REVIEW ARTICLE

Neuroimaging associations with spatial navigation impairment in Alzheimer’s disease continuum: A narrative review

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Abstract

Identifying individuals with incipient Alzheimer’s disease (AD) are critical for early and targeted intervention before the dementia develops as AD progresses. Recently, emerging data have suggested that spatial navigation and neuroimaging could be utilized to identify individuals with prodromal AD. Compared to episodic memory, spatial navigation has fewer cultural and educational discrepancies and could serve as a promising marker for diagnosis and outcome measures in multicenter longitudinal studies with large cohorts. Furthermore, neuroimaging studies have contributed to our understanding of the structural and functional neural basis underlying spatial navigation and provided sensitive and non-invasive neuroimaging markers. The current review summarizes neuroimaging associations with spatial navigation impairment in the AD continuum, their potential pathophysiological mechanisms, and nonpharmacological interventions for spatial navigation impairments. We highlight the promising role of spatial navigation in the early identification of the preclinical and prodromal patients with potential risk of developing AD dementia. Multicenter large-scale longitudinal studies on patients across the AD continuum coupled with a standardized routine assessment of spatial navigation abilities in clinical settings are needed. This review may have implications for clinical practice and future research directions.

Keywords: Spatial navigation; Alzheimer’s disease; Neuroimaging; Functional connectivity
1. Introduction

Alzheimer's disease (AD) has long been a global public health concern\[1\]. Researchers have been diligently searching for sensitive biomarkers for the early diagnosis of AD and interventions to delay disease progression before substantial neuron loss occurs\[2\].

The previous findings have suggested that spatial navigation impairments, which are superior to episodic memory loss with low sensitivity and specificity, could potentially serve as promising markers for AD-related pathology, even in the preclinical stage of AD\[3,4\]. Spatial navigation refers to the process of determining or maintaining a trajectory from one place to another and is prone to decline with normal aging; notably, deficits are more pronounced during the progression of AD\[5,6\]. The navigation system in the brain overlaps substantially with regions that are affected first by AD pathology, and consequently, neurodegeneration in the navigation network results in an inability to create and use cognitive maps\[7,8\]. Furthermore, neuroimaging provides an opportunity for the early and non-invasive detection of structural and functional alterations in spatial navigation neural circuits in the brain, which not only provides sensitive neuroimaging markers but also contributes to the understanding of the neural basis underlying spatial navigation impairment in AD\[9\].

This paper reviews the neuroimaging advances regarding spatial navigation in four aspects: (i) Spatial navigation strategies and neural correlates in normal ageing, (ii) spatial navigation impairment and related neuroimaging alterations, (iii) spatial navigation impairment and related pathophysiological changes, and (iv) nonpharmacological interventions for cognitive and spatial navigation impairment.

The current review offers an overview of the neuroimaging advances regarding spatial navigation impairment in AD. We propose that assessment of spatial navigation impairment is crucial for the early identification of subclinical and preclinical AD with potential risk for AD dementia.

2. Spatial navigation function and neural correlates in normal aging

2.1. Spatial navigation: Definition and strategies

Spatial navigation is an essential ability that helps people determine or maintain routes by means of their own and environmental clues when moving between different locations\[10\]. While navigating the environment, people need to rely on different spatial representations, including two basic navigation strategies, that is, egocentric and allocentric navigation\[5,11\] (Figure 1).

Egocentric navigation strategies encode spatial information with its own location as the center to form an internal representation, which maintains the sense of direction when a person is moving. This sequence of body movements (e.g., remembering left, right, and left) facilitates the ability of route learning, which is primarily based on self-motion perception but can also exploit environmental cues by judging self-to-object relations\[12\]. The temporal sequence of environmental stimuli (e.g., “turn right at the shop”) contributes to landmark-based behavioral responses stored in spatial memory.

Allocentric navigation strategies depend on cognitive maps, which require people to memorize and analyze the geographical parts of the whole space from an exploratory perspective, including the location of spatial landmarks and the distance and direction between the starting point and the target location\[13,14\]. This process requires the recognition of object-to-object relations and is known as path integration\[15\]. Compared to egocentric spatial encoding, the representation of allocentric information is stable and does not change when people move. Consequently, allocentric spatial information may remain constant as long as the information is saved and retrieved properly.

Notably, strategic integration and translation are more common, and the available evidence may not support a strict functional dissociation of egocentric and allocentric reference frames. It should be emphasized that the two navigation strategies are usually inseparable because a
landmark can be identified by egocentric and allocentric reference frames together. Excellent navigators tend to integrate different spatial information to flexibly translate between egocentric and allocentric strategies to maximize navigation efficiency\[16\]. In addition, a study has shown that age, sex, and cultural background have potential influences on strategic preference during navigation\[17\].

2.2. Neural correlates of spatial navigation

The navigation process involves a wide range of brain navigation networks, including the prefrontal lobe, parietal lobe, medial temporal lobe (MTL), caudate nucleus, and thalamus\[3\]. The parietal lobe mainly includes the posterior cingulate cortex (PCC), precuneus, and retrosplenial cortex (RSC); the MTL mainly includes the hippocampus, entorhinal cortex, and parahippocampal cortex (PHC). The previous studies have shown that MTL structures play prominent roles in allocentric navigation, while the parietal lobe and the caudate nucleus mainly contribute to egocentric navigation\[18\]. In addition, the RSC and PCC are crucial for the flexible transformation between egocentric and allocentric reference frames\[19\-21\].

Spatial navigation requires effective neural representations that code location, head direction, speed, and boundaries. The discovery of place, head direction, grid, border, boundary-vector, and speed cells identify these representations\[22\-27\]. At the macroscopic level, functional magnetic resonance imaging (fMRI) has also revealed representations\[24\-26\]. The activity of some hippocampal neurons is closely related to their position in the space of animals or humans\[22\-29\]. These cells are called place cells, which fire in a specific location and contribute to the formation of cognitive maps of the environment. Thus, memories of the environment can be stored as a combination of specific activity in place cells. Later, grid cells were identified in the medial entorhinal cortex\[25\-38\].

These cells are regularly activated in a unique space to calculate vector relationships and distances between spatial locations. Grid cells and place cells work together to form a comprehensive positioning system that could function as the global positioning system (GPS) in the brain. Of note, head direction cells are related to the head direction in the horizontal plane. For instance, a specific neuron might fire whenever a person is facing the west, regardless of the location. In this way, head direction cells could function as a compass. In addition, border cells activate nearby a border\[20\], boundary-vector cells fire at specific distances from a border\[31\], and speed cells contribute to the firing of grid cells through path integration\[27\].

Furthermore, neuroelectrophysiological studies have revealed the phenomenon of phase precession during spatial navigation\[13\]. Phase precession refers to the phase relationship between action potentials and periodic rhythmic field potentials (theta oscillation) of some specific neuron species (e.g., place cells in the hippocampus and grid cells in the entorhinal cortex)\[15\]. Phase precession is a common and critical neuronal mechanism for the coordination of behavior and cognitive processes\[14\].

2.3. Spatial navigation and normal aging

Healthy older adults experience a decrease in navigation ability with aging, which is mainly manifested by impaired abilities of movement self-perception and path integration\[18\,35\-36\]. In both real and virtual navigation, older adults performed worse than younger adults as the task became more difficult; however, the basic cognitive abilities required for successful performance of object-location memory tasks seemed to be preserved in older adults\[37\,38\].

Aging has different effects on egocentric and allocentric strategies. Research shows that healthy older people tend to take a fixed route to avoid entering unfamiliar environments, indicating a preference for egocentric rather than allocentric strategies\[19\]. A similar conclusion was reached by the study conducted by Rodgers et al., which showed that older adults overwhelmingly preferred an egocentric strategy, while younger adults had equally distributed egocentric and allocentric preferences\[40\]. In addition, healthy older adults reached the target location with longer movement paths and spent longer time reaching the destination compared to the young participants in the human version of the Morris Water Maze (hMWM) test. These results demonstrate that aging could affect one’s preference for egocentric navigation strategies, which may be partly attributed to worse impairments in the allocentric reference frames. Furthermore, studies have identified age-related impairments in translation between navigation strategies, not only switching from an egocentric to an allocentric frame, but also switching from an allocentric to an egocentric frame\[41\-43\].

A study based on structural MRI data found that caudate nucleus volumes were reduced in older adults and were positively associated with route learning abilities; thus, a diminution in accurate knowledge of egocentric navigation may be a consequence of atrophy in the caudate nucleus during aging\[44\]. Alterations in the prefrontal and hippocampal functions, which result from atrophy in the prefrontal cortex, hippocampus, and related MTL regions that are crucial for allocentric representations, were also reported to contribute to navigation impairments and strategic preference in healthy elderly individuals during aging\[45\-48\]. Moreover, fMRI studies have shown that the activation of the posterior hippocampus, PHC, RSC, and some parts of the parietal lobe was significantly reduced in
healthy elderly persons compared with young adults during the navigation task, while the activation of the prefrontal cortex was increased\(^{[46,59]}\). In addition, white matter volume in the dorsolateral prefrontal cortex (DLPFC) was positively correlated with navigation performance in the hMWM\(^{[31]}\). Therefore, the structural and functional incompleteness of brain regions responsible for spatial navigation during aging may result in the gradual decline in egocentric and allocentric navigation abilities in healthy elderly individuals.

### 3. Spatial navigation impairment and related neuroimaging alterations in the AD continuum

#### 3.1. AD dementia

The previous studies conducted on AD dementia patients have revealed deficits in both egocentric and allocentric navigation reference frames, which may be attributed to the widespread neurodegeneration involving the medial temporal, frontal, and parietal lobes in the late AD stage\(^{[52-54]}\). These findings suggest that AD patients have impaired abilities to create and use cognitive maps of the environment and to compute body-centered information for self-orientation. In addition, AD patients experience difficulties in translating egocentric parietal and allocentric hippocampal representations, which mainly depend on the RSC and PCC\(^{[56]}\). The reduction in the ability to transition between allocentric and egocentric spatial navigation strategies was more evident than pure egocentric and allocentric navigation, which may suggest the priority to evaluate the allocentric to egocentric translation of spatial coding when a medical professional is making an AD diagnosis\(^{[59]}\). In addition, impaired spatial memory, the ability to encode and store information from egocentric and allocentric representations, has been observed in AD patients, which was not a product of generalized cognitive decline but instead may reflect spatial organization dysfunction\(^{[60]}\). AD could also affect spatial navigation strategies, as the preference for egocentric over allocentric strategies increased with AD severity\(^{[67]}\). The preference for an egocentric strategy may indicate compensatory mechanisms of recruiting extrahippocampal navigation strategies as an adaptation to hippocampal neurodegeneration in AD progression. In addition, spatial navigation tests presented better accuracy than conventional cognitive screening tests in distinguishing AD patients from normal controls (NCs)\(^{[58]}\). More recently, AD patients could be identified based on GPS data of their outdoor navigation patterns in the community, highlighting the potential utility of real-world everyday navigation behavior as an ecologically valid digital marker for AD\(^{[59]}\).

Before the recent development in neuroimaging alterations regarding spatial navigation in AD patients, cumulative structural MRI, task-based fMRI, and resting-state fMRI (rs-fMRI) studies conducted in NCs have suggested that multiple brain regions work collaboratively to guide navigation behaviors\(^{[60-70]}\). Pertinently, neuroimaging deterioration is more pronounced in neurodegenerative diseases such as AD. Voxel-based morphometry analyses based on structural MRI data in AD patients have revealed significant correlations between scene construction impairment and atrophy in the posterior parietal and lateral temporal cortex\(^{[71]}\). Another structural MRI study revealed that basal forebrain atrophy contributed to allocentric navigation impairment independent of hippocampal atrophy in AD patients\(^{[48]}\). As the basal forebrain is a key structure of cholinergic neurons projecting to the hippocampus, amygdala, and cerebral cortex, this study suggested that allocentric disorientation may be related to the loss of cholinergic neurons in AD patients, which corresponds to histopathological findings\(^{[72]}\). Multimodal MRI analyses of grey matter density, glucose metabolism, and white matter axial diffusion have revealed significant converging correlations of the right RSC and PCC with test performance for virtual route learning in a cohort of patients with mild AD\(^{[73]}\). Collectively, AD dementia patients suffer from spatial navigation impairment, which may result from the widespread neurodegeneration in brain regions associated with spatial navigation.

#### 3.2. Mild cognitive impairment (MCI)

MCI is believed to be a predementia stage, and it has been recognized that MCI patients with the amnestic type are more vulnerable to progression to AD dementia than those with the nonamnestic type\(^{[74]}\). Similar to that found in the AD dementia stage, amnestic MCI (aMCI) patients showed spatial navigation dysfunction compared to age-matched NCs\(^{[13,75-78]}\). In addition, patients in the aMCI multiple-domain group performed worse in all subtests of allocentric, egocentric, allocentric, and delayed allocentric navigation, showing high similarity with those of early AD; the aMCI single-domain group was significantly impaired in the subtests of allocentric and delayed allocentric navigation, and patients in the nonamnestic MCI group performed similarly to NCs\(^{[79,80]}\). Spatial navigation tests could further divide aMCI patients into two subgroups: Memory impairment of hippocampal type (hippocampal aMCI) and isolated retrieval impairment (nonhippocampal aMCI); individuals in the former group showed worse performance on spatial navigation, accompanied by an increased risk of AD, compared to the latter group\(^{[81,82]}\). In a longitudinal study with a 2-year follow-up, allocentric spatial memory performance assessed by the Four Mountains Test
could predict conversion from MCI to AD dementia with an accuracy of 0.93, similar to the accuracy of 0.92 by the Tau/amyloid β (Aβ) ratio in cerebrospinal fluid (CSF)

The study provided initial support for the hypothesis that allocentric spatial memory was predictive of progression from MCI to AD dementia. The aforementioned results suggested that spatial navigation impairment was specific for identifying MCI patients with prodromal AD from those with other etiologies and for monitoring disease progression.

Several structural MRI studies of spatial navigation in MCI patients have been conducted. Reduced volumes in the medial part of the entorhinal cortex were related to self-reported spatial navigation performance in MCI patients. The aMCI patients had worse egocentric memory performance measured by a virtual maze, with smaller volumes of the right-sided precuneus indicating worse egocentric memory. Significant associations between allocentric navigation errors and right hippocampal volumes in both real-space and virtual versions were observed in a cohort consisting of aMCI, mild and moderate AD patients, and NCs, controlling for demographic variables and total brain and left hippocampal volumes. The participants in the aMCI group exhibited poorer path integration accuracy than those in the NC group, with hippocampal volume and thickness of the entorhinal cortex and inferior parietal cortex accounting for 37%, 36%, and 45% of the differences, respectively. The result was supported by another study showing that the right hippocampal volume explained 26% of the variance in allocentric navigation in participants in the aMCI group. According to a study that investigated the contribution of hippocampal subregions to spatial navigation, there are significant associations between volumes of the right hippocampal tail and navigation skills in aMCI patients, while the CA2/3 region appears to be more relevant to spatial navigation in NCs.

In addition, the associations among genetic risk factors, spatial navigation, and structural MRI measures have been investigated in MCI patients. Apolipoprotein E (APOE) ε4 is the principal known risk gene that could increase the risk of sporadic AD. Both results of real-space and computer-based hMWM have demonstrated poorer performance on both egocentric and allocentric navigation in participants in the aMCI ε4+ group compared to participants in the aMCI ε4– group, with those in the former group performing similarly to those in the mild AD group, while those in the latter group resemble the NC group, and aMCI patients with APOE ε4 homozygotes were outperformed by those with heterozygotes. The right hippocampal volume could account for the differences in allocentric and delayed allocentric subtests but not in the egocentric subtest, supporting the crucial role of the right hippocampus in allocentric navigation. The brain-derived neurotrophic factor (BDNF) Val66Met polymorphism was believed to be relevant to an increased risk of AD. The combination of APOE ε4 and BDNF Met polymorphisms has been found to be associated with more pronounced egocentric navigation impairments and reduced volumes in the hippocampus and entorhinal cortex in aMCI patients. The very long poly-T variant at rs10524523 of the TOMM40 gene, which encodes the translocase of the outer mitochondrial membrane pore subunit, was reported to be related to allocentric spatial navigation impairments and reduced cortical thickness of the entorhinal cortex and PCC among aMCI individuals with APOE ε3/ε3 homozygotes. Therefore, spatial navigation is associated with multiple genetic polymorphisms, which may exert an effect through alterations in the MTL and parietal lobe structures of MCI patients.

Navigation task-based fMRI studies have revealed reduced activity in aMCI patients in brain regions that are important for navigation, including the hippocampus, caudate, RSC, and precuneus, as well as increased activity in the prefrontal regions, which may serve as compensatory mechanisms. In rs-fMRI analyses, reduced intrinsic activity measured by the amplitude of low-frequency fluctuation (ALFF), fractional ALFF, and regional homogeneity (ReHo) in the subcortical regions was observed in MCI patients. Interestingly, the MCI versus NC group difference can modulate the activity-behavior relationship. More specifically, the correlation between ReHo and allocentric navigation errors differed significantly between participants in the MCI and NC groups, indicating a stage specificity of the brain activity-behavior relationship. Graph theory analysis of the white matter network has revealed significant correlations between network topological properties and navigation errors, with the lower clustering coefficient in the right inferior parietal gyrus predicting larger allocentric navigation errors. The study provided new insight into the neural basis underpinning navigation impairment in MCI patients from the perspective of disruption of white matter network topology. Cumulatively, patients with MCI have deficits in spatial navigation, which varies in subtypes and disease severity and is related to neurodegeneration in the navigation network mainly involving the MTL and parietal lobes.

### 3.3. Preclinical AD

Contrary to the strong evidence supporting spatial navigation impairment in patients with AD dementia and MCI patients, its role in the preclinical AD stage has never been reported.
been extensively investigated. Therefore, spatial navigation has been considered an overlooked cognitive marker for preclinical AD[9]. Nevertheless, spatial navigation impairments are increasingly shown to be present in individuals with incipient AD, which may be related to the high susceptibility of MTL to AD pathology in the preclinical stage[9].

Individuals with subjective cognitive decline (SCD), a self-perceived worsening of cognitive function without objectively detected deficits, have been widely recognized at a higher risk of incipient AD than normal elderly individuals without cognitive complaints[96,97]. Indeed, abundant evidence has suggested significant associations between amyloid pathology, genetic risk of AD, entorhinal cortical thinning, and SCD[98,99]. Spatial navigation complaints are a frequent symptom not only in patients with AD and MCI, but also in individuals with SCD. In particular, 68% of SCD subjects complained about their spatial navigation, which was significantly higher than the 33% in the NC group[99]. The hidden goal task, which has been suggested to show excellent ecological validity and is strongly correlated with real-world navigation difficulty, was applied to evaluate spatial navigation abilities in SCD individuals[79]. In accordance with that observed in AD dementia and MCI patients, both egocentric and allocentric navigation strategies were found to be impaired in individuals with SCD[100,101]. Spatial navigation performance worsened with increasing severity of cognitive impairment in SCD, MCI, and AD dementia patients[102]. The fact that these weak levels of navigation impairment could not be detected objectively using standard neuropsychological evaluations of episodic memory, language, or executive functions indicates that spatial navigation is a specific cognitive domain that is impaired in the earliest stages of AD. The reduced volumes of the basal forebrain, especially in the Ch4p subfield, may serve as a structural basis for allocentric disorientation in SCD individuals independent of hippocampal atrophy[103]. Since the Ch4p subfield of the basal forebrain is a key structure for cholinergic inputs to the cerebral cortex, the results highlighted the potential role of loss of cholinergic neurons in allocentric disorientation. In the rs-fMRI analyses, alterations in functional connectivity between brain regions associated with spatial navigation were observed in SCD individuals. In particular, two spatial navigation brain networks, egonetwork and allo-network, each with 10 selected spherical regions of interest, were defined[100]. Compared with the NCs, participants in the SCD group showed decreased functional connectivity between the right RSC and right prefrontal cortex (PFC) in the egonetwork and decreased functional connectivity between the right RSC and right hippocampus in the allo-network. More interestingly, a logistic regression model based on spatial navigation and functional connectivity measures revealed a big area under the curve (AUC) of 0.880 in differentiating SCD individuals from NCs, indicating the promising role of spatial navigation and related neuroimaging measures in the preclinical detection of incipient AD patients.

In preclinical AD subjects with genetic risk factors for AD, investigations have shown that APOE ε4 noncarriers outperformed ε4 carriers in spatial navigation tests; this finding may be of use to characterize the preclinical phase of cognitive impairment[103,104]. A recent study observed significantly lower functional connectivity between the right entorhinal cortex and PCC in subjects of APOE ε3ε4 group than in those of ε3ε3 group, and the reduced connectivity was correlated with navigation discrepancies[105]. Therefore, the early neurodegenerative processes in APOE ε4 carriers may significantly damage the neural networks that are presumed to be crucial for spatial navigation. Furthermore, the classification accuracy of the path integration test, coupled with connectivity strength between the right entorhinal cortex and PCC, achieved an accuracy of 0.85 to distinguish the APOE ε4 carriers. APOE ε4 could also moderate the indirect effects of basal forebrain volumes on allocentric navigation performance through the MTL and PFC in older adults without dementia[106]. In contrast, APOE ε2 is known to be protective against AD and is associated with a reduced risk and delayed onset of AD[107]. Of note, Konishi et al. found that APOE ε2 carriers tend to use allocentric spatial strategies and have greater hippocampal volumes than APOE ε3 homozygous individuals and APOE ε4 carriers[108]. These findings suggest that the protective effect of the APOE ε2 allele may be expressed in part through increased use of allocentric navigation strategies and greater hippocampal volumes.

Spatial navigation impairments have also been observed in preclinical AD elderly individuals with abnormal AD biomarkers of Aβ compared to those with normal Aβ levels, suggesting that navigation may be particularly sensitive for identifying the earliest pathologic changes in AD[109]. Furthermore, longitudinal studies have provided strong scientific evidence that spatial navigation is specific enough to predict conversion from normal cognition to MCI or dementia[110,111]. More specifically, during an average follow-up period of 4–5 years, baseline performance on cognitive mapping and route learning, which depends on allocentric and egocentric representation, respectively, were predictors of clinical progression of AD[111]. The AUCs of cognitive mapping, route learning, and episodic memory for discriminating progressors from nonprogressors were 0.894, 0.794, and 0.735, respectively. In particular, cognitive mapping tended to perform better...
than episodic memory in identifying progressors. It has been emphasized by the researchers that future work should incorporate neuroimaging and biomarker data to assess whether baseline spatial navigation was related to longitudinal alterations in brain structure, function, and AD biomarkers.

In summary, although spatial navigation was less investigated in the preclinical AD stage, emerging data have suggested that SCD subjects, risk gene carriers, and elderly individuals with abnormal AD biomarkers experience difficulties in spatial navigation compared to the navigation ability of NCs. Decreased functional connectivity measured by rs-fMRI may indicate disruption of navigation networks in subjects with incipient AD.

4. Spatial navigation impairment and related pathophysiological changes

4.1. Spatial navigation impairment and AD pathology of Aβ and Tau

It has been widely recognized that the typical pathological changes in AD are extracellular Aβ deposition and the formation of neurofibrillary tangles caused by Tau hyperphosphorylation. The entorhinal cortex is one of the brain regions first involved in phosphorylated Tau (pTau) [7,112]. Multimodal information from cortices converges in the hippocampus primarily through the entorhinal cortex, with the medial part encoding and transferring spatial information [113]. However, the relationships between spatial navigation impairments and pathological biomarkers of AD in humans have not been clearly illustrated, as most studies have been conducted on animals.

Several studies have been conducted to explore the relationships between Aβ deposits and spatial navigation. A study of APP/PS1 mice found that Y-maze performance worsened before the formation of Aβ deposits; however, despite the increased Aβ load in the hippocampus and cortex, these mice did not show impairment in spatial navigation at 6 or 9 months. This suggested that Aβ deposition alone was not sufficient to cause strong spatial memory impairment in mice of this mixed background ancestry and age [114]. In contrast, a study by Puoliväli et al. showed that total hippocampal Aβ levels in transgenic mice were associated with spatial navigation impairments [113]. The APP/PS1 mice were impaired in water maze acquisition and retention only at the age of 11–12 months. Moreover, the levels of total Aβ1-42 in the hippocampus were negatively correlated with the retention score in mice in the impaired older age group. This was the first study in which significant correlations between age-dependent impairment of memory retention in a traditional water maze and total Aβ in the hippocampus in APP/PS1 mice were observed. The discrepant results of the associations between Aβ deposits and spatial navigation in animal studies may be partly due to the various extent of extrahippocampal pathology and different mechanisms that underlie neuronal dysfunction and spatial navigation impairment at different stages of Aβ pathology [115]. After healthy older adults completed an on-road driving test, the Santa Barbara Sense of Direction scale, and the Driving Habits Questionnaire, Allison et al. found that CSF Aβ42, but not Tau or pTau, was associated with self-reported navigation abilities, which further mediated the relationships between CSF Aβ42 and driving range. These findings indicated that brain Aβ deposition could contribute to patients’ reduced ability to perceive the environment to navigate, which consequently results in older adults with AD pathology having a limited drive range [116].

Interestingly, other studies have focused on the relationships between Tau hyperphosphorylation and spatial navigation impairments. Using a transgenic mouse model, Fu et al. demonstrated that the accumulation of Tau pathology in the entorhinal cortex was associated with excitatory neuron loss, grid-cell dysfunction, and deficits in spatial learning and memory [117]. This was the first study that showed a relationship between Tau pathology and grid cell dysfunction in vivo, which may further provide a link between Tau pathology and spatial navigation impairments in patients with early AD. Notably, the pattern in pTau staining across the parietal-hippocampus network is a powerful predictor of spatial learning and memory performance. Stimmell et al. demonstrated that female mice at 6 months of age had a Tau pathological pattern identified by independent component analysis in the parietal-hippocampus network, with a higher density of pTau-positive cells predicting poorer spatial learning and memory performance in female 3xTg-AD mice [118]. This indicated that spatial disorientation may be attributed to the early accumulation of pTau in the parietal-hippocampus network in AD. Stancu et al. crossed APP/PS1 mice with 5 early-onset familial AD mutation (5xFAD) and TauP301S (PS19) transgenic mice and found that Tau pathology was invariably and robustly aggravated in hippocampal and cortical brain regions [119]. Most importantly, the mice displayed more severe deficits in the spatial navigation task than the controls.

From the above studies, we summarize that spatial navigation impairment may be caused by the deposition of Tau and/or Aβ in the entorhinal cortex, hippocampus, and parietal cortex. More clinical studies are urgently needed to determine the exact relationships between spatial navigation impairments and pathological biomarkers of AD in humans.

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4.2. Spatial navigation impairment and reduced grid cell-like representations

Grid cells have unique hexagonal grid-like firing patterns and play crucial roles in the process of spatial navigation. Since the discovery in the rat brain by Hafting et al. in 2005, the existence of grid cells has been successively confirmed in bats, monkeys, and other animals\(^{25,108}\). Grid cells can receive electrical signals from a variety of neuronal cells involved in spatial navigation and are the primary source of information input to hippocampal place cells\(^{121}\). Tau pathology of AD occurs first in the entorhinal cortex, the medial part of which contains grid cells. Therefore, research that focuses on grid cells in the human brain is of great value for a better understanding of the neural basis underlying spatial navigation impairment in AD.

The process of reading self-motion information and integrating the information of each spatial location to obtain the path to the target position is called path integration, which is an automatic and continuous update process during navigation. Grid cells can form stable grid graphs, and their path integration function does not depend on environmental landmarks but is instead based on ontology motion cues\(^{122}\). Various other cells that are involved in neural circuits for spatial navigation also have typical firing patterns. Border cells fire significantly when animals approach geometric boundaries\(^{123}\); moreover, the firing rate of speed cells increases proportionally with the movement speed of the animal to provide instantaneous speed information\(^{27}\). In addition, the firing of head direction cells is related to the direction of the animal relative to landmarks in the environment\(^{124}\). These cells transmit distance and orientation information to grid cells, which are integrated into the grid map to provide spatial information, including the position in the environment and distances from starting and ending points, and are continuously updating location information based on action cues\(^{14}\).

Fu et al. found that the reduction in grid-cell activation in aged mice was accompanied by the occurrence of spatial memory deficits, and the authors inferred that pathological changes originating from the entorhinal cortex may cause grid-cell dysfunction and lead to spatial navigation impairment in AD patients\(^{117}\). The signals of grid cells have been successfully detected by fMRI, which has greatly facilitated studies of grid cells in humans\(^{234}\). Kunz et al. found that young adults with APOE ε4 exhibited reduced grid-cell activation stability and reduced ability to navigate in virtual scenes\(^{125}\). These results support the hypothesis that impaired grid-cell function is related to spatial disorientation. Bates et al. believed that spatial navigation obstacles were mainly caused by the inaccurate position representation in the navigation system formed by grid cells and place cells\(^{126}\). Carriers of the AD risk gene have a more significant decline in the ability to navigate in the center of the virtual environment than at the border, which may be explained by the reason that navigation in the central area lacks environmental cues that rely more on the path integration function of grid cells\(^{127}\). Pertinently, the increased activation of the hippocampus in risk gene carriers may serve as a compensatory mechanism for spatial memory impairment.

Phase precession has been widely observed in hippocampal place cells and entorhinal grid cells in navigating rodents\(^{32,129}\). Focal dorsal hippocampal Nav1.1 knockout altered the temporal coding properties of place cells, such as theta phase precession, which subsequently degraded the spatial accuracy of rats\(^{129}\). A recent study also provided evidence for spatial phase precession in the human hippocampus and entorhinal cortex during virtual navigation, which exhibited features similar to those observed in rodents\(^{134}\). Thus, we speculate that degradation in the phase precession of grid cells might also contribute to spatial dysfunction in AD patients, which deserves to be further validated.

Emerging evidence has suggested the crucial role of grid cells in spatial navigation, and the application of fMRI in grid cell research has provided a novel entry point and opened a new avenue for the study of neural mechanisms underpinning spatial navigation impairments in AD patients. However, due to the complexity of the relevant data collection and analysis processes, many issues, such as how grid cells encode three-dimensional (3D) spaces and large-scale complex environments in preclinical and prodromal AD patients, remain to be further explored.

5. Nonpharmacological interventions for cognitive and spatial navigation impairment

5.1. Virtual reality (VR)-based training program

Due to the high social burden of AD coupled with the lack of effective treatment, new approaches targeting cognitive and spatial navigation impairment are being sought. VR is defined as a technology that digitally provides a changeable 3D environment in which people can interact with different sensory inputs. VR can be immersive or nonimmersive, and the former allows for a sense of presence in the environment\(^{130}\). VR has been widely recognized as a promising technique that can improve treatment outcomes in patients with neurocognitive disorders, such as AD. Oliveira et al. observed an improvement in overall cognitive function in patients with AD after VR-based cognitive stimulation, with an effect size corresponding to...
a large effect on global cognition[134]. The study suggested that VR-based cognitive stimulation is effective for neurocognitive stimulation in older adults with dementia, contributing to the maintenance of cognitive function in patients with AD. A case study of healthy older adults and MCI patients with unilateral vestibular hypofunction suggested that participants who played a VR racing game in the treated condition (including those with MCI) showed greater improvements in vestibular function than those in the untreated condition[132]. Another study showed that the cognitive function and balancing ability of MCI patients showed a significant increase after exposure to the VR program, which involved 20 sessions for 4 weeks, 30 min/experiment[133]. The results indicated that the VR program is also an effective intervention for elderly individuals with MCI.

More importantly, the VR technique also offers the opportunity to create complex individualized and natural simulated environments in which spatial navigation impairment could be treated precisely. Kober et al. found that different aspects of spatial abilities in neurologic patients with focal brain lesions were improved after VR training in comparison to their spatial performance before VR training[134]. This study showed that guided passive navigation training in VR could enhance general spatial cognition in neurological patients with spatial disorientation as well as in NCs and can thus be used in the rehabilitation of spatial navigation impairments associated with spatial disorientation. Moreover, VR training has been thought of as an advanced embodied tool for the treatment of spatial memory impairment in patients with AD. Serino et al. recruited 20 AD patients who were randomly assigned to either the VR-based training group or the control group, and observed a significant improvement in long-term spatial memory after VR-based training[135]. Another study demonstrated that after experiencing a VR environment, the skill of a man at the onset of AD in navigating while driving improved noticeably in a cognitive treatment program based on spatial navigation[136]. Interestingly, another study showed that the spatial navigation of older adults was enhanced after VR-based physical exercise with two-dimensional exergames[137].

In general, VR training could serve as a promising approach to treat cognitive and spatial navigation impairments in AD. A big advantage of VR is that it enables the development of customized cognitive exercises in meaningful environments, which is especially important since cognitive training can be particularly demanding for AD patients[130]. More specifically, in a virtual environment, cognitive training can be implemented based on specific rehabilitation mechanisms. Despite the preliminary studies mentioned above, further research that adopts methodologies from clinical trials and incorporates behavioral and neurophysiological data are required to provide clear evidence on the effectiveness of VR-based training for cognitive and spatial navigation impairments in AD.

5.2. Neuromodulation

Due to the unsatisfactory effect of drug therapy for AD, neuromodulation technology has gradually attracted the attention of neurologists and physical therapists. Neuromodulation is defined as an intervention intended to alter nervous system function using energy fields, such as electricity, magnetism, or both, with the goal of improving psychiatric symptoms or related conditions[138]. Neuromodulation techniques include deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), transcranial alternating current stimulation, and transcranial focused ultrasound (tFUS). DBS has been widely used to treat Parkinson’s disease and essential tremors, while its application in AD is still under research. In study of DBS targeting the fornix to improve cognition in AD patients, Deeb et al. found that a total of 20 patients (48%) spontaneously reported having vivid experiences of ostensible previous events in their lives after DBS[139]. The high-frequency repetitive TMS (rTMS) protocol at the left DLPFC has been approved for treatment-resistant depression therapy in the United States, and its effectiveness in AD has also been investigated. Of note, after treating aMCI and AD patients with neuro-navigated rTMS targeting the left angular gyrus for 4 weeks, Yang et al. observed significant improvement in episodic memory of aMCI patients and general cognition of both groups[140]. tDCS is the most common choice for transcranial electrical stimulation for treating AD. Another recent study revealed that tDCS to the left DLPFC can enhance verbal episodic memory performance by modulating the memory reconsolidation process in subjects with SCD[141]. In addition, a study suggested that without opening the blood-brain barrier, the regional cerebral metabolic rate of glucose in the superior frontal gyrus, middle cingulate gyrus, and fusiform gyrus increased, and the memory, executive, and global cognitive function improved in patients with AD who received tFUS[142].

A few studies have assessed the effectiveness of neuromodulation on the neural circuits of spatial navigation. Spatial navigation is a complex process that associates with various navigational skills, such as spatial memory. Fyock et al. found that tDCS could modulate spatial memory in cognitively intact adults[143]. The study by Krishnamurthy et al. revealed that tDCS enhanced functional connectivity between the medial superior parietal lobule seeds and
several other areas that are involved in spatial processing and navigation. A recent study showed that network segregation of MCI patients increased to levels similar to that in cognitively intact older adults following active tDCS; this finding suggests that tDCS over the right parietal cortex may normalize the segregation/integration balance of association networks during spatial navigation in MCI patients, highlighting its potential to restore brain activity in patients with AD\cite{145}. The study by Suthana et al. demonstrated that DBS targeting the entorhinal cortex in patients with pharmaco-resistant epilepsy could enhance memory of spatial information during learning\cite{146}.

Collectively, neuromodulation technology showed convincing outcomes in cognition and spatial navigation enhancement in AD treatment. Non-invasive brain stimulations could be the next AD treatment. However, the lack of a standardized protocol is the current challenge in nonpharmacological interventions. Future studies with large cohorts are warranted to determine the exact effects of neuromodulation in cognition and spatial navigation and to standardize the parameters, including target sites, frequency, and duration of each session.

6. Conclusions

In summary, spatial navigation impairment is commonly observed in patients across the AD continuum and is associated with different patterns of structural and functional alterations in the neural networks of navigation revealed by neuroimaging, which could be attributed to the pathophysiological changes in AD progression. In this paper, we highlight the great potential of spatial navigation by providing novel insights into the early detection of AD and reviewing a more general and uniform approach toward future prevention and intervention strategies for AD. More specifically, subjects in memory clinics who complained of difficulties in everyday navigation in previously familiar routes, accompanied by impaired navigational function, as demonstrated in the spatial navigation test, should be considered at a higher risk of incipient AD. Early identification and intervention of incipient AD patients might provide a promising opportunity for a favorable prognosis before the occurrence of substantial neuronal death. Furthermore, spatial navigation presents a novel approach for measuring the efficacy of AD therapy across research sites regardless of cultural and educational discrepancies\cite{147}. Thus, it is of great value to incorporate spatial navigation tests into standard neuropsychological assessments in clinical settings\cite{146,149}.

The development of a standardized and validated testing system that is suitable for routine assessments of spatial navigation abilities in clinical settings for various patient populations is an urgent need\cite{150}. Despite the promising utility of spatial navigation, the current lack of multicenter large-scale longitudinal studies that could corroborate the role of spatial navigation in the progression of the whole AD continuum is an obstacle that requires further investigation. In future studies, multimodal MRI in larger cohorts is needed to further elucidate the mechanisms by which AD pathology influences spatial navigation performance. Additionally, novel spatial navigation training (e.g., immersive VR training) combined with advanced technologies for early spatial rehabilitation interventions, which could serve as effective safeguarding strategies to prevent AD patients from getting lost, remains to be explored\cite{151}.

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Conflict of interest

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