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Getting lost in Alzheimer's disease: A break in the mental frame syncing

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ABSTRACT

Despite the clinical significance of topographical disorientation in Alzheimer's disease, it is not clear which cognitive spatial processes are primarily impaired. Here, we argue that a deficit in "mental frame syncing" between egocentric and allocentric spatial representations causes early manifestations of topographical disorientation in AD. Specifically, patients show impairment in translating from an allocentric hippocampal representation to an egocentric parietal one for the purpose of effective spatial orientation and navigation. We suggest that a break in "mental frame syncing", underpinned by damage to the hippocampus and retrosplenial cortex, may be a crucial cognitive marker both for early and differential diagnosis of AD. Identification of these spatial deficits could facilitate the development of early cognitive rehabilitation interventions and the possibility of identifying individuals most at risk for progression to AD during the preclinical stages.

Background

Getting lost is not just common in Alzheimer's disease (AD), but it is one of its earliest clinical manifestations [1–5]. Episodes of topographical disorientation were reported both in outpatients [6] and patients residing in a community [7]. Moreover, almost 90% of patients with AD had their first incident of disorientation in familiar surroundings [8]. This reflects a deficit in spatial memory, generally defined as the ability to encode, store, and retrieve spatial information in order to build an internal representation of the environment (a "cognitive map") [9]. However, the decline in spatial memory in the elderly is often underestimated, probably because the deficit is more insidious relative to the decline in other cognitive abilities. Elderly individuals with self-perceived difficulties in spatial orientation and navigation can develop several strategies to reduce their likelihood of getting lost, and hence the manifestation of a decline in spatial memory [10]. Moreover, topographical disorientation is an "umbrella term" for a set of heterogeneous cognitive deficits, comprising a difficulty, or inability, to find one's way in familiar and unfamiliar environments, learn new routes, recognize places, describe a pathway verbally, and use a map for self-orientation [11–13].

The cognitive underpininings of topographical disorientation in AD patients are still unclear. Here, we argue that this impairment is caused by AD patients' failure to spontaneously shift from an allocentric hippocampal spatial representation to an egocentric parietal one. This "mental frame syncing" is critical for effective orienting and navigation. A cognitive impairment in the ability to construct a coherent mental image of the space, underpinned by damage to the hippocampus and retrosplenial cortex, may become a crucial cognitive marker both for early and differential diagnosis of AD. Identification of these spatial deficits could facilitate the development of early rehabilitation interventions and the identification of individuals most at risk for progression to AD during the preclinical stages of the disease [14].

Spatial memory: a "mental frame syncing"

Historically, spatial memory has been considered a high-level cognitive process utilizing an "egocentric" reference frame, in which object locations are represented relative to the individual's orientation, and an "allocentric" reference frame, in which object locations are represented irrespective of the individual's orientation [15]. Additionally, one has to consider not just how locations are represented, but how these spatial representations are processed. In a recent review, Avraamides and Kelly [16] argue that spatial relationship processing occurs both on-line, to support immediate actions (e.g., reaching for an object in one's current environment), and off-line, to support the retrieval of previously experienced spatial environments (e.g., planning of a route prior to travelling).

But, how exactly do egocentric and allocentric representations work together to support successful topographical orientating and navigation? According to the "self-reference" model proposed by Sholl [17,18], two subsystems work in parallel to accomplish this goal: the allocentric subsystem codes object-to-object spatial

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relations in long-term memory, while the self-reference system codes and updates egocentric relations to objects using the front–back and left–right axes of the body as reference. The self-reference system operates at both a perceptual-motor (online) and a representational (offline) level. At the perceptual-motor level, the self-reference subsystem represents the locations of objects in the current environment according to egocentric coordinates in order to guide immediate actions. Critically, at the representational level, the self-reference subsystem interfaces with the allocentric subsystem to retrieve allocentric maps from long-term memory and provide them with an orientation. Furthermore, it should be noted that Holmes and Sholl [19] demonstrated that allocentric representations are immediately available in both over-learned and novel environments. The self-reference system uses self-motion cues to update body location and face direction relative to an allocentric, orientation-free, immediately available, object-to-object map.

There is strong neurobiological support for the existence of both egocentric and allocentric representations. As evidenced by Burgess [20], multiple egocentric representations combine, at the level of single neurons, in posterior parietal area 7a of primates [21,22]. Though these neurons respond to visual input corresponding to a specific retinotopic location, their rate of firing is modulated by the animal's orientation within the space [23]. On the other hand, the discovery of place cells primarily in the CA3 subfield in the hippocampus of rats [24], primates [25] and humans [26] provides neurobiological support for the existence of an allocentric representation. These place cells fire when an animal is in a specific location—the cell's 'place field'— regardless of the animal's orientation. Place fields in familiar environments remain stable for several weeks, suggesting that these cells encode a long-term allocentric representation of the environment [27].

Neural mechanisms have also been found to modulate spatial representations of our environment. Head-direction cells, which are found throughout Papez's circuit [28], modulate their rate of firing according to the animal's current head direction, independent of its location in the environment. Boundary vector cells in the subiculum of the hippocampal formation [29,30] modulate their rate of firing according to the presence of an environmental boundary at a specific distance from the animal [31,32]. Grid cells, which are found in the enthorinal cortex [33] and in the pre- and- para subiculum [34], are likely to support the process of "path integration" by updating their rate of firing according to self-motion signals.

Burgess and colleagues have proposed a computational model to identify the neural mechanisms underlying the retrieval of spatial representations [35,36]. Based on the reciprocal connectivity between hippocampus and neocortical regions, their Boundary Vector Cells Model provides support for a crucial role of the hippocampal place cells in retrieving a spatially coherent scene. When prompted by a partial cue revealing the surrounding boundaries and visual textures of a familiar environment, the full spatial representation of this environment can be retrieved through the process of pattern completion [36]. Though allocentric, this spatial representation is translated to an egocentrically coherent image in the medial parietal areas via information updating from other cells: place cells inform the viewpoint location, head-direction cells the viewing direction, and grid cells the self-motion signals. It has also been argued that the retrosplenial cortex (RSC) transforms long-term allocentric representations into egocentric representations by using head direction information to compensate for the rotational offset between different coordinates [35–38].

Based on these theoretical premises and neurobiological evidence, we argue for a critical role of "mental frame syncing", between egocentric and allocentric spatial representations, in spatial mapping. When we orient ourselves in an environment, we identify relevant environmental landmarks (buildings, stores, etc.) and remember their locations with respect to one another. To do so, we create in our mind a cognitive allocentric map, a city-like map that includes all the landmarks' locations. However, as with a real map, its use requires a translation: First, we have to identify our position and the specific destination-landmark on the map. Second, we have to rotate the map to match our egocentric orientation to the landmark. If we are unable to center the map according to our current location, it is useless. Therefore, an allocentric representation (specifying layout in terms of north, south, east, west) has to be translated into an egocentric framework (specifying layout in terms of left, right, ahead) to enable an individual to construct a coherent image of the space suitable for navigation [39]. This "mental frame syncing" requires continuous updating of an individual's body location and face direction relative to the orientation-free allocentric map. If the "mental frame syncing" ceases, even momentarily, the map becomes useless and the individual is more prone to becoming lost.

A break in the "mental frame syncing" in Alzheimer's disease: Insights from brain imaging and lesion studies

Several studies have investigated egocentric and allocentric memory deficits in patients with amnestic Mild Cognitive Impairment (aMCI). Though the studies do not test patients with AD, the results are still informative since patients with aMCI are more likely to develop AD than healthy age-matched controls; for a review, see [40]. In a recent study, Weniger and colleagues [41] compared twenty-nine patients with aMCI to twenty-nine healthy age-matched controls on two virtual reality tasks: subjects learned a route through a virtual park with many landmarks (allocentric memory) and navigated a virtual maze without any landmarks (egocentric memory). In both virtual tasks, but particularly on the latter, the patients' performances were worse than that of the controls.

Burgess and colleagues [42] also tested spatial memory impairment in patients with aMCI. A shifted-viewpoint task can be used to determine which of the two representations (egocentric or allocentric), if any, is impaired: ability to recall a spatial configuration from the point of view at encoding suggests an intact egocentric (viewpoint-dependent) representation; whereas an inability to recall a spatial configuration from any other point of view suggests an impaired allocentric (viewpoint-independent) representation. A virtual reality implementation of the task revealed patients' navigational deficits when allocentric hippocampal-dependent memory, rather than egocentric parietal-dependent memory, was required.

In another interesting study, Hort and colleagues [43] compared the navigational abilities of sixty-five patients divided into five groups: probable AD, amnestic MCI single domain, amnestic MCI multiple domain, nonamnestic MCI, and subjective memory complaints. The authors used a real-world human analog of the Morris water maze test [44] in which the participants were required to to locate an invisible goal using either two landmarks (allocentric) or their own position (egocentric). Like Burgess et al., Hort and colleagues found navigational impairments in aMCI patients only when configurations required allocentric representations. These findings are consistent with findings of medial temporal lobe atrophy in MCI patients [45]. Additionally, amnestic MCI has a higher probability of progression to AD than any of the non-amnestic subtypes [46].

While informative, these studies do not provide conclusive evidence for spatial deficits in AD. Additionally, neither of the aforementioned studies specifically examined whether these impairments occur because of problems translating from allocentric to egocentric representations. However, neuropathological evidence does suggest two possible causes for a "mental frame

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syncing" impairment in AD patients. One, neurofibrillary tangles begin in allocortical areas—e.g., the hippocampus and entorhinal cortex— and later spread in a predictable manner across the isocortex, including the parietal association cortex [47–52]. Furthermore, the hippocampus is known to atrophy in very mild AD [53]. Two, anatomical connectivity of the retrosplenial cortex (RSC) to other brain structures (the dorsolateral prefrontal cortex, parietal and occipital cortex, anterior thalamic nuclei, and hippocampus), as well as evidence of spatial memory deficits in RSC-lesioned humans and animals, provide compelling support that the RSC plays a crucial role in "mental frame syncing" between egocentric and allocentric representations (for a review, [38]). Interestingly, some studies have shown that the earliest metabolic decline in Alzheimer's disease, as measured by using [18] F-fluorodeoxyglucose positron emission tomography (FDG-PET), is localized to the RSC [54–56]. Medial temporal lobes are also hypometabolic in early AD (e.g., [57]); however, when the metabolic rate of the MTL and posterior cingulate cortex was compared in the same cohort, it was observable that the posterior cingulate lesion was considerably more significant [58].

Currently, there are two possible explanations for hypoactivity of the RSC in very early stages of AD: according to Villain and colleagues [56], the posterior cingulate hypometabolism could be a secondary effect of atrophy in brain areas primarily affected by pathological damage in AD or the RSC may itself atrophy early in AD [59,60]. Nestor et al. [60] demonstrated that atrophy in the posterior cingulate cortex is present from the earliest clinical stage of AD. Furthermore, they found the posterior cingulate cortex to be as vulnerable to neurodegeneration as the hippocampus.

Nestor et al. [61] also explored topographical disorientation in AD by developing and testing a new virtual navigation test— the Virtual Route Learning Test (VRLT)— in which participants were required to learn four routes of increasing complexity by following verbal instructions as well as visual pointers. At the end of the route, the experimenter took control of the joystick and navigated back to the starting point along the predefined routes. Hence participants followed the same route from memory, but in reverse. Performance on VRLT demonstrated sensitivity in detecting navigational impairment in very early AD, as well as specificity in discriminating AD patients from patients with Semantic Dementia. The VRLT also demonstrated high ecological validity, since it strongly correlated with caregivers' reports of real world navigation problems. Furthermore, a recent study aimed at exploring the neural basis of performance on VRLT in a cohort of 30 patients with mild AD revealed a significant network level correlation with cerebral metabolism. This included areas common to both activation in normal route learning and early neurodegeneration in AD, specifically, retrosplenial, lateral parietal cortices, and possibly the hippocampal tail [62].

In light of this evidence, we hypothesize that both early damage to allocortical areas and hypometabolism in the RSC provoke a break in the "mental frame syncing" required for spatial navigation. This means that AD patients are not able to translate an allocentric place-cells representation into egocentric coordinates in order to construct a coherent image of the space in which to locate the self and surrounding landmarks. More specifically, AD patients are not able to continuously update their body location and face direction relative to an orientation-free allocentric map. Therefore, they get lost.

Testing the hypothesis

We propose that a cognitive deficit in the "mental frame syncing" between egocentric and allocentric spatial representations, underpinned by damage to the hippocampus and retrosplenial cortex, causes early manifestations of topographical disorientation in AD. According to this premise, AD patients should show impairments in translating an allocentric map into an egocentric coherent image of space for effective spatial orientation and navigation. Specifically, AD patients should not be able to continuously update their body location and face direction relative to an orientation-free allocentric map.

An interesting methodology for investigating this "mental frame syncing" hypothesis is given by Gomaz et al. [63]. Their study compared two path-encoding conditions, (1) encoding through direct path reproduction, in which participants were required to learn a path using both egocentric and allocentric information and (2) encoding via observation of the experimenter who produces a path that the participants can only learn via allocentric information. Participants were then asked to reproduce the path in three different ways: same-way path production (egocentric representation), opposite-way path production (allocentric map), and self-motion cues only (egocentric retrieval). We argue that this methodology may be used to investigate the "mental frame syncing" hypothesis because it permits us to compare two different types of spatial encoding with three different types of spatial memory retrieval. Furthermore, it would be interesting to investigate performance on these three path production conditions in the different stages of AD (as an early diagnosis) and to compare performances of individuals with AD to performances of individuals with other types of dementia (as a differential diagnosis).

Implications for treatment

Cognitive interventions for healthy older people as well as for patients suffering from neurodegenerative disorders have raised much attention in recent years [64–67]. From a preventive viewpoint, a recent systematic review demonstrated that cognitive training in healthy older individuals had persistent protective effects on their longitudinal neuropsychological profile and hence may have prevented the onset of dementia [68]. On the other hand, other evidence demonstrated the efficacy of nonpharmacological therapies in improving quality of life for people with AD and their caregivers [69]. Specifically, several studies showed cognitive training to be efficacious in improving a range of cognitive skills in AD patients (e.g., [70–72]).

From a clinical viewpoint, we argue that there is a "window of possibility" to develop cognitive rehabilitation interventions by detecting and treating the earliest deficits in "mental frame syncing". Virtual Reality (VR) appears to be a suitable medium that offers several requirements for effective cognitive neurorehabilitation interventions: repetitive practice, feedback about performance, multimodal stimulation, and controlled and secure environments [73–75]. Specifically, it is possible to control and manipulate tailored exercises within meaningful and motivating environments using virtual environments (VEs) [76].

Indeed, VR simulations can be highly engaging by supporting a process known as "transformation of flow", defined as a person's ability to exploit an optimal (flow) experience to identify and use new and unexpected psychological resources as sources of involvement [77]. From a psychological perspective, motivation is particularly important for AD patients to consistently engage in demanding and practice-heavy cognitive interventions. Cognitive training can be particularly onerous to a patient whose memory is failing. An individual's response to cognitive training may vary tremendously, depending on the patient's cognitive status. Cognitive rehabilitative strategies should evolve, since different cognitive training may become necessary at different times.

To our best knowledge, there are currently no validated protocols focusing on rehabilitation of spatial memory for AD patients.

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However, McGee has suggested that "older adults with impairments in memory and executive functioning could be presented with hierarchical rehabilitative challenges in a VE more efficiently and consistently than with traditional methods" [78]. Optale et al. [79,80] provided an interesting example, albeit one that is not specific to rehabilitation of spatial abilities. The authors proposed and tested, on twelve patients suffering from aMCI, a cognitive rehabilitation memory training [80]. Rehabilitation treatment consisted of three different listening experiences alternated with three different virtual experiences. Patients were then invited to make an oral summary of their audio or VR experience to enhance their mnemonic abilities. During the immersive VR experience, patients were free to navigate the environments. However, if patients took a "wrong turn" resulting in a dead-end, they were immediately transported back to the point along the VR path immediately before this "wrong turn". This is an interesting virtual spatial task since patients have the chance to train their "mental frame syncing" abilities.

One of the crucial features of VR technology is the interactivity; immersive VEs incorporate highly sensitive head and body tracking system. These sensors update users' positions to provide an egocentric space for the effective translation of long-term allocentric representations of the spatial environment. To navigate effectively in virtual space, the participant must translate an allocentric place-cells representation into egocentric coordinates, hence constructing a coherent image of the environment in which to locate the self and surrounding objects. In fact, the egocentric mental image resulting from "mental frame syncing" is an ongoing process, which may be possible to modify when interactive VEs intercept the sensorimotor links.

In considering protocols for spatial memory rehabiliation, we should heed the warnings of the Cochrane Library report: conclusions about the efficacy of cognitive rehabilitation approaches for people with early-stage AD must be viewed with caution due to the limited number of randomized controlled trials [65]. Controlled trials testing a greater number of participants are needed. Other future challenges include adopting better: inclusion/exclusion criteria, cognitive exercises, control conditions, and standardized outcome measures. Indeed, though current evidence on the efficacy of cognitive trainings in AD patient is limited, it is sufficiently encouraging to justify additional clinical studies in this population.

In a recent review, Riva [81] identified four major issues that may limit the use of the VR system in the assessment and rehabilitation of cognitive impairments:

- The limited possibility of tailoring virtual environments to the specific requirements of the clinical or experimental setting.
- The low availability of standardized protocols that can be shared by the community of clinicians and researchers.
- The high costs (up to $200,000) required for designing and testing a clinical VR application.
- The expensive technical support often required for maintaining a VR system.

To address these logistical challenges, Riva and his team developed NeuroVR (http://www.neurovr.org), a free virtual reality platform based on open source elements [82]. The software allows non-expert users to adapt the content of several pre-designed virtual environments to specific needs of the clinical or experimental setting.

Conclusion and future directions

It is estimated that by 2050, one in eighty-five individuals will be affected by Alzheimer's Disease [83]. As incidence of AD increases, it will become increasingly important to have diagnostic criteria that supports early diagnoses and preventative interventions. Several studies from both genetic at risk-cohorts and clinically normal older individuals suggest that the pathophyshiological cascade of AD begins years before the diagnosis of dementia [14,84]. This long period presents a crucial opportunity for therapeutic and preventative intervention; however, it is important to thoroughly investigate the link between the pathological cascade of AD and the emergence of clinical and cognitive symptoms of dementia.

In the last 30 years, neuropsychological research has tried to identify the most salient and earliest cognitive symptoms characterizing the dementia associated with AD [85–92]. AD pathology is initially marked by damage in limbic areas that are primarily involved in the episodic memory. With the advancing disease, other brain structures are progressively damaged, additional cognitive symptoms emerge, and the full dementia syndrome appears. These studies have suggested a revision of the established research diagnostic criteria for AD dementia [93]. The new diagnostic criteria not only defines the "dementia due to AD" [94], but also introduces an intermediate stage of "mild cognitive impairment due to AD" that precedes the dementia [95] and an earlier stage identified as "preclinical AD" [14]. This prodromal period is characterized by the presence of biomarkers, such as brain amyloid deposition and CSF tau and amyloid, that can be detected in asymptomatic individuals very early before the onset of progressive cognitive decline [14,96,97]. However, the neuropsychological assessment continues to provide reliable cognitive markers of AD that are crucial both for early and differential diagnosis. Spatial memory may also be selectively preserved in patients with semantic dementia, as it is one of the symptoms that can potentially differentiate between different types of dementia [98].

As mentioned above, Nestor and colleagues recently developed and tested the Virtual Route Learning Test (VRLT), which was shown to have sensitivity for detecting navigational impairment in very early AD and specificity in discriminating AD from Semantic Dementia [61]. Bird and colleagues [99] used a recently developed test of spatial memory—the Four Mountains Test—to compare the core cognitive processes underlying topographical disorientation in patients with aMCI and frontotemporal lobar degeneration (FTLD). The authors found a specific impairment in topographical short-term memory that may differentiate AD from FTLD. Finally, from a clinical perspective, we suggested that there is a "window of possibility" to develop cognitive rehabilitation interventions by detecting and treating earliest spatial deficits in "mental frame syncing" between egocentric and allocentric representations. Virtual Reality (VR) appears to be a suitable medium that offers several opportunities for effective cognitive neurorehabilitation interventions. Specifically, since one of its crucial features is interactivity, VR seems to be an "egocentric space" where individuals can train their ability to translate an allocentric representation into egocentric ones.

Conflicts of interest statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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