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New Therapeutic Approaches for Sensory Symptoms in Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is a neurological disorder that results in cellular death within the brain. As there are very few ways to diagnose AD in its earliest stages, research into symptoms of this disease is crucial to better understand its progression. Early detection of these markers in prodromal AD is necessary for early intervention and effective treatment. Changes in sensory symptoms may be indicative of AD. Alterations in sensory feedback are often attributed to aging. However, in prodromal AD, changes in sensory stimulus may have not yet affected a patient's quality of life. Evidence from clinical trials and multiple studies suggests that a decline in sensory function has been associated with prodromal AD. In this review, we will focus on the neuropathological changes that occur within AD for the olfactory, visual, and auditory systems. Additionally, we will analyze the uses of these systems and some subsystems such as time awareness, music, and general sensory routines in slowing down the disease progression. While the initial evidence supporting these systems' usefulness for detecting AD is promising, more studies are required to fully understand their relationship with AD. Understanding symptom advancement is critical to developing non-pharmacological methods for the treatment of clinical AD.

Introduction

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 60-80% of reported cases [1]. The progressive nature of the disease begins with a buildup of AD pathological biomarkers, a congregation of amyloid-β (Aβ) and tau, in the brain [1–4]. Early symptoms are often mistaken with routine aging because of shared symptoms such as memory loss or behavioral changes. During prodromal AD, cognitive performance is normal. However, as the disease progresses, both cognitive functions and sensory systems noticeably decline [2]. The amyloid cascade hypothesis suggests that Aβ in a variety of forms (like Aβ 40 and Aβ42 which only differ in C-terminal residues), cause a cascade harming neurons, leading to dementia. This hypothesis proposes that the Aβ peptide damages synapses and neurons, generating the Aβ plaques and tau tangles [4]. Aβ is formed by the breakdown of the amyloid-β precursor protein (APP) [2,4,5]. Other proteins coded by genes such as *PSEN1, PSEN2, and MAPT* alter the incidence of AD [6–9]. Aβ and tau deposits spread through neural networks disrupting communication and, therefore, result in cognitive dysfunction [3]. Aβ peptides build up within senile plaques while tau proteins accumulate within neurofibrillary tangles [3,6]. Aβ and tau may first appear in areas associated with sensory functions before areas associated with memory [10]. These observations lead to the conclusion that sensory decline may indicate early-stage AD [2]. Currently, while AD has no cure, there has been significant evidence that minimizing Aβ or tau decreases the progression of AD [4,6]. This removal of Aβ and tau slows the degeneration of neurons, as Aβ is known to accelerate tau tangles by clumping into plaques between neurons [11]. On the other hand, the buildup of Aβ and tau proteins could be an indication of AD and potentially serve as a biomarker [5].

Sensory impairments arise from the early onset of AD [2,12]. Evidence from a study done by Meisami and colleagues on the decline of the olfactory systems in aging showed AD sensory impairment is associated with decreased brain volume in sensory areas, as indicated by structural MRIs [2,13,14]. The severity of these sensory disabilities

will progressively increase as the disease advances [2]. Due to the hard-to-detect nature of prodromal AD, the disease progression has been closely examined to determine which demonstrated symptoms correlate to AD [2,11,12]. An increase in sensory deficiencies has become an increasingly efficient way to detect prodromal AD. These symptoms are indicative of AD dementia, and tackling these may help prevent disease advancement. However, similar sensory symptoms are associated with many different neurocognitive disorders, hindering the biomarker's success [2].

AD progresses through seven main stages: normal, normal aged forgetfulness, mild cognitive impairment, mild AD, moderate AD, moderately severe AD, and lastly, severe AD stage [15,16]. As these stages progress, cognitive function declines [16]. Many symptoms throughout AD involve neurological function and sensory deprivation. These symptoms are often present in prodromal AD, but progressively worsen with the disease [15,16]. Another way to stage AD is using the Braak Staging Method. This method focuses on locating neurofibrillary tangles (NFTs) and neuropil threads in intraneuronal lesions. Braak staging has 6 different levels. Stages I and II are characterized by the containment of NFTs to the transentorhinal region of the brain. In stages III and IV, NFTs are in the limbic regions of the brain. Stages V and VI are indicated by the spread of NFTs throughout the neocortical brain regions [16,17]. The accumulation of Aβ and tau in different sensory regions correlates with system impairments [2].

The current treatment regimen for AD includes cholinesterase inhibitors, memantine, and rarely, deep brain stimulation (DBS) [18]. There is also a significant amount of research on Aβ and tau protein removal therapy and buildup prevention in early AD [5,6,9]. Cholinesterase inhibitors act by delaying the degradation of acetylcholine into acetylcholinesterase. This alleviates some symptoms of AD, as higher levels of acetylcholine promote increased communication between nerve cells. Memantine is a N-methyl-D-aspartate antagonist that protects neurons from excitotoxicity. It functions by blocking glutamate receptors, lessening dementia symptoms [5]. DBS is a new experimental treatment method for AD. This neuromodulatory brain stimulation technique places pulse generators in target areas of the brain and is often used to control disorders that are more prevalent in AD, such as obsessive-compulsive disorder (OCD) or attention deficit hyperactivity disorder (ADHD). DBS is mainly utilized as a form of symptom management [18]. Treatment and diagnostics for AD and other neurocognitive disorders are known to have many caveats. Drugs that have proven useful in treating AD cannot always be used due to the drug's inability to cross the blood brain barrier, and it is difficult to detect AD at an early stage because there are not many clinical manifestations and there is a big overlap with what is considered normal age-related changes. More specifically, in gene therapy, translating genetic findings into functional mechanisms and, eventually, into viable targets for therapeutics, has proven to be highly complex [8].

This review is comprised of four sections that analyze current studies associated with the olfactory system, visual system, auditory system, and non-pharmacological interventions/treatments. The individual sections will discuss up-to-date data and clinical results and trials, how they relate to neuroanatomy or neurophysiology, and the uses of such topics in diagnosis or treatment [2,12,19–23].

Olfactory

Olfactory dysfunction has recently been considered an early marker of Alzheimer's disease (AD) [22,24–26]. Although it is not yet labeled a biomarker like amyloid-β42, total-tau, or phosphorylated-tau (causes formation of neurofibrillary tangles and neuropil threads) in cerebrospinal fluid (CSF), its potential use as a biomarker is attractive due to difficulties associated with current diagnostic techniques. Collecting CSF for biomarker testing is an invasive procedure that requires analysis conducted by trained clinicians. CSF biomarkers are considered particularly promising because, unlike blood/plasma biochemical markers, they have direct contact with the brain. However, for CSF biomarkers to be detectable, brain decay has to have already occurred [22,27]. Measuring olfactory dysfunction is simple and can be used for diagnosis prior to brain decay. Researchers measure it using three tests: the University of Pennsylvania Smell Identification Test (UPSIT), the Sniffin' Sticks Test (SST), and the Brief Smell Identification Test(B-SIT) [22,24,28]. The UPSIT is regarded as the choice technique due to its high R correlation value (0.94).

Olfactory dysfunction is a very common symptom in most neurodegenerative disorders, though its connection to AD pathology is unusual [24–26]. A study using a transgenic mouse model that overexpresses the K670N, M671L,

and hAPPsw Swedish mutations in altered humanized amyloid precursor proteins (hAPP), found that mature olfactory receptor neurons (ORN) were extremely sensitive to this buildup, and the ORNs that expressed hAPP underwent apoptosis. A later study of a transgenic Tg2576 mouse model overexpressing hAPP established that the olfactory epithelium (OE) and olfactory glomerular layer expressed a higher activity level of γ-secretase, which aids in the cleavage of amyloid precursor protein that generates the amyloid-beta peptide, and β-secretase respectively [22,29].

Regarding the anatomical connection between the AD and the olfactory bulb, the two main neuronal cells in the OE are immature and mature ORNs [22,25,30]. Mature ORNs have a higher expression of the olfactory marker protein, a cytosolic protein that is involved in odor response [22]. They both have cell bodies that are located in the middle of the OE, a dendrite that expands to the nasal cavity, and an axon that extends toward the olfactory bulb (OB). In the olfactory bulb, olfactory neurons with similar receptors bind with mitral and tufted cells (second-order neurons) to form glomeruli [22,30,31]. Glomeruli and spherical neuropil structures wire both peripheral and central neurons, acting as a map for coding olfactory signals and serving as a gateway to the secondary olfactory pathway [26,32]. Second order neurons like the mitral and tufted cells are located within a close proximity to the hippocampus, which is the main location for early AD pathology accumulation [22]. This proposes that amyloid-β and tau are spreading to the olfactory bulb and interfering with cellular processes [25,26]. Obstructing the olfactory glomerulus map can result in deficits in olfactory-driven behaviors [32]. Additional research has shown that the hippocampus is not the only connection between AD pathology and the olfactory bulb. Other brain regions, mainly the anterior olfactory nucleus, have also shown a buildup of tau amyloid-β through the use of imaging techniques and nasal secretions [22,25]. This study analyzed amyloid-β concentration in nasal samples using interdigitated microelectrode biosensors. It had 35 patients with AD dementia confirmed by a mini-mental state examination (MMSE) score of 15.2. The study concluded that based on the capacitance change index, AD patients had a significantly higher amyloid-β concentration in nasal secretions compared to the control [33].

Olfactory symptoms are one of the more promising potential biomarkers because of the thorough knowledge given by transgenic mouse model studies. Also, the analyses of the olfactory bulb and other brain regions have shown that there is ample evidence to support the conclusion that olfactory symptoms can indicate AD.

Visual

AD neuropathological depositions have been detected in the optic pathways using optical coherence tomography [23]. This visualization showed a reduction of the retinal nerve fiber layer thickness and an accumulation of amyloid-β in the optic nerve [23,34]. Specifically, Aβ42 peptides were found in the optic lens [34]. Other AD-related visual system deteriorations include reduction in the number of retinal ganglion cells (RGC), decrease in thickness of the peripapillary retinal nerve fiber layers (RNFL), depletion of axons in the optic nerve, and the appearance of several senile plaques, but few neurofibrillary tangles, in the visual cortex [23,34]. These deteriorations were found during an *in vivo* study which measured axonal degeneration, demonstrated by p-Phenylenediamine, in the optic nerves of 10 AD patients with optical coherence tomography. The researchers concluded that neuronal degeneration is associated with different filamentous accumulations such as the actin, tubulin, and neurofilament [35,36]. Common visual symptoms reported in AD are decreased color contrast, slow eye movement, impaired reading, difficulty in object/shape recognition, visual hallucinations, and posterior cortical atrophy [23]. During a clinical trial, one of the most common symptoms, visual hallucination, was determined to be caused by sensory deprivation (occipital atrophy) and cortical brain AD pathology in the visual association cortex [37].

The neurosensory retina is an outgrowth of the central nervous system (CNS) and is one of the only parts of the CNS not protected by bone. The neurosensory retina shares structural and pathogenic pathways with the CNS via microvasculature and neural cells. Retinas consist of six layers, including three nerve body layers and three layers of synapses. Photoreceptors inside the retina capture information and transmit it through interneurons to RGCs [38]. RGCs have direct synapse connections with the CNS through optic nerve pathways and are crucial for maintaining a stable circadian rhythm. It is possible that sleep disturbances in AD are directly related to AD pathology accumulation in

these cells. This was further explored in a study done on melanopsinRGC (mRGC), which processes ambient light information before passing it to the brain via the retinohypothalamic tract. The study had 21 AD patients and focused on circadian dysfunction in AD, and found that mRGCs were depleted even with a normal RGC count. The mRGCs were analyzed by postmortem immunohistochemistry in retinas and optic nerve cross-sections. This suggests that AD specifically affects mRGCs, given that they make up only a percentage of total RGCs [23,39]. Significant Aβ deposits were found in the proximity of mRGCs that had abnormal morphology. These mRGCs had substantial loss of axons and dendritic arborization [23]. Using Curcumin, a compound that is fluorescent and binds to Aβ fibrillary tangles, non-invasive retinal imaging can be used for AD diagnosis by utilizing a scanning laser ophthalmoscope [40].

Visual symptoms have made progressions as a potential marker with the strong anatomical evidence provided by an analysis of mRGCs. However, stronger evidence provided by various studies, especially clinical studies, would be beneficial.

Auditory

Multiple epidemiological studies have shown a relationship between compromised auditory function, or presbycusis, and Alzheimer's Disease (reviewed by Llano et al. 2021[20]) [41,42]. These studies have linked 9% of sporadic AD to hearing loss, making hearing a marker for prodromal AD [43]. Out of these studies, one of the most widely accepted hypotheses indicates that hearing loss might lead to sensory deprivation, which is a sign of Alzheimer's dementia [44]. The most studied relationship is between hearing loss and decreased volume in the brainstem and cerebellum. The working theory suggests that AD-related pathology in the brainstem and cerebellum created vulnerabilities in these brain regions to auditory deafferentation-related atrophy. Using volumetric magnetic resonance imaging data, AD subjects were found to have several hindbrain regions that showed volume reductions: brainstem, bilateral cerebellar cortex, and cerebellar white matter [20]. This suggests that AD pathology is causing an interaction between the peripheral auditory system and the central auditory system [20,44,45]. However, reported hearing loss has also been described in mild cognitive impairment (MCI) patients. To disprove this theory a *post hoc* analysis done on both MCI and AD patients revealed that AD patients had a drastically lower volume in these related brain regions [20].

A study done on the transgenic 5xFAD mouse model analyzed auditory startle response (ASR) and the auditory brainstem response (ABR). The 5xFAD mouse model had three mutations, on the amyloid precursor protein (APP) (K670N, I716V, and the V717I mutations), and two presenilin-1 mutations. During the trial, only a small number of wild type (WT) mice showed an extreme response to the acoustic startle, with two males being 3-4 months in age and five males and two females being 9 months in age. After a behavioral test assessing acoustic startle, 24.4% of the mice had large responses, 26% had moderate responses, and 50% of the mice had small responses. Although 75% of WT and 5xFAD mice exhibited a response, 5xFAD mice had decreased responses at all ages, with the number of responses decreasing with age. WT mice did not change in responses with different sets of ages. With the ABR testing, 5xFAD mice had a higher threshold for stimulus compared to WT mice across all ages and frequencies tested. These tests convey that the *APP* and *PSEN1* transgenes are inhibiting the startle response and hearing [46].

Oxidative stress is thought to be a central source of induced hearing loss [43,47]. In the peripheral auditory system, the cochlea is exposed to harm from oxidative stress. This is due to the metabolic demands of mechanoelectrical transduction. This potentially leads to mitochondrial dysfunction, making the auditory receptors prone to an accumulation of reactive oxygen and nitrogen species and causing a decline in auditory function. In addition, oxidative stress damage is thought to precede NFT deposits. Some biomarkers of oxidative stress detected in the CSF in the early stages of AD are lipid peroxidation, protein oxidation, and DNA oxidation. The triggering factors behind oxidative stress are not certain, but it is thought to have to do with Aβ having binding sites to high affinity metals creating an oxidative imbalance [43].

Auditory symptoms still have a great deal to progress before being presented as a biomarker. However, as they are newer than the other sensory symptoms, there is much to analyze, both anatomically and clinically.

Non-pharmacological interventions

There is no current cure for Alzheimer's disease, although drugs and invasive procedures are often used in detecting and treating patients [5,48,49]. On the other hand, there are non-drug interventions that aim to ameliorate symptoms, such as music therapy and virtual reality therapy [49,50]. Along with these, this review will include an exploration into time-processing.

Musical interventions are starting to be studied for their benefits in combating the cognitive decline and behavioral symptoms associated with AD. There is evidence to suggest that musical memory networks can remain intact during cognitive decline caused by AD. First, music activates a broad network of areas in the brain rather than just a specific area. Also, PET scans of AD pathology buildup, of amyloid and glucose metabolism, found that areas of the brain actuated by listening to music experienced less accumulation of pathology [51]. Multiple studies that focused on cognition and behavior were also conducted. The first type of study did not include music therapists and only allowed participants to listen to music individually and without distractions. These studies included 30-41 AD participants confirmed by a mini-mental state exam of 12-25 and a clinical dementia rating of 0.5-1, measured cognitive change such as short-term memory and moral judgment, and behavioral change like depression [52–54]. The second type of study focused on a singular music therapist leading a session. This set of studies consisted of 39-42 AD participants confirmed by a mini-mental state exam above 15 and a clinical dementia rating of 1-2, measured cognitive change such as language and MMSE scores, and behavioral change such as hallucinations and anxiety [55,56]. The MMSE is a cognitive test that is used to indicate the presence of cognitive impairment. The third type of study compared music listening groups to active music therapy led by a group of clinicians. This study had 39 AD participants with a confirmed clinical dementia rating of 3, tested active and receptive music intervention, and measured behavioral change such as emotional state and lasting effects of the study. All of these studies occurred independently and had two sets of participants: those that had individualized music playlists based on interests and those that did not [57]. The results showed that participants who used individualized playlists had improved cognition and behavior. The participants who had generic playlists showed minimal to no improvement in cognition. This suggested that the primary factors for improved AD symptoms for participants was acute arousal thought to be caused by the enjoyment of listening to music of interest and the familiarity of the music playlists [58].

Impairments in spatial navigation are specific to early AD. Virtual reality (VR) uses a combination of spatial cognition, task sequencing, and episodic memory in an attempt to treat AD [59]. A study had AD and amnesia mild cognitive impairment (aMCI) participants enter a VR landscape to assess detail recall, recognition, and episodic memory between AD and aMCI [50,59]. The aMCI group and the AD group in all the categories were both impaired in both detail recall and recognition. However, the AD group was more impaired in all tested categories. The results also proposed that a decline in episodic memory and allocentric recall impairment are good indications of early AD. New studies ranging from 16 to 26 AD participants have tested immersive virtual reality (iVR) environments and their effects on visual memory, auditory recognition, and compensatory postural adjustment. iVR includes all of VR technology with added naturalistic interaction with larger landscapes [59].The research suggests that iVR could be more effective than conventional VR in assessing and diagnosing AD. By using spatial tasks that trigger activation in the medial temporal lobe structures, a site of neurodegeneration in AD, iVR has the potential capability to diagnose and predict the progression of MCI into AD. However, the results of using these immersive tasks are still unclear.

Time distortion, an inability to keep track of the temporal relationship between events, is a commonly observed symptom of dementia. It is also a part of a common cognitive assessment of AD patients: the Mini Mental State Examination [60,61]. A study found that time distortions in AD could be associated with multi-attentional tasks. When a participant was asked to perform three levels of task, increasing in multitasking levels, the AD participant suffered increased distortion as the levels increased [62]. This study highlights the correlation between stress levels and AD. In another study, participants were reading a book, stopped at various time intervals, and asked the time they thought had elapsed in between. The majority of participants struggled with this exercise, prompting the researchers to look at mental time travel, the ability to project ourselves back in time to a prior event. Mental time travel is very

similar to episodic memory. The study, measuring autonoetic consciousness (the ability to mentally project oneself back in subjective time to relive elements), results and the literature suggest that AD patients had a compromised ability to mentally relive past events. This offers the idea that time distortion is correlated to episodic memory impairment [63]. In respect to the anatomy and pathology, the hippocampus is heavily involved in both time and memory processing. It is also one of the main sites for accumulation of AD pathology. The atrophy of the hippocampus then might lead us to the connection between time distortions and memory compromise in AD [61].

Non-pharmacological interventions have had a great deal of progress in the recent years. These methods of intervention are proving to be useful in both treating and detecting AD.

Conclusion

The evidence and current research supporting olfactory, visual, and auditory symptoms as preclinical markers of Alzheimer's disease (AD) is very promising [2,20,22,23]. Olfactory symptoms are currently the most favorable to become prodromal biomarkers because of the strong clinical and anatomical relationship to AD [26]. Auditory symptoms are the most recent and, therefore, least studied out of the sensory symptoms, although it is still an encouraging indication [44]. Visual symptoms have a very strong anatomical connection to AD, and there are many rodent studies currently underway [23,64–70]. Regardless, further research is needed in these areas. Studying the difference in treatment effectiveness between non-pharmacological and pharmacological methods may help narrow down a focus point for treatment. While non-pharmacological methods are also proving to have some significance in diagnosing AD, research suggests that they have more potential in detecting the conversion of dementia and mild cognitive impairment into AD [49,58,59].

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