

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

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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 months 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 months 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:					
	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'	40.2 ± 31.3'	<0.001
Real SN allocentric	36.7 ± 20.2'	67.5 ± 35.3'	<0.001
SSNC score	3.4 ± 4.8	3.8 ± 5.8	0.916

Table 1: Characteristics of SCD and MCI groups. Note: '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'	28.2 ± 28.9'	21.1 ± 7.2'	38.0 ± 28.9'	0.079
Real SN allocentric	55.5 ± 33.6'	57.7 ± 38.2'	40.4 ± 35.1'	57.0 ± 30'	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); '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 whether 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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