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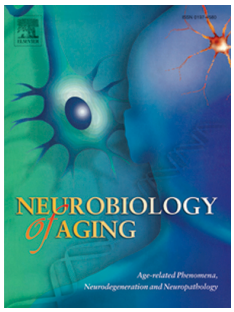

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Exploring the contribution of spatial navigation to cognitive functioning in older adults

Running title: Contribution of spatial navigation to cognitive functioning

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Abstract

Spatial navigation impairment is present early in Alzheimer's disease. We tested whether spatial navigation performance, self-centered (egocentric) and world-centered (allocentric), was distinguishable from performance on established cognitive functions—verbal and non-verbal memory, executive and visuospatial function, attention/working memory and language function. 108 older adults (53 cognitively normal [CN] and 55 with amnestic mild cognitive impairment [aMCI]) underwent neuropsychological examination and real-space navigation testing. Subset (n=63) had automated hippocampal volumetry. In a factor analysis, allocentric and egocentric navigation tasks loaded highly onto the same factor with low loadings on other factors comprising other cognitive functions. In linear regression, performance on other cognitive functions was not, or was only marginally, associated with spatial navigation performance in CN or aMCI groups. After adjustment for age, gender and education, right hippocampal volume explained 26% of the variance in allocentric navigation in aMCI group. In conclusion, spatial navigation, a known cognitive marker of early Alzheimer's disease, may be distinguished from other cognitive functions. Therefore, its assessment along with other major cognitive functions may be highly beneficial in terms of obtaining a comprehensive neuropsychological profile.

Keywords: Alzheimer's disease; mild cognitive impairment; Morris Water Maze; spatial navigation; hippocampus; neuropsychology.

1. Introduction

Alzheimer's disease (AD) is one of the most common and devastating diseases of older age. Among cognitive deficits related to underlying AD pathology, episodic memory dysfunction is considered to be the main early marker of the disease (Mistridis et al., 2015). Recently, an increased attention has been paid to spatial navigation (SN) (Lithfous et al., 2013) as another promising cognitive marker of early AD (Benke et al., 2014). Despite research on the utility of SN in identifying early AD (for review see (Vlcek and Laczo, 2014), only little attention has been paid to how SN fits among the established cognitive functions (deIpolyi et al., 2007). The question remains as to whether SN is a component of the established domains or a distinct function? Two types of SN are recognized—self-centered (egocentric), dependent on an individual's position, and world-centered (allocentric), which is independent of an individual's position and relies on distal cues for navigation (Maguire et al., 1998). Allocentric navigation in particular appears to be impaired in amnestic mild cognitive impairment (aMCI) (Weniger et al., 2011) and preclinical AD (Allison et al., 2016).

Our primary aim was to examine the association between egocentric and allocentric types of SN in relation to established cognitive functions, and to assess the relative contribution of hippocampal volume to the performance on SN and memory functions. We used a sample of 55 cognitively normal (CN) participants and 53 with aMCI to specifically examine whether (1) scores from egocentric and allocentric SN tasks and scores from neuropsychological tests on six established cognitive functions (verbal and non-verbal memory, executive and visuospatial function, attention/working memory and language function) would load on separate factors in a factor analysis, indicating that separate underlying processes may govern SN performance versus other cognitive functions, (2) six established cognitive functions would be associated with egocentric and allocentric navigation and (3) volume of the right hippocampus, a key structure for allocentric navigation (Maguire et al., 1998), which tends to be impaired early in AD (Braak and Braak, 1991), would be associated with allocentric navigation more strongly than with memory performance.

2. Materials and Methods

2.1. Participants

One hundred and eight older adults aged 60 years or more were recruited from the Czech Brain Aging Study, a longitudinal study on risk factors for AD. The detailed recruitment strategies were described previously (Laczo et al., 2015). Participants underwent neuropsychological and SN testing within 2 months of brain MRI. Participants with depression (>5 points on the

15-item Geriatric Depression Scale), history of other major neurological or psychiatric disorders, Hachinski Ischemic Scale score >4 and those meeting criteria for dementia were not included. The participants with aMCI (n=55) met revised Petersen's criteria for aMCI (Petersen, 2004) including memory complaints reported by patient or caregiver, evidence of memory dysfunction on neuropsychological testing, generally intact activities of daily living and absence of dementia. Memory impairment was established when they scored more than 1.5 standard deviations below the mean of age- and education-adjusted norms on any memory test (Laczo et al., 2015). The group included patients with isolated memory impairment (single domain aMCI) and patients with memory impairment and additional deficits in at least one other cognitive domain (multiple domain aMCI). The CN participants (n=53) reported no cognitive problems and scored less than 1.5 standard deviations below the mean of age- and education-adjusted norms on any cognitive test. Above and beyond the exclusion criteria they had normal brain MRI and did not take any psychiatric medication. All participants signed written informed consent approved by the institutional ethics committee.

2.2 Neuropsychological battery

The following tests were included in the neuropsychological battery: 1) the Auditory Verbal Learning Test (AVLT) – trials 1–6 and 30-minute Delayed Recall trial and a 16-item picture version of the Enhanced Cued Recall Test (ECR) – total recall score as the measures of verbal memory; 2) the Rey-Osterrieth Complex Figure Test (ROCF) – the Delayed Recall condition (ROCF-D) as the measure of non-verbal memory; 3) the ROCF – the Copy condition as the measure of visuospatial function; 4) the Trail Making Test (TMT) B and Controlled Oral Word Association Test as the measures of executive function; 5) the Backward Digit Span and TMT A as the measures of attention and working memory; and 6) the Boston Naming Test (30-item version) as the measure of language function. The Mini-Mental State Examination was used to measure global cognitive function. Neuropsychological characteristics are described in Supplementary Table 1.

2.3. Spatial navigation testing

We used the real-space version of a Hidden Goal Task. The Hidden Goal Task is designed as a human analogue of the Morris Water Maze (hMWM) test that allows for to separately evaluate allocentric versus egocentric types of navigation (Hort et al., 2007). The Hidden Goal Task was performed in a real-space setting —the Blue Velvet Arena (Suppl. Fig. 1A) (Kalova et al., 2005). The task for individual participants was to locate the invisible goal on the arena floor using the start position (egocentric) or two distal orientation cues on the wall (allocentric), respectively (Suppl. Fig. 1B). This was

preceded by the initial phase that involved locating the goal using both, the start position and the two distal orientation cues on the arena wall to initially provide maximum available information on the goal position. The egocentric task involved using only the start position to locate the goal with no distal orientation cues displayed. The allocentric task involved using only two distal orientation cues at the arena wall for navigation to the goal from the start position unrelated to the goal position. Both ego- and allocentric tasks had 8 trials and the correct position of the goal was shown after each trial to provide the feedback. The relative positions (distances and directions) of the goal to the start or orientation cues in the egocentric and allocentric tasks remained constant across all trials. After each trial, the goal position, along with the start position and the positions of the cues in the egocentric and allocentric tasks were rotated in a pseudorandom sequence and the participant was instructed to go to the new start position at each consecutive trial. The goal positions and the number of trials were identical across all participants. SN performance derived as distance error in centimeters from the correct hidden goal position was automatically recorded by in-house developed software. The tasks had no time limit.

2.4. MRI acquisition and analysis

Brains were scanned at 1.5T MR scanner (Gyroscan, Philips Medical Systems, Best, The Netherlands). A T1 weighted, three dimensional pulse sequence Fast Field Echo with 170 contiguous coronal partitions and following parameters was used: TE/TR = 5/25 ms, flip angle 30°, FOV = 256 mm, matrix 256 × 256, 1.0 mm slice thickness, no gap, voxel size 1x1x1.25mm and in-plane resolution 1 mm. In the CN (n=27) and aMCI (n=36) groups we used fully automated FreeSurfer algorithm, v 4.4.0 (http://surfer.nmr.mgh.harvard.edu) (Fischl et al., 2004) to compute left and right hippocampal volumes. Volumes were adjusted for the differences in head size (Jack, Jr. et al., 1989).

2.5. Data and statistical analyses

To assess SN performance, we calculated the average distance error across all eight attempts for allocentric and egocentric navigation tasks, respectively. The score for each individual cognitive function was expressed as a unit-weighted composite z-score from the relevant neuropsychological tests. The values from TMT A and B expressed in seconds to completion of these tests were reversed before the z-scores were generated. All data were found to be adequate for parametric analysis. Initially, we examined descriptive statistics and correlations (Pearson) among study variables. To delineate SN and other specific cognitive functions, we performed an exploratory factor analysis separately for CN and aMCI groups. Principal components factor extraction with Varimax rotation was used to derive common underlying factors. Rotated factors with

eingenvalues >1 were extracted. Associations between particular cognitive function and allocentric or egocentric navigations were evaluated for CN and for aMCI groups using multivariate linear regression controlling for age, gender and education. Change in model fit, reported as change in r-squared (ΔR^2), was assessed by adding individual cognitive function score to a covariate-adjusted model. Identical approach was used to explore the association between hippocampal volumes and memory tests (AVLT, ECR and ROCF-D), allocentric or egocentric navigation. Significance was set at two-tailed .05. All analyses were conducted with IBM SPSS 20.0 software.

3. Results

3.1. Descriptive analysis

Descriptive statistics and the results of correlation analyses of demographic variables, neuropsychological, SN scores and volumes of right and left hippocampi are displayed in Supplementary Tables 1, 2 and 3.

3.2. Factor analysis

Results of the factor analysis in the CN and aMCI groups showing the highest loading for each item are summarized in Table 1. Both analyses yielded 5 factors with eigenvalues >1. Allocentric and egocentric navigation loaded highly onto the same single factor ("SN") and showed low loadings on other factors in both CN and aMCI groups. Conversely, each of the neuropsychological tests showed low loading on (or low relation with) the SN factor in both CN and aMCI groups. Although other factors were represented by different variables across the CN and aMCI groups, the SN factor remained the same.

3.3. Association between individual cognitive functions and SN

In the CN group (Suppl. Table 4), the established cognitive functions were not associated with allocentric or egocentric navigation. In the aMCI group (Suppl. Table 5), executive function was associated with allocentric navigation and explained 11% of its variance above and beyond the covariates. There was a trend for association between visuospatial function and allocentric navigation. Verbal memory was associated with egocentric navigation and explained 9% of its variance.

3.4. Association between hippocampal volumes, SN and memory tests

In the CN group (Suppl. Table 6), hippocampal volumes were not associated with either performance on SN or memory tests. In the aMCI group (Suppl. Table 7), both right and left hippocampal volumes were associated with allocentric navigation and explained 26% and 12%, respectively, of its variance after adjustment for the covariates. Left hippocampal volume was associated with performance on AVLT and ECR and explained 9-14% of their variance. In addition, right hippocampal volume was associated with performance on ECR and explained 13% of its variance. The associations between hippocampal volumes, egocentric navigation and ROCF-R were not significant.

4. Discussion

We examined the notion that SN may be distinguished from other cognitive functions by using a data reduction technique (factor analysis) to identify discrete factors as well as by linear regression to test associations (a) between established cognitive functions and SN and (b) between SN, memory performance and hippocampal volume, the known biomarker of AD. Using a real-space hMWM to assess SN, we found that allocentric and egocentric navigation scores loaded on its own factor that was separate from six established cognitive functions (verbal and non-verbal memory, executive and visuospatial function, attention/working memory and language function) in an exploratory factor analysis. Therefore, it appears that SN shares only limited variance with other cognitive abilities. Further, SN performance was not associated with performance on any established cognitive function among the CN older adults. Only executive function was associated with allocentric navigation and verbal memory was associated with egocentric navigation among those with aMCI. Still, these associations accounted only for a small proportion of the variance in SN (11% and 9%, respectively). Finally, left and right hippocampal volumes were not found to be associated with SN or any other cognitive function among CN older adults. However, among participants with aMCI, both left and right hippocampal volumes were associated with allocentric navigation, and explained 12% and 26%, respectively, of the variance in allocentric navigation after adjustment for age, gender and education.

Although hippocampal volumes were also related to memory tests, especially the tests of episodic memory, volumes did not explain more than 14% of the variance in memory performance, which is in line with previous findings (Sarazin et al., 2010). Therefore, hippocampal volumes explained substantially smaller proportion of the variance in memory than in allocentric navigation. Together, these findings support the notion that SN may be distinguished from other cognitive functions and that its testing provides additional relevant information about the cognitive profile beyond the established neuropsychological tests. Our findings build on previous research suggesting that SN is impaired early in the course of AD

(Benke et al., 2014) and that right hippocampal atrophy indicates the severity of SN impairment (Nedelska et al., 2012). Given the central role of the hippocampus in AD pathology (Braak and Braak, 1991), these results further underscore the utility and additional value of SN testing in the assessment of people at risk for AD. Among participants with aMCI, our findings for the associations between right and left hippocampal volumes and allocentric, but not for egocentric, navigation performance also fit into the current knowledge about spatial navigation which indicates that allocentric navigation relies more on the hippocampus (Nedelska et al., 2012), whereas egocentric navigation relies more on the medial parietal regions (Weniger et al., 2011).

This study is not without limitations. First, our results are based on SN testing in real-space hMWM, which may be somewhat difficult to implement broadly. However, it is likely that the presented results would be replicated with an easier-to-use computerized hMWM that provided almost identical results in the previous studies (Laczo et al., 2014) and strongly correlated with the real-space setting (Laczo et al., 2012). Second, brain MRI volumetry was not performed in all subjects and was restricted to the hippocampus. This may limit power to detect significant associations between cognitive performance and brain morphometric characteristics and reduces generalizability of our findings. Third, spatial navigation and spatial memory, which was unavailable in this study, may form the same construct. While we focused on a standard battery of well-established neuropsychological tests that measures established cognitive functions, the overlap with spatial memory should be studied in future research. However, the finding that spatial navigation and memory together form a distinct construct may only underscore the need for a more widespread assessment of these abilities. Finally, it would be of interest to elucidate the underlying cognitive factors assessed by different neuropsychological tests in cognitively normal and impaired older adults. This should be also the focus of future studies.

In conclusion, our results suggest that SN may be distinguished from other cognitive functions and its assessment is beneficial when characterizing cognitive performance in older adults, particularly in those at risk for AD. These results can serve as a basis for future research to further improve our understanding of SN, its relation to other cognitive functions and its utility in detecting early signs and monitoring the course of AD.

Disclosure statement

Dr Harrison has consulted for Abbvie, Astra-Zeneca, Avraham, Boehringer Ingelheim, Bracket (Clinical), CRF Health, EnVivo Pharma, ePharmaSolutions, Eisai, Eli Lilly, Heptares, Janssen AI, Kyowa Hakko Kirin, Lundbeck, MedAvante, Merck, MyCognition, Novartis, Nutricia, Orion Pharma, Pharmanet/i3, Pfizer, Prana Biotech, ProStrakan, Reviva, Shire, Servier, TCG and TransTech Pharma & Velacor. Dr Hort consulted for Pfizer, Merck, Axon, Sotio, Elan, Novartis, Ipsen, Janssen and Zentiva. Dr Laczó, Dr Andel, Dr Nedelska, Dr Vyhnalek, Dr Vlcek and Dr Crutch report no disclosures.

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Table 1

Factor analyses of spatial navigation tasks and neuropsychological tests

	Cognitively normal older adults[a]					**Amnestic mild cognitive impairment[b]**				
	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Egocentric task	-0.19	-0.27	0.44	**0.65**	0.28	-0.18	0.01	**0.93**	-0.05	0.11
Allocentric task	0.03	-0.01	0.03	**0.90**	-0.06	0.37	0.02	**0.78**	0.31	0.04
AVLT sum of trials 1-6	-0.01	**0.97**	0.14	-0.04	0.01	**0.90**	0.21	-0.20	-0.12	-0.14
AVLT 30	0.10	**0.81**	0.29	-0.06	0.08	**0.77**	-0.12	-0.15	0.07	0.44
ECR Total Recall score	-0.12	0.07	-0.04	0.04	**0.89**	**0.59**	-0.28	-0.36	0.43	0.26
ROCF-D	0.19	0.18	**0.71**	0.16	-0.14	**0.86**	-0.21	0.03	0.37	-0.01
ROCF Copy condition	-0.05	0.20	**0.72**	0.13	0.10	0.02	-0.06	-0.13	0.14	**-0.90**
Trail Making Test B	**0.72**	0.07	0.14	-0.13	0.05	0.21	0.13	0.05	**0.88**	-0.04
COWAT	**0.62**	0.01	0.15	-0.21	-0.13	0.23	**0.74**	0.10	0.33	-0.21
Backward Digit Span	**0.92**	0.05	-0.11	0.11	-0.06	-0.01	**0.95**	0.03	-0.8	0.09
Trail Making Test A	**0.57**	0.02	0.32	0.04	0.43	-0.13	-0.09	-0.48	**0.65**	-0.01
Boston Naming Test	**-0.54**	-0.44	-0.09	0.44	0.15	0.07	0.03	0.49	**-0.72**	0.36
Eigenvalue	3.30	2.86	2.18	1.58	1.15	3.63	3.06	2.44	2.31	1.42

[a]Note. N = 53. These 5 factors explained 73.7% of total variance in the model. Factor 1 = working memory, attention, executive and language; Factor 2 = verbal memory without cueing; Factor 3 = visuospatial and non-verbal memory; Factor 4 = spatial navigation; Factor 5 = verbal memory with cueing. The tests within the same factor are highlighted in bold.

[b]Note. N = 55. These 5 factors explained 85.7% of total variance in the model. Factor 1 = memory; Factor 2 = attention and executive; Factor 3 = spatial navigation; Factor 4 = executive, working memory and language; Factor 5 = visuospatial. The tests within the same factor are highlighted in bold. Key: AVLT, Auditory Verbal Learning Test; AVLT 30, AVLT 30-minute Delayed Recall; ECR, Enhanced Cued Recall Test; COWAT, Controlled Oral Word Association Test; ROCF, Rey-Osterrieth Complex Figure Test; ROCF-D, ROCF Delayed Recall condition.

Highlights (maximum 85 characters, including spaces)

- We recruited older adults with and without mild cognitive impairment
- We examined association between spatial navigation and other cognitive functions
- We examined association between hippocampal volume, spatial navigation and memory
- Allocentric and egocentric navigation related poorly to other cognitive functions
- Hippocampal volume explained more variance in allocentric navigation than in memory