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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).

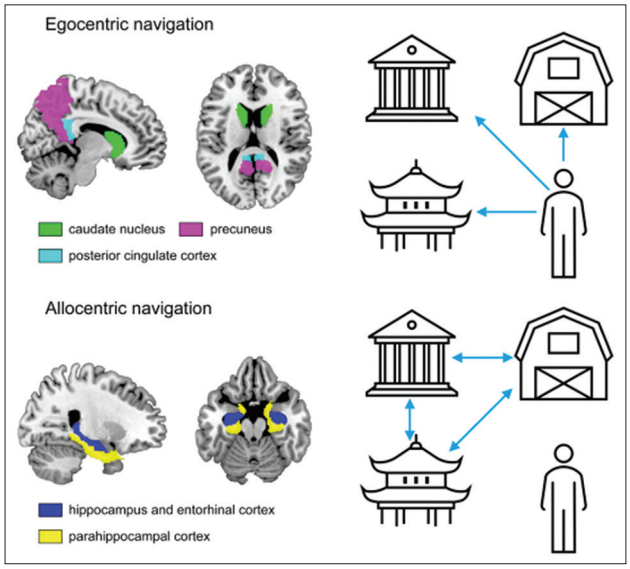

Figure 1. Egocentric and allocentric spatial coding. Egocentric navigation relies on parietal lobes and encodes spatial information with self-to-object relations, while allocentric navigation relies on MTLs and encodes spatial information with object-to-object relations.

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[24,28]. 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[25,30]. 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[26], 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[32]. 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)[33]. Phase precession is a common and critical neuronal mechanism for the coordination of behavior and cognitive processes[34].

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[39]. 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[49,50]. In addition, white matter volume in the dorsolateral prefrontal cortex (DLPFC) was positively correlated with navigation performance in the hMWM[51]. 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[16]. 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[55]. 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[56]. AD could also affect spatial navigation strategies, as the preference for egocentric over allocentric strategies increased with AD severity[57]. 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[46]. 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 allo-egocentric, 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)[83]. 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[10,84].

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[85]. 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[86]. 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[13]. 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[87]. 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[88]. 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[89].

In addition, the associations among genetic risk factors, spatial navigation, and structural MRI measures have been investigated in MCI patients[90-92]. Apolipoprotein E (*APOE*) ε4 is the principal known risk gene that could increase the risk of sporadic AD[93]. 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[90,92]. 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[13]. 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[94]. The very long poly-T variant at rs10524523 of the *TOMMO40* 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[91]. 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[95]. 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[75]. Interestingly, the MCI versus NC group difference can modulate the activity-behavior relationship. More specifically, the correlation slopes 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[76]. 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 extensively investigated. Therefore, spatial navigation has been considered an overlooked cognitive marker for preclinical AD[3]. 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[7].

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[9,98]. 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[101]. 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, ego-network 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 ego-network 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[115]. 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 $A\beta_{1\text{-}42}$ 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 $A\beta_{42}$, but not Tau or $pTau_{181}$, was associated with self-reported navigation abilities, which further mediated the relationships between CSF $A\beta_{42}$ 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.

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[25,120]. 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[18].

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[24]. 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[32,128]. Focal dorsal hippocampal Nav1.1 knockdown 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[34]. 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[131]. 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 hypoactivity 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[135]. 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[144]. 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[145]. The study by Suthana *et al.* demonstrated that DBS targeting the entorhinal cortex in patients with pharmacoresistant epilepsy could enhance memory of spatial information during learning[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[147]. Thus, it is of great value to incorporate spatial navigation tests into standard neuropsychological assessments in clinical settings[148,149].

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[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[151].

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Conflict of interest

The authors report no conflicts of interest.

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Further disclosure

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References

1. Dubois B, Villain N, Frisoni GB, *et al.*, 2021, Clinical diagnosis of Alzheimer's disease: Recommendations of the international working group. *Lancet Neurol*, 20(6): 484–496.

   https://doi.org/10.1016/s1474-4422(21)00066-1

2. Jack CR Jr., Bennett DA, Blennow K, *et al.*, 2018, NIA-AA research framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement*, 14(4): 535–562.

   https://doi.org/10.1016/j.jalz.2018.02.018

3. Coughlan G, Laczo J, Hort J, *et al.*, 2018, Spatial navigation deficits overlooked cognitive marker for preclinical Alzheimer disease? *Nat Rev Neurol*, 14(8): 496–506.

   https://doi.org/10.1038/s41582-018-0031-x

4. Gellersen HM, Coughlan G, Hornberger M, *et al.*, 2021, Memory precision of object-location binding is unimpaired in APOE ε4-carriers with spatial navigation deficits. *Brain Commun*, 3(2): fcab087.

   https://doi.org/10.1093/braincomms/fcab087

5. Tuena C, Mancuso V, Stramba-Badiale C, *et al.*, 2021, Egocentric and allocentric spatial memory in mild cognitive impairment with real-world and virtual navigation tasks: A systematic review. *J Alzheimers Dis*, 79(1): 95–116.

   https://doi.org/10.3233/jad-201017

6. Lithfous S, Dufour A, Després O, 2013, Spatial navigation in normal aging and the prodromal stage of Alzheimers disease: Insights from imaging and behavioral studies. *Ageing Res Rev*, 12(1): 201–213.

   https://doi.org/10.1016/j.arr.2012.04.007

7. Braak H, Del Tredici K, 2015, The preclinical phase of the pathological process underlying sporadic Alzheimer's disease. *Brain*, 138(Pt 10): 2814–2833.

   https://doi.org/10.1093/brain/awv236

8. Howett D, Castegnaro A, Krzywicka K, *et al.*, 2019, Differentiation of mild cognitive impairment using an entorhinal cortex-based test of virtual reality navigation. *Brain*, 142: 1751–1766.

   https://doi.org/10.1093/brain/awz116

9. Wang X, Huang W, Su L, *et al.*, 2020, Neuroimaging advances regarding subjective cognitive decline in preclinical Alzheimer's disease. *Mol Neurodegene*, 15(1): 55.

   https://doi.org/10.1186/s13024-020-00395-3

10. Gazova I, Vlcek K, Laczó J, *et al.*, 2012, Spatial navigation-a unique window into physiological and pathological aging. *Front Aging Neurosci*, 4: 16.

    https://doi.org/10.3389/fnagi.2012.00016

11. Boccia M, Nemmi F, Guariglia C, 2014, Neuropsychology of environmental navigation in humans: Review and meta-analysis of FMRI studies in healthy participants. *Neuropsychol Rev*, 24(2): 236–251.

    https://doi.org/10.1007/s11065-014-9247-8

12. Muffato V, Meneghetti C, 2020, Learning a path from real navigation: The advantage of initial view, cardinal North and visuo-spatial ability. *Brain Sci*, 10(4): 204.

    https://doi.org/10.3390/brainsci10040204

13. Nedelska Z, Andel R, Laczo J, *et al.*, 2012, Spatial navigation impairment is proportional to right hippocampal volume. *Proc Natl Acad Sci U S A*, 109(7): 2590–2594.

    https://doi.org/10.1073/pnas.1121588109

14. O'Keefe J, Nadel L, 1978, The Hippocampus as a Cognitive Map. Oxford: Clarendon Press Chicago.

15. Loomis JM, Klatzky RL, Golledge RG, *et al.*, 1993, Nonvisual navigation by blind and sighted: Assessment of path integration ability. *J Exp Psychol Gen*, 122(1): 73–91.

    https://doi.org/10.1037//0096-3445.122.1.73

16. Serino S, Riva G, 2013, Getting lost in Alzheimer's disease: A break in the mental frame syncing. *Med Hypotheses*, 80(4): 416–421.

    https://doi.org/10.1016/j.mehy.2012.12.031

17. Coutrot A, Silva R, Manley E, *et al.*, 2018, Global determinants of navigation ability. *Curr Biol*, 28(17): 2861–2866.e2864.

    https://doi.org/10.1016/j.cub.2018.06.009

18. Lester AW, Moffat SD, Wiener JM, *et al.*, 2017, The aging navigational system. *Neuron*, 95(5): 1019–1035.

    https://doi.org/10.1016/j.neuron.2017.06.037

19. Vann SD, Aggleton JP, Maguire EA, 2009, What does the retrosplenial cortex do? *Nat Rev Neurosci*, 10(11): 792–802.

    https://doi.org/10.1038/nrn2733

20. Vass LK, Epstein RA, 2013, Abstract representations of location and facing direction in the human brain. *J Neurosci*, 33(14): 6133–6142.

    https://doi.org/10.1523/JNEUROSCI.3873-12.2013

21. Clark BJ, Simmons CM, Berkowitz LE, *et al.*, 2018, The retrosplenial-parietal network and reference frame coordination for spatial navigation. *Behav Neurosci*, 132(5): 416–429.

    https://doi.org/10.1037/bne0000260

22. O'Keefe J, Dostrovsky J, 1971, The hippocampus as a spatial

map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Res*, 34: 171–175.

https://doi.org/10.1016/0006-8993(71)90358-1

23. Taube JS, Muller RU, Ranck JB Jr., 1990, Head-direction cells recorded from the postsubiculum in freely moving rats. I. Description and quantitative analysis. *J Neurosci*, 10(2): 420–435.

https://doi.org/10.1523/JNEUROSCI.10-02-00420.1990

24. Doeller CF, Barry C, Burgess N, 2010, Evidence for grid cells in a human memory network. *Nature*, 463: 657–661.

https://doi.org/10.1038/nature08704

25. Hafting T, Fyhn M, Molden S, *et al.*, 2005, Microstructure of a spatial map in the entorhinal cortex. *Nature*, 436(7052): 801–806.

https://doi.org/10.1038/nature03721

26. Solstad T, Boccara CN, Kropff E, *et al.*, 2008, Representation of geometric borders in the entorhinal cortex. *Science*, 322(5909): 1865–1868.

https://doi.org/10.1126/science.1166466

27. Kropff E, Carmichael JE, Moser MB, *et al.*, 2015, Speed cells in the medial entorhinal cortex. *Nature*, 523(7561): 419–424.

https://doi.org/10.1038/nature14622

28. Kunz L, Schroder TN, Lee H, *et al.*, 2015, Reduced grid-cell-like representations in adults at genetic risk for Alzheimer's disease. *Science*, 350(6259): 430–433.

https://doi.org/10.1126/science.aac8128

29. Ekstrom AD, Kahana MJ, Caplan JB, *et al.*, 2003, Cellular networks underlying human spatial navigation. *Nature*, 425(6954): 184–188.

https://doi.org/10.1038/nature01964

30. Diehl GW, Hon OJ, Leutgeb S, *et al.*, 2017, Grid and nongrid cells in medial entorhinal cortex represent spatial location and environmental features with complementary coding schemes. *Neuron*, 94(1): 83–92 e86.

https://doi.org/10.1016/j.neuron.2017.03.004

31. Lever C, Burton S, Jeewajee A, *et al.*, 2009, Boundary vector cells in the subiculum of the hippocampal formation. *J Neurosci*, 29(31): 9771–9777.

https://doi.org/10.1523/JNEUROSCI.1319-09.2009

32. Okeefe J, Recce ML, 1993, Phase Relationship between hippocampal place units and the eeg theta-rhythm. *Hippocampus*, 3(3): 317–330.

https://doi.org/10.1002/hipo.450030307

33. Buzsaki G, 2002, Theta oscillations in the hippocampus. *Neuron*, 33(3): 325–340.

https://doi.org/10.1016/s0896-6273(02)00586-x

34. Qasim SE, Fried I, Jacobs J, 2021, Phase precession in the human hippocampus and entorhinal corex. *Cell*, 184(12): 3242–3255.e3210.

https://doi.org/10.1016/j.cell.2021.04.017

35. Harris MA, Wolbers T, 2012, Ageing effects on path integration and landmark navigation. *Hippocampus*, 22(8): 1770–1780.

https://doi.org/10.1002/hipo.22011

36. Mahmood O, Adamo D, Briceno E, *et al.*, 2009, Age differences in visual path integration. *Behav Brain Res*, 205(1): 88–95.

https://doi.org/10.1016/j.bbr.2009.08.001

37. Korman M, Weiss PL, Hochhauser M, *et al.*, 2019, Effect of age on spatial memory performance in real museum vs. computer simulation. *BMC Geriatr*, 19(1): 165.

https://doi.org/10.1186/s12877-019-1167-2

38. Head D, Isom M, 2010, Age effects on wayfinding and route learning skills. *Behav Brain Res*, 209(1): 49–58.

https://doi.org/10.1016/j.bbr.2010.01.012

39. Bryden KJ, Charlton JL, Oxley JA, *et al.*, 2013, Self-reported wayfinding ability of older drivers. *Accid Anal Prev*, 59: 277–282.

https://doi.org/10.1016/j.aap.2013.06.017

40. Rodgers MK, Sindone JA 3rd, Moffat SD, 2012, Effects of age on navigation strategy. *Neurobiol Aging*, 33(1): e215–e222.

https://doi.org/10.1016/j.neurobiolaging.2010.07.021

41. Harris MA, Wiener JM, Wolbers T, 2012, Aging specifically impairs switching to an allocentric navigational strategy. *Front Aging Neurosci*, 4: 29.

https://doi.org/10.3389/fnagi.2012.00029

42. Harris MA, Wolbers T, 2014, How age-related strategy switching deficits affect wayfinding in complex environments. *Neurobiol Aging*, 35(5): 1095–1102.

https://doi.org/10.1016/j.neurobiolaging.2013.10.086

43. Carelli L, Rusconi ML, Scarabelli C, *et al.*, 2011, The transfer from survey (map-like) to route representations into virtual reality mazes: Effect of age and cerebral lesion. *J Neuroeng Rehabil*, 8: 6.

https://doi.org/10.1186/1743-0003-8-6

44. Moffat SD, Kennedy KM, Rodrigue KM, *et al.*, 2007, Extrahippocampal contributions to age differences in human spatial navigation. *Cereb Cortex*, 17(6): 1274–1282.

https://doi.org/10.1093/cercor/bhl036

45. Driscoll I, Davatzikos C, An Y, *et al.*, 2009, Longitudinal pattern of regional brain volume change differentiates normal aging from MCI. *Neurology*, 72(22): 1906–1913.

https://doi.org/10.1212/WNL.0b013e3181a82634

46. Kerbler GM, Nedelska Z, Fripp J, *et al.*, 2015, Basal forebrain atrophy contributes to allocentric navigation impairment in Alzheimer's disease patients. *Front Aging Neurosci*, 7: 185.

https://doi.org/10.3389/fnagi.2015.00185

47. Lovden M, Schaefer S, Noack H, *et al.*, 2012, Spatial navigation training protects the hippocampus against age-related changes during early and late adulthood. *Neurobiol Aging*, 33(3): 620 e629–620 e622.

https://doi.org/10.1016/j.neurobiolaging.2011.02.013

48. Colombo D, Serino S, Tuena C, *et al.*, 2017, Egocentric and allocentric spatial reference frames in aging: A systematic review. *Neurosci Biobehav Rev*, 80: 605–621.

https://doi.org/10.1016/j.neubiorev.2017.07.012

49. Konishi K, Etchamendy N, Roy S, *et al.*, 2013, Decreased functional magnetic resonance imaging activity in the hippocampus in favor of the caudate nucleus in older adults tested in a virtual navigation task. *Hippocampus*, 23(11): 1005–1014.

https://doi.org/10.1002/hipo.22181

50. Moffat SD, Elkins W, Resnick SM, 2006, Age differences in the neural systems supporting human allocentric spatial navigation. *Neurobiol Aging*, 27(7): 965–972.

https://doi.org/10.1016/j.neurobiolaging.2005.05.011

51. Antonova E, Parslow D, Brammer M, *et al.*, 2009, Age-related neural activity during allocentric spatial memory. *Memory (Hove, England)*, 17(2): 125–143.

https://doi.org/10.1080/09658210802077348

52. Jheng SS, Pai MC, 2009, Cognitive map in patients with mild Alzheimer's disease: A computer-generated arena study. *Behav Brain Res*, 200(1): 42–47.

https://doi.org/10.1016/j.bbr.2008.12.029

53. Zanco M, Plácido J, Marinho V, *et al.*, 2018, Spatial navigation in the elderly with Alzheimer's disease: A cross-sectional study. *J Alzheimers Dis*, 66(4): 1683–1694.

https://doi.org/10.3233/jad-180819

54. Pai MC, Jan SS, 2020, Have i been here? Sense of location in people with Alzheimer's disease. *Front Aging Neurosci*, 12: 582525.

https://doi.org/10.3389/fnagi.2020.582525

55. Morganti F, Stefanini S, Riva G, 2013, From allo-to egocentric spatial ability in early Alzheimer's disease: A study with virtual reality spatial tasks. *Cogn Neurosci*, 4(3–4): 171–180.

https://doi.org/10.1080/17588928.2013.854762

56. Serino S, Morganti F, Di Stefano F, *et al.*, 2015, Detecting early egocentric and allocentric impairments deficits in Alzheimer's disease: An experimental study with virtual reality. *Front Aging Neurosci*, 7: 88.

https://doi.org/10.3389/fnagi.2015.00088

57. Parizkova M, Lerch O, Moffat SD, *et al.*, 2018, The effect of Alzheimer's disease on spatial navigation strategies. *Neurobiol Aging*, 64: 107–115.

https://doi.org/10.1016/j.neurobiolaging.2017.12.019

58. Plácido J, Ferreira JV, Araújo J, *et al.*, 2021, Beyond the mini-mental state examination: The use of physical and spatial navigation tests to help to screen for mild cognitive impairment and Alzheimer's disease. *J Alzheimers Dis*, 81(3): 1243–1252.

https://doi.org/10.3233/jad-210106

59. Ghosh A, Puthusseryppady V, Chan D, *et al.*, 2022, Machine learning detects altered spatial navigation features in outdoor behaviour of Alzheimer's disease patients. *Sci Rep*, 12(1): 3160.

https://doi.org/10.1038/s41598-022-06899-w

60. Hao X, Huang Y, Li X, *et al.*, 2016, Structural and functional neural correlates of spatial navigation: A combined voxel-based morphometry and functional connectivity study. *Brain Behav*, 6(12): e00572.

https://doi.org/10.1002/brb3.572

61. Chadwick MJ, Jolly AE, Amos DP, *et al.*, 2015, A goal direction signal in the human entorhinal/subicular region. *Curr Biol*, 25(1): 87–92.

https://doi.org/10.1016/j.cub.2014.11.001

62. Hirshhorn M, Grady C, Rosenbaum RS, *et al.*, 2012, The hippocampus is involved in mental navigation for a recently learned, but not a highly familiar environment: A longitudinal fMRI study. *Hippocampus*, 22(4): 842–852.

https://doi.org/10.1002/hipo.20944

63. Viard A, Doeller CF, Hartley T, *et al.*, 2011, Anterior hippocampus and goal-directed spatial decision making. *J Neurosci*, 31(12): 4613–4621.

https://doi.org/10.1523/jneurosci.4640-10.2011

64. Xu J, Evensmoen HR, Lehn H, *et al.*, 2010, Persistent posterior and transient anterior medial temporal lobe activity during navigation. *Neuroimage*, 52(4): 1654–1666.

https://doi.org/10.1016/j.neuroimage.2010.05.074

65. Ramanoël S, York E, Le Petit M, *et al.*, 2019, Age-related differences in functional and structural connectivity in the spatial navigation brain network. *Front Neural Circuits*, 13: 69.

https://doi.org/10.3389/fncir.2019.00069

66. Boccia M, Sulpizio V, Nemmi F, *et al.*, 2017, Direct and indirect parieto-medial temporal pathways for spatial navigation in humans: Evidence from resting-state functional connectivity. *Brain Struct Funct*, 222(4): 1945–1957.

https://doi.org/10.1007/s00429-016-1318-6

67. Hao X, Wang X, Song Y, *et al.*, 2018, Dual roles of the hippocampus and intraparietal sulcus in network integration and segregation support scene recognition. *Brain Struct Funct*, 223(3): 1473–1485.

https://doi.org/10.1007/s00429-017-1564-2

68. Sulpizio V, Boccia M, Guariglia C, *et al.*, 2016, Functional connectivity between posterior hippocampus and retrosplenial complex predicts individual differences in navigational ability. *Hippocampus*, 26(7): 841–847.

https://doi.org/10.1002/hipo.22592

69. Izen SC, Chrastil ER, Stern CE, 2018, Resting state connectivity between medial temporal lobe regions and intrinsic cortical networks predicts performance in a path integration task. *Front Hum Neurosci*, 12: 415.

https://doi.org/10.3389/fnhum.2018.00415

70. Zajac L, Burte H, Taylor HA, *et al.*, 2019, Self-reported navigation ability is associated with optic flow-sensitive regions' functional connectivity patterns during visual path integration. *Brain Behav*, 9(4): e01236.

https://doi.org/10.1002/brb3.1236

71. Irish M, Halena S, Kamminga J, *et al.*, 2015, Scene construction impairments in Alzheimer's disease a unique role for the posterior cingulate cortex. *Cortex*, 73: 10–23.

https://doi.org/10.1016/j.cortex.2015.08.004

72. Mesulam MM, Mufson EJ, Levey AI, *et al.*, 1983, Cholinergic innervation of cortex by the basal forebrain: Cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey. *J Comp Neurol*, 214(2): 170–197.

https://doi.org/10.1002/cne.902140206

73. Pengas G, Williams GB, Acosta-Cabronero J, *et al.*, 2012, The relationship of topographical memory performance to regional neurodegeneration in Alzheimer's disease. *Front Aging Neurosci*, 4: 17.

https://doi.org/10.3389/fnagi.2012.00017

74. Csukly G, Sirály E, Fodor Z, *et al.*, 2016, The differentiation of amnestic type MCI from the non-amnestic types by structural MRI. *Front Aging Neurosci*, 8: 52–52.

https://doi.org/10.3389/fnagi.2016.00052

75. Qing Z, Li W, Nedelska Z, *et al.*, 2017, Spatial navigation impairment is associated with alterations in subcortical intrinsic activity in mild cognitive impairment: A resting-state fMRI Study. *Behav Neurol*, 2017: 6364314.

https://doi.org/10.1155/2017/6364314

76. Li W, Zhao H, Qing Z, *et al.*, 2021, Disrupted network topology contributed to spatial navigation impairment in patients with mild cognitive impairment. *Front Aging Neurosci*, 13: 630677.

https://doi.org/10.3389/fnagi.2021.630677

77. Keynejad RC, Marková H, Šiffelová K, *et al.*, 2018, Spatial navigation deficits in amnestic mild cognitive impairment with neuropsychiatric comorbidity. *Neuropsychol Deve Cogn B Aging, Neuropsychol Cogn*, 25(2): 277–289.

https://doi.org/10.1080/13825585.2017.1290212

78. Boccia M, Di Vita A, Diana S, *et al.*, 2019, Is losing one's way a sign of cognitive decay? Topographical memory deficit as an early marker of pathological aging. *J Alzheimers Dis*, 68(2): 679–693.

https://doi.org/10.3233/jad-180890

79. Hort J, Laczó J, Vyhnálek M, *et al.*, 2007, Spatial navigation deficit in amnestic mild cognitive impairment. *Proc Natl Acad Sci U S A*, 104(10): 4042–4047.

https://doi.org/10.1073/pnas.0611314104

80. Rusconi ML, Suardi A, Zanetti M, *et al.*, 2015, Spatial navigation in elderly healthy subjects, amnestic and non amnestic MCI patients. *J Neurol Sci*, 359(1-2): 430–437.

https://doi.org/10.1016/j.jns.2015.10.010

81. Laczó J, Vlcek K, Vyhnálek M, *et al.*, 2009, Spatial navigation testing discriminates two types of amnestic mild cognitive impairment. *Behav Brain Res*, 202(2): 252–259.

https://doi.org/10.1016/j.bbr.2009.03.041

82. Laczó J, Andel R, Vyhnalek M, *et al.*, 2012, From morris water maze to computer tests in the prediction of Alzheimer's disease. *Neurodegener Dis*, 10(1-4): 153–157.

https://doi.org/10.1159/000333121

83. Wood RA, Moodley KK, Lever C, *et al.*, 2016, Allocentric spatial memory testing predicts conversion from mild cognitive impairment to dementia: An initial proof-of-concept study. *Front Neurol*, 7: 215.

https://doi.org/10.3389/fneur.2016.00215

84. Vlček K, Laczó J, 2014, Neural correlates of spatial navigation changes in mild cognitive impairment and Alzheimer's disease. *Front Behav Neurosci*, 8: 89.

https://doi.org/10.3389/fnbeh.2014.00089

85. Hallab A, Lange C, Apostolova I, *et al.*, 2020, Impairment of everyday spatial navigation abilities in mild cognitive impairment is weakly associated with reduced grey matter volume in the medial part of the entorhinal cortex. *J Alzheimers Dis*, 78(3): 1149–1159.

https://doi.org/10.3233/jad-200520

86. Weniger G, Ruhleder M, Lange C, *et al.*, 2011, Egocentric and allocentric memory as assessed by virtual reality in individuals with amnestic mild cognitive impairment. *Neuropsychologia*, 49(3): 518–527.

https://doi.org/10.1016/j.neuropsychologia.2010.12.031

87. Mokrisova I, Laczo J, Andel R, *et al.*, 2016, Real-space path integration is impaired in Alzheimer's disease and mild cognitive impairment. *Behav Brain Res*, 307: 150–158.

https://doi.org/10.1016/j.bbr.2016.03.052

88. Laczó J, Andel R, Nedelska Z, *et al.*, 2017, Exploring the contribution of spatial navigation to cognitive functioning in older adults. *Neurobiol Aging*, 51: 67–70.

https://doi.org/10.1016/j.neurobiolaging.2016.12.003

89. Peter J, Sandkamp R, Minkova L, *et al.*, 2018, Real-world navigation in amnestic mild cognitive impairment: The relation to visuospatial memory and volume of hippocampal subregions. *Neuropsychologia*, 109: 86–94.

https://doi.org/10.1016/j.neuropsychologia.2017.12.014

90. Laczó J, Andel R, Vyhnalek M, *et al.*, 2014, APOE and spatial navigation in amnestic MCI: Results from a computer-based test. *Neuropsychology*, 28(5): 676–684.

https://doi.org/10.1037/neu0000072

91. Laczó J, Andel R, Vyhnalek M, *et al.*, 2015, The effect of TOMM40 on spatial navigation in amnestic mild cognitive impairment. *Neurobiol Aging*, 36(6): 2024–2033.

https://doi.org/10.1016/j.neurobiolaging.2015.03.004

92. Laczó J, Andel R, Vlček K, *et al.*, 2011, Spatial navigation and APOE in amnestic mild cognitive impairment. *Neurodegener Dis*, 8(4): 169–177.

https://doi.org/10.1159/000321581

93. Xu WL, Caracciolo B, Wang HX, *et al.*, 2013, Accelerated progression from mild cognitive impairment to dementia among APOE epsilon4epsilon4 carriers. *J Alzheimers Dis*, 33(2): 507–515.

https://doi.org/10.3233/JAD-2012-121369

94. Laczó J, Cechova K, Parizkova M, *et al.*, 2020, The combined effect of APOE and BDNF Val66Met polymorphisms on spatial navigation in older adults. *J Alzheimers Dis*, 78(4): 1473–1492.

https://doi.org/10.3233/jad-200615

95. Migo EM, O'Daly O, Mitterschiffthaler M, *et al.*, 2016, Investigating virtual reality navigation in amnestic mild cognitive impairment using fMRI. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*, 23(2): 196–217.

https://doi.org/10.1080/13825585.2015.1073218

96. Jessen F, Amariglio RE, van Boxtel M, *et al.*, 2014, A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers Dement*, 10(6): 844–852.

https://doi.org/10.1016/j.jalz.2014.01.001

97. Jessen F, Amariglio RE, Buckley RF, *et al.*, 2020, The characterisation of subjective cognitive decline. *Lancet Neurol*, 19(3): 271–278.

https://doi.org/10.1016/s1474-4422(19)30368-0

98. Hu X, Teunissen CE, Spottke A, *et al.*, 2019, Smaller medial temporal lobe volumes in individuals with subjective cognitive decline and biomarker evidence of Alzheimer's disease-data from three memory clinic studies. *Alzheimers Dement*, 15(2): 185–193.

https://doi.org/10.1016/j.jalz.2018.09.002

99. Cerman J, Andel R, Laczo J, *et al.*, 2018, Subjective spatial navigation complaints a frequent symptom reported by patients with subjective cognitive decline, mild cognitive impairment and Alzheimers disease. *Curr Alzheimer Res*, 15(3): 219–228.

https://doi.org/10.2174/1567205014666171120145349

100. Chen Q, Qing Z, Jin J, *et al.*, 2021, Ego and allo-network disconnection underlying spatial disorientation in subjective cognitive decline. Cortex, 137: 35–48.

https://doi.org/10.1016/j.cortex.2020.12.022

101. Chen Q, Wu S, Li X, *et al.*, 2021, Basal forebrain atrophy is associated with allocentric navigation deficits in subjective cognitive decline. *Front Aging Neurosci*, 13: 596025.

https://doi.org/10.3389/fnagi.2021.596025

102. Tangen GG, Engedal K, Bergland A, *et al.*, 2015, Spatial navigation measured by the floor maze test in patients with subjective cognitive impairment, mild cognitive impairment, and mild Alzheimer's disease. *Int Psychogeriatr*, 27(8): 1401–1409.

https://doi.org/10.1017/s1041610215000022

103. Berteau-Pavy F, Park B, Raber J, 2007, Effects of sex and APOE epsilon4 on object recognition and spatial navigation in the elderly. *Neuroscience*, 147(1): 6–17.

https://doi.org/10.1016/j.neuroscience.2007.03.005

104. Coughlan G, Coutrot A, Khondoker M, *et al.*, 2019, Toward personalized cognitive diagnostics of at-genetic-risk Alzheimer's disease. *Proc Natl Acad Sci U S A*, 116(19): 9285–9292.

https://doi.org/10.1073/pnas.1901600116

105. Coughlan G, Zhukovsky P, Puthusseryppady V, *et al.*, 2020, Functional connectivity between the entorhinal and posterior cingulate cortices underpins navigation discrepancies in at-risk Alzheimer's disease. *Neurobiol Aging*, 90: 110–118.

https://doi.org/10.1016/j.neurobiolaging.2020.02.007

106. Lerch O, Laczó M, Vyhnálek M, *et al.*, 2022, APOEε4 allele moderates the association between basal forebrain nuclei volumes and allocentric navigation in older adults without dementia. *J Alzheimers Dis*, 86(1): 155–171.

https://doi.org/10.3233/jad-215034

107. Serrano-Pozo A, Qian J, Monsell SE, *et al.*, 2015, APOEepsilon2 is associated with milder clinical and pathological Alzheimer disease. *Ann Neurol*, 77(6): 917–929.

https://doi.org/10.1002/ana.24369

108. Konishi K, Bhat V, Banner H, *et al.*, 2016, APOE2 Is associated with spatial navigational strategies and increased gray matter in the hippocampus. *Front Hum Neurosci*, 10: 349.

https://doi.org/10.3389/fnhum.2016.00349

109. Allison SL, Fagan AM, Morris JC, *et al.*, 2016, Spatial navigation in preclinical Alzheimer's disease. *J Alzheimers Dis*, 52(1): 77–90.

https://doi.org/10.3233/jad-150855

110. Verghese J, Lipton R, Ayers E, 2017, Spatial navigation and risk of cognitive impairment: A prospective cohort study. *Alzheimers Dement*, 13(9): 985–992.

https://doi.org/10.1016/j.jalz.2017.01.023

111. Levine TF, Allison SL, Stojanovic M, *et al.*, 2020, Spatial navigation ability predicts progression of dementia symptomatology. *Alzheimers Dement*, 16(3): 491–500.

https://doi.org/10.1002/alz.12031

112. Hu W, Zhang X, Tung YC, *et al.*, 2016, Hyperphosphorylation determines both the spread and the morphology of tau pathology. *Alzheimers Dement*, 12(10): 1066–1077.

https://doi.org/10.1016/j.jalz.2016.01.014

113. Li Y, Xu J, Liu Y, *et al.*, 2017, A distinct entorhinal cortex to hippocampal CA1 direct circuit for olfactory associative learning. *Nat Neurosc*, 20(4): 559–570.

https://doi.org/10.1038/nn.4517

114. Leigh A. Holcomb MN, Jantzen P, *et al.*, 1999, Behavioral changes in transgenic mice expressing both amyloid precursor protein and presenilin-1 mutations: Lack of association with amyloid deposits. *Behav Genet*, 29(3): 177–185.

https://doi.org/10.1023/a:1021691918517

115. Puoliväli J, Wang J, Heikkinen T, *et al.*, 2002, Hippocampal A beta 42 levels correlate with spatial memory deficit in APP and PS1 double transgenic mice. *Neurobiol Dis*, 9(3): 339–347.

https://doi.org/10.1006/nbdi.2002.0481

116. Allison S, Babulal GM, Stout SH, *et al.*, 2018, Alzheimer disease biomarkers and driving in clinically normal older adults role of spatial navigation abilities. *Alzheimer Dis Assoc Disord*, 32: 101–106.

https://doi.org/10.1097/WAD.0000000000000257

117. Fu H, Rodriguez GA, Herman M, *et al.*, 2017, Tau pathology induces excitatory neuron loss, grid cell dysfunction, and spatial memory deficits reminiscent of early Alzheimer's Disease. *Neuron*, 93(3): 533–541.

https://doi.org/10.1016/j.neuron.2016.12.023

118. Stimmell AC, Xu Z, Moseley SC, *et al.*, 2021, Tau pathology profile across a parietal-hippocampal brain network is associated with spatial reorientation learning and memory performance in the 3xTg-AD mouse. *Front Aging*, 2: 655015.

https://doi.org/10.3389/fragi.2021.655015

119. Stancu IC, Ris L, Vasconcelos B, *et al.*, 2014, Tauopathy contributes to synaptic and cognitive deficits in a murine model for Alzheimer's disease. *FASEB J*, 28(6): 2620–2631.

https://doi.org/10.1096/fj.13-246702

120. Killian NJ, Jutras MJ, Buffalo EA, 2012, A map of visual space in the primate entorhinal cortex. *Nature*, 491(7426): 761–764.

https://doi.org/10.1038/nature11587

121. Rowland DC, Roudi Y, Moser MB, *et al.*, 2016, Ten years of grid cells. *Annu Rev Neurosci*, 39: 19–40.

https://doi.org/10.1146/annurev-neuro-070815-013824

122. McNaughton BL, Battaglia FP, Jensen O, *et al.*, 2006, Path integration and the neural basis of the "cognitive map". *Nat Rev Neurosci*, 7(8): 663–678.

https://doi.org/10.1038/nrn1932

123. Van Wijngaarden JB, Babl SS, Ito HT, 2020, Entorhinal-retrosplenial circuits for allocentric-egocentric transformation of boundary coding. *Life*, 9: e59816.

https://doi.org/10.7554/eLife.59816

124. Sargolini F, Fyhn M, Hafting T, *et al.*, 2006, Conjunctive representation of position, direction, and velocity in entorhinal cortex. *Science*, 312(5774): 758–762.

https://doi.org/10.1126/science.1125572

125. Kunz L, Lee H, Montag C, *et al.*, 2015, Reduced grid-cell-like representations in adults at genetic risk forAlzheimer's disease. *Science*, 350(6259): 430–433.

https://doi.org/10.1126/science.aac8128

126. Bates SL, Wolbers T, 2014, How cognitive aging affects multisensory integration of navigational cues. *Neurobiol Aging*, 35(12): 2761–2769.

https://doi.org/10.1016/j.neurobiolaging.2014.04.003

127. Muessig L, Hauser J, Wills TJ, *et al.*, 2015, A developmental switch in place cell accuracy coincides with grid cell maturation. *Neuron*, 86(5): 1167–1173.

https://doi.org/10.1016/j.neuron.2015.05.011

128. Reifenstein ET, Kempter R, Schreiber S, *et al.*, 2012, Grid cells in rat entorhinal cortex encode physical space with independent firing fields and phase precession at the single-trial level. *Proc Natl Acad Sci U S A*, 109(16): 6301–6306.

https://doi.org/10.1073/pnas.1109599109

129. Sakkaki S, Barrière S, Bender AC, *et al.*, 2020, Focal dorsal hippocampal nav1.1 knock down alters place cell temporal coordination and spatial behavior. *Cereb Cortex*, 30(9): 5049–5066.

https://doi.org/10.1093/cercor/bhaa101

130. Moreno A, Wall KJ, Thangavelu K, *et al.*, 2019, A systematic review of the use of virtual reality and its effects on cognition in individuals with neurocognitive disorders. *Alzheimers Dement (NY)*, 5: 834–850.

https://doi.org/10.1016/j.trci.2019.09.016

131. Oliveira J, Gamito P, Souto T, *et al.*, 2021, Virtual reality-based cognitive stimulation on people with mild to

moderate dementia due to Alzheimer's disease: A pilot randomized controlled trial. *Int J Environ Res Public Health*, 18(10): 5290.

https://doi.org/10.3390/ijerph18105290

132. Micarelli A, Viziano A, Micarelli B, *et al.*, 2019, Vestibular rehabilitation in older adults with and without mild cognitive impairment: Effects of virtual reality using a head-mounted display. *Arch Gerontol Geriatr*, 83: 246–256.

https://doi.org/10.1016/j.archger.2019.05.008

133. Hwang J, Lee S, 2017, The effect of virtual reality program on the cognitive function and balance of the people with mild cognitive impairment. *J Phys Ther Sci*, 29(8):1283–1286.

https://doi.org/10.1589/jpts.29.1283

134. Kober GW, Hofer D, Kreuzig W, *et al.*, 2013, Virtual reality in neurologic rehabilitation of spatial disorientation. *J NeuroEng Rehabil*, 10(1): 17.

135. Serino S, Pedroli E, Tuena C, *et al.*, 2017, A novel virtual reality-based training protocol for the enhancement of the "Mental frame syncing" in individuals with Alzheimer's disease: A development-of-concept trial. *Front Aging Neurosci*, 9: 240.

https://doi.org/10.3389/fnagi.2017.00240

136. White PJ, Moussavi Z, 2016, Neurocognitive treatment for a patient with Alzheimer's disease using a virtual reality navigational environment. *J Exp Neurosci*, 10: 129–135.

https://doi.org/10.4137/JEN.S40827

137. Oliveira LM, Evangelista ES, Alves MR, *et al.*, 2020, 2D virtual reality-based exercise improves spatial navigation in institutionalized non-robust older persons: A preliminary data report of a single-blind, randomized, and controlled study. *Front Neurol*, 11: 609988.

https://doi.org/10.3389/fneur.2020.609988

138. Aaronson ST, Philip NS, 2018, Neuromodulation. *Psychiatr Clin North Am*, 41(3): 13–16.

https://doi.org/10.1016/j.psc.2018.06.001

139. Deeb W, Salvato B, Almeida L, *et al.*, 2019, Fornix-region deep brain stimulation induced memory flashbacks in Alzheimer's disease. *N Engl J Med*, 381(8): 783–785.

https://doi.org/10.1056/NEJMc1905240

140. Yang Z, Sheng X, Qin R, *et al.*, 2022, Cognitive improvement via left angular gyrus-navigated repetitive transcranial magnetic stimulation inducing the neuroplasticity of thalamic system in amnesic mild cognitive impairment patients. *J Alzheimers Dis*, 86(2): 537–551.

https://doi.org/10.3233/JAD-215390

141. Manenti R, Sandrini M, Gobbi E, *et al.*, 2017, Strengthening of existing episodic memories through non-invasive stimulation of prefrontal cortex in older adults with subjective memory complaints. *Front Aging Neurosci*, 9: 401.

https://doi.org/10.3389/fnagi.2017.00401

142. Jeong H, Im JJ, Park JS, *et al.*, 2021, A pilot clinical study of low-intensity transcranial focused ultrasound in Alzheimer's disease. *Ultrasonography*, 40(4): 512–519.

https://doi.org/10.14366/usg.20138

143. Fyock C, England HB, Hampstead BM, *et al.*, 2015, Transcranial direct current stimulation modulates spatial memory in cognitively intact adults. *Behav Brain Res Int J*. 283:191–195.

https://doi.org/10.1016/j.bbr.2015.01.044

144. Krishnamurthy V, Gopinath K, Brown GS, *et al.*, 2015, Resting-state fMRI reveals enhanced functional connectivity in spatial navigation networks after transcranial direct current stimulation. *Neurosci Lett*, 604: 80–85.

https://doi.org/10.1016/j.neulet.2015.07.042

145. Iordan AD, Ryan S, Tyszkowski T, *et al.*, 2022, High-definition transcranial direct current stimulation enhances network segregation during spatial navigation in mild cognitive impairment. *Cereb Cortex*, 00: 1–12.

https://doi.org/10.1093/cercor/bhac010

146. Suthana N, Haneef Z, Stern J, *et al.*, 2012, Memory enhancement and deep-brain stimulation of the entorhinal area. *N Engl J Med*, 366(6): 502–510.

https://doi.org/10.1056/NEJMoa1107212

147. Laczó J, Markova H, Lobellova V, *et al.*, 2017, Scopolamine disrupts place navigation in rats and humans: A translational validation of the hidden goal task in the morris water maze and a real maze for humans. *Psychopharmacology*, 234(4): 535–547.

https://doi.org/10.1007/s00213-016-4488-2

148. Poos JM, van der Ham IJM, Leeuwis AE, *et al.*, 2021, Short digital spatial memory test detects impairment in Alzheimer's disease and mild cognitive impairment. *Brain Sci*, 11(10): 1350.

https://doi.org/10.3390/brainsci11101350

149. Laczó M, Wiener JM, Kalinova J, *et al.*, 2021, Spatial navigation and visuospatial strategies in typical and atypical aging. *Brain Sci*, 11(11): 1421.

https://doi.org/10.3390/brainsci11111421

150. Da Costa RQ, Pompeu JE, Moretto E, *et al.*, 2021, Two immersive virtual reality tasks for the assessment of spatial orientation in older adults with and without cognitive impairment: Concurrent validity, group comparison, and accuracy results. *J Int Neuropsychol Soc*, 28(5): 460–472.

https://doi.org/10.1017/s1355617721000655

151. Puthusseryppady V, Emrich-Mills L, Lowry E, *et al.*, 2020, Spatial disorientation in Alzheimer's disease: The missing path from virtual reality to real world. *Front Aging Neurosci*, 12: 550514.

https://doi.org/10.3389/fnagi.2020.550514