory neural pathways, and motor systems provide the means by which organisms manifest behavioral responses to these stimuli. The cognitive component of these neural systems processes the incoming sensory input transmitted by the sensory end organs and then formulates and directs the responses by specifically regulating the motor neural pathways. In addition, the cognitive component may also modulate the sensory neural pathways to refine the sensory input through mechanisms of top-down regulation [331–335]. The interconnections among sensory, cognitive, and motor neural pathways suggest that when one neural pathway is impaired, the function of the other neural systems will be altered as well. For instance, an impairment in a sensory pathway may reduce the quality of input received by the cognitive domain thus compromising cognitive function, for example, hippocampal function [336–339]; an impairment in the cognitive domain could reduce its modulatory effect on the sensory pathway and diminish its control of motor output generation, leading to both altered sensory responses and motor output patterns, whereas an impairment in the motor pathway may impede the proper transmission of the commands from the cognitive domain, thus resulting in uncoordinated motor patterns and inefficient capture of environmental signals. Given this interdependence of sensory, motor, and cognitive systems, changes in sensory or motor function may either cause or reflect subtle deficits in the cognitive processes before the progression to more severe cognitive impairment conditions. Hence, effective treatment of any of these neural systems may decrease the overall burden of age-related diseases, such as AD.

The elemental nature of the neural networks that underlie sensory perception and motor output has motivated investigators to develop powerful tools to interrogate their function, some of which were recently standardized as the NIH toolbox [340]. When instruments for measurement of sensory and motor function have been applied to aging individuals or those with impending or clinically diagnosed AD, important evidence of neural system dysfunction has emerged from each sensory modality and the motor system. Functionally, the compromise of sensory and motor systems seen in aging

individuals diminishes their quality of life and increases risk for additional comorbidities, such as falls. Fortunately, a number of rehabilitation or intervention strategies for vision, hearing, and motor function have been developed to ameliorate the declines in some of the sensory and motor systems for older adults. These strategies afford the opportunity to address the question of whether treating these age-related sensory or motor declines would prevent or reduce the progression of AD.

Despite the collective body of evidence from epidemiologic and clinical studies assembled in this review and our current understanding of the principles governing neural circuitry connections, the role of sensory and motor signs and mechanisms in the diagnosis and pathophysiology of AD has been understudied for a number of reasons. We discuss three major concerns about the importance of sensory and motor dysfunctions in AD and propose a number of testable hypotheses to promote future investigations to address the issues.

The first major concern stems from the fact that one sensory or motor dysfunction does not fully capture the entire population of AD patients, for example, the sensitivity issue. Because memory loss and cognitive impairment are the most common functional changes among AD patients, the canonical view is that AD begins with degeneration of the cognitive system. Yet, some individuals with preclinical AD may first manifest visual symptoms, for example, PCA, hearing loss, diminished sense of smell, or slowing of gait, whereas others do not present with sensory or motor declines before the onset of memory loss. In light of the revised diagnostic criteria for AD, where targeting cognitive impairments for AD treatment may be considered too late, we may want to consider alternative hypotheses regarding the relationship between sensory and motor dysfunctions and AD. One alternative view is that AD is a heterogeneous disease with many different initiation points in the central nervous system often with early clinical signs in the sensory and motor domains. Cognitively normal older adults with a particular type of sensory or motor dysfunction may represent a discrete subgroup of individuals at risk for developing AD. The methodology to probe sensory and motor systems is more sensitive to changes because our understanding of the underlying neural systems is more advanced. To test this hypothesis, strong support was provided by the group of workshop attendees for systematic prospective cohort studies to assess a battery of carefully chosen sensory, motor, and cognitive tests in a healthy middle-aged population as they age to determine the clinical course and the composition of early sensory and motor dysfunctions among those who eventually develop AD dementia. The development and refinement of means to quantify sensory and motor functional declines in our aging population remains an important goal of current research [340]. These measures afford investigators reliable tools to test interventions that may reduce the impact of

sensory and motor dysfunction. Furthermore, these measures may afford the clinician the opportunity to counsel and intervene in a preventive manner to reduce the impact of sensory and motor deficits on cognitive performance or ADLs.

The second major concern states that sensory or motor dysfunctions are not specific to AD. This lack of specificity has long undercut the potential utility of these sensory or motor changes to serve as biomarkers for AD, especially preclinical and prodromal AD. As outlined previously in this review, a number of sensory and motor dysfunctions increase the risk (or OR) for developing AD substantially. Moreover, as discussed in the olfactory system section, findings from a number of recent studies suggest that functional assessment of sensory and motor neural systems may provide additional diagnostic accuracy of prodromal AD when coupled with molecular, genetic, or imaging biomarkers. The diagnosis and management of preclinical AD is a pressing concern with current projections of disease burden of AD over the next several decades. Current methodology to visualize amyloid deposition in the brain [341], quantify markers of neurodegeneration in the cerebral spinal fluid [342], and determine volume loss in the cortex [343] provides independent means to detect the pathogenesis of AD in its preclinical stage. However, individuals have significant variations to accommodate the pathologic burden of AD, and the correlations between these biomarkers and concurrent neural system failure have not been consistent [344]. In other words, individuals may harbor similar degrees of pathologic burden with very different functional states. This variability for individuals to harbor AD pathology asymptomatically implies that the determination of the magnitude of pathologic markers solely may not accurately predict impending neural system failure. Functional measures may provide a means to detect impending neural system failure. Efforts to include sensory and motor assessments have begun in individual cohorts, but an examination of these measures of sensory and motors systems in larger multicenter cohorts, for example, Alzheimer's disease Neuroimaging Initiative (ADNI), Alzheimer's Disease Research Centers (ADRC), or Dominantly Inherited Alzheimer's Network (DIAN) cohorts, which afford the comparison with other biomarkers of AD pathology, will have sufficient power to test the hypothesis that specific sensory and motor signs in the setting of a positive biomarker screen portends neural system failure and symptom development. With further validation, functional measures could be incorporated into clinical trial designs to identify individuals on the brink of neural system failure and monitor the efficacy of the therapeutic intervention on the function of a neural system [345]. Sensory and motor functional markers could be coupled with other molecular, genetic, and imaging biomarkers to generate an algorithm to predict conversion to the MCI and dementia phases of AD [1].

The third major concern lies in the distribution patterns of AD neuropathology across sensory, motor, and cognitive neural pathways. As discussed in earlier sensory and motor sections, the distributions of AD pathologies are not consistent across all sensory or motor neural pathways. For example, although AD pathologies have been detected in the peripheral olfactory pathway, the eye, and the visual association areas, even before the onset of cognitive impairment and in the absence of pathologies in the cognitive brain regions, they are mostly lacking in the auditory pathway, especially the periphery, in the early phase of AD. Furthermore, little is known at the human level whether the presence of AD pathologies in sensory areas is associated with sensory functional declines. In contrast, there is a correlation between the presence of NFTs in the EC and hippocampus and the presence of cognitive impairment in all AD patients. This clinicopathologic correlation for the cognitive system, along with the relative lack of evidence for a clinicopathologic correlation in humans for the sensory and motor systems, has thus long favored the idea that cognitive system is the most vulnerable neural system in AD. However, as presented in the olfaction and vision sections, a number of animal model studies have demonstrated a strong correlation between the presence of AD pathologies in the sensory neural pathway and the functional changes of the sensory system. In addition, in motor systems, studies have shown that the presence of tau pathology in SN correlates with the presence of extrapyramidal motor signs in AD patients. Therefore, additional work is needed to examine the clinicopathologic correlations for sensory systems in AD. If AD is a heterogeneous disease with distinct sensory or motor endophenotypes at its preclinical stage, understanding the etiology of sensory and motor dysfunctions in preclinical AD is warranted to improve early diagnosis and to tailor therapeutic interventions that are specific to the underlying disease process and to modality-specific rehabilitation to maintain functional capacity.

To further contemplate how dysfunctions in the sensory or motor pathway would eventually progress into cognitive impairments as observed in all AD patients, the workshop participants explored two general possibilities. The first hypothesis was whether the AD pathologic process initiated in one sensory or motor system for each individual could eventually propagate to other brain regions, especially the EC and hippocampus. Clinically, the evolution of cognitive deficits in MCI and AD patients suggests that neural system failure propagates through the brain as the disease progresses, starting in the EC and spreading through the hippocampal formation toward other cortical areas. From a pathogenic perspective, it has been proposed that the disease comprises two fundamental stages: an initiating stage in which the pathologic cascade is ignited and a propagation stage in which the pathologic cascade spreads to inflict additional neural circuits ultimately leading to

neural system failure [346]. This view is based on seminal pathologic case series [347]. A thorough examination of this hypothesis will require experiments in circuit- or network-based animal models. For instance, a model of limited tau overexpression enriched in the EC and demonstrated the propagation of tau pathology to distal hippocampal regions in the network [59,60,348]. Moreover, vulnerable sensory or motor neural circuits may be fertile ground to test hypotheses related to initiation and propagation in animal models. These circuits offer a plethora of experimental tools for subtly perturbing vulnerable circuits with disease genes and for analyzing the structural and functional consequences of these perturbations in the olfactory neural network of mice [37,56]. A cell culture approach complements these in vivo approaches to investigate mechanisms of disease propagation as the spread of pathologic tau conformations by nucleating species [349]. One clinical implication of this formulation predicts that a functional survey of the sensory and motor neural systems will be more sensitive than surveying only one or subset of the systems. For instance, the elucidation of the changes at the circuit and network levels caused by AD—and the compensatory strategies used by the brain to maintain function in response to these assaults—is necessary to bridge alterations at the molecular and cellular levels with clinical (cognitive and behavioral) observations. The complexity of the nervous system at the circuit and network levels is daunting, but new approaches in systems neuroscience in both animal models and humans are rendering this objective increasingly feasible.

The second hypothesis was whether altered sensory and motor inputs into the EC/hippocampus and association cortices contribute to the dysfunction arising from these areas. If the data from the proposed longitudinal studies confirm dysfunction in sensory and motor systems in the asymptomatic phase of AD, two mechanistic possibilities arise. One view is that the dysfunction occurs in parallel with the development of the disease in the association cortices and hippocampus. By contrast, the dysfunction in the sensory systems may represent a primary disturbance to the expected input into the association cortices and the hippocampus, which triggers pathologic plasticity processes [339]. For instance, altered neuronal activity was shown to reduce the transport and release of the brain-derived neurotrophic factor in the study by Chen et al. [350]. A provocative proposal by T.H. postulated that a reopening of the critical period resulting in enhanced plasticity may contribute to the development of AD pathology. Indeed, the expression of genes and synthesis of gene products implicated in the closing of the critical period are inverted in AD pathogenesis. Moreover, many epidemiologic risk factors for AD such as head trauma and cerebrovascular insults evoke cortical plasticity responses to affect repair. Mechanistic investigations to test this and related hypotheses at the circuit and network

levels will likely be performed in the next generation of animal models. These new animal models are based on the facility of genetic manipulation of sensory and motor circuits to express disease genes under spatial and temporal control and to deploy functional markers at strategic locations within these circuits and networks. Furthermore, these investigations can be extended to humans with increasing sophisticated functional neuro-imaging techniques.

In summary, there is considerable evidence that the interrogation of sensory and motor systems in aging individuals reveals deficits. Combined with neuro-psychological, imaging, and CSF outcomes, these indices of sensory and motor function may be used to accurately identify asymptomatic individuals with impending neural system failure due to smoldering AD pathology. Moreover, these functional indices may serve as potential outcomes for clinical trials in the preclinical phase of the disease. A comprehensive understanding of the damage inflicted by AD comprising all levels of the functional hierarchy of the nervous system, from the molecular and cellular through the circuit and network to the cognitive, behavioral, and social levels, will provide mechanistic insights into its pathogenesis. It is likely that this comprehensive understanding will inform the development and refinement of much needed effective and affordable therapeutic strategies. Further investigation of genetically tractable sensory and motor circuits in animal models of aging and prodromal AD will enhance our knowledge of these disorders at circuit and networks levels. Taken together, we recommend continued investigations of sensory and motor systems in aged individuals and animal models. We anticipate that the results from these studies will contribute to preclinical detection of neurodegenerative disease and will lead to the development and implementation of effective preventive and therapeutic modalities for AD, thereby reducing the burden of this devastating disease.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jalz.2014.04.514.

RESEARCH IN CONTEXT

1. Systematic Review: The participants of a "Sensory and Motor Dysfunctions in Aging and Alzheimer's Disease" exploratory workshop at the NIA have joined together to summarize the advances in each neural system, outline research priorities, provide a conceptual framework, and outline testable hypotheses.

2. Interpretation: Based on the increasing and converging data from each neural system, it is clear that sensory and motor regions of the CNS are affected by Alzheimer pathology and that interventions targeting amelioration of sensory-motor deficits in AD may enhance patient function as AD progresses.

3. Future Directions: Key research directions are outlined at the end of each section focused on a sensory or motor system. The consensus view is that longitudinal studies of asymptomatic, at risk individuals are needed to follow the natural history of the deficits and evaluate therapeutic interventions, and more research in animal models, harnessing the rich methods to interrogate these neural systems in the context of changes related to Alzheimer's, will further elucidate the early pathogenic events.

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