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Real-world navigation in amnestic mild cognitive impairment: The relation to visuospatial memory and volume of hippocampal subregions

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ABSTRACT

Spatial disorientation is a frequent symptom in Alzheimer's disease and in mild cognitive impairment (MCI). In the clinical routine, spatial orientation is less often tested with real-world navigation but rather with 2D visuoconstructive tasks. However, reports about the association between the two types of tasks are sparse. Additionally, spatial disorientation has been linked to volume of the right hippocampus but it remains unclear whether right hippocampal subregions have differential involvement in real-world navigation. Yet, this would help uncover different functional roles of the subregions, which would have important implications for understanding the neuronal underpinnings of navigation skills.

We compared patients with amnestic MCI (aMCI; n = 25) and healthy elderly controls (HC; n = 25) in a real-world navigation task that engaged different spatial processes. The association between real-world navigation and different visuoconstructive tasks was tested (i.e., figures from the Consortium to Establish a Registry for Alzheimer's Disease; CERAD, the Rey-Osterrieth Complex Figure task; and clock drawing). Furthermore, the relation between spatial navigation and volume of right hippocampal subregions was examined. Linear regression and relative weight analysis were applied for statistical analyses.

Patients with aMCI were significantly less able to correctly navigate through a route compared to HC but had comparable map drawing and landmark recognition skills. The association between visuoconstructive tasks and real-world navigation was only significant when using the visuospatial memory component of the Rey figure. In aMCI, more volume of the right hippocampal tail was significantly associated with better navigation skills, while volume of the right CA2/3 region was a significant predictor in HC.

Standard visuoconstructive tasks (e.g., the CERAD figures or clock drawing) are not sufficient to detect real-world spatial disabilities in aMCI. Consequently, more complex visuoconstructive tasks (i.e., the Rey figure) should be routinely included in the assessment of cognitive functions in the context of AD. Moreover, in those elderly individuals with impaired complex visuospatial memory, route finding behaviour should be evaluated in detail. Regarding the contribution of hippocampal subregions to spatial navigation, the right hippocampal tail seems to be particularly important for patients with aMCI, while the CA2/3 region appears to be more relevant in HC.

1. Introduction

In Alzheimer's disease (AD) and its prodromal stage, mild cognitive impairment (MCI), getting lost in new (but also familiar) environments is a frequent symptom of considerable relevance as it severely impairs daily life. Spatial disorientation is related to early degeneration of right medial temporal lobe structures, including the hippocampus (Vlček and Laczó, 2014), which runs along a posterior-to-anterior axis in humans (Strange et al., 2014) and consists of multiple sub-regions, including the hippocampal tail, the cornu ammonis areas (CA1-CA4), the dentate

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Table 1
Socio-demographic data and group comparison for visuoconstructive memory functions in a sample of healthy elderly controls and patients with amnestic mild cognitive impairment (aMCI). Student's *t*-tests were used for group differences unless stated otherwise.

	Healthy controls		aMCI		*p*-value
	Mean	SD	Mean	SD	
n (m/f)	25 (15/10)		25 (12/13)		0.39 (χ^2 test)
Age (years)	69.2	5.3	73.1	5.2	0.01
Education (years)	14.8	3.3	13.5	3.2	0.18
MoCA (0–30)	27.0	1.9	22.7	2.9	< 0.0001
Clock drawing (score 0–5)	/	/	2.09	0.92	
CERAD visuoconstruction (drawing; 0–11 points)	/	/	10.4	1.5	
CERAD visuoconstructive memory (recall; 0–11 points)	/	/	5.4	2.7	
ROCF visuoconstruction (drawing; 0–36 points)	35.4	0.8	31.8	7.2	0.02
ROCF visuoconstructive memory (recall; 0–36 points)	18.1	6.6	10.6	6.7	0.0002
BDI-II	6.2	5.0	7.8	4.8	0.23
GDS	1.2	1.5	1.8	1.7	0.12

Note: SD = standard deviation, aMCI = amnestic mild cognitive impairment, MoCA = Montreal Cognitive Assessment, CERAD = Consortium to Establish a Registry for Alzheimer's disease, ROCF = Rey-Osterrieth Complex Figure. For the MoCA, a score ≥ 26 was used as a cut-off between healthy aging and mild cognitive impairment and a score ≥ 17 was used as a cut-off between mild cognitive impairment and dementia.

gyrus (DG), and the subiculum (Strange et al., 2014). Besides the hippocampus, other parts of the brain (e.g. parietal or frontal) seem to also play a role in spatial navigation (Maguire et al., 1998; Wolbers and Wiener, 2014) but the utilization of information to create a map first occurs in the right hippocampus (Lisman et al., 2017). Other areas might to be more important during passive viewing of navigation-related stimuli (i.e., the parietal cortex), for spatial subtask components, or during planning (i.e., the prefrontal cortex) (Epstein et al., 2017). Previous studies have associated parietal areas with egocentric[1] processing and the hippocampus with allocentric processing (but see Ekstrom et al., 2014; Wolbers and Wiener, 2014 for a critical review). Recently, spatial disorientation in real-world navigation tasks was suggested to be particularly sensitive at detecting the earliest cognitive signs of AD (Allison et al., 2016) and to predict development of pre-dementia syndromes (Verghese et al., 2017). Yet, real-world navigation is not included in the assessment of cognitive functions in the clinical routine, mostly due to limited time and the lack of ecologically valid approaches. Instead, 2D visuoconstructive paper-pencil tasks are typically applied to assess spatial abilities, although their usefulness in detecting real-world spatial disorientation remains unclear. Common tasks to assess spatial abilities in the clinical routine are clock drawing tests (Shulman et al., 1986), figures from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al., 1989), the pentagons from the Mini Mental Status Examination (MMSE; Folstein et al., 1975), or the Rey-Osterrieth Complex Figure task (ROCF; Rey, 1941). The last three include copying (typically activating parietal regions) and later recall (consistently activating temporal areas, including the hippocampus) (Wicking et al., 2014). Clock drawing, on the other hand, contains drawing a picture ‘from memory’, which means that an internal representation of space and clock appearance has to be retrieved. Left (time setting) and right (number placement and spatial organisation) parietal regions as well as left temporal regions (semantic memory; i.e., clock appearance) seem to be primarily responsible for accurate clock drawing (Leyhe et al., 2009; Tranel et al., 2008). So far, no study had compared the predictive value of different 2D visuoconstructive tasks for 3D real-world navigation.

Regarding right hippocampal activity in spatial orientation, one previous real-world navigation study in AD (n = 13) and MCI (n = 21) found an association between less volume of the right hippocampus and enhanced navigation impairment, which was suggested to reflect a specific pattern of neural atrophy in the right-lateralised human navigation network (DeIpolyi et al., 2007). The authors did not further specify which area of the right hippocampus (i.e., which subregion) was associated with getting lost on the route. A further characterisation of right hippocampal subregions for spatial navigation in aging and MCI would extend current knowledge as no specific functional roles have been distinguished yet. Certainly, some authors believe that the right hippocampal tail (i.e., the posterior hippocampus) is crucial for precise spatial behaviour (e.g., Wolbers et al., 2014) while others have found the cornu ammonis area 1 (CA1) to be essential (Suthana et al., 2009).

The aims of our study were to investigate the predictive value of different 2D visuoconstructive tasks for 3D real-world navigation and to assess the relation between real-world navigation and volume of right hippocampal subregions in a sample of patients with aMCI. Our aim was not to differentiate between allocentric and egocentric processes although we see this as an interesting approach in the current literature. Since we focused on subregions of the right hippocampus (in order to uncover different functional roles of those), we did not consider other brain areas (e.g. parietal regions). We hypothesize that (1) healthy elderly controls would outperform patients with aMCI in navigation abilities, (2) the diverse visuoconstructive tasks would have different predictive value for 3D navigation, and (3) subregions of the hippocampus would be differentially involved in 3D navigation.

2. Materials and methods

2.1. Participants

Twenty-five patients with aMCI (73.1 ± 5.2 years, range: 60–82; 12 females, 13.5 ± 3.2 years of education, range: 8–20) and 25 healthy gender-, and education-matched controls (69.2 ± 5.3 years, range: 61–81; 10 females; 14.8 ± 3.3 years of education, range: 7–20) were included in our study (Table 1). Patients with aMCI were recruited from the Center for Geriatric Medicine and Gerontology of the University Medical Center Freiburg. The proportion of single-domain vs. multiple-domain amnestic MCI was 7/18. To increase diagnostic certainty, a clinical follow-up was implemented after 12 months. At clinical follow-up almost all participants were again diagnosed with MCI while two participants progressed to AD (corresponding to an annual conversion rate of 8%, which is in line with the current literature; e.g., Mitchell and Shiri-Feshki, 2009). None of our patients with MCI reverted to normal cognition at clinical follow-up. Healthy controls were community-dwelling citizens, recruited via newspaper advertisement and flyers circulated in Freiburg. The study was approved by the Ethics Committee of the University Medical Center Freiburg and conducted

[1] Spatial information such as direction or distance can be coded egocentrically (i.e., relative to an observer) or in an allocentric way (i.e., in a reference frame independent of the observer's position and orientation).