Spatial navigation deficits – overlooked cognitive marker for preclinical Alzheimer disease?

Gillian Coughlan[1], Jan Laczó[2,3], Jakub Hort[2,3], Anne-Marie Minihane[1] and Michael Hornberger[1,4] *****

[1]*Norwich Medical School, University of East Anglia, Norwich, UK*

[2]*Memory Clinic, Department of Neurology, Charles University, 2nd Faculty of Medicine and Motol University Hospital, Prague, Czech Republic*

[3]*International Clinical Research Center, St. Anne's University Hospital Brno, Brno, Czech Republic*

[4]*Dementia and Complexity in Later Life, NHS Norfolk and Suffolk Foundation Trust, UK*

*****email m.hornberger@uea.ac.uk

Abstract

Detection of incipient Alzheimer disease (AD) pathophysiology is critical to identify preclinical individuals and target potentially disease-modifying therapies towards them. Current neuroimaging and biomarker research is strongly focused in this direction, with the aim of establishing AD fingerprints to identify individuals at high risk of developing this disease. By contrast, cognitive fingerprints for incipient AD are virtually nonexistent as diagnostics and outcomes measures are still focused on episodic memory deficits as the gold standard for AD, despite their low sensitivity and specificity for identifying at-risk individuals. This Review highlights a novel feature of cognitive evaluation for incipient AD by focusing on spatial navigation and orientation deficits, which are increasingly shown to be present in at-risk individuals. Importantly, the navigation system in the brain overlaps substantially with the regions affected by AD in both animal models and humans. Notably, spatial navigation has fewer verbal, cultural and educational biases than current cognitive tests, and could enable a more uniform, global approach towards cognitive fingerprints of AD and better cognitive treatment outcome measures in future multicentre trials. The current Review appraises the available evidence for spatial navigation and/or orientation deficits in preclinical, prodromal and confirmed AD, as well as identifying research gaps and future research priorities.

[H1] Introduction

Alzheimer disease (AD) is the most common form of dementia, with increasing worldwide prevalence[1,2]. Accurate early diagnosis is crucial as it provides the chance to intervene at an early stage before substantial neuronal death occurs. This approach is particularly relevant in an era in which research is focused on the efficacy of upcoming pharmacological[3–5] and non-pharmacological prevention and treatment strategies[6], which might allow intervention when neuronal loss is at its minimum to stop or delay the progress of the pathophysiology.

Current 'gold standard' clinical diagnostic and outcome measures for AD are strongly focused on episodic memory[7]. Episodic memory loss is one of the most common features of AD and is considered the most sensitive and specific cognitive marker of underlying AD pathophysiology[8]. However, it is becoming increasingly clear that decline in memory is so common in healthy ageing that early detection of incipient AD pathophysiology is difficult[9], which in turn often delays diagnosis as clinicians schedule follow-up appointments in an attempt to confirm a progressive decline in memory performance. The situation is further complicated by the fact that other brain diseases,[10–12] such as frontotemporal dementia (FTD), can manifest with substantial memory deficits, despite having a different underlying pathology[13].

Given this limited specificity of episodic memory deficits for incipient underlying AD pathophysiology, a new approach is required. Emerging data reveals that spatial navigation and orientation deficits have higher specificity than episodic memory in distinguishing AD from other dementias, particularly FTD[14,15]. More specifically, in animal studies AD pathophysiology has been shown to affect navigation-specific brain areas before episodic memory areas are affected[16]. Further, healthy older adults do not experience topographical disorientation in well-known environments, which contrasts starkly with the spatial disorientation seen in early AD[1718]. Finally, analysis of spatial performance allows better translation of animal intervention studies to human clinical trials as conceptualization of episodic memory is difficult to apply to nonhuman species[19]. Despite these highly promising findings, the utility of such spatial navigation deficits for diagnosis in preclinical

individuals with a high genetic risk of AD or with mild cognitive impairment (MCI) **[G]** remains underexplored[20,21]. The current Review appraises the available evidence for spatial navigation deficits in preclinical, prodromal and confirmed AD, as well as identifying research gaps and future research priorities.

[H1] AD diagnosis and criteria

[H3] Diagnostic criteria

According to the National Institute on Aging (2011), AD diagnostic criteria include a history of worsening amnestic and nonamnestic symptoms in the visuospatial, language and executive function domains that reflect the amyloid-β (Aβ) burden and neurodegeneration in the brain[22]. Positive test results for cerebrospinal fluid (CSF) biomarkers and PET amyloid imaging increase confidence in the clinical diagnosis and predict AD progression from prodromal stages[23]. Importantly, Aβ plaque deposition has been observed in post-mortem evaluations of individuals who were not judged to be symptomatic in their lifetime[24,25], highlighting the complexity of the underlying AD pathology and time lag to clinical manifestation . A further complication is that biomarkers are not brain region-specific, and do not equate to clinical outcomes or have real-life symptom relevance for patients[26,27]. Thus, the role of cognitive evaluations is important in the early diagnostic process and has great potential to complement established biomarkers. Given that the amnestic syndrome continues to appear as a 'core' criterion to support diagnosis of the most typical form of AD, we discuss the issues surrounding the use of memory tests in clinical settings below (for atypical AD see elsewhere[28]).

[H3] Neuropathology over the lifetime

At a biological level, AD clinical symptoms are associated with the accumulation of extracellular Aβ plaques and intracellular tau tangles, leading to neuronal apoptosis. The extracellular deposition of Aβ plaques usually occurs first in prefrontal brain regions but becomes widespread over the cortex even in healthy ageing. By contrast, the intraneuronal neurofibrillary tangles of tau protein show a highly specific spreading pattern through the brain in AD[29]. Typically, tangles first develop in the most superficial cellular layer of the transentorhinal cortex (Braak & Del Tredici Stage I) advancing to the

entorhinal cortex and Ammon's horn in the hippocampus (Stage II), later spreading to the amygdala, the anterodorsal thalamic nucleus and the rest of the hippocampal formation (Stage III). Finally, tau tangles continue to spread to neighbouring regions within the cerebral cortex causing neocortical atrophy[23] (Stages IV–VI). The interaction of Aβ and tau leads to progressive neuronal loss, which in turn is believed to underlie AD symptomology, such as forgetfulness, disorientation and confusion[28]. The reason for the pronounced directional expansion of the tau pathological process in typical AD as well as the tau– Aβ interplay is still unknown.

[H3] Limitations of episodic memory for AD diagnosis

Given that patients with AD present with profound symptoms of forgetfulness and substantial Aβ load in the medial temporal lobe (MTL), it is not surprising that episodic memory is currently the gold standard for diagnosing probable AD[7]. Indeed, patients with substantial memory problems are highly likely to have underlying AD pathology. However, the reliance on episodic memory deficits for diagnosis in the prodromal or even preclinical stages is problematic, because episodic memory peaks in very early adulthood[30] and progressively declines with normal ageing. Indeed, diagnosis can be challenging in people >75 years of age, in whom memory and associated MTL structures show considerable age-related changes not due to pathophysiological processes[31]. As a result, cognitive decline in healthy older people >75 years might have been considerably underestimated by longitudinal studies[32]. Moreover, delayed recall ability, one of the current main cognitive diagnostic indicators of AD, progressively declines in healthy adults aged ≥65 years[33], highlighting the potential difficulties with the sensitivity of episodic memory to diagnose and predict AD pathophysiology in an older population. Similarly, as mentioned above, it is becoming increasingly recognised that patients with other forms of dementia can also show significant episodic memory problems. For example, FTD subtypes — such as the behavioural variant of FTD (bvFTD) — often manifest with similar deficits of episodic memory as AD, even for pathologically confirmed cases of bvFTD[12,34–36], which can make the differential diagnosis difficult[9,13,15,37]. Differential diagnosis is important when determining the underlying pathology and choosing the correct treatment strategy to manage symptoms. An early and differential diagnosis is particularly problematic for patients with AD who

exhibit neuropsychiatric symptoms, who can be very difficult to clinically distinguish from patients with bvFTD[37].

Unlike episodic memory impairments, spatial navigation or orientation problems are rarely reported in healthy older adults[38] or non-AD dementias, and experimental studies have shown that spatial navigational paradigms that are independent of mnemonic process can differentiate patients with AD from individuals with other dementias and healthy control groups[14,39]. This finding is not surprising given that the neuropathology of AD starts in the entorhinal areas, which are crucial for successful navigation[16,40–43]. This evidence raises the question as to whether such symptoms might be more sensitive and specific to underlying AD pathophysiology, even at a preclinical (that is, pre-memory symptom onset) stage. In the following sections, we briefly introduce current knowledge of navigation strategies and their neural correlates before reviewing the evidence in normal ageing and AD.

[H1] Spatial navigation

[H3] Navigation strategies

Spatial navigation is the process of determining and maintaining a trajectory between different points in our environment. Successful navigation relies on two co-dependent strategies: allocentric and egocentric navigation. These strategies use different types of spatial reference frames but are highly correlated[44] (Figure 1).

Egocentric strategies **[G]** are generally used when the same route is followed over and over again[45,46]. These self-centred navigation frames encode spatial information from the viewpoint of the person navigating to form an internal representation that is based on a sequence of bodily movements. This sequence of movements allows the navigator to maintain their route-goal trajectory relatively free of conscious control. Perceptual processing is required, as available visual input, bodily distance from landmarks, sensorimotor and vestibular knowledge about position in space and self-motion are all utilised as navigational cues. The temporal order in which environmental stimuli are encountered is

important and facilitates the landmark-based behavioural responses that are stored in spatial memory (for example, turn left at a supermarket and right at the lights).

On the other hand, when traveling a lesser known or novel route, spatial representations of sequential bodily movements are not available, and allocentric, world-centred strategies are employed instead. Allocentric strategies **[G]** are based on the navigator's perception of landmark positions relative to other landmarks. These positions are memorised and estimated by the navigator, contributing to an internal representation or 'cognitive map' that enables an individual to plan shorter routes regardless of their starting point[46,47]. Allocentric representations of self-location are updated by self-motion on the basis of visual, auditory, vestibular and proprioceptive information[48,49], in a process known as path integration. This process has a pivotal role in an individual's ability to successfully maintain movement through the environment[42,50].

The ability to use environmental landmarks to navigate also relies on the translation of egocentric to allocentric information (for example 'I am 20 meters from the church' to 'the supermarket is to the left of the church') and vice versa. For example, when one's location in an environment has been determined, the navigation system calculates subsequent routes on the basis of a combination of egocentric and allocentric information. For instance, self-motion, distance travelled, head direction during the journey[51], and temporal order of observed stimuli are combined across navigation frames. This strategic translation between allocentric and egocentric reference frames is a core determinant of one's navigational ability and might be of particular importance for detecting very early signs of disorientation by clinical examination.

Thus, egocentric and allocentric navigation strategies integrate for optimal performance in daily functioning and are associated with a network of brain regions that operate conjointly but can also be dissociated from each other [52]. Indeed, successful navigation can be achieved by employing just one of these navigation processes at a time. For example, employing only egocentric navigation, it is possible to go from one landmark to another without knowing the relationship between landmarks

(allocentric information), as the overall path might be stored in a series of visual snapshots or scene memories[53,54]. Similarly, egocentric navigation is also not required for allocentric navigation. When walking from one's house to the garden, the ability to measure bodily distance from landmarks (egocentric strategy) might not be necessary if a cognitive representation of the spatial trajectory already exists. Such a dissociation is often employed in experimental navigation tests by asking participants to remember locations on the basis of direction information while background cues are rotated or removed[54–56]. Evidence also suggests inter-individual differences for navigation preference, such that individuals preferentially choose specific strategies or reference frames when attempting to solve spatial tasks[52]. Outside the experimental paradigm, however, the human navigation system encourages the natural interaction (or strategic translation) of egocentric and allocentric strategies and, therefore, it is important to identify translational impairment in the clinical setting.

[H3] Neural correlates of spatial navigation

Advances in the field have shown that a large network of brain regions, involving MTL regions (hippocampus, entorhinal cortex and parahippocampal cortex[57]), parietal lobe regions (posterior cingulate, precuneus[58] and retrosplenial cortex (RSC)[59,60]), frontal lobe regions[61], and subcortical structures (caudate nucleus[46] and thalamus [62,63]) underlie our ability to navigate (Figure 2). Electrophysiological recordings in freely moving rodents offered the original insights into spatially tuned neurons that independently code for various aspects of navigation such as place location, head direction, speed and environmental boundaries. Likewise, in humans these sophisticated cells together form the neural architecture that underlies the navigation system.

Allocentric navigation strategies are thought to be represented by highly selective cell ensembles commonly found in the hippocampal CA1 and CA3 regions of the MTL. These so-called 'place cells' contribute to the formation of cognitive maps of the environment, providing local information about one's location within that environment. Both rodent and human models show that place cells become stable and more spatially restricted with repeated exposure to an environment (that is, as one becomes more familiar with the surrounding area). On the other hand, large-scale spatial information is

provided by grid cells located primarily in the medial entorhinal cortex, which can encode grid-like representations of distinct positions in space (self-location) and calculate routes between locations[41,43,64]. Grid cells represent a core component of the neural system that underlies path integration, as they also seem to measure 'distance travelled' akin to an odometer[64,65].

In addition, head direction cells (which were first identified in the postsubiculum of the rat) encode orientation in space and are activated whenever one is facing a certain direction (the reference direction [66] . Since their first discovery in rats, these cells have been found in the posterior parietal cortex, RSC, dorsal presubiculum, postsubiculum and anterior thalamus in humans **[Au: OK?]** [67,68]. Boundary vector cells[69] and cells coding specifically for self-motion (path integration)[43,50,70], complement other spatial representations and together might be used to rapidly form goal-independent maps of the environment.

Previous work suggests that the posterior cingulate region, RSC and precuneus have major roles in the integration of egocentric and allocentric spatial information streams[71]. For example, the rodent posterior cingulate receives dense direct hippocampal connections from the subiculum and is thus considered an integrative hub for projections from the hippocampus and anterior thalamic nuclei[72]. Interactions between the egocentric parietal and allocentric MTL systems are mediated by the RSC[51,73–75] as it projects to the parahippocampal gyrus and other areas including the entorhinal cortex, presubiculum, thalamus and posterior parietal cortex.[76,77] Moreover, the medial prefrontal cortex has been shown to receive information from the posterior parietal cortex and the hippocampus and may be involved in upstream processing of the spatial information generated [78,79].

Functional imaging studies in rodents and humans have shown that the RSC is a major contributor to navigational performance, especially accurate path integration in darkness[80], recognizing permanent environmental objects[59], binding together multiple cues within the environment[71], and encoding and storing spatial information[72]. In healthy individuals, the RSC responds selectively to environmental objects with high permanence such as telephone booths or street lights[59,81]. However, self-reported 'poor navigators' show reduced retrosplenial cortex activation in response to high-permanence landmarks and have more difficulty estimating object permanency compared with self-reported 'good

navigators'[60]. Moreover, the functional connectivity between the RSC and anterior thalamus nuclei is reduced in poor navigators[60], consistent with the literature from rodent studies[63]. The ability to recognise permanent objects in the environment is a general skill required to make appropriate decisions related to navigation, thus emphasising the important role, within the wider posterior cingulate region, of the RSC in spatial navigation. Understanding spatial navigation performance in healthy individuals is a crucial starting point before inferences can be drawn about initial sites of functional abnormality in patients with AD or preclinical individuals.

[H3] Ageing and spatial navigation

The majority of research on spatial navigation in normal ageing supports a general consensus that human and rodent navigational ability, especially allocentric processing,[82,83] declines with age[18,84,85]. Reduced resting-state blood flow[86], long-term potentiation of rodent synaptic function[87], and decreased hippocampal volumes in humans[88] are some of the mechanisms that underpin this gradual decline. Along with these age-related neural changes, deficits in place learning[83], perception of self-motion, [89]and retrieval of spatial memories[90] have been reported in humans. Based on rodent studies, such navigational errors are believed to be a consequence of computational changes within neural circuits of the medial prefrontal cortex and CA1 and CA3 regions of the hippocampus[91]. These age-related changes give rise to deficits in spatial working memory as well as difficulties maintaining and retrieving allocentric representations.[91,92] Interestingly, reduced allocentric processing, mostly related to spatial memory (that is, encoding and retrieval of route trajectories and environmental maps) is suggested to lead to a compensatory shift toward egocentric or path integration navigational processes, as they do not rely on memory per se[84,93]. This idea is consistent with the finding that older adults between 60-80 years of age actually outperform younger adults on egocentric[94] and allocentric distance tasks for example, manually adjusting the length of a line until its length matches the distance of a target [95]. The preservation of these spatial processes in healthy ageing might therefore have important implications for the effective discrimination of age-related and AD-related decline in

navigational ability[84], and also has implications for navigational rehabilitation strategies for AD in the future.

[H1] Spatial navigation as a diagnostic tool

Early identification — based on navigational difficulties — of individuals who are likely to develop AD is currently complicated by the challenges of measuring different features of spatial navigation in humans. Reliable tests of spatial navigation that are suitable for clinical settings across centres and different patient populations are still in development, as most experimental tests are not feasible for clinical evaluation. Validated, simple visuospatial tests such as the widely used Mental Rotation Test[96] and the Money Road Map test[97] have been shown to be poor predictors of navigational abilities[98,99] and cognitive decline[100]. Newly developed virtual reality or real-world tests of spatial cognition have proven more sensitive in identifying spatial navigation deficits in patient populations. In particular, virtual reality testing can be applied as an alternative to real-world reality tests (that are difficult to administer with space constraints in clinical settings) to measure navigational abilities in younger and older age groups[101], patients with MCI and early AD[102]. These computer-generated virtual environments provide tightly controlled testing conditions and also enable manipulation of navigational parameters, such as landmark availability and navigation complexity. The adoption of tablet computers by clinical services for cognitive testing will make the testing of spatial navigation deficits more sophisticated and sensitive in everyday clinical practice. Furthermore, extraction of critical features from these virtual reality tests might enable development of further pencil & paper or bedside assessments.

[H3] Early AD

Previous studies using virtual reality techniques have shown that spatial disorientation in patients with AD typically includes both egocentric and allocentric impairments linked to widespread neurodegeneration in medial temporal, parietal and frontal brain regions[17,103–106] (Figure 2). In accordance with these findings, both types of navigational strategy have been found to be impaired in

early AD dementia, alongside impairments in the translation of both reference frames[105] and the ability to construct novel scenes from spatial and contextual information, which is dependent on posterior parietal regions such as the supramarginal and angular gyrus [106]. Virtual reality studies found that patients with early AD were unable to store an allocentric viewpoint-independent representation and to synchronize this representation with the allocentric viewpoint dependent representation (e.g., memorize the position of the plant and retrieve the plant's position from a different location)[17] probably as a result of reduced hippocampal neuronal density particularly in CA1 and CA3 subregions[107]. Egocentric impairments are also present, mainly as a result of hypometabolism and structural medial parietal changes, which are signature features of AD[108]. Surprisingly, these medial parietal changes and associated egocentric impairments have been much less investigated in AD, despite having potentially much higher specificity for AD pathology. Indeed, retrosplenial (Brodmann areas 29 and 30) volumetric changes have been shown to efficiently distinguish AD from FTD, even in patients with similar hippocampal atrophy [14,109].

As noted above, patients with AD also experience difficulty translating between allocentric and egocentric reference frames, a function that strongly correlates with RSC and posterior cingulate dysfunction and has been shown to distinguish AD from FTD[14,105] . Given the role of the RSC in integrating different navigational frames, orientation and visual information from the occipital lobes, its dysfunction in early AD is in agreement with deficits in translation between allocentric and egocentric representations that occur at early clinical stages of the disease and are highly specific to underlying AD pathophysiology[110]. For this reason, the RSC is often considered an initial site of functional abnormality in patients with AD or in preclinical individuals.

[H3] Prodromal AD and MCI

Similar to early AD, patients with MCI often show spatial navigation impairments[111]. Although the exact trajectory from MCI to AD is still under discussion[112], a large number of studies show functional and structural changes in the MTL and parietal cortex in patients with MCI[18,108,113–116].

Investigations of egocentric and allocentric memory in individuals with amnestic MCI (aMCI) indicate that these patients have substantial volume reductions in the hippocampus, right-sided precuneus and inferior parietal cortex, and are severely impaired at learning both allocentric and egocentric tasks[108]. Indeed, path integration in spatial navigation tests is substantially impaired among prodromal cohorts and might represent a cognitive marker for AD[117]. Furthermore, a study employing a human real-life version of the Morris water maze **[G]** found that patients with AD had problems navigating and using both allocentric and egocentric orientation; aMCI groups were more severely impaired on allocentric trials[111], probably due to the stronger emphasis on memory in these trials[118].

Interestingly, genetic vulnerability interacts with aMCI to influence spatial navigation performance. The apolipoprotein E ε4 allele (*APOE ε4*), which is a known genetic risk factor for AD, has high prevalence but low penetrance in the population, with a threefold increased risk of developing AD in *APOE ε3*/*ε4* heterozygotes and a tenfold increased risk in *APOE ε4*/*ε4* homozygotes compared with *APOE ε4* non-carriers (see genetics section later, and for more details see elsewhere[119]. On a computerised human analogue of the Morris water maze test (Hidden Goal Task), aMCI *APOE ε4* homozygous carriers are poorer on all spatial navigation subtasks, including allocentric (hippocampus-dependent) and egocentric subtasks, compared with aMCI *APOE ε4* heterozygous carriers[120].

Despite the strong focus on MTL contributions to navigational deficits in AD, findings suggest an increasingly important role for the posterior cingulate cortex and RSC; these areas are affected early in the course of AD[121] and in patients at early MCI stages[122,123], especially those who then progress to AD[116,122,124,125]. However, questions around the contributions of the RSC and associated posterior cingulate areas to spatial navigation deficits in early AD remain unanswered. In addition, whether changes in the RSC reflect a compensatory mechanism that occurs as a result of early AD pathology in the transentorhinal cortex and hippocampus at the microscopic level remains unclear. Such a finding would not be surprising, however, as the entorhinal cortex has a strong anatomical connection with the RSC[126].

[H3] Preclinical AD

Although evidence is emerging that spatial navigation is impaired in early AD and MCI, its integrity in preclinical populations is less well understood. Various attempts have been made to determine spatial neural and cognitive biomarkers in individuals as young as 45 years who have an elevated sporadic or genetic risk of progressing to AD [127]. Preclinical investigations have reported functional MRI abnormalities in the resting-state default mode network, including reduced functional connectivity in posterior cingulate cortices and precuneus regions[128,129], both of which underlie egocentric ability and egocentric to allocentric translation.

Studies in sporadic preclinical AD have partially relied on CSF Aβ levels. For example, a study from 2016[20] investigated spatial navigation as a marker for AD, using two non-immersive desktop virtual maze environments for allocentric and egocentric conditions. Individuals were considered preclinical if they had low CSF Aβ levels (<500 pg/ml)[130], with no cognitive deficits. Selective deficits in allocentric strategy among preclinical individuals were reported relative to individuals with a normal Aβ level in the CSF (>500 pg/ml). Despite allocentric acquisition impairments, the preclinical group retained sufficient information to solve the wayfinding task. However, the exact contribution of decreased CSF Aβ levels to impairment of allocentric and egocentric processing is uncertain, as increasing evidence suggests that the tau protein has a critical role in the generation of cognitive deficits [131,132]. Experiments in aged transgenic mice expressing human tau suggest that the interaction of reduced excitatory grid cell firing in the dorsal medial entorhinal cortex and increased activity of inhibitory cells in response to enhanced theta oscillations results in the spatial memory deficits seen in early AD[16]. This finding links the destabilization of grid cell fields (which code for route trajectories and update spatial information) with the earliest stage of tau pathology. The significance of this finding in relation to preclinical AD, however, remains to be determined (see Figure 3)

In human studies, preclinical individuals carrying mutations in the presenilin 1 and amyloid precursor protein genes show entorhinal and posterior cingulate cortical thickness changes up to 8 years before

disease onset[133]. However, to our knowledge, spatial navigational ability has not been investigated in these particular preclinical patients. These predictive MRI findings underline the strong need for longitudinal investigations to examine the sensitivity of cortical thickness changes as neural markers for AD and the manifestation of spatial navigation disparities for predicting later conversion to MCI and early AD.

Most navigation studies in cohorts of patients with genetic risk factors for AD have been conducted with *APOE*-genotyped individuals. The association between the *APOE ε4* allele and AD risk has spurred a growing number of studies investigating the cognitive and neurophysiological effect of *APOE ε4* in younger 18-24 year olds,[134,135] middle-aged 40-60 year olds [136–139] and elderly 60-90 year old individuals [140] adults, also in relation to spatial performance and hippocampal volume[120].

A study examined a possible link between *APOE ε4* and spatial navigation in genetically at-risk young healthy adults. Reduced grid-cell-like representation was observed in *APOE ε3*/*ε4* carriers compared with *APOE ε3*/*ε3* individuals, suggesting functional (but no structural) differences between young *APOE ε4* carriers and non-carriers. Grid-cell representations were temporally unstable in young adult carriers as functional connectivity between the right entorhinal cortex and hippocampus was impaired, leading to a behavioural preference to navigate along the border of the virtual environment. The authors proposed a potential compensatory mechanism of the hippocampus due to neuronal loss in the entorhinal cortex and reduced grid-cell representations which enabled young adult carriers to navigate successfully and complete the task [21,141]. Clearly, preclinical cohorts are of great interest for future navigation research in AD pathophysiology, not only for individuals at genetic risk, but also for sporadic high-risk groups.

An alternative approach is to investigate preclinical cognitive forms of AD via healthy elderly participants who have significant memory concerns (SMCs) **[G]** but do not reach cut-offs for objective memory impairment on standard neuropsychological measures. Such SMCs are a potential harbinger of AD pathology[142]. However, it should be emphasised that no gold standard tool currently

exists to identify SMCs, and no threshold values to suggest clinically relevant SMCs have been established. Unsurprisingly, few studies have explored spatial navigation in SMC cohorts[111]. However, evidence does suggest a positive association between amyloid pathology, genetic risk of AD, entorhinal cortex integrity and SMCs[143,144], which might ignite new interest in whether SMCs and navigational difficulties are comorbid among genetically at-risk cohorts.

[H1] Conclusions

This review underscores the presence of spatial navigation impairments in early AD and its prodromal and preclinical forms. The evidence reviewed clearly highlights the great potential of spatial navigation and orientation deficits as diagnostic measures and predictors of incipient AD pathophysiology. The findings should not be surprising as MTL and posterior parietal regions, which constitute the core network for navigation, are highly susceptible to AD pathophysiology even in the prodromal and preclinical stages of the disease. An urgent need exists to revisit the notion that episodic memory should be the gold standard for early AD diagnosis and outcome intervention studies. Specifically, the literature indicates that spatial navigation deficits can identify individuals at risk of developing AD, which has obvious implications for clinical practice. For example, routine assessment of spatial navigation complaints should be considered a priority in memory clinics[38]. If subjective complaints are present, particularly when accompanied by behavioural symptoms that manifest as everyday difficulties navigating previously familiar routes and/or using public transport, the patient should be considered at high risk of developing AD. Identification of incipient AD might provide an earlier opportunity to begin potentially disease-modifying treatment before more substantial and deadly brain changes occur.

Spatial navigation parameters could also have an important role in animal to human translational research. Drug development for AD has been hampered by the failure to replicate success in animal models (tested with spatial navigation measures) in phase II or III clinical trials. A 3-month open-label study has shown that a computerized human analogue of the Morris water maze has the potential to measure the effects of donepezil in mild AD[145]. Subsequent research has shown that the disruptive

effect of scopolamine on place navigation can be reverted by donepezil, a finding that was demonstrated using both rodent and human versions of the Morris water maze[146].

The past few years have seen a considerable shift in interest towards patients with prodromal AD, and some of the conventional neuropsychological tests for AD might be subject to a ceiling effect in these patients. Only a few subtests of current measures have the potential to show differences in the effects of drugs and placebo in patients with prodromal AD or MCI. Therefore, spatial navigation, as a sensitive and specific marker of AD, presents a window of opportunity in these patients. Furthermore, in the era of cross-cultural clinical trials, tests that are independent of language and culture (such as those for spatial navigation) facilitate comparison across research sites.

From a social care perspective, the findings presented offer important information for dementia care organisations. Disorientation leads to patients getting lost in everyday environments, resulting in distress for patients and family members and often the involvement of the emergency services and in extreme cases leading to death from exposure. Thus, the identification of individuals with spatial navigation deficits might enable better safeguarding to be put in place for those individuals.

Despite clear clinical applications of the research, spatial navigation has several limitations as a diagnostic tool for AD. One major question is whether spatial deficits occur before episodic memory deficits or whether both deficits manifest concurrently in humans. Navigation and orientation tests can only be considered superior to episodic memory tests if they are shown to be more sensitive and specific for AD pathology. However, given that the normal ageing process will probably give rise to complaints around memory of past events, as opposed to ability to navigate and orientate oneself in space, disorientation should be further investigated as a potentially more valuable (specific) marker to distinguish pathological ageing from normal ageing. This rationale leads to a pressing need to develop a standardized and validated diagnostic spatial test battery that does not rely on topographical memory. These tests might also be used as a clinical diagnostic tool and outcome marker in upcoming treatment efficacy trials, as current navigation tools are limited and not standardized across research centres. Given the multifactorial nature of the navigation system, such a battery of tests should consider not only mnemonic processes, but also higher mental functions mediated by the frontal lobe

such as planning, motivation and maintenance of spatial representations that influence navigational ability. This approach is especially important when considering a differential diagnosis, for example, between AD and FTD syndromes.

Importantly, spatial navigation studies in AD might be limited in their comparability, as many of the studies predate the publication of robust diagnostic criteria for AD[7]. As a result, the potential for mixed or other forms of dementia to confound an established cohort of patients with AD cannot be ruled out. It is also difficult to say with certainty that cut-off points for disease staging (preclinical, early MCI, late MCI) are consistent across studies published before the 2014 guidelines[7]. In addition, heterogeneity in the definition of patient cohorts and differences in spatial navigation paradigms and testing procedures have created inconsistencies across studies.

The current lack of epidemiological data from healthy populations for spatial navigation is a further obstacle. Inter-individual differences in spatial navigation remain elusive, with no population-level data available to rectify conflicting ideas around, for example, sex differences in navigational abilities. One notable exception is the launch of Sea Hero Quest (http://www.seaheroquest.com), an online mobile game to measure spatial navigation (Box 1). To date (April 2018), Sea Hero Quest has been played by over 3.7 million people, in 193 countries between the ages of 19 and 95 years[132]. Initial results from Sea Hero Quest show that not only age but also gender and cultural background have a substantial effect on navigation behaviour, which clearly needs to be investigated further[147]. There is considerable scope to use the data from the game to create the first population benchmarks for healthy navigation abilities across ages, gender and countries. Benchmark scores will allow us to develop easy-to-administer, sensitive spatial navigation tools validated against benchmark population data and also to relate it to real-life navigation problems that patients encounter. Already, navigational pattern changes, in preclinical groups defined as genetically-at risk of AD, have been uncovered on Sea Hero Quest. This demonstrates the game's utility to detect cognitive changes that precede the expected onset of AD Taken together, the presented evidence highlights the enormous potential of spatial navigation for AD diagnosis, which in turn could have a major impact on clinicians, patients and their families.

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Key points

- Episodic memory has limited utility as a diagnostic and outcome measure for preclinical AD
- Spatial navigation deficits have the potential to detect underlying pathophysiology in preclinical AD
- The brain areas affected earliest by AD pathophysiology are key nodes in the spatial navigation network
- Genetically at-risk individuals show altered spatial navigation patterns before any episodic memory symptom onset
- Spatial navigation emerges as a potential cost effective cognitive biomarker to detect AD in the preclinical stages, which has significant implications for future diagnostics and treatment approaches
- Future spatial navigation benchmarks and standardisation of spatial navigation tests are needed to realise this goal

Competing interests

The authors declare no competing interests.

Author contributions

M.H. and G.C. contributed to all aspects of the manuscript. J.L. and J.H. contributed to reviewing/editing the manuscript before submission. A.M.M. contributed to writing the manuscript.

Reviewer information

Nature Reviews Neurology thanks Thomas Brandt, Katherine Possin and Thomas Wolbers for their contribution to the peer review of this work.

Further information

Sea Hero Quest: www.seaheroquest.com

Box 1 | Sea Hero Quest

Sea Hero Quest (SHQ) is a mobile app-based cognitive task that enables the collection of spatial navigation data on a population level. SHQ has been downloaded by 3.7 million people in 193 different countries worldwide. As people advance in the game, they face challenges in different navigation domains, including visuospatial skills, path integration, spatial short-term memory and allocentric and /or egocentric navigational strategy.

Game performance can be divided into two main domains: wayfinding and egocentric path integration. In wayfinding levels, players are initially presented with a map indicating start location and the location of several checkpoints to find in a set order. The two variables of interest are trajectory distance and time taken to complete each level. In path integration levels, participants navigate along a river with bends to find a flare gun and then choose the correct direction back to the starting point from a choice of three options. Depending on their accuracy, players receive one, two or three stars. The game also controls for video gaming proficiency, which might otherwise bias performance by giving players familiar with similar games an advantage.

Current preliminary findings for the population-level navigation data can be found here:

https://www.biorxiv.org/content/early/2018/01/21/188870

Glossary

Allocentric Navigation Allocentric strategies are based on the navigator's perception of landmark positions relative to other landmarks

Egocentric Navigation Egocentric self-centred navigation frames encode spatial information from the viewpoint of the navigator

Episodic memory Episodic memory refers to our memory of events represented by aspects of the past not present in other memories, such as the time, place, or social context.

Mild Cognitive Impairment Mild cognitive impairment (MCI) is a prodromal or intermediate stage between the expected cognitive decline of normal aging and the more-serious decline of dementia.

Morris water maze: The Morris water maze is a test of spatial learning examining rodent ability to navigation from different starting locations around an open swimming arena to location a submerged escape platform using only distal cues. For more information see elsewhere[148]

Subjective Cognitive Decline: Subjective Cognitive Decline (SCD) refers to a self-experienced persistent decline in cognitive abilities in comparison with a prior normal status and occurs in the absence of objective impairment on standardised neuropsychological tests