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Spatial orientation tasks show moderate to high accuracy for the diagnosis of mild cognitive impairment: a systematic literature review

Tarefas de orientação espacial têm acurácia moderada a alta para o diagnóstico de comprometimento cognitivo leve: uma revisão sistemática

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ABSTRACT

Spatial disorientation has been observed in mild cognitive impairment (MCI) and is associated with a higher risk of progression to Alzheimer's disease (AD). However, there is no gold standard assessment for spatial orientation and paper-and-pencil tests lack ecological validity. Recently, there has been an increasing number of studies demonstrating the role of spatial disorientation as a cognitive marker of pathological decline, shedding new light on its importance for MCI. This systematic review aimed to investigate the accuracy of spatial orientation tasks for the diagnosis of MCI by comparison with cognitively healthy elderly. The search was conducted in the databases Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed), Web of Science, Scopus, Excerpta Medica Database (Embase), Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs) and Scientific Electronic Library Online (SciELO). Only original studies reporting spatial orientation assessment in MCI patients compared to a healthy control group were included. Studies were excluded if the MCI classification did not follow well described criteria and/or if accuracy results of spatial orientation assessment were not provided. Seven studies met the eligibility criteria, describing a variety of spatial orientation assessments including questionnaires, paper-and-pencil, office-based route learning, and computer-based and virtual reality tasks. Spatial orientation tasks demonstrated moderate to high accuracy in detecting elderly with MCI compared to cognitively healthy elderly, with areas under the curve (AUC) ranging from 0.77 to 0.99. However, important methodological issues were found in the selected studies which should be considered when interpreting results. Although the inclusion of spatial orientation assessments in MCI evaluations seems to have significant value, further studies are needed to clarify their true capacity to distinguish pathological from non-pathological aging.

Keywords: Cognitive Dysfunction; Orientation, Spatial; Spatial Navigation; Alzheimer Disease; Sensitivity and Specificity.

RESUMO

A ocorrência de desorientação espacial foi observada no comprometimento cognitivo leve (CCL) e está associada a um maior risco de progressão para a doença de Alzheimer (DA). No entanto, não há um padrão ouro para avaliação da orientação espacial e os testes em papel e caneta não apresentam validade ecológica. Recentemente, um número cada vez maior de estudos têm apontado o papel da desorientação espacial como um marcador cognitivo do declínio patológico, lançando uma nova luz sobre sua importância para o CCL. Esta revisão sistemática teve como objetivo investigar a acurácia de tarefas de orientação espacial para se estabelecer o diagnóstico de CCL entre idosos cognitivamente saudáveis. A pesquisa foi realizada através das bases de dados Medline/PubMed, Web of Science, Scopus, Embase, Lilacs e Scielo. Apenas artigos originais que reportassem avaliação da orientação espacial em idosos CCL comparados a um grupo controle saudável foram incluídos. Foram excluídos os estudos que não utilizassem a classificação de CCL segundo critérios bem

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Authors' contributions: RQMC and LAPV conducted the review and independently selected papers based on the eligibility criteria. SMDB arbitrated any unresolved disagreements at that stage. RQMC and LAPV read the selected papers in full and wrote the manuscript supervised by SMDB and JEP. SMDB and JEP revised the final version of the manuscript.

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descritos e/ou que não reportassem resultados de acurácia da avaliação da orientação espacial. Sete estudos atenderam aos critérios de elegibilidade, descrevendo uma variedade de formas de avaliação da orientação espacial, incluindo questionários, tarefas em papel e lápis, tarefas de aprendizado de rotas no escritório, tarefas baseadas em computador e com realidade virtual. As tarefas de orientação espacial demonstraram acurácia moderada a alta na detecção de CCL em comparação com idosos cognitivamente saudáveis, com áreas sob a curva (*area under the curve* — AUC) variando de 0,77 a 0,99. No entanto, um viés metodológico importante foi identificado nos estudos selecionados, o que deve ser levado em consideração na interpretação dos resultados. Apesar da inclusão da orientação espacial na avaliação cognitiva em CCL parecer ter um valor significativo, mais estudos são necessários para esclarecer sua verdadeira capacidade de distinguir o envelhecimento patológico do não patológico.

Palavras-chave: Disfunção Cognitiva; Orientação Espacial; Navegação Espacial; Doença de Alzheimer; Sensibilidade e Especificidade.

Mild cognitive impairment (MCI) is a heterogeneous clinical entity, currently the focus of multiple research studies aiming to identify preclinical stages of Alzheimer's disease (AD) and other dementias[1,2]. Diagnosis of MCI is established in the presence of a cognitive complaint, along with an objective measure of cognitive impairment, without any evidence of functional decline or impairment in activities of daily living (*i.e.* in the absence of dementia)[3]. According to the type of cognitive impairment presented, MCI patients can be classified into amnestic MCI (aMCI), if memory is considered impaired, or non-amnestic MCI (naMCI) if other cognitive domain(s) is/are considered impaired, but memory is not affected[3].

Spatial disorientation, defined as a defect in the ability to establish relations among positions, directions, movements of objects, and points in space, has been frequently reported in AD, commonly being one of the earliest symptoms[4,5,6,7]. Several studies have also demonstrated spatial disorientation in MCI patients, with a prevalence as high as 41.4%[8,9,10,11]. Changes in hippocampal volume or metabolism, considered particularly important predictors of conversion from MCI to AD, are known to mediate spatial orientation skills[9,12,13,14]. It has been hypothesized that spatial disorientation in MCI patients could reflect an underlying neurodegenerative process in key areas for AD pathology, which would justify its inclusion in regular cognitive evaluation[5,11,15,16].

In order to assess spatial orientation abilities, investigators should keep in mind that, besides preserved visual and spatial perception as well as attention and executive functions[16,17,18], the ability to orient oneself in familiar and unfamiliar surroundings encompasses two different kinds of spatial orientation: egocentric and allocentric. Egocentric orientation involves self-centered navigation and includes sensorimotor information about the position of the body in space, providing spatial information from the viewpoint of the navigator[16,19]. Allocentric orientation, on the other hand, results from the survey perspective of the environment. It includes the positions of landmarks relative to other salient aspects of the surroundings, as well as distances and directions estimated by the navigator[5,16]. Contrary to egocentric orientation, allocentric representations are centered on the object rather than the observer and depend on the formation and use of a cognitive map[16,17]. For an individual to navigate successfully, both kinds of processing — egocentric and allocentric reference frames — must be preserved[16,19].

Key brain regions, affected early by the pathological accumulation of plaques and tangles in AD, are involved in spatial orientation processing and are consistent with navigational deficits[20,21]. Allocentric orientation is mediated by the medial temporal lobe, particularly the hippocampus, whereas egocentric orientation processing relies on the integrity of parietal lobe structures[13,22]. Recently, a study by Peter et al.[14] described that subregions CA1/2 of the right hippocampus were predictive of participant performance in an ecological route-learning task, whereas the right hippocampal tail seemed to be involved only in aMCI participants. In addition, the retrosplenial cortex, which has also been implicated in AD pathology, plays a particular role in the integration of allocentric and egocentric information, allowing the formation of an efficient path and orientation strategy[19,23,24].

There are multiple ways to assess spatial orientation, and to date, there is no gold standard. Investigators have used questionnaires, traditional paper-and-pencil testing, real-world route learning or landmark recall, map drawing, and even virtual reality[25,26,27]. A growing number of research groups are creating new ways to test spatial orientation skills and several new tasks have been proposed over the years[10,28,29,30,31].

With new spatial orientation tasks and the increasing number of studies investigating the role of spatial orientation deficits in MCI, it is important to understand the predictive power of spatial orientation deficits for differentiating pathological from non-pathological aging[12,16,32,33,34]. Following this line of thought, the current systematic review aimed to investigate the accuracy of spatial orientation tasks for the diagnosis of MCI among cognitively healthy elderly (CHE).

METHODS

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[35] and the review protocol was registered at the international

prospective register of systematic reviews (PROSPERO), under registration number CRD42018110616.

Eligibility criteria

Only original studies reporting spatial orientation assessment (using either traditional or innovative tasks) in MCI patients compared to a control group of CHE (*i.e.* without a diagnosis of MCI, stroke, dementia, or another neurodegenerative process) were included. Studies were excluded if they: (1) investigated a sample of participants with MCI in other disorders and/or not classified according to Petersen's criteria; (2) focused on intervention or rehabilitation rather than diagnostic features; (3) focused on imaging findings and did not describe participants' performance in spatial orientation tasks; (4) did not use any statistical method to report the diagnostic accuracy of spatial orientation performance by group (MCI *vs.* CHE); (5) were case series and case reports; (6) provided empirical data reported for a second time; or (7) were not written in English or Portuguese languages.

Search strategy and study selection

A systematic literature search was conducted for studies that assessed the accuracy of spatial orientation tasks for the diagnosis of MCI in the international databases Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed), Web of Science, Scopus, Excerpta Medica Database (Embase), and the Latin-American databases Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs) and Scientific Electronic Library Online (SciELO) in June 2019 using the index terms or descriptors for the keywords "aged" and "spatial orientation" and "sensitivity and specificity" and "mild cognitive impairment". To provide an example of the search strategy utilizing the descriptors for the keywords mentioned above, in the Web of Science database the final strategy was "TÓPICO:(Aged OR Elderly OR Older adult OR Older adults OR Older people OR Elder OR Elders) AND TÓPICO:(Orientation, Spatial OR Spatial Orientation OR spatial navigation OR spatial visualization OR spatial ability OR spatial orientation assessment OR visual-spatial ability test OR visual-spatial ability testing OR mental navigation tests) AND TÓPICO:(sensitiv* OR sensitivity and specificity OR diagnose OR diagnosed OR diagnoses OR diagnosing OR diagnosis OR diagnostic OR diagnosis, differential) AND TÓPICO:(Cognitive Dysfunction OR cognitive decline OR cognitive impairments OR cognitive impairment OR mental deterioration OR mild cognitive impairment OR mild neurocognitive disorder OR cognition disorders OR cognition disorder)".

Two of the authors (R.Q.M.C. and L.P.V.) independently screened the titles and abstracts of all papers according to the pre-established eligibility criteria. Those studies not excluded in the first screening were read in full for further evaluation. The two authors discussed any disagreement about the inclusion of a study, and a third senior author (S.M.D.B.) arbitrated any unresolved disagreements.

Data collection and methodological quality assessment

One review author (R.Q.M.C) extracted the data listed below from the included studies and a second author (L.P.V) checked them. Data was extracted into a data extraction sheet (using Microsoft Excel® version 2013) and included first author's name, year of publication, study title and journal, number of participants in the MCI and CHE groups, participant characteristics in each group (including number of women, age, and years of education), MCI classification (aMCI, naMCI or indistinct), name given by the author to the spatial orientation task(s), type and/or setting in which the task was performed (questionnaire, paper-and-pencil test, computer-based task, virtual reality or real-world task), task's classification as ecological or non-ecological, and results from the accuracy analysis. It should be mentioned that if the study provided results from different subgroups of MCI participants, only data from the aMCI subgroup was considered for extraction (and not from naMCI or comorbid MCI participants). Authors of included studies were contacted for additional information or clarification when needed.

To identify risk of bias and applicability concerns in the selected studies, a methodological quality assessment was performed according to the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) protocol[36]. Risk of bias was assessed in the following four domains: (1) patient selection, (2) index test, (3) reference standard, and (4) flow and timing. Applicability concerns were evaluated in domains (1), (2) and (3) only. Both reviewers (L.P.V. and R.Q.M.C) independently scored the included studies. Disagreements were discussed and resolved.

For the qualitative review, the primary outcome measure was accuracy of the spatial orientation task for the correct identification of the MCI group compared to the CHE group (reported as area under the curve — AUC, sensitivity and specificity or Odds Ratio — OR). Meta-analysis was conducted if risk of bias across studies was deemed low and if variation across study outcomes was considered adequate.

RESULTS

Using the search strategy described above, 2,629 studies were found. One was identified through additional sources (reference lists). After removal of duplicates, 2,225 studies remained. Seven matched the eligibility criteria and were included in the final qualitative review (Table 1). All papers included in the final review were considered diagnostic case-control studies, since MCI diagnosis was based on the criteria developed by Petersen et al.[3] prior to the experimental spatial orientation assessment. The selection flow diagram is summarized in Figure 1.

Table 1. Studies selected for qualitative review.

Study (ref)	Sample						Spatial task	Assessment type or task setting	Assessment classification	Accuracy		
	MCI (n)	CHE (n)	MCI classification	Women (n)	Age (M±SD)	Education, years (M±SD)				AUC (SE)	Sens × Spec	OR
				MCI / CHE	MCI / CHE	MCI / CHE						
Caffò et al.[40]	51	53	aMCI	32 / 29	71.15±5.0 / 68.06±6.0	7.78±4.4 / 9.7±4.3	Virtual reorientation task	Virtual reality	Ecological	0.90 (0.03)	0.80 × 0.94	-
Cerman et al.[31]	61	13	aMCI	31 / 8	71.96±8.7 / 69.54±4.0	14.25±3.2 / 15.54±2.1	Subjective spatial navigation complaints	Questionnaire	Non-ecological	-	-	2.43
Howett et al.[41]	45	41	N/A	33 / 26	71.7±8.3 / 69.3±7.5	14.2±3.4 / 14.8±3.6	Path integration task	Virtual reality	Ecological	0.82 (0.04)	0.84 × 0.68	-
Mitolo et al. [25]	20	14	N/A	10 / 10	74.75±6.9 / 68.64±4.5	7.85±4.4 / 8.57±4.9	Objects recognition and location (Location subtest)	Paper-and-pencil	Non-ecological	0.94 (0.03)	-	-
							Map learning (first location subtest)	Paper-and-pencil	Non-ecological	0.88 (0.06)	-	-
							Route learning (from vision subtest)	Office-based route learning	Ecological	0.91 (0.05)	-	-
							Route learning (from action subtest)			0.90 (0.06)	-	-
							Sense of direction questionnaire	Questionnaire	Non-ecological	0.77 (-)	-	-
Ritter et al[33]	11	15	aMCI	6 / 9	63.4±3.6 / 62.2±4.6	13.1±3.1 / 11.9±3.3	Topographical recognition memory test	Paper-and-pencil	Non-ecological	-	0.64 × 0.73	-
Tarnanas et al.[38]	25	25	aMCI	18 / 20	78±4.7 / 77.2±4.9	5±1.9 / 5±1.7*	Virtual action planning museum (Egocentric query)	Virtual reality	Ecological	-	0.94 × 0.73	-
							(Allocentric query)			-	0.92 × 0.97	-
Wang et al[37]	30	30	aMCI	14 / 14	73.7±7.4 / 71.0±7.0	8.43±3.4 / 8.93±4.1	Modified spatial-context memory test	Computer-based	Non-ecological	0.99 (0.007)	-	-
							Spatial location memory subtest			0.90 (0.77)	-	-

MCI: mild cognitive impairment; CHE: cognitively healthy elderly; aMCI: amnestic mild cognitive impairment; M: mean; SD: standard deviation; SE: standard error; AUC: area under the curve; Sens: sensitivity; Spec: specificity; OR: *Odds Ratio*; N/A: no classification reported; *education results provided as "level of education" instead of total years; (-) no information provided.

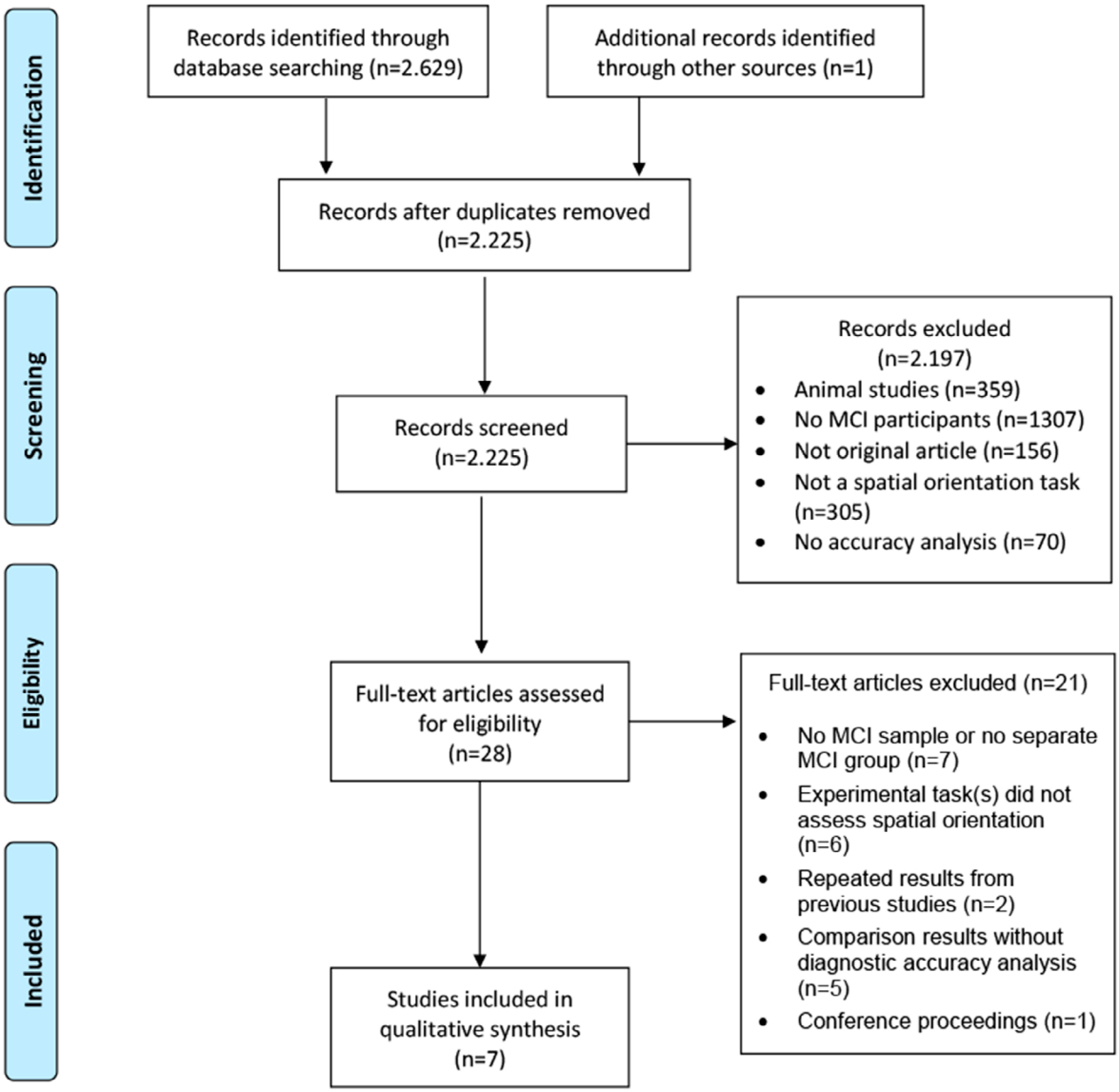

Figure 1. Selection flow diagram.

Qualitative review

All seven studies selected for the qualitative review were case-control, observational and published in English. Participants' mean age varied between 62.2 (±4.6) to 78 (±4.7) and mean years of education ranged from 7.78 (±4.4) to 15.54 (±2.1). One study reported the education of participants in levels rather than total years. Five had a group of aMCI participants (either the MCI sample was composed of only aMCI or the study included a subgroup of aMCI) and two did not further stratify MCI participants into aMCI or naMCI (Table 1).

Because studies' spatial orientation tasks, participants, and reported outcome measures varied markedly, we focused on describing their findings, kinds of tasks used, accuracy results, applicability, strengths and limitations in a qualitative synthesis rather than a meta-analysis. Moreover, methodological quality assessment identified considerable risk of bias (Table 2). Reported results were considered to be influenced by selection and information bias, therefore summarizing data was not recommendable.

The following section will stratify results from the selected studies by categorizing spatial orientation tasks (index test) into three different sections: (1) traditional paper-and-pencil tests or questionnaires; (2) computer-based tests; and (3) ecological tests.

Spatial orientation assessment using traditional "paper-and-pencil" tests or questionnaires

One manuscript was selected which used "paper-and-pencil" tests, one employed questionnaires and one relied

Table 2. Methodological quality assessment using the Quality Assessment of Diagnostic Accuracy Studies 2 tool.

First author	Risk of BIAS				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Ritter, E.	High	Unknown	Low	Low	Low	Low	Low
Wang, H.	High	High	Low	Low	Low	Low	Low
Caffò, A.	High	High	Low	High	Low	Low	Low
Mitolo, M.	High	High	Low	Low	Low	Low	Low
Howett, D.	High	High	Low	Low	Low	Low	Low
Tarnanas, I.	High	High	Low	Unknown	Low	Low	Low
Cerman, J.	High	High	Low	Unknown	Low	Low	Low

High Unknown Low

Domains from the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) second version. Each domain is assessed in terms of risk of bias, and the first three domains are also assessed in terms of concerns regarding applicability, presented here separately.

on both kinds of assessment[25,31,33]. Descriptions are detailed below to provide a better understanding of these approaches.

Cerman et al.[31] proposed a spatial orientation questionnaire focused on navigation impairment reported by participants in the previous three months. The 15-item sheet explored complaints of self-perceived spatial navigation decline in familiar and unfamiliar surroundings, as well as its direct impact on daily functioning. The questionnaire severity scores were demonstrated to be a significant factor for diagnostic category prediction in the aMCI group (OR=3.64; p=0.014), but not in the naMCI group (OR=6.41; p=0.055), when controlled for age, sex, education and anxiety levels[31].

Ritter et al.[33] proposed a topographical recognition memory test for the detection of MCI, while accounting for the influence of depressive symptoms. As argued by the research group, topographical recognition tasks selectively recruit the parahippocampal gyrus — involved in the pathological process of AD, but not in major depression — in contrast to commonly used verbal recall memory tasks. The topographical recognition memory task (TRMT) consisted of 30 color photographs of places, which participants were required to recognize and select immediately after using a three-choice format. As predicted by the group, the "aMCI" group factor, but not the "Depression" group factor had a significant effect on the TRMT scores. In addition, when using a cut-off score of 1.5 standard deviation (SD) below the control group mean score in the TRMT, the task correctly classified 65% of aMCI (among which 63.6% without comorbid depression and 66.8% with depression). To provide a comparison, a 12-word-list immediate recall task was able to correctly classify only 30% of aMCI (among which 36.4% without comorbid depression and 22.2% with depression)[33].

Mitolo et al.[25] investigated several aspects of visuospatial memory and orientation abilities. Among the different tasks used, the object recognition and location test, the self-rating spatial questionnaire, and the Map Learning task are detailed in this section. The object and location test consisted of showing participants a picture of a room with twelve objects. After studying the picture carefully, participants were asked to recall all twelve objects and locate them in a picture of the same room, now empty. Receiver Operating Characteristic (ROC) curve analysis showed elevated discriminative power for the object location phase of this test, with an AUC of 0.94 (95% confidence interval [95%CI] 0.86–1.00). The Spatial questionnaire used by Mitolo et al. comprised four categories: *attitude toward spatial environmental tasks*, *spatial anxiety*, *self-efficacy toward environmental tasks* and *sense of direction*. The questionnaire demonstrated weaker discriminative power compared to the object location test, with an AUC of 0.77 for the *sense of direction* category.

The Map Learning test involved eight landmarks on a map (e.g., pharmacy, school, cinema). After looking at the map for five minutes, participants were asked to write down all the landmarks they remembered and to locate each in its correct position on the map. The task showed high classification accuracy for MCI compared to cognitively healthy elderly, with an AUC of 0.88 (95%CI 0.75–1.00)[25].

Spatial orientation assessment using computer-based tests

Wang et al.[37] described a computer-based modified Spatial-Context Memory Test (SCMT) in a group of aMCI participants. One subtask of the SCMT, in which participants were shown a city map with different blocks of buildings, investigated spatial location memory. After selecting one specific block with a flashing red dot, participants were shown the image of a particular building — present on that block. This sequence was shown six times. A query stage then began, in which participants were asked to recall where each building should be found on the city map. In general, the computer-based modified SCMT was considered effective for distinguishing aMCI from cognitively healthy elderly.

Specifically, the subtask of spatial location memory had an AUC of 0.90 (95%CI 0.82–0.98) and was demonstrated to be of great value for detecting aMCI compared to cognitively healthy elderly[37].

Ecological assessment of spatial orientation

In the study from Tarnanas et al.[38], a real archeological museum (the Museum of Aiani in Greece) was reproduced in a virtual environment, so participants could explore exhibitions and navigate freely. After becoming familiar with the equipment and virtual surroundings, they were given a list of five archeological artifacts with written directions on how to locate them. Once this part of the task was completed, participants were asked to verbally recall different aspects of the items, as well as details of where they were found. Taking into account only the spatial orientation aspects of the task, participants were required to situate the recalled artifact in relation to other items, or topographical aspects of their surroundings (allocentric memory) as well as to remember if they turned right or left after encountering the artifact (egocentric memory). The Virtual Action Planning Museum (VAP-M) was able to significantly differentiate aMCI participants from CHE. The allocentric query showed 92% sensitivity and 97% specificity, while the egocentric query showed 94% sensitivity and 73% specificity[38].

In resemblance to the traditional Morris Water Maze used by behavioral psychology studies with rodents[39], Caffò et al.[40] proposed a virtual spatial orientation task named the "Virtual Reorientation Test" (VReoT). In it, participants were required to find a yellow sphere that was hidden inside a blue box in one of the four corners of a virtual room. The participants' starting position facing the room was changed randomly across the twelve trials of the test, in order to control for any egocentric memorizing interference. The VReoT was composed of five subtests, each providing different landmark information for finding the hidden yellow sphere. One particular characteristic of this test was the assessment of different kinds of allocentric orientation, since landmark cues directly and indirectly related to the goal position were provided and egocentric interference was controlled. A cut-off score of >7 in the VReoT demonstrated 80.4% sensitivity and 94.3% specificity for the detection of aMCI compared to cognitively health elderly, but failed to distinguish single-domain from multiple-domain MCI participants[40].

Besides the objects and location recognition test, the self-rating spatial questionnaire, and the Map Learning Task described previously, Mitolo et al.[25] proposed yet another form of spatial orientation assessment: the route-learning task consisted of a visual span offering the possibility of actually walking through a twenty-five dot (5X5) matrix route. Using a growing span sequence (two, then three, then four, etc.), participants first learned the route by walking together with the examiner (route learning from action) and were asked to repeat it alone afterward. Secondly, participants learned the route by observing the examiner (route learning from vision) and finally, they learned the route on a map (route learning from a map). Interestingly, by dividing the route-learning task into these three components, investigators were able to obtain an allocentric frame of reference (route learning from vision and from a map), and an egocentric frame of reference (route learning from action). Two route-learning tasks demonstrated strong discriminative power, with AUCs of 0.90 (95%CI 0.77–1.00) for route learning from action and 0.91 (95%CI 0.80–1.00) for route learning from vision[25].

More recently, Howett et al.[41] described an entorhinal-based navigation task using an immersive virtual reality environment: the path integration task. To complete it, participants were required to walk in the virtual environment following a sequence of three visually-displayed cones in the virtual landscape and then return to the first location without any visual clues. Path integration performance was assessed by calculating the absolute distance error, defined as the Euclidean distance between the participant's estimate of the first cone location and the actual location where the first cone had appeared. Test scores were able to successfully differentiate the MCI participants from CHE, as well as MCI participants with AD biomarkers in the cerebrospinal fluid (CSF) from negative ones (AUC of 0.9 using absolute distance errors). Absolute distance errors in the path integration task yielded a sensitivity of 0.84 and a specificity of 0.68 (with an AUC of 0.82) for the classification of MCI (without biomarker status distinction) among CHE[41].

DISCUSSION

Overall, few studies have investigated the accuracy power of spatial orientation tasks for the diagnosis of MCI. Spatial orientation tasks varied significantly in terms of task setting, ecological or non-ecological type of assessment, and even the kind of spatial orientation ability being evaluated. Studies investigated route-learning abilities, path integration, allocentric orientation, egocentric orientation, object location and self-reported measures of spatial orientation functioning. Although most studies provided results for a group of aMCI participants, some chose not to stratify into aMCI and naMCI categories, and therefore may have included naMCI participants in the MCI group.

Despite the diversity of tasks, good accuracy results for the detection of MCI among CHE were reported, varying from moderate to strong. Studies reporting AUC found results ranging from 0.77 to 0.99. Sensitivity of spatial orientation tasks was found between 0.64 and 0.94, and specificity varied from 0.68 to 0.97. One study reported an OR of 2.43 for a self-report measure of spatial abilities[31].

To the best of our knowledge, this is the first systematic review specifically aimed at the diagnostic accuracy of spatial orientation tasks for the diagnosis of MCI compared to

a healthy control group. Although the findings presented in this review do not permit a final statement regarding the predictive power of spatial orientation tasks for this purpose, they contribute to the growing discussion on the importance of investigating spatial (dis)orientation in older adults, and evidence the need for more standardized forms of evaluation of this cognitive domain.

The diagnosis of MCI is an important first step in identifying individuals at a higher risk of conversion to AD[2,42,43]. However, MCI is a heterogeneous clinical entity, which encompasses different underlying conditions[44,45]. Spotting which individuals among those with the broad classification of MCI are more likely to convert to AD can be challenging. Biological markers, such as amyloid or tau positron emission tomography (PET), glycolytic metabolism in fluorodeoxyglucose PET (FDG-PET), reduced hippocampal volume on magnetic resonance imaging, and AD biomarkers in CSF have been shown to correlate with worse cognitive functioning and/or a higher risk of conversion to AD[46,47,48]. Among the selected studies, three included biomarkers (magnetic resonance imaging of the brain with voxel-based morphometry[25], event-related potential in electroencephalography[38], and levels of amyloid-β_{1-42}, total tau and phosphorylated tau in cerebrospinal fluid[41]), but only the study of Howett et al.[41] described the accuracy results of the spatial orientation task taking into account the biomarker status of MCI participants.

Besides the use of biomarkers, further classification of MCI patients into aMCI or naMCI, and single or multiple-domain, is also considered valuable for the identification of those at a higher risk of conversion to AD[2]. Biomarkers are usually costly and/or invasive, which limits their use in the clinical setting, especially in low and middle-income countries. Finding a cognitive marker would fill an important gap in the detection of pathological cognitive decline, and could be easily applied anywhere in the world. For this purpose, spatial orientation deficits appear to be characteristic of an underlying pathology of the AD type among MCI patients. Spatial orientation engages the same brain areas involved early in AD — medial temporal and parietal lobes — and has been described to differentiate higher-risk MCI individuals[41,49,50,51]. Classifications used by the authors of the selected studies to stratify MCI participants included aMCI[31,33,37,38,40], MCI with or without AD cerebrospinal fluid biomarkers[41], MCI with or without comorbid Depression[33], and single and multiple-domain aMCI[40].

Several studies have reported that only aMCI patients appear to present spatial orientation deficits, while naMCI patients seem to perform similarly to CHE[5,26,51,52]. Among the studies included in this review, only that of Cerman et al.[31] included a sample of naMCI participants. Although their Subjective Spatial Navigation Complaints Questionnaire showed that 64% of naMCI participants complained about their spatial navigation abilities (16% being major complaints), its predictive power proved to be non-significant for this group after controlling for anxiety symptoms. This finding is in line with different studies demonstrating no significant spatial orientation deficits in naMCI patients[26,28,51,52]. In contrast, predictive power for the aMCI group remained significant after controlling for either anxiety or depression symptoms.

In agreement with other studies demonstrating that spatial orientation tasks successfully differentiate MCI participants with and without biomarkers[49,50,51], the path integration task used by Howett et al.[41] effectively distinguished MCI patients with positive CSF biomarkers from MCI without biomarkers and the healthy control group. This seems particularly promising for studies aiming to stratify aMCI patients according to a higher risk of conversion to AD, based on cognitive assessment. The study of Ritter et al.[33] also demonstrated that the "amnestic MCI" factor had a significant effect on spatial orientation deficits, while the "depression" factor did not, pointing to a distinctive characteristic of spatial orientation deficits in elderly cognitive decline.

The study of Caffò et al.[40], on the other hand, failed to differentiate single-domain aMCI from multiple-domain aMCI subgroups. This could be explained, at least partially, by the kind of spatial orientation assessment chosen by the authors. Allocentric orientation tasks have proven to be a valid tool for differentiating aMCI patients from cognitively healthy elderly, and for identifying preclinical stages of AD[53], but have failed to differentiate subgroups of aMCI at a higher risk of conversion to AD[26,49,54]. Apparently, the earliest spatial deficits in preclinical AD seem to be the translation of allocentric information to egocentric information, a process known to be mediated by the retrosplenial cortex[7,19,55]. Also sensitive to early decline is the process of path integration[41]. Path integration tasks are known to recruit grid cells from the entorhinal cortex, an area known to be related to the accumulation of tau protein in AD pathology[20,41].

Furthermore, spatial orientation tasks are expected to present fewer educational and cultural biases[52,53]. Education level varied between samples, with three studies reporting participants' mean years of education below 10 and the other four studies reporting higher levels of education among participants. Strong accuracy results of spatial orientation tasks were found in both kinds of samples.

Although interesting and promising findings were identified in this review, significant quality issues in the methodologies of selected studies limit the interpretation of reported results. The small number of studies, small number of participants, and patient selection and information biases are likely to have influenced the accuracy of results, which must be interpreted with caution. Longitudinal studies should be conducted in order to better understand the true value of spatial orientation deficits as cognitive markers of pathological aging. In addition, more studies aiming to associate cognitive assessment with biomarkers and neuroimaging techniques are required to corroborate the accuracy of

spatial orientation for the detection of MCI (or even a high-risk group of MCI patients) among cognitively healthy elderly.

Although applicability concerns were considered rather low, high heterogeneity in the methods of spatial orientation assessment used by each research group also limits interpretation of the results and their extrapolation to clinical practice. It is important to keep in mind that both allocentric and egocentric processing are involved in spatial processing, as well as the correct integration of both reference frames[56,57]. These aspects of spatial cognition engage distinct brain areas and are known to be affected differently by pathological and non-pathological aging[17]. In this review, the majority of the described spatial orientation tasks did not separate those two aspects of spatial processing, which may have influenced the overall understanding of results[58]. There is an evident need for more uniform ways of assessing spatial orientation abilities or for the establishment of a gold standard. Additionally, further studies with different populations and heterogeneous ethnic and cultural backgrounds are necessary, as well as with diverse educational levels.

Finally, it is important to recognize the growing number of studies using computer-based and virtual reality tasks for the assessment of spatial orientation abilities[37,38,40,41]. Researchers and health care providers have increasingly questioned the utility of traditional "paper-and-pencil" tests or questionnaires to assess a participant's spatial orientation abilities, since they may not adequately represent daily navigation impairments[16,26,59]. In recent years, researchers have proposed innovative ways to assess these abilities in order to address this issue[26,28,60]. In particular, with the advent of virtual reality technology, new possibilities for the ecological assessment of spatial orientation have emerged, renewing the field of spatial orientation studies[41,53,61,62,63]. Virtual reality technology also allows for the isolation of specific spatial orientation processes and may be a helpful tool for unifying and standardizing spatial orientation assessment.

In conclusion, more studies are needed to confirm the accuracy of spatial orientation assessment for the diagnosis of MCI and there is an urgent need for standardized ways of ecologically assessing spatial orientation abilities. Understanding of this cognitive domain and its relation to pathological ageing must be advanced. Virtual reality technology and the possibility it offers of creating more ecological forms of evaluation appears to be a promising tool to fill this gap. There is a small but growing number of studies demonstrating the utility of spatial orientation assessment for the identification of MCI, and discussions around this topic should be encouraged.

References

1. Portet F, Ousset PJ, Visser PJ, Frisoni GB, Nobili F, Scheltens P, et al. Mild cognitive impairment (MCI) in medical practice: a critical review of the concept and new diagnostic procedure. Report of the MCI Working Group of the European Consortium on Alzheimer's Disease. J Neurol Neurosurg Psychiatry. 2006 Jun;77(6):714-8. https://doi.org/10.1136/jnnp.2005.085332
2. Petersen RC. Mild cognitive impairment. Continuum (Minneap Minn). 2016 Apr;22(2 Dementia):404-18. https://doi.org/10.1212/CON.0000000000000313
3. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med. 2004 Sep;256(3):183-94. https://doi.org/10.1111/j.1365-2796.2004.01388.x
4. Guariglia CC, Nitrini R. Topographical disorientation in Alzheimer's disease. Arq Neuro-Psiquiatr. 2009 Dec;67(4):967-72. http://dx.doi.org/10.1590/S0004-282X2009000600001
5. Iachini I, Iavarone A, Senese VP, Ruotolo F, Ruggiero G, Iachini T, et al. Visuospatial memory in healthy elderly, AD and MCI: a review. Curr Aging Sci. 2009 Mar;2(1):43-59. https://doi.org/10.2174/1874609810902010043
6. Deipolyi AR, Fang S, Palop JJ, Yu G-Q, Wang X, Mucke L. Altered navigational strategy use and visuospatial deficits in hAPP transgenic mice. Neurobiol Aging. 2008 Feb;29(2):253-66. https://doi.org/10.1016/j.neurobiolaging.2006.10.021
7. Serino S, Cipresso P, Morganti F, Riva G. The role of egocentric and allocentric abilities in Alzheimer's disease: A systematic review. Ageing Res Rev. 2014 Jul;16:32-44. https://doi.org/10.1016/j.arr.2014.04.004
8. Brien CO, Ph D, Smith GE, Ivnik RJ, Boeve BF. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. Neurology. 1999 Apr;52(7):1397-403. https://doi.org/10.1212/wnl.52.7.1397
9. Nedelska Z, Andel R, Laczó J, Vlcek K, Horinek D, Lisy J, et al. Spatial navigation impairment is proportional to right hippocampal volume. Proc Natl Acad Sci U S A. 2012 Feb;109(7):2590-4. https://doi.org/10.1073/pnas.1121588109
10. Moodley K, Minati L, Contarino V, Prioni S, Wood R, Cooper R, et al. Diagnostic differentiation of mild cognitive impairment due to Alzheimer's disease using a hippocampus-dependent test of spatial memory. Hippocampus. 2015 Aug;25(8):939-51. https://doi.org/10.1002/hipo.22417
11. Lim T-S, Iaria G, Moon SY. Topographical disorientation in mild cognitive impairment: a voxel-based morphometry study. J Clin Neurol. 2010 Dec;6(4):204-211. https://doi.org/10.3988/jcn.2010.6.4.204
12. delpolyi AR, Rankin KP, Mucke L, Miller BL, Gorno-Tempini ML. Spatial cognition and the human navigation network in AD and MCI. Neurology. 2007 Sep;69(10):986-97. https://doi.org/10.1212/01.wnl.0000271376.19515.c6.
13. Vlček K, Laczó J. Neural correlates of spatial navigation changes in mild cognitive impairment and Alzheimer's disease. Front Behav Neurosci. 2014 Mar;8:1-6. https://doi.org/10.3389/fnbeh.2014.00089
14. Peter J, Sandkamp R, Minkova L, Schumacher LV, Kaller CP, Abdulkadir A, et al. Real-world navigation in amnestic mild cognitive impairment: the relation to visuospatial memory and volume of hippocampal subregions. Neuropsychologia. 2018 Jan;109:86-94. https://doi.org/10.1016/j.neuropsychologia.2017.12.014
15. Devier DJ, Villemarette-Pittman N, Brown P, Pelton G, Stern Y, Sano M, et al. Predictive utility of type and duration of symptoms at initial presentation in patients with mild cognitive impairment. Dement Geriatr Cogn Disord. 2010;30(3):238-44. https://doi.org/10.1159/000320137

16. Lithfous S, Dufour A, Després O. Spatial navigation in normal aging and the prodromal stage of Alzheimer's disease: Insights from imaging and behavioral studies. Ageing Res Rev. 2013 Jan;12(1):201-13. https://doi.org/10.1016/j.arr.2012.04.007

17. Colombo D, Serino S, Tuena C, Pedroli E, Dakanalis A, Cipresso P, et al. Egocentric and allocentric spatial reference frames in aging: a systematic review. Neurosci Biobehav Rev. 2017 Sep;80:605-21. https://doi.org/10.1016/j.neubiorev.2017.07.012

18. Korthauer L, Nowak N, Frahmand M, Driscoll I. Cognitive correlates of spatial navigation: Associations between executive functioning and the virtual Morris Water Task. Behav Brain Res. 2017 Jan;317:470-8. https://doi.org/10.1016/j.bbr.2016.10.007

19. Lester AW, Moffat SD, Wiener JM, Barnes CA, Wolbers T. The Aging navigational system. Neuron. 2017 Aug;95(5):1019-35. https://doi.org/10.1016/j.neuron.2017.06.037

20. Braak H, Braak E. Demonstration of amyloid deposits and neurofibrillary changes in whole brain sections. Brain Pathol. 1991 Apr;1(3):213-6. https://doi.org/10.1111/j.1750-3639.1991.tb00661.x

21. Bird CM, Chan D, Hartley T, Pijnenburg YA, Rossor MN, Burgess N. Topographical short-term memory differentiates Alzheimer's disease from frontotemporal lobar degeneration. Hippocampus. 2010 Oct;20(10):1154-69. https://doi.org/10.1002/hipo.20715

22. Peters-Founshtein G, Peer M, Rein Y, Merhavi SK, Meiner Z, Arzy S. Mental-orientation: A new approach to assessing patients across the Alzheimer's disease spectrum. Neuropsychology. 2018 Sep;32(6):690-9. https://doi.org/10.1037/neu0000463

23. Pengas G, Patterson K, Arnold RJ, Bird CM, Burgess N, Nestor PJ. Lost and found: Bespoke memory testing for Alzheimer's disease and semantic dementia. J Alzheimers Dis. 2010;21(4):1347-65. https://doi.org/10.3233/jad-2010-100654

24. Vann SD, Aggleton JP, Maguire EA. What does the retrosplenial cortex do? Nat Rev Neurosci. 2009 Nov;10(11):792-802. https://doi.org/10.1038/nrn2733

25. Mitolo M, Gardini S, Fasano F, Crisi G, Pelosi A, Pazzaglia F, et al. Visuospatial memory and neuroimaging correlates in mild cognitive impairment. J Alzheimers Dis. 2013;35(1):75-90. https://doi.org/10.3233/JAD-121288

26. Laczó J, Andel R, Vyhnalek M, Vlcek K, Magerova H, Varjassyova A, et al. Human analogue of the morris water maze for testing subjects at risk of Alzheimer's Disease. Neurodegener Dis. 2010;7(1-3):148-52. https://doi.org/10.1159/000289226

27. Weniger G, Ruhleder M, Lange C, Wolf S, Irle E. Egocentric and allocentric memory as assessed by virtual reality in individuals with amnestic mild cognitive impairment. Neuropsychologia. 2011 Feb;49(3):518-27. https://doi.org/10.1016/j.neuropsychologia.2010.12.031

28. Rusconi ML, Suardi A, Zanetti M, Rozzini L. Spatial navigation in elderly healthy subjects, amnestic and non amnestic MCI patients. J Neurol Sci. 2015 Dec;359(1-2):430-7. https://doi.org/10.1016/j.jns.2015.10.010

29. Migo EM, O'Daly O, Mitterschiffthaler M, Antonova E, Dawson GR, Dourish CT, et al. Investigating virtual reality navigation in amnestic mild cognitive impairment using fMRI. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2016;23(2):196-217. https://doi.org/10.1080/13825585.2015.1073218

30. da Costa RQM, Pompeu JE, de Mello DD, Moretto E, Rodrigues FZ, Dos Santos MD, et al. Two new virtual reality tasks for the assessment of spatial orientation: Preliminary results of tolerability, sense of presence and usability. Dement Neuropsychol. 2018 Apr-Jun;12(2):196-204. http://dx.doi.org/10.1590/1980-57642018dn12-020013

31. Cerman J, Ross A, Laczo J, Martin V, Zuzana N, Ivana M, et al. Subjective Spatial navigation complaints - a frequent symptom reported by patients with subjective cognitive decline, mild cognitive impairment and Alzheimer's disease. Curr Alzheimer Res. 2018;15(3):219-28. https://doi.org/10.2174/1567205014666171120145349

32. Mitolo M, Gardini S, Caffarra P, Ronconi L, Venneri A, Pazzaglia F. Relationship between spatial ability, visuospatial working memory and self-assessed spatial orientation ability: a study in older adults. Cogn Process. 2015 May;16(2):165-76. https://doi.org/10.1007/s10339-015-0647-3

33. Ritter E, Després O, Monsch AU, Manning L. Topographical recognition memory sensitive to amnestic mild cognitive impairment but not to depression. Int J Geriatr Psychiatry. 2006 Oct;21(10):924-9. https://doi.org/10.1002/gps.1581

34. Laczó J, Andel R, Vlček K, Maťoška V, Vyhnálek M, Martin T, et al. Spatial navigation and APOE in amnestic mild cognitive impairment. Neurodegener Dis. 2011;8(4):169-77. https://doi.org/10.1159/000321581

35. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015 Jan;4(1):1. https://doi.org/10.1186/2046-4053-4-1

36. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011 Oct;155(8):529-36. https://doi.org/10.7326/0003-4819-155-8-201110180-00009

37. Wang H-M, Yang C-M, Kuo W-C, Huang C-C, Kuo H-C. Use of a modified spatial-context memory test to detect amnestic mild cognitive impairment. pLoS One. 2013 Feb;8(2):e57030. https://doi.org/10.1371/journal.pone.0057030

38. Tarnanas I, Laskaris N, Tsolaki M, Muri R, Nef T, Mosimann UP. On the Comparison of a Novel Serious Game and Electroencephalography Biomarkers for Early Dementia Screening. Adv Exp Med Biol. 2015;821:63-77. https://doi.org/10.1007/978-3-319-08939-3_11

39. Barnhart CD, Yang D, Lein PJ. Using the Morris water maze to assess spatial learning and memory in weanling mice. PLoS One. 2015 Apr;10(4):e0124521. https://doi.org/10.1371/journal.pone.0124521

40. Caffò AO, De Caro MF, Picucci L, Notarnicola A, Settanni A, Livrea P, et al. Reorientation deficits are associated with amnestic mild cognitive impairment. Am J Alzheimers Dis Other Demen. 2012 Aug;27(5):321-30. https://doi.org/10.1177/1533317512452035

41. Howett D, Castegnaro A, Krzywicka K, Hagman J, Marchment D, Henson R, et al. Differentiation of mild cognitive impairment using an entorhinal cortex-based test of virtual reality navigation. Brain. 2019 Jun;142(6):1751-66. https://doi.org/10.1093/brain/awz116

42. Levey A, Lah J, Goldstein F, Steenland K, Bliwise D. Mild cognitive impairment: an opportunity to identify patients at high risk for progression to Alzheimer's disease. Clin Ther. 2006 Jul;28(7):991-1001. https://doi.org/10.1016/j.clinthera.2006.07.006

43. Landau SM, Harvey D, Madison CM, Reiman EM, Foster NL, Aisen PS, et al. Comparing predictors of conversion and decline in mild cognitive impairment. Neurology. 2010 Jul;75(3):230-8. https://doi.org/10.1212/WNL.0b013e3181e8e8b8

44. Hugo J, Ganguli M. Dementia and cognitive impairment: epidemiology, diagnosis, and treatment. Clin Geriatr Med. 2014 Aug;30(3):421-42. https://doi.org/10.1016/j.cger.2014.04.001

45. Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. JAMA. 2014 Dec;312(23):2551-61. https://doi.org/10.1001/jama.2014.13806

46. Altomare D, Ferrari C, Caroli A, Galluzzi S, Prestia A, van der Flier WM, et al. Prognostic value of Alzheimer's biomarkers in mild cognitive impairment: the effect of age at onset. J Neurol. 2019 Oct;266(10):2535-45. https://doi.org/10.1007/s00415-019-09441-7

47. Cognat E, Mouton Liger F, Troussière A-C, Wallon D, Dumurgier J, Magnin E, et al. What is the clinical impact of cerebrospinal fluid biomarkers on final diagnosis and management in patients with mild cognitive impairment in clinical practice? Results from a nation-wide prospective survey in France. BMJ Open. 2019 May;9(5):e026380. https://doi.org/10.1136/bmjopen-2018-026380

48. Eliassen CF, Reinvang I, Selnes P, Grambaite R, Fladby T, Hessen E. Biomarkers in subtypes of mild cognitive impairment and subjective cognitive decline. Brain Behav. 2017 Sep;7(9):e00776. https://doi.org/10.1002/brb3.776

49. Laczó J, Andel R, Vyhnalek M, Vlcek K, Nedelska Z, Matoska V, et al. APOE and spatial navigation in amnestic MCI: results from a computer-based test. Neuropsychology. 2014 Sep;28(5):676-84. https://doi.org/10.1037/neu0000072

50. Laczó J, Andel R, Vyhnalek M, Matoska V, Kaplan V, Nedelska Z, et al. The effect of TOMM40 on spatial navigation in amnestic mild cognitive impairment. Neurobiol Aging. 2015 Jun;36(6):2024-33. https://doi.org/10.1016/j.neurobiolaging.2015.03.004

51. Hort J, Laczó J, Vyhnálek M, Bojar M, Bures J, Vlcek K. Spatial navigation deficit in amnestic mild cognitive impairment. Proc Natl Acad Sci U S A. 2007 Mar;104(10):4042-7. https://doi.org/10.1073/pnas.0611314104

52. Laczó J, Vlcek K, Vyhnálek M, Vajnerová O, Ort M, Holmerová I, et al. Spatial navigation testing discriminates two types of amnestic mild cognitive impairment. Behav Brain Res. 2009 Sep;202(2):252-9. https://doi.org/10.1016/j.bbr.2009.03.041

53. Coughlan G, Coutrot A, Khondoker M, Minihane AM, Spiers H, Hornberger M. Toward personalized cognitive diagnostics of at-genetic-risk Alzheimer's disease. Proc Natl Acad Sci U S A. 2019 May;116(19):9285-92. https://doi.org/10.1073/pnas.1901600116

54. Coughlan G, Laczó J, Hort J, Minihane AM, Hornberger M. Spatial navigation deficits — Overlooked cognitive marker for preclinical Alzheimer disease? Nat Rev Neurol. 2018 Aug;14(8):496-506. https://doi.org/10.1038/s41582-018-0031-x

55. Lopez A, Caffò AO, Bosco A. Memory for familiar locations: the impact of age, education and cognitive efficiency on two neuropsychological allocentric tasks. Assessment. 2020 Oct;27(7):1588-603. https://doi.org/10.1177/1073191119831780

56. Wallach A, Harvey-Girard E, Jaeyoon Jun J, Longtin A, Maler L. A time-stamp mechanism may provide temporal information necessary for egocentric to allocentric spatial transformations. Elife. 2018 Nov 22;7:e36769. https://doi.org/10.7554/eLife.36769

57. Gramann K, Onton J, Riccobon D, Mueller HJ, Bardins S, Makeig S. Human brain dynamics accompanying use of egocentric and allocentric reference frames during navigation. J Cogn Neurosci. 2010 Dec;22(12):2836-49. https://doi.org/10.1162/jocn.2009.21369

58. Ekstrom AD, Arnold AEGF, Iaria G. A critical review of the allocentric spatial representation and its neural underpinnings: toward a network-based perspective. Front Hum Neurosci. 2014 Sep;8:803. https://doi.org/10.3389/fnhum.2014.00803

59. Cogné M, Taillade M, N'Kaoua B, Tarruella A, Klinger E, Larrue F, et al. The contribution of virtual reality to the diagnosis of spatial navigation disorders and to the study of the role of navigational aids: A systematic literature review. Ann Phys Rehabil Med. 2017 Jun;60(3):164-76. https://doi.org/10.1016/j.rehab.2015.12.004

60. Benke T, Karner E, Petermichl S, Prantner V, Kemmler G. Neuropsychological deficits associated with route learning in Alzheimer disease, MCI, and normal aging. Alzheimer Dis Assoc Disord. Apr-Jun 2014;28(2):162-7. https://doi.org/10.1097/WAD.0000000000000009

61. Allison SL, Fagan AM, Morris JC, Head D. Spatial navigation in preclinical Alzheimer's disease. J Alzheimers Dis. 2016 Feb;52(1):77-90. https://doi.org/10.3233/JAD-150855

62. Tascón L, Castillo J, León I, Cimadevilla JM. Walking and non-walking space in an equivalent virtual reality task: Sexual dimorphism and aging decline of spatial abilities. Behav Brain Res. 2018 Jul;347:201-8. https://doi.org/10.1016/j.bbr.2018.03.022

63. Ranjbar Pouya O, Byagowi A, Kelly DM, Moussavi Z. Introducing a new age-and-cognition-sensitive measurement for assessing spatial orientation using a landmark-less virtual reality navigational task. Q J Exp Psychol (Hove). 2017 Jul;70(7):1406-19. https://doi.org/10.1080/17470218.2016.1187181