Working memory assessment using Cambridge neuropsychological test automated battery can help in the diagnosis of mild cognitive impairment: a systematic review and meta-analysis

Zahra Sabahi1, Mehdi Farhoudi, Amirreza Naseri, Mahnaz Talebi

ABSTRACT. Mild cognitive impairment (MCI) is an interstitial state between normal aging and dementia. Objective: In this study, we investigated working memory (WM) profiles of MCI patients using the Cambridge Neuropsychological Test Automated Battery (CANTAB). We also examined the diagnostic accuracy and possible associated factors as secondary outcomes of the study. Methods: We conducted an electronic search on EMBASE, PubMed, and ScienceDirect databases. Studies with MCI participants and using CANTAB battery subtests for the assessment of WM were included. Meta-analysis was conducted using the CMA2 software. Results: Out of 1537 records, 14 studies were covered in this systematic review, and 7 of them were included in the meta-analysis. There was a significant difference between MCI patients and healthy controls in spatial working memory (SWM) (SDM: 0.535; 95%CI 11–96; p-value=0.014), spatial span (SSP) (SDM: 0.649 95%CI 0.297–0.100; p-value<0.01), and rapid visual information processing (RVP) (SDM: 0.52; 95%CI 0.386–0.654; p-value<0.01). WM function of MCI patients was associated with the cerebrospinal fluid (CSF) levels of tau-protein and amyloid-beta (Aβ). Conclusions: WM is an impaired cognitive domain in MCI. CANTAB WM subtests including SSP, SWM, and RVP are accurate enough to be used as a proper assessment tool for the diagnosis of MCI in clinical settings. Tau-protein and Aβ are associated with lower WM scores in MCI patients; however, sex, age, psychiatric disorders, apolipoprotein 4 allele, and functional activity scores cannot affect WM.

Keywords: Cognitive Dysfunction; Memory, Short-Term; Neuropsychological Tests; Systematic Review; Meta-Analysis.
INTRODUCTION

Mild cognitive impairment (MCI) is known as a transitional state between normal aging and dementia in the age continuum in which patients experience memory loss more than healthy age-matched older adults, but do not fulfill defined criteria for dementia diagnosis. Based on manifestations and disease course, MCI includes different subtypes: amnestic or non-amnestic MCI and single- or multiple-domain MCI. The amnestic MCI is typically associated with an increased risk of conversion to Alzheimer’s disease (AD); however, non-amnestic subtypes, which may progress to non-AD dementias, may also evolve to AD.

Several studies have estimated the prevalence of MCI from 12 to 18% in older people over the age of 60 years. With the global increase in life expectancy, early diagnosis and precise application of disease-modifying treatments for MCI have turned into a priority for the health systems. Previous studies following MCI patients for 6 years found that 80% of patients progress to AD with an annual rate of 10–15%, which is 10-fold higher than the conversion rate in the normal population.

Several cognitive domains such as learning, short- and long-term memory, social cognition, language, perceptual motor, complex attention, or executive functioning are characteristically affected by the pathogenesis of AD along with disease progression. Working memory (WM) can be defined as a component of short-term memory with a restricted capacity that depends on central executive functions and attention, utilizing stored information and linking them to long-term memory. Unlike short memory which provides short-term storage of information, WM has been proposed as a multicomponent structure that stores incoming information and operates them to a more complicated cognitive function. WM is highly associated with daily functioning abilities and has shown an explicit linear decreasing relationship with age, so it can be used as a measure for early diagnosis of dementia.

Previous studies have shown impairment of WM in the early stage of dementia, which makes it a good factor for early diagnosis of the disease and prevention of disease progression. Classic paper-pencil tests like Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) are widely being used for the assessment of MCI; however, these tests have shown some serious drawbacks with standardization of administration, the accuracy of response measurement, and demographic factors, importantly years of education and illiteracy.

The Cambridge Neuropsychological Test Automated Battery (CANTAB) is a computerized neuropsychological test with a game-like and non-verbal environment that assesses the different cognitive domains like memory, attention, executive functions, learning, and problem-solving. Among various subtests of CANTAB, spatial span (SSP) and spatial working memory (SWM) account for the assessment of WM. Also, rapid visual processing (RVP) accounts for sustained attention and target detection that has a small WM component that is sensitive to parietal and frontal lobe dysfunction.

In this systematic review and meta-analysis study, we aimed to study the WM function in MCI patients using CANTAB to determine the severity of WM impairment in MCI patients, as the primary outcome, and compare it with healthy matched older adults, to define the diagnostic accuracy of WM profiles of CANTAB in the detection of MCI. Also, as another secondary outcome, we investigated the associated factors of WM function in MCI patients.

METHODS

This study was conducted following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. This systematic review was designed to assess the WM function in MCI patients using the CANTAB, and the meta-analysis was conducted to compare the differences between MCI and healthy participants in WM subtests of the CANTAB.

Search

Two independent researchers (Z.S. and A.N.) conducted a systematic literature search on EMBASE, PubMed, and ScienceDirect databases combining the keywords “Cognitive dysfunction, cognitive decline, cognitive impairment, mental deteriorations, mild cognitive impairment, CANTAB, Cambridge Neuropsychological Test Automated Battery, neuropsychological test, working memory, immediate memory, short-term memory,” on December 16, 2020. For the sake of comprehensiveness, the references of each included study were checked for any additional related papers.

Study selection

Search results were imported to the EndNote reference manager. After deleting duplicated studies, two independent authors (Z.S. and A.N.) started screening and selecting papers by title/abstract in the first stage and full text in the second stage. In case of any conflicts, investigators tried to convince each other or ask for a third expert researcher’s comment (M.T. or M.F.).

Inclusion criteria were as follows:

1. Original journal articles,
2. MCI diagnosis at the baseline based on the clinical criteria,
3. Using CANTAB subtests that evaluate WM, and
4. Studies in English.

Exclusion criteria were as follows:
1. Studies in other languages, and
2. Other types of articles such as review articles, editorials, letters,
3. Conference abstracts, and
4. Animal studies.

Data extraction
Data were extracted by two independent authors (Z.S. and A.N.) in a pre-specified format using a data extraction table, including the name of the first author of the study, publication year, study design, the overall number of participants as well as the number of patients in each group of the study, mean age, years of education, diagnostic criteria, MMSE score, mean and standard deviations (SD) of CANTAB WM subtests in MCI group and the healthy control group, and finally associated and non-associated factors with WM function. We could not examine amnesic and non-amnesic subtypes separately since they were not described in most of the included articles. The online version of Web Plot Digitizer was used for extracting the exact values from the graphs. Extracted data were reviewed by a third author (M.T. or M.F.) and, in case of any disagreements about results, it was determined between authors or by a judgment of a third author.

Risk of bias in individual studies
The risk of bias (RoB) and methodological quality were evaluated (by Z.S. and A.N. separately) with Joanna Briggs Institute (JBI) checklist that contains eight questions, evaluating inclusion criteria, detailed study subjects and setting, the validity of exposure, the standard measurement of the condition, and the outcome, identifying and dealing with confounding factors and statistical analysis.

Statistics
In this study, meta-analysis was performed using comprehensive meta-analysis (CMA) version 2.0. The confidence interval was considered at 95% and 0.05 level of significance for the p-value. Studies that used SWM total errors, SSP length, as well as A’ or latency measures of RVP subtest of CANTAB in MCI patients and healthy control group were included in the quantitative analysis. The I² model was also utilized for assessing the level of heterogeneity among included studies. Whenever any of the studies had reported data for MCI by subgroups (subjective MCI, amnestic MCI, single-domain MCI, multiple-domain MCI), we merged them using an excel code. The mean, SD, and the number of the individuals in each group were imported into CMA, and both the random-effect model (REM) and fixed-effect model (FEM) were utilized for assessing the difference between the groups. Also, the results of the study were reported in funnel plots in Supplementary Material.

RESULTS

Search results and selection process
The electronic search identified 1,235 records through databases and 655 records added from other resources. After removing duplicates, 1,537 records were screened, and 1,434 records were excluded. Out of 66 studies that were assessed in the full-text stage, 14 studies were included in this systematic review, and 7 of them met our inclusion criteria for the meta-analysis. The PRISMA flow diagram is presented in Figure 1. Table 1 is a summary of the characteristics and findings of included studies.

Characteristics of the studies and participants
Five of included studies were cross-sectional and nine were cohorts. Only baseline data of the cohort studies are taken into account. In sum, 930 out of 1670 participants were diagnosed with MCI, and 527 were healthy controls. The mean age of the participants was between 55 and 75 years. The years of education varied from 7 to 14, and the male ratio varied between 8 and 56%.

MCI diagnosis
In this study, most of the researchers used MMSE for the diagnosis of MCI, and the rest of the studies used the other tests or criteria, such as Petersen criteria, MOCA, Rey Auditory Verbal Learning Test, and Dementia Rating Scale.

CANTAB tests for WM
Regarding the tests for WM in CANTAB, 11 of the included studies reported SWM, and 9 of them reported SSP for assessing WM. As mentioned before, RVP has a small WM component and was used in nine of our included studies. Only one study reported that used delayed matching to sample (DMS) subtest of CANTAB as an assessment tool for WM.

Factors associated with WM in MCI
In terms of factors associated with WM functions of MCI patients, sex, age, psychiatric disorders such as
depression, apolipoprotein 4 (ApoE4), and functional activity scores were not significantly correlated to CANTAB WM scores, while a higher cerebrospinal fluid (CSF) levels of tau-protein and amyloid-beta (Aβ) were associated with a lower function in WM tests.

**Meta-analysis**

Out of 14 included studies, 3 of them did not include any healthy participants for control group and 4 others did not report our intended component of CANTAB subtests to be included in the quantitative synthesis; hence, they were excluded from the meta-analysis. Seven remaining studies were included in the meta-analysis. The forest plots of the meta-analyses are shown in Figures 2–4. The quantitative synthesis of studies using CANTAB subtests to assess WM showed a significant difference between MCI and healthy controls in SWM (REM SDM: 0.535; 95%CI 0.110–0.960; p=0.014, FEM SDM: 0.450; 95%CI 0.270–0.630; p<0.01; test for heterogeneity I²: 81.28%; p<0.01), SSP (REM SDM: 0.649; 95%CI 0.297–1.000; p<0.01, FEM SDM: 0.510 95%CI 0.654–0.365; p<0.01; test for heterogeneity I²: 82.76%; p<0.01), and RVP (REM SDM: 0.583; 95%CI 0.244–0.922; p<0.01, FEM SDM: 0.590; 95%CI 0.401–0.870; p<0.01; test for heterogeneity I²: 46.49%; p=0.05). Also, RVP A' (REM SDM: 0.583; 95%CI 0.244–0.922; p<0.01, FEM SDM: 0.590; 95%CI 0.401–0.870; p<0.01; test for heterogeneity I²: 67.87%; p=0.01) and RVP latency (REM and FEM SDM: 0.449; 95%CI 0.259–0.639; p<0.01; test for heterogeneity I²: 0%; p=0.50) were significantly different between patients with MCI and healthy controls.
Table 1. Characteristics and summary of findings of included studies.

| Author (year) | Study design | Sample size | Mean age | Gender ratio (%) | MMSE score | Eligibility criteria MCI | Eligibility criteria-control | CANTAB subtests for WM | MCI Mean | SD n | Control Mean | SD n | Associated factors | Non-associated factors |
|---------------|--------------|-------------|----------|------------------|------------|--------------------------|-----------------------------|-------------------------|----------|-----|-------------|-----|----------------|----------------------|
| Nathan et al. 2014 | Cross-sectional | 145 | 68 ±7.37 | 46.9% above 10 years of education | 42.8 | 26.6±1.9 (24 to 30) | Age 55–90 years; subjective memory complaint verified by a family relative; at least 1 standard deviation deficit in a measure of episodic memory; an MMSE score of 2–4; a CDR scale score of 0.5 (with a score of 0.5 for the memory subscale); a clinical diagnosis of amnestic MCI, but preservation of general cognitive and functional performance to not meet clinical criteria for AD; GDS scale score ≤6; and Hachinski Modified Ischemic Scale score ≤4 | SWM between errors | 27.7 | 8.3 | - | - | - | - |
| Saunders and Summers et al. 2014 | Cross-sectional | 131 | Control: 69.3±5.83 S-MCI: 71.1±7.56 A-MCI: 71.8±7.02 | Control: 13.5±3.14 S-MCI: 13.00±3.52 A-MCI: 13.1±3.35 | 48.09 | - | Memory problems, with a history of decline from a former level; preserved cognitive functioning; intact activities of daily living; no history of significant medical, neurological, or psychiatric condition; no history of major risk factors for vascular disease; and no history of alcohol abuse, sensory impairment, or impairment of hand mobility. | SWM total errors (S-MCI) | 42.06 | 15.05 | 32 | 33.68 | 13.08 | Age, WTR (a-MCI), DRS II (a-MCI), NART delayed (a-MCI) | Education, sex, WIAT (S-MCI), WAIS-R, TTS, GDS, BNT, CERAD delayed (S-MCI), BNT (S-MCI), DRS II delayed (S-MCI) |
| Egerházi et al. 2014 | Cross-sectional | 40 | 55±6 | - | 47.5 | 28±0.6 | No neurological symptoms or other physical disorders, amnestic MCI diagnosis according to the criteria of Petersen, CDR ≥0.5, mild short-term memory loss, with symptoms insufficient for the diagnosis of dementia according to the criteria of the DSM-IV, MMSE≥26, normal CT/MRI, no medication intake | SWM (Z-score) | -0.871 | - | - | - | - | - | - |
| Collie et al. 2020 | Cohort | 46 | Control: 65.9±5.37 MCI: 67.8±7.75 | Control: 12.3±3.7 MCI: 11.6±3.86 | 45.65 | 28.12±1.42 | Age ≥50 years, no psychiatric and neurological diagnosis. Exclusion criteria at this stage included a history of respiratory, circulatory, or endocrine disease, personal or family history of psychiatric illness, head injury or substance abuse. MCI based on CERAD neuropsychological battery | SWM total errors (A-MCI) | 33.3 | 15.81 | 23 | 25.19 | 12.24 | 23 | Age, sex, education, MMSE, depression, CERAD, CFA, WMS-R, state and trait anxiety test, and NART |
| Facal et al. 2014 | Cross-sectional | 145 | MDA-MCI: 70.4±9.49 SDA-MCI: 67.8±9.40 | Control: 10.22±5.05 | 37.93 | 27.00±1.81 | MMSE ≥20, no history of clinical stroke, traumatic brain injury, motor sensory defects, alcohol or drug abuse/dependence, not diagnosed with any significant medical or psychiatric illnesses, GDS <10. | SWM Correct items (MDA-MCI) | 21.76 | 7.09 | 44 | - | - | - | - | - |

Continue...
| Author (year) | Study design | Sample size | Mean age | Education | Male ratio (%) | MMSE score | Eligibility criteria MCI | Eligibility criteria-control | CANTAB subtests for WM | MCI | Control | Associated factors | Non-associated factors | Age, education, Visual acuity |
|--------------|--------------|-------------|----------|-----------|----------------|------------|--------------------------|-----------------------------|--------------------------|-----|---------|------------------|--------------------------|--------------------------|
| Juncos-Rabadán et al. 2014 | Cross sectional | 170 | - | 68.1±8.75 | Healthy control: 68.1±8.75 | MDA-MCI: 71.0±6.36 | SDA-MCI: 68.9±8.69 | MDA-MCI: 22.4±1.59 | No prior diagnosis of dementia, psychiatric or neurological disorders, severe illness, death or blindness, not receiving chemotherapy, not consuming of substances or alcohol, informant-corroborated memory complaints, performance of 1.5 SDs below age norms on the Spanish version of (CVLT), no significant or minimal impact on activities of daily living assessed by the Lawton and Brody Index, not demented according the NINCDS-ADRA and DMS-N criteria. Normal or corrected-to-normal vision and hearing and visual acuity | No prior diagnosis of dementia, psychiatric or neurological disorders, severe illness, death or blindness, not receiving chemotherapy, not consuming of substances or alcohol, informant-corroborated memory complaints, performance of 1.5 SDs below age norms on the Spanish version of (CVLT), no significant or minimal impact on activities of daily living assessed by the Lawton and Brody Index, not demented according the NINCDS-ADRA and DMS-N criteria. Normal or corrected-to-normal vision and hearing and visual acuity | Memory complaints (informant), MMSE, CVLT, Language, Attention, calculation, Praxis | 54 | Age, education, Visual acuity |
| Summers and Saunders cohort 2012 | Cohort | 106 | Control: 73.80±7.9 | Control: 71.04±7.1 | Progressed MCI: 14.60±3.5 | Progressed: 12.55±3.0 | 46.25 | Memory problems with a history of decline; preserved cognitive functioning; intact activities of daily living; no history of significant medical, neurological, or psychiatric condition; no history of major risk factors for vascular disease; and no history of alcohol abuse, sensory impairment, or impairment to hand mobility | Memory problems with a history of decline; preserved cognitive functioning; intact activities of daily living; no history of significant medical, neurological, or psychiatric condition; no history of major risk factors for vascular disease; and no history of alcohol abuse, sensory impairment, or impairment to hand mobility | Memory complaints (informant), MMSE, CVLT, Language, Attention, calculation, Praxis | 25 | Age, education, FSIQ, DRS, sex, WAIS–RAVLT, BNT |
| Kleeckiuk and Summers cohort 2014 | Cohort | 118 | 60–90 | - | 38.98 | No previous medical, neurological, or psychological conditions, no evidence of dementia, AEMSS score ≥, preserved activities of daily living, subclinical impairment as a performance 1.28 standard deviations or greater below age-appropriate normative references. | No previous medical, neurological, or psychological conditions, no evidence of dementia, AEMSS score ≥, preserved activities of daily living, subclinical impairment as a performance 1.28 standard deviations or greater below age-appropriate normative references. | Memory complaints (informant), MMSE, CVLT, Language, Attention, calculation, Praxis | 49 | Age, education, sex, HADS Depression |
| Author (year)               | Study design | Sample size | Mean age | Education | Male ratio (%) | MMSE score | Eligibility criteria MQI | Eligibility criteria-control | CANTAB subtests for WM | MCI | Control | Associated factors | Non-associated factors |
|----------------------------|--------------|-------------|----------|-----------|----------------|------------|--------------------------|-----------------------------|------------------------|-----|---------|-------------------|------------------------|
| Cacciamani et al. 2018     | cohort 25    | 46          | 27.04±0.31 | 40        |                |            |                          |                             | SWM Strategy (overall MCI) | 37.44 | 0.72    | 25                |                        |
|                           |              |             |          |           |                |            |                          |                             | SWM strategy (MCI-AD)     | 38.17 | 0.95    | 12                |                        |
|                           |              |             |          |           |                |            |                          |                             | SWM strategy (MCI-ambiguous) | 36.77 | 1.06    | 13                |                        |
|                           |              |             |          |           |                |            |                          |                             | SWM errors (overall MCI)   | 53.96 | 4.25    | 25                |                        |
|                           |              |             |          |           |                |            |                          |                             | SWM errors (MCI-AD)       | 59.92 | 5.73    | 12                |                        |
|                           |              |             |          |           |                |            |                          |                             | SWM errors (MCI-ambiguous) | 48.46 | 6.04    | 13                |                        |
|                           |              |             |          |           |                |            |                          |                             | RVP A (overall MCI)        | 0.81  | 0.02    | 25                |                        |
|                           |              |             |          |           |                |            |                          |                             | RVP A (MCI-AD)             | 0.81  | 0.03    | 12                |                        |
|                           |              |             |          |           |                |            |                          |                             | RVP A (MCI-ambiguous)      | 0.82  | 0.01    | 12                |                        |
| Cacciamani et al. 2018     | cohort 263   | 68.3±9.1    | 10.4±4.5 | 56        | 25±5±3.9       |            |                          |                             | Age, sex, education, FAQ, MMSE, CDR, GDS, Hachinski Modified Ischemic Scale, Logical Memory II, Mental Deterioration Battery, MMSE |              |          |                   |                        |
|                           |              |             |          |           |                |            |                          |                             | Total-tau, phospho-tau     |              |          |                   |                        |
| Reijs et al. 2017          | cohort 263   | 68.3±9.1    | 10.4±4.5 | 56        | 25±5±3.9       |            |                          |                             | Age, sex, education, FAQ, MMSE, CDR, Aβ, 42, FSIQ, DRS-2, Digit Span (forward and backward) |              |          |                   |                        |
|                           |              |             |          |           |                |            |                          |                             | Wordlist learning and delayed recall and recognition, animal fluency |              |          |                   |                        |
| Klecociuk and Summers et al. 2014 | cohort 122 | 70.6±17.99 |                | a-MCI: 70.5±15.97 | a-MO: 70.5±15.97 | 14.4±3±1.16 | 14.4±3±1.16 | 69.2±16.56 | Control: 72.6±16.52 | 12.4±8±3.53 | 12.4±8±3.53 | 39.34 | -       |                   |                        |
|                           |              |             |          |           |                |            |                          |                             | Presence of cognitive complaints (e.g., memory, attention); preserved general cognition (as assessed by the DRS-2, self-reported capacity to maintain independent daily functioning (confirmed by an informant); no history of major medical, neurological, or psychiatric illness); no history of major risk factors for vascular disease and no history of sensory impairment or impairment to hand mobility. |              |          |                   |                        |
|                           |              |             |          |           |                |            |                          |                             | SWM total errors (a-MCI)   | 20.29 | 17.77   | 23                |                        |
|                           |              |             |          |           |                |            |                          |                             | SWM total errors (na-MCI)  | 32.04 | 18.83   | 26                | 29.42 | 18.52   |                        |
|                           |              |             |          |           |                |            |                          |                             | SWM total errors (na-MCI+) | 36.63 | 18.96   | 23                |                        |
|                           |              |             |          |           |                |            |                          |                             | SSP length (MCI-AD)        | 5.52  | 0.91    | 23                |                        |
|                           |              |             |          |           |                |            |                          |                             | SSP length (na-MCI)        | 4.73  | 0.71    | 25                |                        |
|                           |              |             |          |           |                |            |                          |                             | SSP length (a-MCI+)        | 4.74  | 0.71    | 23                |                        |
|                           |              |             |          |           |                |            |                          |                             | RVP latency (a-MCI)        | 480.92 | 112.31  | 23                |                        |
|                           |              |             |          |           |                |            |                          |                             | RVP latency (na-MCI)       | 545.36 | 108.20  | 26                | 46.04 | 89.73   |                        |
|                           |              |             |          |           |                |            |                          |                             | RVP latency (a-MCI+)       | 519.02 | 152.07  | 23                |                        |
|                           |              |             |          |           |                |            |                          |                             | RVP A (a-MCI)              | 0.90  | 0.047   | 23                |                        |
|                           |              |             |          |           |                |            |                          |                             | RVP A (na-MCI)             | 0.87  | 0.05    | 26                | 0.902 | 0.042   |                        |
|                           |              |             |          |           |                |            |                          |                             | RVP A (a-MCI+)             | 0.85  | 0.047   | 23                |                        |

Table 1. (Continued.)
| Author (year)            | Study design | Sample size | Mean age | Education | Male ratio (%) | MMSE score | Eligibility criteria MCI | CANTAB subtests control | MCI | Control | Associated factors | Non-associated factors |
|-------------------------|--------------|-------------|----------|-----------|----------------|------------|--------------------------|------------------------|-----|---------|-------------------|------------------------|
| Saunders and Summers et al. 2011 | cohort 106 | 69.8±7.75 | 71.4±7.22 | a-MCI: 70.9±6.85 | 13.50±3.09 | 7.14±3.50 | - | - | Memory problems with a history of decline; preserved cognitive functioning; intact activities of daily living; no history of significant medical, neurological, or psychiatric condition; no history of major risk factors for vascular disease; no history of alcohol abuse, sensory impairment, or impairment to hand mobility | SWM strategy (a-MCI) 37.61 | 23.56 | 52 | 35.42 | 15.29 |
| | | 6.9±7.75 | 7.14±3.50 | na-MCI: 6.9±7.75 | 13.17±3.50 | 7.14±3.50 | - | - | SWM strategy (na-MCI) 38.2 | 10.7 | 29 | | |
| | | 7.14±3.50 | 7.14±3.50 | a-MCI: 7.14±3.50 | 13.04±3.39 | 7.14±3.50 | - | - | SWM errors (a-MCI) 50.5 | 14.56 | 52 | 35.2 | 12.84 |
| | | 7.14±3.50 | 7.14±3.50 | na-MCI: 7.14±3.50 | 14.56±1.7 | 7.14±3.50 | - | - | SWM total errors (na-MCI) 43.39 | 14.75 | 29 | | |
| | | 7.14±3.50 | 7.14±3.50 | a-MCI: 7.14±3.50 | 14.56±1.7 | 7.14±3.50 | - | - | SSP length (a-MCI) 5.2 | 0.57 | 29 | 5.82 | 0.76 |
| | | 7.14±3.50 | 7.14±3.50 | na-MCI: 7.14±3.50 | 0.57±0.57 | 7.14±3.50 | - | - | SSP length (na-MCI) 5.2 | 0.57 | 29 | 5.82 | 0.76 |
| | | 7.14±3.50 | 7.14±3.50 | a-MCI: 7.14±3.50 | 14.56±1.7 | 7.14±3.50 | - | - | RVP latency (a-MCI) 0.87 | 0.07 | 52 | 0.33 | 0.05 |
| | | 7.14±3.50 | 7.14±3.50 | na-MCI: 7.14±3.50 | 0.07±0.07 | 7.14±3.50 | - | - | RVP latency (na-MCI) 0.85 | 0.05 | 29 | 0.33 | 0.05 |
| | | 7.14±3.50 | 7.14±3.50 | a-MCI: 7.14±3.50 | 14.56±1.7 | 7.14±3.50 | - | - | SWM total hits 10.61 | 5.23 | 29 | 13.68 | 4.57 |
| | | 7.14±3.50 | 7.14±3.50 | na-MCI: 7.14±3.50 | 5.23±0.52 | 7.14±3.50 | - | - | RVP total hits 10.61 | 5.23 | 29 | 13.68 | 4.57 |
| Stanojlova et al. 2020 | cohort 45 | 68.3±8.37 | 68.3±8.37 | - | - | 8.88 | - | - | MCI diagnosis based on the criteria of the MCI Working Group of the European Consortium on Alzheimer’s disease, age between 45 and 90 years, with a TMSE score of >23, (MoCA)-Thai score of <25 | SWM between errors | 53.48 | 13.10 | 51.45 | 14.81 |
| | | 68.3±8.37 | 68.3±8.37 | - | - | 8.88 | - | - | SWM total errors | 55.39 | 13.31 | 52.64 | 15.51 |
| | | 68.3±8.37 | 68.3±8.37 | - | - | 8.88 | - | - | RVP mean latency | 2.77 | 0.12 | 2.72 | 0.11 |
| | | 68.3±8.37 | 68.3±8.37 | - | - | 8.88 | - | - | RVP total hits | 10.61 | 5.23 | 13.68 | 4.57 |
| Campos-Magdaleno et al. 2021 | cohort 208 | 64.2±8.3 | 70.9±7.54 | - | - | 35.13 | - | - | No previous diagnosis of neurologic disorders, normal adults in general functioning and specific domain tests, attending primary care health centers with self-reported cognitive concerns; confirmation of these concerns by the short Spanish version of the questionnaire for subjective memory complaints | SSP (MCI-stable) | 4.5 | 2.82 | 32 | | |
| | | 70.9±7.54 | 70.9±7.54 | - | - | 35.13 | - | - | SSP (MCI-worsened) | 3.9 | 2.87 | 27 | 5.0 | 3.84 |

"In this study, "Progressed" is used for the participants who were classified at baseline as a-MCI or na-MCI but were reclassified as a-MCI following the 20-month assessment; "Subjects with mild cognitive impairment and Alzheimer’s disease like CSF profiles; "MCI+ defined as multiple domains amnestic mild cognitive impairment in this study; CANTAB: Cambridge Neuropsychological Test Automated Battery; MMSE: Mini-Mental State Examination; WM: working memory; MCI: mild cognitive impairment; SWM: spatial working memory; SSP: spatial span; RVP: rapid visual information processing; DMS: delayed matching to sample; S-MCI: subjective MCI; A-MCI: amnestic MCI; NPQ: Neuropsychiatric Inventory Questionnaire; FAQ: Functional Activities Questionnaire; APOE: apolipoprotein E; A: amyloid-beta; SDA-MCI: single-domain MCI; CFG: Cognitive Failures Questionnaire; MDA-MCI: multiple-domain amnestic MCI; NMDA-MCI: multiple-domain non-amnestic MCI; GDS: Geriatric Depression Scale; BNT: Boston Naming Test; TMSE: Thai Mental State Examination; MoCA: Montreal Cognitive Assessment; CERA: Consortium to Establish a Registry for Alzheimer’s Disease; CAMCOG: Cambridge Cognitive Examination; CVLT: California Verbal Learning Test; DRS: dementia rating scale; RCFT: Rey Auditory Verbal Learning Test; RCF: Rey Complex Figure Test; FSQ: Full Scale Intelligence Quotient; WAB: Wechsler test of adult reading; CCI: Charlson Comorbidity Index; DSP: Digit Span; WAIS-III: Wechsler Adult Intelligence Scale, 3rd edition; LNS: Letter-Number Sequencing; MMSE: Mini Mental State Examination; CD-R: Clinical dementia rating; FAQ: the Functional Assessment Questionnaire; WMS: Wechsler Memory Scale; S-CM: specific memory complaints questionnaire; SD: standard deviation; MINICD: ADRDA; the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association; TMSE: Thai mental state examination; MOANS: Mayo Older American Normative; AEMSS: age- and education-corrected MOANS scaled scores (AEMSS) score."
Figure 2. Meta-analysis of comparing patients with mild cognitive impairment and healthy controls based on "total errors" measure of spatial working memory (SWM) test of Cambridge Neuropsychological Test Automated Battery. The purple indicator is the final result. (Test for heterogeneity: I²: 81.28%; p<0.01).

Figure 3. Meta-analysis of comparing patients with mild cognitive impairment and healthy controls based on "length" measure of spatial span (SSP) test of Cambridge Neuropsychological Test Automated Battery. The purple indicator is the final result. (Test for heterogeneity: I²: 82.76%; p<0.01).

Figure 4. Meta-analysis of comparing patients with mild cognitive impairment and healthy controls based on "A’ and mean latency" measures of Rapid Visual Processing (RVP) test of Cambridge Neuropsychological Test Automated Battery. The purple indicators are the final results. (Test for heterogeneity: overall I²: 46.49%; p-value=0.05; A’ I²: 67.87 %; p=0.01; Latency I²: 0%; p=0.50).
Risk of bias
The results of the RoB assessments are shown in Table 2. There was not any exposure studied in our systematic review; so, the third question of the checklist, which assessed the validity of the exposure measurement, was not applicable. Furthermore, we only considered MMSE, Petersen, and MoCA as standard index tests for MCI diagnosis. Because of that, the overall rate of standard measurement of conditions was low. Besides, only 35.7% of the studies mentioned the setting properly. Briefly, there were no considerable levels of bias in most of the included studies.

DISCUSSION
This study assessed the WM function of patients with MCI and compared it between MCI patients and healthy people using the CANTAB. Also, influencing factors on WM were considered. SWM, SSP, and RVP were the most commonly used subtests of CANTAB for assessing the WM. The results of quantitative synthesis revealed a significant difference between healthy controls and patients with MCI regarding the CANTAB-based WM assessments. Also, the available evidence suggested a significant correlation between CSF levels of tau-protein and Aβ with WM function in patients with MCI.

| Study                     | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 |
|---------------------------|----|----|----|----|----|----|----|----|
| Nathan et al., 2017       | Yes| No | NA | Yes| Yes| Yes| Yes| Yes|
| Saunders and Summers, 2010| Yes| No | NA | No | Yes| No | Yes| Yes|
| Égerházi et al., 2007     | No | No | NA | Yes| Yes| Yes| Yes| No |
| Collie et al., 2002       | Yes| No | NA | Yes| Yes| Yes| Yes| Yes|
| Facal et al., 2014        | Yes| No | NA | Yes| Yes| Yes| Yes| Yes|
| Juncos-Rabadán et al., 2014| Yes| Yes| NA | Yes| Yes| Yes| Yes| Yes|
| Summers and Saunders, 2012| Yes| No | NA | No | Yes| No | Yes| Yes|
| Klekociuk and Summers, 2014| Yes| Yes| NA | No | Yes| Yes| Yes| Yes|
| Cacciamani et al., 2017   | Yes| No | NA | Yes| Yes| Yes| Yes| Yes|
| Reijs et al., 2017        | Yes| Yes| NA | Yes| Yes| Yes| Yes| Yes|
| Klekociuk and Summers, 2014| Yes| Yes| NA | No | Yes| Yes| Yes| Yes|
| Saunders and Summers, 2011| Yes| No | NA | No | Yes| Yes| Yes| Yes|
| Stonesaovapak et al. 2020| No | No | NA | Yes| Yes| Yes| Yes| Yes|
| Campos-Magdaleno et al., 2020| Yes| Yes| NA | Yes| Yes| Yes| Yes| Yes|

Overall: 85.7% 35.7% 57.1% 100% 85.7% 100% 92.8%

NA: not applicable.

One of the preclinically deteriorated domains in AD and MCI is WM. WM comprises a cognitive spectrum from attention allocation to specific stimuli to complex decision-making. Some studies have suggested WM as an early predictor of AD. Regardless of the method of assessment, WM function is found to significantly deteriorate in MCI. WM is subdivided into verbal and visual components. Emrani et al. found that the visual component of WM is more sensitive than verbal WM, for distinguishing between MCI patients and healthy older adults. Align with the aforementioned study, our quantitative synthesis reveals that the WM of MCI patients based on SWM, SSP, and RVP is impaired significantly, so it can be suggested as a proper diagnostic evaluation for MCI.

CANTAB is a novel neuropsychological battery for evaluating cognitive state. This battery has shown promising outcomes in the diagnosis of cognitive function in healthy older adults, MCI, AD, or any other possible diseases that may compromise cognition. It has several benefits over traditional paper-pencil tests, such as reducing the risk of human error and data noise, recording reaction times precisely, lowering data storing problems, easing task scoring, and having access to normative comparison. Also, CANTAB has a non-verbal structure that makes it more convenient for people with different languages. Regarding the
disadvantages, CANTAB is a time-consuming test, and providing the test instruments imposes an extra cost to the clinicians, which limits its usage in resource-limited settings. The accuracy of WM tests of CANTAB battery in distinguishing between MCI patients and healthy older adults was studied in our review and CANTAB has shown to be a proper battery for MCI diagnosis.

As a secondary outcome of the study, we assessed related factors with WM function in MCI patients. Aging is one of the confirmed predictors of cognitive decline61. Although WM function is found to be affected by age62, in most of our included studies, age was not associated with the WM scores of the patients. This may be because most of the participants in our study were older people while there is a need for the participation of patients with a wider age range to survey the age differences.

The relation between CSF biomarkers and cognitive state is one of the interest areas for research. Soldan et al. in a cohort study investigated the performance of cognitively healthy adults on CANTAB-PAL and found that it was associated with CSF p-tau levels63. This study suggested that the AD-related CSF biomarker can predict specific cognitive dysfunctions. In our included studies, Aβ and tau-protein were associated biomarkers with WM functions of MCI patients. On the contrary, ApoE4, which is one of the most studied genetic factors associated with human cognition and one of the well-known predictors of AD64, was not associated with WM function of MCI patients, as reported in two studies39,40.

This study is a novel and unprecedented review of WM assessment of MCI patients with CANTAB. One of the challenges related to this study was that the included studies did not report the sensitivity and specificity of CANTAB for the diagnosis of WM deficits in MCI patients. This should be considered in future studies. The other related limitation was that the included studies used heterogeneous criteria for baseline diagnosis of MCI; thus, the results cannot be generalized to all of the considered populations. Nevertheless, a comprehensive review of available evidence with a systematic approach was the main strength of this study.

This study reveals that WM is an impaired cognitive domain at MCI. Based on our assessment, WM subtests of CANTAB, including SWM, SSP, and RVP, can pinpoint deficits in MCI patients, so CANTAB-based WM assessment can help the clinicians in the diagnosis of MCI. Also, WM functions of MCI patients are associated with some of the AD-associated biomarkers, such as tau-protein and Aβ. There is a need for future well-designed studies on this topic to reach a comprehensive conclusion in terms of both diagnostic accuracies of WM profiles of CANTAB battery and factors that can affect the WM in MCI patients.

Authors’ contributions. ZS, MF: These two authors contributed equally to this work and both of them should be considered as shared co-first authorship. ZS: formal analysis, investigation, project administration, resources, writing – original draft. MF: formal analysis, investigation, project administration, resources, writing – original draft. AN: formal analysis, investigation, project administration, resources, writing – original draft. MT: conceptualization, validation, writing – review & editing.

REFERENCES

1. Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, et al. Current concepts in mild cognitive impairment. Arch Neurol. 2001;58(12):1985-92. https://doi.org/10.1001/archneur.58.12.1985
2. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med;2004;256(3):240-6. https://doi.org/10.1111/j.1365-2958.2004.01380.x
3. Kropman DS, Arrieu H, Petersen RC, Chételat G, Holtzman DM, Hyman BT, et al. Alzheimer disease. Nat Rev Dis Primers. 2015;1(1):33. https://doi.org/10.1038/nrdp.2014.021-00269-y
4. Busse A, Hensel A, Gühne U, Angermeyer MC, Riedel-Heller SG, MCI. Mild cognitive impairment: long-term course of four clinical subtypes. Neurology. 2006;67(12):2176-85; https://doi.org/10.1212/01.wnl.0000249117.23318.e1
5. Di Carlo A, Lamassa M, Baldereschi M, Inzitari M, Scalfato E, Farchi G, et al. CIND and MCI in the Italian elderly: frequency, vascular risk factors, progression to dementia. Neurology. 2007;68(12):1099-106. https://doi.org/10.1212/01.wnl.0000263132.99055.0
6. Ganguli M, Chang CCH, Snitz BE, Saxton JA, Vanderbilt J, Lee CW. Prevalence of mild cognitive impairment by multiple classifications: The Monongahela-Youghiogheny Healthy Aging Team (MYHAT) project. Am J Geriatr Psychiatry. 2010;18(8):874-83. https://doi.org/10.1016/j.jgp.2010.03.018
7. Larrieu S, Letermeur L, Orrego-Jo M, Fabrigoule C, Arrieu H, Le Carret N, et al. Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. Neurology. 2002;59(10):1594-9. https://doi.org/10.1212/0000249117.000000000000000000000
8. Lopez OL, Jagust WJ, DeKosky ST, Becker JT, Fitzpatrick A, Dulan C, et al. Prevalence and classification of mild cognitive impairment in the cardiovascular health study cognition study: part 1. Arch Neurol. 2003;60(10):1385-9. https://doi.org/10.1001/archneur.60.10.1385
9. Prince M, Wimo A, Guerchet M, Ali GC, Wu YT, Prina M. World Alzheimer Report 2015. The global impact of dementia: an analysis of prevalence, incidence, costs and trends. London: Alzheimer’s Disease International; 2015. [cited on Jun 17, 2022]. Available from: https://www.alzint.org/WorldAlzheimerReport2015.pdf
10. Reis BJ, Ramakers IHGB, Köhler S, Teunissen CE, Kool-Simmelink M, Nathan PJ, et al. Memory correlates of Alzheimer’s disease cerebrospinal fluid markers: a longitudinal cohort study. J Alzheimers Dis. 2017;60(3):1119-28. https://doi.org/10.3233/JAD-160766
11. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol. 1999;56(3):303-8. https://doi.org/10.1001/archneur.56.3.303.
12. Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Mild cognitive impairment. Lancet. 2006;367(9518):1262-70. https://doi.org/10.1016/S0140-6736(06)68542-5
55. Cronin DA, Peacock CE, Henderson JM. Visual and verbal working memory loads interfere with scene-viewing. Atten Percept Psychophys. 2020;82(6):2814-20. https://doi.org/10.3758/s13414-020-02078-1

56. Emrani S, Wasserman V, Matusz E, Miller D, Lamar M, Price CC, et al. Visual versus verbal working memory in statistically determined patients with mild cognitive impairment: on behalf of the consortium for clinical and epidemiological neuropsychological data analysis (CENDA). J Int Neuropsychol Soc. 2019;25(10):1001-10. https://doi.org/10.1017/S1355617719000388

57. Fray PJ, Robbins TW, Sahakian BJ. Neuropsychiatric applications of CANTAB. Journal of Geriatric Psychiatry. 1996;11(4):329-36. https://doi.org/10.1034/s13414-020-02078-1

58. Lenehan ME, Summers MJ, Saunders NL, Summers JJ, Vickers JC. Does the Cambridge Automated Neuropsychological Test Battery (CANTAB) distinguish between cognitive domains in healthy older adults? Assessment. 2016;23(2):163-72. https://doi.org/10.1177/1073191115581474

59. Gonçalves MM, Pinho MS, Simões MR. Construct and concurrent validity of the Cambridge neuropsychological automated tests in Portuguese older adults without neuropsychiatric diagnoses and with Alzheimer’s disease dementia. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2018;25(2):290-317. https://doi.org/10.1080/13825585.2017.1294851

60. Robbins TW, James M, Owen AM, Sahakian BJ, McInnes L, Rabbitt P. Cambridge Neuropsychological Test Automated Battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers. Dementia. 1994;5(5):266-81. https://doi.org/10.1159/000106735

61. Murman DL. The impact of age on cognition. Semin Hear. 2015;36(3):111-21. https://doi.org/10.1055/s-0035-1555115

62. Economou A, Papageorgiou S, Karageorgiou C. Working-delayed memory difference detects mild cognitive impairment without being affected by age and education. J Clin Exp Neuropsychol. 2006;28(4):528-35. https://doi.org/10.1080/13803390590949340

63. Soldan A, Pettigrew C, Moghekar A, Albert M, BiOCARD Research Team. Computerized cognitive tests are associated with biomarkers of Alzheimer’s disease in cognitively normal individuals 10 years prior. J Int Neuropsychol Soc. 2016;22(10):968-77. https://doi.org/10.1017/S1355617716000722

64. Emrani S, Arain HA, DeMarshall C, Nuriel T. APOE4 is associated with cognitive and pathological heterogeneity in patients with Alzheimer’s disease: a systematic review. Alzheimers Res Ther. 2020;12(1):141. https://doi.org/10.1186/s13195-020-00712-4