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Czech Brain Aging Study (CBAS): prospective multicentre cohort study on risk and protective factors for dementia in the Czech Republic

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AbStrACt

Purpose Identification of demographic, physical/physiological, lifestyle and genetic factors contributing to the onset of dementia, specifically Alzheimer disease (AD), and implementation of novel methods for early diagnosis are important to alleviate prevalence of dementia globally. The Czech Brain Aging Study (CBAS) is the first large, prospective study to address these issues in Central/Eastern Europe by enrolling non-demented adults aged 55+ years, collecting a variety of personal and biological measures and tracking cognitive function over time.

Participants The CBAS recruitment was initiated in 2011 from memory clinics at Brno and Prague University Hospitals, and by the end of 2018, the study included 1228 participants. Annual follow-ups include collection of socioeconomic, lifestyle and personal history information, neurology, neuropsychology, laboratory, vital sign and brain MRI data. In a subset, biomarker assessment (cerebrospinal fluid (CSF) and amyloid positron emission tomography) and spatial navigation were performed. Participants were 69.7±8.1 years old and had 14.6±3.3 years of education at baseline, and 59% were women. By the end of 2018, 31% finished three and more years of follow-up; 9% converted to dementia. Apolipoprotein E status is available from 95% of the participants. The biological sample bank linked to CBAS database contained CSF, serum and DNA.

Findings to date Overall, the findings, mainly from cross-sectional analyses, indicate that spatial navigation is a promising marker of early AD and that it can be distinguished from other cognitive functions. Specificity of several standard memory tests for early AD pathology was assessed with implications for clinical practice. The relationship of various lifestyle factors to cognition and brain atrophy was reported.

Future plans Recruitment is ongoing with secured funding. Longitudinal data analyses are currently being conducted. Proposals for collaboration on specific data from the database or biospecimen, as well as collaborations with similar cohort studies to increase sample size, are welcome. Study details are available online (www.cbas.cz).

Strengths and limitations of this study

► The Czech Brain Aging Study (CBAS) is a prospective longitudinal study of cognitive and brain ageing that combines prospective data on lifestyle, genetic, neuropsychological, social, physical and biological factors with neuropsychological and imaging data in the context of Alzheimer disease (AD) biomarkers.

► Although biomarkers are available for most cognitively impaired participants, only a subsample of participants with subjective memory complaints and cognitively normal controls has biomarkers available.

► Participants come from university hospital-based memory clinics from two major Czech cities—Brno and Prague—which limits generalisability, although universal healthcare coverage promotes university hospital visits by a more diverse patient population with respect to urban/rural living and socioeconomic status.

► CBAS has the potential to serve as a crucial, comprehensive source of information about markers of cognitive decline and impairment and can represent a model for studying risk/protective factors for AD in other Central and Eastern European countries.

IntroduCtIon

A gradual increase in the prevalence of dementia has been one of the trends accompanying the growth in life expectancy seen across the globe over the past few decades. Dementia affects 1% of those 60–65 years of age and about 45% of those aged 90–95 years,[1 2] although there is also evidence suggesting that the prevalence, as well as incidence of dementia, has decreased in the last decade.[3 4] This downward trend may be the result of treatment of hypertension and diabetes, as well as greater attention to lifestyle factors stemming from the increasing awareness of its impact on cognitive and overall health among the general public. Still dementia remains a major public health issue.

Currently, the course of dementia can only be modified by symptomatic therapies and no causal treatment for its most common form, Alzheimer disease (AD), or for other neurodegenerative disorders is available. A crucial step in the effective management of dementia, including AD, is to better understand the underlying neuropathological mechanisms and the differences in ethnic and lifestyle risk factors. An important effort in this context involves the identification of the extent to which demographic, physical/physiological, lifestyle and genetic factors contribute to the onset of dementia and AD specifically.

A parallel effort to searching for risk factors includes early identification of cognitive impairment. To further alleviate dementia incidence on the global level, novel diagnostic methods need to be implemented to define the risk factors for conversion from preclinical to early symptomatic (prodromal) stage and to dementia. Presumably, an early, accurate diagnosis is a crucial, yet still elusive, step in the pursuit of effective treatments for dementia.

The Czech Brain Aging Study (CBAS) is the first large, prospective study to address these issues in Eastern Europe. CBAS was designed to study potential early biomarkers and risk/protective factors of cognitive decline and dementia by enrolling a large number of older adults; collecting a variety of information about personal and family history, past and current lifestyle, genetic, physical and biological measures; and tracking cognitive function and status and brain MRI of the participants over time. The Czech Republic (CR) has approximately 150 000 patients with dementia among its roughly 10.6 million inhabitants. CR, like other Eastern European countries, is unique in a number of ways, including a relatively high prevalence of cardiovascular issues. However, since the 1980s, the frequency of common vascular risk factors is continuously decreasing, and the mortality associated with vascular risk factors in CR and neighbouring countries such as Poland has been significantly lower compared with other Eastern European countries, such as Russia. Although the cause of this remains mainly unexplained, improved prevention and education are especially suggested.[5 6]

Another unique feature of healthcare delivery in the CR is a care delivery system that favours memory clinic visits from a wide spectrum of the patient population. In turn, prodromal stages of the disease are mostly handled by neurologists, whereas postdiagnostic patients are more often seen by geriatricians and psychiatrists.[7] Neurologists generally tend to employ more sophisticated diagnostic tools for detecting early stages of cognitive deficit and assessment of its aetiology than psychiatrists/geriatricians.

Building on this model, CBAS was established using recruitment from two memory clinics at two independent neurology departments based at university hospitals in Prague and Brno, respectively. Data collection started in 2005 in Prague, and the extension to a multicenter design was possible in 2011, thanks to the European Union Regional Development Fund. The main aim of both memory clinics is to diagnose and treat neurological disorders that lead to cognitive disorders and dementia. Both centres are harmonised in terms of neuropsychological battery, multimodality MRI, positron emission tomography (PET) imaging, genetic testing, blood tests and cerebrospinal fluid (CSF) analysis, the set of questionnaires, and a participant database system.

Although CBAS lacks the advantages of a population-based study, it uses the only a currently feasible design for this type of study in the CR. In addition, it provides access to a relatively large number of clinical patients. A population-based study would need to include much larger numbers to recruit the same number of at-risk patients, which would deem the study unfeasible under the current funding mechanisms.

The overarching objectives of CBAS were to help understand lifestyle, genetic and biological factors influencing variability in the onset of cognitive impairment, including AD, and finding novel ways of early AD diagnosis. The specific aims were (1) to explore epidemiological risk factors for cognitive decline and dementia in the CR; (2) to evaluate spatial navigation and other experimental neuropsychological tests as early markers of AD pathology; (3) to define structural, metabolic and functional biomarkers of neurodegenerative diseases in older adults; and (4) to explore non-pharmacological interventions in the prevention of cognitive decline.

Cohort deSCrIPtIon
Settings
CBAS is a prospective longitudinal memory clinic-based multicentre study recruiting non-demented adults 55+ years of age. Both CBAS centres work as a low-threshold facility; hence, the participants are mostly volunteers who come as a self-referral with memory complaints expressed by themselves or the family or who were referred by general practitioners, local specialists or the Czech Alzheimer Society to one of the memory clinics.

eligibility criteria
All participants entering the two memory clinics undergo neurological examination, brain CT or MRI, and cognitive assessment, excluding subjects with dementia. All non-demented subjects aged 55+ years who are able to undergo MRI examination and are eligible (see further for exclusion criteria) are initially offered to participate in CBAS. About 95% of these subjects agreed to enter the study. The additional exclusion criteria are severe depression (participants with a recent bout of mild depression are included), a diagnosis of neurological or other psychiatric disorder, a systemic condition potentially causing cognitive impairment or a recent history of stroke. Participants referred for newly developed cognitive complaints in whom no objective cognitive deficit is found are categorised as subjective cognitive decline (SCD). Participants with objective cognitive decline are classified as mild cognitive impairment (MCI) based on

2011 National Institute on Aging and Alzheimer's Association guidelines by Albert and colleagues.[8]

Cognitively healthy controls or normal controls (NCs), defined as subjects with no significant cognitive complaints verified by memory complaints questionnaires and by a structured clinical interview and with no objective cognitive deficit, are recruited from adults taking continuing education classes under the University of the Third Age at Charles University and from relatives of employees or of study participants.

Written informed consent was obtained from each participant prior to entering the study.

Cohort characteristics

Between January 2011 and December 2018, 1228 subjects who fulfilled the CBAS criteria agreed to enter the study. Brno has contributed 496 and Prague 732 participants so far, with enrolment accelerated at both sites more recently. The basic characteristics of this cohort are presented in table 1; the frequency of vascular risk factors is in figure 1. The frequencies of these vascular risk factors in CBAS are similar to national reports and studies, almost solely conducted by cardiologists and internal medicine specialists in CR,[5] although the proportion of smokers is lower in CBAS compared with the national average reported in 2004.

Apolipoprotein E4 (apolipoprotein E (APOE) and its ε4 allele, specifically) is the strongest genetic risk factor for late-onset AD and is associated with impairments in cerebral metabolism and cerebrovascular function. About 30% of the participants carry at least one APOE ε4 allele. The dataset includes 15.2% of APOE ε4 allele heterozygotes and 5.4% homozygotes in MCI subjects, 7.2% heterozygotes and 2.1% homozygotes in SCD subjects, and only 1.2% heterozygotes in NC subjects. About 25% of the subjects are living alone, and the rest are living with a spouse, friend or a family member. All participants are community dwelling. The age of the cohort reflects the age distribution of older adults in the CR, with 12% of the subjects 80+ years of age, and 4% 85+ years of age at baseline. There are 3.3 million people aged 55+ years living in the CR, 12% of whom are 80+ years and 6% are 85+ years according to the 2018 Czech Census data. Education of our cohort is slightly higher than the average education level of 55+ population in the CR; 7.3% of the CBAS participants finished basic education (vs 26% in the CR), 68% finished secondary (high school) education (vs 62% in the CR) and 48% achieved college/university degree (vs 9% in the CR). Efforts are under way to recruit a more diverse cohort.

Aside from the CBAS cohort defined earlier, the 'CBAS Plus' database is also available, containing baseline data from 155 Brno and 283 Prague subjects who did not meet the CBAS inclusion criteria due to mild dementia of various neurodegenerative origins, depression and history of stroke and who signed informed consent. Dementia aetiology (AD dementia, frontotemporal lobar degeneration, Parkinsonian syndromes and vascular

Table 1 Basic characteristics of the Czech Brain Aging Study cohort at baseline

	Total			SCD			MCI			NC		
	Mean (SD) or ratio	Median or %	IQR	Mean (SD) or ratio	Median or %	IQR	Mean (SD) or ratio	Median or %	IQR	Mean (SD) or ratio	Median or %	IQR
Number of participants	1228			428			732			68		
Gender (M/F)	502/726	40.9% M		146/282	34.1% M		329/403	44.9% M		27/41	39.7% M	
Age (years)	69.7 (8.0)	70	64–75	67.1 (7.9)	66	61–72	71.2 (7.9)	72	66–77	68.9 (7.1)	69	64–73
Education (years)	14.6 (3.3)	14	12–17	15.2 (3.0)	15	13–18	14.3 (3.4)	13	12–17	16.1 (3.4)	16	13–17
Depression (GDS)[42]	3.86 (3.1)	3	2–5	3.9 (3.0)	3	2–5	4.0 (3.2)	3	2–6	1.6 (1.3)	1	0–1

F, female; GDS, Geriatric Depression Scale; M, male; MCI, mild cognitive impairment; NC, normal control; SCD, subjective cognitive decline.

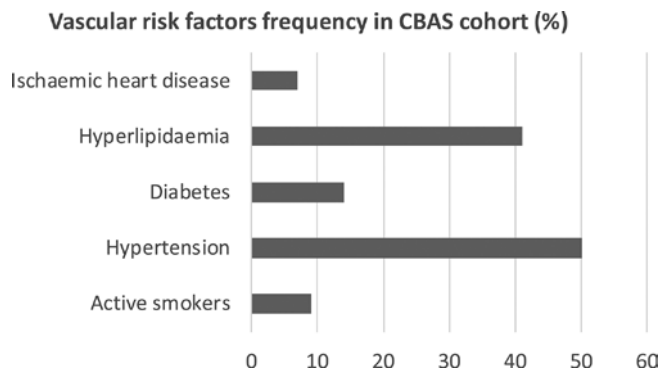**Vascular risk factors frequency in CBAS cohort (%)**

Figure 1 Frequency of vascular risk factors in the CBAS cohort. CBAS, Czech Brain Aging Study.

disorders) is diagnosed according to established guidelines.[9] The CBAS Plus cohort reflects a real memory clinic patient profile and therefore can provide clinically relevant and important data about a wide spectrum of neurological brain diseases leading to dementia and the role of vascular risk factors and psychiatric comorbidity.

Methods

At each visit, all study participants undergo a standard set of procedures. Neurological and comprehensive neuropsychology examinations, including Uniform Data Set battery, are administered[10 11]; laboratory and vital function assessments are also performed. Sociodemographic, personal, pharmacological and family history data are collected. Participants and their informants complete multiple questionnaires about cognitive complaints and lifestyle factors. MRI scans of 1.5 or 3 T are performed every 24 months or earlier when a participant converts to dementia or progresses towards cognitive impairment at an unusual rate. Volumetric MRI is analysed in all patients to obtain measures of regional cortical thickness and subcortical volumes cross-sectionally and longitudinally using Freesurfer image analysis suite V.5.3 (http://surfer.nmr.mgh.harvard.edu/). The details of Freesurfer image processing have been published elsewhere,[12–14] including previous studies by our group.[15 16] A subset of MRI volumes has been previously measured using manual tracing, and a subset of participants' MRI volumes is used to measure the atrophy of the cholinergic basal forebrain nuclei.[17] Genotyping is carried out at baseline. In a subset, CSF and/or amyloid PET is performed and additional data are collected from experimental neuropsychology, spatial navigation and personality trait assessment. The detailed procedures including their timelines are presented in table 2.

The CBAS is complemented by a biological sample bank linked to data from the CBAS and CBAS Plus cohorts. The cerebrospinal fluid (CSF) collection and storage are carried out according to the widely recognised consensus protocol for the standardisation of CSF collection and biobanking.[18] Eighteen aliquots of 0.2 mL CSF and 5–9 aliquots of serum are stored for each participant. All samples are stored at −80C. Commercial ELISA kits

(Innogenetics) are used for dementia biomarker analyses (Aβ1–42, protein tau and phospho-tau), and cut-off values derived from validation study are used.[19] The characteristics of the biobank as of December 2018 are listed in table 3.

Follow-up

Participants are examined annually; they are invited for a follow-up via a letter mailed to their permanent address. Subsets of SCDs and NC who are cognitively stable for the first three visits are followed up every other year. At each follow-up visit, all participants undergo a standard set of procedures described in the Methods section; see table 2 for additional details. Standard criteria-based consensus diagnosis is performed based on each visit. MCI and dementia aetiology is based on biomarkers.[8 9]

Progression from NC/SCD to MCI or to dementia and from MCI to dementia is the main outcome, along with longitudinal quantitative measures of cognitive performance, which are used for evaluation of early markers of AD and risk factors for progression. Participants are censored when they progress to dementia as ascertained by panel consensus conference or if they can no longer undergo an MRI examination. Between entering the study and the end of 2018, 31% of the total of 1228 participants already completed at least three full yearly evaluations (baseline+2 follow-up visits) with at least two brain MRI sessions. Additionally, 9% of all participants converted to dementia at some timepoint within their follow-up and were no longer followed up, and 16% of the participants were lost to follow-up for various reasons (loss of interest, newly acquired MRI intolerance, worsening health condition and change of residence address not allowing invitation for follow-up). From all participants recruited by the end of 2018, 931 (75%) continue in the study. The recruitment is ongoing with secured funding. We have just reached a sufficient number of longitudinally followed up participants to begin with longitudinal data analyses, which will contribute significantly to the fulfilment of most of the study aims.

Patient and public involvement

Patient involvement was crucial in questionnaire implementation. Initial versions of the questionnaires were consulted with a pilot group of patients and their caregivers. Based on their feedback, we excluded McNair's questionnaire of activities of daily living. The adaptation of the Mild Behaviour Impairment Checklist was graphically reworked after being consulted, with our participants increasing the rate of successful completion considerably. In the tests developed by our team, such as the Famous Landmark Identification Test[20] or the Subjective Spatial Memory Complaints Questionnaire,[21] we consulted our participants during the entire development process, including the selection of relevant items. Some of the items were generated from qualitative research, which always preceded the development of new questionnaires. These procedures ensured high participation and validity.

Table 2 The Czech Brain Aging Study procedures

Frequency	Procedure	Specification
Annually	Clinical exam	Standard complex neurology examination
Annually	Standard neuropsychology	Uniform Data Set[10 11]: Mini-Mental State Examination, digit span forward and backward, digit symbol, Trail Making Tests A and B, animal list generation, vegetable list generation, Boston Naming Test (30 odd items), logical memory and story A Premorbid ability estimation: National Adult Reading Test[43] Memory assessment: Enhanced cued recall test,[44] Rey Auditory Verbal Learning Test,[45] Brief Visuospatial Memory Test—Revised[46] and ROCFT recall[47] Executive functions: Prague Stroop Test,[48] similarities (Wechsler Adult Intelligence Scale - Revised),[49] Controlled Oral Word Association Test,[50] Visuoconstruction: Clock Test[51] and ROCFT copy[47] Functional scales: Clinical Dementia Rating Scale[52] and Functional Assessment Questionnaire[53] Symptoms of anxiety and depression: Geriatric Depression Scale (15 items version)[42] and Beck Anxiety Inventory[54]
Annually	Laboratory	Fasting glucose, lipid profile, homocysteine, vitamin B_{12}, thyroid hormones, folic acid, renal and liver functions, C reactive protein and glycosylated haemoglobin
Annually	Vital functions	Blood pressure, pulse frequency, waist:hips ratio and Body Mass Index
Annually	Socioeconomic data	Marital status, type of living and current occupation
Annually	Questionnaires	Subjective cognitive complaints (Questionnaire de PLainte Cognitive),[55] physical/mental activity at midlife and currently, Becke's Habitual Physical Activity,[56] Epworth Sleepiness Scale[57] and Falls Self-Efficacy Scale—International[58]
Biannually	MRI	1.5T protocol: plane localiser, standard clinical T2, T1 three-dimensional isometric MPRAGE with isometric voxe, FLAIR, T2* and echoplanar imaging for diffusion tensor imaging with 32 directions 3T protocol: plane localiser; standard clinical T1 and T2; T1 three-dimensional isometric MPRAGE with isometric voxel; echoplanar imaging for diffusion tensor imaging with 64 directions; FLAIR; T2 fast spin echo; T2*; resting state functional MRI; switch to 3T MRI since 2015 in Brno, since 2019 in Prague
At baseline	Demography	Age, education, occupation and laterality
At baseline, all optional	Genotyping	Apolipoprotein E TOMM40, BDNF, CD36, BuChE, KIBRA, TREM2, PSEN 1, PSEN 2, APP, TARDBP, MAPT, GRN, C9orf72
Subset at both centres	CSF	Amyloid β-42, total, tau, p-tau, oligoclonal bands, CSF biochemistry
Subset at both centres	Amyloid PET	PET/MRI or PET/CT (visual assessment), flutemetamol, dual-phase ('perfusion') PET
Prague cohort all	Spatial navigation[22 23 27]	Hidden goal task, simple navigation task, path integration task, Y-maze assessment, intersections task, sea hero quest and spatial tasks in virtual reality/augmented virtual reality
Prague cohort optional	Experimental neuropsychology	Facial emotion recognition,[59 60] famous faces identification,[60] FNAME 12 items version,[61] Memory Binding Test[62] and spatial pattern separation task[63] In-house developed tests: Famous Landmarks Identification,[20] Episodic-like Memory Test[64] and Arena Perspective-Taking Task[65]
Brno cohort, all at baseline	Specific questionnaires	Spiritual Well-being Questionnaire,[66] OPD-2 (OPD Working Group)[67] and early life trauma assessment

CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery; MPRAGE, magnetisation-prepared rapid gradient echo; OPD, Operationalized Psychodynamic Diagnostics; PET, positron emission tomography; ROCFT, Rey-Osterrieth Complex Figure Test.

Wider public engagement is ensured by public lectures regularly performed by the CBAS team members, which inform the public about the study, its goals and procedures. Partial results concerning lifestyle are discussed. The information about the study and the possibilities to join are communicated to the public via various channels, including the Concept Alzheimer Café and the CBAS webpage. We also closely cooperate with the Czech Alzheimer Association (CAA) connecting dementia specialists with patients and their caregivers. Many CAA

Table 3	Biobank characteristics	
	Aliquots per patient stored at −80C	Participants (n)
Cerebrospinal fluid	18×0.2 mL	75 in Brno/350 in Prague
Serum	5−9×0.5 mL	145 in Brno/350 in Prague
DNA	Concentration>100 ng/µL	95% of all participants

members and participants of the study help disseminate information about the study, which facilitates recruitment.

FIndIngS to dAte

Data collected from the CBAS and CBAS plus cohorts have spurred more than 60 publications so far, mainly from cross-sectional analyses, primarily in impacted neurology and neuroscience journals (the complete list is available at www.cbas.cz). We highlight the most significant ones here in the context of the aims of the study.

early markers of Ad
Spatial navigation
Spatial navigation testing is part of the baseline CBAS protocol[22 23] (for details, see table 2). Outcomes of this comprehensive examination have been compared with results of structural brain MRI and genetic and laboratory assessments. Our cross-sectional studies using clinically and biomarker-defined individuals with AD[24] have shown that spatial navigation is a distinct cognitive function and a promising cognitive marker of early stages of AD, the assessment of which may add important information to a comprehensive neuropsychological profile of individuals in the CBAS study[25 26] and may be useful for early and differential diagnosis of AD or for evaluating the effect of therapies.[27 28] This longitudinal study aimed to provide evidence for this notion. It should be noted that other copathologies may negatively impact on spatial navigation performance in individuals with AD.[29 30]

We have found that impairment of spatial navigation is associated with structural changes of the right hippocampus, entorhinal cortex, posterior parietal lobe and basal forebrain, that is, the structures that are impaired very early in AD,[15 17 25] and that it can be influenced by genetic background[31 32] and cardiovascular risk factors.[33]

Experimental neuropsychology
We have shown that our 'in-house' developed the Famous Landmarks Identification Test, created with the help from our participants, could be useful in recognising early stages of AD.[20] We have also tested the specificity of several standard memory tests for estimating hippocampal atrophy in the CBAS participants, which could have immediate implications for clinical practice.[34]

Lifestyle factors and Ad
We have recently completed the first longitudinal MRI analysis from CBAS[35] showing that the level of spiritual well-being can influence the atrophy rates in regions affected by AD pathology, as well as those associated with attention and with behavioural symptoms. The manuscript is being prepared for publication. Previous studies have included examinations of cholesterol[36] and blood glucose[37] in relation to cognitive outcomes.

non-pharmacological interventions
We have completed an intervention study with mindfulness-based stress reduction (MBSR) therapy and cognitive training in members of CBAS with MCI. We have shown that MBSR is a suitable intervention for subjects with mild cognitive decline,[38] and findings regarding its effect on cognition, immunology profile and depression suggest that MBSR could be effective in secondary prevention. The manuscript is submitted for publication.

StrengthS And LIMItAtIonS
CBAS represents a unique effort to study cognitive and brain ageing in Central and Eastern Europe. It is a prospective study of a relatively culturally and genetically homogenous Czech population based mainly on recruitment of volunteers who come to a memory clinic in one of the two largest cities in the country, Prague and Brno. The study includes a large biological sample bank (sera, CSF and DNA) that can enhance diagnostic accuracy and improve predictive validity of analyses with other AD risk factors, such as lifestyle factors and vascular risk factors. Despite several studies on vascular risk factors, the reasons for the high frequency of vascular problems in Eastern Europe, as well as the association between vascular factors and cognitive performance,[39] remain poorly understood. We believe that data from our study can contribute important information on this topic.

The study also has limitations. While having two sites involved in participant recruitment is an advantage, it does not create population representation. However, it is also of note that due to the nature of healthcare delivery in the CR, attendance at the two memory clinics is far from restricted to the close geographical proximity. Rather, older adults of all ages and backgrounds visit the clinics from a variety of geographical areas. This could increase the bias as usually it is the least deprived that access tertiary expertise in most healthcare settings. Therefore, coding of demographics and participant residence (urban vs rural or by region) can enrich analyses and help increase interpretability of any findings, and potentially ameliorate this limitation to at least some extent. Given the recruitment from university hospital-based clinics, one may assume that the sample could attract relatively young patients.[40] However, although the average age for patients with MCI is substantially lower than the UK-based Cognitive Function and Ageing Studies, it is roughly similar to studies from Italy, Spain

and Australia, and those studies conducted in Asia.[41] Still, results of longitudinal analyses are likely to be affected by selective attrition. Additionally, the current sample is relatively highly educated, and efforts are under way to recruit participants with more diverse educational attainment. However, there are also other advantages to basing recruitment on memory clinics, such as the access to much higher rates of at-risk patients than is typical for a population-based study, making the recruitment approach crucial in terms of study feasibility under the current CBAS funding structure.

Although brain imaging is available for most participants, biomarkers are available only for a subsample. Efforts are under way to increase biomarker data availability. Detailed information is missing on subjects lost to follow-up. Despite these limitations, to the best of our knowledge, CBAS remains the largest coordinated effort to collect longitudinal data in the context of cognitive and brain ageing in the CR and in Eastern Europe in general. CBAS is also unique in its richness of prospective data on lifestyle, genetic, neuropsychological, social, physical and biological factors as predictors of cognitive decline in the context of AD biomarkers. Until a population-based study with the same aim can be carried out within Eastern Europe, the CBAS may serve as the only source of information about a wide variety of risk factors for cognitive impairment in this geographical region.

In conclusion, CBAS has the potential to serve as a crucial, comprehensive source of information about markers of cognitive decline and impairment and can represent a model for studying risk/protective factors for AD in other Central and Eastern European countries.

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Famous Landmark Identification in Amnestic Mild Cognitive Impairment and Alzheimer's Disease

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Abstract

Background: Identification of famous landmarks (FLI), famous faces (FFI) and recognition of facial emotions (FER) is affected early in the course of Alzheimer's disease (AD). FFI, FER and FLI may represent domain specific tasks relying on activation of distinct regions of the medial temporal lobe, which are affected successively during the course of AD. However, the data on FFI and FER in MCI are controversial and FLI domain remains almost unexplored.

Objectives: To determine whether and how are these three specific domains impaired in head to head comparison of patients with amnestic MCI (aMCI) single domain (SD-aMCI) and multiple domain (MD-aMCI). We propose that FLI might be most reliable in differentiating SD-aMCI, which is considered to be an earlier stage of AD pathology spread out, from the controls.

Patients and Methods: A total of 114 patients, 13 with single domain (SD–aMCI) and 30 with multiple domains (MD–aMCI), 29 with mild AD and 42 controls underwent standard neurological and neuropsychological evaluations as well as tests of FLI, FER and FFI.

Results: Compared to the control group, AD subjects performed worse on FFI (p = 0.020), FER (p ﹥ 0.001) and FLI (p ﹥ 0.001), MD-aMCI group had significantly worse scores only on FLI (p = 0.002) and approached statistical significance on FER (0.053). SD-aMCI group performed significantly worse only on FLI (p = 0.028) compared to controls.

Conclusions: Patients with SD-aMCI had an isolated impairment restricted to FLI, while patients with MD–aMCI showed impairment in FLI as well as in FER. Patients with mild dementia due to AD have more extensive impairment of higher visual perception. The results suggest that FLI testing may contribute to identification of patients at risk of AD. We hypothesize that clinical examination of all three domains might reflect the spread of the disease from transentorhinal cortex, over amygdala to fusiform gyrus.

Introduction

Alzheimer disease (AD) is considered to be a continuum from preclinical stage through the prodromal stage represented by mild cognitive impairment (MCI) syndrome to the dementia syndrome [1,2,3]. The difference between MCI and dementia is in preserved functional capacity of MCI individuals whereas cognitive impairment is present in both stages. It is well accepted that beside the impairment of episodic memory, there are also other cognitive domains affected in early stages of AD, such as semantic memory, executive functions, attention, language, visuo-constructive skills and spatial navigation [4,5,6,7].

The individuals with MCI form a heterogeneous group, where those with memory impairment – amnestic MCI (aMCI), seem to be more vulnerable to convert to AD with estimated average rate of conversion 12% per year [8]. Some of aMCI subjects present with isolated memory impairment – aMCI single domain (SD-aMCI), while others present with impairment in additional domains to memory – aMCI multiple domain (MD-aMCI) [9]. Individuals with MD-aMCI are more likely to convert to dementia than SD-aMCI subjects [10] and might thus represent a more

advanced stage of AD pathology than SD-aMCI subjects. However, not all of the individuals with aMCI syndrome convert to dementia; some may remain stable or even reverse back to normal cognition. Therefore much effort is spent to identify subjects at higher risk with putative underlying AD pathology who are considered to be at prodromal stages of AD.

Besides the structural and functional neuroimaging, focused on the hippocampus and related structures, and the cerebrospinal fluid assessment of amyloid-b peptide, tau, and phosphorylated tau proteins, specific memory tests play an important role in identification of the high risk MCI subjects. Specifically, "amnestic syndrome of the hippocampal type" [11] seems to be characteristic for prodromal stages of AD [12,13]. Besides clinically well-established episodic memory tests [14], there has been ongoing search for novel instruments aiming even for earlier AD related changes with highest possible sensitivity and specificity.

Higher visual perception, which includes identification and recognition of faces and landmarks as well as recognition of facial emotions, is dependent on the medial temporal lobe structures that are affected early in the course of AD. There is some empirical evidence that these domains might be affected already in the MCI subjects [15,16,17].

Studies on famous faces identification (FFI) report consistently impairment of this domain in subjects with dementia due to AD [18,19,20] while studies with MCI subjects report rather inhomogeneous results [15,16,21,22].

Another domain affected early in patients with AD is recognition of facial emotions (FER) [17,23]. Reports on FER impairment in MCI are controversial [24,25,26,27]. However, evidence favors the hypothesis that worse FER is associated with MCI compared to normal aging [28].

Only very sporadic data exists on famous landmark identification (FLI) in AD – casuistic report is available of an AD patient with impaired discrimination between famous and unknown buildings despite of preserved identification of faces [29]. The single study with FLI in MCI [16] found that MCI subjects were impaired in naming of famous buildings, famous faces, and of well-known objects compared to controls.

The inconsistent results of FLI, FFI and FER impairment in MCI might be the result of different study populations: Some studies compared subgroups of patients with amnestic MCI while the others also included those with non-amnestic MCI. In addition, these studies use different paradigms exploring each specific domain. Some studies rely on testing the naming of famous faces/objects which also involves some semantic processing [15,16] while others use face matching tasks, comparing similarities or differences in facial features or emotions [17,21,22].

Recognizing famous faces, famous landmarks and emotions is probably domain specific task. Imaging studies in cognitively healthy subjects have shown category specific activation in medial temporal structures during tasks with buildings, emotion and famous faces recognition. Parahippocampal/lingual gyri are more responsive to buildings [30]; amygdala and adjacent cortex are activated during emotion recognition [31,32], while the fusiform gyri are preferentially responsive to famous faces [22,33].

Clinical staging of AD corresponds with spread of tau pathology (formation of typical argyrophilic neurofibrillary tangles and neuropil threads within the neurons) characterized in Braak staging [34], where stage I-IV corresponds with the spread of pathology in the direction from transentorhinal and parahippocampal cortices, to hippocampus, fusiform gyrus and beyond [35]. We suggest that the impairment in identification of these domain specific categories (FER, FFI and FLI) could appear based on their structural correlates in a timely manner during the course of AD

following the Braak stages. We have used well defined groups of patients (SD-aMCI, MD-aMCI and mild AD).

The aim of our study was to perform head to head comparison of these three domain specific paradigms relying on various medial temporal lobe structures in well-defined subgroups of aMCI and mild AD and to assess whether these tests can reliably distinguish SD-aMCI and MD-aMCI from controls. Based on the domain specific structural correlates, we expected that all 3 tasks will be affected in mild AD, while only FER and FLI would be impaired in aMCI compared to controls. Assuming that SD-aMCI might be an earlier stage of AD pathology then MD-aMCI, we hypothesize that FLI, which is relying on the parahippocampal gyrus, a brain region affected very early in the course of AD, might be more reliable in distinguishing SD-aMCI from controls.

Materials and Methods

1. Participants

The study was approved by the institutional ethics committee of University Hospital Motol and all participants provided a written informed consent. In demented people a research consent form was approved and signed on the patient's behalf by the caregiver. A total of 114 subjects were recruited at the Memory Clinic of the University Hospital Motol, 29 patients with mild AD, 43 patients with aMCI (13 SD–aMCI and 30 MD–aMCI), and 42 cognitively healthy controls. Cognitively healthy participants were recruited from the older adults attending University of the Third Age at Charles University in Prague or from relatives of patients of the Memory Clinic, Motol University Hospital in Prague. Subjects with memory complaints, history of neurological or psychiatric disease, psychiatric medication usage, or abnormal neurological examination including gait or movement difficulties were not included. Participants meeting DSM IV-TR criteria for dementia, Petersen's criteria for MCI [36] or scoring more than 1.5 SD below the age- and education-adjusted norms on neuropsychological examination were not included into the control group. MCI and AD subjects were referred to the clinic by general practitioners, neurologists, psychiatrists, and geriatricians. AD patients met the NINDS ADRDA diagnostic criteria and all participants with aMCI met published revised clinical criteria for MCI [36] including memory problem reported by patient or caregiver, generally intact activities of daily living, evidence of cognitive dysfunction with predominant memory involvement on neuropsychological testing, and absence of dementia. The aMCI patients scored in memory tests 1.5 standard deviation points below the mean of age- and education-adjusted norms. The aMCI subjects were further classified into SD-aMCI and MD-aMCI. SD-aMCI patients had an isolated memory deficit. Cognitive impairment in attention and executive function, language skills, or visuospatial skills in addition to memory impairment was used to classify subjects as having MD-aMCI. Patients with a Hachinski Ischemic Scale score ₋4 [37] or with a history of other neurological or psychiatric disorders including depression – scoring ₋5 in the short 15 items Geriatric depression scale [38] were not included in the study. All participants underwent standard neurological and laboratory evaluations, 1.5T magnetic resonance brain imaging, clinical scaling Mini Mental State Examination (MMSE) [39] and complex neuropsychological testing. Patients with extensive vascular changes – Fazekas score 3 [40], lacunar stroke, meningioma or other severe structural pathology on brain MRI were excluded from the study.

2. Neuropsychological evaluation

The neuropsychological battery was covering 1) memory, measured by Auditory Verbal Learning Test trials 1–6 and the Auditory Verbal Learning Test Delayed Recall [41,42], Rey-Osterrieth Complex Figure Recall condition [43] and modified version of FCSRT called Enhanced Cued Recall (ECR test in Czech validated version) [13,44]; 2) attention/processing speed, measured with the Digit Span Backwards [45] and Trail Making Test A [46]; 3) executive functions, measured with the Trail Making Test B [46] and Controlled Oral Word Association (COWAT) test [47]; 4) language, measured with the Boston Naming Test [48]; and 5) visuospatial functions measured with the Rey-Osterrieth Complex Figure Copy condition [43]. The score for each domain was expressed as a unit weighted composite score from the relevant tests. The Trail Making Test subtasks, which are expressed in seconds to completion, were reverse scored before the means were generated. Boston Naming Test scores were used only for MCI patient classification. The MMSE was administered to measure global cognitive functions.

3. Test of famous faces identification

This test was adapted from Keane's study [49] and adjusted for a Czech population [50]. Faces of 10 highly famous persons (politicians, actors, musicians, etc.) and 10 unfamiliar faces were presented to the subjects in a fixed pseudo-random order. We used pictures of famous people from visual media. For each face, the participant decided whether the person was familiar or not. The performance was measured by the number of faces correctly recognized as familiar or unfamiliar (correct rejections) with possible scores ranging from 0–20. The battery of famous faces was composed only from Czech personalities. The test was administered by a single qualified test administrator to avoid interrater variability.

4. Test of famous landmarks identification (Fig.1)

The famous objects were depicted considering Czech generally well known buildings and international buildings well-known within the Czech population. Identification of these objects was previously tested on a set of elderly cognitively healthy volunteers. Items which were not recognized by 20% or more of the volunteers were not included in the test. The administration of the test was fully computer based to avoid interrater variability.

Figure 1. Test of famous landmarks identification. Illustration of two famous places for the Czech population and two similar but unfamiliar places. For each place, the participant decided whether the place was familiar or not.
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Pictures of 25 highly famous places worldwide (buildings, bridges, statues etc.) and 25 matched pictures of unfamiliar places were presented in a fixed pseudo-random order. For each place, the participant decided whether the place was generally familiar or not. Each correctly recognized place as familiar or unfamiliar (correct rejections) was scored with one point – score range 0-50.

5. Test of facial emotions recognition

Pictures from the Ekman and Friesen series [51] representing five basic emotions, i.e., happiness, anger, sadness, fear and disgust were used to measure recognition of facial emotions. Each category of the five emotions was presented by using five pictures of different faces. The description of each emotion was printed under each picture in a random order in multiple choices. The participants were asked to point to the emotion which correlated best with the facial expression shown above. There were 25 trials (five for each emotion) with possible scores ranging from 0–25. The emotions were randomly presented and no target picture was used more than once.

6. Statistical evaluation

Inferential statistics involved a one-way analysis of variance (ANOVA) to evaluate between-group differences in age, MMSE, and neuropsychological tests. The x^2 test was used to evaluate differences in proportions (gender). The between-group differences in the main analyses with FFI, FER and FLI were evaluated using a general linear model (GLM). As the groups differed in the level of education, education was used as a covariate in these models. In the second GLM model we controlled for global cognitive functioning by adding a MMSE score to the previous model. All post hoc analyses were carried out with the Sidak test.

In the correlation analyses, first, zero-order Pearson correlation with Holm-Bonferroni correction for multiple comparisons was used to assess the relationship between the FFI, FER and FLI and neuropsychological tests. Subsequently, partial Pearson correlation with Holm-Bonferroni correction was used to control for the effect of group membership. Due to low variability of the scores across the groups, we used all participants within one correlation analysis. This step did not affect the results. The significance level was set at two-tailed 0.05. All analyses were run using SPSS 13.0 for Windows.

Results

The groups did not differ in age (F[3,110] = 2.11; p = 0.103) and gender (x^2(3) = 3.03; p = 0.387), but in education (F[3,110] = 8.65; p > 0.001), specifically AD (p > 0.001) and SD-aMCI (p = 0.023) had less years of education than the control group. The demographical and neuropsychological characteristics are presented in Table 1.

There was a moderate positive correlation between FER and FLI, and a low positive correlation between FFI and FLI and between FFI and FER. Correlations between FFI, FER, FLI, MMSE and cognitive domains are presented in Table 2. When we controlled for a group membership in the correlation analyses, only a low positive correlation between FER and FFI and between FER and FLI together with a moderate positive correlation between FLI and MMSE remained significant; see Table 2.

In the main GLM analysis controlling for education, we found significant main effects for group in FFI (F[3,109] = 3.54; p = 0.017), FER (F[3,109] = 12.00; p > 0.001) and FLI (F[3,109] = 15.60; p > 0.001) tests. Specifically, the SD-aMCI was impaired only in FLI (p = 0.028) compared to the control group. Further, the MD-aMCI had lower performance in FLI (p = 0.002)

Table 1. Demographic characteristics of the groups.

	Controls (n = 42)	SD-aMCI (n = 13)	MD-aMCI (n = 30)	mild AD (n = 29)	P value	Effect size
Age	71.55 (4.95)	72.62 (7.68)	71.93 (9.18)	74.41 (8.44)	0.103[a]	0.054[c]
Sex W/M	25/17 (0.60)	9/4 (0.69)	13/17 (0.43)	17/12 (0.59)	0.387[b]	0.162[d]
Education	15.79 (2.59)	13.23 (2.89)*	14.83 (3.44)	12.59 (2.21)***	˃ 0.001[a]	0.190[c]
MMSE	28.54 (1.44)	27.04 (2.32)	26.02 (2.86)***	19.79 (3.26)***	˃ 0.001[a]	0.617[c]
FCSRT	15.88 (0.33)	12.25 (2.71)	13.81 (3.03)*	9.00 (1.41)***	˃ 0.001[a]	0.362[c]
AVLT 1-6	58.41 (12.15)	30.75 (9.71)***	29.00 (6.57)***	30.0 (2.83) ***	˃ 0.001[a]	0.701[c]
AVLT 30	10.18 (3.38)	1.25 (1.49)***	2.24 (1.64)***	0.50 (0.71) ***	˃ 0.001[a]	0.752[c]
ROCF - R	18.38 (6.17)	6.80 (4.10)***	8.95 (5.16)***	1.50 (2.12)***	˃ 0.001[a]	0.501[c]
DSB	4.94 (0.97)	4.50 (1.41)	4.19 (1.66)	4.50 (0.71)**	0.003[a]	0.193[c]
TMT A	40.68 (8.72)	45.63 (30.66)	60.14 (23.80)	65.00 (32.53)**	0.001[a]	0.172[c]
TMT B	87.56 (19.74)	113.75 (36.51)	186.62 (119.79)**	355.00 (205.06)***	˃ 0.001[a]	0.353[c]
COWAT	43.24 (11.86)	37.88 (9.99)	30.76 (10.40)**	25.50 (7.78)***	˃ 0.001[a]	0.249[c]
ROCF - C	31.76 (1.79)	31.88 (2.03)	26.95 (5.24)*	16.75 (9.55)***	˃ 0.001[a]	0.448[c]
BNT err.	2.50 (1.89)	5.25 (2.44)	6.19 (3.81)*	12.40 (5.76)***	˃ 0.001[a]	0.800[c]
FFI	18.61 (1.48)	18.38 (1.66)	17.66 (2.72)	16.79 (2.90)*	0.017	0.098[c]
FER	21.93 (2.23)	20.00 (2.20)	20.03 (2.54)	17.13 (4.02)***	˃ 0.001	0.223[c]
FLI	42.27 (3.79)	37.62 (4.25)*	37.90 (4.72)**	33.17 (5.91)***	˃ 0.001	0.317[c]

Mean values (SD); Auditory Verbal Learning Test (AVLT) trials 1–6 and AVLT Delayed Recall (AVLT 30), Rey-Osterrieth Complex Figure Copy (ROCF - C) and Recall (ROCF – R), Free and Cued Selective Reminding Test (FCSRT) total recall, Digit Span Backward (DSB), Trail Making Test (TMT) A and B, Controlled Oral Word Association (COWAT), Boston Naming Test errors (BNT err.); one-way ANOVA - between-group differences.
[a]ANOVA, [b]X^2 test, [c]Partial eta ^{2}, [d]Cramér's V, * p ˃ .05, ** ˃ .01, *** ˃ .001 (compared to the control group) Note: Partial eta^2 of 0.2 corresponds to Cohen's d of 1.0 with our sample size, Cramér's V of about 0.175 corresponds to Cohen's d of 0.356.
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compared to the control group. Differences between the MD-aMCI and the control group in FER approached statistical significance (p = 0.053). Finally, the AD group had lower performance in all three main tests, FFI (p = 0.020), FER (p ˃ 0.001) and FLI (p ˃ 0.001), compared to the control group. There were no differences between the SD-aMCI and MD-aMCI groups. For the differences in the performance among the groups see in Figure 2, 3, 4. In the second GLM analysis controlling for education and MMSE score, the main significant effect remained for the FLI (F[3,108] = 5.97; p = 0.001) and FER (F[3,108] = 5.38; p = 0.002) tests, but not for the FFI (F[3,108] = 2.21; p = 0.091). Specifically, the differences between the SD-aMCI and the control

group approached statistical significance in FLI (p = 0.057). Further, the differences between the MD-aMCI and the control group remained significant for FLI (p = 0.013), but not for FER (p = 0.083). Finally, the differences between the AD and the control group remained significant for FER (p = 0.001) and FLI (p = 0.001) tests. The differences between the SD-aMCI and MD-aMCI groups remained non-significant.

Discussion

The findings indicate that SD-aMCI patients performed significantly worse than controls on FLI but not on FER and

Table 2. Correlations of FFI, FER and FLI with cognitive domains (EGM – correlations controlled for effect of group membership).

		FFI	FER	FLI
MMSE	EGM	0.127	0.114	0.407**
		0.313*	0.411**	0.681***
memory	EGM	0.220	0.171	0.139
		0.370**	0.438**	0.531***
attention	EGM	0.248	0.248	0.177
		0.309*	0.333*	0.299*
executive	EGM	0.092	0.228	0.245
		0.247	0.425**	0.511***
visuospatial	EGM	20.094	20.110	0.228
		0.104	0.181	0.504***

* p ˃ 0.05, ** ˃ 0.01, *** ˃ 0.001 values in bold indicate significant correlations after Holm-Bonferroni correction for multiple comparisons. The tests used for testing each cognitive domain are closely described in the methods.
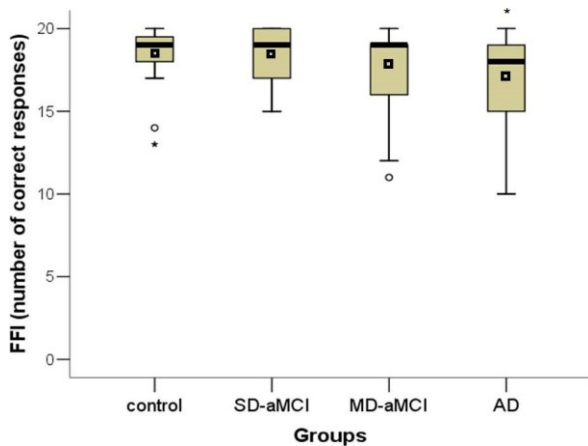doi:10.1371/journal.pone.0105623.t002

Figure 2. Differences across groups in the FFI test. The total number of faces correctly recognized as familiar or unfamiliar (correct rejections) in each group is depicted. * p ˃ 0.05. Note: mean, median and interquartile ranges characterise performance of each group. FFI = Test of famous faces identification, SD-aMCI = single domain amnestic mild cognitive impairment, MD-aMCI = multiple domain amnestic mild cognitive impairment, AD = Alzheimer's disease dementia.
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Figure 3. Differences across groups in the FER test. The total number of correctly recognized emotions in each group is depicted. * p ˃ 0.05, *** p ˃ 0.001. Note: mean, median and interquartile ranges characterise performance of each group. FER = Test of facial emotions recognition, SD-aMCI = single domain amnestic mild cognitive impairment, MD-aMCI = multiple domain amnestic mild cognitive impairment, AD = Alzheimer's disease dementia.
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FFI, MD-aMCI scored worse on FLI and approached statistical significance in FER performance. Further, AD patients exhibited impairment in all 3 visual domains. The findings could not be explained by differences in education but were partially modified by MMSE.

In our previous work we have shown that FER but not FFI may be impaired in MD-aMCI and that neither FER nor FFI is impaired in SD–aMCI [27] which is consistent with the results of this study using different patients' cohort. Similar finding was reported from the study of University of California Los Angeles, which also compared two groups of aMCI subtypes [26]. However, FLI seems to be impaired in both SD-aMCI as well as MD-aMCI group of patients compared to controls and no differences in FLI performance seem to be present between SD-aMCI and MD-aMCI patients. This suggests that FLI could be helpful in combination with other scales in cognitive screening for aMCI in geriatric population.

On the contrary, impairment of FFI does not seem to be very sensitive for MCI. Studies with face matching tasks in MCI subjects suggested no differences in the number of correct answers, but only longer completion time when compared to normal controls [21,22]. This is consistent with our results where no impairment of FFI compared to controls was found in any of the aMCI subtype and both, SD-aMCI as well as MD-aMCI group, performed similarly when compared with each other.

On the other hand, the Barcelona group [15] reported that slight FFI impairment may be predictive of dementia due to AD developed 2 years later and the Cambridge group did report impairment of FFI in MCI [16]. The different results can be explained by using of different paradigm. Both studies relay the testing of these categories on naming faces and/or buildings, which involves a complex processing network including involvement of stored semantic knowledge about the people or buildings. Psychological studies have suggested that the task of fully identifying and naming a famous person is achieved by a cascade of sequential processing stages [52]: the pre-semantic stage, when recognition of famous faces is impaired only in the visual domain, the semantic stage, when loss of biographical information about known people (person-specific semantics) occurs regardless of the
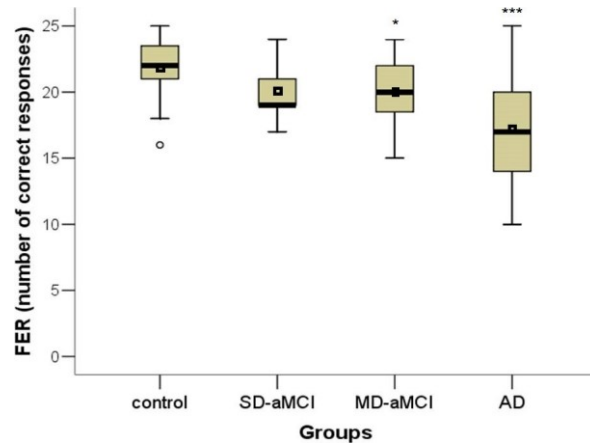
stimulus modality; and the post-semantic lexical retrieval stage, when name retrieval is impaired but semantic information is retrieved correctly. In our study however, subjects did not name the faces/buildings, they were just deciding whether the presented item was famous or not. This is similar to paradigm used in a different Cambridge study [19], which indicated that pure recognition and sense of familiarity can occur independently of accessing semantic information.

Results of our present study show that impairment of FLI is present in aMCI subjects and it can discriminate both aMCI subtypes from controls. There are very few studies on recognizing famous or familiar buildings or landmarks in AD and MCI [16,29]; the results of these studies correspond with our findings of
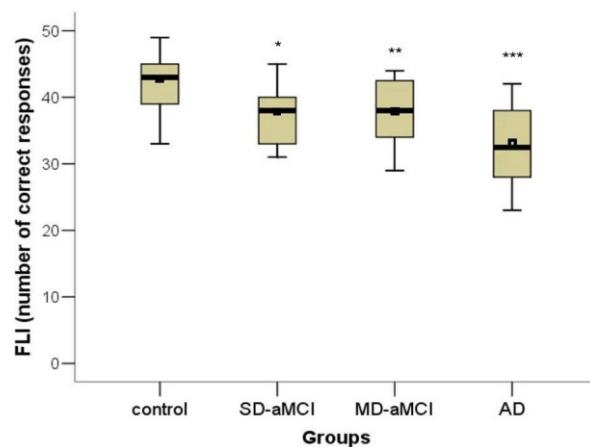
Figure 4. Differences across groups in the FLI test. The total number of correctly recognized places as familiar or unfamiliar (correct rejections) in each group is depicted. * p ˃ 0.05, ** p ˃ 0.01, *** p ˃ 0.001. Note: mean, median and interquartile ranges characterise performance of each group. FLI = Test of famous landmarks identification, SD-aMCI = single domain amnestic mild cognitive impairment, MD-aMCI = multiple domain amnestic mild cognitive impairment, AD = Alzheimer's disease dementia.
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FLI impairment in AD as well as in MCI and to a more pronounced FLI than FFI impairment in these subjects [53].

According to the literature the FLI, FER and FFI depends on various anatomical structures [17,21,30,31,32,54] therefore the differences in the impairment of specific domains among the groups of patients with different severity of cognitive impairment might be caused by distinct neuropathological correlates involved in each paradigm. According to Braak and Braak [35], underlying AD pathology spreads gradually; affecting medio-temporal structures in the typical order and clinical staging corresponds with tau pathology and Braak staging [34]. Our results could be interpreted in this context. FLI refers to parahippocampal/lingual gyri [30].

Lesion of the parahippocampal gyrus may lead to inability to recognize salient environmental landmarks during spatial navigation and may thus cause significant spatial navigation deficits [54].

Transentorhinal cortex, a part of parahippocampal gyrus is the first affected by the AD pathology. This corresponds with a view that SD-aMCI is an earlier stage than MD-aMCI, where besides FLI also FER is impaired. FER depends on the function of the amygdala [31,32] which is affected later in the course of AD [35]. Spreading of the pathology beyond the mesiotemporal struc- tures in subjects with dementia would correspond to our observation that FFI impairment relying on more lateral regions within temporal neocortex [17,21] was present together with FLI and FER impairment only in demented subjects.

Our study shares limitation with similar studies in the field which is the absence of neuroimaging correlates. Further, we used a relatively small sample size, which could also influence the results. Especially, due to the small sample size we failed to find differences between SD-aMCI and MD-aMCI groups in FER, although MD-aMCI patients seem to be impaired unlike SD-aMCI patients when compared to the control group. We could not exclude problems with familiarity assessment as an influencing factor, similarly like the other studies on familiarity cited in this article. We acknowledge that some studies in aMCI reported difficulties with assessing familiarity in these subjects [55] and over-reliance on familiarity as well [56]. However other studies did not find impaired familiarity-based recognition in contrary to impaired recognition based on recollection in MCI subjects, suggesting that recollection and familiarity might be independent processes associated with distinct anatomical substrates [57,58]. PET studies also show that the distinction of famous and non–famous stimuli independently of its category [30,59,60,61] relies on anterior temporal pole, which as a part of associative neocortex is affected later in the course of AD pathology spread out (Braak IV). This might suggest that the statistical differences observed in aMCI subjects reflect the domain specific differences in the task rather than difficulties in familiarity assessment. We cannot also exclude a ceiling effect in the FFI task, which could cover up some of the group differences in performance within this task. The selection of participants is limited because the diagnosis of aMCI was based only on a complex neuropsychological examination and no imaging or biochemical biomarkers were used. Therefore we could not exclude subjects which would not convert to AD in a short time.

However, this study has potential implications for future research. We have introduced a new paradigm on famous landmark identification which allows direct comparison with analogical paradigm described in Keane's study [49] on identification of famous faces. This is to our knowledge the first head to head comparison of these 3 paradigms, which allows interpretation of the usefulness of each paradigm for distinguishing aMCI patients from the controls. The tasks of FLI, FER and FFI probably involve segregated neurocognitive networks part of

which are affected in prodromal stages of AD and future research is needed to test this hypothesis. Especially studies with the employment of functional neuroimaging would be of a great advantage. The early spread-out of pathology through the visual ventral stream is a specific feature for AD therefore assessment of these domains could also help in early differential diagnosis of AD versus other forms of dementia such as frontotemporal lobar degeneration where ventral visual stream is spared and diffuse Lewy body disease where dorsal visual stream is early involved.

Another important future implication for research would be to assess how FLI impairment correlates with real spatial navigation difficulties. Spatial orientation difficulties is a well-known and stressful feature reported by caregivers of individuals with dementia due to AD and impairment in spatial navigation is one of the early markers of MCI due to AD pathology while it correlates with hippocampal type of memory impairment [62] and with right hippocampal volume [63]. FLI is related to the ability of recognizing landmarks important for navigation. Recent findings indicated that learning and subsequent recalling or recognition of landmarks or famous places may not be dependent on the way how and in which environment they were perceived. In the study addressing this issue [64] similar results were found when landmarks or places visited by subjects were learned in the real-world and virtual environment, respectively, and also when they were subsequently recalled or recognized from photographs and video clips. The more unique an object is within an environment and the more it is perceived as having a stable spatial position, the more likely it is that it will be used as a landmark. Objects rated as more stable (larger and less "portable") automatically evoked landmark-based neural processes in the study subjects [65]. In line with this, it has also been shown that making spatial judgments with reference to stable environmental objects (e.g., a large buildings) compared with unstable objects (e.g., a ball) elicit greater activity in navigationally relevant medial parietal and temporal brain regions, including the hippocampus (for review see [66,67]). Objects included in our FLI test fulfil both of these criteria (shape uniqueness and stability) hence could be relevant for testing one part of complex spatial navigation behaviour used in. Objects used for navigation in the neighbourhood and town are usually landmarks learned long time ago. Therefore difficulties in recognizing them as familiar could be part of the problem everyday navigation scenario of AD subjects. Establishing the relationship between FLI and spatial navigation impairment might confirm the usefulness of FLI in assessment in MCI at high risk for conversion to AD dementia. The practical implication may be that being impaired in the FLI can reflect the difficulties with orientation in the real environment, which may contribute to driving impairments and getting lost.

Conclusions

Our results suggest that the tasks with recognizing famous landmarks, facial emotions and familiar faces involve segregated neurocognitive networks and might be impaired in a time order in relation to the course of AD. Since these tests refer to different brain structures which are considered to be related to various stages of the disease, assessment of FLI, FER and FFI may provide valuable clinical information indirectly reflecting underlying pathology. Future research is needed to match pathological changes, test performance and longitudinal data.

Acknowledgments

Author Contributions

Conceived and designed the experiments: JL MV KV JA JH. Performed the experiments: IM MV. Analyzed the data: KS RA JA. Contributed reagents/materials/analysis tools: KV JL. Contributed to the writing of the manuscript: KS JL MV RA KV IM JA JH.

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Neuropsychological Correlates of Hippocampal Atrophy in Memory Testing in Nondemented Older Adults

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Abstract.
Background and Objective: Cognitive deficits in older adults attributable to Alzheimer's disease (AD) pathology are featured early on by hippocampal impairment. Among tests used to evaluate memory, verbal memory tests with controlled encoding and cued recall are believed to be specific for hippocampal impairment. The objective of this study was to assess the relation between left and right hippocampal volumes and several frequently used memory tests.
Methods: Fifty six nondemented older adults (30 with amnestic mild cognitive impairment and 26 cognitively healthy older adults) underwent neuropsychological testing including: 1) The Enhanced Cued Recall test (ECR), a memory test with controlled encoding and recall; 2) the Auditory Verbal Learning Test (AVLT), a verbal memory test without controlled encoding and with delayed recall; and 3) The Rey-Osterrieth Complex Figure test (ROCF), a visuospatial memory test–recall condition. 1.5T brain MRI scans were used to measure estimated total intracranial volume (eTIV) along with hippocampal right and left volumes, which were measured with quantitative volumetry using FreeSurfer package (version 4.4.0). Spearman partial correlation controlled for age was used to correct for non-normal score distribution and effect of age.
Results: We found moderate correlations of hippocampal volumes with AVLT 1–5 scores, AVLT delayed recall, ECR free and total recall, and ROCF reproduction. Total recall in ECR using cued recall was not superior to any of the free recall tests. No correlation in any memory test was achieved with eTIV.
Conclusion: Verbal memory tests, either with controlled encoding and cued delayed recall (ECR), or without it (AVLT), as well as nonverbal memory test with delayed recall (ROCF), equally reflect hippocampal atrophy in nondemented older adults.

Keywords: Amnestic mild cognitive impairment, episodic memory, hippocampus, MRI

INTRODUCTION

Impairment of episodic memory is known to be an early sign of Alzheimer's disease (AD) [1, 2] and a core criterion in the proposed diagnostic AD criteria [3, 4]. Verbal episodic memory impairment is among the first symptoms of a typical form of AD [5]. There

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is evidence that in addition to verbal episodic memory, nonverbal episodic memory declines in the early stages of AD [5–9].

Subjective and objective memory impairment in older adults does not occur only in AD and therefore must be distinguished from non-AD related impairment that can also affect delayed recall. Impairment of delayed recall may include inefficient retrieval strategies associated with normal aging [10] or other dementias [11, 12].

Memory impairment is already present in patients with amnestic mild cognitive impairment (aMCI), a prodromal stage of AD [13]. Patients with aMCI are at increased risk of conversion to dementia. However, the diagnosis of MCI may be problematic. Research evidence is mixed concerning the prevalence of MCI in the population, as well as conversion rates of MCI to dementia [14]. Further, diagnosis of MCI may be unreliable, in part because of the absence of a standard neuropsychological MCI testing battery and the border between cognitively healthy older adults and patients with MCI is often blurred [15]

As demonstrated by neuropathological studies, memory decline in early AD is considered to result mainly from degeneration of the hippocampus [16]. The degeneration of other brain structures (mainly frontal lobe and its circuitry) may also contribute to memory dysfunction in the later stages of dementia due to AD [17].

Degeneration of the hippocampus is reflected by hippocampal atrophy, which can be identified by MRI even in the prodromal aMCI stage [18, 19]. Measurement of hippocampal volume and its change over the time by means of the quantitative volumetry have been found to predict disease progression and AD diagnosis [20–22]. Fully automated software tools are now available that can measure hippocampal volume efficiently and reproducibly [23–25]. Overall, the selection of the most sensitive memory tests that are strongly associated with hippocampal atrophy appear to be of crucial importance for an accurate diagnosis of pathological aging.

Various memory tests are used to assess memory impairment in older adults. The tests differ by stimulus modality (verbal or nonverbal), by method of encoding (presence of controlled learning/encoding), and by type of recall (free recall, controlled cued recall, or recognition). Word-list learning tests with multiple trials (e.g., Auditory Verbal Learning Test, AVLT) reveal the rate of learning over time, as well as the maximum amount of information acquired over the course of the learning trials. Other verbal learning tests include

immediate and delayed paragraph recall, e.g., Logical Memory from Wechsler Memory Scale III.

Some guidelines recommend the use of memory tests with a controlled encoding paradigm [3, 26], in which controlled learning/encoding with semantic cues diminishes the influence of attention, strategy, and working memory during the encoding part of the test, based on the encoding specificity principle [27]. Researchers suggest that a low free and total recall performance reflects hippocampal impairment with higher specificity and is the core neuropsychological marker of prodromal AD [3, 28].

The most widely used neuropsychological test with controlled encoding and cued recall is the Free and Cued Selective Reminding Test (FCSRT), which includes free and total recall subtests [29]. The FCSRT uses category cues at both acquisition and retrieval in an attempt to ensure semantic encoding and enhance recall. The FCSRT (especially total recall) has been identified to be the most sensitive and specific test for identifying convertors to AD among MCI patients [30].

In a longitudinal population study of nondemented older adults the FCSRT subtests of free and total recall showed high negative predictive value. However, positive predictive values were low, and many subjects with poor free and total recall scores on the FCSRT remained free of dementia at 5 years [31]. In another longitudinal aging study, a decline in free recall was detected 7 years before the diagnosis of dementia [32]. In summary, the clinical utility of this widely used test seems to be evident in numerous studies; however, it has yet to be directly compared with other verbal memory tests (without controlled learning/encoding and cued recall) among older adults in the predementia stage.

The Enhanced Cued Recall test (ECR) has been recognized as an alternative version of FCSRT, using the same paradigm.

Other widely used assessments of memory impairment in older adults do not use the controlled learning/encoding paradigm. The AVLT [33] assesses learning and retention using a five-trial presentation of a 15-word list (list A), plus two post-interference recall trials (one immediate and one delayed) and recognition [17].

The test is considered to be highly sensitive, with impairment of AVLT total learning and long-term delayed recall demonstrated even in cognitively healthy APOE4 carriers [34]. In particular, learning and delayed recall after 30 minutes has been shown to be a highly sensitive measure of memory decline in early AD [35–38].

Although numerous studies use verbal memory tests, proof is lacking of the superiority of cued learning/recall tests, such as the FCSRT, over the tests based purely on free recall (without controlled learning/encoding and cued recall), such as AVLT, in diagnosing cognitive deficits in nondemented older adults [39].

Non-verbal memory is assessed neuropsychologically with visual memory tests. Probably the most widely used neuropsychological test of nonverbal memory is the Rey-Osterrieth Complex Figure test (ROCF). Recall of the complex figure typically follows the copy trial.

The perturbation of recall ROCF has been found in patients representing a range of impairment, including patients with AD [40] or MCI [41], and even in healthy APOE4 carriers aged 50–59 years [34].

To our knowledge, no study has examined the relation between various types of memory tests and hippocampal volumes in nondemented older adults.

The aim of the study was to correlate performance on frequently used memory tests (the AVLT, the short version of the FCSRT, and the ROCF) with left and right hippocampal volumes to find which of the tests better reflects hippocampal atrophy in nondemented older adults. First, we compared correlations between hippocampal atrophy and two different types of verbal memory tests, those with controlled encoding and those without. Second we compared correlations between hippocampal atrophy and tests with free recall versus cued recall. Third we compared correlations between hippocampal atrophy and verbal versus non-verbal memory tests. Due to small variability in memory scores among patients with aMCI and a small overall sample size, we adopted a similar analytical approach as used in previous imaging studies [42–45]; that is, we treated non-demented older adults as a single group.

MATERIALS AND METHODS

Subjects

A total of 56 nondemented older adults were recruited and followed prospectively with annual examinations at the Memory Disorders Clinic at Motol University Hospital in Prague, Czech Republic between 2009 and 2013. The group consisted of 30 participants with clinically confirmed aMCI and 26 cognitively healthy elderly.

Subjects with aMCI [13] underwent standard neurological, internal, and laboratory evaluations, clinical

scaling, brain MRI, and neuropsychological examination. These participants were referred to the clinic by general practitioners, neurologists, psychiatrists, and geriatricians based on memory complaint from the patient or the caregiver. They also met published clinical criteria for aMCI, including memory complaints reported by a patient or caregiver, evidence of memory dysfunction on neuropsychological testing, generally intact activities of daily living, and absence of dementia [13]. Memory impairment was established when the patient scored more than 1.5 standard deviations below the mean of age- and education-adjusted norms on any memory test [46]. Participants with depression (>5 points on the 15-item Geriatric Depression Scale) [47] and those meeting the Diagnostic and Statistical Manual of Mental Disorders IV-TR criteria for dementia were not included.

Cognitively healthy participants were recruited from the older adults attending University of the Third Age at Charles University in Prague or from relatives of patients of the Memory Clinic, Motol University Hospital in Prague. Subjects with memory complaints, history of neurological or psychiatric disease, psychiatric medication usage, or abnormal neurological examination including gait or movement difficulties were not included. Participants meeting DSM IV-TR criteria for dementia, Petersen's criteria for MCI [13], or scoring more than 1.5 SD below the age- and education-adjusted norms on neuropsychological examination were not included.

All participants in this study had signed written informed consent that was approved by a local ethics committee.

The basic characteristics of the group and subgroups are summarized in Table 1.

Neuropsychological assessment

All subjects were interviewed using the following questionnaires: Clinical Dementia Rating, Activities of Daily Living, Hachinski Ischemic Scale, and Geriatric Depression Scale. The neuropsychological battery included the Mini Mental State Examination (MMSE), the Clock Drawing Test, Digit Span forward and backward tests, Initial Letter Fluency – COWAT, and the Trail-Making Tests (TMT) A and B.

Three memory tests were used:

1) Memory test with controlled encoding and recall: a modified version of FCSRT called Enhanced Cued Recall (ECR test in Czech validated version) [48, 49]

The test uses category cues at both acquisition and retrieval in an attempt to ensure semantic encoding

Table 1
Descriptive statistics of the sample

Variable	Non demented elderly	Non demented elderly	
		aMCI ($n = 30$)	Cognitively healthy elderly ($n = 26$)
Demographic characteristics			
Gender (male/female)	21/35	16/14	5/21
		Mean $\pm$ sd	
Age	72.02 $\pm$ 8.64	75.00 $\pm$ 8.57	68.58 $\pm$ 7.48
Education	14.98 $\pm$ 3.08	14.20 $\pm$ 3.00	15.92 $\pm$ 2.96
Test scores			
MMSE	27.90 $\pm$ 2.34	26.67 $\pm$ 2.54	29.31 $\pm$ 0.84
AVLT 1	4.84 $\pm$ 1.92	4.07 $\pm$ 1.28	5.73 $\pm$ 2.16
AVLT 5	10.07 $\pm$ 3.38	7.67 $\pm$ 2.23	12.85 $\pm$ 2.11
AVLT 1-5	40.55 $\pm$ 12.67	31.97 $\pm$ 7.00	50.46 $\pm$ 10.28
AVLT 30	6.45 $\pm$ 5.19	2.63 $\pm$ 2.74	10.85 $\pm$ 3.60
ECR-FR	7.33 $\pm$ 3.80	5.00 $\pm$ 3.16	9.92 $\pm$ 2.58
ECR-TR	14.58 $\pm$ 2.77	13.34 $\pm$ 3.37	15.96 $\pm$ 0.20
ROCF-R	12.81 $\pm$ 7.33	7.67 $\pm$ 4.79	17.94 $\pm$ 5.65
ROCF-C	29.21 $\pm$ 4.58	28.06 $\pm$ 4.81	30.37 $\pm$ 4.10
TMT A	22.89 $\pm$ 10.14	27.48 $\pm$ 11.60	17.68 $\pm$ 4.28
TMT B	135.85 $\pm$ 147.22	229.58 $\pm$ 176.85	74.64 $\pm$ 34.65
F-DigitSpan-NM	6.02 $\pm$ 1.30	5.67 $\pm$ 1.35	6.42 $\pm$ 1.14
F-Digit Span-SC	9.23 $\pm$ 2.35	8.57 $\pm$ 2.34	10.00 $\pm$ 2.15
R-DigitSpan-NM	4.41 $\pm$ 1.26	3.97 $\pm$ 1.07	4.92 $\pm$ 1.29
R-DigitSpan-SC	5.98 $\pm$ 2.19	5.30 $\pm$ 1.84	6.77 $\pm$ 1.84
COWAT	39.07 $\pm$ 13.31	33.03 $\pm$ 10.09	46.04 $\pm$ 13.33
Volumes			
HPC – L	2.31 $\pm$ 0.39	2.08 $\pm$ 0.29	2.57 $\pm$ 0.32
HPC – R	2.28 $\pm$ 0.37	2.07 $\pm$ 0.34	2.52 $\pm$ 0.25
eTIV	1529979 $\pm$ 129111	1540856.43 $\pm$ 146640.68	1517428.07 $\pm$ 106880.27

MMSE, total score; AVLT 1, trial 1 recall; AVLT 5, trial 5 recall; AVLT 1–5, sum of trials 1 to 5; AVLT 30, recall after 30 minutes; ECR-FR, free recall; ECR-TR, total recall after cueing; ROCF-R, visual reproduction after 3 minutes; ROCF-C, copy score (Meyers & Meyers, 1995); TMT A given in seconds; TMT B, given in seconds; F-DigitSpan-NM, forward Digit Span - numbers; F-Digit Span-SC, forward Digit Span – score; R-DigitSpan-NM, reversed Digit Span – numbers; R-DigitSpan-SC, reversed Digit Span – score; COWAT, Czech version with "N", "K", "P" letters; HPC – L, left hippocampal volume – corrected; HPC – R, right hippocampal volume – corrected; eTIV, estimated total intracranial volume.

and enhance recall. The subject is asked to search a card containing line drawings of four objects and to identify the one that belongs to a category named by the examiner, such as fruit. Each of the 16 items to be learned appears on one of four cards that are used. After each item on the first card is correctly identified, the card is removed and immediate recall of the four items is tested by cueing with the category prompt. Errors are corrected. The other 12 items are presented four at a time in the same manner. A learning phase and subsequent interfering task (clock test) was followed by one free trial and subsequent cued recall for items not spontaneously reported. Free recall (ECR-FR) and total recall (ECR-TR = free + cued recall) were evaluated.

2) Verbal memory test without controlled encoding and delayed recall: auditory verbal learning test (AVLT) [50, 51]

The examiner reads a list of 15 words from List A at the rate of one per second after instructing the participant to listen and remember them. The examiner writes down the words recalled then rereads the test for trials II to V with immediate recall recorded after every trial. After the fifth trial, words from the List Bare read and recalled. Following the List B trial, the examiner asks the patient to recall as many words from List A as possible (trial VI). A 30-minute delayed recall trial is administered to measure retention. In our study, word span under overload conditions (trial I: AVLT 1), final acquisition level (trial V: AVLT 5), total acquisition (E I-V: AVLT 1–5), and delayed recall after 30 minutes (trial VII- AVLT 30) were analyzed.

3) Visuospatial memory test: Rey-Osterrieth Complex Figure (ROCF) [52]

Participants are asked to copy and later recall a line drawing of a figure. In our study, a recall task was administered 5 minutes after the copy task. The subject had not been previously instructed to memorize the figure. Copy and reproduction were scored by an independent rater (neuropsychologist) using the Meyers

system. Both copy and reproduction were evaluated in the final analysis.

Results of the neuropsychological battery including memory tests are summarized in Table 1.

MRI Data acquisition and analysis

Brain images were performed at 1.5T (Avanto, Siemens AG, Erlangen, Germany) using T1-weighted 3-dimensional high resolution magnetization-prepared rapid acquisition with gradient echo (MP RAGE) sequence in sagittal plane with the following parameters: repetition time/echo time/inversion time = 2000/3.08/1100 ms, flip angle 15°, 192 contiguous partitions, slice thickness 1.0 mm and no gap, TE/TR = 5/25 ms, flip angle 30, and in-plane resolution 1 mm. Scans were visually inspected by a single neuroradiologist blinded to the diagnosis and clinical or cognitive measures, in order to ensure appropriate data quality and to exclude patients with relevant brain pathology such as cortical infarctions, neoplasm, subdural hematoma, or hydrocephalus. Those with lacunar infarcts or leukoaraiosis were excluded. Volumes of the left and right hippocampus were computed using fully automated FreeSurfer algorithm, version 4.4.0, installed on local Mac OS X (Apple) workstation and described in details elsewhere [23] (http://surfer.nmr.mgh.harvard.edu). We have visually checked the outputs of FreeSurfer's segmentation for potential errors in in the delineation of hippocampal region of interest segmentation [23]. We further checked the distribution of hippocampal volumes and did not identify any overly influential outliers. We finally adjusted hippocampal volumes for estimated total intracranial volume (eTIV) using the following formula: Adjusted hippocampal volume = raw hippocampal volume mm^3/eTIV mm^3 * 1000 [53]. The hippocampus ROI was chosen not only for its implication in AD and relevance to memory functions, but it has well defined borders and its volume can be consistently measured with various available tools [54]. Another reason for atlas-based approach was that we wanted to correlate hippocampal volume with performance on memory tests, in keeping with our hypothesis.

Statistical analysis

The Kolmogorov Smirnov test was used to assess the distribution normality of the neuropsychological test scores. The scores with non-normal distribution were: MMSE, AVLT 1, AVLT 5, ECR-total recall, ROCF-copy, TMT B. Other scores showed normal distributions. Spearman rather than Pearson correlation was used to correlate neuroimaging measures to indices of memory among the nondemented older adults because of the non-normally distributed variables. Partial correlation was used to control for the effect of age. All statistical analyses were conducted using SPSS v 13.0 for Windows. The magnitude of correlations was compared using SISA-Steiger's Z for two dependent correlations from a single sample [55]. To assess whether multiple comparisons affected the results, we applied the Holm-Bonferroni method to correct statistical significance (*p*-value) for the number of correlations with hippocampal volumes that were calculated [56]. This is a sequential variant of the conventional Bonferroni correction method in which *p*-values are sorted from lowest to highest, then the lowest *p*-value is multiplied by the number of correlations, the second lowest *p*-value is multiplied by the number of correlations minus one, the third lowest *p*-value is multiplied by the number of correlations minus two and so on until the 0.05 threshold of significance is reached or exceeded.

RESULTS

Descriptive information of the nondemented participants and the subgroups is presented in Table 1.

The results of all correlation analyses for the combined nondemented group are summarized in Table 2. We found moderate correlations of hippocampal volumes with the total learning score (results for left and right hippocampal volume: AVLT 1–5, $r_L = 0.414$, $r_R = 0.281$), recall in the last trial in the learning sequence (AVLT 5, $r_L = 0.501$, $r_R = 0.314$), long-term delayed recall (AVLT 30, $r_L = 0.514$, $r_R = 0.431$), the ECR free and total recall ($r_L = 0.442$, $r_R = 0.415$, and $r_L = 0.356$, $r_R = 0.334$, respectively), and the ROCF reproduction ($r_L = 0.427$, $r_R = 0.488$). No significant correlation was found between hippocampal volumes and recall in the first learning trial (AVLT 1, $p = 0.14$ and $p = 0.08$ for left and right side, respectively). The eTIV did not correlate with any memory tests (all *p*'s>0.10).

The results of all correlation analyses are summarized in Table 2. Verbal memory scores tended to correlate better with the left hippocampus; however, the difference between the magnitude of correlation parameters was significant only for the recall in the last learning trial (AVLT 5, $p = 0.021$). The strongest correlation was found between left hippocampal volume and long-term delayed recall (AVLT 30, $r_L = 0.514$).

Table 2
Non parametric partial correlations – Spearman rho: controlled for age

	AVLT 1	AVLT 5	AVLT 1–5	AVLT 30	ECR -FR	ECR TR	ROCF-R	ROCF-C	HPC -L	HPC -R
AVLT 5	0.520***									
AVLT 1–5	0.722***	0.922***								
AVLT 30	0.448***	0.854***	0.791***							
ECR-FR	0.377**	0.656***	0.601***	0.752***						
ECR-TR	0.104 ns	0.605***	0.476***	0.628***	0.640***					
ROCF-R	0.210 ns	0.701***	0.611***	0.718***	0.768***	0.622***				
ROCF-C	0.044 ns	0.266 ns	0.245 ns	0.322*	0.205 ns	0.194 ns	0.403**			
HPC-L	0.242 ns	0.501***	0.414**	0.514***	0.442***	0.350**	0.427**	0.410**		
HPC-R	0.203 ns	0.314**	0.281*	0.431***	0.415**	0.334**	0.408**	0.357**		
eTIV	−0.170 ns	0.026 ns	0.025 ns	−0.033 ns	0.116 ns	0.227 ns	0.134 ns	−0.012 ns	−0.323*	−0.219 ns

Control variable, Age; ns, not significant; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$. AVLT 1, trial 1 recall; AVLT 5, trial 5 recall; AVLT 1–5, sum of trials 1 to 5; AVLT 30, recall after 30 minutes; ECR-FR, free recall; ECR-TR, total recall after cuing; ROCF-R, visual reproduction after 3 minutes; ROCF-C; HPC – L, left hippocampal volume – corrected; HPC – R, right hippocampal volume – corrected; eTIV, estimated total intracranial volume.

However, the difference in magnitude of correlation was not significantly greater compared to the total learning score in the same test.

Comparing the magnitude of correlations among free recall scores in three tests, there was a significant difference in the magnitude of correlations among recall in the first trial (AVLT 1) and free recall in ECR (ECR free) and AVLT 1-ROCF copy, respectively, with both hippocampal volumes (p's < 0.05). However, correlations with other indices of free recall in AVLT (AVLT 5 and AVLT 1–5) did not significantly differ in magnitude from free recall scores used in two other memory tests. Correlation with the ECR total recall score was not superior compared to free recall scores procedures in all three tests.

Finally, when we applied the Holm-Bonferroni method to correct for the number of correlations with hippocampal volumes that were calculated, the results remained significant with the exception of the correlation between right hippocampal volume and AVLT 1–5.

DISCUSSION

We compared three memory tests, two widely used verbal memory tests with different encoding paradigms and one nonverbal memory test, in order to assess which test most appropriately reflected hippocampal atrophy in nondemented older adults and could thus serve as the best functional measure of early AD development [57].

We found moderate correlation of hippocampal volumes with free recall in all three tests (AVLT 1–5, ECR-free, ROCF-R). When we compared the magnitude of correlations in these three tests, we did not find any significant differences.

We did not find the total recall procedure with cueing (ECR–TR) to better correlate with hippocampal atrophy than the learning free recall procedure of all three tests. Moreover, the opposite was evident, as the correlation between the ECR–TR and hippocampus volume was lower than with free recall in all three tests; however, the difference in magnitude of correlation parameters was not significant.

Contrary to our expectations, we did not demonstrate the superiority of the ECR test using the controlled encoding/learning and cued recall paradigm over the free recall verbal tests (AVLT). Further comparing by modality, the visual memory test ROCF with recall equally reflected hippocampal atrophy compared to both verbal memory tests.

To our knowledge, this is the first study comparing two frequently used verbal memory tests in nondemented older adults while also assessing the tests' correlations with hippocampal atrophy. In agreement with other studies, we found that hippocampal volumes in nondemented older adults were correlated with all memory scores except AVLT 1, which represents mainly working memory that does not rely on the hippocampus [58].

Another study using patients with dementia due to AD found free and total recall in the FCSRT test using the same paradigm as the ECR to correlate moderately with hippocampal volume, but no comparison was made with other types of verbal memory tests [59]. Our study found no obvious differences in magnitude of correlations of hippocampal volumes with free recall in two verbal word list memory tests (one with controlled encoding, the other without this procedure). Previous studies suggested that using tests with controlled learning/encoding and cued recall could improve specificity by eliminating the effect of strategy and attention

during word acquisition and recall [3, 28]. This concept has been demonstrated in patients with dementia, wherein AD could be differentiated from frontotemporal dementia [11] and progressive supranuclear palsy, in which strategy and working memory deficit is the most prominent [12]. This concept, however, had not been studied in an MCI stage.

In the ECR procedure of controlled learning/encoding, reinforcement is given through the use of category cues at acquisition to ensure semantic encoding, whereas in AVLT the process of learning/encoding is reinforced by repeated presentation of the same stimuli without correcting the participant. Our results show that these two paradigms are likely to be comparably effective in nondemented older adults.

The other explanation of our results is that working memory remains relatively stable in the earliest stages of AD and thus may not play such an important role in memory encoding failure among nondemented older adults, compared to those in the later stages of AD with deeply pronounced long-term episodic memory impairment [60].

Previously, moderate correlations were found between FCSRT total recall and left hippocampal volume [59] and left and right hippocampal volumes [61] in patients with mild AD. There were no significant correlations between hippocampal volumes and FCSRT free recall in these two studies, which could probably be explained by a floor effect of free recall among participants with dementia and by the low number of subjects in each study (35 and 18 respectively). In Sarazin's study [59], there was a correlation between both free and total recall in the FCSRT and volumes of CA1 subfield, which has been considered to be more specific for memory function [62].

In our study, cueing was very efficient in most of the cognitively healthy participants and in a large portion of those with aMCI. Total recall in the ECR test thus showed a pronounced ceiling effect, which was demonstrated previously in studies of aging using the FCSRT [63]. That is probably why the potential of the FCSRT to reflect hippocampal atrophy in nondemented older adults was found to be inferior to the free recall procedures, contrary to findings from previous dementia studies. In conclusion, it seems likely that detecting hippocampal atrophy in nondemented elderly may be done with free recall procedures, irrespective of the controlled learning/encoding paradigm, because its contribution is not specific enough to enhance the diagnostic value.

Contrary to the studies performed in patients with traumatic brain lesions [64] and epilepsy [65] that found a clear lateralization of verbal and nonverbal memory, our study found that verbal and nonverbal tests correlated moderately with both hippocampal volumes, and the difference between the magnitude of correlation of both sides was not significant. A possible explanation is that in normal aging and aMCI, the asymmetry of the hippocampal atrophy is not clinically significant and that degeneration of both hippocampi is relatively symmetrical in early AD [66]. This was also shown in our study by the high intercorrelation between volumes of the left and right hippocampi and is in agreement with studies in AD dementia [61].

Correlations of hippocampal volumes with the ROCF were similar to those with verbal tests, which is in accordance with similar studies [67]. In particular, the copy, as well as the recall, in ROCF are influenced by executive and visuoconstructive functions. Thus, ROCF task performance reflects the influence of many brain networks, which may hinder the interpretation of neuropsychological test scores [17]. In the present study, these multiple factors probably do not play an important role in nondemented older adults, and the test seems to be an important marker of hippocampal atrophy and episodic memory impairment. If rigorous scoring criteria are used [49], its correlation is similar to the verbal memory tests in this group.

Our study has the following limitations. First we combined two heterogeneous populations with different recruitment strategies (cognitively healthy older adults and a clinically based MCI population), as our aim was to cover the whole range of nondemented subjects from normal to pathological aging.

Second, since hippocampus is implicated very early in AD, and has been shown to be a practical and anatomically well-defined imaging marker, we made an educated choice and focused on this structure and did not assess other, cortical regions with arbitrary boundaries.

Longitudinal study comparing both types of verbal memory tests is necessary to confirm which type of memory test predicts better conversion to dementia due to AD in nondemented older adults.

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Spatial navigation in young versus older adults

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Older age is associated with changes in the brain, including the medial temporal lobe, which may result in mild spatial navigation deficits, especially in allocentric navigation. The aim of the study was to characterize the profile of real-space allocentric (world-centered, hippocampus-dependent) and egocentric (body-centered, parietal lobe dependent) navigation and learning in young vs. older adults, and to assess a possible influence of gender. We recruited healthy participants without cognitive deficits on standard neuropsychological testing, white matter lesions or pronounced hippocampal atrophy: 24 young participants (18–26 years old) and 44 older participants stratified as participants 60–70 years old ($n = 24$) and participants 71–84 years old ($n = 20$). All underwent spatial navigation testing in the real-space human analog of the Morris Water Maze, which has the advantage of assessing separately allocentric and egocentric navigation and learning. Of the eight consecutive trials, trials 2–8 were used to reduce bias by a rebound effect (more dramatic changes in performance between trials 1 and 2 relative to subsequent trials). The participants who were 71–84 years old ($p < 0.001$), but not those 60–70 years old, showed deficits in allocentric navigation compared to the young participants. There were no differences in egocentric navigation. All three groups showed spatial learning effect ($p' \leq 0.01$). There were no gender differences in spatial navigation and learning. Linear regression limited to older participants showed linear ($\beta = 0.30$, $p = 0.045$) and quadratic ($\beta = 0.30$, $p = 0.046$) effect of age on allocentric navigation. There was no effect of age on egocentric navigation. These results demonstrate that navigation deficits in older age may be limited to allocentric navigation, whereas egocentric navigation and learning may remain preserved. This specific pattern of spatial navigation impairment may help differentiate normal aging from prodromal Alzheimer's disease.

Keywords: spatial navigation, aging, allocentric navigation, egocentric navigation, spatial learning, gender, Alzheimer's disease, hippocampus

INTRODUCTION

Aging involves accumulation of adverse biological, psychological, and social changes over time (Bowen and Atwood, 2004) that may or may not signal pathology. Because of the long preclinical period of Alzheimer's disease (AD), recognizing normal and pathological aging has been challenging and the frontier between these two conditions is blurred (Sperling et al., 2011). The relatively high prevalence of AD makes this an important public health issue. Age-related changes interfere unevenly with cognitive functioning (Gazova et al., 2012). While certain cognitive domains do show a decline, other may remain stable (Burke and Barnes, 2006).

Navigation in space is a complex cognitive function that is essential for independence, safety, and quality of life. Differences in spatial navigation between young and older adults were demonstrated by previous research (Barrash, 1994; Wilkniss et al., 1997; Burns, 1999; Newman and Kaszniak, 2000; Moffat and Resnick, 2002; Driscoll et al., 2005; Iaria et al., 2009; Head and Isom, 2010; Jansen et al., 2010). The decline in spatial navigation was shown to be apparent after 60 years of age and further accelerated after

70 years of age (Barrash, 1994). Studies performed in virtual reality showed a specific pattern of spatial navigation deficits in older adults restricted to allocentric navigation (Moffat and Resnick, 2002; Iaria et al., 2009). Allocentric navigation is world-centered processing of spatial information, when individuals have to rely on a "spatial map" using distant landmarks. It was shown to be dependent on medial temporal lobe structures, especially the hippocampus (Grön et al., 2000; Moffat et al., 2006). According to functional neuroimaging studies, reduced hippocampal activation occurs during spatial navigation tasks in older adults compared to their young counterparts (Moffat et al., 2006; Antonova et al., 2009). Therefore, hippocampal dysfunction may be responsible for any allocentric deficits in older adults. Egocentric, or body-centered, spatial navigation where distance and directions from individuals' body position are used for navigation, is instead parietal lobe dependent (Maguire et al., 1998) and was shown not to be affected in older adults (Rodgers et al., 2012).

However, studies in real-space environment testing separately allocentric and egocentric navigation in older adults are lacking.

General spatial navigation learning seems to be unimpaired in older age according to some studies (Barrash, 1994; Newman and Kaszniak, 2000). However, specific comparison of allocentric and egocentric navigation in the real-space setting has not yet been reported. Due to specific age-related changes in spatial navigation, older individuals may avoid new environments and become restricted to well-known familiar places.

Further, there is evidence suggesting that the ability of spatial navigation and spatial learning is severely impaired in patients with AD and contributes to the loss of functional independence. This impairment is present very early in the course of AD, even in pre-dementia stages with the same pattern as in the clinical dementia stage (Mapstone et al., 2003; deIpolyi et al., 2007; Hort et al., 2007; Laczó et al., 2009, 2011, 2012), where atrophy of the hippocampus (Nedelska et al., 2012) and parietal cortex (Weniger et al., 2011), known biomarkers for AD, is the likely culprit. However, differentiation between age-related spatial navigation changes and spatial navigation impairment in the very early, preclinical, stage of AD may be challenging. Furthermore, the situation is complicated by white matter (WM) lesions that are commonly present in the brain of AD patients and also cognitively normal elderly people and may influence spatial navigation performance (Weniger et al., 2011).

Although much work has been done in the field of age-related spatial navigation changes, some issues still remain unsolved. Recent studies showing spatial navigation deficits in older adults were performed in the virtual reality settings that lack vestibular and proprioceptive feedback and therefore may not fully reflect navigation in the real world. On the other hand, original studies investigating spatial navigation in older adults that were performed in the real-space settings did not discriminate between allocentric and egocentric spatial navigation and learning.

Further, findings of spatial navigation changes in the older adults may be biased when using an unselected cohort of older patients defined as normal only on the basis of neuropsychological test results. Because WM lesions and hippocampal atrophy suggestive of preclinical stage of AD may impair spatial navigation, it is desirable to exclude participants with these pathologies to get a more homogeneous cohort of healthy and cognitively normal older adults. Beside age, gender may also influence spatial navigation as indicated by previous research, where men outperformed women in several spatial navigation tasks (Moffat et al., 1998; Astur et al., 1998; Saucier et al., 2002; Chai and Jacobs, 2009; Woolley et al., 2010), especially in allocentric navigation (Saucier et al., 2002), where a possible explanation may lie in a different activation of the left hippocampus in men and women (Grön et al., 2000). However, a recent study performed in a real-world setting reported no gender differences in spatial navigation (Burke et al., 2012). Although research exploring the link between gender and spatial navigation has been extensive in the past 20 years, the majority of studies were performed in virtual reality settings with young participants, and thus studies conducted in the real-space environment separating allocentric and egocentric navigation and focused on elderly are still lacking.

Using the real-space human analog of the Morris Water Maze (hMWM) that allows for separate testing of two basic spatial navigation strategies and using a selected cohort of older adults without pronounced hippocampal atrophy (indicative of incipient AD) or WM lesions that may affect spatial navigation performance, we assessed the differences between young and older adults and possible influence of gender on real-space allocentric and egocentric spatial navigation and learning.

Specifically, the first aim of this study was to characterize the profile of spatial navigation performance and learning in young versus older adults. The older adults were further stratified based on previous spatial navigation research (Barrash, 1994) into participants 60–70 years old and those 71–84 years old, all of whom were free of WM lesions or pronounced hippocampal atrophy to reflect genuine physiological spatial navigation deficit in older age. We hypothesized that in older adults spatial navigation performance would be worse compared to young adults, mainly in allocentric navigation. The second aim was to evaluate the influence of gender on the real-space navigation performance and learning irrespective of age, given that female gender was also reported to interfere with allocentric navigation (Astur et al., 1998; Saucier et al., 2002). The third aim was to assess whether allocentric and egocentric navigation performance would decline in a linear or curvilinear (quadratic) fashion in participants 60 years of age and older.

MATERIALS AND METHODS
PARTICIPANTS
Older adult participants (60–84 years, $n = 62$) without memory complaints, neurological and psychiatric disorders and psychiatric medication were recruited from the seniors attending University of the Third Age at Charles University in Prague or from relatives of patients of the Memory Clinic, Motol University Hospital in Prague. Young adult participants (18–26 years, $n = 24$) were mostly students of medicine or psychology and were selected to be matched to elderly participants by sex and education. All subjects underwent standard medical and neurological examination, complex neuropsychological and spatial navigation testing. Subjects with memory complaints, history of neurological or psychiatric disease, psychiatric medication, abnormal neurological examination including gait or movement difficulties, were not included. Elderly subjects further underwent magnetic resonance imaging (MRI) brain scan.

Participants meeting DSM IV-TR criteria for dementia ($n = 1$), Petersen's criteria for mild cognitive impairment (Petersen, 2004) ($n = 3$) or scoring more than 1.5 SD below the age- and education-adjusted norms on neuropsychological examination ($n = 7$) were excluded. Seven more participants were excluded due to abnormal images of the brain (see Magnetic resonance imaging for details).

Therefore, the final sample included 68 participants: 24 young participants 18–26 years old and 44 older participants were included in the analyses. The older adult participants were further stratified into two subgroups–participants 60–70 years old ($n = 24$) and participants 71–84 years old ($n = 20$). This stratification was adopted from a study by Barrash (1994) in which apparent changes in spatial navigation were observed after age 60 and even greater changes after age 70. Similar stratification was used in some neuropsychological studies (e.g., Whelihan and Lesher, 1985).

Finally, this stratification corresponds to neuropsychological findings suggesting that decline in cognitive domains such as executive function, working memory, and long-term memory becomes empirically observable after 60 years of age (Treitz et al., 2007; Park et al., 2002), and working memory decline appears further accelerated after 70 years of age (Park et al., 2002).

All participants involved in this study had signed written informed consent that was approved by a local ethics committee.

NEUROPSYCHOLOGICAL TESTING

Comprehensive neuropsychological battery that was used to assess all cognitive domains of participants consisted of Auditory Verbal Learning Test, Free and Cued Selective Reminding Test, Logical Memory II, Brief Visuospatial Memory Test – Revised, Rey–Osterrieth Complex Figure Test (Copy and Recall Condition), Clock Drawing Test, Digit Span Task (Forward and Backward), Digit Symbol–Coding Test, Stroop test (Victoria version), Trail Making Test (A and B), Controlled Oral Word Association Test, Semantic Fluency Test, Boston Naming Test. Mini-Mental State Examination was used to evaluate global cognitive functions.

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging was performed using a 1.5T MRI scanner (Gyroscan; Philips Medical Systems, The Netherlands). Scans were inspected by a neuroradiologist to ensure appropriate data quality. Two participants with relevant brain pathology (meningioma) were excluded. Visual scoring was performed to evaluate hippocampal atrophy (Scheltens et al., 1992) and WM lesions (Fazekas et al., 1991) on a MRI brain scan. WM lesions were evaluated using Fazekas scale (Fazekas et al., 1991) on axial sections of T2-weighted and FLAIR sequences. Fazekas scale is a 4-point visual scale (0–3), where "0" signifies absence of WM lesions, "1" signifies sporadic WM lesions, "2" signifies confluence of WM lesions, and "3" signifies severe WM lesions. Subjects with moderate to severe WM lesions – Fazekas score $\geq$ 2 points were excluded ($n = 2$). Hippocampal atrophy was evaluated using Scheltens visual scale (Scheltens et al., 1992) on coronal sections of T1-weighted 3D FFE sequences. Scheltens visual scale is a 5-point medial temporal lobe atrophy (MTA) rating scale (0–4), where

grades are assessed according to width of temporal horn, length of chorioidal fissure, and preservation of height of hippocampus, with "0" signifying no atrophy and "4" signifying the most severe atrophy. The MTA scores were assessed for the right and left side of the brain separately. The images were evaluated by two experienced raters blinded to the clinical diagnosis and results of neuropsychological and spatial navigation tests. A definite score was assigned when consensus was reached. Subjects with hippocampal atrophy – MTA score above the age-adjusted cut-offs (Scheltens et al., 1992) – $\geq$ 2 on any side in subjects $\leq$ 75 years ($n = 1$) and $\geq$ 3 in subjects >75 years ($n = 1$) were excluded. One subject with simultaneous WM lesions and hippocampal atrophy was also excluded.

SPATIAL NAVIGATION TESTING

Spatial navigation tests were performed in the Laboratory of Spatial Cognition in the Department of Neurology, 2nd Faculty of Medicine, Charles University in Prague, Czech Republic, a joint workplace with Institute of Physiology Academy of Sciences of the Czech Republic v.v.i., Prague, Czech Republic. The hMWM is designed to separately test two basic types of navigation– allocentric and egocentric. Allocentric (world-centered) navigation, hippocampus-dependent, that is independent of an individual's position and where salient distal cues (landmarks) are used for navigation (Astur et al., 2002). Egocentric (body-centered) navigation is considered parietal cortex-dependent, and relies on an individual's position and the start location (Maguire et al., 1998). The participants were tested in the real-space version of the hMWM that was located in the navigation setting called the Blue Velvet Arena – a fully enclosed cylindrical arena 2.8 m in diameter surrounded by a 2.9 m high dark blue velvet curtain (**Figure 1A**). The design of the Blue Velvet Arena and the real-space testing procedure were described in detail elsewhere (Laczó et al., 2009; Laczó et al., 2010). The aim was to locate the invisible goal in three different subtasks using the start position or two distal orientation cues, respectively (**Figure 1B**).

The allocentric–egocentric subtask was a training task to make the subject familiar with the test and involved locating the goal using its spatial relationship with both the start position and the two distal orientation cues. The egocentric subtask involved
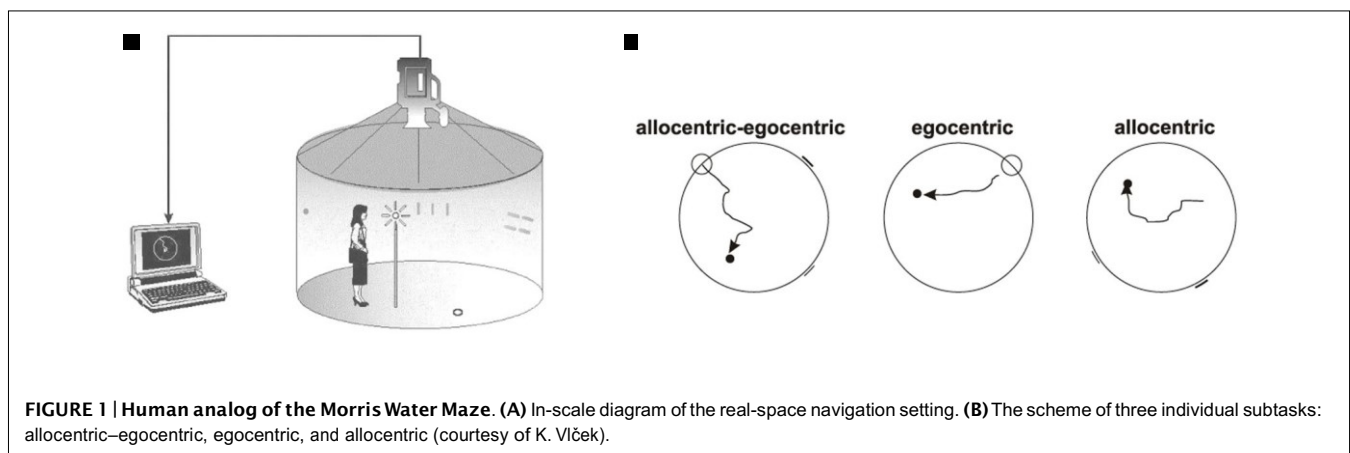

FIGURE 1 | Human analog of the Morris Water Maze. (A) In-scale diagram of the real-space navigation setting. **(B)** The scheme of three individual subtasks: allocentric–egocentric, egocentric, and allocentric (courtesy of K. Vlček).

using only the start position to locate the goal with no distal orientation cues displayed. The allocentric subtask involved using only two distal orientation cues at the perimeter for navigation to the goal as the start position was unrelated to the goal position. Each subtask involved eight trials. The relative positions of the goal, start position, and both orientation cues were identical across all trials. The correct position of the goal as well as its relationship to the start position and to the orientation cues was shown after each trial in each subtask to facilitate learning. The performance was measured as the distance error between the subject's final position and the actual goal location (in centimeters). There was no time limit to find the goal, mainly to reduce bias by differences in cognitive, sensory, and physical functioning.

STATISTICAL ANALYSIS

An analysis of variance (ANOVA) with *post hoc* Tukey's test of honestly significant differences (HSD) evaluated mean differences between the groups in gender, years of education, and neuropsychological measures. A χ^2 test evaluated differences in proportions (gender). The distance between the participant's final position and the correct goal location (distance error) measured in centimeters was used in the analyses as the measure of navigational accuracy (dependent variable), whereas group status was the independent variable. These main analyses included the assessment of between-group and between-gender differences in spatial navigation performance and learning effects in the egocentric and allocentric subtasks separately. We used a repeated measures (RM) ANOVA with two between-subjects factors (group: young versus young–old versus old–old and gender: female versus male) and one within-subjects factor (trial: trials 2–8). Note that trial 1 was not used in the analyses to reduce possible bias by a rebound effect, whereby the performance changes more dramatically between the first and second trial relative to subsequent trials. Again, *post hoc* Tukey's test was used to compare individual groups.

Linear regression was used to evaluate age-related differences in spatial navigation in participants 60–84 years old, where spatial navigation accuracy was the dependent variable and age (linear effect) and age $\times$ age (quadratic effect) were the independent variables.

Statistical significance was set at two-tailed (alpha) of 0.05. All analyses were conducted by using SPSS for Windows.

RESULTS

The groups did not differ in gender and education (p's > 0.05). The descriptive comparisons regarding demographic characteristics and neuropsychological measures are displayed in the **Table 1**.

In the main analyses, we first addressed our first hypothesis that spatial navigation performance would be impaired in older participants. We found a significant main effect for group performance in the allocentric subtask ($F[2,64] = 9.40$; $p < 0.001$), where the participants 71–84 years old consistently exhibited poorer overall spatial navigation accuracy than the participants 60–70 years old ($p < 0.001$; **Figure 2**). There were no differences in the allocentric navigation accuracy between the young participants and those 60–70 years old ($p = 0.182$). Differences between the

participants 60–70 years old and those 71–84 years old were significant ($p = .043$). The main effect for group performance in the egocentric subtask was not significant ($F[2,64] = 1.74$; $p = 0.184$) indicating no differences in egocentric navigation across groups. However, the resultant performance was not due to failure to execute the task as a learning effect, based on a change in performance across consecutive trials in the sample overall, was observed for all groups in the allocentric ($F[6,384] = 2.72$, $p = 0.022$) and the egocentric ($F[6,384] = 3.50$, $p = 0.020$) subtasks. There were no significant group-by-trial interactions, suggesting no differences in learning among the groups in the allocentric ($F[12,384] = 1.50$; $p = 0.140$) and egocentric ($F[12,384] = 0.99$; $p = 0.429$) subtasks.

We next addressed the second hypothesis, that gender would influence spatial navigation performance. We did not find any main effect for gender in the allocentric ($F[2,64] = 0.08$; $p = 0.777$) and egocentric ($F[2,64] = 0.15$; $p = 0.704$) subtasks. Further, there were no significant gender-by-trial interactions, suggesting there were no gender differences in learning in the allocentric ($F[6,384] = 1.18$; $p = 0.319$) or egocentric ($F[6,384] = 0.50$; $p = 0.664$) subtasks. There were also no significant gender-by-group-by-trial interactions, suggesting no gender differences in learning among the groups in the allocentric ($F[6,384] = 0.51$; $p = 0.484$) and egocentric ($F[6,384] = 0.332$; $p = 0.906$) subtasks.

Finally, linear regression analyses were used to address the third hypothesis regarding whether greater error distance on allocentric and egocentric spatial navigation tasks would be associated with age in participants 60 years of age and older, and whether the decline would be linear or quadratic. We found that scores in allocentric navigation performance did get progressively worse for the older participants (standardized regression coefficient $[\beta] = 0.30$, $p = 0.045$). We also found a quadratic effect ($\beta = 0.30$, $p = 0.046$), indicating that worsening of spatial navigation performance was further accelerated in older ages. There was no linear ($\beta = 0.06$, $p = 0.722$) or quadratic ($\beta = 0.06$, $p = 0.713$) effect of age on egocentric navigation.

DISCUSSION

We used a real-space hMWM to investigate the differences in spatial navigation performance between young and older participants and to assess the influence of gender on spatial navigation and learning. We compared young participants (18–26 years old) with two groups of cognitively normal older participants: participants 60–70 years old and those 71–84 years old who did not present with WM lesions or pronounced hippocampal atrophy. Consistent with our hypotheses, we found spatial navigation deficits in allocentric navigation in participants 71–84 years old. There were no significant differences between young and older participants in egocentric navigation. Both allocentric and egocentric spatial learning was preserved in older participants compared to young participants. Further, we found that gender did not influence spatial navigation or learning in the real-space environment. Finally, we found that worsening of allocentric navigation with age was gradual, with further acceleration in older ages.

Our results are consistent with previous studies describing general spatial navigation deficits in older adults compared to

Table 1 | Characteristics of the Sample by Age Group.

Variables	Participants 18–26 years old	Participants 60–70 years old	Participants 71–84 years old
Age, mean (SD), years	22.45 (4.9)	67.74 (5.6)	75.50 (5.8)
Education, mean (SD), years	15.55 (0.6)	14.84 (0.5)	16.19 (0.6)
Women, No (%)	15 (62.5)	17 (70.8)	13 (65.0)
Mini-Mental State Examination, mean (SD)	29.73 (0.5)	29.16 (1.4)	28.31 (1.2)**
Geriatric Depression Scale, mean (SD)	1.36 (1.8)	2.32 (3.5)	2.00 (2.2)
Auditory Verbal Learning Test 1–5, mean (SD)	60.75 (6.5)	50.95 (9.413)	41.56 (7.394)***
Auditory Verbal Learning Test 30, mean (SD)	13.18 (1.6)	10.58 (3.0)*	8.50 (2.6)***†
Free and Cued Selective Reminding Test – free recall, mean (SD)	10.18 (0.8)	9.84 (0.4)	10.19 (0.5)
Free and Cued Selective Reminding Test – total recall, mean (SD)	15.82 (0.4)	15.95 (0.2)	15.94 (0.3)
FAS Verbal Fluency Test, mean (SD)	40.36 (11.0)	47.11 (10.7)	42.94 (11.1)
Trail Making Test A, mean (SD)	30.55 (5.7)	35.56 (15.0)	38.96 (8.8)
Trail Making Test B, mean (SD)	64.55 (19.0)	78.63 (25.2)	105.06 (23.5)***††
Digit Span Forward Task – points, mean (SD)	10.00 (2.8)	10.21 (2.2)	8.31 (1.9)*†
Digit Span Backward Task – points, mean (SD)	8.45 (2.3)	7.26 (1.6)	5.50 (2.3)***†
Rey Osterrieth Complex Figure Test – recall condition, mean (SD)	26.18 (5.2)	17.61 (3.9)***	16.13 (5.1)***
Egocentric Navigation Test, mean (SD), cm	18.88 (1.0)	26.35 (3.6)	27.27 (3.7)
Allocentric Navigation Test, mean (SD), cm	22.86 (2.0)	31.41 (2.7)	41.80 (4.9)***

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ compared to participants 18–26 years old. †$p < 0.05$, ††$p < 0.01$ compared to participants 60–70 years old. SD, standard deviation; cm, centimeters.

their younger counterparts (Barrash, 1994; Wilkniss et al., 1997; Burns, 1999; Newman and Kaszniak, 2000; Moffat and Resnick, 2002; Driscoll et al., 2005; Iaria et al., 2009; Head and Isom, 2010; Jansen et al., 2010) and later studies in virtual reality showing selective allocentric navigation impairment (Moffat and Resnick, 2002; Iaria et al., 2009) accompanied by a compensatory shift from hippocampus-dependent (allocentric) to non-hippocampal (egocentric) strategy (Rodgers et al., 2012).
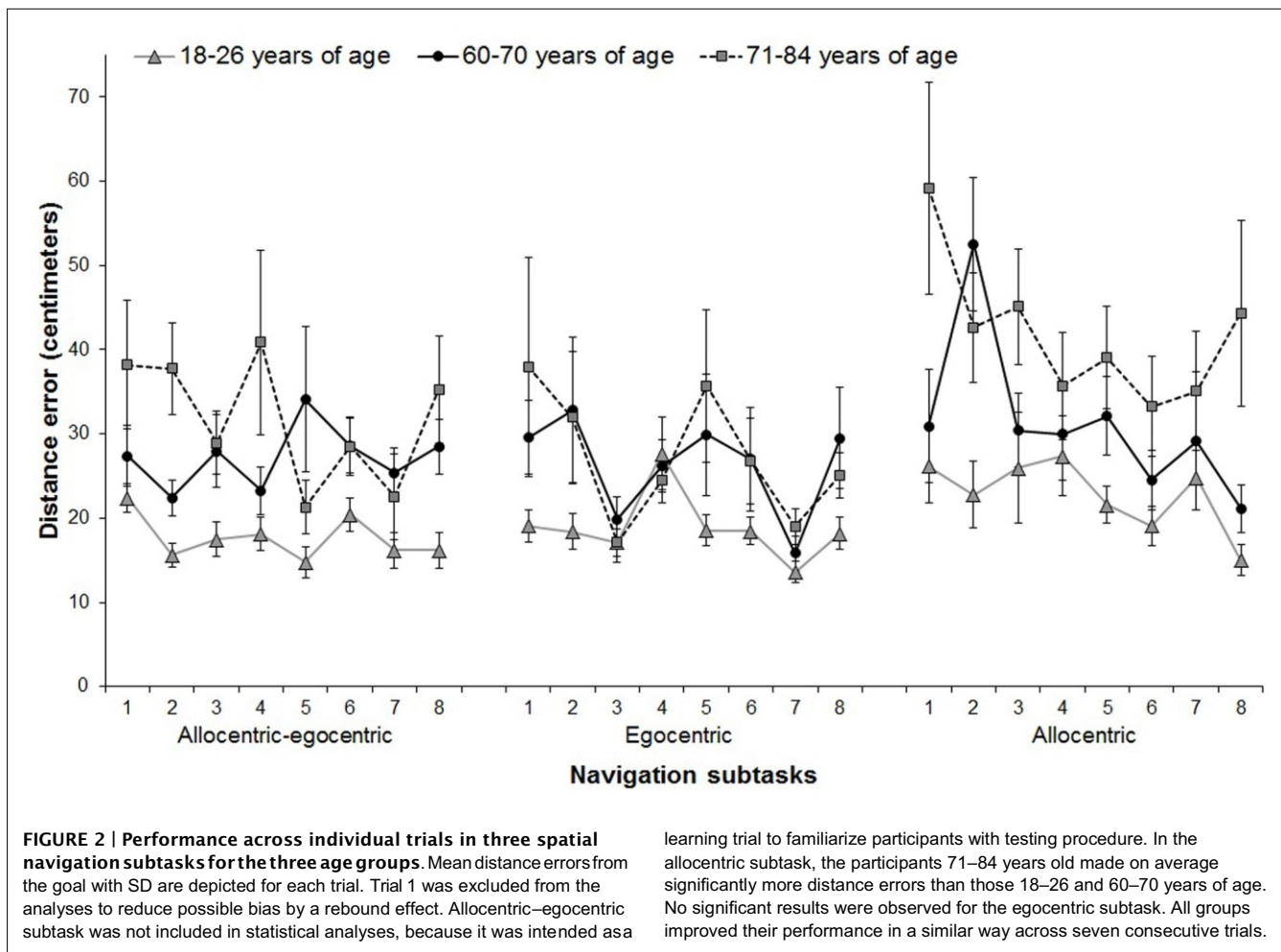
From the clinical point of view, it is important to be able to differentiate between physiological spatial navigation deficit in older age and spatial navigation impairment in prodromal or even preclinical stages of AD. These differences may lie in a different pattern and quantity of spatial navigation impairment (Mapstone et al., 2003; deIpolyi et al., 2007; Hort et al., 2007; Laczó et al., 2009, 2010, 2011, 2012). Specifically, even very early in the course of AD, besides profound allocentric navigation impairment, egocentric navigation is also affected, presumably due to atrophy of parietal cortex, especially precuneus (Weniger et al., 2011). However, differentiation between age- and AD-related spatial navigation changes, especially in the preclinical stage of AD remains challenging.

In our study cognitively normal participants demonstrated spatial learning effect (by presenting improvement across seven consecutive trials in allocentric and egocentric navigation) compared to patients in the early stage of AD, where spatial learning was found to be impaired (Hort et al., 2007; Laczó et al., 2009, 2011, 2012). Thus, spatial learning does not seem to be influenced by age in cognitively normal adults, differentiating them

from patients with early stage AD where pronounced hippocampal atrophy (Nedelska et al., 2012), accumulation of pathological tau (Braak and Braak, 1991) and beta amyloid proteins are present in the brain.

We did not find any effect of gender on allocentric or egocentric spatial navigation performance and learning. Our results are in concordance with current literature showing that male and female participants can learn spatial tasks equally well (Astur et al., 1998; Moffat et al., 1998; Saucier et al., 2002; Chai and Jacobs, 2009; Woolley et al., 2010). However, spatial navigation performance and navigation strategies were found to be gender dependent, with men showing an advantage over women (Astur et al., 1998; Moffat et al., 1998). Specifically, women tended to make more errors relative to men in use of the allocentric navigation (Saucier et al., 2002). A possible cause of gender differences in spatial navigation was may be different levels of activation of the left hippocampus and the right parietal and prefrontal cortex between men and women (Grön et al., 2000). However, all studies reporting superiority of males in spatial navigation were conducted with young participants and decreased levels of testosterone are associated with worse spatial navigation (Driscoll et al., 2005). Thus our findings suggesting no relation between gender and spatial navigation performance may be caused partially by recruitment of older cohort in which hormonal differences are less pronounced.

Furthermore, the previously reported effects of gender on spatial navigation in young participants was observed only in

FIGURE 2 | Performance across individual trials in three spatial navigation subtasks for the three age groups. Mean distance errors from the goal with SD are depicted for each trial. Trial 1 was excluded from the analyses to reduce possible bias by a rebound effect. Allocentric–egocentric subtask was not included in statistical analyses, because it was intended as a learning trial to familiarize participants with testing procedure. In the allocentric subtask, the participants 71–84 years old made on average significantly more distance errors than those 18–26 and 60–70 years of age. No significant results were observed for the egocentric subtask. All groups improved their performance in a similar way across seven consecutive trials.

the virtual reality setting (Astur et al., 1998; Moffat et al., 1998; Saucier et al., 2002; Chai and Jacobs, 2009; Woolley et al., 2010) and a recent study performed in a real-world setting reported no between-gender differences in spatial navigation (Burke et al., 2012), similar to our findings. More studies are thus needed to solve the issue of gender influence on spatial navigation in the real-world setting.

One strength of our study is the use of the real-space hMWM, which allows for separate evaluation of two basic navigation strategies (allocentric and egocentric) and spatial learning effect. The real-space setting mimics very well navigation in the real world due to vestibular and proprioceptive feedback that contributes to successful navigation. Further cognitively normal older participants were precisely selected to be free of WM lesions and pronounced hippocampal atrophy that were found to affect spatial navigation performance (Weniger et al., 2011; Nedelska et al., 2012). In the absence of WM lesions and pronounced hippocampal atrophy in our older adult sample, we speculate that allocentric navigation deficits in participants 71–84 years of age may be a result of reduced hippocampal activation in response to a spatial navigation task, as previously demonstrated by functional neuroimaging studies (Moffat et al., 2006; Antonova et al., 2009).

Some limitations of this study should be mentioned. Due to the lack of availability of participants 27–59 years old we were not able to assess age-related changes in spatial navigation through the entirety of the life course. However, it is possible that we still captured most of the age-related differences in spatial navigation as previous research suggests that decline in cognitive domains such as executive function, working memory, and long-term memory may become apparent only after 60 years of age (Park et al., 2002; Treitz et al., 2007). Still, a future study with participants representing all decades of adult life should be conducted. Additional limitation is the use of a cross-sectional design, which makes it impossible to evaluate longitudinal changes. Therefore, we are not able to fully exclude the possibility of future development of cognitive impairment eventually leading to dementia despite the current absence of hippocampal atrophy or WM lesions. Future research that adopts a longitudinal design may be needed.

CONCLUSION

In summary, our results suggest that, in cognitively healthy older adults, spatial navigation deficit in the real-space environment may be limited to allocentric navigation. Egocentric spatial navigation and learning appear to be preserved in older age. This specific

pattern of spatial navigation impairment may help differentiate normal aging from prodromal AD.

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Neuropsychology

APOE and Spatial Navigation in Amnestic MCI: Results From a Computer-Based Test

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Objective: We investigated the association between APOE ε4 status and spatial navigation in patients with amnestic mild cognitive impairment (aMCI) and assessed the role of hippocampal volume in this association. ***Method:*** Participants were 74 patients with clinically confirmed aMCI (33 APOE ε4 noncarriers, 26 heterozygous, and 15 homozygous ε4 carriers). Body-centered (egocentric) and world-centered (allocentric) spatial navigation in a computerized human analogue of the Morris Water Maze was assessed. Brain MRI with

subsequent automated hippocampal volumetry was included. ***Results:*** Groups were similar in neuropsychological profile. Controlling for age, sex, education, and free memory recall, the APOE ε4 carriers performed more poorly on all spatial navigation subtasks ($ps < .05$). APOE ε4 homozygotes performed worse than heterozygotes ($p = .021$). Right hippocampal volume accounted for the differences in allocentric and delayed subtasks ($ps > .05$), but not in the egocentric subtask ($p < .001$). ***Conclusions:*** Using an easy-to-use, computer-based tool to assess spatial navigation, we found spatial navigation deficits to worsen in a dose-dependent manner as a function of APOE ε4 status. This was at least partially due to differences in right hippocampal volume.

Dementia due to Alzheimer's disease (AD) is preceded by the prodromal stage of mild cognitive impairment (MCI). Diversity of symptomology and the scarcity of easy to use, reliable instruments designed to predict conversion rates from MCI to dementia due to AD have been major obstacles to the development of preventive and therapeutic strategies (Andrieu et al., 2008). Impaired orientation in space is a frequently reported symptom in AD patients and recent studies have confirmed spatial navigation impairment in AD and MCI patients in both real-space (Cherrier, Mendez, & Perryman, 2001; Monacelli, Cushman, Kavcic, & Duffy, 2003; deIpolyi, Rankin, Mucke, Miller, & Gorno-Tempini, 2007) and virtual (Cushman, Stein, & Duffy, 2008) environments, with similar results (Cushman et al., 2008; Kalová, Vlček, Jarolímová, & Bureš, 2005; Hort et al., 2007). For example, cognitively intact APOE ε4 noncarriers were found to outperform APOE ε4 carriers on spatial navigation and on object recognition tasks, yet performed similarly on a number of other cognitive measures (Berteau-Pavy, Park, & Raber, 2007). Although the underlying neurostructural correlates of this association were not assessed, hippocampal dysfunction, a known early finding in AD (Dubois et al., 2007; Jack et al., 2011) is the likely culprit. Further, APOE ε4 has been associated with greater atrophy of the right hippocampus (Farlow et al., 2004; den Heijer et al., 2002), which plays a major role in spatial navigation (Astur, Taylor, Mamelak, Philpott, & Sutherland, 2002).

In our previous study (Laczó et al., 2011), we used a real-space version of the Hidden Goal Task (HGT). The HGT is a human analogue of the Morris Water Maze. We found that APOE ε4 carriers with amnestic MCI (aMCI) had poorer spatial navigation accuracy, mirroring the performance of patients with early-stage AD, yet their neuropsychological profile was similar to APOE ε4 noncarriers with aMCI. However, real-space navigation testing takes time, special equipment, and substantial effort to administer. Therefore, we aimed to compare performance of APOE ε4 carriers and noncarriers with aMCI in a computerized 2-dimensional version of the HGT, which is a more practical, easier-to-administer diagnostic tool to measure spatial navigation in clinical settings.

An advantage of both versions of the HGT is the ability to allow for separate and more refined measurements of two basic navigation strategies (egocentric and allocentric) that rely on different brain structures (Astur et al., 2002; Aguirre & D'Esposito, 1999). Another important point is that the computerized version appears to be a good approximation of the real-space version. Specifically, in our original article (Hort et al., 2007), we reported that the two versions yielded almost the same results when used within one study. Specifically, both versions reliably distinguished different patterns of spatial navigation impairment in patients with aMCI.

Further, in the following studies, we reported strong correlations between the results from the computerized and real-space versions for allocentric (Laczó et al., 2012; Nedelska et al., 2012) and egocentric (Laczó et al., 2012) navigation, respectively. Additionally, Nedelska and colleagues (2012) found almost an identical pattern of results for the association between spatial navigation and hippocampal volume using the real-space and computerized test.

We build on previous research by presenting the initial investigation of the structural correlates of variations in computer-based spatial navigation performance as a function of APOE status. Our goals were to examine: (a) Whether spatial navigation performance in a computerized setting would vary in a dose-dependent manner across APOE ε4 noncarriers (ε4−/−), APOE ε4 heterozygous carriers (ε4+/−), and homozygous carriers (ε4+/+) and, if so, (b) whether these APOE-based differences in spatial navigation would be accounted for by volume reduction of the right hippocampus, a center for spatial navigation and topographical memory (Spiers et al., 2001). We hypothesized that APOE ε4 noncarriers would outperform APOE ε4 carriers, particular the homozygous carriers. In addition, we hypothesized that right hippocampal volume would at least partially account for these differences.

Method

Participants

Seventy-four right-handed participants with clinically confirmed amnestic MCI (aMCI) were recruited at the Memory Disorders Clinic at Motol University Hospital in Prague, Czech Republic, and underwent standard neurological, internal, and laboratory evaluations, clinical scaling, brain MRI, neuropsychological examination, and computer-based spatial navigation testing in the HGT. Participants were referred to the clinic by general practitioners, neurologists, psychiatrists, and geriatricians. Referral to the memory clinic was triggered by memory complaint from the patient or the caregiver. All participants met published clinical criteria for aMCI including memory complaints reported by a patient or caregiver, evidence of memory dysfunction on neuropsychological testing, generally intact activities of daily living (measured by Functional Activities Questionnaire), and absence of dementia (Petersen, 2004). All aMCI patients had Clinical Dementia Rating global score no greater than 0.5, which commonly designates MCI (Morris, 1993). Memory impairment was established when the patient scored more than 1.5 standard deviations below the mean of age- and education-adjusted norms on any memory test. The aMCI patients included patients with aMCI

single domain (aMCIs; $n = 26$), with isolated memory impairment, and patients with aMCI multiple domain (aMCIm; $n = 48$), with additional impairment in any other nonmemory domain. Participants with depression (>5 points on the 15-item Geriatric Depression Scale; Yesavage, 1988; $n = 8$), those meeting the *Diagnostic and Statistical Manual of Mental Disorders IV-TR* criteria for dementia ($n = 1$), and those unable or unwilling to complete the spatial navigation task were excluded ($n = 5$). The 74 aMCI patients were further stratified into three groups based on the APOE genotype—ε4 noncarriers (aMCI ε4−/−; $n = 33$), ε4 heterozygous carriers (aMCI ε4+/−; $n = 26$) and ε4 homozygous carriers (aMCI ε4+/+; $n = 15$). Those in the aMCI ε4−/− group represented ε3/ε3 homozygotes ($n = 27$) and ε2/ε3 ($n = 6$) heterozygotes. Those in the aMCI ε4+/− group represented ε2/ε4 ($n = 1$) and ε3/ε4 ($n = 25$) heterozygotes. The distribution of APOE alleles was similar in patients with aMCIs (ε4−/−, $n = 11$; ε4+/−, $n = 8$; ε4+/+, $n = 7$) and aMCIm (ε4−/−, $n = 22$; ε4+/−, $n = 18$; ε4+/+, $n = 8$).

The study was approved by an institutional ethical committee and the participants have signed written informed consent.

Neuropsychological Tests

The psychometric battery included the Mini-Mental State Examination (MMSE), the Rey Auditory Verbal Learning Test (RAVLT): Trials 1– 6 (sum of the five learning trials and the delayed recall Trial 6) and the 30-min delayed recall trial, Trail Making Tests A and B, Controlled Oral Word Association Test, Forward and Backward Digit Spans and Benton's Visual Retention Test (*BVRT*): A and C administration.

APOE Genotyping

To determine the APOE genotype, DNA was isolated from blood samples and genotyping was performed using a polymerase chain reaction-based assay (Laczó et al., 2011; Hixson & Vernier, 1990).

MRI Acquisition and Automated Volumetry

Brain images were obtained on a 1.5T scanner (Gyroscan, Philips Medical Systems, Best, The Netherlands) using T1-weighted 3-dimensional Fast Field Echo sequence in coronal plane with 170 contiguous partitions, with slice thickness 1.0 mm and no gap, TE/TR = 5/25 ms, flip angle 30°, field of view = 256 mm, matrix 256 X 256 and in-plane resolution 1 mm. Scans were visually inspected by a neuroradiologist to ensure appropriate data quality and to exclude patients with relevant brain pathology such as cortical infarctions, neoplasm, subdural hematoma or hydrocephalus. Volumes of the left and right hippocampus were computed using fully automated FreeSurfer algorithm (Fischl et al., 2002) v4.4.0 (http://surfer.nmr.mgh.harvard.edu) installed on local Mac OS X (Apple) workstation. We have visually checked the outputs of FreeSurfer's segmentation for potential errors in hippocampal ROI segmentation. We also assessed the distribution of hippocampal volumes and did not identify any substantial outliers. Finally, we normalized hippocampal volumes with estimated total intracranial volume (eTIV) using following formula: Normalized hippocampal volume = raw hippocampal volume mm^3/eTIV mm^3 * 1000.

Spatial Navigation Testing With the Hidden Goal Task—the Human Analogue of the Morris Water Maze Test

Spatial navigation testing was performed in the Laboratory of Spatial Cognition, a joint workplace of the Department of Neurology, 2nd Faculty of Medicine, Charles University in Prague, Czech Republic and Institute of Physiology, Academy of Sciences of the Czech Republic v.v.i., Prague, Czech Republic. The HGT was designed to test separately two basic types of navigation. The first type is allocentric (world-centered) navigation, which is hippocampus-dependent and independent of an individual's position and where salient distal cues (landmarks) are used for navigation (Astur et al., 2002). The second type is egocentric (body-centered) navigation, which is parietal cortex-dependent, and relies on an individual's position and the start location (Weniger, Ruhleder, Wolf, Lange, & Irle, 2009). The HGT has two versions—the 2-dimensional computerized version and the real-space version performed in the real-space navigation setting called the Blue Velvet Arena (BVA) described in detail in our previous studies (Hort et al., 2007; Laczó et al., 2011) and also in our last study (Hort et al., 2014), where the apparatus was described under a different name. In this study we used the 2-dimensional computerized version of the HGT, where a map-view of the arena (used in the real-space testing procedure) was projected on a 17-inch computer touch screen (Laczó et al., 2012). The arena in the computerized version was shown as a large white circle with the start position (medium-sized red circle) and two orientation cues (red and green lines) on its perimeter. A small red circle inside the arena represented the goal (Figure 1a).

The aim was to locate the invisible goal in four different subtasks using the start position or two distal orientation cues, respectively (Figure 1b). On the computer touch screen, the participants were requested to move a pointer directly from their start position at the arena's perimeter to the goal position inside the arena, which was briefly visible (approximately 10 –15 seconds) just prior to the trial, and to finish on the presumed goal position. The allocentric-egocentric subtask involved locating the goal using its spatial relationship with both the start position and the two distal orientation cues. This was considered a training subtask designed to familiarize participants with the testing procedure. The egocentric subtask involved using only the start position to locate the goal with no distal orientation cues displayed. The allocentric subtask involved using only two distal orientation cues at the perimeter for navigation to the goal as the start position was unrelated to the goal position. Finally, the delayed subtask was a repeat of the allocentric subtask administered 30 minutes after the initial allocentric subtask was completed (see Table 1).

Each subtask involved eight trials performed in direct sequence. The delayed subtask involved only two trials. The positions of the goal were consistent across trials relative to (a) the positions of the start location and both orientation cues in the allocentric-egocentric subtask, (b) positions of the start location in the egocentric subtask, and (c) positions of both orientation cues in the allocentric and delayed subtask. Each consecutive trial involved a 45-degree clockwise rotation around the virtual arena. For example, in the allocentric-egocentric task (Figure 1a), the two cues positioned at about 7:30 o'clock and 10:30 o'clock, respectively, and the start location positioned at about 4:30 o'clock all rotated
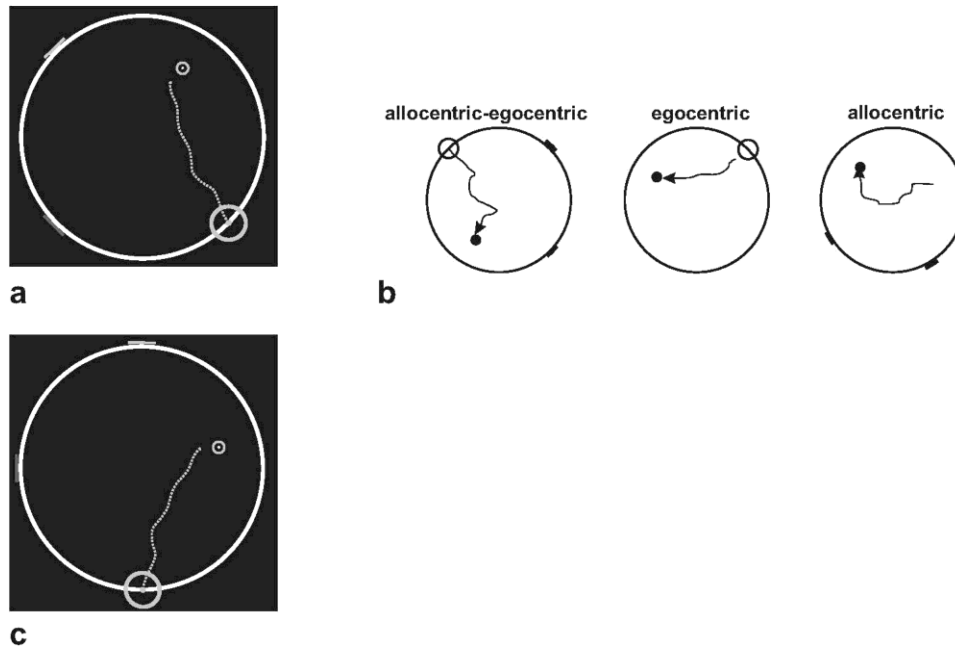
Figure 1. The Hidden Goal Task. (a) Computerized version—a computer screen view with the largest circle representing the arena, the small circle in the arena representing the goal position, the midsize circle on the edge of the arena representing the start position and the two lines on the edge of the arena representing the cues. The line representing tracking by a subject between the start and the goal positions is also depicted. (b) The scheme of the first three individual subtasks: allocentric-egocentric, egocentric, and allocentric. The delayed subtask (not shown here) is the same as the allocentric subtask. (c) A computer screen view of the arena rotated 45 degrees clockwise from the previous trial shown in Figure 1a.

clockwise by 45 degrees between two trials. This rotation is expressed Figure 1c with the cues moved to 9 o'clock and 12 o'clock and the start position moved to 6 o'clock. The goal position also moved correspondingly. The correct position of the goal was visible for 10–15 seconds after each trial in each subtask as feedback to enable continual learning of the goal position. It

was, however, not shown anytime during the delayed subtask. Thus, all tasks except for the delayed subtask allowed for learning across trials.

Performance was measured automatically by the computer as the distance error between the estimated position on the screen and the actual goal location (in screen pixels, the diameter of the map-view of the arena was 280 pixels). There was no time limit to find the goal, mainly to reduce bias by differences in cognitive, sensory, and physical functioning. Examiners were blinded to the results of the other examinations and they supervised the correct performance of the task without interference beyond standard instructions.

Table 1
Description of Spatial Navigation Subtasks

Key characteristics	Spatial navigation subtasks			
	Allocentric-egocentric	Egocentric	Allocentric	Delayed allocentric
Number of trials	8	8	8	2
Start related to the goal[a]	Yes	Yes	No	No
Orientation cues[b]	Yes	No	Yes	Yes
Learning[c]	Yes	Yes	Yes	No

Note. Allocentric-egocentric navigation subtask = both the positions of the start and orientation cues are used for navigation to the goal; egocentric navigation subtask = only the start position is used for navigation; allocentric navigation subtask = only the position of the orientation cues is used for navigation; delayed allocentric subtask = similarly to allocentric subtask only orientation cues are used for navigation.
[a] The goal is a consistent distance away from the starting position, the goal is always in the same distance and direction from the starting position. [b] Orientation cues are visible at the sides of the circle to facilitate orientation, they always appear at the same angle and distance from the goal position. [c] Each trial was followed by feedback to facilitate learning.

Statistical Analyses

An analysis of variance (ANOVA) with post hoc Tukey's test evaluated mean differences between groups in age, years of education, the MMSE, neuropsychological tests, and left and right hippocampal volumes. The x^2 test evaluated differences in proportions (gender).

To properly account for the repeated measures structure of the data, we used linear mixed effects regression (Littell, Milliken, Stroup, Wolfinger, & Schabenberger, 2006; Singer & Willett, 2003). This method of analysis yields the same output as repeated measures ANOVA but it is also more versatile, properly handling repeated measures and allowing specification of best-fitting covariance structure accounting for random effects.

The distance between the participant's choice of the goal position and the correct goal position (distance error) measured in pixels on each of the eight spatial navigation trials (allocen- tric or egocentric), or the two delayed allocentric trials was entered as the outcome in linear mixed effects models. APOE status was the independent variable. The models yielded main effect for group (aMCI ε4−/− vs. aMCI ε4+/− vs. aMCI ε4+/+) and trial (Trials 1– 8 for the egocentric or allocentric subtasks, or Trials 1–2 for the delayed subtask). All distance error values were converted into z-scores ($M = 0$, standard deviation = 1), which allowed us to present the main results in standard deviation units.

Age, gender, and education, which may affect spatial naviga- tion, were controlled to provide more conservative estimates of the hypothesized associations. Because spatial navigation can be in- fluenced by memory impairment, we subsequently also controlled for free verbal memory recall, measured with the sum of two indices from the RAVLT (sum of the five learning trials and the Trial 6) and for free nonverbal memory recall, measured with the index from the BVRT administration A (total number of errors). To assess the influence of right hippocampal volume, we esti- mated the same linear mixed effects models while also control- ling for the right hippocampal volumes. The same models were estimated separately for women and men. The intercept and a person identifier were specified as random effects. Based on model fit, the final models used the compound symmetric covariance structure.

We examined the proportion of the association accounted for by right hippocampal volume with the following formula: % ac- counted for = (adjusted mean difference$_{basic\ model}$ − adjusted mean difference$_{model\ with\ hippocampal\ volume}$ / adjusted mean difference$_{basic\ model}$) * 100.

Statistical significance was set at 2-tailed (alpha) of .05. Effect sizes were reported using Cramér's V for the x^2 test (Cramér, 1999) and partial eta^2 for ANOVA and linear mixed effects re- gression analyses (Tabachnick & Fidell, 2007). Partial eta^2 of 0.2 corresponds to Cohen's d of 1.0. With our sample size, Cramér's V of about 0.47 corresponds to Cohen's d of 1.0. All analyses were conducted by using IBM SPSS for Windows version 20.0.

Results

The groups did not differ in age, education, MMSE and GDS scores or any neuropsychological test, but there were more men in the aMCI ε4−/− group than in the ε4+/− and ε4+/+ groups (33% vs. 73% and 73%, $x^2 = 11.74$; $p = .003$; Cramér's V = 0.40). The aMCI groups did not differ in left hippocampal volume ($F(2, 71) = 2.48$; $p = .096$; partial eta$^2 = 0.10$), but differed in right hippocampal volume ($F(2, 71) = 3.99$; $p = .026$; partial eta$^2 = 0.19$). Specifically, the aMCI ε4+/+ group had smaller right hippocampal volume com- pared to the aMCI ε4−/− group (see Table 2).

APOE ε4 Genotype and Spatial Navigation in aMCI

Controlling for age, gender and education, we found significant main effects for group in all spatial navigation subtasks—in the egocentric ($F(2, 68) = 19.44$; $p < .001$; partial eta$^2 = 0.40$), allocentric ($F(2, 68) = 6.74$; $p = .001$; partial eta$^2 = 0.36$) and

Table 2

Demographic, Neuropsychological and MRI Volumetric Characteristics of Study Participants

Variables	aMCI ε4−/− (n = 33)	aMCI ε4+/− (n = 26)	aMCI ε4+/+ (n = 15)	Effect sizes
Women, n (%)	11 (33)	19 (73)	11 (73)	0.40**
Age in years, mean (SD)	74.4 (10.8)	74.9 (7.3)	71.7 (7.3)	0.02
Education in years, mean (SD)	13.4 (2.4)	13.6 (2.9)	12.7 (3.0)	0.02
MMSE raw score, mean (SD)	27.0 (2.1)	26.7 (2.6)	25.5 (2.4)	0.07
GDS raw score, mean (SD)	4.2 (3.2)	3.1 (1.6)	2.5 (1.7)	0.08
RAVLT 1–6 raw score, mean (SD)	35.4 (9.3)	35.7 (11.6)	32.0 (9.1)	0.02
RAVLT 30 raw score, mean (SD)	4.0 (2.9)	2.9 (3.3)	2.1 (2.3)	0.06
TMT A score (in seconds), mean (SD)	24.7 (11.2)	27.0 (12.8)	32.3 (12.7)	0.05
TMT B score (in seconds), mean (SD)	178.1 (85.1)	182.0 (83.4)	167.5 (95.0)	0.01
COWAT raw score, mean (SD)	33.2 (11.6)	34.8 (11.8)	38.4 (9.6)	0.03
Digit span total numbers recalled, mean (SD)	6.7 (3.2)	6.4 (1.3)	6.0 (1.2)	0.01
Reversed digit span total numbers recalled, mean (SD)	4.2 (1.3)	4.5 (1.1)	3.9 (1.0)	0.05
BVRT A errors' raw score, mean (SD)	7.8 (4.9)	10.7 (3.2)	8.7 (4.7)	0.05
BVRT C errors' raw score, mean (SD)	1.1 (1.6)	1.1 (1.0)	0.7 (1.2)	0.01
Egocentric navigation subtask (pixels), mean (SD)	39.4 (29.9)	78.5 (43.6)§	96.7 (30.1)§	0.40***
Allocentric navigation subtask (pixels), mean (SD)	73.2 (40.5)	97.7 (32.3)†	113.7 (26.5)‡	0.36**
Delayed navigation subtask (pixels), mean (SD)	65.7 (46.4)	101.5 (52.3)†	110.9 (50.9)‡	0.29*
Left hippocampal volume normalized with eTIV, mean (SD)	2276 (685)	2302 (361)	1767 (235)	0.10
Right hippocampal volume normalized with eTIV, mean (SD)	2371 (509)	2223 (436)	1776 (259)†	0.19*

Note. MCI = mild cognitive impairment; aMCI ε4−/− = amnestic MCI ε4 negative; aMCI ε4+/− = amnestic MCI ε4 heterozygotes; aMCI ε4+/+ = amnestic MCI ε4 homozygotes; MMSE = Mini-Mental State Examination; GDS = Geriatric Depression Scale; RAVLT = Rey Auditory Verbal Learning Test; RAVLT 1–6 = trials 1 to 6 total; RAVLT 30 = word recall after 30 minutes; TMT A and B = Trail Making Tests A and B; COWAT = Controlled Oral Word Association Test; BVRT A and C = Benton's Visual Retention Test A and C administration; eTIV = estimated total intracranial volume. Neuropsychological characteristics of the groups. Values are mean (SD) except for gender. Effect sizes indicating the differences among all groups were calculated as Cramér's V for chi-square (gender) and partial eta-squared for ANOVA comparisons (all other variables). For p indicating the level of significance for the size effects are: * $p < .05$. ** $p < .01$. *** $p < .001$. For p indicating the level of significance compared with aMCI ε4−/− group are: † $p < .05$. ‡ $p < .01$. § $p < .001$.
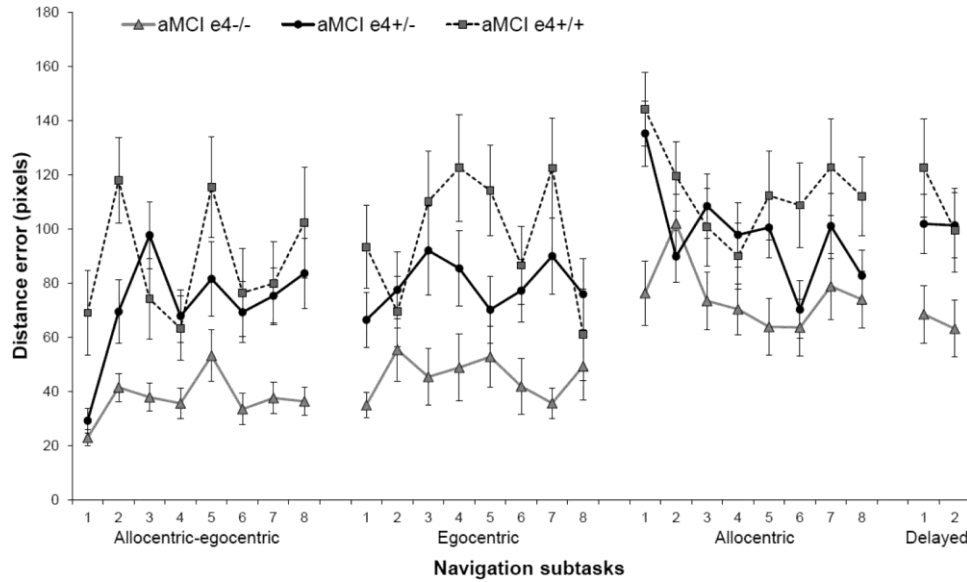
Figure 2. Spatial navigation performance across trials. Mean distance errors from the goal and *SD* are depicted.

delayed ($F(2, 68) = 4.85$; $p = .012$; partial eta^2 = 0.29). Specifically, the aMCI ε4+/+ group exhibited poorer overall navigation accuracy than the aMCI ε4−/− group in the egocentric, allocentric and delayed subtasks (see Figure 2). In addition, the aMCI ε4+/− group exhibited poorer overall navigation accuracy than the aMCI ε4−/− group in the egocentric, allocentric and delayed subtasks. The aMCI ε4+/+ group also exhibited poorer overall navigation accuracy than the aMCI ε4+/− group in the egocentric subtask, whereas differences in the allocentric and delayed subtasks were not significant (see Table 3).

The main effects for trial in the egocentric and allocentric subtasks were not significant, indicating no significant learning effect across consecutive trials in the sample overall ($F(1, 476) = 0.06$; $p = .812$; partial eta^2 = 0.02 and $F(1, 476) = 0.46$; $p = .422$; partial eta^2 = 0.02, for egocentric and allocentric subtasks, respectively). Finally, there were no significant group-by-trial interactions, suggesting no differences in learning between the groups in the egocentric ($F(2, 476) = 0.43$; $p = .650$; partial eta^2 = 0.03) and allocentric ($F(2, 476) = 0.26$; $p = .769$; partial eta^2 = 0.06) subtasks. In the subsequent analyses, we used the same models

while also adding the RAVLT score (sum of Trials 1 to 6) and BVRT score from administration A (total number of errors), respectively, as a covariate to control for free verbal and nonverbal memory recall. This adjustment did not change the results in any spatial navigation subtask.

The linear mixed effects models analyses conducted for women and men separately yielded results similar to those with the overall sample. Specifically, significant main effects for group in both men and women were found in egocentric ($F(2, 36) = 11.76$; $p < .001$; partial eta^2 = 0.37 and $F(2, 28) = 13.92$; $p < .001$; partial eta^2 = 0.48, respectively) and delayed ($F(2, 36) = 4.86$; $p = .016$; partial eta^2 = 0.25 and $F(2, 28) = 6.57$; $p = .007$; partial eta^2 = 0.33, respectively) subtasks. Only in the allocentric subtask the differences between groups were driven mainly by men ($F(2, 28) = 8.16$; $p < .001$; partial eta^2 = 0.35) and not by women ($F(2, 36) = 1.88$; $p = .155$; partial eta^2 = 0.20).

The main effects for trials and for group-by-trial interactions in the linear mixed effects models analyses conducted for women and men separately remained nonsignificant for women (ps > .50) and men (ps > .60), which mimics the results with the overall sample.

Table 3

Comparisons of Adjusted Mean Error Distances From the Goal Across Groups

(I) Group code	(J) Group code	Egocentric subtask		Allocentric subtask		Delayed subtask	
		Mean difference (I–J)	Effect size	Mean difference (I–J)	Effect size	Mean difference (I–J)	Effect size
aMCI ε4−/−	aMCI ε4+/−	−0.71	0.76***	−0.41	0.50*	−0.63	0.71*
	aMCI ε4+/+	−1.24	1.55***	−0.74	0.91**	−0.85	0.98*
aMCI ε4+/−	aMCI ε4+/+	−0.54	0.64*	−0.33	0.59	−0.22	0.26

Note. aMCI = amnestic Mild Cognitive Impairment; ε4−/− = APOE ε4 noncarriers; ε4+/− = APOE ε4 heterozygous carriers; ε4+/+ = APOE ε4 homozygous carriers.
Linear mixed models adjusted for age, gender and education. Mean differences are measured in standard deviation units. Effect sizes were calculated as Cohen's *d* using standardized mean differences and pooled standard deviation. For *p* indicating the level of significance for the size effects are: * $p < .05$. ** $p < .01$. *** $p < .001$.

The Role of Hippocampal Volume in the Association Between APOE Ε4 Genotype and Spatial Navigation in aMCI

In models adjusted for age, gender, and education, the right hippocampal volume accounted for the association between ε4 status and spatial navigation on the allocentric ($F(2, 67) = 1.78$; $p = .170$; partial eta^2 = 0.13) and delayed ($F(2, 67) = 1.22$; $p = .306$; partial eta^2 = 0.07) subtasks, but not on the egocentric subtask ($F(2, 67) = 15.69$; $p < .001$; partial eta^2 = 0.34). Specifically, the aMCI ε4+/+ group still exhibited poorer overall navigation accuracy than the aMCI ε4−/− group in the egocentric, but not in the allocentric and delayed subtasks (see Figure 2). Further, also the aMCI ε4+/− group still exhibited poorer overall navigation accuracy than the aMCI ε4−/− group in the egocentric, but not in the allocentric and delayed subtasks. Differences between aMCI ε4+/+ and aMCI ε4+/− groups were reduced to the trend in the egocentric subtask, and remained nonsignificant in the allocentric and delayed subtasks (see Table 4).

Using the formula to calculate the proportion of the group difference in adjusted mean value accounted for right hippocampal volume (see values in Tables 3 vs. 4), we found that right hippocampal volume accounted for 50% of the association between being a ε4+/+ carrier (as opposed to ε4−/− carrier) and spatial navigation on the allocentric subtask, 69% of the association on the delayed subtask, and 4% of the association on the egocentric subtask. Further, right hippocampal volume accounted for 41% of the association between being a ε4+/− carrier and spatial navigation on the allocentric subtask, 33% of the association on the delayed subtask, and 1% of the association on the egocentric subtask.

The main effects for trial in the egocentric ($F(1, 469) = 0.38$; $p = .540$; partial eta^2 = 0.02) and allocentric ($F(1, 469) = 0.14$; $p = .708$; partial eta^2 = 0.02) subtasks, as well as the group-by-trial interactions in the egocentric ($F(2, 469) = 0.06$; $p = .938$; partial eta^2 = 0.05) and allocentric ($F(2, 469) = 0.50$; $p = .607$; partial eta^2 = 0.05) subtasks, remained nonsignificant.

Discussion

We examined the influence of APOE ε4 genotype on spatial navigation using a computerized version of the human variant of the Morris Water Maze in patients with amnestic MCI (aMCI). Consistent with our hypothesis, patients with aMCI who carried at least one APOE ε4 allele performed significantly worse on spatial navigation than their counterparts without this allele irrespective of age, gender, education, and degree of verbal and nonverbal memory impairment. Further, spatial navigation in this aMCI sample was sensitive to the influence of APOE ε4 in a dose-dependent manner, particularly in the egocentric (body-centered) type of navigation, whereby APOE ε4 homozygotes were more impaired than APOE ε4 heterozygotes and APOE ε4 noncarriers.

The results for allocentric (world-centered) navigation as a function of APOE ε4 categorization were not significant. One possibility is that these results were affected by the floor effect. Specifically, the APOE ε4 heterozygotes scored rather poorly on this task, recording large distance errors from the goal. Although the APOE ε4 homozygotes scored even more poorly than the APOE ε4 heterozygotes, they sometimes reached the threshold for the magnitude of the error allowed by the program, presumably preventing the difference between these two groups from reaching the threshold for statistical significance.

Overall, these findings map on our previous findings showing poor navigation by APOE ε4 heterozygous carriers with aMCI in the real space (Laczó et al., 2010, 2011) and extend them to an easy-to-use computerized variant that has much greater clinical utility. Furthermore, they show that spatial navigation may be sensitive to the number of APOE ε4 alleles. Therefore, these findings strengthen the notion that APOE genotype is an important determinant of spatial navigation performance in nondemented older adults, possibly in a similar way as it affects spatial attention and spatial working memory (Parasuraman, Greenwood, & Sunderland, 2002; Greenwood, Lambert, Sunderland, & Parasuraman, 2005).

There are notable differences between the studies by Parasuraman et al. (2002) and Greenwood et al. (2005) and our study. Both Parasuraman and Greenwood focused on spatial working memory where the task revolves around the ability to recognize whether a dot on a screen is located on the same (match) or a different (nonmatch) location from an attached location cue dot over a delay of 2 seconds, with reaction time (RT) being the main outcome. The task we used here revolves around the assessment of spatial navigation per se and its two basic components— egocentric (using a start position to find a hidden goal) and allocentric (using a configuration of landmarks in relation to the position of the hidden goal). Also, by using the human analogue of the Morris Water Maze, the subjects are asked to imagine navigating themselves

Table 4

Comparisons of Adjusted Mean Error Distances From the Goal Across Groups Controlled for Right Hippocampal Volume

(I) Group code	(J) Group code	Egocentric subtask		Allocentric subtask		Delayed subtask	
		Mean difference (I–J)	Effect size	Mean difference (I–J)	Effect size	Mean difference (I–J)	Effect size
aMCIε4−/−	aMCI ε4+/−	−0.70	0.75***	−0.24	0.29	−0.42	0.47
	aMCI ε4+/+	−1.19	1.48***	−0.37	0.46	−0.26	0.30
aMCIε4+/−	aMCI ε4+/+	−0.49	0.57	−0.14	0.25	−0.16	0.19

Note. aMCI = amnestic Mild Cognitive Impairment; ε4−/− = APOE ε4 noncarriers; ε4+/− = APOE ε4 heterozygous carriers; ε4+/+ = APOE ε4 homozygous carriers.
Linear mixed models adjusted for age, gender, education, and right hippocampal volume. Mean differences are measured in standard deviation units. Effect sizes were calculated as Cohen's *d* using standardized mean differences and pooled standard deviation. For *p* indicating the level of significance for the size effects are: * $p < .05$. ** $p < .01$. *** $p < .001$.

within a defined space (or an arena). Finally, we were interested in spatial navigation accuracy rather than time to completion to minimize the influence of spatial attention and psychomotor speed. Therefore, this study provides a new view of the utility of spatial tasks in the examination of the association between APOE ε4 and cognitive function.

Our findings are in line with research indicating that spatial navigation may be an important indicator of cognitive impairment. Notably, AD patients have approximately 3–4 times higher prevalence of APOE ε4 genotype compared to the general population, and APOE ε4 is a significant risk factor for conversion from MCI to AD (Xu et al., 2013). Future research should investigate spatial navigation impairment as an important indicator of cognitive impairment among individuals with APOE ε4.

Right hippocampal volume was decreased in APOE ε4 homozygous carriers, which is consistent with studies reporting a greater atrophy of the hippocampus among nondemented APOE ε4 carriers (Farlow et al., 2004; den Heijer et al., 2002). Because the hippocampus is known to play a major role in spatial navigation (Astur et al., 2002; Aguirre & D'Esposito, 1999), we hypothesized that its volume loss could be at least partially responsible for spatial navigation impairment in the APOE ε4 carriers. In fact, decreased right hippocampal volume accounted for a substantial portion of the association between APOE ε4 status and poorer allocentric and allocentric delayed navigation accuracy. Specifically, 50% and 69% of the covariate-adjusted effect showing poor navigation on the allocentric and allocentric delayed subtasks among APOE ε4 homozygous carriers was accounted for by differences in right hippocampal volume. In parallel, 41% and 33% of the covariate-adjusted effect for the APOE ε4 heterozygous carriers on the same subtasks was accounted for by right hippocampal volume. This finding is consistent with our hypothesis and with previous evidence for the role of the right hippocampus for allocentric navigation (Feigenbaum & Morris, 2004; Nedelska et al., 2012). Allocentric navigation with the computerized test directly examines functional, but reflects also structural changes of the (primarily right) hippocampus (Gazova et al., 2012).

Combined with the relative simplicity of administration compared to the real-space version, we propose that the computerized test based on the MWM paradigm may be a useful tool for evaluation of spatial navigation deficits and may be a more appropriate cognitive task than traditional tests for examination of the role of APOE in human cognition. However, with respect to study limitations, it should be noted that the real-space and computerized 2-dimensional versions are inherently not fully interchangeable, as the computerized spatial navigation tasks lack vestibular and proprioceptive feedback that is normally available in the real-world navigation tasks and that contributes to successful navigation (Hort et al., 2007). Second, we used a cross-sectional design, which does not allow for tracking aMCI patients for risk of dementia diagnosis. Third, the diagnostic criteria used to define aMCI vary across studies to at least some extent, which reduces generalizability of our findings. Finally, we were unable to evaluate the association between egocentric navigation and parietal cortex, which is associated with poorer egocentric navigation performance in aMCI patients (Weniger et al., 2011). Future studies where these data are available may provide a more refined look at the mechanisms underlying egocentric navigation. Along

the same lines, the relationship between APOE status and egocentric navigation in patients with MCI is still underexplored and should be a focus of future studies.

Conclusion

Our findings indicate that APOE genotype influences spatial navigation in aMCI patients in a computerized version of the HGT, similar to our previous findings with the real-space version of this test, in a dose-dependent manner. Spatial navigation impairment in APOE ε4 carriers with aMCI was independent of demographic variables and neuropsychological profile, but was partially accounted for by differences in right hippocampal volume. Future studies are needed to correlate performance on this test with real life spatial navigation outcomes such as driving impairments, getting lost and misplacing items. If such correlation was demonstrated, this test could serve as a clinical screening tool for evaluation of spatial navigation deficits in people at risk of AD.

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Differences in Subjective Cognitive Complaints Between Non-Demented Older Adults from a Memory Clinic and the Community

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Abstract.
Background: Subjective cognitive complaints (SCCs) may represent an early cognitive marker of Alzheimer's disease (AD). There is a need to identify specific SCCs associated with an increased likelihood of underlying AD.
Objective: Using the Questionnaire of Cognitive Complaints (QPC), we evaluated the pattern of SCCs in a clinical sample of non-demented older adults in comparison to cognitively healthy community-dwelling volunteers (HV).
Methods: In total, 142 non-demented older adults from the Czech Brain Aging Study referred to two memory clinics for their SCCs were classified as having subjective cognitive decline (SCD, $n = 85$) or amnestic mild cognitive impairment (aMCI, $n = 57$) based on a neuropsychological evaluation. Furthermore, 82 age-, education-, and gender-matched HV were recruited. All subjects completed the QPC assessing the presence of specific SCCs in the last six months.
Results: Both SCD and aMCI groups reported almost two times more SCCs than HV, but they did not differ from each other in the total QPC score. *Impression of memory change* and *Impression of worse memory in comparison to peers* were significantly more prevalent in both SCD and aMCI groups in comparison to HV; however, only the latter one was associated with lower cognitive performance.

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Conclusion: The pattern of QPC-SCCs reported by SCD individuals was more similar to aMCI individuals than to HV. A complaint about memory change seems unspecific to pathological aging whereas a complaint about worse memory in comparison to peers might be one of the promising items from QPC questionnaire potentially reflecting subtle cognitive changes.

INTRODUCTION

Subjective cognitive complaints (SCCs) in older adults have been widely studied in patients in prodromal Alzheimer´s disease (AD). Concerns regarding a change in cognition obtained from the patient or from an informant became a part of core clinical criteria for mild cognitive impairment (MCI) [1, 2]. In line with the efforts to identify patients with AD as early as possible, even in the preclinical stage of the disease, SCCs in individuals without measurable cognitive deficit have become one of the primary research interests.

In longitudinal studies, SCCs have been found to predict accelerated cognitive decline [3, 4] and increased risk of subsequent dementia [5] (for review, see [6]). Further, in cross-sectional studies, SCCs in cognitively normal older adults have been shown to be associated with the presence of neuroimaging and metabolic biomarker abnormalities consistent with AD pathology [7–10]. Along with these findings, SCCs in the absence of cognitive impairment have been considered the earliest clinical manifestation of AD, preceding the MCI stage. As a result, the concept of subjective cognitive decline (SCD) was introduced in a recent conceptual framework for research of preclinical AD by the SCD-Initiative Workgroup (SCD-I) [11].

However, community-based studies showed a high prevalence of SCCs in older adults [4, 12–15] and only a portion of those complaining individuals will develop AD dementia. This may account for some researchers viewing the significance of the SCD concept in preclinical AD as controversial [16]. It may also imply that the current SCD definition is broad and unspecific constituting a heterogeneous population, although it is important to note that most of the studies probably have not specifically reflected the SCD-I criteria yet. Thus, sensitivity and specificity of the true SCD population remains to be further explored.

Different ways how to recruit SCD subjects were shown to bring different associations with AD biomarkers and affective symptomatology. In a recent cross-sectional study by Perrotin and colleagues studying SCD individuals from a memory clinic and community-recruited cognitively normal older adults, amyloid-β deposition was observed in both groups with similarly high level of SCCs; however, SCD individuals from a memory clinic reported more depressive symptoms and had more pronounced hippocampal atrophy [8]. Medical help-seeking behavior may be stimulated by worry associated with SCCs. The so-called cognitive worry was shown to be associated with the greatest risk for conversion to MCI or dementia compared to SCCs without associated worry and no SCCs in cognitively normal older adults at baseline [17, 18].

Classification of SCD is largely based on a subjective report in the context of normal cognitive functioning; however, a standardized assessment of SCCs is still absent [19]. A recent systematic review compared cognitive self-report measures used by 19 international studies [20]. The authors brought preliminary recommendations for instrument selection and expressed a particular need for further research to identify relevant specific items associated with an increased likelihood of early AD.

The Questionnaire of Cognitive Complaints (QPC; from French Le Questionnaire de Plainte Cognitive) was originally developed to help physicians in primary care identify individuals with cognitive impairment due to AD [21, 22]. It is a brief and easy to administer tool which is listed on the French Greco database as one of the screening questionnaires and widely used in clinical praxis in France. It comprises three types of questions that have been recently proposed to differentiate between normal and pathological aging [20, 23]: 1) decline in memory compared to the previous level; 2) memory functioning compared to individuals of the same age group; and 3) other specific cognitive complaints beyond memory. Prevalence and distribution of QPC-SCCs in a sample of cognitively healthy community-dwelling volunteers aged 60 or older was shown in our recent study [15]. The total QPC score

reflected more closely depressive symptomatology than cognitive performance. Lower memory performance was specifically linked to *Impression of worse memory in comparison to peers* and *Spatial orientation difficulties*. The most prevalent complaints (*Word finding difficulties, Difficulties with recalling past events*, and *Impression of memory change*) were not related either to depressive symptomatology or cognition in that sample. As we discussed, these findings support the notion that some complaints are specific for pathological aging, while others seem to be part of normal aging. It also supports recommendations of the SCD-I Workgroup [20] who stimulated researchers to focus rather on individual items than the total score which usually does not allow to weight endorsement of individual complaints. However, findings from a community-dwelling sample are not easily transferred into the clinical setting, unless confirmed in the clinical setting. Studies on the medical-help seeking SCD population are lacking.

Building on our previous research [15] and following the recommendations of the SCD-I, we aimed to analyze the pattern of SCCs using the Czech version of the QPC in a sample of 1) individuals seeking help at a memory clinic for their cognitive complaints without cognitive deficit based on a comprehensive neuropsychological assessment (SCD), 2) individuals seeking help at a memory clinic for their cognitive complaints, who fulfilled criteria for amnestic MCI (aMCI), and to compare it to 3) cognitively healthy community-dwelling volunteers without SCCs for which they would seek for medical help (HV). Second, we aimed to examine the total QPC score and specific QPC-SCCs in relation to depressive symptomatology and cognitive performance.

We hypothesized a continuum in the frequency of QPC-SCCs ranging from HV to SCD and aMCI individuals and searched for QPC-SCCs specific for each of those groups: we expected *Memory change* and *Impression of worse memory in comparison to peers* to be particularly linked to cognitive performance.

METHODS

Participants

The clinical study sample (SCD and aMCI) consisted of 142 subjects aged 60 and older participating in the Czech Brain Aging Study (CBAS) and was recruited at two centers: 1) Memory Clinic, Department of Neurology, 2nd Faculty of Medicine, Charles University and Motol University Hospital; 2) Memory Center by International Clinical Research Center, St. Anne's University Hospital Brno. Patients were referred to these memory clinics by general practitioners, neurologists, psychiatrists, and geriatricians for SCCs reported by the patients and/or by their informants. The nature and intensity of complaints were verified by a semi-structured interview with an experienced clinician. All patients underwent clinical and laboratory evaluations, brain MRI, and comprehensive neuropsychological examination. A cognitive neurologist together with a clinical neuropsychologist classified the patients as aMCI or SCD based on results of neuropsychological examination during the standard diagnostic meeting.

aMCI patients ($n = 57$) met published clinical criteria for aMCI, including memory complaints reported by a patient or a caregiver, evidence of memory dysfunction on neuropsychological testing, generally intact activities of daily living, and absence of dementia [1]. Memory impairment was established when the patients scored ≥5 SD on at least one memory test below the mean of age- and education-adjusted norms [24]. Both single domain (memory impairment only) and multiple domain (memory impairment plus impairment of at least one other cognitive domain) MCI patients were included in the aMCI group. To diminish the risk of self-perception bias caused by anosognosia only individuals with Mini-Mental State Exam (MMSE) ≥24 were included [25].

SCD patients ($n = 85$) met published criteria for SCD [11] including a self-experienced persistent decline in cognitive capacity within the last 5 years in comparison with a previously normal status and unrelated to an acute event and normal age-, gender-, and education-adjusted performance on standardized cognitive tests. Cognitively unimpaired individuals were not included into the SCD group if their main motivation for the consultation at the memory clinic was positive family history of dementia, but not subjective cognitive complaints.

Individuals with a history of neurological disease potentially leading to cognitive impairment and disturbances in mobility (history of stroke, traumatic brain injury, neuroinfection, Parkinson's disease, etc.), psychiatric diseases including major depressive disorder, or abnormal neurological examination were not included. Furthermore, individuals with significant vascular changes on MRI (Fazekas scale >2), or with major depressive symptomatology on 15-item Geriatric Depression Scale (GDS-15 > 10) were not

included in either of the medical-help seeking groups (aMCI, $n = 15$; SCD, $n = 22$).

HV group comprised 82 community-dwelling volunteers without SCCs for which they would ever seek or intended to seek for medical help which was ascertained in a structured interview by an experienced clinician. They were age, education, and gender matched to SCD individuals and were chosen from the participants of a normative study of healthy aging (NANOK) [26]. General exclusion criteria for NANOK were history of neurological disease potentially causing brain impairment and disturbances in mobility (history of stroke, traumatic brain injury, neuroinfection, Parkinson's disease, etc.), an acute phase of serious mental disorder (e.g., major depressive disorder), current radiotherapeutic or chemotherapeutic treatment, alcohol or substance abuse, and impaired sensory perception not possible to be corrected by sensory aids. Additionally, only those participants were included in whom the absence of cognitive impairment was ascertained. Probable cognitive impairment was established when the subjects scored 1.5 SD below the mean of age- and education-adjusted norms on at least one of the following tests: MMSE, Rey Auditory Verbal Learning Test sum of trials 1–5 (RAVLT 1–5), RAVLT delayed recall after 30 minutes, and Trail Making Test A and B. The cut-off score of 1.5 SD was set so that it resembles that used for the aMCI group. All HV participants completed a comprehensive neuropsychological battery in a single assessment.

All participants in this study signed written informed consent that was approved by a local ethics committee (Motol University Hospital, St. Anne´s University Hospital Brno, and National Institute of Mental Health). The procedures were in accordance with the Helsinki Declaration of 1975 and later revision in 2000.

Measures

Evaluation of SCCs: QPC

All participants were administered the Czech version of the QPC, which was based on an original French 10-item yes/no questionnaire assessing the presence of cognitive difficulties in the last six months [22, 27]. The Czech version was made based on a translation from French to Czech by an experienced translator, followed by a back-translation from Czech to French by a translator blinded to the original French version. The discrepancies were consulted and based on the consensus between the two trans-

lations the final version was developed to preserve the original meaning as accurately as possible. The QPC was translated into English in cooperation with a native English speaker and the final English version was approved by the author of the questionnaire, already for the purpose of our previous study [15]. The first two items of the QPC inquire about general memory abilities, while the remaining eight items inquire about more particular cognitive complaints with a focus on memory. The items also cover difficulties with spatial orientation, language, instrumental activities, or personality change. The exact wording of all items is presented in Fig. 1. For each item, we indicate a key name for ease in reporting findings.

Neuropsychological measures

All participants underwent a comprehensive neuropsychological battery that included measures of global cognitive function (MMSE [28]), attention (Trail Making Test A (TMT A) [29]; Prague Stroop Test – Dots, (PST-D) [30]), memory (RAVLT [31]), executive function (Trail Making Test B (TMT B) [29]; Prague Stroop Test–Color (PST-C) [30]), and language (phonemic verbal fluency – letters N, K, P; semantic verbal fluency–animals [32]). All participants were also administered a self-report GDS-15 [33] to evaluate the severity of depressive symptomatology. We adjusted the GDS-15 by subtracting the cognitive item from the total score [item number 10: "Do you feel you have more problems with memory than most?"; (adjusted GDS-15)], so that the analyses exploring the association between SCCs, depressive symptomatology and cognition are not biased by a shared variance between the QPC and GDS-15 measures.

Statistical analyses

To evaluate between-groups differences in age and years of education, we performed a parametric one-way analysis of variance (ANOVA), with Tukey *post hoc* test, as the assumption of normality was not violated (values of skewness and curtosis ranged from −1 to +1). The Pearson Chi-Square test evaluated differences in gender proportions. To evaluate between-groups differences in background neuropsychological characteristics and severity of depressive symptomatology, we performed a non-parametric Kruskal-Wallis H test followed by pairwise Mann-Whitney *U* tests with a Bonferroni correction for multiple comparisons, as the assumption of normality was violated (values of skewness and curtosis

1.	Have you experienced any memory change during the last six months?	Impression of memory change
2.	Do you feel like your memory is worse in comparison to your peers?	Impression of worse memory in comparison to peers
3.	Do you feel like you are getting worse in remembering recent events and/or you hear your family say more often "I have already told you"?	Difficulties with recalling past events
4.	Have you forgotten about an important appointment?	Forgetting about appointments
5.	Do you lose things more often than in the past, or do you take longer to find them than usual?	Losing things
6.	Have you experienced any difficulties with spatial orientation or failed to recognize a place you were previously familiar with?	Spatial orientation difficulties
7.	Have you completely forgotten about an event and were unable to recall it even when your close relatives/friends were talking about it or when you saw photos from the event?	Forgetting about past experiences
8.	Do you have difficulties finding words (this does not apply to names) and have you felt like the word was on the tip of your tongue but you could not recall it, forcing you to say "this" or "that" more frequently?	Word finding difficulties
9.	Have you limited your activities (or asked for help) because of concerns that you may make a mistake? *(such as filling tax declaration, paying bills etc.)*	Limitation in daily activities
10.	Have you noticed any changes in your personality? *(such as turning inward, reducing contacts with others or being less interested in things)*	Personality change

Fig. 1. QPC, Questionnaire of cognitive complaints. Exact phrasing and key names. Questions are related to last six months.

ranged outside -1 to $+1$). To evaluate between-groups differences in the total QPC score, we performed a parametric one-way ANOVA, with Tukey *post hoc* test, as the assumption of normality was not violated (values of skewness and curtosis ranged from -1 to $+1$). Between-groups differences in frequency of reported specific QPC-SCCs were compared using the Pearson Chi-Square test, to control for multiple comparisons the Bonferroni correction was applied. To evaluate the relation between SCCs, depressive symptomatology and cognition the non-parametric Spearman rank-order correlation was performed, followed by the non-parametric partial rank correlation. Demographic characteristics (age, education, and gender) were not associated with the total QPC score or the specific QPC-SCCs, so only adjusted GDS-15 was used as a covariate. Additional Multiple Linear Regression was conducted to determine whether both depressive symptomatology (adjusted GDS-15) and the diagnostic group predicted the total QPC score (outcome variable).

The significance level (alpha) was set at ($p \leq 0.05$) throughout the analyses; the adjusted level of

significance according to Bonferroni correction for multiple comparisons is reported for each analysis in the Results section. To report effect sizes, partial eta² was calculated for ANOVA and Kruskal-Wallis H test, Cohen's d for Tukey *post hoc* test, effect size r score for Mann-Whitney U test, and Cramer's V for Pearson Chi-Square test. Cognitive scores were transformed into z-scores. Cognitive composite z-score of memory, attention, executive function, and language were calculated as the averages of z-score of administered neuropsychological tests for each cognitive domain. The scores for TMT A, TMT B, and PST were reversed before being transformed into z-scores.

All statistical analyses were run using IBM SPSS Statistics 20 for Windows.

RESULTS

Demographic and neuropsychological characteristics of groups

Demographic and neuropsychological characteristics of groups are summarized in Table 1. There

Table 1
Demographic and neuropsychological characteristics of groups

	aMCI (*n* = 57)			SCD (*n* = 85)		HV (*n* = 82)
	Mean (SD)	d[a]	d[b]	Mean (SD)	d[a]	Mean (SD)
Age	73.6 (5.9)***,†††	0.71	0.69	69.2 (6.7)	0.02	69.4 (5.9)
Education	13.7 (3.2)	0.22	0.33	14.7 (2.7)	0.11	14.4 (2.9)
Female, n (%)	29 (50.9)			58 (68.2)		54 (65.9)
QPC	3.7 (2.2)***	0.98	0.16	4.0 (2.3) ***	1.13	1.8 (1.6)
	Mean (SD)	r[a]	r[b]	Mean (SD)	r[a]	Mean (SD)
GDS-15	3.1 (2.1)‡	0.14	0.00	3.2 (2.4)‡	0.14	1.6 (1.7)
Adjusted GDS-15	2.5 (1.9)‡	0.08	0.00	2.6 (2.3)‡	0.08	1.4 (1.6)
MMSE	27.1 (1.5)‡,‡‡	0.25	0.33	28.9 (1.1)	0.01	28.6 (1.2)
RAVLT 1–5	32.4 (9.2)‡,‡‡	0.47	0.56	51.9 (7.8)‡	0.04	48.7 (8.2)
RAVLT 30	3.3 (3.3)‡,‡‡	0.54	0.56	10.6 (2.8)	0.01	10.1 (2.4)
TMT A	54.2 (22.5)‡,‡‡	0.13	0.10	40.6 (12.6)	0.00	38.7 (9.5)
TMT B	177.1 (109.3)‡,‡‡	0.37	0.28	91.5 (30.5)	0.03	81.2 (25.9)
PST-D	16.2 (3.5)‡,‡‡	0.10	0.27	13.8 (2.9)	0.02	14.1 (2.4)
PST-C	42.8 (18.0)‡,‡‡	0.23	0.19	30.3 (9.7)	0.00	28.9 (8.4)
S-VF	17.9 (6.3)‡,‡‡	0.16	0.20	23.6 (5.9)	0.00	22.7 (5.5)
P-VF	35.3 (12.3)‡,‡‡	0.20	0.18	46.3 (11.2)	0.00	47.5 (12.9)

*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$; in comparison to HV; †††$p \leq 0.001$, in comparison to SCD (one-way Analysis of Variance with Tukey *post hoc* test); ‡$p < 0.016$, statistically significant difference after Bonferroni correction for multiple comparison in comparison to HV; ‡‡$p < 0.016$, statistically significant difference after Bonferroni correction for multiple comparison in comparison to SCD (Mann–Whitney U test); d[a]: Cohen's d effect size in comparison to HV; d[b]: Cohen's d effect size in comparison to SCD; r[a]: Effect size r score in comparison to HV; r[b]: Effect size r score in comparison to SCD; GDS-15, Geriatric Depression Scale, 15-item version; adjusted GDS-15, the cognitive item subtracted; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test, sum of trials 1–5; RAVLT, Rey Auditory Verbal Learning Test, delayed recall after 30 minutes; TMT, Trail Making Test; PST-D, Prague Stroop Test – dots; PST-C, Prague Stroop Test – color; S-VF, semantic verbal fluency (animals); *P*-VF, phonemic verbal fluency (letters N, K, P).

were no group differences in years of education ($F(2, 220) = 1.94$, $p = 0.14$, partial eta² = 0.08). As expected, there was a main effect of group on age ($F(2, 221) = 9.92$, $p < 0.001$, partial eta² = 0.08). Tukey *post hoc* tests indicated that SCD and HV were younger than aMCI (both *ps* < 0.001) but they were not significantly different from each other ($p = 0.98$). There were no group differences in gender proportions ($\chi^2(2) = 4.876$, $p = 0.087$). Further, a Kruskal-Wallis H test showed that there was a statistically significant between-group difference in adjusted GDS-15 score ($\chi^2(2) = 15.04$, $p = 0.001$; partial eta² = 0.07). *Post hoc* pairwise Mann-Whitney U tests showed that aMCI and SCD reported more depressive symptoms on adjusted GDS-15 than HV ($U = 1204.5$, $p = 0.002$, and $U = 1828.5$, $p = 0.001$, respectively), with significant differences even after Bonferroni correction for multiple comparisons (both ps < 0.016), but aMCI and SCD were not significantly different from each other ($U = 1402.0$, $p = 0.86$). As for neuropsychological background, aMCI performed significantly worse than SCD and HV in all neuropsychological measures ($ps \leq 0.016$), SCD and HV did not differ from each other, except for RAVLT 1–5 in which HV surprisingly performed worse ($U = 2599.0$, $p = 0.012$).

Pattern of SCCs according to groups

There was a significant main effect of group on the total QPC score ($F(2, 221) = 27.82$, $p < 0.001$, partial eta² = 0.20). Both clinical groups, aMCI and SCD, reported two times more QPC-SCCs relative to HV (both *ps* ≤ 0.003), but they did not differ from each other ($p = 0.441$); see Table 1.

Specific QPC-SCCs endorsement according to groups is presented in Fig. 2. Both clinical groups (aMCI and SCD) reported with significantly higher frequency than HV seven out of ten specific QPC-SCCs (*Impression of memory change, Impression of worse memory in comparison to peers, Difficulties with recalling past event, Spatial orientation difficulties, Forgetting about past experiences, Limitation in daily activities, and Personality change),* but they did not differ from each other, except for *Difficulties with recalling past events,* which was the only QPC-SCC reported with significantly higher frequency by aMCI than by SCD. There were two QPC-SCCs (*Word finding difficulties*, and *Forgetting about appointments)* reported with significantly higher frequency by SCD in comparison to both aMCI and HV but with similar level of frequency by aMCI and HV. *Losing things* was reported with higher frequency by SCD and
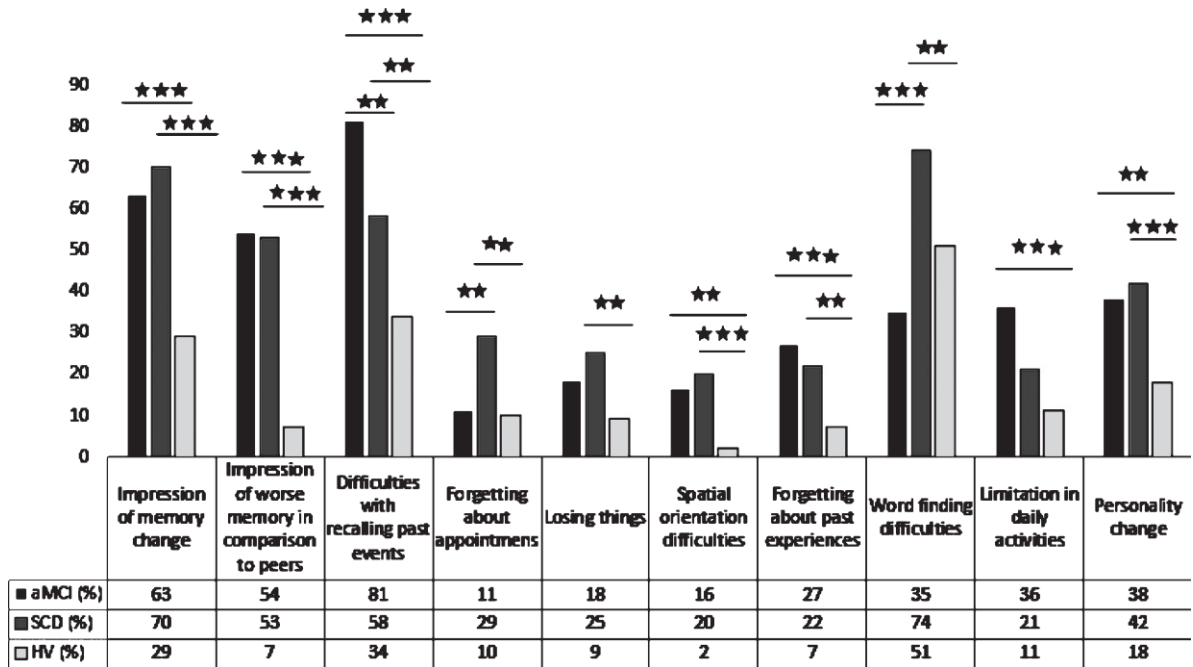
Fig. 2. Between-group differences in frequency of self-reported specific QPC-SCCs using the Pearson Chi-Square Test; $**p \leq 0.016$, $***p \leq 0.001$, statistically significant difference after Bonferroni correction for multiple comparison (alpha level adjusted for comparison of 3 groups: 0.05/3 = 0.016).

	Impression of memory change	Impression of worse memory in comparison to peers	Difficulties with recalling past events	Forgetting about appointmens	Losing things	Spatial orientation difficulties	Forgetting about past experiences	Word finding difficulties	Limitation in daily activities	Personality change
■ aMCI (%)	63	54	81	11	18	16	27	35	36	38
■ SCD (%)	70	53	58	29	25	20	22	74	21	42
□ HV (%)	29	7	34	10	9	2	7	51	11	18

aMCI in comparison to HV, however, the difference between aMCI and HV did not reach statistical significance. The between-groups differences should be treated cautiously in the complaints with low prevalence (*Forgetting about appointments, Losing things, Spatial orientation difficulties* and *Forgetting about past experiences*).

Total QPC score in relation to depressive symptomatology and cognition

The total QPC score was not associated with any of the demographic characteristics (age, education, and gender; all $ps \geq 0.106$), so that these variables were not used as covariates in further analyses. Higher total QPC score was moderately associated with higher depressive symptomatology (adjusted GDS-15; $\rho = 0.43$, $p < 0.001$); this association remained significant after Bonferroni correction for multiple comparisons (alpha level adjusted for comparison of 9 variables, $p \leq 0.005$). According to the additional Multiple Linear Regression, the combination of the adjusted GDS-15 score and the diagnostic group significantly predicted the total QPC score, F(2,188) = 21.13, $p < 0.001$. 18% of the total QPC score was explained by the model. However, only the adjusted GDS-15 score significantly contributed

to the model (adjusted GDS-15: $\beta = 0.43$, $p < 0.001$; diagnostic group: $\beta = 0.01$, $p = 0.88$). Exploring the Collinearity Statistics, the variables did not account for an overlapping variance.

The total QPC score was not associated with MMSE or cognitive domains, which remained the same even after adjusting for depressive symptomatology (all $ps \geq 0.067$). Table 2 displays the associations between the total QPC score, demographic characteristics, depressive symptomatology, global cognitive functioning, and cognitive domains.

Specific QPC-SCCs and their relation to depressive symptomatology and cognition

Globally, all the specific QPC-SCCs were weakly to moderately associated with higher depressive symptomatology, the associations remained significant after Bonferroni correction for multiple comparisons (all $ps \leq 0.007$), except for *Forgetting about appointments* ($p = 0.047$) and *Limitation in daily activities* ($p = 0.032$).

The associations between specific QPC-SCCs and depressive symptomatology and cognitive performance are displayed in Table 3a and 3b. Five out of ten QPC-SCCs were weakly associated with at least one cognitive domain or global cognition measure

Table 2
The association between the total QPC score and demographic
variables, depressive symptomatology, and cognition

	rho[1]	B Correction	rho[2]
Age	0.10	ns	–
Education	0.0023	ns	–
Gender	0.086	ns	–
adjusted GDS-15	0.43***	sig.	–
MMSE	−0.12	ns	−0.12
Memory[†]	−0.045	ns	−0.022
Attention[†]	−0.11	ns	−0.069
Executive function[†]	−0.11	ns	−0.13
Language[†]	−0.10	ns	−0.098

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; [1]non-parametric Spearman rank-order correlation; [2]non-parametric partial rank correlation, controlled for adjusted GDS-15; [†]values expressed in composite scores, calculated as the averages of z-score of administered neuropsychological tests for each cognitive domain; adjusted GDS-15, Geriatric Depression Scale, 15-item version, the cognitive item subtracted; MMSE, Mini-Mental State Examination; B Correction, Bonferroni Correction for multiple comparisons (alpha level adjusted for comparison of 9 variables: $0.05/9 = 0.005$); numbers are rounded to two significant figures.

(*Impression of worse memory in comparison to peers, Difficulties with recalling past events, Forgetting about past experiences, Limitation in daily activities, and Personality change*), three of them remained significant even after the stringent Bonferroni correction for multiple comparison (*Impression of worse memory in comparison to peers, Difficulties with recalling past events, and Limitation in daily activities*).

After adjusting for depressive symptomatology, all the five QPC-SCCs remained associated with worse cognitive performance (*Limitation in daily activities, Difficulties with recalling past events, Impression of worse memory in comparison to peers, Forgetting about past experiences,* and *Personality change*), however, only recognition of *Limitation in daily activities* was significantly associated with worse executive performance ($\rho = -0.24$, $p < 0.001$, and worse MMSE score, $\rho = -0.24$, $p < 0.001$), after applying the stringent Bonferroni correction for multiple comparisons.

DISCUSSION

The QPC is a relatively brief and easy to administer tool for SCCs assessment which is listed in the French Greco database as one of the screening questionnaires recommended to be used in clinical praxis for SCCs assessment. Despite the recommendation studies on the population of SCD individuals have been lacking. Using the QPC, SCD and aMCI individuals did

not differ from each other in the number of SCCs or depressive symptoms, but both medical-help seeking groups reported two times more SCCs and three times more depressive symptoms in comparison to demographically matched and cognitively similar healthy community-dwelling volunteers. In terms of the total QPC-score, current results do not support the hypothesized continuum ranging from healthy volunteers to SCD and aMCI individuals in our sample. Instead, SCD individuals seem to be closer to aMCI individuals, which is congruent with findings of a previous study [34].

The total QPC score was significantly related to higher depressive symptomatology but not to cognitive performance, the diagnostic group itself was not predictive of the QPC score. This result is in agreement with previous findings [8, 35] and can be explained by the same level of higher depressive symptomatology and cognitive complaints in both clinical groups compared to HV, but differences in cognitive performance in standard neuropsychological battery between aMCI and SCD group where aMCI individuals scored by definition lower than SCD.

The causality of relationship between SCCs and depressive symptomatology in non-demented older adults has not been clarified yet. Some authors argue that particularly in SCD individuals depressive symptomatology is the primary cause of SCCs [16]. Second, depressive symptoms may be triggered by awareness of cognitive decline in comparison to previous level not captured using traditional neuropsychological tests originally designed for identification of cognitive deficit at the MCI stage; or third, depressive symptoms may also be an independent early manifestation of underlying AD neuropathological process in both aMCI and SCD individuals [23, 36]. The last-mentioned hypothesis was supported by findings of two recent longitudinal studies with a 14- and 28-year follow-up [38, 39]. The largest risk of dementia was associated with depressive symptoms occurring approximately 5 years before dementia onset, while depression occurring earlier throughout the lifespan did not significantly increase the risk of dementia. In a recent cross-sectional study [8], subclinical depression together with hippocampal atrophy was indeed more prevalent in medical-help seeking SCD individuals compared to community-recruited older adults with similarly high levels of SCCs. The authors suggested that cognitively normal older adults with a higher level of depressive symptomatology in whom SCCs are

Table 3a
The associations between specific QPC-SCCs, depressive symptomatology, and cognition, without controlling for depressive symptomatology

	Adjusted GDS-15	MMSE	Memory[†]	Attention[†]	Executive[†]	Language[†]
Specific QPC-SCCs			**rho (p)**			
1 Impression of memory change	**0.29 (<0.001)***	–0.088 (0.19)	0.036 (0.60)	–0.021 (0.76)	–0.013 (0.84)	0.004 (0.95)
2 Impression of worse memory in comparison to peers	**0.25 (<0.001)***	–0.12 (0.060)	–0.11 (0.10)	–0.13 (0.054)	**–0.19 (0.0045)***	**–0.15 (0.020)**
3 Difficulties with recalling past events	**0.28 (<0.001)***	**–0.15 (0.021)**	**–0.18 (0.0058)***	**–0.16 (0.014)**	**–0.19 (0.0031)***	**–0.14 (0.030)**
4 Forgetting about appointments	**0.14 (0.047)**	0.023 (0.73)	0.20 (0.0026)*	0.14 (0.029)	0.15 (0.027)	0.087 (0.19)
5 Losing things	**0.19 (0.0065)***	–0.097 (0.16)	0.024 (0.72)	0.017 (0.80)	0.024 (0.72)	–0.038 (0.57)
6 Spatial orientation difficulties	**0.19 (0.0066)***	–0.063 (0.35)	–0.048 (0.47)	–0.012 (0.85)	–0.53 (0.43)	–0.069(0.30)
7 Forgetting about past experiences	**0.20 (0.0053)***	–0.055 (0.42)	–0.095 (0.16)	–0.087 (0.19)	**–0.17 (0.010)**	–0.031(0.64)
8 Word finding difficulties	**0.20 (0.0054)***	0.25 (<0.001)*	0.22 (<0.001)*	–0.020 (0.76)	**–0.20 (0.0028)***	0.14 (0.033)
9 Limitation in daily activities	**0.15 (0.032)**	**–0.24 (<0.001)***	**–0.20 (0.0027)***	**–0.16 (0.016)**	**–0.25 (<0.001)***	**–0.15 (0.017)**
10 Personality change	**0.43 (<0.001)***	**–0.15 (0.026)**	–0.052 (0.44)	–0.13 (0.041)	–0.12 (0.067)	**–0.16 (0.013)**

Non-parametric Spearman rank-order correlation; [†]values expressed in composite scores, calculated as the averages of z-score of administered neuropsychological tests for each cognitive domain; * $p \leq 0.008$, statistically significant correlation coefficient after Bonferroni correction for multiple comparisons [alpha level adjusted for comparison of 6 variables (adjusted GDS-15, MMSE and cognitive domains), 0.05/6 = 0.008]; adjusted GDS-15, Geriatric Depression Scale, 15-item version, the cognitive item subtracted; MMSE, Mini-Mental State Examination; numbers are rounded to two significant figures.

Table 3b
The associations between specific QPC-SCCs and cognition, controlling for depressive symptomatology

	MMSE	Memory[†]	Attention[†]	Executive[†]	Language[†]
Specific QPC-SCCs		**rho (p)**			
1 Impression of memory change	–0.087 (0.23)	0.070 (0.33)	0.030 (0.68)	0.0073 (0.92)	0.026 (0.72)
2 Impression of worse memory in comparison to peers	–0.12 (0.081)	–0.088 (0.23)	–0.093 (0.20)	**–0.18 (0.013)**	**–0.14 (0.047)**
3 Difficulties with recalling past events	**–0.15 (0.031)**	**–0.16 (0.026)**	–0.12 (0.088)	**–0.18 (0.011)**	–0.13 (0.072)
4 Forgetting about appointments	0.026 (0.72)	0.22 (0.0023)*	0.17 (0.017)	0.16 (0.027)	0.099 (0.17)
5 Losing things	–0.095 (0.19)	0.046 (0.53)	0.051 (0.48)	0.038 (0.60)	–0.025 (0.73)
6 Spatial orientation difficulties	–0.061 (0.40)	–0.028 (0.70)	0.021 (0.77)	–0.040 (0.58)	–0.056 (0.44)
7 Forgetting about past experiences	–0.052 (0.47)	–0.076 (0.30)	–0.055 (0.45)	**–0.16 (0.025)**	–0.017 (0.81)
8 Word finding difficulties	0.26 (<0.001)*	0.25 (<0.001)*	0.013 (0.85)	0.21 (0.0025)*	0.16 (0.027)
9 Limitation in daily activities	**–0.24 (<0.001)***	**–0.18 (0.010)**	–0.14 (0.056)	**–0.24 (<0.001)***	**–0.15 (0.039)**
10 Personality change	**–0.15 (0.030)**	–0.0076 (0.91)	–0.074 (0.31)	–0.10 (0.15)	**–0.15 (0.039)**

Non-parametric partial rank correlation, controlling for adjusted GDS-15; [†]values expressed in composite scores, calculated as the averages of z-score of administered neuropsychological tests for each cognitive domain; * $p \leq 0.008$, statistically significant correlation after Bonferroni correction for multiple comparisons [alpha level adjusted for comparison of 6 variables (adjusted GDS-15, MMSE and cognitive domains), 0.05/6 = 0.008]; MMSE, Mini-Mental State Examination; numbers are rounded to two significant figures.

associated with medical-help seeking behavior may be further along the AD trajectory in comparison to subjects who do not evaluate their SCCs to be distressing enough to seek for medical help. Taken together, the stronger association between the total QPC score and depressive symptomatology in adjusted GDS-15 questionnaire in comparison to cognitive performance in our sample cannot be explained as only depression causing the SCCs and further studies are needed to clarify the causality of relationship.

The pattern of specific QPC-SCCs reported by SCD individuals was also much closer to the pattern of QPC-SCCs endorsed by aMCI individuals than by healthy volunteers. *Impression of memory change* and *Impression of worse memory in comparison to peers* are complaints earlier proposed as potentially

useful for identifying individuals at preclinical and prodromal stage of AD [23]. In our sample, they were reported with the almost highest prevalence by both medical-help seeking groups in comparison to relatively low prevalence in healthy community-dwelling volunteers.

There was an association between *Impression of worse memory in comparison to peers* and worse cognitive performance. The association remained significant after accounting for depressive symptomatology, but it did not survive the Bonferroni correction. With respect to its comparably high prevalence in both medical-help seeking groups, we consider the association with cognitive performance as an important finding. Thus, these findings support the presumed potential of the complaint to reflect subtle cognitive changes.

Impression of memory change was not associated with cognitive performance and was reported almost by one third of healthy volunteers consistently with our previous paper [15]. In a previous cohort-based study by Amariglio, a complaint about *Change in memory* was acknowledged by more than 50% of non-demented subjects [14]. In line with that and with our previous study showing such a high prevalence in cognitively healthy older adults, it seems that a complaint about memory change as worded in the QPC questionnaire does not specifically reflect pathological aging. However, in a cross-sectional study acknowledgement of progressive memory change was shown to differentiate cognitively healthy older adults with high amyloid-β load, who are supposed to be in the preclinical stage of AD, from those with low amyloid-β load [40]. Further, in a longitudinal study acknowledgement of worsening memory which was associated with worry was shown to be a greater risk factor for conversion to dementia compared to worsening memory without worry in cognitively healthy participants [17]. Thus, based on our results and previous reports it is possible that simple complaint about memory change is rather nonspecific, unless associated with progressive nature or worry.

We identified one specific QPC-SCC, *Difficulties with recalling past events,* showing the hypothesized continuum in prevalence (HV < SCD < aMCI). There was another one, *Limitation in daily activities,* showing the same trend, although the difference between aMCI and SCD did not reach the statistical significance. The frequency with which these two QPC-SCCs were reported by groups was reflected in the association with worse MMSE, memory and executive performance, which remained significant for *Limitation in daily activities* even after adjusting for depressive symptomatology. It suggests that endorsement of these two complaints may reflect more severe cognitive decline. This assumption is supported by results of a previous study using QPC, showing a higher prevalence of complaint about *Limitation in daily activities* in patients with early and mild AD in comparison to cognitively healthy controls [22].

Despite our expectations, *Forgetting about appointments* and *Word finding difficulties* were reported with significantly higher prevalence by SCD individuals compared to both aMCI and healthy controls. *Word finding difficulties* were acknowledged by three quarters of SCD individuals which is reflected by association with better cognitive performance. The similar prevalence in aMCI and community-dwelling cognitively healthy

older adults supports the notion that subjective word finding difficulty constitutes rather a part of normal aging and does not necessarily relate to anomia due to AD neuropathology which is present rather later on the AD trajectory [41].

The three remaining complaints, *Losing things, Spatial orientation difficulties*, and *Forgetting about past experiences*, were reported by a smaller portion of participants relative to other QPC-SCCs and were not associated with cognition. Though, they were also reported with a significantly higher prevalence by both medical help-seeking groups than by healthy controls. We suppose that difficulties with *Losing things* and *Forgetting about past experiences* do not appear in prodromal stages of AD. In the current study, only aMCI individuals with MMSE ≥ 24 were included to diminish the risk of self-perception bias caused by anosognosia occurring in late prodromal and dementia stage of the disease [25]. On the other hand, findings about prevalence of spatial orientation complaints are not consistent. The relatively low prevalence reported by all groups is in contrast to findings of another recent study [42], where 55% of aMCI, 68% of SCD, and even 33% of healthy controls complained about their spatial navigation. However, spatial navigation difficulties were evaluated on a four-point Likert scale and it is likely that individuals may tend to endorse more difficulties when evaluating on a scale in comparison to yes/no decision. Still, spatial orientation impairment has been already well-established as an AD cognitive marker occurring very early in the course of the disease [43]. Thus, a complaint about spatial orientation difficulty should be treated with concern.

In a recent commentary by Buckley and colleagues, the question of how to utilize the SCD concept in terms of its predictive information about the risk of cognitive decline was discussed [44]. To analyze individual complaints and seriously consider the recruitment setting is the recent direction in SCD research. Medical help-seeking SCD individuals were shown to have a more pronounced marker of neurodegeneration [8] and to be more likely to progress to MCI than SCD individuals from the general population [18], thus, they were proposed to be further along the AD trajectory [8, 19]. Building on these assumptions, the current study examining the pattern of QPC-SCCs in a clinical sample of aMCI and SCD subjects expands on our previous one [15] which studied the prevalence of individual QPC-SCCs and their relation to depressive symptomatology and cognition in a sample of

community-dwelling cognitively healthy volunteers. Still, there are several limitations that need to be considered in the interpretation of the current results.

The absence of AD biomarker evidence in our current cross-sectional study does not allow us to determine in what portion of our individuals SCD is really AD-related despite the increasing evidence that SCCs are more likely to be related to AD pathology when acknowledged by worried medical help-seeking cognitively healthy individuals. In our medical-help seeking SCD group, 30% of the SCD individuals did not report memory change and 47% of the SCD individuals did not report worse memory in comparison to peers. This could suggests that these individuals do not fit the traditional definition of SCD [11]. One explanation could be a discrepancy between information provided by the individuals in a structured questionnaire and during the clinical interview. Another possible explanation of this discrepancy could be that SCD individuals who did not report memory change and worse memory in comparison to peers experienced decline in other than memory domain. The main inclusion criterion to classify a subject as SCD was the intensity of recently developed cognitive complaints (not limited only to memory domain) that motivated the consultation at a memory clinic which was verified by a semi-structured interview with an experienced clinical. Further research is needed to investigate positive and negative predictive value of specific QPC-SCCs in a clinical sample of SCD individuals in a longitudinal setting, ideally in individuals with AD biomarker evidence. The self-perception bias caused by anosognosia is commonly associated with the dementia stage; however, it may be present even at the MCI stage [45, 46]. Although we tried to diminish the risk, still, it is possible that in some aMCI individuals the self-report was slightly affected by their reduced self-awareness. As for the selection of the HV group, it should be noted that the cognitive criterion was overly strict and the HV group is not fully representative of the cognitively healthy older population. However, the cut-off score of −1.5 SD was set with the aim to select cognitively healthy volunteers from the community who were psychometrically comparable to the SCD group as much as possible.

Conclusion

In conclusion, the pattern of cognitive complaints reported by medical help-seeking SCD individuals is similar to that of aMCI individuals. Both

medical help-seeking groups endorsed not only a higher number of SCCs, but also a higher number of depressive symptoms in comparison to demographically matched and cognitively similar community-dwelling healthy volunteers, despite not meeting criteria for clinical diagnosis of depressive disorder. Our findings support the notion that analysis of the pattern of reported QPC-SCCs seems to be more informative than the total score when evaluating the risk of non-normative cognitive decline. A complaint about memory change seem to be unspecific to pathological aging whereas a complaint about worse memory in comparison to peers might be one of the promising items from QPC questionnaire potentially reflecting subtle cognitive changes.

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RESEARCH ARTICLE

Subjective Spatial Navigation Complaints - A Frequent Symptom Reported by Patients with Subjective Cognitive Decline, Mild Cognitive Impairment and Alzheimer's Disease

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Abstract: ***Background:*** Great effort has been put into developing simple and feasible tools capable to detect Alzheimer's disease (AD) in its early clinical stage. Spatial navigation impairment occurs very early in AD and is detectable even in the stage of mild cognitive impairment (MCI).

Objective: The aim was to describe the frequency of self-reported spatial navigation complaints in patients with subjective cognitive decline (SCD), amnestic and non-amnestic MCI (aMCI, naMCI) and AD dementia and to assess whether a simple questionnaire based on these complaints may be used to detect early AD.

Method: In total 184 subjects: patients with aMCI (n=61), naMCI (n=27), SCD (n=63), dementia due to AD (n=20) and normal controls (n=13) were recruited. The subjects underwent neuropsychological examination and were administered a questionnaire addressing spatial navigation complaints. Responses to the 15 items questionnaire were scaled into four categories (no, minor, moderate and major complaints).

Results: 55% of patients with aMCI, 64% with naMCI, 68% with SCD and 72% with AD complained about their spatial navigation. 38-61% of these complaints were moderate or major. Only 33% normal controls expressed complaints and none was ranked as moderate or major. The SCD, aMCI and AD dementia patients were more likely to express complaints than normal controls (p's<0.050) after adjusting for age, education, sex, depressive symptoms (OR for SCD=4.00, aMCI=3.90, AD dementia=7.02) or anxiety (OR for SCD=3.59, aMCI=3.64, AD dementia=6.41).

Conclusion: Spatial navigation complaints are a frequent symptom not only in AD, but also in SCD and aMCI and can potentially be detected by a simple and inexpensive questionnaire.

1. INTRODUCTION

Recently, a great effort has been put into developing a reliable tool for early diagnosis of AD. Following some promising results, diagnostic criteria involving new metabolic biomarkers, neuropsychological tests and imaging studies have been created [1, 2]. However, despite undeniable usefulness of these diagnostic tools, their utilization is challenging and often limited to well-equipped specialized centers. In primary healthcare settings, application of these tools is difficult given their expensive and time consuming nature. Although primary healthcare screening should be the first step in successful early AD diagnosis, these efforts often produce misleading results as practitioners lack a brief and simple screening tool [3-5].

Spatial navigation impairment is typically a very early indicator of oncoming AD [6, 7]. Patients with early signs of AD are frequently getting lost, particularly in unfamiliar places or in situations challenging in terms of spatial navigation (*e.g.* parking lots, supermarkets). Therefore, it is possible that inquiring about self-reported spatial navigation complaints may provide useful clues to improve accuracy of cognitive screening without a great burden on clinicians. Spatial navigation impairment in patients with AD has been well documented in a number of studies using the human analogue of Morris Water Maze [8, 9]. However, these studies also show that impairment similar in quality and quantity with early AD may already be present in MCI subjects with

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hippocampal type of memory impairment, a prodromal stage of AD [8, 9].

Furthermore, in recent years there is a great effort to detect patients at risk of developing AD in the earliest possible stage. Therefore, to characterize patients who do not have cognitive impairment on neuropsychological testing and thus do not meet criteria for the MCI diagnosis, but who self-report cognitive difficulties, the term subjective cognitive decline (SCD) has been established. Recently, it has been also proposed that SCD may represent preclinical stage of AD, thus preceding the MCI stage (2014, the SCD initiative) [10].

However the prevalence of self-perceived cognitive problems is relatively high [11, 12]. In a large study of 16 900 women the complaint about spatial navigation was one of two complaints that was strongly and systematically associated with cognitive impairment [13]. Inquiring about subjective spatial navigation complaints (SSNC) may therefore represent a more direct approach to detect patients at risk of developing AD, however in order to develop a clinically useful tool, the extent of self-perceived spatial navigation difficulties needs to be assessed and understood first.

The aim of this study was:

1) To compare the frequency of SSNC as a symptom in patients with AD, MCI and SCD.

2) To examine whether significant differences exist on a self-reported questionnaire assessing SSNC across patients with SCD, MCI and AD versus healthy controls, above and beyond the effect of potentially important covariates such as age, sex, education, depressive symptoms and anxiety. If differences could be found, this symptom could be used in further studies to create and validate an inexpensive screening tool that can be used in primary healthcare settings and guide further decision making about patients with self-reported memory complaints.

3) To relate SSNC to well-established cognitive domains (attention, language, visuo-spatial function, executive function, verbal memory and non-verbal memory) in order to assess whether SSNC adds a new, potentially useful diagnostic information.

We hypothesized that SSNC may be a relatively frequent symptom in AD and aMCI patients given the already documented objective spatial navigation impairment in these groups. Although we would expect spatial navigation impairment to increase in intensity with disease progression, the frequency of any self-perceived spatial navigation complaints may not necessarily increase in parallel with disease progression due to developing anosognosia [14-18]. We also expected that some SCD patients would express SSNC.

Although spatial navigation impairment is usually present early in AD and amnestic MCI, it has not been unambiguously documented in non-amnestic MCI patients [9, 19]. Because this patients' group is relatively heterogeneous, we hypothesized that SSNC may not be present in this group as consistently as in patients with AD and amnestic MCI, providing further evidence for keeping the non-amnestic MCI as a separate diagnostic category.

2. MATERIAL AND METHODS

2.1. Subjects and Settings

In total 184 subjects, amnestic MCI (aMCI, n=61), non-amnestic MCI (naMCI, n=27), subjective cognitive decline (SCD, n=63) and patients with dementia due to AD (n=20) were recruited from the Memory Clinic in Motol University Hospital, Prague, Czech Republic during years 2011-2015. Normal controls without subjective cognitive complaints (n=13) were recruited from volunteers attending the University of the Third Age, an education program for older adults. The controls were recruited to approximately match patients with AD, SCD, aMCI and naMCI in age, sex and education (Table 4).

Patients had been referred to our clinic by general practitioners, neurologists, psychiatrists, geriatricians and contact sites of the Czech Alzheimer Society. All subjects signed an informed consent approved by hospital ethics committee and underwent brain MRI, clinical and laboratory evaluations, a semi-structured interview, and the following neuropsychological tests: 1) memory: a) verbal memory – measured with the Auditory Verbal Learning Test (AVLT; trials 1–5 and Delayed Recall), and the Free and Cued Selective Reminding Test (FCSRT; Free Recall and Total Recall), b) non-verbal memory: the Benton Visual Retention Test (BVRT) and Rey-Osterrieth Complex Figure (ROCF) Recall Condition; 2) attention/processing speed – measured with the Digit Span (Forward and Backward) and Trail Making Test (TMT) A; 3) executive function – measured with the TMT B and Controlled Oral Word Association (COWAT); 4) language – measured with the Boston Naming Test (BNT); and 5) visuospatial function – measured with the ROCF Copy Condition. Performance on TMT was measured in time to completion. The Mini-mental State Examination (MMSE) and the Czech version of Addenbrooke's Cognitive Screening were administered to measure global cognitive functioning [20, 21]. Hachinski ischemic scale was also administered to all subjects.

The classification of patients into MCI, SCD, AD was clinically based and included the results of neuropsychological tests mentioned above and self-reported cognitive difficulties, which included any subjective cognitive complaints actively mentioned by subject. Diagnosis of MCI was established according to Petersen´s criteria for MCI [22]. Patients with MCI were further classified as 1) amnestic (aMCI) when they scored more than 1.5 standard deviations below the mean of age- and education-adjusted norms on any memory test and 2) non-amnestic (naMCI) when they scored more than 1.5 standard deviations below the mean of age- and education-adjusted norms on any non-memory test (attention/processing speed, executive, language or visuo-spatial). The MCI subjects had Clinical Dementia Rating (CDR) score of maximum 0.5. SCD was defined with consideration of previous research [10, 23, 24] as individuals actively seeking medical help for cognitive complaints perceived by themselves or their caregiver who did not show objective cognitive deficit characterized by scoring less than 1.5 standard deviations below the mean of age- and education-adjusted norms on any cognitive test [23] (therefore not meeting criteria for MCI). To evaluate cognitive complaints a structured interview by an experienced clinician with the

patient and caregiver was used, taking into account the qualitative and quantitative aspect of complaints as well as the reported timing of their onset and change over time. Diagnosis of dementia due to AD (n=61) was made according to National Institute on Aging – Alzheimer's Association (NIA-AA) criteria [24] and only patients with probable AD were included in the study. The diagnosis of dementia due to AD was supported by CSF biomarker analysis (tau, p-tau and beta-amyloid levels) in 20% of subjects [25].

Subjects in the control group did not report any cognitive difficulties and this was confirmed by neuropsychological testing. They were selected to have similar age, education and sex ratio as the other groups. Subjects with other primary neurological or psychiatric disorders were not included in this study. Subjects with Hachinski ischemic scale score above 4 and GDS above 6 were excluded from the study.

2.2. Questionnaire Regarding Subjective Spatial Navigation Complaints

The questionnaire was designed at our memory clinic based on clinical experience and our previous research. The questionnaire was administered to the subjects at the beginning of the examination. The subjects were asked to choose the most suitable answer with a particular emphasis on the "last 3 months" timeframe. Reasonable assistance was provided by trained person when needed. Otherwise no other general instructions were provided. Questions were formulated to address the extent (*e.g.* difficulties in neighborhood or outside of own town) and frequency of spatial navigation complaints with an emphasis on navigational skills necessary in everyday functioning.

The questionnaire consisted of 15 items across seven sections (see Table **1**): (1) Self-perceived difficulties with navigation in four different environments ordered from the most familiar (own home) to the more challenging (out of own town). Every item (environment) was scored according to the severity of symptoms (0-4 points; never = 0, every day = 4). (2) In the second section we inquired whether subjects actually got lost in the specific environment. This section was scored the same as the previous one. (3) Self-perceived decline of spatial navigation skills in relatively well known places (0-3 points; same or better = 0, significantly worse = 3). (4) Self-perceived decline of spatial navigation skills in relatively less known places (scored the same as previous one). (5) Decline in spatial navigation skills that resulted in seeking more help (0-4 points; never = 0, every day = 4). (6) A question specifically addressing navigational skills at more challenging places (supermarket), scored according to the severity of symptoms (0-4 points; never = 0, every day = 4). The final section (7) investigates whether and how much these self-perceived difficulties influence everyday general functioning. This sections contains dichotomous (yes/no) questions (Each "yes" answer on dichotomous questions was coded as 1 point; "no" as 0 points)

Total composite score (SSNC composite) was calculated as the sum of all points from all items (possible maximum 49 points). Scores in this sample ranged from zero to 31. The sample averaged 3.07 points (SD=5.06 points). In the subsequent analysis, each question (item) was evaluated separately

as well (SSNC specific questions). The Cronbach's alpha for the combined scores was 0.894.

2.3. Covariates

Covariates were age, sex, years of education, depressive symptoms and anxiety. Depressive symptoms were measured with 15-item Geriatric Depression Scale (GDS), (26) and anxiety was measured with Beck Anxiety Inventory (BAI) (27). Both the GDS and BAI were administered during the neuropsychological test session and standardized official Czech translations were used.

2.4. Statistical Analysis

One-way analysis of variance (ANOVA) with diagnostic category as a single factor followed by Tukey's Honestly Significant post-hoc test was used to examine between-group differences in age, education, depressive symptoms and anxiety. Chi-Square was used to determine differences in sex.

To correct for non-linear distribution of the SSNC composite, the SSNC severity scale was categorized based on the SSNC composite as 'no complaints' (SSNC composite = 0, coded as SSNC severity scale 0, 39% of the sample), 'minor complaints' (SSNC composite = 1, coded as 1, 17% of the sample), 'moderate complaints' (SSNC composite 2-4, coded as 2, 23% of the sample), and 'major complaints' (SSNC composite greater than 4, coded as 3, 21% of the sample – see Table **2**).

Correlations among neuropsychological tests, age, sex, education, depressive symptoms, anxiety and SSNC severity scale were assessed using Pearson correlation for continuous measures and Spearman correlation for ordinal measures.

Finally, four multinominal logistic regression models were used to estimate differences in SSNC severity scale and SSNC specific questions between the groups. First, an unadjusted model was built only with diagnostic category as dependent variable and SSNC severity scale as the fixed factor (Model 1). The second model was adjusted for age, sex, education and either depressive symptoms (Model 2a) or anxiety (Model 2b) to avoid bias due to multicollinearity (high level of correlation between the depressive symptoms and anxiety).

In the next model (Model 3) we examined the possible interaction between GDS and SSNC severity scale in a model based on Model 2a (adjusted for adjusted for age, sex, education, depressive symptoms).

3. RESULTS

3.1. Cohort Characteristics

The group of patients with SCD was younger (F=4.832, p=0.001) than patients with AD (p=0.001) and aMCI (p=0.031). We found no significant differences in age compared to controls in any group. In education, the only difference among the groups (F=2.74, p=0.030) was between the SCD group and AD patients (p=0.031), who achieved lower education. As expected, the AD patients achieved lower score in MMSE (F=86.579, p<0.001) as compared to any

Table 1.   **Patients´ version of SSNC questionnaire. Please note, that reliability of presented wording has been based on reversed translation from Czech language to English and back to Czech language.**

I have had difficulties in the last 3 months with:					
Orientation in my home					
	never	less than once a week	approximately once a week	several times a week	every day
Orientation in my neighborhood					
	never	less than once a week	approximately once a week	several times a week	every day
Orientation in my town					
	never	less than once a week	approximately once a week	several times a week	every day
Orientation outside of my town					
	never	less than once a week	approximately once a week	several times a week	every day
I have been lost in the last 3 months:					
in my flat					
	never	less than once a week	approximately once a week	several times a week	every day
in my neighborhood					
	never	less than once a week	approximately once a week	several times a week	every day
in my town					
	never	less than once a week	approximately once a week	several times a week	every day
in the other town, than where I live					
	never	less than once a week	approximately once a week	several times a week	every day
With respect to places that I visit every day or almost every days, in the last 3 months, my ability to orient myself has been _____ compared to when I was young:					
	same or better	little worse	much worse	significantly worse	
With respect to places that I visit several times a year, in the last 3 months, my ability to orient myself has been _____ compared to when I was young:					
	same or better	little worse	much worse	significantly worse	
In the last 3 months, I have had to ask for directions more often than in the past:					
	never	less than once a week	approximately once a week	several times a week	every day
In the last 3 months, I have had difficulties getting oriented in my supermarket:					
	never	less than once a week	approximately once a week	several times a week	every day
Because of worries that I may get lost, I have had to:					
	reduce traveling out of my town.			yes	no
	reduce traveling to my relatives and friends.			yes	no
	reduce activities around my home (shopping, go to post, *etc.*).			yes	no

other group and there was no difference in MMSE between SCD, aMCI, naMCI or controls. The aMCI (p=0.004), naMCI (p<0.001) and SCD (p=0.017) scored higher in GDS (F=4.682, p=0.001) compared to the control group, however, we found no difference between AD patients and the control group. The only difference in anxiety (F=2.646, p=0.036) was between the control group and the naMCI patients (p=0.022) who reported more anxious symptoms. The groups did not differ in sex ratio (Table **4**).

3.2. Differences in Subjective Spatial Navigation Complaints

    The basic frequencies of no complaints, minor, moderate - and major complaints were compared among the groups. The

Table 2. SSNC severity scale categorization.

SSNC severity scale	Frequency	SSNC composite	Percent
0 (no complaints)	73	0	39
1 (minor complaints)	32	1	17
2 (moderate complaints)	43	2-4	23
3 (major complaints)	39	≥ 5	21

Table 3. Correlations among SSNC, neuropsychological tests, age, sex, education, depressive symptoms anxiety.

	Age	MMSE	EDU	GDS	BAI	SSNC sev. s.	AVLT 1-5	Del. R.	TMT A	TMT B	COW AT	ROCF C	ROCF R	Digit Sp. F	Digit Sp. B	FCSRT F	FCSRT T	BNT
Age	-																	
MMSE	-0.253**	-																
EDU	0.028	0.291**	-															
GDS	-0.162*	-0.036	-0.161*	-														
BAI	-0.276**	0.011	-0.139	0.704**	-													
SSNC sev. s.	-0.163*	-0.058	0.006	0.235**	0.362**	-												
AVLT 1-5	-0.313**	0.635**	0.210**	-0.024	0.076	0.181*	-											
Del. R.	-0.289**	0.475**	0.098	0.105	0.158	0.100	0.721**	-										
TMT A	0.144	-0.489**	-0.063	0.178*	0.143	0.030	-0.297**	-0.229**	-									
TMT B	-0.254**	-0.686**	-0.171*	0.076	-0.065	0.037	-0.438**	-0.304**	0.498**	-								
COWAT	-0.106	0.343**	0.384**	0.018	0.104	0.036	0.453**	0.432**	-0.365**	-0.317**	-							
ROCF C	-0.214**	0.400**	-0.021	-0.012	0.011	0.015	0.164*	0.176*	-0.401**	-0.293**	0.167*	-						
ROCF R	-0.418**	0.615**	0.232**	-0.086	0.100	-0.062	0.539**	0.500**	-0.251**	-0.446**	0.332**	0.570**	-					
Dig Sp. F	-0.024	0.285**	0.176*	-0.104	-0.106	-0.112	0.263**	0.236**	-0.221**	-0.165*	0.376**	0.045	0.160*	-				
Dig Sp. B	-0.144	0.457**	0.183*	-0.195*	-0.156	-0.013	0.418**	0.286**	-0.268**	-0.330**	0.353**	0.178*	0.286**	0.584**	-			
FCSRT F	-0.295**	0.614**	0.268**	0.034	0.160	-0.037	0.691**	0.572**	-0.208**	-0.438**	0.435**	0.339**	0.662**	0.215**	0.294**	-		
FCSRT T	-0.287**	0.719**	0.267**	0.073	0.133	-0.054	0.536**	0.502**	-0.217**	-0.510**	0.253**	0.278**	0.543**	0.203**	0.299**	0.693**	-	
BNT	0.426**	-0.417**	-0.264**	0.180*	0.031	-0.012	-0.360**	-0.327**	0.318**	0.456**	-0.363**	-0.283**	-0.451**	-0.157*	-0.270**	-0.324**	-0.397**	-
BVRT	-0.382**	0.136	0.557**	-0.171*	-0.063	0.029	0.668**	0.499**	-0.262**	-0.443**	0.367**	0.319**	0.600**	0.186*	0.368**	0.611**	0.477**	0.398*

Note: Pearsons correlation are shown except for SSNC sev. s. where Spearman correlation coefficient is shown
*. Correlation is significant at the 0.05 level (2-tailed), **. Correlation is significant at the 0.01 level (2-tailed).
Abbreviations: MMSE – Mini-mental State Examiantion, EDU – Education; GDS – Geriatric Depression Scale; SSNC sev. s.– Subjective Spatial Navigation Complaints Severity Scale; AVLT – Auditory Verbal Learning Test trials 1–5; Delayed R. – AVLT Delayed Recall; TMT A, B – Trail Making Test (A, B); COWAT – Controlled Oral Word Association; ROCF C, R – Rey-Osterrieth Complex Figure Copy, Recall Condition; Dig Sp. F, B – Forward and Backward; FCSRT F– Free and Cued Selective Reminding Test Free Recal; FCSRT T – Free and Cued Selective Reminding Test Total Recall; BNT – Boston Naming Test; BVRT – Benton Visual Retention Test.

highest percentage of no complaints and minor complaints were in the control group (67% and 33%), whereas highest percentage of major complaints was in the SCD group (29%) and moderate complaints in the AD group (44%) respec-tively. Overall, the lowest percentage of no complaints and minor complaints was in the AD group. (Fig. **1**).

SSNC score correlated depressive symptoms (r=0.235, p=0.003) and anxiety (r=0.362, p<0.001). The scale did not correlate with any of the neuropsychological tests except the very weak and correlation with AVLT (1-5 trials; r = 0.165, p=0.04; see Table **3**).
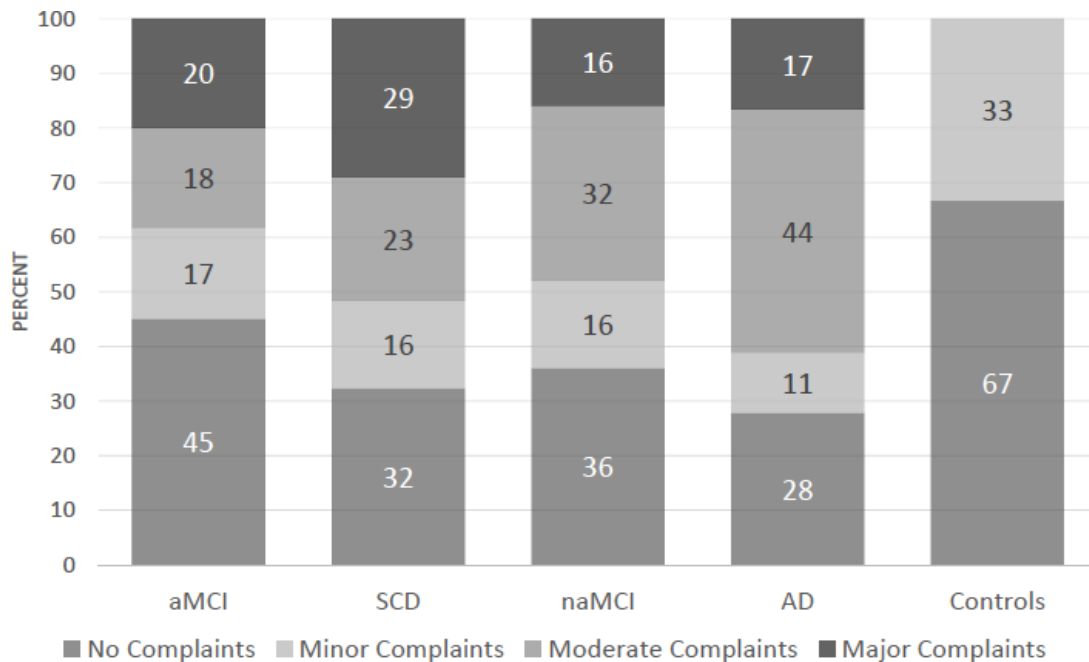
Fig. (1). Distribution of SSNC across diagnostic categories.

Table 4.   Characteristics of the Sample by Diagnostic Category.

	Total		**AD**		**SCD**		**aMCI**		**naMCI**		**Controls**	
	n= 184		n=20		n=63		n=61		n=27		n=13	
Female, n (%)	103	(56)	10	(50)	39	(62)	31	(51)	15	(56)	8	(62)
Age, mean (SD)	70.38	(9.07)	74.88[*]	(6.17)	67.40[*,†]	(9.43)	71.96[†]	(8.74)	71.36	(8.99)	69.54	(4.01)
Education, mean (SD)	14.67	(3.14)	13[*]	(2.73)	15.32[*]	(2.79)	14.25	(3.19)	14.89	(3.97)	15.54	(2.07)
MMSE, mean (SD)	26.48	(3.63)	19.3[*,†,‡,‡]	(3.31)	28.55[*]	(1.25)	25.60[†]	(2.97)	27.77[‡]	(1.76)	28.92[‡]	(1.19)
GDS, mean (SD)	3.96	(3.17)	3.40	(2,01)	3.85[†]	(2.89)	4.26[*]	(3.41)	5.28[‡]	(3.37)	0.92[*,†,‡]	(1.04)
Beck, mean (SD)	11.89	(10.72)	8.56	(8.67)	12.3	(10.38)	11.53	(10.62)	16.36[*]	(12.54)	5.38[*]	(6.17)

Notes. *, †, ‡, ‡. Two corresponding symbols indicate that the mean difference between two specific diagnostic categories is significant at the 0.05 level.

The SSNC severity sscale was a significant factor for di-agnostic category prediction in all groups in the unadjusted Model 1 (SCD OR=3.14, p=0.008; aMCI OR=2.43, p=0.040; naMCI OR=2.71, p=0.027; and AD OR=3.18, p=0.013) and in Model 2a, which was adjusted for age, sex, education and depressive symptoms (SCD OR=4.00, p=0.032; aMCI OR=3.90, p=0.037; naMCI OR=3.83, p=0.046; and AD OR=7.02, p=0.007).

In Model 2b, which was adjusted for age, sex, education and anxiety, the SSNC severity scale was significant in SCD (OR=3.59, p=0.014,), aMCI (OR=3.64, p=0.014;), and AD (OR=6.41, p=0.03) groups and non-significant in the naMCI group (OR=6.41, p=0.055). Although the greatest effect was observed for AD vs. the control group, the effects were com-

parable in magnitude when confidence intervals around the odds ratios were considered (Table 5).

Depressive symptoms was the only covariate that consis-tently conferred association with diagnostic classification, with depressive symptoms being higher for SCD, aMCI and naMCI (but not AD) compared to the control group. The interaction of depressive symptoms by SSNC severity scale was not significant for SCD (p=0.923), aMCI (p=0.931), naMCI (p=0.949) and AD (p=0.882).

Only one specific question (difficulty with orientation in places that are not often visited) was associated with the di-agnostic category in the unadjusted model, however this as-sociation became insignificant after correction for covariates (education, age, sex, depressive symptoms and anxiety).

Table 5.   SSNC Severity Scale multinominal logistic regression models.

	SCD			aMCI			naMCI			AD		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Model 1[†]	3.14	1.35–7.32	0.008	2.43	1.04–5.67	0.040	2.71	1.12–6.56	0.027	3.18	1.28-7.88	0.013
Model 2a[††]	4.00	1.13–14.20	0.032	3.90	1.09–14.02	0.037	3.83	1.03–14.26	0.046	7.02	1.72–28.68	0.007
Model 2b[†††]	3.59	1.30–9.90	0.014	3.64	1.30–10.20	0.014	2.87	0.98–8.40	0.055	6.41	1.91–21.51	0.003
Model 3[††††]	1.05	0.36–3.05	0.923	1.05	0.36–3.03	0.931	1.04	0.36–3.00	0.949	1.09	0.37–3.23	0.882

[†] Unadjusted SSNC Severity Scale model
[††] SSNC Severity Scale adjusted for age, sex, education and depressive symptoms
[†††] SSNC Severity Scale adjusted for age, sex, education and anxiety
[††††] Interaction between GDS and SSNC scale (adjusted for age, sex, education, depressive symptoms and SSNC severity scale)
Participants in the control group were the reference category.

4. DISCUSSION

The aim of this study was to describe and compare the frequency of SSNC as a symptom in patients with AD, MCI and SCD and as such imply utility as a potential screening tool. To address these aims, we proposed a simple 15-item self-reported questionnaire that was administered to the patients and healthy controls as well. Using a four-level scale classification of self-reported spatial navigation complaints (no complaints, minor, moderate, and major complaints), we found that 55% of patients with aMCI, 64% with naMCI, 68% with SCD and 72% with AD complained about their spatial navigation. 38-61% of these complaints were moderate or major on our scale. These results are in strong contrast to the healthy controls group, where only 33% subjects complained about their spatial navigation and none was ranked as moderate or major on our scale.

We also found that subjects expressing significantly more complaints on the SSNC severity scale are more likely to be associated with other diagnostic category other than normal controls (SCD, aMCI or AD). The odds ratios became even larger after controlling for age, education and gender and depressive symptoms or anxiety. The odds ratios were similar in both models controlled for either depressive symptoms or anxiety. The subjects were approximately 3-4x times more likely to be diagnosed with SCD or aMCI for each point at the SSNC severity scale (odds ratios 4.00 for SCD and 3.90 in the model controlled for depressive symptoms and 3.59 and 3.64 in the model controlled for anxiety) and 6-7x more likely to belong to the AD group (odds ratios 7.02 and 6.41 – Table **5**) in comparison to the controls. These findings support the potential diagnostic value of the SSNC screening tool.

Our results are consistent with previous reported findings indicating that patients with dementia due AD experience difficulties in spatial navigation in everyday activities [28, 29].This may also be true for some patients with aMCI [30, 31]. Studies describing subjective spatial navigation impairment in patients with SCD are lacking. Although patients with SCD by definition do not suffer from any objective impairment, in our study they expressed complaints about spatial navigation ability that appear more similar to patients with aMCI than to normal controls.

Our previous study showed that objective spatial navigation impairment is present very early in both aMCI and AD patients and undetectable in patients with SCD [8]. However, based on recent advances in the biomarker model of the AD, it has been proposed that the SCD stage may represent preclinical stage AD, where cognitive changes are already present, but undetectable by standardized diagnostic tools [10, 32]. Recent metaanalysis also showed they are at twofold increased risk of developing dementia as compared to controls without SCD. Our screening tool based on SSNC was able to detect these patients.

The relationship between depressive symptoms, anxiety and self-reported cognitive complaints in general is well documented in literature [33-35]. Patients with SCD, MCI and dementia due AD report frequently depressive symptoms [36, 37]. This is consistent with our findings, where both depressive symptoms and SSNC severity scale were associated with diagnostic category. Our group has also shown previously that anxiety influences subjective perception of spatial navigation abilities in non-demented elderly, regardless of their objective spatial navigation deficit [38]. However, depressive symptoms and SSNC appear to act independently of each other as we found no interaction between these two variables and their correlation was very weak (r_s=0.235; p<0.01). SSNC may reflect the ongoing pathological process with depressive symptoms accompanying it.

The SSNC severity scale did not correlate with any of the well-established cognitive domains tested (attention, language, visuo-spatial function, executive function, verbal memory and non-verbal memory). Except for the correlation between AVLT 1-5 and SSNC severity scale that was very weak and of a low statistical and clinical value. Our results may thus indicate that SSNC can enrich standardized neuropsychological testing which focuses on the traditional cognitive domains.

4.1. Limitations and Further Research

Our main objective was to examine whether simple tool based on the frequency of SSNC can discriminate between healthy controls and subjects in risk of developing AD. In order to be usable in clinical practice such a tool needs to be kept as simple as possible.

Given the relatively stringent definition of the SCD in our study and despite our great effort we were not able to recruit more subjects who would meet the inclusion criteria for the control group.

Based on the SSNC severity scale, the questionnaire could not distinguish between patients with SCD, MCI or AD. In our previous studies, we found a clearer pattern of results with objective spatial navigation tests, whereby it was possible to differentiate between patients with SCD, naMCI and AD based on their results in egocentric and allocentric subtests and their learning curve. Objective spatial navigation impairment in patients with early AD and aMCI appears to be similar in quality and quantity [8, 39]. SSNC did not elucidate diagnosis-based differences in the same manner, either as a result of limited explanatory power of the categories representing SSNC or because potential limited sensitivity of the SSNC. Future research should investigate SSNC to confirm or refute its clinical utility. The score in the SSNC questionnaire is subjective in its nature and cannot be used interchangeably with real spatial navigation testing. Patients with SCD may tend to exacerbate their complaints [40] (they even complained more frequently than patients with aMCI). On the other hand, patients with AD and aMCI may not be able to realize the full extent of their impairment due to limited awareness and anosognosia [14-18].

The difference in the SSNC severity scale between the naMCI group and the controls was reduced to non-significant after correcting for anxiety, but it was significant when controlling for all other covariates including depressive symptoms. The association between the likelihood of being in the naMCI group compared to the control group was initially relatively weak. We also found that the correlation between SSNC severity scale and anxiety was quite strong (r=0.362). Therefore, controlling for anxiety could be expected to affect this result in particular. Overall, the naMCI group is a very heterogeneous group of patients [41] who may progress into vascular dementia or frontotemporal lobar degeneration that presents with relatively spared spatial navigation and this may be reflected in the SSNC questionnaire [42].

It appears that global SSNC severity scale is a good indicator of the diagnostic category. However, items from the scale may not offer the same validity as the overall scores. In our clinical experience, the spatial navigation complaints are often very individual in their nature as every patient describes his symptoms in his unique way. In our study none of SSNC specific question yielded significant differences across the diagnostic categories but some of them appear to be potentially promising (i.e. difficulty with orientation in places that are not often visited or difficulty with orientation in situations challenging for spatial navigation). Based on these results, in further studies a more sensitive set of questions could be proposed and subsequently validated on a larger number of subjects.

It needs to be highlighted that although the questionnaire identified subjects likely at the highest risk of developing AD, its predictive value was not tested in this cohort study. The question of which subjective measure has greater predictive value of conversion to AD, memory or navigation falls beyond the scope of this study. However, the predictive

value of a SSNC-based questionnaire and perhaps also sensitivity and reliability of a SSNC-based screening tool may be tested in future, preferably longitudinal, studies. Given the relatively high prevalence of SCD in the population of older adults, the clinical significance of self-perceived general cognitive complaints is yet to be fully understood. Using the SSNC and the frequency of these complaints may offer a more direct pathway to identifying individuals at risk of developing AD.

It should be noted, that this questionnaire may not replace spatial navigation testing and comprehensive neuropsychological examination.

Also, given the association of depressive symptoms with diagnostic category in our analysis, we would propose that in the clinical settings the GDS, BAI and SSNC questionnaire are administered together as they both add different valuable information. Depressive symptoms may affect the subjects' performance in cognitive tests and are also associated with an increased risk of AD [43, 44]. The SSNC questionnaire has been shown to detect early AD stages in our study.

CONCLUSION

According to our findings, the subjective spatial navigation complaints are a frequent symptom reported by SCD, MCI and AD patients. This symptom may be exploited to create an inexpensive screening tool that can be used in primary healthcare settings. We proposed a simple questionnaire that was able to distinguish healthy controls from patients with SCD, aMCI and AD and thus detect early AD stages in our study.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

Prof. Hort consulted for Pfizer, Janssen, Merck, Novartis, Elan, Zentiva, Ipsen and Polyhymnia-TS.

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Depression & Anxiety

Spatial Navigation Complaints are Associated with Anxiety Regardless of the Real Performance in Non-Demented Elderly

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Abstract

Objective: Memory complaints in non-demented elderly are reported frequently and are often associated with depression/anxiety. The relationship between depression/anxiety, memory complaints and risk of dementia is unclear. Spatial disorientation is a common problem reported by patients with early Alzheimer´s disease (AD). Objective testing of spatial navigation (SN) in human analogue of Morris water maze showed that subject with mild cognitive impairment (MCI) present with identical SN impairment as AD patients. There is not much known about how subjective perception of spatial navigation skills reflects the real SN performance and whether depression/anxiety plays a role in this association. We investigated whether subjects with MCI reported more subjective spatial navigation complaints (SSNC) than individuals with subjective cognitive decline (SCD) with no cognitive deficit and whether SSNC reporting depends on anxiety or/and depression regardless of real SN performance.

Methods: A total of 123 non-demented participants, including 52 with SCD and 71 with MCI underwent spatial navigation (SN) testing, neuropsychological examination and completed SSNC questionnaire, Geriatric Depression Scale (GDS), and Beck Anxiety Inventory (BAI).

Results: There were no differences in GDS and BAI scores between MCI and SMC groups. The MCI group did not report more SSNC than SMC group regardless of worse real-SN performance in the MCI group (p<0.001). Anxiety explained most of the SSNC (p<0.001). A median split by BAI (≤ 10) and GDS (≤ 4) scores were used to classify participants into 4 groups- normal (n=44), anxious (n=18), depressive (n=13) and anxious/depressive (n=34). The anxious/depressive and anxious groups reported more SSNC than normal (p=0.006; p=0.036) and depressive groups (p=0.018; p=0.031).

Conclusion: General complaints about SN performance do not rely on actual cognitive status. Anxiety rather than depression influences subjective perception of SN abilities in non-demented elderly, regardless of their objective SN deficit. Screening for anxiety, rather than only for depression, may be useful to evaluate subjective complaints.

Keywords: Anxiety; Spatial navigation; MCI; Subjective memory complaints

Introduction

In the recent years, there has been a shift in clinical practice toward earlier identification of Alzheimer's disease (AD) inspired by wider public awareness, larger professional effort, patients' initiatives and growing scientific evidence. DSM V manual and new research guidelines for AD consider AD as a continuum ranging from preclinical, stage, over prodromal stage characterized by minor cognitive changes referred to as mild cognitive impairment (MCI) to dementia syndrome characterized by major cognitive deficit and impaired functioning. Memory and executive functions impairments are recognized as early symptoms of the disease [1] and new challenging neuropsychological tests are thus being sought to improve early diagnosis. Apart from objective performance in neuropsychological tests, subjective symptoms of memory complaints and slowing of thinking (which may refer to executive dysfunction) are in the center of clinical and research interest.

Memory complaints are a frequent symptom in older adults [2,3] and may reflect both healthy and pathological ageing since they are not always associated with objective impairment in cognitive tests [4]. Furthermore, many studies with non-demented subjects report associations between memory complaints and depression/anxiety [5-10]. The relationship between depression/anxiety, memory complaints and risk of dementia is unclear. Follow-up studies with non-demented subjects report higher rate of conversion to dementia as well as higher

incidence of depression/anxiety in subjects with memory complaints compared to non-complainers [2,11-14]. However, this area is even more complex while also depression alone was considered as a risk factor of dementia in some studies; possibly via toxic effects of increased glucocorticoid levels on the hippocampus [15-17]. There is also no consistency in terminology and assessment of subjective memory impairment [18], with some studies using simple yes/no question while other studies using complex questionnaires. Furthermore, studies on subjective memory impairment often do not distinguish cognitively healthy subjects from those with MCI. Many elderly also report problems in other cognitive domains like language, visuo-constructive functions, clumsiness/apraxia, attention, slowing of thinking, or agnosia, despite normal neuropsychological examination. Therefore a new concept was proposed for research of this entity. The concept of

subjective cognitive decline (SCD) comprises subjective change in time in any of the cognitive domains in cognitively healthy individuals [19].

Besides the previously mentioned cognitive domains, we reported earlier that allocentric (i.e., with respect to external cues without regard to subject's own position) spatial navigation (SN) impairment correlates with right hippocampal volume [20], with hippocampal type of memory impairment [21] in MCI as well as with ApoE 4 status [22], putting SN impairment among possible early markers of AD. Spatial disorientation or even being lost is also a well-known and stressful feature reported by caregivers of individuals with dementia due to Alzheimer disease (AD). This suggests potential usefulness of the assessment of SN difficulties on a subjective level, an area not represented in most memory complaints questionnaires.

Data on the relationship between subjective SN complaints (SSNC) and objective cognitive and SN performance in non-demented subjects are limited. Little is also known about the role of depression/anxiety in subjective perception of SN skills. We have developed 15 item SSNC questionnaire assessing navigation performance in one's daily life and we analyzed the correlation of SSNC with real SN performance in the human analogue of Morris water maze. We hypothesized that according to SCD, depression and anxiety also play a critical role in SSNC reporting.

We investigated 1) whether subjects with MCI report more SSNC than subjects with SCD and 2) whether SSNC reporting and real SN performance depends on depression or/and anxiety.

Methods

Subjects

The institutional ethics committee of Motol Hospital approved the study and all participants provided a written informed consent. All procedures comply with the ethical rules for human experimentation that are stated in the Declaration of Helsinki from 1997. Total of 186 individuals with memory complaints were referred to Memory clinic by general practitioners, families or contact sites of Czech Alzheimer Society in 2011-2014. Subjects with a history of neurological or psychiatric disease, psychiatric medication, abnormal neurological examination including gait or movement difficulties, were excluded. All underwent standard neurological and laboratory evaluations, structural magnetic resonance (MR) imaging, clinical scaling and complex neuropsychological testing as well as SN testing. Participants meeting DSM IV -TR criteria for dementia (n=28) were excluded. For the final analyses we also excluded subjects (n=35) which were not able or not willing to undergo any part of the protocol (SN test, neuropsychological examination or fill in the questionnaires). Therefore, the final sample included 123 participants, 71 with MCI and 52 subjects with SCD without detectable objective cognitive impairment.

Neuropsychology

Comprehensive neuropsychological battery was used to assess all cognitive domains including: 1) memory, measured by Auditory Verbal Learning Test [23], Brief Visuospatial Memory Test-Revised [24] and Enhanced cued recall test Test in Czech validated version [25,26]; 2) attention/processing speed, measured with the Digit Span Backwards [27] and Trail Making Test A [28]; 3) frontal/executive functions, measured with the Trail Making Test B [28] and Controlled Oral Word Association [29]; 4) language, measured with the Boston Naming Test[30]; and 5) visuospatial functions measured with the Rey-Osterreith Complex Figure [24]– copy condition. All participants with MCI met clinical criteria for MCI [31] including cognitive complaints

reported by patient or caregiver, evidence of cognitive dysfunction on neuropsychological testing, generally intact activities of daily living, and absence of dementia. Cognitive impairment was established when they scored more than 1.5 standard deviations below the mean of age- and education-adjusted norms on any neuropsychological tests.

Subjective Spatial Navigation Complaints (SSNC) assessment (Figure 1)

Since the area of SN research is not standardized, candidate questions were chosen and combined in order to be able to be administered in a novel questionnaire. This multiple choice 15 item SSNC questionnaire assessing SN performance in one's daily life was developed at Memory Clinic, Motol University Hospital in Prague using content validity criteria. Five experienced clinicians assessing older adults at a memory clinic and an expert on spatial navigation research were involved in development and testing of the questionnaire. It contains questions on subjectively perceived difficulties during spatial orientation, questions on impact of navigational difficulties on everyday life activities, and questions on the impact of certain subjective concerns on everyday life performance. The instrument had a high degree of internal consistency (Cronbach's alpha=0.894). SSNC was administered together with Geriatric Depression Scale (GDS) [32] and Beck Anxiety Inventory (BAI) [33].

Spatial navigation testing

SN was tested within 2 months period from all other examinations. The real-space navigation setting is called the Blue Velvet Arena located in the Laboratory of Spatial Cognition, a joint workplace of the Department of Neurology, 2nd Faculty of Medicine, Charles University in Prague, and Institute of Physiology, Academy of Sciences of the Czech Republic, Prague. The design of the Blue Velvet Arena and the real-space testing procedure were described in detail elsewhere [34,35]. Briefly, it is a fully-enclosed cylindrical arena 2.8 meters in diameter surrounded by a 2.9 meter high dark blue velvet curtain and it is designed to test two subtypes of navigation; allocentric (world-centered) navigation, which is considered hippocampus-dependent, and where salient distal cues (landmarks) are used for navigation irrespective of an individual's position [36]. Egocentric (self-centered) navigation is considered parietal cortex-dependent, and relies on an individual's position and the start location [37]. The egocentric subtask involved using only the start position to locate the goal with no distal orientation cues displayed. The allocentric subtask involved using only two distal orientation cues at the perimeter for navigation to the goal as the start position was unrelated to the goal position. Each subtask involved eight trials. The relative positions of the goal, start position, and both orientation cues were identical across all trials. The performance was measured as the distance error between the subject's final position and the actual goal location (in centimeters). There was no time limit to find the goal, mainly to reduce bias by differences in cognitive, sensory, and physical functioning. All subjects were tested for both allocentric and egocentric navigation.

Statistical analysis

All analyses were conducted by using IBM SPSS for Windows version 20.0. First, all variables were examined for normality of distribution. Except for SSNC questionnaire composite score, no variable presented significant deviation from normal score distribution. Therefore for SSNC analysis we used non-parametric tests (Mann-Whitney U test and Kruskal-Wallis one-way analysis of variance with post hoc Holm-Bonferroni correction for multiple comparisons. For analysis of other variables we used parametric tests (an independent

I have had difficulties in the last 3 months with:

orientation in my flat

	never	less than once a week	approximately once a week	several times a week	every day

orientation in my neighborhood

	never	less than once a week	approximately once a week	several times a week	every day

orientation in my town

	never	less than once a week	approximately once a week	several times a week	every day

orientation out of my town

	never	less than once a week	approximately once a week	several times a week	every day

I have been lost in the last 3 months:

in my flat

	never	less than once a week	approximately once a week	several times a week	every day

in my neighborhood

	never	less than once a week	approximately once a week	several times a week	every day

in my town

	never	less than once a week	approximately once a week	several times a week	every day

in the other town, than where I live

	never	less than once a week	approximately once a week	several times a week	every day

At the places which I have visited every days or almost every days, my orientation in the last 3 moths has been in compare when I was young:

	same or better	little worse	much worse	significantly worse	

At the places which I have visited several times a year, my orientation in the last 3 moths has been in compare when I was young:

	same or better	little worse	much worse	significantly worse	

I have had to ask for the right way more often than before in the last 3 months:

	never	less than once a week	approximately once a week	several times a week	every day

I have had difficulties with orientation in my supermarket in the last 3 months:

	never	less than once a week	approximately once a week	several times a week	every day

Because of my worries I get lost, I have had to:

		yes	no
	reduce traveling out of my town.	yes	no
	reduce traveling to my relatives and friends	yes	no
	reduce the activities around my home (shopping, go to post, etc.)	yes	no

Figure 1: Subjective spatial navigation complaints questionnaire.

samples t-test and one way analysis of variance with post hoc Tukey's test). The χ^2 test evaluated differences in proportions (gender). To assess for the influence of depression and anxiety on SSNC scores irrespective of age, gender, education, the real SN performance and cognitive status, we used an ordered logistic regression. Specifically, the SSNC global score was entered into ordered logistic regression model as the outcome variable with the GDS and BAI scores being the main independent variables.

We also examined whether the association between BAI and SSNC was modified by GDS by creating a categorical variable to reflect combinations of anxiety and depression using the median for BAI ($\leq$

10) and GDS (≤ 4) as follows: not anxious/not depressed (0; reference), anxious/not depressed (1), not anxious/depressed (2) and anxious/depressed (3). We controlled for the same covariates as in the main regression model.

Results

There were no differences in GDS and BAI scores between MCI and SCD groups. As expected, the MCI group performed worse in the real SN testing in both egocentric (p<0.001) and allocentric (p<0.001) navigation tasks compared to SCD group. However, MCI subjects did not report more SSNC than SCD subjects (p=0.916) (Table 1 for the characteristics of the MCI and SCD groups).

When we performed ordered logistic regression including all the subjects using SSNC global score as dependent variable and GDS and BAI score as an independent variable, anxiety significantly increased the likelihood of reporting more spatial navigation complaints controlling for cognitive status, real SN performance, and depression (Estimate=0.077, p<0.001). In the same model, the association between depression and the likelihood of reporting spatial navigation complaints was not statistically significant (Estimate=-0.069, p=0.311). When age, gender, and education were also controlled (Appendix 1), greater anxiety was still associated with an increased likelihood of reporting spatial navigation complaints (Estimate=0.105, p=0.003; Appendix 1). Depression showed the opposite trend, whereby greater depression was related to lower likelihood of reporting spatial navigation complaints when all study covariates and anxiety were controlled, although this association was not statistically significant (Estimate=-0.196, p=0.079).

In order to learn more about the effect of depression and anxiety on subjective perception of spatial navigation deficit we divided the sample regardless of cognitive status based on median BAI (≤ 10) and GDS (≤ 4) scores into 4 groups – not anxious/not depressed (n=44), anxious/not depressed (n=18), not anxious/depressed (n=13) and anxious/depressed (n=34). These 4 groups characterized by GDS and BAI scores did not differ in age, MMSE score or the real SN performance. The main characteristics of these 4 groups are displayed in Table 2. Results with "anxiety/depression" combinations as the main independent variable are shown in Appendix 2. We found that those in the anxious/not depressed group were significantly more likely to report spatial navigation complaints than those in the not anxious/not depressed group (Estimate=2.011, p=0.012). In addition, we observed greater likelihood of spatial navigation complaints in the anxious/depressed group, but this result did not reach our preset threshold for statistical significance (Estimate=1.039, p=0.078).

Discussion

We found that anxiety rather than depression influenced subjective

	SCD N=52	MCI N=71	p
Gender M/F	19/33	29/42	0.629
Age/years	68.3 ± 9.3	71.6 ± 9.5	0.035
MMSE	28.3 ± 1.2	26.5 ± 2.6	<0.001
GDS	3.9 ± 3.1	4.9 ± 3.8	0.079
BAI	12.0 ± 9.0	14.8 ± 12.9	0.153
Real SN egocentric	22.6 ± 9.2[1]	40.2 ± 31.3[1]	<0.001
Real SN allocentric	36.7 ± 20.2[1]	67.5 ± 35.3[1]	<0.001
SSNC score	3.4 ± 4.8	3.8 ± 5.8	0.916

Table 1: Characteristics of SCD and MCI groups. Note: [1]Mean distance from the correct position of the goal in cm; MMSE: Minimental state evaluation; GDS: Geriatric depression scale; BAI: Beck anxiety inventory); Normal ranges: MMSE 27-30, GDS 0-4, BAI 0-10, BVA ego 0-29, BVA allo 0-39, SSNC - not set.

Groups	Normal n=44	Depressive n=13	Anxious n=18	Anxious/ Depressive n=34	p
Gender M/F	26/18	3/10	8/10	11/37	0.003
Age	70.3 ± 9.9	71.5 ± 8.3	70.7 ± 7.7	69.4 ± 10.3	0.987
MMSE	26.9 ± 2.5	27.9 ± 1.7	28.1 ± 2.1	27.2 ± 2.1	0.152
Real SN egocentric	32.9 ± 25.2[1]	28.2 ± 28.9[1]	21.1 ± 7.2[1]	38.0 ± 28.9[1]	0.079
Real SN allocentric	55.5 ± 33.6[1]	57.7 ± 38.2[1]	40.4 ± 35.1[1]	57.0 ± 30[1]	0.091
SSNC score	2.4 ± 4.1	1.1 ± 1.5	4.6 ± 5.0*[†]	5.2 ± 6.6**[†]	0.008

Table 2: Groups according to depression and anxiety (median GDS ≤ 4, median BAI ≤ 10). Note: **p<0.01, *p<0.05 (compared to normal group); [†]p<0.05 (compared to depressive group); [1]Mean distance from the correct position of the goal in cm; MMSE (Minimental state evaluation); Normal ranges: MMSE 27-30, GDS 0-4, BAI 0-10, BVA ego 0-29, BVA allo 0-39, SSNC - not set.

perception of SN abilities in non-demented elderly, regardless of age, sex, education, real-space SN performance and objective cognitive abilities. We also found that the association between anxiety and SSNC did not vary as a function of depression, but rather that the association between anxiety and SSNC showed a relatively consistent magnitude across levels of depression. Finally, we found that SSNC scores were not reliably related to age and gender of participants. We also found that higher education was associated with greater SSNC, but this relationship did not reach statistical significance (p=0.068). It may be that more educated individuals are more aware of spatial navigation problems, possible as a result of greater daily geographical mobility.

In our study, patients with SCD did not have impaired SN performance, which is in agreement with our previously published data where SCD subjects performed similarly to healthy controls [38] and patients with MCI had similar quality and magnitude of SN impairment as patients with mild AD[34,35]. Interestingly, the difference in the real performance in Blue Velvet Arena was not reflected by a difference of SSNC total score between these two groups, MCI subjects did not report generally more difficulties than SCD subjects in the SSNC questionnaire. This corresponds to the findings from cross-sectional studies on non-demented elderly where subjectively perceived memory problems do not usually reflect a true cognitive deficit[4,5,8]. However, some limitation of those studies might be a different sensitivity of the psychometric tools used for the detection of the underlying cognitive deficit in memory complainers [39]. In this regard, studies with SCD subjects suggest that not all cognitive complaints are of equal significance for the risk of future cognitive decline; hence it is important which questions are asked [40]. More research is needed to determine which concrete complaints may be most significant for future cognitive decline and which are purely associated with anxiety. Our cross sectional data do not allow to analyze weather SSNC which is not associated with anxiety would lead to increased risk of dementia, however this is going to be a question of farther research using data from the longitudinal follow up of these patients.

It is also well documented that memory complaints are often associated with depression [5,7,8]. Therefore, it was surprising that we did not observe such an effect of depression on subjective SN complaints. The post hoc analyses revealed that most of the SSNC were anxiety driven. The finding that greater depressive symptoms were associated with lower likelihood of spatial navigation complaints, albeit not significantly, also deserves comment. It may be that more depressed patients live in a more restricted life-space, hence not "testing" their spatial navigation in real life situations as much as individuals with low depressive symptoms. This finding also provides additional evidence for the notion that anxiety rather than depression may be the more reliable indicator of spatial navigation problems.

The relationship between anxiety and memory complaints, or between anxiety and SN complaints, has been studied in few studies. In a study with 283 community-dwelling people in which authors examined correlations of personality variables of conscientiousness and neuroticism in relation to subjective memory in older adults, anxiety together with self-consciousness explained almost one third of the variance in subjective memory complaints while only 4% unique variance was associated with the objective memory measure [9,10].

On a practical level, subjective memory complaints may interfere with activities of daily living and quality of life in a different way. Those with subjective SN complaints, rather than subjects with subjective memory complaints, may be more fixed to their home environment resulting in reduced capacity of independent shopping, socializing or searching for medical services. These are the reasons why SN capacity and its objective grounding should be of a thorough and separate assessment beyond and above of subjective memory complaints. The focus on patients' history and self-reporting including that of subjective memory complaints and subjective SN complaints combines benefits of easy to perform and potentially efficient screening tool.

Another issue is every day functioning of individuals with anxiety. Regardless of their otherwise preserved memory and navigational abilities, individuals with increased anxiety might be avoiding situations in which they feel insecure and this might have an impact on their quality of life.

There are some limitations. The self-reported questionnaire may have a ceiling effect for MCI subjects, whereby we may have observed more severe complaints in this group otherwise. In addition, decreased awareness of cognitive problems in cognitively impaired individuals (i.e., anosognosia) may have affected the results. We found that MCI patients and participants with SCD did not differ with respect to anxiety, depression, or memory complaints. We also found that patients with MCI performed worse on the objectively measured navigation tasks, suggesting possible lack of awareness of spatial navigation problems in the MCI subgroup. Future research should examine this possibility.

Conclusion

General subjective complaints about SN performance do not distinguish patients with MCI with objective cognitive decline from subjects with SCD reporting memory complaints but no impaired cognition. Depression but mainly anxiety appears to play a role in subjective perception of navigational skills. Our results suggest that screening for anxiety, and not only for depression, may be useful to elucidate the relevance of subjective cognitive complaints in elderly, specifically SSNC. In the clinical setting, specific questions may yield different clinically useful information as it needs not reflect functional impairment, but may be associated with anxiety. This is important in the context that otherwise SSNC may be associated with real SN deficits which are present early in AD and which may interfere with quality of life and everyday functioning. Decision-making on further examination and management of non-demented subjects who frequently report SSNC needs to consider anxiety as an important contributor to patients' way of self-assessment.

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Meditation's impact on cognitive functions in mild cognitive impairment: A pilot study

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Background. Effect of meditation on various domains of cognition in aging and patients at risk of dementia is receiving growing attention. The potential of mindfulness to reduce, slow down or prevent cognitive decline in patients with high risk of developing dementia is a curious topic of discussion with vast clinical implications. However, the effect of Mindfulness-Based Interventions (MBIs) on cognitive functions in patients with cognitive decline is very poorly understood.
Aim. The aim of this study was to examine effects of Mindfulness-Based Stress Reduction (MBSR) program on cognitive functions in patients with mild cognitive impairment (MCI).
Methods. 14 MCI patients participated in the program. The severity of their cognitive decline was assessed by CogState cognitive tests.
Results. Results showed that, when comparing values before and after completing MBSR, MCI patients significantly improved in cognitive task assessing psychomotor functions, but not in tasks assessing attention, visual learning, or working memory.
Conclusion. Data suggest that mindfulness may positively influence certain cognitive domains in MCI patients. However, further studies with larger sample size, follow-up data and active control group are needed.

Key words: mindfulness, meditation, cognition, MCI, neurodegeneration, Mindfulness-Based Stress Reduction

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INTRODUCION

Prevalence of dementia increases every year due to the increasing age of the world's population. It has been predicted that number of people with dementia may double every 20 years[1]. Most common cause to dementia are neurodegenerative diseases, especially Alzheimer's disease (AD) (ref.[2]). Considering that there is no current cure for this disease, multiple studies are searching for preventative strategies that could effectively delay its onset. It has been stated that such prevention may even be more effective than current pharmacological treatment[3,4]. Mild Cognitive Impairment (MCI), the symptomatic pre-dementia stage, has been an object of multiple trials in hope finding an effective therapy to slow down, or even prevent the progression to AD (ref.[5]).

There is a growing interest in studying effects of meditation as a potential strategy for preventing cognitive decline[6,7]. Interventions using meditation techniques based on the concept of mindfulness have been the mostly researched[7]. Mindfulness refers to awareness emerging through paying attention, purposely, in the present moment, and without judgement to the unfolding of experience moment by moment[8]. Systematic review discussing the topic of effect of mindfulness-based interventions (MBIs) on cognitive functions showed that MBIs might influence various domains of cognition, such as attention, memory and executive functions[9]. There is, however, very limited number of studies assessing the effect of MBIs

on cognition in MCI (ref.[10]). Data from one study examining 7 MCI patients have suggested trend towards improvement of cognition[11], assessed by Alzheimer's Disease Assessment Scale cognitive subscale. This subscale, widely used in AD, has, however, been reported to be less responsive to change when used in patients with MCI (ref.[12]). The same study has also reported increased functional connectivity between the left hippocampus, posterior cingulate cortex and bilateral medial prefrontal cortex and trends of less hippocampal volume atrophy when compared to control participants. Authors concluded that MBSR may reduce hippocampal atrophy and improve functional connectivity in the brain areas also mostly affected by AD. It has also been concluded that further studies with larger sample size are needed[13].

The aim of this prospective study was to examine effects of MBSR on cognitive functions in MCI and to expand our knowledge about which cognitive domains are mostly influenced.

METHODS

Patients diagnosed with MCI were selected from the Czech Brain Aging Study (for details, see table 1), epidemiological study based on longitudinal follow up of non-demented older subjects with cognitive complaints. 109 patients with MCI were invited over the phone to participate in this study. 14 participants accepted the invitation.

The sample consisted of 9 men and 5 women, aged 65-85 years (M = 74.36, SD = 7.24).

Participants were tested twice, immediately prior to commencement of the 8-week MBSR course and then again 2-3 days after its completion. Four computer CogState cognitive tests were administered assessing: attention (Identification Test), psychomotor functions (Detection Test), visual learning (One Card Learning Test), working memory (One Back Test) (ref.[14]). CogState tests are designed for repeated administration with minimal practice or learning effects, so it was possible to use them repeatedly in 8 weeks' distance.

Table 1. Study sample.

Participants	
n	13
Gender	8 male, 5 female
	Average ± Standard deviation
Age	74.69 ± 7.42
Years of education	14.38 ± 3.15

Statistical analysis

One patient was further eliminated as an outlier. Statistical analysis was therefore conducted on 13 patients. To compare pre-intervention and post-intervention values within the group, Wilcoxon test was used. Statistical analysis was performed using R and RStudio and the chosen significance level was α = 0.05.

RESULTS

Preliminary data analysis (see Table 2.) showed that comparison of pre-intervention and post-intervention values within the group revealed that MCI patients showed significant improvement of CogState Detection Test (observed P-value 0.0479). Values from CogState Identification Test, One Card Learning Test and One Back Test did not show any significant differences before and after the therapy.

Table 2. Results.

Task	P
Cogstate DET	0.0479
Cogstate IDN	0.3396
Cogstate OCL	0.6355
Cogstate OBT	0.8241

DET - Detection Test, IDN - Identification Test, OCL - One Card Learning Test, OBT - One Back Test

DISCUSSION

This study linked up to previous research[11] by assessing a curious, but insufficiently researched topic of impact of mindfulness on cognitive functions in MCI. By almost doubling the sample size in comparison to previous research[11] and by measuring various domains of cognition we were able to deepen our insight into possible impact of meditation on cognition in elders suffering from cognitive decline. Data suggest that participation in MBSR might be related to an improvement of psychomotor functions, but not in other domains, such as attention, visual learning, or working memory. Previous research on MCI have showed trend towards improvement in cognition[11] in task which primarily assesses global cognition in response to antidementia therapies[12]. By using cognitive tests which have been previously defined as useful for identifying memory impairment related to MCI and no learning effect[15], we have been able to assess a topic of mindfulness's impact on cognition more thoroughly. Our data suggest that mindfulness might influence certain aspects of cognition in MCI and might therefore be relevant when considering non-pharmacological approach to cognitive decline in this population.

These preliminary results stimulate need for future research of this topic in order to better understand the impact and relevance of meditation for MCI. Major limitation when interpreting these preliminary data is a current lack of data from an active control group, which makes it difficult to estimate the difference between test-retest effect, placebo effect and effect of MBSR intervention. There is a need for further studies, that would use larger sample size, compare results with an active control group and to make follow-up measurements later after the intervention has ended. Another topic curious topic to be researched is how to effectively deliver MBI with respect to particular characteristics of this population - manuscript assessing data related to this topic has already been submitted for review. Even though an adapted mindfulness intervention for patients suffering from dementia has been found feasible in past, authors declared that before adapted implementation is widely recommended, there is a need for more research to further assess its effectiveness[16].

CONCLUSION

This pilot study found that elders with MCI completing MBSR may improve in cognition, particularly in psychomotor functions. Despite limitations of these preliminary results, such as small sample size, non-comparison to active control group, and current lack of follow-up data, this study is a next step towards revealing the question of impact of MBI on cognitive functions in those, who are already diagnosed with onset of cognitive decline.

Ethical approval

This study has been approved by ethics committee of St. Anne's University Hospital. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Auhor contribution: RS: manuscript writing, data interpretation, mindfulness state assessment; KS: creating study protocol, data interpretation, manuscript writing; RM: data interpretation, neuropsychological examination, manuscript writing; AJ: teaching MBSR intervention; MJ: data analysis, tables; JH: data interpretation, management of research group.

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