This is a "preproof" accepted article for *Journal of Clinical and Translational Science*.
This version may be subject to change during the production process.
10.1017/cts.2024.525

Early Sensory Deficits in Alzheimer's Disease: A Review of Potential Integrating Diagnostic Methods

Yang Yang [1*]

[1]Department of Surgery, Yale School of Medicine, New Haven, CT, United States.

* Email address: yang.yang.yy687@yale.edu, telephone number: +1 (254)-242-4027

Author contributions

Y.Y takes responsibility for the manuscript.

Funding statement

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflicts of interest:

I have no conflicts of interest to disclose.

Abstract

Alzheimer's Disease (AD) is the most common cause of dementia globally, leading to memory loss and cognitive decline. Accumulating studies have uncovered the correlation between sensory impairments and AD, suggesting that changes in sensory functions could be early biomarkers of the disease. Utilizing sensory biomarkers for AD detection offers a privileged approach since sensory tests could be more rapid, portable, earlier, and less invasive compared to traditional clinical diagnostic methods. However, solely relying on sensory deficits from a single sensory system has significant limitations, particularly regarding accuracy, as sensory impairments can vary among individuals and can easily be influenced by other non-AD-related factors such as environment and aging. Therefore, a more holistic and integrating multidimensional approach is necessary for early diagnosis of AD using sensory biomarkers. This review explores changes in the sensory system of AD patients, and the earliest time point of detectable sensory deficits in various AD transgenic mouse models focusing on olfactory, visual, and auditory functions. The aim is to integrate sensory testing combined with other diagnostic methods such as conventional methods and artificial intelligence models to develop a systematic and reliable early detection of AD through sensory systems.

Keywords: Alzheimer’s Disease, sensory biomarkers, AD diagnosis, transgenic mouse model, artificial intelligence.

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is the most prevalent cause of dementia globally, accounting for 60-80% of all dementia cases. With about 5 million new cases occurring annually, it is estimated that the number of people with AD and AD-related dementia will increase by more than 3-fold (~131 million) by 2050 [1]. AD is indeed a significant burden on the burden and public health [2,3], as the number of patients is rapidly increasing. Thus, early diagnosis and treatment methods are crucial in addressing this challenge. AD is clinically characterized by a progressive cognition decline and dementia, in addition to the two required pathologies hallmarks, amyloid-β (Aβ) plaque aggregation and hyperphosphorylated tau tangles [4]. The traditional clinical criteria for AD diagnosis were originally founded upon cognitive assessments, based on the belief that there are no motor, sensory, or coordination deficits early in the disease, and cannot be determined by laboratory tests [5]. However, accumulating clinical evidence indicates that AD may have early symptoms other than cognitive decline. In 2011, the National Institute on Aging and Alzheimer's Association (NIA-AA) created separate diagnostic recommendations for the preclinical, mild cognitive impairment, and dementia stages of Alzheimer's disease, labeled as "research framework" [6]. This proposed AD diagnostic criteria focuses on the diagnosis of AD with biomarkers grouped into amyloid-β deposition, pathologic tau, and neurodegeneration, also known as the AT(N) classification system [7]. Based on the AT(N) system, several methods can be conducted to diagnose AD prior to cognitive symptomatology, including cerebrospinal fluid (CSF) analysis, positron emission tomography (PET), and magnetic resonance imaging (MRI) [8]. Although capable of identifying early changes during the asymptomatic stage, these core clinical criteria are more generally reliable and provide high diagnostic accuracy in most patients for the advanced stages of AD. In early diagnosis, these methods are still premature and have drawbacks such as overdiagnosis, increased cost, and invasiveness of the assessment [9].

Recently, accumulated evidence revealed that sensory changes, including olfactory, auditory, visual, tactile, and gustatory dysfunction are associated with AD pathological processes, and usually emerge prior to the mild cognitive symptoms [10-15]. Thus, the impairment in sensory systems could be potentially used as biomarkers for the early detection and intervention of AD. However, the examination of sensory function alone may not provide sufficient accuracy for the

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

clinical AD diagnosis, since it can also be caused by various non-AD-related factors, such as neutral aging, environmental factors, and other neurological disorders like Parkinson's disease [16]. Thus, integrating comprehensive sensory alteration across the pathological progression could lead to reliable and early detection of AD, and pave the way to establish an early non-invasive AD diagnostic method. Furthermore, sensory deficits may also promote AD pathology, while early interventions and corrections may alleviate cognitive decline and slow down the AD pathological process. Recent studies in both human and animal models revealed that visual impairments, or hearing loss (induced by cochlear ablation in mouse models) are associated with an increased likelihood of developing dementia [17-19]. Preventive actions for vision problems, such as eye exams, eyeglasses, and cataract surgery, may reduce the risk for AD and related dementias [20]. Hearing intervention might also reduce cognitive change over 3 years in populations of older adults at increased risk for cognitive decline [21]. These findings suggest the promise of implementing several early interventions targeting sensory alterations to potentially reduce the risk of AD.

This review aims to collate current research on sensory changes caused by AD in the olfactory, visual, and auditory systems in both patients and transgenic mouse models of AD, exploring their relationship with established AD sensory biomarkers during the AD pathologic process, and outlining a potential integration diagnostic technique for AD identification at early stages.

2. Pathogenesis and Diagnosis of AD

2.1 The pathogenesis of AD

AD is an irreversible, highly complex, and progressive neurodegenerative disease. It was first described in 1907, with neurotic plaques, neurofibrillary tangles, and amyloid angiopathy in the cerebral cortex [22]. These autopsy characterizations were then become the hallmarks of AD. Over the past several decades, numerous hypotheses have been made for AD pathogenesis. The amyloid cascade hypothesis postulates that neurodegeneration in AD is caused by abnormal accumulation of amyloid beta (Aβ) plaques in the cerebral cortex [23]. Aβ is cleavage from the amyloid precursor protein (APP), the defective intracellular cleavage of APP is thought to be the predominant cause of plaque formation. The tau theory focuses on the aggregation of intracellular neurofibrillary tangles (NFTs) formed by accumulated tau protein in a

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

hyperphosphorylated state [24]. The tau hypothesis suggests that the hyperphosphorylation of tau (P-tau) induces the formation of neurofibrillary tangles, which is another hallmark pathology of AD [25,26]. Calcium dysregulation seems to generate large amounts of tau [27]. The inflammatory hypothesis is based on the observation that the increased inflammatory markers in AD patients, such as pro-inflammatory cytokines interleukin-1β, (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor α (TNF α) [28]. Increased oxidative stress in the AD brain is characterized by increased lipid peroxidation, increased protein, and DNA oxidation, these data support the oxidative stress hypothesis [29,30]. Mitochondrial disturbances are also associated with both oxidative stress and AD plaque formation [28].

2.2 The diagnosis of AD

In 2011, the National Institute on Aging-Alzheimer's Association (NIA-AA) conceptualized the pathophysiological process of AD in 2 stages, that is preclinical stages and clinical stages based on whether the patients have overt symptoms of dementia and cognitive impairment [7]. The diagnosis of AD in the clinical stage is clear in the guidelines, but the recommendations for preclinical AD which could potentially be decades before the symptoms become noticeable [31] were not established. Furthermore, accumulated evidence indicates that the neurodegeneration and cognitive decline in AD is a continuous pathophysiological process that should be regarded as a continuum rather than two distinct preclinical and clinical entities [6,32]. This concept is recognized widely, indicating the importance of early AD diagnosis methods.

In 2011 NIA-AA guidelines, several methods have been established for identifying and assessing the progression of AD in clinical stages (**Figure 1**). These methods can be clustered into two divisions, clinical assessments, and neuroimaging techniques. The clinical assessments of AD rely on patient informant history, mental state examination, thorough physical examination, bedside cognitive testing including mini-mental state examination (MMSE) and Montreal cognitive assessment (MoCA), and some neuropsychologic and psychiatric tests such as memory, attention, language, problem-solving skills, attention [33]. AD can be further diagnosed with firm clinical evidence provided by neuroimaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) scans [34,35], or direct biomarker tests including cerebrospinal fluid (CSF) analysis and blood tests [36,37]. All these traditional methods

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

have a certain limitation, as these methods always work after the symptoms presented, such as memory loss and cognitive decline. Furthermore, these diagnostic techniques could be invasive procedures, or require radiation exposure, posing a risk of side effects. Also, certain methods need specialized and costly equipment that is less available. Additionally, AD can only be noticed by families 4 years before a firm diagnosis is made, and this delay is often longer and includes misdiagnosis in the variants and early onset groups [38].

3. Early Biomarkers of AD in the Sensory System

In recent years, more and more results have shown that the sensory system can be affected in AD patients. For example, several studies have revealed that olfactory function was profoundly affected by AD in the clinical stages, revealing that the impairment of olfactory function could be a potential biomarker for cognitive impairment and neurodegeneration [39-43]. Visual manifestations can also be observed in AD patients, with decreased visual acuity, reduced contrast sensitivity, poor color discrimination, and abnormal ocular motor function [44]. AD also manifests with hearing loss [45], even though the causation between hearing loss and dementia remains unknown, evidence shows that the intervein of age-related hearing loss could prevent AD, making hearing loss another high-risk factor for AD [46]. In this section, we started with a concise summary of the structure composition of different sensory systems, then we aimed to provide an overview of early sensory biomarkers related to AD in preclinical research. Following this, we encapsulated the sensory deficits reported in the symptomatic stage of AD and concluded by describing the discoveries related to sensory impairments in preclinical AD patients.

3.1 Structural overview of sensory pathways

Olfaction is a highly conservative primary sensory system [47]. Olfactory can be clustered as the peripheral and central system [48]. Odorants are first received by olfactory sensory neurons (OSNs) located on the olfactory epithelium (OE), where the chemical signals are converted to neuro-electrical signals [49]. The electrical potentials are then transferred to the mitral cells and tuft cells (M/T) on the surface of the olfactory bulb (OB) via OSNs projection [50], and then handover to olfactory cortical areas, including the piriform cortex (PCX), the medial olfactory cortex, and the amygdala [51].

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

About half of the neuronal pathway in the brain subserves visual function, light signals are transduced to the neuronal signals via photoreceptors, the cones, and rods which are located on the outer nuclear layer of the retina. It is then passed to the inner nuclear layer, including [52], followed by ganglion cells on the last layer. The axon of ganglion cells projects to the brain cortex via the lateral geniculate nucleus, and superior colliculus, and finally reaches the visual cortex.

The auditory system can be divided into two main components, peripheral and central systems, both are essential for normal hearing function. The peripheral auditory system includes external, middle, and inner ears, approximately 70% of hearing loss is caused by various pathologies in the inner ear and auditory nerve [53]. A specialized hearing organ in the inner ear, the cochlea, transduces the sound vibrations to neuronal electrical signals, this process is also known as mechanotransduction [54]. The main sensory cells for mechanotransduction in the cochlea are hair cells. The ion homeostasis of the cochlea and hair cells (e.g. K^+ and Ca^{2+}) is required for normal hearing function and the development of the auditory system [55-58]. After mechanotransduction, the spiral ganglion neurons transmit the acoustic information from the cochlea to the central auditory system via the superior olivary complex, lateral lemniscus, inferior colliculus, medial geniculate nucleus, and the auditory cortex [59].

3.2 Preclinical research revealed early sensory biomarkers related to AD

AD animal models, primarily rodent models, have provided valuable insights into the disease and contributed to preclinical research. Since rodents do not develop AD, introducing human AD pathogenic genes is essential to model the AD pathology in mice. Thus, mouse models of AD can be generally classified as follows based on what gene is engineered, and each of these models is slightly difference in AD pathophysiology. Here, we briefly summarized the pathogenesis of 5 main AD mouse models, including the APP transgenic model, APP/PS1 transgenic model, 5xFAD transgenic model, Tau transgenic model, and 3xTg mouse model.

Interestingly, numerous studies have also demonstrated that early sensory impairments are present in AD mouse models, highlighting the utility of these AD mouse models for exploring sensory deficits as potential early indicators of AD. The impairment of sensory systems can be assessed through behavioral tests, such as odor discrimination, identification, threshold test [60,61], Morris water maze [62,63], acoustic startle response (ASR), and pre-pulse inhibition (PPI) tests [64].

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

Behavioral tests, however, may suffer from certain limitations such as variability in sensitivity, and environmental factors, and may not always directly correlate to the function being assessed. Electrophysiologic tests of sensory functions provide a non-invasive diagnosis [65]. Here, we highlighted the earliest point at which the cerebral Aβ deposition, coupled with cognition decline can be detected in each AD mouse model, which is, as previously described, the hallmark for the transition from the pre-clinical to clinical stages of AD **(Table 1)**. We also summarized the earliest time points at which sensory impairments manifest, based on the primary research papers we have reviewed, this includes Aβ/P-tau aggregation in different sensory systems, functional-related behavioral deficits, and electrophysiologic changes within sensory systems including olfactory, auditory, and visual impairment (**Table 2**).

3.2.1 APP transgenic model

APP transgenic models overexpress the mutation of human APP, which is associated with familial AD (FAD), such as the famous Tg2576 mouse model that overexpress Swedish mutation (K670M/N671L) [66]. Tg2576 mice exhibit a large number of failures in the Morris water maze test with visible platforms starting from 6-11 months [67] and exhibit cognitive decline around 6 months of age [68]. At this age, the soluble Aβ levels in the brain cortex start to increase [69]. However, the actual cerebral Aβ plaques can be observed around 6-10 months old, typically by 9-12 months [70]. Another APP transgenic mouse model is TgCRND8. Similar to Tg2576, TgCRND8 mice encode Swedish mutation (K670M/N671L) and Indiana mutations (V717F) APP protein [71]. With the extra expression of mutant Aβ peptides, TgCRND8 shows an earlier onset of AD pathology compared to the Tg2576 model. The Aβ deposits can be detected as early as 3 months old, accompanied by the early onset of memory and learning impairment [71].

Tg2576 transgenic mice exhibited sensory impairment at the early stage of AD. In the APP transgenic model Tg2576, the soluble human Aβ is detectable in the OB as early as 2 months old, which is before the deposition in the PCX, entorhinal cortex (EC), or hippocampus [72,73]. The nonfibrillar Aβ deposition can be observed within the olfactory bulb (OB) around 3 months of age in Tg2576 mice [74]. Mistargeted OSN connection in Tg2576 mice can be observed at ages from 12 months down to even postnatal day 10 [75]. Furthermore, the decline of olfactory function is also revealed by the impairment of odor-related behaviors in Tg2576 mice. 4-month-old Tg2576 mice showed a significant impairment in the olfactory working memory task when more

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

odors were applied [76]. 4-month-old Tg2576 mice are also impaired at object placement, an EC-dependent cognitive task [72]. These results indicate that the Aβ deposition in the olfactory system is earlier than it is in the brain cortex, and the impairment of olfactory function also emerges much earlier compared to the MCI and neurodegeneration. Tg2576 mice also show changed electrophysiology characters in the olfactory system before the cognitive impairment. 3-month-age Tg2576 mice exhibit hyperactive odor-evoked activity in the PCX, which is shown to be involved in higher-order olfactory functions, and increased OB-PCX functional connectivity [77]. The hyperactivity can be also seen in both OB and PCX, with significantly increased beta and gamma band power of spontaneous local field potential (LFP) activity [77]. The single-unit spontaneous activity in PCX shows a trend toward increased baseline firing starting from 3 months of age [78]. This data reveals a hyperactive activity persisted during the early stage of AD, before converting to a hyporesponsive state [77]. However, in 18-21-month-old APP knock-in mice (harboring three familial AD mutations from Swedish, Iberian, and Arctic), no significant differences were observed for the olfactory-related mRNA expression [79], indicating that the correlation might only be observed at the early stage of AD and could be overlapped by the normal aging process. We discussed the aging factor during AD pathologies in the following section.

The APP transgenic model exhibited visual impairment at the early stage of AD. APP immunoreactivity can be observed as early as the 7.8-month-old Tg2576 mice ganglion cell layer and the inner nuclear layer of the retina [80]. Aβ can be detected in the retina of 12-month-old Tg2576 mice [81,82]. Tg2576 mice were impaired in visible platform recognition at 9 months of age and increased activity measures as early as 3 months old [83]. Other research confirmed that at both 6 and 14 months of age, the Tg2576 mice were not affected using water maze spatial reference memory and T-maze working memory [84].

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

3.2.2 APP/PS1 transgenic model

APP/PS1 is another AD mouse model that harbors a chimeric mouse/human APP (Mo/HuAPP695swe) and a mutant human presenilin 1 (PS1-dE9), both are associated with early-onset AD [85]. Compared to APP transgenic mice, APP/PS1 mice show an early onset of Aβ plagues and AD pathology. APP/PS1 mice express cerebral Aβ deposition in APP/PS1 mice can be detected as early as 3 months of age, the significant memory deficits start from 5 months old [86].

APP/PS1 mice exhibit olfactory deficits but not cognitive impairment at 3-4 months of age, with soluble Aβ deposition aggregates and morphology changes in granule cells (GCs) and mitral cells (MCs) in OB [87]. At this age, APP/PS1 mice show impaired odor-related behavioral performance in odor sensitivity tests and discrimination tests [87]. APP/PS1 mice also have an altered electrophysiology in the olfactory system at the early stage of AD. MCs exhibit increased spontaneous firing rates as early as 3 months induced by the inhibitory defects of pre-synapses in OB [88]. 3-month-old APP/PS1 mice show altered LFP activity, with a reduced theta band and increased low gamma oscillatory activity that can be detected in OB slices from 3-month-old APP/PS1 mice [89]. Others reported reduced low and high gamma oscillations with or without odor stimulation using the LFP analysis in the anterior piriform cortex (aPCX) from 3-month-old APP/PS1 mice [90].

Aβ can be detected in 6 months of age APP/PS1 mice [81]. Another report indicates that Aβ levels in the retina correlate with cerebral levels that can be detected as early as 5 months [91]. Substantial color and contrast-mode alternation deficits appear in APP/PS1 mice as early as 8.5 months of age [92]. APP/PS1 mice exhibit altered electroretinogram and optical coherence tomography starting from 3 months, the retinal pathology, with a reduced inner retinal thickness measured by optical coherence tomography (OCT), can be observed as early as 9 months [93].

It has been reported that APP/PS1 mice showed an early-onset of hearing loss as early as 2 months old, starting from the high-frequency region, and appears to be whole-frequency range later on, similar to the age-related hearing loss [94,95]. However, another study has reported that there is no significant change in both ABR and DPOAE thresholds even in 13 months of age APP/PS1 mice. A recent study showed progressive age-related hearing loss in both WT and APP/PS1 mice after shame operation (SO) of cochlear ablation, the ABR thresholds were

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

compatible at 4, 6, 9, and 12 months of ages between WT and APP/PS1 mice with SO [18]. One possible reason for the different outcomes could be that different backgrounds of mice were utilized. C57 mice typically show a faster onset of age-related hearing loss, while CBA/CaJ mice exhibit a longer hearing lifespan due to the cdh23 mutation [96]. Thus, the difference may be obscured by normal aging, given the inherent age-related hearing loss in some mouse backgrounds. For the auditory-related behavioral test, no significant difference between APP and APP/PS1 mice and wild-type mice at 6 months old [97]. This data is also confirmed using a 7-month-old APP/PS1 mouse model that a non-significant trend of altered ASR but no changes in PPI can be found [98]. [99]. another report also showed that APP/PS1 mice exhibited normal ASR and PPI at 3 months old, but significantly lower PPI starting from 7 months of age [100]. APP protein expression in the auditory cortex can be detected as early as 2 months old, accompanied by decreased auditory-evoked cortical potential (AECP) [13]. These data indicate that hearing loss and reduced auditory cortical response could be early biomarkers for AD in this mouse model.

3.2.3 5xFAD transgenic models

5xFAD mouse model co-express 5 FAD mutations, 3 APP mutations (mutant human APP with Swedish (K670N, M671L), Florida (I716V), and London (V717I) mutations), and 2 PS1 mutation (M146L, L286V) (Oakley et al., 2006). 5xFAD mouse model is designed for the early onset of AD, as it displays strong Aβ pathologies, with plaques appearing in the brain from 2-4 months of age, resulting in robust synaptic and neuronal loss [101]. Early cognitive deficits related to the frontal cortex appear at 4 months of age [102].

The odor-related behavioral change can be detected in 3-month-old 5xFAD mice, with [103]. The Aβ deposition in this model can be seen at 2 months of age [104] and is high in the OSNs located in the olfactory epithelial ectoturbinate and the ventral olfactory bulb glomeruli at 3 months of age [103]. Another report shows that Aβ is co-localized with synaptic markers on olfactory bulb glomeruli as early as 2-4 months of age, but the olfactory memory is not impaired from 3 to 15 months of age [105]. However, other research shows an impaired olfactory function starting from 3 months and can be detected at 6 and 8 months of age [61,106]. OSNs from 5xFAD mice at 3 months of age show reduced responses to odorant stimulation measured by Ca^{2+} signals [103].

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

5xFAD mice show reduced ganglion cell responses to light as early as 6 months of age, with a thicker inner plexiform layer [107]. This mouse model exhibits impaired spatial learning in water maze tests starting at 6 months of age [108]. The changed full-field ERGs can be observed as early as 3 months of age [108].

In 5xFAD mice, Aβ deposition and intracellular accumulation can first be found in the primary auditory cortex as early as postnatal day 21 (p21), the extracellular plaques appear later by age p90 [109,110]. The Aβ accumulation occurs at cortical levels and the upper auditory brainstem as early as 3 months of age, but at lower levels of the brainstem such as the cochlear nucleus [99]. Using ASR and PPI test, 5xFAD mice exhibit an age-related decline in acoustic startle as early as 3 months of age before any hearing loss symptom [111], but no significant reduction of PPI at 3-4 months of age [112]. 13-month-old 5xFAD mice have increased auditory brainstem response (ABR) thresholds, indicating an early-onset of hearing loss [111]. 5xFAD mice also exhibit gap detection deficits in startle response tests as early as 2 months of age [113], with degraded gap responses and baseline firing rates in the auditory cortex [114]. All these results demonstrate early-onset impairments of the central auditory system in 5xFAD mice. However, it has also been reported that at 3 months of age, 5xFAD mice are indistinguishable from the control in central auditory activity and hearing threshold, but at 6 months of age, the central gain was significantly increased (p4:p1) in 5xFAD mice [99]. Overall, 5xFAD mice exhibit delayed ASR, which could be a potential biomarker for early AD diagnosis [115].

3.2.4 Tau transgenic model

The tau pathology and synaptic failure correlate with cognitive decline [116]. Thus, overexpression of incorrect tau protein could also induce AD in mouse models. Tau transgenic model exhibits mutant tau protein, the P301S (PS19) mice model, for example, expressing P301S mutation Tau driven by mouse prion protein promoter (*Prnp*), gives rise to neurofibrillary tangles and neurodegeneration by 9 -12 months of age [117,118]. Hyperphosphorylated Tau (P-tau) can be detected in the hippocampus and cortex at 6 months of age [119]. Memory deficits can be identified around 5 months of age in P301S mice [120]. Spatial learning deficits can be observed as early as 4 months of age [121]. P301S mice do not typically develop Aβ plaques since it is designed for tau pathology research. However, it has been reported that the intracerebral injection of Aβ1-42

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

increases tau phosphorylation, cleavage, and aggregation [122]. Co-expression of soluble Aβ (Aβ4-42) in the P301S tau transgenic model worsens spatial memory deficits and motor performance [123]. These data demonstrate that Aβ promotes tau pathogenesis.

Tau transgenic mice (P301S) show increased P-tau expression levels in the OB and PCX as early as 1 month of age, the MC layer is severely affected [124]. A progressive neuronal cell loss in OB and PCX can be observed during aging [125]. The olfactory impairment starts as early as 2 months of age using the food-seeking test [61,124]. 3-month-old P301S mice show a reduction in gamma frequency oscillation and severe early impairments in the theta-gamma phase-amplitude coupling in the OB area, but the LFP oscillatory activities do not show any difference in EC [126].

Hyperphosphorylated tau starts to accumulate in the nerve fiber layer in the P301S mouse model at 2 months of age, and aggregates into filamentous inclusions in retinal ganglion cells [127]. P301S mice show a worse learning curve compared to wild-type mice at 2.5 months of age [120]. Another study reports early and persistent spatial working memory deficits, with hyperactivity in the Y-maze test with less alternation, and this trend can be seen as early as 2 months of age [128].

P301S mice express phosphorylated tau in the auditory cortex, amygdaloid nucleus, and ventral hippocampus as early as 4 months of age, with the enhancement of the PPI test [119]. Other studies show that P301L mice exhibit unaltered ASR but reduced PPI (or increased %PPI) at 3 months of age [119,129]. Whether the tau pathway affects auditory electrophysiology needs further investigation.

Overall, in four commonly utilized AD mouse models, a consistent pattern can be observed that sensory system impairments were detectable earlier than the cerebral Aβ deposition and cognitive decline (**Table 1-2**). Furthermore, most of these models exhibited multiple sensory deficits at the early stage of AD, suggesting the possibility of using an integrated assessment of sensory system impairments as a non-invasive diagnostic tool.

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

3.3 Sensory deficits and aging in the symptomatic stage of AD

Transitioning from the exploration of sensory deficits in the research animal models to the symptomatic stage marks a critical juncture in understanding the disease's progression. During the pre-clinical phase, subtle sensory changes may begin to emerge, often unnoticed or dismissed as benign age-related decline. However, as AD advances to its symptomatic stage, these sensory impairments become more pronounced, directly impacting patients' quality of life and their ability to interact with the world around them (**Table 3**).

A variety of ocular abnormalities have been observed in AD patients in the MCI stage, indicating a strong association between AD and visual impairment [130]. In the clinical stage, a large number of visual disorders and their association with Aβ burden have been reported in AD patients [131], such as lower visual acuity in recognition of low luminance and low spatial frequency pictures [132], reduced visual contrast sensitivity [133], altered color vision [134], retinal hemodynamic parameters [135], visual field loss [136] , and poor ocular motor function [137]. A deteriorated olfactory function can be observed in AD patients [138]. Furthermore, olfactory dysfunction is associated with Aβ burden, several studies have reported early olfactory impairment in AD patients also known as hyposmia [139], these patients exhibit a reduced ability to detect, discriminate, and identify odors, coupled with abnormal odor coding [140,141]. As many as 60% of older adults with AD and ADRD have hearing loss [142]. All these sensory impairments could be used to evaluate the AD pathophysiology and should be taken into consideration for the AD clinical diagnosis. Multiple epidemiological studies have revealed that hearing loss is correlated with pathological cognitive decline and dementia [59,143]. Hearing loss is a risk factor for cognition impairment. It has been reported that mild to severe hearing loss significantly increases the dementia risk [144,145]. Elderly individuals with hearing loss symptoms have a higher risk of AD, which is also associated with loss of brainstem and cerebellar volume [146]. Furthermore, AD could cause a faster onset of hearing loss. Individuals' AD risks can be evaluated using a polygenic risk score (PRS) [147], high PRS individuals are more likely to experience hearing difficulty than those with lower PRS [148]. However, the causation between AD and hearing loss is still controversial. Several hypotheses might explain the relationship between AD and hearing loss. Firstly, hearing loss could cause cognitive decline, and eventually dementia. Indeed, hearing loss induced by noise exposure exacerbates cognitive decline [149], expressing Aβ derivatives in the cochlear hair

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

cells leads to an early onset of hearing loss, especially in high-frequency regions, similar to age-related hearing loss [111]. Overexpression of tau synergistically worsens the Aβ-induced hearing defects [111]. These data indicate that Aβ and tau are both toxic to the peripheral auditory system, and overexpression of Aβ might accelerate the process of age-related hearing loss. Furthermore, hearing loss leads to less engagement in social and leisure activities which results in dementia. Lastly, both hearing loss and cognitive decline could be caused by a 'common factor' [150], and might share the same pathway with age-related hearing loss, or presbycusis [151]. Despite the unclear causation between AD and auditory impairment, it has been reported that inducing gamma oscillations in the auditory cortex improved spatial and recognition memory and reduced Aβ in AC [152], indicating the auditory pathway could be a potential target to ameliorate AD-associated pathology.

Noticeably, all the sensory impairments mentioned above could also be the comorbidities of the natural aging process [153]. This confluence of sensory impairments with aging complicates the differential diagnosis of AD from normal age-related changes, necessitating a nuanced understanding of pathological versus physiological decline. Moreover, the overlap of sensory impairments with AD is not uniquely induced by the aging process but could also be induced by other neurodegenerative diseases such as Parkinson's Disease (PD) and Dementia with Lewy Bodies (DLB) [154,155]. Critical to advancing this differentiation is the longitudinal study of sensory deficits, utilizing both animal models and human subjects, to delineate the specific markers of AD-related sensory degradation. The challenge remains to disentangle the intricate web of aging and disease-specific sensory changes, requiring innovative methodologies and interdisciplinary approaches. Integrating multi-sensory assessments with cognitive evaluations and biomarker analysis could enhance the specificity of early AD diagnoses. Ultimately, this comprehensive approach will not only improve our understanding of AD progression but also pave the way for the development of targeted interventions to mitigate sensory deficits and improve the quality of life for individuals with AD.

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

3.4 Sensory impairments in preclinical AD patients

The impairment of the sensory system in AD patients may occur in the preclinical stage, well before the emergence of the onset of clinical symptoms (**Figure 1**). Olfactory dysfunction is associated with a higher Aβ burden in older people, early olfactory impairment in AD patients also known as hyposmia [139], patients exhibit a reduced ability to detect, discriminate, and identify odors, coupled with abnormal odor coding [140,141], elucidating the potential contribution of olfactory testing to detect preclinical AD [156]. In clinically normal elderly individuals, worse olfactory function was associated with decreased hippocampal volume, thinner entorhinal cortex, and a trend associated with greater Aβ burden [155]. Another study showed that reduced odor identification (OI) was associated with lower cognitive score and older age, and increased CSF tau and Aβ, revealing that OI could be an affordable biomarker of AD pathology [157]. The visual deficit is considered a high-risk factor for AD and is increasingly supported by evidence linking visual system alterations to the early stage of AD [158]. For the preclinical stage, substantial visual deficits have been reported in AD patients, [44,159]. Potential measurable functional, structural, metabolic, and vascular changes have been identified in the retina during the early stages of AD [160], indicating vision could be another biomarker for early detection of AD. As another high-risk factor of AD, hearing loss was also associated with higher Aβ and tau burden. A study indicated that worsened hearing was related to the increased Aβ and tau burden [161].

Above all, the evidence supporting sensory deficits as early indicators of AD suggests a paradigm shift in the approach to diagnosing and managing this complex condition in the pre-clinical stages.

4. Integrating Sensory Detection in Early AD Diagnosis

4.1 The Imperative of Incorporating Sensory Detection

In our comprehensive review of early changes in various AD mouse models, notable early alternations take place in sensory systems prior to the cognition decline and the cerebral Aβ/P-tau aggregation. Here we listed out the early time point of alternation in different sensory systems using different AD mouse models **(Table 2)**. This trend is consistent in olfactory, visual, and auditory systems across different AD models. Further, we also found a trend of hyperactivity status across sensory systems before the onset of neurodegeneration and cognition decline. The

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

soluble Aβ oligomers induced hyperactivity on memory performance, cell death, epileptiform activity, gamma oscillations, and slow wave activity can be observed in both AD mouse models and human patients [162], consistent with early detection of soluble Aβ in sensory organs. The hyperactivity status of sensory functions, also known as network hyperexcitability [163], could be a biomarker for AD.

However, we also found results may vary in different research due to the diversity of methodologies and sensory systems. Indeed, some tests have certain limitations. For example, the behavioral test can be affected easily by handling and environmental factors and can be stressful for animals [164,165]. Additionally, the accurate measurement and diagnosis of AD using sensory deficits may be complicated by other variables, including natural aging processes, Parkinson's Disease (PD), Dementia with Lewy Bodies (DLB), and various other neurodegenerative conditions, which can introduce significant variability into the assessment of sensory impairments. The variability and uncertainty indicate the necessity of integrating sensory function tests and the combination of sensory tests and other test methods to increase the accuracy of early AD diagnosis. To achieve this, multidisciplinary approaches that incorporate neuropsychological, neurobiological, and genetic analyses are essential. Implementing these strategies will improve the accuracy of early AD diagnosis through sensory deficit detection and contribute to a more nuanced understanding of the disease's pathophysiology. For instance, the combination of vision and hearing deficits in older people experience higher rates of cognitive impairment [166]. Thus, the simultaneous application of visual and auditory assessments could potentially enhance the precision of pre-clinical AD diagnosis, offering a more robust framework for identifying early indicators of cognitive impairment. Above all, sensory tests have demonstrated potential as supplementary tools for the diagnosis of AD and MCI. For instance, odor identification screening (Sniffin' Sticks Odor Identification Test, SS-OIT) can improve the diagnostic accuracy of AD and MCI when combined with MoCA, providing additional information for clinical categorization of AD and MCI [167]. Visuospatial measures show a significant diagnostic and prognostic potential in dementia, which means visuospatial tests could also improve the diagnosis of AD [168]. Central auditory testing might be another suitable biomarker for identifying people at risk for dementia combined with electrophysiologic testing [169].

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

Nevertheless, before these approaches can be adopted clinically, extensive validation steps are essential. This encompasses replicating findings across diverse studies to ensure reproducibility, alongside rigorous comparisons with established diagnostic benchmarks to clinical implementation. Additionally, defining precise diagnostic thresholds for sensory tests is crucial to delineate AD-related sensory impairments from those attributable to other causes. Moreover, evaluating the predictive value of these tests in foreseeing disease progression is essential. The pathway towards clinical adoption involves meticulous steps, including the elaboration of a clear context of use, submission of a comprehensive qualification package to regulatory bodies, and achieving a consensus on standards for test performance [170-173]. These processes are instrumental in ensuring the reliability, efficacy, and clinical relevance of sensory detection methods, thereby facilitating the integration into the diagnostic repertoire for early AD.

4.2 integrating Sensory Change Detection with Artificial Intelligence

Utilizing artificial intelligence (AI) in predicting AD is a rapidly evolving field. AI aids early detection and diagnosis based on a variety of machine learning-trained models. Based on the cognitive tests, imaging techniques, and CSF test, AI can improve the accuracy of traditional diagnostic methods, such as analyzing PET and MRI scan images [28], and new biomarkers analysis beside Aβ42 and P-tau using the CSF database [174]. AI can also do end-to-end detection without using additional diagnostic methods. A pre-trained data2vec model can perform a self-supervised algorithm that works for speech, vision, and text [175]. An integrating pre-trained model that can access multimodal sensory test data would be a potential method for rapid, non-invasive AD diagnosis during the early detection window (**Figure 2**).

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

5. Conclusion

In conclusion, we have thoroughly reviewed the changes in multiple sensory systems in the early stage of AD, focusing on olfactory, visual, and auditory functions. Changes in these sensory systems manifest significantly in both AD patients and various AD mouse models, the alternations of the sensory system appear much earlier than the typical neurodegeneration and cognitive decline. These results shed light on the importance of multiple sensory tests for early and non-invasive AD diagnosis. Moreover, the potential integration of multi-sensory examination and the combination with traditional diagnostic methods and/or AI prediction presents a promising methodology for the improvement of accuracy and rapid AD detection in the future.

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

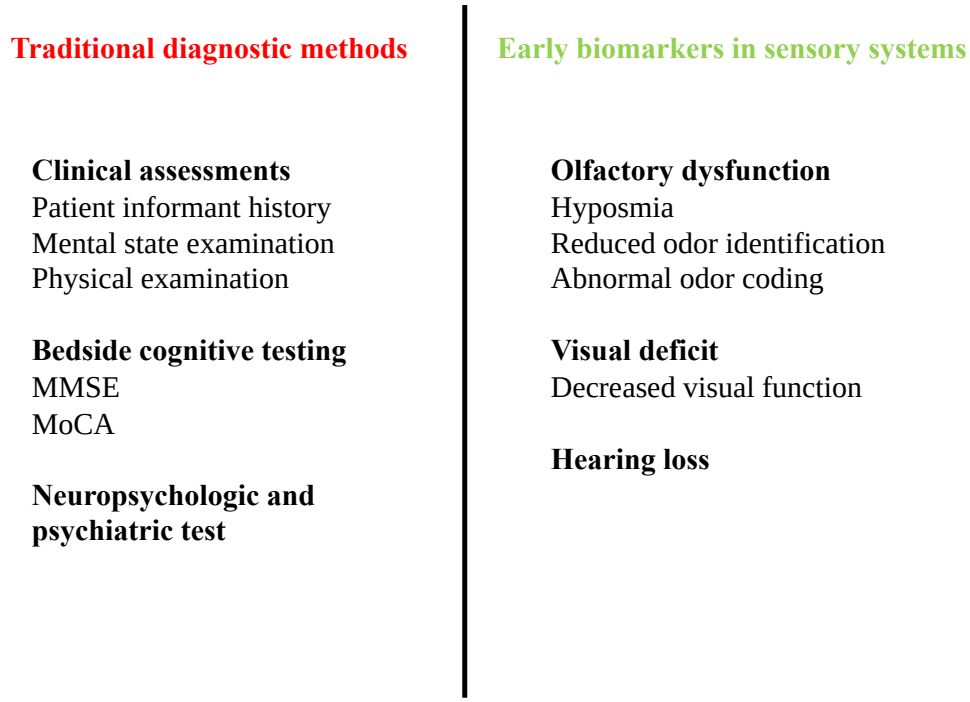

Figure 1. Overview of traditional diagnostic methods and early biomarkers in sensory systems. MMSE: Mini-mental State Examination. MoCA: Montreal Cognitive Assessment.

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

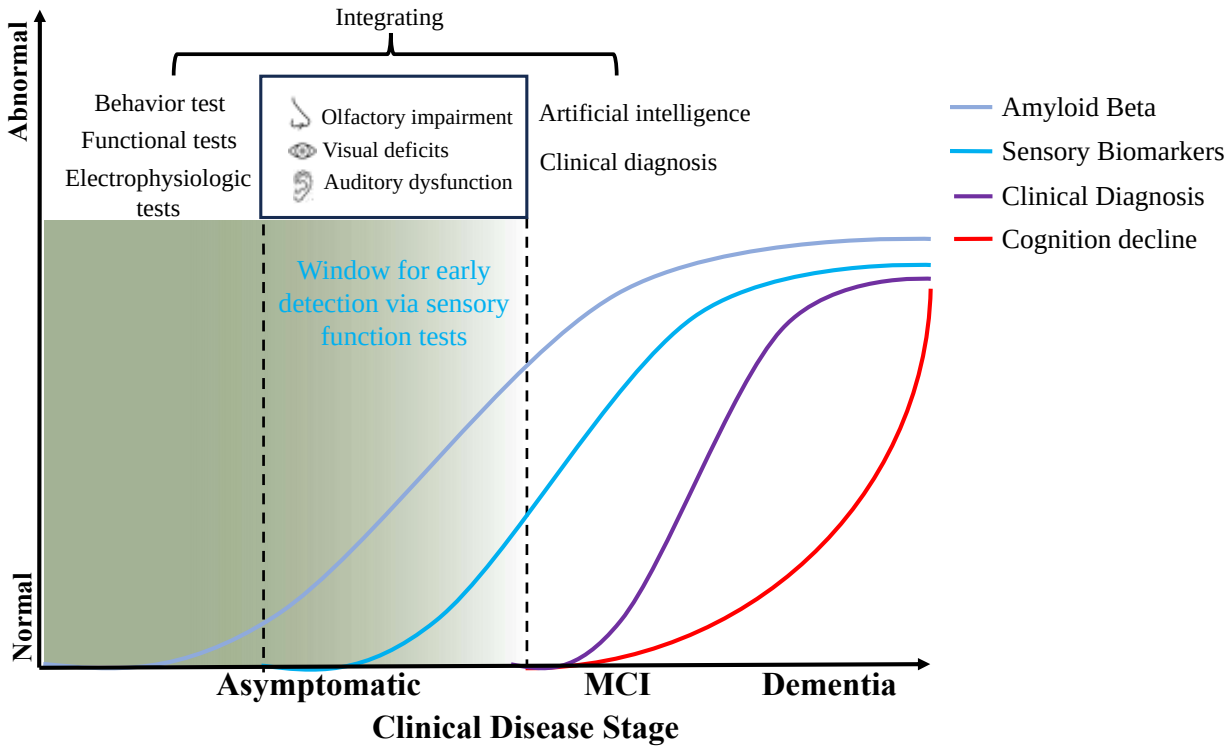

Figure 2: Schematic of Alzheimer's Disease (AD) Stages. Amyloid beta (Aβ) begins to accumulate many years before cognitive decline, marking the asymptomatic stage. This accumulation of Aβ starts to impair the sensory system's function, including olfactory, visual, and auditory systems, before the onset of Mild Cognitive Impairment (MCI). After the asymptomatic stage, some clinical diagnostic methods become applicable. However, by this point, patients start to experience cognitive decline, which, at this stage, is irreversible. Therefore, the window for early detection through sensory function tests is crucial. Integrating these tests with common clinical diagnostics and artificial intelligence (AI) could enhance the accuracy of early AD diagnosis before the onset of cognitive decline.

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

Table 1 Earliest Detection Points of symptoms in AD mouse models

AD model mice	Cerebral Aβ/P-tau	Cognition decline
APP transgenic models (Tg2576)	6 Mo [70]	6 Mo [68]
APP/PS1	3 Mo [86]	5 Mo [86]
5xFAD	2 Mo [101]	4 Mo [102]
Tau transgenic models (P301S)	6 Mo [119]	4 Mo [121]

Mo: month of age

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

Table 2 Earliest Detection Points of sensory deficits in AD mouse models

Mo: month of age, N.A: not applicable.

AD model mice	**Olfactory**			**Visual**			**Auditory**		
	APP/Aβ/P-tau aggregation	Behaviors	EP	APP/Aβ/P-tau aggregation	Behaviors	EP	APP/Aβ/P-tau aggregation	Behaviors	EP
APP transgenic models (Tg2576)	2 Mo [72]	4 Mo [76]	3 Mo [77]	7.8 Mo [80]	9 Mo [83]	N.A	N.A	N.A	N.A
APP/PS1	3 Mo [176]	3 Mo [177]	3 Mo [90]	5 Mo [91]	8.5 Mo [92]	3 Mo [93]	2 Mo [94]	7 Mo [100]	2 Mo [13]
5xFAD	2 Mo [105]	3 Mo [103]	3 Mo [106]	6 Mo [107]	6 Mo [108]	3 Mo [108]	1 Mo [109]	2 Mo [113]	6 Mo [99]
Tau transgenic models (P301S)	1 Mo [124]	2 Mo [124]	3 Mo [126]	2 Mo [127]	2.5 Mo [120]	N.A	4 Mo [119]	3 Mo [129]	N.A

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

Table 3 Sensory deficits in the symptomatic stage of AD

Sensory system	Sensory deficits	Reference
Vision	Difficulty reading, loss of contrast sensitivity	Lee et al., [178]
Vision	Decreased visual field and/or contrast sensitivity, and fixation problems	Ikram et al., [179]
Vision	Changed topological organization of higher-level visual	Deng et al., [180]
Vision	Loss of retinal ganglion cells	Kirby et al., [181]
Olfactory	Increased olfactory threshold	Serby et al., [41,182]
Olfactory	Smaller OB volumes	Jobin et al., [183]
Olfactory	Impaired olfactory identification	Vyhnalek et al., [139]
Hearing	Cannot recognize or misinterpret environmental sounds	Dietz et al., [184]
Hearing	Changes N200 and P300 latencies	Cintra et al., [185]

https://doi.org/10.1017/cts.2024.525 Published online by Cambridge University Press

Reference:

1. Tiwari S, Atluri V, Kaushik A, Yndart A, Nair M. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. *International Journal of Nanomedicine*. 2019-07-01 2019;Volume 14:5541-5554. doi:10.2147/ijn.s200490
2. Skaria AP. The economic and societal burden of Alzheimer disease: managed care considerations. *Am J Manag Care*. Sep 2022;28(10 Suppl):S188-S196. doi:10.37765/ajmc.2022.89236
3. Tobore TO. On the Etiopathogenesis and Pathophysiology of Alzheimer's Disease: A Comprehensive Theoretical Review. *J Alzheimers Dis*. 2019;68(2):417-437. doi:10.3233/JAD-181052
4. Murphy MP, Levine H. Alzheimer's Disease and the Amyloid-β Peptide. *Journal of Alzheimer's Disease*. 2010-01-06 2010;19(1):311-323. doi:10.3233/jad-2010-1221
5. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. Jul 1984;34(7):939-44. doi:10.1212/wnl.34.7.939
6. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia*. 2018-04-01 2018;14(4):535-562. doi:10.1016/j.jalz.2018.02.018
7. Petersen RC, Wiste HJ, Weigand SD, et al. NIA-AA Alzheimer's Disease Framework: Clinical Characterization of Stages. *Annals of Neurology*. 2021-06-01 2021;89(6):1145-1156. doi:10.1002/ana.26071
8. Mckhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*. 2011-05-01 2011;7(3):263-269. doi:10.1016/j.jalz.2011.03.005
9. Ferreira D, Perestelo-Perez L, Westman E, Wahlund LO, Sarria A, Serrano-Aguilar P. Meta-Review of CSF Core Biomarkers in Alzheimer's Disease: The State-of-the-Art after the New Revised Diagnostic Criteria. *Front Aging Neurosci*. 2014;6:47. doi:10.3389/fnagi.2014.00047

10. Martín ISM, Barato VP, Oliva SL, et al. Body Composition, Dietary, and Gustatory Function Assessment in People With Alzheimer's Disease. *American Journal of Alzheimer's Disease & Other Dementiasr*. 2018-12-01 2018;33(8):508-515. doi:10.1177/1533317518782173

11. Suzuki M, Tatsumi A, Otsuka T, et al. Physical and Psychological Effects of 6-Week Tactile Massage on Elderly Patients With Severe Dementia. *American Journal of Alzheimer's Disease & Other Dementiasr*. 2010-12-01 2010;25(8):680-686. doi:10.1177/1533317510386215

12. Prandota J. Possible link between Toxoplasma gondii and the anosmia associated with neurodegenerative diseases. *American Journal of Alzheimer's Disease & Other Dementiasr*. 2014-05-01 2014;29(3):205-214. doi:10.1177/1533317513517049

13. Mei L, Liu L-M, Chen K, Zhao H-B. Early Functional and Cognitive Declines Measured by Auditory-Evoked Cortical Potentials in Mice With Alzheimer's Disease. *Frontiers in Aging Neuroscience*. 2021-09-13 2021;13doi:10.3389/fnagi.2021.710317

14. Risacher SL, Wudunn D, Yoder K, et al. Visual and auditory changes are associated with neuroimaging biomarkers during prodromal stages of Alzheimer's disease. *Alzheimer's & Dementia*. 2014-07-01 2014;10(4S_Part_6):P54-P55. doi:10.1016/j.jalz.2014.05.102

15. Füllgrabe C. Auditory Biases in Cognitive Assessment: Insights from a Hearing-Loss Simulation for the Screening of Dementia due to Alzheimer's Disease. *Journal of Alzheimer's Disease*. 2023-01-17 2023;91(2):537-541. doi:10.3233/jad-215695

16. Permezel F, Alty J, Harding IH, Thyagarajan D. Brain Networks Involved in Sensory Perception in Parkinson's Disease: A Scoping Review. *Brain Sciences*. 2023-11-06 2023;13(11):1552. doi:10.3390/brainsci13111552

17. Kuźma E, Littlejohns TJ, Khawaja AP, Llewellyn DJ, Ukoumunne OC, Thiem U. Visual Impairment, Eye Diseases, and Dementia Risk: A Systematic Review and Meta-Analysis. *Journal of Alzheimer's Disease*. 2021-09-28 2021;83(3):1073-1087. doi:10.3233/jad-210250

18. Pan L, Li C, Meng L, et al. GDF1 ameliorates cognitive impairment induced by hearing loss. *Nature Aging*. 2024-03-15 2024;doi:10.1038/s43587-024-00592-5

19. Zhao H-B, Yang Y. Hearing loss promotes Alzheimer's disease. *Nature Aging*. 2024-03-15 2024;doi:10.1038/s43587-024-00606-2

20. Ehrlich JR, Goldstein J, Swenor BK, Whitson H, Langa KM, Veliz P. Addition of Vision Impairment to a Life-Course Model of Potentially Modifiable Dementia Risk Factors in the US. *JAMA Neurology*. 2022-06-01 2022;79(6):623. doi:10.1001/jamaneurol.2022.0723

21. Lin FR, Pike JR, Albert MS, et al. Hearing intervention versus health education control to reduce cognitive decline in older adults with hearing loss in the USA (ACHIEVE): a multicentre, randomised controlled trial. *Lancet*. Sep 2 2023;402(10404):786-797. doi:10.1016/s0140-6736(23)01406-x

22. Bondi MW, Edmonds EC, Salmon DP. Alzheimer's Disease: Past, Present, and Future. *Journal of the International Neuropsychological Society*. 2017-10-01 2017;23(9-10):818-831. doi:10.1017/s135561771700100x

23. Barage SH, Sonawane KD. Amyloid cascade hypothesis: Pathogenesis and therapeutic strategies in Alzheimer's disease. *Neuropeptides*. Aug 2015;52:1-18. doi:10.1016/j.npep.2015.06.008

24. Hampel H, Mesulam M-M, Cuello AC, et al. REVISITING THE CHOLINERGIC HYPOTHESIS IN ALZHEIMER'S DISEASE: EMERGING EVIDENCE FROM TRANSLATIONAL AND CLINICAL RESEARCH. *The Journal Of Prevention of Alzheimer's Disease*. 2018-01-01 2018:1-14. doi:10.14283/jpad.2018.43

25. Mohandas E, Rajmohan V, Raghunath B. Neurobiology of Alzheimer's disease. *Indian J Psychiatry*. Jan 2009;51(1):55-61. doi:10.4103/0019-5545.44908

26. Kametani F, Hasegawa M. Reconsideration of Amyloid Hypothesis and Tau Hypothesis in Alzheimer's Disease. *Frontiers in Neuroscience*. 2018-01-30 2018;12doi:10.3389/fnins.2018.00025

27. Arnsten AFT, Datta D, Del Tredici K, Braak H. Hypothesis: Tau pathology is an initiating factor in sporadic Alzheimer's disease. *Alzheimers Dement*. Jan 2021;17(1):115-124. doi:10.1002/alz.12192

28. Aberathne I, Kulasiri D, Samarasinghe S. Detection of Alzheimer's disease onset using MRI and PET neuroimaging: longitudinal data analysis and machine learning. *Neural Regen Res*. Oct 2023;18(10):2134-2140. doi:10.4103/1673-5374.367840

29. Markesbery WR. Oxidative stress hypothesis in Alzheimer's disease. *Free Radic Biol Med*. 1997;23(1):134-47. doi:10.1016/s0891-5849(96)00629-6

30. Pratico D. Oxidative stress hypothesis in Alzheimer's disease: a reappraisal. *Trends Pharmacol Sci*. Dec 2008;29(12):609-15. doi:10.1016/j.tips.2008.09.001

31. Monsell SE, Mock C, Hassenstab J, et al. Neuropsychological changes in asymptomatic persons with Alzheimer disease neuropathology. *Neurology*. 2014-07-29 2014;83(5):434-440. doi:10.1212/wnl.0000000000000650

32. Dubois B, Hampel H, Feldman HH, et al. Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimer's & Dementia*. 2016-03-01 2016;12(3):292-323. doi:10.1016/j.jalz.2016.02.002

33. Eratne D, Loi SM, Farrand S, Kelso W, Velakoulis D, Looi JC. Alzheimer's disease: clinical update on epidemiology, pathophysiology and diagnosis. *Australas Psychiatry*. Aug 2018;26(4):347-357. doi:10.1177/1039856218762308

34. Islam J, Zhang Y. Brain MRI analysis for Alzheimer's disease diagnosis using an ensemble system of deep convolutional neural networks. *Brain Informatics*. 2018-12-01 2018;5(2)doi:10.1186/s40708-018-0080-3

35. Valotassiou V, Malamitsi J, Papatriantafyllou J, et al. SPECT and PET imaging in Alzheimer's disease. *Annals of Nuclear Medicine*. 2018-11-01 2018;32(9):583-593. doi:10.1007/s12149-018-1292-6

36. Bouwman FH, Frisoni GB, Johnson SC, et al. Clinical application of CSF biomarkers for Alzheimer's disease: From rationale to ratios. *Alzheimers Dement (Amst)*. 2022;14(1):e12314. doi:10.1002/dad2.12314

37. Schneider P, Hampel H, Buerger K. Biological marker candidates of Alzheimer's disease in blood, plasma, and serum. *CNS Neurosci Ther*. Winter 2009;15(4):358-74. doi:10.1111/j.1755-5949.2009.00104.x

38. Draper B, Cations M, White F, et al. Time to diagnosis in young-onset dementia and its determinants: the INSPIRED study. *Int J Geriatr Psychiatry*. Nov 2016;31(11):1217-1224. doi:10.1002/gps.4430

39. Jung HJ, Shin IS, Lee JE. Olfactory function in mild cognitive impairment and Alzheimer's disease: A meta-analysis. *Laryngoscope*. Feb 2019;129(2):362-369. doi:10.1002/lary.27399

40. Dan X, Wechter N, Gray S, Mohanty JG, Croteau DL, Bohr VA. Olfactory dysfunction in aging and neurodegenerative diseases. *Ageing Res Rev*. Sep 2021;70:101416. doi:10.1016/j.arr.2021.101416

41. Djordjevic J, Jones-Gotman M, De Sousa K, Chertkow H. Olfaction in patients with mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging*. May 2008;29(5):693-706. doi:10.1016/j.neurobiolaging.2006.11.014

42. Fusetti M, Fioretti AB, Silvagni F, et al. Smell and preclinical Alzheimer disease: study of 29 patients with amnesic mild cognitive impairment. *J Otolaryngol Head Neck Surg*. Apr 2010;39(2):175-81.

43. El Haj M, Laroi F. Olfactory hallucinations in Alzheimer's disease. *Acta Neuropsychiatrica*. 2021-02-01 2021;33(1):37-42. doi:10.1017/neu.2020.33

44. Javaid FZ, Brenton J, Guo L, Cordeiro MF. Visual and Ocular Manifestations of Alzheimer's Disease and Their Use as Biomarkers for Diagnosis and Progression. *Frontiers in Neurology*. 2016-04-19 2016;7doi:10.3389/fneur.2016.00055

45. Li S, Cheng C, Lu L, et al. Hearing Loss in Neurological Disorders. *Front Cell Dev Biol*. 2021;9:716300. doi:10.3389/fcell.2021.716300

46. Shityakov S, Hayashi K, Stork S, Scheper V, Lenarz T, Forster CY. The Conspicuous Link between Ear, Brain and Heart-Could Neurotrophin-Treatment of Age-Related Hearing Loss Help Prevent Alzheimer's Disease and Associated Amyloid Cardiomyopathy? *Biomolecules*. Jun 17 2021;11(6)doi:10.3390/biom11060900

47. Ache BW, Young JM. Olfaction: Diverse Species, Conserved Principles. *Neuron*. 2005-11-01 2005;48(3):417-430. doi:10.1016/j.neuron.2005.10.022

48. Smith TD, Bhatnagar KP. Anatomy of the olfactory system. *Handb Clin Neurol*. 2019;164:17-28. doi:10.1016/B978-0-444-63855-7.00002-2

49. Duchamp-Viret P, Chaput MA, Duchamp A. Odor response properties of rat olfactory receptor neurons. *Science*. Jun 25 1999;284(5423):2171-4. doi:10.1126/science.284.5423.2171

50. Firestein S. How the olfactory system makes sense of scents. *Nature*. 2001-09-01 2001;413(6852):211-218. doi:10.1038/35093026

51. Giessel AJ, Datta SR. Olfactory maps, circuits and computations. *Curr Opin Neurobiol*. Feb 2014;24(1):120-32. doi:10.1016/j.conb.2013.09.010

52. Chaya T, Matsumoto A, Sugita Y, et al. Versatile functional roles of horizontal cells in the retinal circuit. *Sci Rep*. Jul 17 2017;7(1):5540. doi:10.1038/s41598-017-05543-2

53. Strenzke N, Pauli-Magnus D, Meyer A, Brandt A, Maier H, Moser T. [Update on physiology and pathophysiology of the inner ear: pathomechanisms of sensorineural hearing loss]. *HNO*. Jan 2008;56(1):27-36. Update zur Physiologie und Pathophysiologie des Innenohrs : Pathomechanismen der sensorineuralen Schwerhorigkeit. doi:10.1007/s00106-007-1640-7

54. Stover T, Diensthuber M. [Molecular biology of hearing]. *Laryngorhinootologie*. Mar 2011;90 Suppl 1:S22-34. Molekularbiologie des Gehors. doi:10.1055/s-0030-1270444

55. Schmiedt RA. Effects of aging on potassium homeostasis and the endocochlear potential in the gerbil cochlea. *Hear Res*. Dec 1 1996;102(1-2):125-32. doi:10.1016/s0378-5955(96)00154-2

56. Climer LK, Hornak AJ, Murtha K, et al. Deletion of Oncomodulin Gives Rise to Early Progressive Cochlear Dysfunction in C57 and CBA Mice. *Front Aging Neurosci*. 2021;13:749729. doi:10.3389/fnagi.2021.749729

57. Murtha KE, Yang Y, Ceriani F, et al. Oncomodulin (OCM) uniquely regulates calcium signaling in neonatal cochlear outer hair cells. *Cell Calcium*. Jul 2022;105:102613. doi:10.1016/j.ceca.2022.102613

58. Yang Y, Murtha K, Climer LK, et al. Oncomodulin regulates spontaneous calcium signalling and maturation of afferent innervation in cochlear outer hair cells. *The Journal of Physiology*. 2023-10-01 2023;601(19):4291-4308. doi:10.1113/jp284690

59. Jayakody DMP, Friedland PL, Martins RN, Sohrabi HR. Impact of Aging on the Auditory System and Related Cognitive Functions: A Narrative Review. *Frontiers in Neuroscience*. 2018-03-05 2018;12doi:10.3389/fnins.2018.00125

60. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. 'Sniffin' Sticks': Olfactory Performance Assessed by the Combined Testing of Odour Identification, Odor Discrimination and Olfactory Threshold. *Chemical Senses*. 1997-01-01 1997;22(1):39-52. doi:10.1093/chemse/22.1.39

61. Zhang J, Zhao Z, Sun S, et al. Olfactory Evaluation in Alzheimer's Disease Model Mice. *Brain Sciences*. 2022-05-06 2022;12(5):607. doi:10.3390/brainsci12050607

62. Lissner LJ, Wartchow KM, Toniazzo AP, Goncalves CA, Rodrigues L. Object recognition and Morris water maze to detect cognitive impairment from mild hippocampal damage in rats: A reflection based on the literature and experience. *Pharmacol Biochem Behav*. Nov 2021;210:173273. doi:10.1016/j.pbb.2021.173273

63. Leinonen H, Tanila H. Vision in laboratory rodents-Tools to measure it and implications for behavioral research. *Behav Brain Res*. Oct 15 2018;352:172-182. doi:10.1016/j.bbr.2017.07.040

64. Wendt J, Kuhn M, Hamm AO, Lonsdorf TB. Recent advances in studying brain-behavior interactions using functional imaging: The primary startle response pathway and its affective modulation in humans. *Psychophysiology*. 2023-12-01 2023;60(12)doi:10.1111/psyp.14364

65. Danjou P, Viardot G, Maurice D, et al. Electrophysiological assessment methodology of sensory processing dysfunction in schizophrenia and dementia of the Alzheimer type. *Neurosci Biobehav Rev*. Feb 2019;97:70-84. doi:10.1016/j.neubiorev.2018.09.004

66. Hsiao K, Chapman P, Nilsen S, et al. Correlative memory deficits, Abeta elevation, and amyloid plaques in transgenic mice. *Science*. Oct 4 1996;274(5284):99-102. doi:10.1126/science.274.5284.99

67. Westerman MA, Cooper-Blacketer D, Mariash A, et al. The Relationship between Aβ and Memory in the Tg2576 Mouse Model of Alzheimer's Disease. *The Journal of Neuroscience*. 2002-03-01 2002;22(5):1858-1867. doi:10.1523/jneurosci.22-05-01858.2002

68. Lesné S, Koh MT, Kotilinek L, et al. A specific amyloid-β protein assembly in the brain impairs memory. *Nature*. 2006-03-16 2006;440(7082):352-357. doi:10.1038/nature04533

69. Nyul-Toth A, Delfavero J, Mukli P, et al. Early manifestation of gait alterations in the Tg2576 mouse model of Alzheimer's disease. *GeroScience*. 2021-08-01 2021;43(4):1947-1957. doi:10.1007/s11357-021-00401-6

70. Kawarabayashi T, Younkin LH, Saido TC, Shoji M, Ashe KH, Younkin SG. Age-Dependent Changes in Brain, CSF, and Plasma Amyloid β Protein in the Tg2576 Transgenic Mouse Model of Alzheimer's Disease. *The Journal of Neuroscience*. 2001-01-15 2001;21(2):372-381. doi:10.1523/jneurosci.21-02-00372.2001

71. Chishti MA, Yang D-S, Janus C, et al. Early-onset Amyloid Deposition and Cognitive Deficits in Transgenic Mice Expressing a Double Mutant Form of Amyloid Precursor Protein 695. *Journal of Biological Chemistry*. 2001-06-01 2001;276(24):21562-21570. doi:10.1074/jbc.m100710200

72. Duffy ÁM, Morales-Corraliza J, Bermudez-Hernandez KM, et al. Entorhinal cortical defects in Tg2576 mice are present as early as 2–4 months of age. *Neurobiology of Aging*. 2015-01-01 2015;36(1):134-148. doi:10.1016/j.neurobiolaging.2014.07.001

73. Wilson DA, Yan X. Sleep-like states modulate functional connectivity in the rat olfactory system. *J Neurophysiol*. Dec 2010;104(6):3231-9. doi:10.1152/jn.00711.2010

74. Wesson DW, Levy E, Nixon RA, Wilson DA. Olfactory Dysfunction Correlates with Amyloid-β Burden in an Alzheimer's Disease Mouse Model. *The Journal of Neuroscience*. 2010-01-13 2010;30(2):505-514. doi:10.1523/jneurosci.4622-09.2010

75. Cao L, Schrank BR, Rodriguez S, et al. Aβ alters the connectivity of olfactory neurons in the absence of amyloid plaques in vivo. *Nature Communications*. 2012-08-21 2012;3(1):1009. doi:10.1038/ncomms2013

76. Young JW, Sharkey J, Finlayson K. Progressive impairment in olfactory working memory in a mouse model of Mild Cognitive Impairment. *Neurobiol Aging*. Sep 2009;30(9):1430-43. doi:10.1016/j.neurobiolaging.2007.11.018

77. Wesson DW, Borkowski AH, Landreth GE, Nixon RA, Levy E, Wilson DA. Sensory Network Dysfunction, Behavioral Impairments, and Their Reversibility in an Alzheimer's β-Amyloidosis Mouse Model. *The Journal of Neuroscience*. 2011-11-02 2011;31(44):15962-15971. doi:10.1523/jneurosci.2085-11.2011

78. Xu W, Lopez-Guzman M, Schoen C, et al. Spared Piriform Cortical Single-Unit Odor Processing and Odor Discrimination in the Tg2576 Mouse Model of Alzheimer's Disease. *PLoS ONE*. 2014-09-02 2014;9(9):e106431. doi:10.1371/journal.pone.0106431

79. Narukawa M, Mori Y, Nishida R, et al. Expression of Olfactory-Related Genes in the Olfactory Epithelium of an Alzheimer's Disease Mouse Model. *Journal of Alzheimer's Disease*. 2022-06-28 2022;88(1):29-35. doi:10.3233/jad-220213

80. Ning A, Cui J, To E, Ashe KH, Matsubara J. Amyloid-beta deposits lead to retinal degeneration in a mouse model of Alzheimer disease. *Invest Ophthalmol Vis Sci*. Nov 2008;49(11):5136-43. doi:10.1167/iovs.08-1849

81. Dutescu RM, Li QX, Crowston J, Masters CL, Baird PN, Culvenor JG. Amyloid precursor protein processing and retinal pathology in mouse models of Alzheimer's disease. *Graefes Arch Clin Exp Ophthalmol*. Sep 2009;247(9):1213-21. doi:10.1007/s00417-009-1060-3

82. Liu B, Rasool S, Yang Z, et al. Amyloid-peptide vaccinations reduce beta-amyloid plaques but exacerbate vascular deposition and inflammation in the retina of Alzheimer's transgenic mice. *Am J Pathol*. Nov 2009;175(5):2099-110. doi:10.2353/ajpath.2009.090159

83. King DL, Arendash GW. Behavioral characterization of the Tg2576 transgenic model of Alzheimer's disease through 19 months. *Physiol Behav*. Apr 15 2002;75(5):627-42. doi:10.1016/s0031-9384(02)00639-x

84. Zhuo JM, Prescott SL, Murray ME, Zhang HY, Baxter MG, Nicolle MM. Early discrimination reversal learning impairment and preserved spatial learning in a longitudinal study of Tg2576 APPsw mice. *Neurobiol Aging*. Aug 2007;28(8):1248-57. doi:10.1016/j.neurobiolaging.2006.05.034

85. Jankowsky JL, Fadale DJ, Anderson J, et al. Mutant presenilins specifically elevate the levels of the 42 residue β-amyloid peptide in vivo: evidence for augmentation of a 42-specific γ secretase. *Human Molecular Genetics*. 2004-01-15 2004;13(2):159-170. doi:10.1093/hmg/ddh019

86. Zhu S, Wang J, Zhang Y, et al. The role of neuroinflammation and amyloid in cognitive impairment in an <scp>APP</scp>/<scp>PS</scp>1 transgenic mouse model of Alzheimer's disease. *CNS Neuroscience & Therapeutics*. 2017-04-01 2017;23(4):310-320. doi:10.1111/cns.12677

87. Li W, Li S, Shen L, et al. Impairment of Dendrodendritic Inhibition in the Olfactory Bulb of APP/PS1 Mice. *Front Aging Neurosci*. 2019;11:2. doi:10.3389/fnagi.2019.00002

88. Hu B, Geng C, Guo F, Liu Y, Zong YC, Hou XY. GABA(A) receptor agonist muscimol rescues inhibitory microcircuit defects in the olfactory bulb and improves olfactory function in APP/PS1 transgenic mice. *Neurobiol Aging*. Dec 2021;108:47-57. doi:10.1016/j.neurobiolaging.2021.08.003

89. Chen M, Chen Y, Huo Q, et al. Enhancing GABAergic signaling ameliorates aberrant gamma oscillations of olfactory bulb in AD mouse models. *Mol Neurodegener*. Mar 4 2021;16(1):14. doi:10.1186/s13024-021-00434-7

90. Shen J, Li M, Long C, Yang L, Jiang J. Altered Odor-Evoked Electrophysiological Responses in the Anterior Piriform Cortex of Conscious APP/PS1 Mice. *J Alzheimers Dis*. 2022;90(3):1277-1289. doi:10.3233/JAD-220694

91. Mei X, Yang M, Zhu L, et al. Retinal Levels of Amyloid Beta Correlate with Cerebral Levels of Amyloid Beta in Young APPswe/PS1dE9 Transgenic Mice before Onset of Alzheimer's Disease. *Behav Neurol*. 2020;2020:1574816. doi:10.1155/2020/1574816

92. Vit JP, Fuchs DT, Angel A, et al. Color and contrast vision in mouse models of aging and Alzheimer's disease using a novel visual-stimuli four-arm maze. *Sci Rep*. Jan 13 2021;11(1):1255. doi:10.1038/s41598-021-80988-0

93. Georgevsky D, Retsas S, Raoufi N, Shimoni O, Golzan SM. A longitudinal assessment of retinal function and structure in the APP/PS1 transgenic mouse model of Alzheimer's disease. *Transl Neurodegener*. 2019;8:30. doi:10.1186/s40035-019-0170-z

94. Liu Y, Fang S, Liu L-M, et al. Hearing loss is an early biomarker in APP/PS1 Alzheimer's disease mice. *Neuroscience Letters*. 2020-01-01 2020;717:134705. doi:10.1016/j.neulet.2019.134705

95. Ruan Q, Chen B, Panza F. Which Came First, Age-Related Hearing Loss with Tinnitus or Cognitive Impairment? What are the Potential Pathways? *Journal of Integrative Neuroscience*. 2023-08-04 2023;22(5):109. doi:10.31083/j.jin2205109

96. Kane KL, Longo-Guess CM, Gagnon LH, Ding D, Salvi RJ, Johnson KR. Genetic background effects on age-related hearing loss associated with Cdh23 variants in mice. *Hear Res*. Jan 2012;283(1-2):80-8. doi:10.1016/j.heares.2011.11.007

97. Pietropaolo S, Delage P, Lebreton F, Crusio WE, Cho YH. Early development of social deficits in APP and APP-PS1 mice. *Neurobiol Aging*. May 2012;33(5):1002 e17-27. doi:10.1016/j.neurobiolaging.2011.09.012

98. Cheng D, Logge W, Low JK, Garner B, Karl T. Novel behavioural characteristics of the APP(Swe)/PS1DeltaE9 transgenic mouse model of Alzheimer's disease. *Behav Brain Res*. May 15 2013;245:120-7. doi:10.1016/j.bbr.2013.02.008

99. Na D, Zhang J, Beaulac HJ, et al. Increased central auditory gain in 5xFAD Alzheimer's disease mice as an early biomarker candidate for Alzheimer's disease diagnosis. *Frontiers in Neuroscience*. 2023-05-26 2023;17doi:10.3389/fnins.2023.1106570

100. Wang H, He J, Zhang R, et al. Sensorimotor gating and memory deficits in an APP/PS1 double transgenic mouse model of Alzheimer's disease. *Behav Brain Res*. Jul 15 2012;233(1):237-43. doi:10.1016/j.bbr.2012.05.007

101. Jawhar S, Trawicka A, Jenneckens C, Bayer TA, Wirths O. Motor deficits, neuron loss, and reduced anxiety coinciding with axonal degeneration and intraneuronal Abeta aggregation in the 5XFAD mouse model of Alzheimer's disease. *Neurobiol Aging*. Jan 2012;33(1):196 e29-40. doi:10.1016/j.neurobiolaging.2010.05.027

102. Girard SD, Baranger K, Gauthier C, et al. Evidence for early cognitive impairment related to frontal cortex in the 5XFAD mouse model of Alzheimer's disease. *J Alzheimers Dis*. 2013;33(3):781-96. doi:10.3233/JAD-2012-120982

103. Son G, Yoo SJ, Kang S, et al. Region-specific amyloid-beta accumulation in the olfactory system influences olfactory sensory neuronal dysfunction in 5xFAD mice. *Alzheimers Res Ther*. Jan 4 2021;13(1):4. doi:10.1186/s13195-020-00730-2

104. Ziegler-Waldkirch S, Friesen M, Loreth D, et al. Seed-induced Abeta deposition alters neuronal function and impairs olfaction in a mouse model of Alzheimer's disease. *Mol Psychiatry*. Oct 2022;27(10):4274-4284. doi:10.1038/s41380-022-01686-5

105. O'Leary TP, Stover KR, Mantolino HM, Darvesh S, Brown RE. Intact olfactory memory in the 5xFAD mouse model of Alzheimer's disease from 3 to 15 months of age. *Behav Brain Res*. Sep 1 2020;393:112731. doi:10.1016/j.bbr.2020.112731

106. Girard SD, Jacquet M, Baranger K, et al. Onset of hippocampus-dependent memory impairments in 5XFAD transgenic mouse model of Alzheimer's disease. *Hippocampus*. Jul 2014;24(7):762-72. doi:10.1002/hipo.22267

107. Lim JKH, Li QX, He Z, et al. Retinal Functional and Structural Changes in the 5xFAD Mouse Model of Alzheimer's Disease. *Front Neurosci*. 2020;14:862. doi:10.3389/fnins.2020.00862

108. Patil SA, Grossman S, Kenney R, Balcer LJ, Galetta S. Where's the Vision? The Importance of Visual Outcomes in Neurologic Disorders: The 2021 H. Houston Merritt Lecture. *Neurology*. Jan 31 2023;100(5):244-253. doi:10.1212/WNL.0000000000201490

109. Weible AP, Wehr M. Amyloid Pathology in the Central Auditory Pathway of 5XFAD Mice Appears First in Auditory Cortex. *J Alzheimers Dis*. 2022;89(4):1385-1402. doi:10.3233/JAD-220538

110. Oakley H, Cole SL, Logan S, et al. Intraneuronal beta-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: potential factors in amyloid plaque formation. *J Neurosci*. Oct 4 2006;26(40):10129-40. doi:10.1523/JNEUROSCI.1202-06.2006

111. Omata Y, Tharasegaran S, Lim Y-M, et al. Expression of amyloid-β in mouse cochlear hair cells causes an early-onset auditory defect in high-frequency sound perception. *Aging*. 2016-03-07 2016;8(3):427-439. doi:10.18632/aging.100899

112. O'Leary TP, Shin S, Fertan E, et al. Reduced acoustic startle response and peripheral hearing loss in the 5xFAD mouse model of Alzheimer's disease. *Genes Brain Behav*. Jun 2017;16(5):554-563. doi:10.1111/gbb.12370

113. Kaylegian K, Stebritz AJ, Weible AP, Wehr M. 5XFAD Mice Show Early Onset Gap Detection Deficits. *Frontiers in Aging Neuroscience*. 2019-04-02 2019;11doi:10.3389/fnagi.2019.00066

114. Weible AP, Stebritz AJ, Wehr M. 5XFAD mice show early-onset gap encoding deficits in the auditory cortex. *Neurobiology of Aging*. 2020-10-01 2020;94:101-110. doi:10.1016/j.neurobiolaging.2020.05.013

115. Story D, Chan E, Munro N, Rossignol J, Dunbar GL. Corrigendum to "Latency to startle is reduced in the 5xFAD mouse model of Alzheimer's disease" [Behav. Brain Res. 359 (2019) 823-827]. *Behav Brain Res*. Apr 19 2019;362:338. doi:10.1016/j.bbr.2019.01.020

116. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med*. Sep 2011;1(1):a006189. doi:10.1101/cshperspect.a006189

117. Yoshiyama Y, Higuchi M, Zhang B, et al. Synapse Loss and Microglial Activation Precede Tangles in a P301S Tauopathy Mouse Model. *Neuron*. 2007-02-01 2007;53(3):337-351. doi:10.1016/j.neuron.2007.01.010

118. Allen B, Ingram E, Takao M, et al. Abundant Tau Filaments and Nonapoptotic Neurodegeneration in Transgenic Mice Expressing Human P301S Tau Protein. *The Journal of Neuroscience*. 2002-11-01 2002;22(21):9340-9351. doi:10.1523/jneurosci.22-21-09340.2002

119. Takeuchi H, Iba M, Inoue H, et al. P301S Mutant Human Tau Transgenic Mice Manifest Early Symptoms of Human Tauopathies with Dementia and Altered Sensorimotor Gating. *PLoS ONE*. 2011-06-15 2011;6(6):e21050. doi:10.1371/journal.pone.0021050

120. Xu H, Rosler TW, Carlsson T, et al. Memory deficits correlate with tau and spine pathology in P301S MAPT transgenic mice. *Neuropathol Appl Neurobiol*. Dec 2014;40(7):833-43. doi:10.1111/nan.12160

121. Przybyla M, Van Eersel J, Van Hummel A, et al. Onset of hippocampal network aberration and memory deficits in P301S tau mice are associated with an early gene signature. *Brain*. 2020-06-01 2020;143(6):1889-1904. doi:10.1093/brain/awaa133

122. Hu X, Li X, Zhao M, Gottesdiener A, Luo W, Paul S. Tau pathogenesis is promoted by Aβ1-42 but not Aβ1-40. *Molecular Neurodegeneration*. 2014-01-01 2014;9(1):52. doi:10.1186/1750-1326-9-52

123. Zampar S, Wirths O. Characterization of a Mouse Model of Alzheimer's Disease Expressing Aβ4-42 and Human Mutant Tau. *International Journal of Molecular Sciences*. 2021-05-14 2021;22(10):5191. doi:10.3390/ijms22105191

124. Li S, Li W, Wu X, et al. Olfactory deficit is associated with mitral cell dysfunction in the olfactory bulb of P301S tau transgenic mice. *Brain Res Bull*. May 2019;148:34-45. doi:10.1016/j.brainresbull.2019.03.006

125. Yang S, Kuan WL, Spillantini MG. Progressive tauopathy in P301S tau transgenic mice is associated with a functional deficit of the olfactory system. *Eur J Neurosci*. Sep 2016;44(6):2396-403. doi:10.1111/ejn.13333

126. Ahnaou A, Rodriguez-Manrique D, Biermans R, Embrechts S, Manyakov NV, Drinkenburg WH. Functional Alterations in the Olfactory Neuronal Circuit Occur before Hippocampal Plasticity Deficits in the P301S Mouse Model of Tauopathy: Implications for Early Diagnosis and Translational Research in Alzheimer's Disease. *International Journal of Molecular Sciences*. 2020-07-30 2020;21(15):5431. doi:10.3390/ijms21155431

127. Gasparini L, Crowther RA, Martin KR, et al. Tau inclusions in retinal ganglion cells of human P301S tau transgenic mice: effects on axonal viability. *Neurobiol Aging*. Mar 2011;32(3):419-33. doi:10.1016/j.neurobiolaging.2009.03.002

128. Ahmad F, Mein H, Jing Y, Zhang H, Liu P. Behavioural Functions and Cerebral Blood Flow in a P301S Tauopathy Mouse Model: A Time-Course Study. *Int J Mol Sci*. Sep 8 2021;22(18)doi:10.3390/ijms22189727

129. Koppel J, Jimenez H, Azose M, et al. Pathogenic tau species drive a psychosis-like phenotype in a mouse model of Alzheimer's disease. *Behav Brain Res*. Dec 15 2014;275:27-33. doi:10.1016/j.bbr.2014.08.030

130. Papageorgiou E, Tsirelis D, Lazari K, Siokas V, Dardiotis E, Tsironi EE. Visual disorders and driving ability in persons with dementia: A mini review. *Front Hum Neurosci*. 2022;16:932820. doi:10.3389/fnhum.2022.932820

131. Golzan SM, Goozee K, Georgevsky D, et al. Retinal vascular and structural changes are associated with amyloid burden in the elderly: ophthalmic biomarkers of preclinical Alzheimer's disease. *Alzheimer's Research & Therapy*. 2017-12-01 2017;9(1)doi:10.1186/s13195-017-0239-9

132. Lee YT, Pai MC. Recognition of personally familiar scenes in patients with very mild Alzheimer's disease: effects of spatial frequency and luminance. *J Alzheimers Dis*. 2012;29(2):441-8. doi:10.3233/JAD-2011-111601

133. Gilmore GC, Groth KE, Thomas CW. Stimulus contrast and word reading speed in Alzheimer's disease. *Exp Aging Res*. Jan-Mar 2005;31(1):15-33. doi:10.1080/03610730590882828

134. Kim HJ, Ryou JH, Choi KT, Kim SM, Kim JT, Han DH. Deficits in color detection in patients with Alzheimer disease. *PLoS One*. 2022;17(1):e0262226. doi:10.1371/journal.pone.0262226

135. Berisha F, Feke GT, Trempe CL, Mcmeel JW, Schepens CL. Retinal Abnormalities in Early Alzheimer's Disease. *Investigative Opthalmology & Visual Science*. 2007-05-01 2007;48(5):2285. doi:10.1167/iovs.06-1029

136. Bateman R. Alzheimer's disease and other dementias: advances in 2014. *Lancet Neurol*. Jan 2015;14(1):4-6. doi:10.1016/S1474-4422(14)70301-1

137. Crawford TJ, Devereaux A, Higham S, Kelly C. The disengagement of visual attention in Alzheimer's disease: a longitudinal eye-tracking study. *Front Aging Neurosci*. 2015;7:118. doi:10.3389/fnagi.2015.00118

138. Dibattista M, Pifferi S, Menini A, Reisert J. Alzheimer's Disease: What Can We Learn From the Peripheral Olfactory System? *Front Neurosci*. 2020;14:440. doi:10.3389/fnins.2020.00440

139. Vyhnalek M, Magerova H, Andel R, et al. Olfactory identification in amnestic and non-amnestic mild cognitive impairment and its neuropsychological correlates. *J Neurol Sci*. Feb 15 2015;349(1-2):179-84. doi:10.1016/j.jns.2015.01.014

140. Yaffe K, Freimer D, Chen H, et al. Olfaction and risk of dementia in a biracial cohort of older adults. *Neurology*. Jan 31 2017;88(5):456-462. doi:10.1212/WNL.0000000000003558

141. Li W, Howard JD, Gottfried JA. Disruption of odour quality coding in piriform cortex mediates olfactory deficits in Alzheimer's disease. *Brain*. Sep 2010;133(9):2714-26. doi:10.1093/brain/awq209

142. Powell DS, Reed NS, Wolff JL. Care for Hearing Loss and Best Principles of Dementia Care: The Time is Right for Inclusion. *J Am Med Dir Assoc*. Dec 2022;23(12):e13-e14. doi:10.1016/j.jamda.2022.10.003

143. Tarawneh HY, Menegola HK, Peou A, Tarawneh H, Jayakody DMP. Central Auditory Functions of Alzheimer's Disease and Its Preclinical Stages: A Systematic Review and Meta-Analysis. *Cells*. Mar 16 2022;11(6)doi:10.3390/cells11061007

144. Lin FR, Metter EJ, O'Brien RJ, Resnick SM, Zonderman AB, Ferrucci L. Hearing Loss and Incident Dementia. *Archives of Neurology*. 2011-02-01 2011;68(2)doi:10.1001/archneurol.2010.362

145. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. Aug 8 2020;396(10248):413-446. doi:10.1016/S0140-6736(20)30367-6

146. Llano DA, Kwok SS, Devanarayan V. Reported Hearing Loss in Alzheimer's Disease Is Associated With Loss of Brainstem and Cerebellar Volume. *Frontiers in Human Neuroscience*. 2021-09-24 2021;15doi:10.3389/fnhum.2021.739754

147. Jansen IE, Savage JE, Watanabe K, et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nature Genetics*. 2019-03-01 2019;51(3):404-413. doi:10.1038/s41588-018-0311-9

148. Mitchell BL, Thorp JG, Evans DM, Nyholt DR, Martin NG, Lupton MK. Exploring the genetic relationship between hearing impairment and Alzheimer's disease. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*. 2020-01-01 2020;12(1)doi:10.1002/dad2.12108

149. Paciello F, Rinaudo M, Longo V, et al. Auditory sensory deprivation induced by noise exposure exacerbates cognitive decline in a mouse model of Alzheimer's disease. *Elife*. Oct 26 2021;10doi:10.7554/eLife.70908

150. Amieva H, Ouvrard C. Does Treating Hearing Loss in Older Adults Improve Cognitive Outcomes? A Review. *Journal of Clinical Medicine*. 2020-03-16 2020;9(3):805. doi:10.3390/jcm9030805

151. Chern A, Golub JS. Age-related Hearing Loss and Dementia. *Alzheimer Dis Assoc Disord*. Jul-Sep 2019;33(3):285-290. doi:10.1097/WAD.0000000000000325

152. Martorell AJ, Paulson AL, Suk HJ, et al. Multi-sensory Gamma Stimulation Ameliorates Alzheimer's-Associated Pathology and Improves Cognition. *Cell*. Apr 4 2019;177(2):256-271 e22. doi:10.1016/j.cell.2019.02.014

153. Liu Y, Tan Y, Zhang Z, Yi M, Zhu L, Peng W. The interaction between ageing and Alzheimer's disease: insights from the hallmarks of ageing. *Transl Neurodegener*. Jan 23 2024;13(1):7. doi:10.1186/s40035-024-00397-x

154. Lad M, Sedley W, Griffiths TD. Sensory Loss and Risk of Dementia. *Neuroscientist*. Apr 2024;30(2):247-259. doi:10.1177/10738584221126090

155. O'Callaghan C, Firbank M, Tomassini A, Schumacher J, O'Brien JT, Taylor JP. Impaired sensory evidence accumulation and network function in Lewy body dementia. *Brain Commun*. 2021;3(3):fcab089. doi:10.1093/braincomms/fcab089

156. Growdon ME, Schultz AP, Dagley AS, et al. Odor identification and Alzheimer disease biomarkers in clinically normal elderly. *Neurology*. May 26 2015;84(21):2153-60. doi:10.1212/WNL.0000000000001614

157. Lafaille-Magnan ME, Poirier J, Etienne P, et al. Odor identification as a biomarker of preclinical AD in older adults at risk. *Neurology*. Jul 25 2017;89(4):327-335. doi:10.1212/WNL.0000000000004159

158. Hawkins KM, Goyal AI, Sergio LE. Diffusion tensor imaging correlates of cognitive-motor decline in normal aging and increased Alzheimer's disease risk. *J Alzheimers Dis*. 2015;44(3):867-78. doi:10.3233/JAD-142079

159. Katz B, Rimmer S. Ophthalmologic manifestations of Alzheimer's disease. *Surv Ophthalmol*. Jul-Aug 1989;34(1):31-43. doi:10.1016/0039-6257(89)90127-6

160. Gupta VB, Chitranshi N, den Haan J, et al. Retinal changes in Alzheimer's disease-integrated prospects of imaging, functional and molecular advances. *Prog Retin Eye Res*. May 2021;82:100899. doi:10.1016/j.preteyeres.2020.100899

161. Zheng M, Yan J, Hao W, et al. Worsening hearing was associated with higher beta-amyloid and tau burden in age-related hearing loss. *Sci Rep*. Jun 21 2022;12(1):10493. doi:10.1038/s41598-022-14466-6

162. Hector A, Brouillette J. Hyperactivity Induced by Soluble Amyloid-beta Oligomers in the Early Stages of Alzheimer's Disease. *Front Mol Neurosci*. 2020;13:600084. doi:10.3389/fnmol.2020.600084

163. Tok S, Ahnaou A, Drinkenburg W. Functional Neurophysiological Biomarkers of Early-Stage Alzheimer's Disease: A Perspective of Network Hyperexcitability in Disease Progression. *J Alzheimers Dis*. 2022;88(3):809-836. doi:10.3233/JAD-210397

164. Gouveia K, Hurst JL. Optimising reliability of mouse performance in behavioural testing: the major role of non-aversive handling. *Sci Rep*. Mar 21 2017;7:44999. doi:10.1038/srep44999

165. Fonio E, Golani I, Benjamini Y. Measuring behavior of animal models: faults and remedies. *Nat Methods*. Dec 2012;9(12):1167-70. doi:10.1038/nmeth.2252

166. Davidson JGS, Guthrie DM. Older Adults With a Combination of Vision and Hearing Impairment Experience Higher Rates of Cognitive Impairment, Functional Dependence, and Worse Outcomes Across a Set of Quality Indicators. *J Aging Health*. Jan 2019;31(1):85-108. doi:10.1177/0898264317723407

167. Quarmley M, Moberg PJ, Mechanic-Hamilton D, et al. Odor Identification Screening Improves Diagnostic Classification in Incipient Alzheimer's Disease. *J Alzheimers Dis*. 2017;55(4):1497-1507. doi:10.3233/JAD-160842

168. Salimi S, Irish M, Foxe D, Hodges JR, Piguet O, Burrell JR. Can visuospatial measures improve the diagnosis of Alzheimer's disease? *Alzheimers Dement (Amst)*. 2018;10:66-74. doi:10.1016/j.dadm.2017.10.004

169. Gates GA, Anderson ML, Feeney MP, McCurry SM, Larson EB. Central auditory dysfunction in older persons with memory impairment or Alzheimer dementia. *Arch Otolaryngol Head Neck Surg*. Jul 2008;134(7):771-7. doi:10.1001/archotol.134.7.771

170. Cummings J, Kinney J. Biomarkers for Alzheimer’s Disease: Context of Use, Qualification, and Roadmap for Clinical Implementation. *Medicina*. 2022-07-19 2022;58(7):952. doi:10.3390/medicina58070952

171. Hampel H, Elhage A, Cummings J, et al. The AT(N) system for describing biological changes in Alzheimer's disease: a plain language summary. *Neurodegenerative Disease Management*. 2022-10-01 2022;12(5):231-239. doi:10.2217/nmt-2022-0013

172. Hampel H, O’Bryant SE, Molinuevo JL, et al. Blood-based biomarkers for Alzheimer disease: mapping the road to the clinic. *Nature Reviews Neurology*. 2018-11-01 2018;14(11):639-652. doi:10.1038/s41582-018-0079-7

173. Goldsack JC, Coravos A, Bakker JP, et al. Verification, analytical validation, and clinical validation (V3): the foundation of determining fit-for-purpose for Biometric Monitoring

Technologies (BioMeTs). *npj Digital Medicine*. 2020-04-14 2020;3(1)doi:10.1038/s41746-020-0260-4

174. Chang CH, Lin CH, Lane HY. Machine Learning and Novel Biomarkers for the Diagnosis of Alzheimer's Disease. *Int J Mol Sci*. Mar 9 2021;22(5)doi:10.3390/ijms22052761

175. Agbavor F, Liang H. Artificial Intelligence-Enabled End-To-End Detection and Assessment of Alzheimer's Disease Using Voice. *Brain Sci*. Dec 23 2022;13(1)doi:10.3390/brainsci13010028

176. Li W, Li S, Shen L, et al. Impairment of Dendrodendritic Inhibition in the Olfactory Bulb of APP/PS1 Mice. *Frontiers in Aging Neuroscience*. 2019-01-24 2019;11doi:10.3389/fnagi.2019.00002

177. Chen B, Wang Q, Zhong X, et al. Structural and Functional Abnormalities of Olfactory-Related Regions in Subjective Cognitive Decline, Mild Cognitive Impairment, and Alzheimer's Disease. *International Journal of Neuropsychopharmacology*. 2022-05-27 2022;25(5):361-374. doi:10.1093/ijnp/pyab091

178. Lee AG, Martin CO. Neuro-ophthalmic findings in the visual variant of Alzheimer's disease. *Ophthalmology*. Feb 2004;111(2):376-80; discussion 380-1. doi:10.1016/S0161-6420(03)00732-2

179. Ikram MK, Cheung CY, Wong TY, Chen CP. Retinal pathology as biomarker for cognitive impairment and Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. Sep 2012;83(9):917-22. doi:10.1136/jnnp-2011-301628

180. Deng Y, Shi L, Lei Y, Wang D, Alzheimer's Disease Neuroimaging I. Altered topological organization of high-level visual networks in Alzheimer's disease and mild cognitive impairment patients. *Neurosci Lett*. Sep 6 2016;630:147-153. doi:10.1016/j.neulet.2016.07.043

181. Kirby E, Bandelow S, Hogervorst E. Visual impairment in Alzheimer's disease: a critical review. *J Alzheimers Dis*. 2010;21(1):15-34. doi:10.3233/JAD-2010-080785

182. Serby M, Larson P, Kalkstein D. The nature and course of olfactory deficits in Alzheimer's disease. *Am J Psychiatry*. Mar 1991;148(3):357-60. doi:10.1176/ajp.148.3.357

183. Jobin B, Boller B, Frasnelli J. Volumetry of Olfactory Structures in Mild Cognitive Impairment and Alzheimer's Disease: A Systematic Review and a Meta-Analysis. *Brain Sci*. Jul 30 2021;11(8)doi:10.3390/brainsci11081010

184. Dietz B, Kohl S, Mayer J, Metzger C, Forstl H, Diehl-Schmid J. [Impaired recognition of environmental sounds in patients with dementia : I can hear but I do not understand]. *Z Gerontol Geriatr*. Jul 2018;51(5):495-500. Storung des Erkennens von Umweltgerauschen bei Demenz : Ich hore aber ich verstehe nicht. doi:10.1007/s00391-017-1216-4

185. Cintra MTG, Avila RT, Soares TO, et al. Increased N200 and P300 latencies in cognitively impaired elderly carrying ApoE epsilon-4 allele. *Int J Geriatr Psychiatry*. Feb 2018;33(2):e221-e227. doi:10.1002/gps.4773