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Title: Spatial navigation deficits in amnesic mild cognitive impairment with neuropsychiatric co-morbidity

Running head: Spatial navigation in aMCI with comorbidity

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Abstract

Aims: To find out whether neuropsychiatric comorbidity (comMCI) influences spatial navigation performance in amnesic mild cognitive impairment (aMCI).

Methods: We recruited aMCI patients with (n=21) and without (n=21) neuropsychiatric comorbidity or alcohol abuse, matched for global cognitive impairment and cognitively healthy elderly participants (HE, n=22). They completed the Mini-Mental State Examination and a virtual Hidden Goal Task in egocentric, allocentric and delayed recall subtests.

Results: In allocentric navigation, aMCI and comMCI performed significantly worse than HE and similarly to each other. Although aMCI performed significantly worse at egocentric navigation than HE, they performed significantly better than patients with comMCI.

Conclusions: Despite the growing burden of dementia and the prevalence of neuropsychiatric symptoms in the elderly population, comMCI remains under-studied. Since trials often assess “pure” aMCI, we may underestimate patients’ navigation and other deficits. This finding emphasizes the importance of taking account of the cognitive effects of psychiatric disorders in aMCI.

Keywords: Mild Cognitive Impairment; neuropsychiatric comorbidity, spatial navigation; spatial memory

Introduction

Spatial navigation is often defined as a process of determining and maintaining a trajectory from one place to another (Sékoléne, Dufour, & Després, 2012). Two types of navigational strategies are distinguished, with evidence of distinct underlying brain structures: egocentric and allocentric navigation (Morris, Garrud, Rawlins, & O'Keefe, 1982; Chersi & Burgess, 2015). Egocentric navigation is self-centered, viewpoint-dependent navigation, associated with response learning from one's own position. It uses distances or angles to and from individual landmarks, is associated with navigation of well-known paths, and is thought to rely on parietal-cortical and striatal brain regions (Wolbers, Weiller, & Büchel, 2004). Allocentric navigation is independent of the individual's viewpoint, referring instead to distal cues. It encompasses the spatial layout of an environment from a survey or "bird's eye view" perspective, learning the position of landmarks in relation to other landmarks. Allocentric navigation relies on the medial temporal lobe, particularly the hippocampus (Burgess, Maguire, & O'Keefe, 2002); more recent studies have demonstrated a correlation between basal forebrain volume and spatial accuracy in allocentric but not egocentric navigation (Kerbler et al., 2015).

The Morris water maze is a classic test used to study spatial learning and memory in rats (Morris, 1981), who learn to find a hidden platform under the surface of a pool, using visual cues placed around the room. Successful completion of the Morris water maze is highly sensitive to hippocampal damage. The Hidden Goal Task (HGT) is a human analogue of Morris water maze, of which real-world and virtual versions exist (Kalova, Vlček, Jarolimova, & Bureš, 2005). Studies using the HGT have demonstrated spatial navigation impairment in patients diagnosed with Alzheimer's disease and mild cognitive impairment of different sub-types (Hort, et al., 2007; Laczó et al., 2009), when compared with cognitively healthy control participants.

Amnesic mild cognitive impairment (aMCI) is characterized by memory deficits beyond those expected for normal aging, which may be selective (single-domain aMCI) or accompanied by deficits

in at least one other cognitive domain, such as language, attention, executive function or visuospatial skills (multiple-domain aMCI), and is associated with an elevated risk of developing Alzheimer's disease (Petersen, 2004). Spatial navigation impairment is an early feature of Alzheimer's disease (Henderson, Mack, & Williams, 1989; Hort et al., 2007) and may result from hippocampal atrophy, which is also observed in aMCI (Shi et al., 2009).

Different sub-tests of the HGT can be used to assess egocentric and allocentric navigation. Using both virtual and real-world formats, differential patterns of spatial navigation deficits have been demonstrated in patients with multiple-domain aMCI and those with single-domain aMCI (Hort et al., 2007). Both real-space and computerized versions of the HGT reliably identify aMCI (Laczó et al., 2012) and it is sensitive enough to detect disease progression in the clinical setting (Laczó et al., 2009). A recent functional imaging study found that in comparison to controls, patients with aMCI showed reduced activity in the hippocampus bilaterally, retrosplenial cortex and left dorsolateral prefrontal cortex during a virtual reality analogue of the radial arm maze, despite relatively normal task performance (Migo et al., 2016). Increased right dorsolateral prefrontal cortex activity in aMCI patients was thought to indicate a potential mechanism to compensate for underactivity in other brain regions.

Mild cognitive impairment can often be accompanied by other neuropsychiatric conditions but such patients are usually excluded from research participation (Stephan, Brayne, Savva & Matthews, 2011). Whilst there is evidence that psychiatric disorders, such as depression, anxiety, and alcohol use also affect spatial cognition (see below), the effect of these neuropsychiatric comorbidities on spatial navigation is under-researched, especially in humans. Moreover, the presence of these neuropsychiatric complaints can result in missed or erroneous diagnoses in the clinical setting.

The role of the hippocampus in the etiology of neuropsychiatric disorders such as depression is an area of growing research interest (Sahay & Longmore, 2007). Spatial memory, a key component of spatial navigation, has been demonstrated to be significantly poorer in depressed patients when compared to healthy controls using a novel virtual reality navigation task (Gould, Holmes, Fantie,

Luckenbaugh, Pine, et al., 2007), whilst a virtual Morris water maze task showed impaired allocentric spatial navigation in depressed patients (Cornwell et al., 2010). Such spatial navigation deficits in depressed patients have been linked to hippocampal structural and functional abnormalities (Campbell, Marriott, Nahmias, & MacQueen, 2004; Videbech, & Ravnkilde, 2004).

A number of studies have reported multiple-domain cognitive impairment in patients with alcohol dependence syndrome during short-term abstinence, with spatial processing deficits most common (Knight & Longmore, 1994; Ceccanti et al., 2015). Selective spatial processing deficits seem to remain even after long-term abstinence in middle-aged patients after recovery from alcohol dependence (Fein, Torres, Price, & Sclafani, 2006). However, no deficits in spatial processing were found in long-term abstinent elderly patients after recovery from alcohol dependence, relative to age- and gender- comparable light or non-drinking controls (Fein, & McGillivray, 2007). The direct impact of chronic alcohol misuse on spatial navigation in humans is under-researched, despite inconsistent findings about the effect of alcohol consumption on spatial navigation in rodents (Matthews, Simson, & Best, 1996; Santín, Rubio, Begega, & Arias, 2000; Steigarwald & Miller, 1997).

The aim of this study was to characterize spatial navigation deficits in patients with amnesic mild cognitive impairment and a neuropsychiatric co-morbidity (depression, anxiety and history of alcohol abuse: comMCI) compared with amnesic MCI without neuropsychiatric co-morbidity (aMCI) and healthy controls. For this purpose, we used the Hidden Goal Task (HGT), a human analogue of the Morris water maze, to assess spatial navigation performance.

Method

Participants

A total of 65 patients without a diagnosis of dementia were recruited from St Thomas' Hospital Neuropsychiatry and Memory Disorders Clinic, London, United Kingdom (UK), and from Motol University Hospital Memory Clinic, Prague, Czech Republic (CZ). The sample comprised 21 patients with aMCI and co-morbid mood disorder or alcohol abuse (comMCI), 21 patients with aMCI without neuropsychiatric co-morbidity, and 22 cognitively healthy elderly (HE) participants.

ComMCI and aMCI participants were referred to specialist clinics by general practitioners, neurologists, psychiatrists, and geriatricians based on cognitive complaints reported by the patient or the caregiver. HE participants were recruited from the University of the Third Age, an educational institution for older adults, and relatives of patients.

A neuropsychiatrist (UK site) or a cognitive neurologist (CZ site) together with a clinical neuropsychologist evaluated each participant in a consensus diagnostic session incorporating the patient's medical history, collateral history from a knowledgeable informant, neuropsychological testing, and neuroimaging.

Inclusion and Exclusion Criteria

Inclusion criteria for aMCI were age between 55 and 80 and cognitive deficit meeting established revised clinical criteria (Petersen, 2004; Table 1). Participants assigned to the comMCI group met criteria for aMCI and had a clinical history of mood, psychotic disorder or schizoaffective disorder, or history of alcohol abuse (daily alcohol consumption >40 g for women and > 80 g for men). The corresponding ICD-10 categories for comorbidities were F32: depressive episode, F20: schizophrenia, F25: schizoaffective disorders, F41: other anxiety disorders and F10.1: mental and behavioral disorders due to use of alcohol: harmful use. The HE group comprised participants reporting no subjective cognitive difficulties, who did not score lower than 1.5 standard deviations

below mean age- and education-adjusted norms on neuropsychological tests of working memory, episodic memory, executive function, language, and visuospatial skills.

Consenting participants were assigned to groups using a combination of their clinical history, clinically performed neuropsychological assessments, and Beck anxiety and/or depression scores, where available. Verbal recall, visual recall and executive function had been measured during clinical assessments across the two sites, but using different rating scales. Raw scores were therefore converted to Z-scores at each site. Depressive symptoms were measured using the Beck Depression Inventory (BDI-II; UK site) and the 15 item Geriatric Depression Scale (GDS-15; CZ site). Scores on each measure were categorized for severity of depression according to published norms.

Table 1

Exclusion criteria were current acute psychotic episode, acute major depressive episode, acute intoxication during assessment, severe visual and auditory impairment, a history of stroke, severe cranio-cerebral trauma, epilepsy, multiple sclerosis, or non-cooperation.

Participant groups were matched, based on age, Mini-Mental State Examination (MMSE) score and years in education (Table 2).

Ethics

Ethical approval for UK recruitment was obtained from the Camberwell St Giles Research Ethics Committee (ref:13/LO/1101). Ethical approval for CZ recruitment was obtained from the Motol University Hospital Ethics Committee. All participants gave written, informed consent.

Procedure

An initial interview obtained demographic information about the participant's age, education and subjective difficulties with spatial navigation. Participants then completed the computerized

Hidden Goal Task (HGT) and an MMSE (Folstein, 1975) to screen for the severity of any cognitive impairment, before the delayed recall (allocentric) subtest of the HGT.

The HGT is a well-validated method designed to measure egocentric and allocentric navigation (Kalova, Vlček, Jarolimova, & Bureš, 2005). Participants were required to learn where a goal (small purple circle, 10 arbitrary units in diameter) was located within an “arena” (larger white circle, 280 arbitrary units in diameter), by using its relationship to the starting point’s position (filled red circle outside the arena) and the orientation cues (red and green lines parallel to the arena’s contour) and try to find it again when it was hidden. They did so by dragging the cursor from the starting point to its anticipated location.

Participants were required to locate a hidden goal in three different subtests of the HGT (Figure 1): egocentric (using the starting point’s position for orientation), allocentric (using external orientation cues) and delayed recall (allocentric). The process was demonstrated by the researcher before trials began, for each subtest.

Egocentric and allocentric subtests featured eight trials. The configuration of the starting point, orientation cues, and goal remained the same during the task, and was displayed on a demonstration screen once before testing commenced. During each trial, the screen image rotated into different positions, equally spaced around the arena in a fixed order. Before each trial, the participant was reminded to locate the goal in its position, relative to the starting point or orientation cues (depending on the subtest). After the participant had selected the location of the hidden goal, its correct position was displayed, and he or she was reminded to take note of its relative position to the starting point and orientation cues, if present.

The delayed recall subtest was similar to the allocentric subtest but consisted of only two trials administered 30 minutes after the end of the allocentric subtest, in which the correct goal position was not displayed.

There was no time limit to locate the goal. The outcome measure was the distance error from the goal in pixels, where a smaller number indicated better performance.

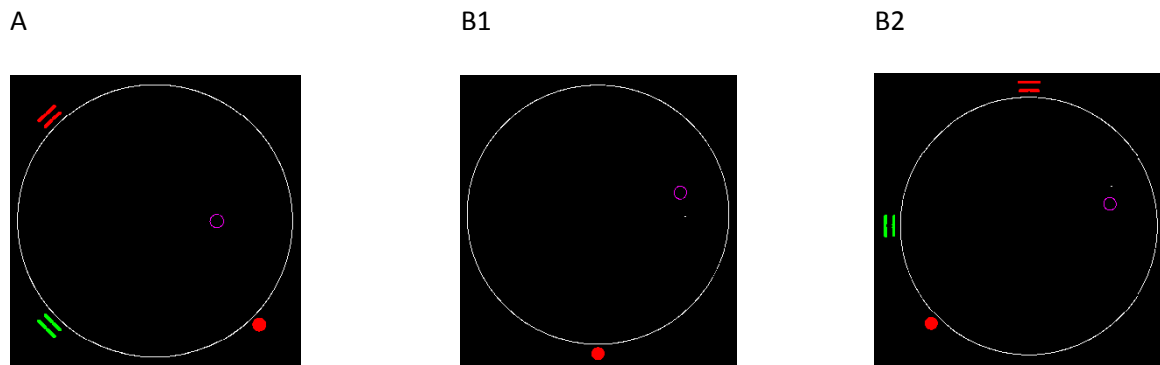


Figure 1: Hidden Goal Task Screens: (A) Arena (large white circle) as displayed on the demonstration screen before testing, with starting point (red filled circle), orientation cues (red and green lines) and goal (purple circle) marked; (B1) Egocentric trial; (B2) Allocentric trial.

Analysis

The distances between participants' selected location for the hidden goal and its true location were used to calculate mean distance errors for each individual and then group. As the assumption of normality was not breached (values of skewness and kurtosis ranged from -1 to +1), we performed a parametric one-way ANOVA, with Tukey post hoc test, to evaluate between-groups differences in demographic characteristics, and mean distance errors in egocentric, allocentric and delayed recall subtests. To compare background neuropsychological characteristics between the two patient groups (aMCI and comMCI), raw scores for visual recall, verbal recall and executive function available across both sites were converted to Z-scores according to published age- and education-adjusted norms. As the assumption of normality had been breached (values of skewness and kurtosis ranged outside -1 to +1), Z-scores were compared using the non-parametric Mann-Whitney U test. The independent samples T-Test was additionally performed, for confirmation. To report effect sizes, Cohen's d was calculated. Depressive symptoms were categorized as minimal, mild, moderate or severe, according to published norms for each rating scale. The two patient groups (aMCI and comMCI) were compared in terms of severity of depression across these categories using the Chi-Square test.

The rank-based nonparametric Kruskal-Wallis H Test was performed to determine if there were statistically significant differences in egocentric, allocentric and delayed recall performance between comMCI participants with different comorbid clinical diagnoses. The significance level (alpha) throughout the analyses was set at .05. All statistics analyses were run using SPSS Statistics 20 for Windows.

Results

Demographic characteristics

All groups were well matched on background demographic characteristics (Table 2). There were no group differences in age, $F(2, 61) = 2.54$, $MSE = 66.02$, $p = .087$, or years of education, $F(2, 61) = 1.87$, $MSE = 12.49$, $p = .163$. However, as expected, there was a significant main effect of group on MMSE, $F(2, 61) = 10.79$, $MSE = 6.90$, $p < .001$. Tukey post hoc tests indicated that aMCI and comMCI scored less than HE ($ps \leq .001$; $d = 1.32$ and $d = 1.34$, respectively) but they were not significantly different from each other ($p = .827$; $d = .13$). There was no significant difference between aMCI and comMCI on any background neuropsychological measure (Table 3), nor in the severity of depression according to published categories of depressive symptom severity, $\chi^2(3) = 3.17$, $p = .37$. comMCI patients had diagnoses of aMCI with comorbid clinical diagnoses of depression (10), anxiety (4), mixed anxiety and depression (4) and alcohol misuse (3).

Table 2

Table 3

Mean Distance Errors

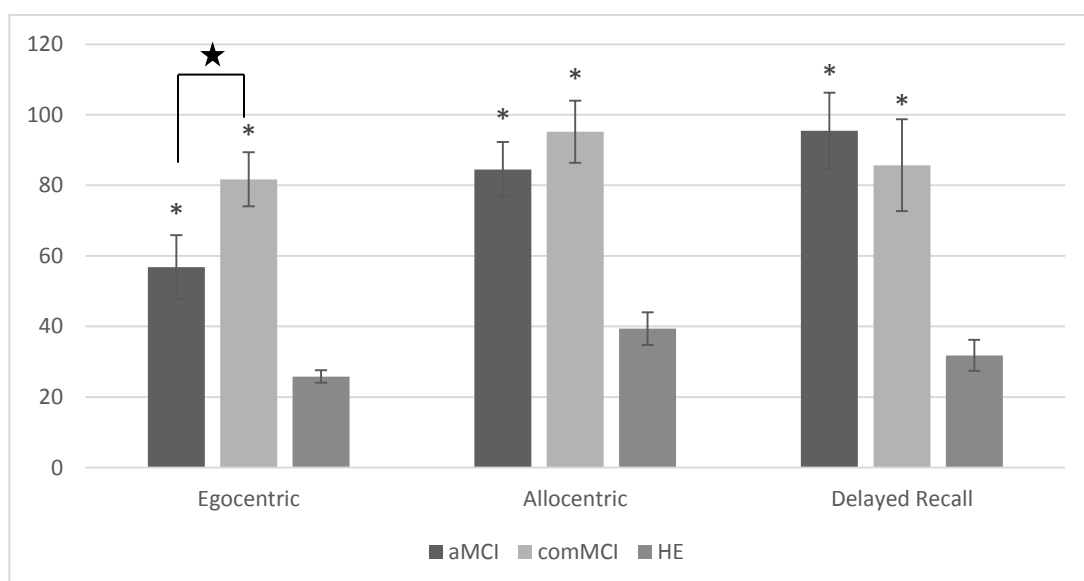
We calculated mean distance errors for each group's performance on each subtest of the HGT (Table 4; Figure 2).

Table 4

Significant differences in mean distance errors were present across groups in egocentric, $F(2, 61) = 17.00$, $MSE = 993.24$, $p < .001$, and allocentric subtests, $F(2, 61) = 17.02$, $MSE = 1114.07$, $p < .001$. In the egocentric subtest, comMCI and aMCI groups were impaired relative to HE participants ($p < .001$; $d = 2.19$ and $p = .006$; $d = 1.03$; respectively), but aMCI performed significantly better than comMCI ($p = .034$; $d = .65$). In the allocentric subtest, both comMCI and aMCI groups were impaired

in comparison to HE participants (both p s < .001; d = 1.72 and d = 1.53, respectively), but aMCI performed similarly to comMCI (p = .554; d = .28). In the delayed recall subtest, there were significant group differences in mean distance errors, $F(2, 57) = 12.11$, $MSE = 2039.93$, $p < .001$, with both comMCI and aMCI impaired relative to HE (p = .001; d = 1.20 and $p < .001$; d = 1.68; respectively) but there was no difference between comMCI and aMCI groups (p = .784; d = .18). In summary, aMCI and comMCI groups performed significantly worse than controls in all conditions. The comMCI and aMCI groups differed on the egocentric subtest, where comMCI participants performed significantly worse. Interpretation of differences in mean distance errors by comorbidity was limited by sample size. There was an indication that errors were lower in participants with comMCI and anxiety disorder than in those with comMCI and depression, depression and anxiety or alcohol misuse (Supplementary Table 1). However, Kruskal-Wallis H Tests showed no statistically significant differences in performance between comMCI sub-groups across HGT subtests, egocentric: $\chi^2(3) = 1.147$, $p = .766$, allocentric: $\chi^2(3) = 4.582$, $p = .205$, and delayed recall: $\chi^2(3) = .655$, $p = .884$.

Figure 2: Mean distance errors by group in each Hidden Goal Task (HGT) subtest. Asterisks represent significant differences ($p < .05$) from HE group. Star represents a significant difference between aMCI and comMCI



Discussion

As expected, there were significant differences in egocentric and allocentric navigation between healthy elderly participants, patients with aMCI and patients with comMCI. In viewpoint-dependent egocentric navigation, patients with aMCI performed significantly worse than healthy controls but significantly better than patients with comMCI, despite comparable background neuropsychological and depression scores between the two MCI groups. On viewpoint-independent allocentric navigation and delayed recall (also allocentric), patients with aMCI and comMCI did not differ significantly from each other, but both performed significantly worse than healthy controls. This indicates that aMCI with comorbid neuropsychiatric disorder was associated with significantly worse egocentric but not allocentric navigation than the 'aMCI alone' group.

Previous research has suggested that egocentric navigation relies on cortico-striatal brain regions (Wolbers et al., 2004) and allocentric navigation on the medial temporal lobes (Burgess et al., 2002) and basal forebrain (Kerbler et al., 2015). This raises the possibility that comorbid neuropsychiatric disorders may interact with aMCI to differentially affect spatial cognition and potentially its underlying neurocircuitry. Egocentric navigation is relatively more preserved than allocentric navigation in individuals with aMCI (Hort et al. 2007), which could explain comparatively better performance in participants with aMCI without comorbid neuropsychiatric disorders than those with comMCI. Participants with aMCI commonly progress to Alzheimer's dementia (Albert et al., 2011). Disruption of the cholinergic system is an early neuropathological hallmark of Alzheimer's disease (Schliebs & Arendt, 2011) and may also underlie spatial navigation deficits in aMCI (Kerbler et al., 2015). In comorbid neuropsychiatric disorders, more extensive disruption of neurotransmission systems is present, encompassing serotonin and dopamine mediators (Gordon & Hen, 2004; Kapur & Mann, 1992; Mann, 1999; Noble, 1996). These mediators have a reported role in the regulation of cognitive processes (Olvera-Cortés, Anguiano-Rodríguez, López-Vázquez, & Alfaro, 2008). This may result in more complex deficits in spatial navigation and explain the more profound egocentric navigation impairment in participants with comMCI, compared to aMCI. It is also possible

that there are underlying neuroanatomical differences, despite similar levels of cognitive impairment to those with aMCI. This would require a study involving neuroimaging to examine this hypothesis. The similarity between aMCI and comMCI groups on the allocentric subtest could have resulted from both groups' distance errors approaching the limits of arena size. It would therefore be of interest to repeat this study with more extensive neuropsychological assessments, and/or with functional neuroimaging to visualize brain regions active during the performance of each subtest, and on easier tests of allocentric navigation.

Because of the relatively small numbers of participants with different neuropsychiatric conditions, detailed comparison between spatial navigation performance of sub-groups was limited. Although there were no significant differences in performance between comMCI sub-groups across HGT sub-tests, there was a trend for better performance in participants with comorbid anxiety than in those with depression, mixed depression and anxiety or alcohol abuse. Based on previous literature, we might have expected these sub-groups to differ, with more profound spatial navigation impairment in participants with depression and alcohol dependence anticipated than in those with anxiety disorder.

Whilst multiple-domain cognitive impairment in patients with depression or alcohol dependence is already well-established, their spatial navigation performance on complex tasks, such as the HGT, may be modulated by different processes. In animal studies of ethanol consumption, both mild thiamine deficiency and chronic alcohol intake have been shown to modulate spatial memory performance on the Morris water maze, and the activity of acetylcholinesterase (Oliveria-Silva et al., 2015). Studies using alternative tasks to the HGT have established impaired spatial and temporal order recall in participants with alcohol-induced Korsakoff Syndrome (Kopelman, Stanhope, and Kingsley, 1997; Kessels, Postma, Wijnalda, and de Haan, 2000; Postma, van Asselen, Keuper, Wester, and Kessels, 2006). Similar profiles of episodic and working memory deficits have been demonstrated in participants with alcohol dependence with and without a diagnosis of

Korsakoff's syndrome (Pitel et al., 2008). A review identified that participants diagnosed with Korsakoff's syndrome demonstrate impaired explicit processing of contextual (spatial and temporal) information and in binding of target to contextual information in long-term and working memory (Kessels & Kopelman, 2012).

A study of healthy participants found that experimentally-induced anxiety enhanced spatial navigation performance on a virtual Morris water maze task, associated with increased left posterior hippocampal theta rhythm activity on magnetoencephalography (MEG; Cornwell et al., 2012). Despite growing interest in hippocampal function in specific conditions such as post-traumatic stress disorder (Karl et al., 2006), there is a paucity of studies of spatial navigation in anxiety disorders more generally. There is evidence to suggest that symptoms of anxiety but not depression affect subjective spatial navigation complaints in elderly individuals, irrespective of objective spatial navigation performance (Sheardova et al., 2015). Moreover, in a study demonstrating impaired allocentric navigation in depressed patients using a virtual Morris water maze task, 47% had a current anxiety disorder, complicating interpretation of differences in hippocampal activity (Cornwell et al., 2010). It will therefore be important that future studies systematically assess for individual neuropsychiatric disorders to investigate their relationship to spatial navigation deficits and complaints.

The burden of dementia is growing (Alzheimer's Society, 2014; Czech Alzheimer's Society, 2015) and the current cost to the United Kingdom is £26.3 billion per year. Clinically significant psychiatric symptoms are more prevalent in older adults than discrete psychiatric disorders, with sleep difficulties, anxiety disorders and depression the most common (Hybels & Blazer, 2015; Kopelman & Crawford, 1996). There is a higher than expected frequency of binge drinking among older adults (Blazer & Wu, 2011) and suicide rates are higher in older men, especially of white ethnicity in American samples (Hybels & Blazer, 2015). Despite the burden of both dementia and psychiatric symptoms in older adults, specific effects on spatial navigation of comorbid neuropsychiatric disorders in the context of aMCI have not been well-studied. Patients with comorbid psychiatric

disorders are frequently excluded from dementia research due to concerns about confounding effects (Stephan et al., 2011), but this limits the generalizability of findings to the clinical population, in whom comorbidity is the norm rather than the exception.

A strength of this study was its use of the HGT, a validated human analogue of the Morris water maze, frequently used to assess spatial navigation in animals. This behavioral test enables comparison between human and animal study findings and generation of hypotheses which can be tested in both groups. However, our findings are limited by sample size and use of only the MMSE (within the study itself) to quantify cognitive impairment. Because clinical data were gathered at two different memory clinics using different background neuropsychological batteries, the interpretation of our findings was limited. Our comMCI group was selected for clinical evidence of comorbid depression, anxiety or alcohol misuse. However, cases of acute depression were excluded, and this may explain why, on the rating scales, aMCI and comMCI groups did not differ significantly in terms of the proportion of patients falling in the different categories of depression severity. Replication in a larger cohort with detailed neuropsychological assessment, and the use of consistent clinical assessment and rating scales across sites to evaluate current and lifelong mental health problems, would enhance our understanding of the interactions between aMCI and comorbid neuropsychiatric disorders. Expansion of this research to include functional neuroimaging might further elucidate the neuroanatomical processes underlying egocentric and allocentric navigation in patients with comMCI and aMCI alone.

Conclusions

Despite the growing burden of dementia and the prevalence of psychiatric symptoms in the elderly population, spatial navigation has not previously been compared in patients with aMCI and comMCI. Our study indicated worse egocentric navigation in patients with comMCI in comparison to patients with aMCI only, despite similar levels of global cognitive impairment. These findings highlight the additional problems experienced by patients with concomitant psychiatric disorder, as well as the need for further research examining the nature of spatial navigation impairment in comMCI. Since trials often assess 'pure' aMCI only, we may underestimate navigation and other deficits, for which support may be needed. Future research might involve a larger sample size, perhaps including neuroimaging techniques to visualize affected brain regions.

References

- Albert, M.S., DeKosky, S.T., Dickson, D., Feldman, H.H., Fox, N.C., Gamst, A. ... Phelps, C.H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, 7(3), 270-279.
- Alzheimer's Society. (2014). Dementia 2014: Opportunity for change. Accessed on 25 February 2016 from: https://www.alzheimers.org.uk/site/scripts/download_info.php?fileID=2317
- Blazer, D.G., Wu, L.T. (2011). The epidemiology of alcohol use disorders and subthreshold dependence in a middle-aged and elderly community sample. *American Journal of Geriatric Psychiatry* 19(8):685-694.

Burgess, N., Maguire, E. A., & O'Keefe, J. (2002). The human hippocampus and spatial and episodic memory. *Neuron*, 35(4), 625-641.

Ceccanti, M., Hamilton, D., Coriale, G., Carito, V., Aloe, L., Chaldakov, G. ... Fiore, M. (2015). Spatial learning in men undergoing alcohol detoxification. *Physiology & Behavior*, 149, 324-330.

Gordon, J.A., Hen, R. (2004). The serotonergic system and anxiety. *Neuromolecular medicine*, 5(1), 27-40.

Chersi, F., Burgess, N. (2015). The cognitive architecture of spatial navigation: Hippocampal and striatal contributions. *Neuron*, 88, 64-77.

Campbell, S., Marriott, M., Nahmias, C., & MacQueen, G.M. (2004). Lower hippocampal volume in patients suffering from depression: a meta-analysis. *American Journal of Psychiatry*, 161(4), 598-607.

Cornwell, B.R., Arkin, N., Overstreet, C., Carver, F.W., & Grillon, C. (2012). Distinct contributions of human hippocampal theta to spatial cognition and anxiety. *Hippocampus*, 22(9), 1848-1859.

Cornwell, B.R., Salvatore, G., Colon-Rosario V., Latov, D.R., Holroyd, T., Carver, F.W. ... Grillon, C. (2010). Abnormal Hippocampal Functioning and Impaired Spatial Navigation in Depressed Individuals: Evidence From Whole-Head Magnetoencephalography. *American Journal of Psychiatry*, 167(7), 836-844.

Czech Alzheimer's Society (2015). Zpráva o stavu demence 2015. Accessed on 10 March 2016 from: <http://www.alzheimer.cz/tiskove-zpravy/zprava-o-stavu-demence-2015>

Fein, G., & McGillivray, S. (2007). Cognitive Performance in long-term abstinent elderly alcoholics. *Alcoholism: Clinical and Experimental Research*, 31(11), 1788-1799.

Fein, G., Torres, J., Price, L., & Di Sclafani, V. (2006). Cognitive Performance in Long-Term Abstinent Alcoholics. *Alcoholism: Clinical and Experimental Research*, 30(9), 1538-1544.

Folstein, M. F., Folstein, S. E., & McHugh, P.R. (1975). "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12(3), 189-198.

Behavioral Brain Research, 159(2), 175-186.

Gould, N.F., Holmes, M.K., Fantie, B.D., Luckenbaugh, D.A., Pine, D.S., Gould, T.D. ... Zarate, C.A. (2007). Performance on a Virtual Reality Spatial Memory Navigation Task in Depressed Patients. *The American Journal of Psychiatry*, 164(3), 516-519.

Henderson, V. W., Mack, W., & Williams, B. W. (1989). Spatial disorientation in Alzheimer's disease. *Archives of Neurology*, 46, 391 –394. doi:10.1001/archneur.1989.00520400045018

Hort, J., Laczó, J., Vyhnálek, M., Vyhnálek, M., Bojar, M., Bureš, J., Vlček, K. (2007). Spatial navigation deficit in amnesic mild cognitive impairment. *PNAS*, 104(10), 4042-4047.

Hybels, C.F., Blazer, D.G. (2015). Demography and Epidemiology of Psychiatric Disorders in Late Life. In: *The American Psychiatric Publishing Textbook of Geriatric Psychiatry (Fifth Edition)*. American Psychiatric Publishing, Arlington, VA, USA.

Kalova, E., Vlček, K., Jarolimova, E., & Bureš, J. (2005). Allothetic orientation and sequential ordering of places is impaired in early stages of Alzheimer's disease: corresponding results in real space tests and computer tests.

Kapur, S., Mann, J.J. (1992). Role of the dopaminergic system in depression. *Biological Psychiatry*, 32(1), 1-17.

Karl, A., Schaefer, M., Malta, L.S., Dorfel, D., Rohleder, N., & Werner, A. (2006). A meta-analysis of structural brain abnormalities in PTSD. *Neuroscience & Biobehavioral Reviews*, 30, 1004-1031.

Kelly, S., J., Goodlett, Ch., R., Hulsether, S., A., West, J.R. (1988). Impaired spatial navigation in adult female but not adult male rats exposed to alcohol during the brain growth spurt. *Behavioral Brain research*, 27(3), 247-257.

Kerbler, G.M., Nedelska, Z., Fripp, J., Laczó, J., Vyhnálek, M., Lisý, J., ... Coulson, E.J. (2015). Basal forebrain atrophy contributes to allocentric navigation impairment in Alzheimer's disease patients. *Frontiers in Aging Neuroscience*, 7:185.

Kessels, R.P.C., & Kopelman, M.D. (2012). Context memory in Korsakoff's syndrome. *Neuropsychology Review*, 22: 117.

Kessels, R.P.C, Postma, A., Wijnalda, E.M., & de Haan, E.H.F. (2000). Frontal-lobe involvement in spatial memory: evidence from PET, fMRI, and lesion studies. *Neuropsychology Review*, 10: 101-113.

Knight, R.G., & Longmore, B.E. (1994). *Clinical Neuropsychology of Alcoholism*. Lawrence Erlbaum Associates Ltd: Hove, United Kingdom.

Kopelman, M.D., & Crawford, S. (1996). Not all memory clinics are dementia clinics. *Neuropsychological Rehabilitation*, 6(3), 187-202.

Kopelman, M.D., Stanhope, N., & Kingsley, D. (1997). Temporal and spatial context memory in patients with focal frontal, temporal lobe, and diencephalic lesions. *Neuropsychologia*, 35: 1533-1545.

Laczó, J., Andel, R., Vyhnálek, M., Vlček, K., Magerova, H., Varjassyova, A. ... Hort, J. (2012). From Morris Water Maze to Computer Tests in the Prediction of Alzheimer's Disease. *Neurodegenerative Diseases*, 10, 153-157.

Laczó, J., Vlček, K., Vyhnálek, M., Vajnerová, O., Ort, M., Holmerová, I. ... Hort, J. (2009). Spatial navigation testing discriminates two types of amnesic mild cognitive impairment. *Behavioral and brain research*, 202(2), 252-259.

Mann, J.J. (1999). Role of the serotonergic system in the pathogenesis of major depression and suicidal behavior. *Neuropsychopharmacology*, 21(2 Suppl), 99S-105S.

Matthews, D. B., Simson, P. E., & Best, P. J. (2006). Ethanol Alters Spatial Processing of Hippocampal Place Cells: A Mechanism for Impaired Navigation When Intoxicated. *Alcoholism: Clinical and Experimental Research*, 20(2), 404-407.

Morris, R. G., Garrud, P., Rawlins, J.N., & O'Keefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. *Nature*, 297(5868), 681-683.

Migo, E.M., O'Daly, O., Mitterschiffthaler, M., Antonova, E., Dawson, G.R., Dourish, C.T. ... Morris, R.G. (2016). Investigating virtual reality navigation in amnesic mild cognitive impairment using fMRI. *Aging, Neuropsychology, and Cognition*, 23(2), 196-217.

Morris, R.G.M. (1981). Spatial localization does not require the presence of local cues. *Learning and Motivation*, 12(2), 239-261.

- Nadel, L., & Hardt, O. (2004). The Spatial Brain. *Neuropsychology*, 18(3), 473-476.
- O'Keefe, J., & Nadel, L. (1978). *The hippocampus as a cognitive map*. Oxford, England: Clarendon Press.
- Noble, E.P. (1996). Alcoholism and the dopaminergic system: a review. *Addiction Biology*, 1(4), 338-348.
- Oliveria-Silva, I.D.F., Pereira, S.R.C., Fernandes, P.A., Ribeiro, A.F., Pires, R.G.W., & Ribeiro, A.M.R. (2015). Mild thiamine deficiency and chronic ethanol consumption modulate acetylcholinesterase activity change and specific memory performance in a water maze task. *Journal of Molecular Neuroscience*, 55: 217-226.
- Olvera-Cortés, M.E., Anguiano-Rodríguez, P., López-Vázquez, M.A., & Alfaro, J.M. (2008). Serotonin/dopamine interaction in learning. *Progress in Brain Research*, 172, 567-602.
- Petersen, R., C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine*, 256, 183-194.
- Pitel, A.L., Beaunieux, H., Witkowski, T., Vabret, F., de la Sayette, V., Viader, F., ... Eustache, F. (2008). Episodic working memory deficits in alcoholic Korsakoff patients: the continuity theory revised. *Alcoholism: Clinical and Experimental Research*, 32: 1229-1241.
- Postma, A., van Asselen, M., Keuper, O., Wester, A.J., Kessels, & R.P.C. (2006). Spatial and temporal order memory in Korsakoff patients. *Journal of the International Neuropsychological Society*, 12: 327-336.
- Sahay, A., & Hen, R. (2007). Adult hippocampal neurogenesis in depression. *Nature Neuroscience*, 10, 1110-1115.
- Santin, L., J., Rubio, S., Begega, A., & Arias, J., L. (2000). Effects of chronic alcohol consumption on spatial and working memory tasks. *Alcohol*, 20(2), 149-159.
- Schliebs, R., & Arendt, T. (2011). The cholinergic system in aging and neuronal degeneration. *Behavioural Brain Research*, 221(2), 555-563.

- Sékoléne, L., Dufour, A., & Després, O. (2012). Spatial navigation in normal aging and the prodromal stage of Alzheimer's disease: Insights from imaging and behavioral studies. *Aging Research Reviews*, 405, 1-13.
- Sheardova, K., Laczó, J., Vynhalek, M., Mokrisova, I., Telensky, P., Andel, R., & Hort, J. (2015). Spatial navigation complaints are associated with anxiety regardless of the real performance in non-demented elderly. *Journal of Depression & Anxiety*, 4(4): 205.
- Shi, F., Liu, B., Zhou, Y., Yu, C., & Jiang, T. (2009). Hippocampal volume and asymmetry in mild cognitive impairment and Alzheimer's disease: Meta-analyses of MRI studies. *Hippocampus*, 19, 1055–1064. doi:10.1002/hipo.20573
- Steigerwald, E.S., & Miller, M.W. (1997). Performance by adult rats in sensory-mediated radial arm maze tasks is not impaired and may be transiently enhanced by chronic exposure to ethanol. *Alcoholism Clinical and Experimental Research*, 21(9), 1553-1559.
- Stephan, B.C.M., Brayne, C., Savva, G.M., Matthews, F.E. (2011). Occurrence of medical co-morbidity in mild cognitive impairment: implications for generalization of MCI research. *Age and Ageing*, 40 (4), 501-507.
- Tolman, E. C. (1948). Cognitive maps in rats and men. *Psychological Review*, 55, 189-208.
- Videbech, P., & Ravnkilde, B. (2004). Hippocampal volume and depression: a meta-analysis of MRI studies. *American Journal of Psychiatry*, 161(11), 1957-66.
- Wolbers, T., & Büchel, C. (2005). Dissociable retrosplenial and hippocampal contributions to successful formation of survey representations. *Journal of Neuroscience*, 25, 3333-3340.
- Wolbers, T., Weiller, C., Büchel C. (2004). Neural foundations of emerging route knowledge in complex spatial environments. *Cognitive Brain Research*, 21 (3), 401-411.

Tables

Table 1: Inclusion criteria for amnesic Mild Cognitive Impairment (aMCI)

aMCI criteria (Petersen, 2004)
1. Memory complaint usually corroborated by an informant
2. Objective memory impairment for age
3. Essentially preserved general cognitive function
4. Largely intact functional activities
5. Not dementia

Table 2: Demographic characteristics of the sample: Means (Standard Deviations in brackets)

	HE	comMCI	d ¹	aMCI	d ¹	d ²
N	22 (6 male)	21 (12 male)		21 (8 male)		
Age	65.8 (6.4)	62.5 (7.6)	.47	68.1 (10.1)	.27	.63
Education	15.8 (2.7)	14.0 (4.1)	.52	14.1 (3.7)	.52	.03
MMSE	29.1 (1.4)	25.7 (3.3)**	1.34	26.1 (2.9)**	1.32	.13

** $p \leq 0.001$: Tukey post hoc significance compared to HE (One-Way ANOVA); d: Cohen's d effect size: ¹ in comparison to HE, ² in comparison to comMCI.

Table 3: Background neuropsychological data comparisons (comMCI and aMCI)

Cognitive function	Mean (Standard Deviation)		Mann-Whitney U test		T-test		
	comMCI	aMCI	U	P	t	p	d
Verbal recall [‡]	-1.43 (.89)	-1.13 (1.18)	147.50	.359	-.89	.377	.29
Visual recall ^{‡‡}	-1.01 (1.05)	-1.16 (.92)	176.00	.941	.48	.635	.15
Executive function ^{‡‡‡} (composite score)	-1.08 (.86)	-1.00 (1.08)	156.00	.509	-.25	.803	.08

[‡] UK site – Doors and People (D&P), CZ site – Rey Auditory Verbal Learning Test (RAVLT), recall of the first trial;

^{‡‡} UK site – D&P, CZ site – Rey-Osterrieth Complex Figure, recall after three minutes; ^{‡‡‡} UK site – mean of Z-scores from FAS test, Hayling and Brixton tests, error score; CZ site – mean of Z-scores from FAS test (Czech version, letters N, K, P), Trail Making Test, part B; d: Cohen's d effect size.

Table 4: Distance errors throughout HGT subtests: Means (Standard Deviations in brackets)

	HE (n=22)	comMCI (n=21)	d ¹	aMCI (n=21)	d ¹	d ²
Egocentric	25.8 (8.2)	81.7 (35.1)**	2.19	56.8 (41.6)* †	1.03	.65
Allocentric	39.4 (21.8)	95.2 (40.4)**	1.72	84.5 (35.6)**	1.53	.28
Delayed Recall	31.8 (20.8)	85.7 (59.8)**	1.20	95.5 (49.5)**	1.68	.18

** $p \leq .001$, * $p \leq .01$: Tukey post hoc significance compared to HE; † $p \leq .05$: Tukey post hoc significance

compared to comMCI; d: Cohen's d effect size: ¹ in comparison to HE, ² in comparison to comMCI.

Supplementary Table 1: Distance errors throughout HGT subtests in comMCI subgroups: Means (Standard Deviations in brackets)

	comMCI depression (n=10)	comMCI anxiety (n=4)	comMCI depression + anxiety (n=4)	comMCI alcohol (n=3)
MMSE	25.0 (3.1)	28.5 (1.3)	23.3 (4.1)	27.3 (1.2)
Egocentric	83.7 (40.5)	64.9 (39.4)	85.5 (28.9)	92.5 (23.9)
Allocentric	92.6 (37.8)	67.0 (39.3)	115.7 (53.5)	114.1 (16.5)
Delayed Recall	86.2 (56.9)	63.7 (38.4)	86.6 (95.7)	112.7 (75.0)

Figure captions

Figure 1: Hidden Goal Task Screens: (A) Arena (large white circle) with start point (red filled circle), orientation cues (red and green lines) and goal (purple circle) marked; (B1) Egocentric trial; (B2) Allocentric trial.

Figure 2: Mean distance errors by group in each Hidden Goal Task (HGT) subtest.