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A Review on the Comparison of Working Memory Performance, Cognitive Function, and Behavioral, and Psychological Symptoms across Normal Aging, Mild Cognitive Impairment, and Alzheimer's Disease

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Abstract

This study explores the roles of working memory, cognitive functions, and behavioral and psychological symptoms in the contexts of aging, mild cognitive impairment (MCI), and Alzheimer's disease (AD). Employing a systematic review approach, insights were synthesized from diverse research perspectives. Furthermore, we aimed to investigate the association between changes in brain metabolism and cognitive score in ADNI dataset. Key findings indicate that assessment of recognition memory performance serves as a critical indicator for identifying MCI and tracking its progression to AD. Additionally, evaluating spatial working memory performance proves essential in monitoring advancement from MCI to AD stages. Furthermore, the study underscores that trends in performance on the Digit Symbol Substitution Test and the Sequencing Test among healthy adults, those with MCI, or dementia tend to converge around the age of 100. In instances of accelerated aging, neuronal loss varies across different cell groups and brain regions. The research concludes that in individuals experiencing mild to severe cognitive impairment, performance in balance, strength, and aerobic fitness correlates closely with working memory while showing no significant association with episodic memory.

Keywords: Working Memory, Cognitive Function, Behavioral Symptoms, Normal Aging

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Introduction

Population aging represents a prominent societal shift in the 21st century, marked by a rapid increase in the proportion of older adults within the global population (1). This demographic transformation has led to a heightened prevalence of age-related neurological conditions, implying to significant socio-economic implications (2–5). Presently, approximately 50 million individuals live with dementia worldwide, with associated costs estimated at around 818 billion USD (6). According to the Centers for Disease Control and Prevention (CDC), Alzheimer's disease (AD) ranks as the sixth leading cause of death overall and

the fifth among individuals aged over 65 in the United States (7). The risk of developing AD escalates notably with advancing age (8), AD constituting the primary cause of dementia, encompassing 60 to 70 percent of all cases of cognitive impairment and dementia among older adults (9,10). In 2020, an estimated 6.7 million individuals aged 65 and older were affected by AD, a number projected to increase to 13.8 million by 2060 (11). Globally, this figure is expected to reach 80 million by 2040 (12).

Alzheimer's disease (AD) is a progressive neurological disorder characterized by impairments in working memory (WM), episodic memory, and executive function. These include challenges in selective and divided attention, difficulty inhibiting interfering stimuli, and deficiencies in manipulation skills. While episodic memory impairment is widely recognized and central to AD diagnosis, recent research has increasingly focused on the decline in WM and executive function observed in mild cognitive impairment (MCI), the preclinical stage of AD. Studies suggest that AD can be seen as a continuum, beginning with MCI and progressing to full AD, with subtle symptoms possibly emerging even before the MCI diagnosis (13). Symptoms of AD typically manifest in individuals over 65 years old, although early-onset AD can start between ages 30 and 60 (14). Despite the significant societal impact of AD, its exact causes remain unclear, and current treatments have limited effectiveness in halting or slowing its progression (15-19). Understanding the progression of AD is crucial, as most diagnoses occur in advanced stages when neurological damage is irreversible (18,20). It is now recognized that AD may initiate decades before clinical symptoms manifest (21). As observed in neuroimaging studies, early indicators of AD include memory impairment and atrophy in memory-related mesial temporal lobe (MTL) structures, particularly the hippocampus (22). Recent research underscores the loss of synaptic plasticity as a significant characteristic of AD, necessary for complex cognitive functions such as learning, abstract thinking, and memory (23). Mild cognitive impairment (MCI) is viewed as a transitional phase between normal cognitive aging and early dementia (24). It is characterized by subjective memory complaints and objective evidence of cognitive decline, typically in memory, while daily functional abilities remain intact (25-27). MCI represents a critical period during which cognitive restructuring and neuroplasticity, such as compensation mechanisms, are still possible, making cognitive therapies potentially beneficial in slowing AD progression during this stage. Monitoring tasks related to WM and executive function can signal the transition from normal cognition to MCI and eventually to AD (13). Nearly 50% of individuals with MCI progress to AD within five years (28). Concerns about cognitive changes and maintaining independence in daily activities are diagnostic criteria for MCI, with clinical presentations varying depending on the presence of memory impairment (9).

Despite extensive efforts, significant strides in altering the course of AD remain elusive, largely due to pathological changes that begin decades before clinical symptoms emerge (10). Early detection of cognitive disorders presents a challenging yet crucial opportunity for making informed decisions regarding early interventions (24). There is a growing urgency to predict AD based on neurocognitive abnormalities that appear before disease onset (29).

Given the global impact of this issue, this study investigates working memory performance, cognitive functions, and behavioral and psychological symptoms across the spectrum of normal aging, mild cognitive impairment (MCI), and Alzheimer's disease (AD). Reviewing research in this area is crucial to understanding cognitive decline. It provides insights into differences at various stages of cognitive impairment, aiding in early detection and intervention strategies. Ultimately, this research is essential for improving diagnostic and treatment strategies, and enhancing the quality of life for those impacted by cognitive decline. The subsequent sections include a comprehensive literature review, research methodology, findings, discussion, and conclusions. Furthermore, we aimed to investigate the association between changes in brain metabolism and cognitive score in ADNI dataset.

Literature

Mild cognitive impairment (MCI) is often marked by symptoms such as learning and memory issues, difficulties with executive functions, slower processing speeds, and problems with semantic language (30,31). Researchers divide MCI into three subtypes based on cognitive and pathological criteria (32,33): amnestic-MCI (a-MCI), multiple domains amnestic-MCI (a-MCI+), and nonamnestic-MCI (na-MCI). Individuals with a-MCI display clear episodic memory impairments, those with a-MCI+ have both episodic memory and other cognitive deficits, while those with na-MCI experience cognitive impairments that do not affect episodic memory (30). Recent studies suggest that early signs of visual episodic memory issues, executive function difficulties, linguistic/semantic memory challenges, attention problems, and WM deficits are significant predictors of the transition from MCI to AD (30,34).

Schneider-Garces et al. (35) showed that controlling for differences in WM load provides a dependable measure of WM capacity regardless of age. Kochan et al. (36) suggested that evaluating WM decline in preclinical populations compared to healthy adults could shed light on how pre-AD pathogenesis impacts WM. To investigate the onset of executive function and WM deficits, Belleville et al. (37) assessed attentional control using tasks that measured divided attention, online manipulation of stimuli, and inhibition of irrelevant stimuli in participants with a-MCI and a-MCI+. They discovered that individuals with AD performed significantly worse on all attentional control tasks compared to age-matched healthy adults, whereas MCI participants only showed poorer performance on the Brown-Peterson task with a 30-second delay in recall. Later, Belleville et al. (37) reported that MCI participants who later developed AD performed significantly worse than controls on tasks requiring manipulative skills and divided attention. Through cognitive and neuropsychological assessments, researchers were able to better predict which MCI participants were likely to progress to AD. These assessments demonstrated that tests of sustained attention, semantic

Table 1. Results of Spatial Working Memory, Pattern Recognition Memory, and Paired-Associate Learning Between the Alzheimer's Disease, Mild Cognitive Impairment, and Normal Groups a (29).

CANTAB Tests	Variables	AD	MCI	Normal	P Value	Comparison Between Each 2 Groups	P Value	Correlation with MMSE	
								Correlation Coefficient	P Value
SWM	Between errors	78.86 ± 24.59	60.11 ± 17.22	48.86 ± 14.98	0	Normal and MCI	0.101	-0.563	0
						Normal and AD	0.000		
						MCI and AD	0.008		
	Total errors	82.26 ± 28.11	65.66 ± 18.10	52.33 ± 15.26	0.001	Normal and MCI	0.076	-0.543	0
						Normal and AD	0.000		
						MCI and AD	0.029		
	Strategy	38.20 ± 9.29	39.94 ± 3.07	38.20 ± 3.48	0.348			0.181	0.218
PRM	Mean correct latency	4580.9 ± 1731.11	3271.4 ± 835.56	2855.2 ± 862.24	0.004	Normal and MCI	0.354	-0.596	0
						Normal and AD	0.007		
						MCI and AD	0.037		
	Correct number	14.86 ± 3.60	18.72 ± 3.10	20.93 ± 2.57	0	Normal and MCI	0.049	0.749	0
						Normal and AD	0.000		
						MCI and AD	0.001		
PAL	First trial memory score	4.20 ± 3.00	12.50 ± 4.17	15.66 ± 3.26	0	Normal and MCI	0.015	0.812	0
						Normal and AD	0.000		
						MCI and AD	0		
	Mean errors to success	8.52 ± 2.29	5.69 ± 2.98	3.82 ± 2.32	0	Normal and MCI	0.044	-0.733	0
						Normal and AD	0.000		
						MCI and AD	0.003		
	Total error adjusted	156.00 ± 46.42	55.55 ± 42.16	28.73 ± 16.01	0	Normal and MCI	0.052	-0.834	0
						Normal and AD	0.000		
						MCI and AD	0		

Abbreviations: CANTAB, Cambridge Neuropsychological Test Automated Battery; AD, Alzheimer disease; MCI, mild cognitive impairment; MMSE, Mini-mental State Examination; SWM, spatial working memory; PRM, pattern recognition memory; PAL, paired-associate learning.
a Values are expressed as mean ± SD.

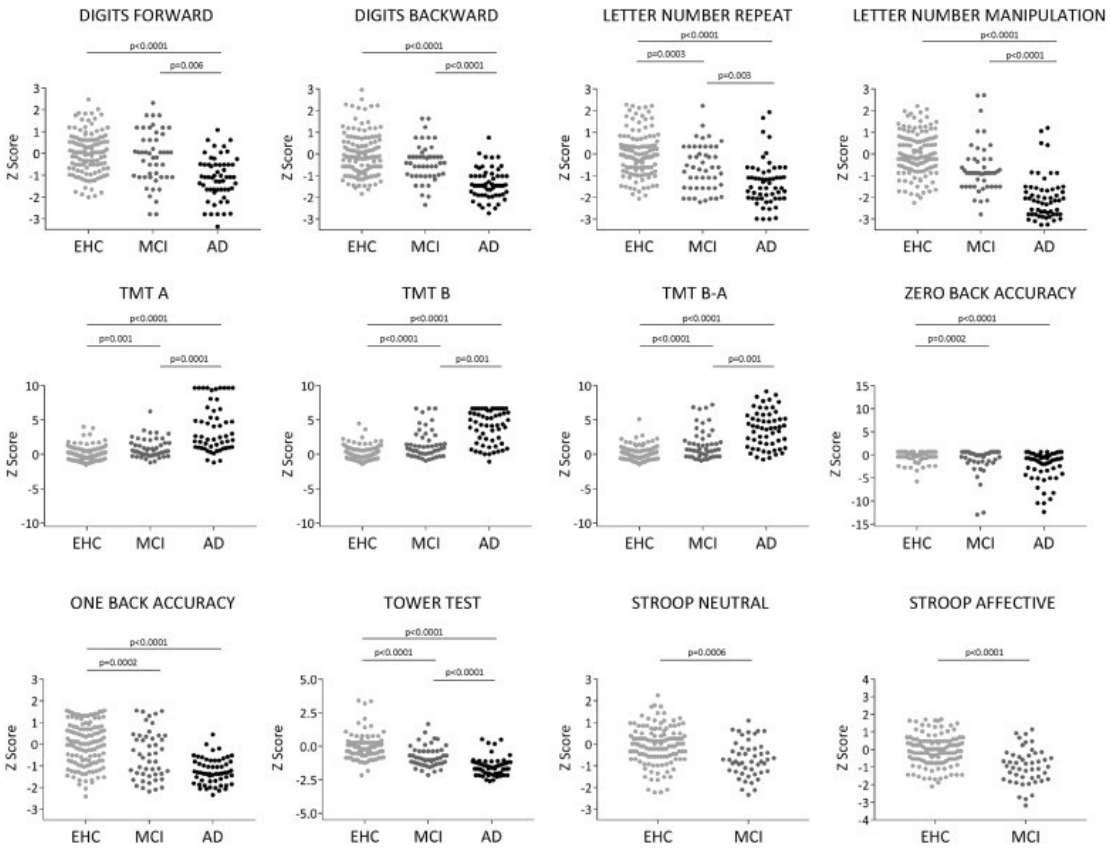

Figure 1. Frequency of WM/EF impairment in MCI and AD groups. Distribution of z scores between groups for each of the tests. Each dot in the graphs represents a subject. P values have been obtained through $\chi 2$ tests comparing the proportion of subjects below and above −1 z score between groups. Bonferroni adjustment for level of significance was set at P = .004. Note that there was a trend to significance in the comparison of EHC and MCI on digits backward (P = .009). Abbreviations: EHC, elderly healthy controls; MCI, mild cognitive impairment; AD, Alzheimer's disease; P, P value (57).

memory, WM, episodic memory, and selective attention could predict MCI or unimpaired functioning with 80% accuracy. Such assessments are valuable in clinical settings for monitoring cognitive function and detecting declines in executive function and WM over time, particularly in relation to episodic memory deterioration. The authors proposed that the a-MCI+ subtype might be the only true form of MCI since both episodic memory and cognitive function declines are uniquely associated with this condition. WM is crucial for cognitive activities ranging from selective attention to complex decision-making (13). It enables the short-term active maintenance of information for subsequent access and manipulation, incorporating both auditory information through the phonological loop and visual information via the visuospatial sketchpad. WM capacity can be evaluated using behavioral tasks that measure memory span, requiring participants to encode a list of stimuli (such as letters, numbers, words, or pictures), often involving selective or divided attention tasks to enhance WM capacity (38). Neuroimaging tools allow comparisons of brain activity during WM tasks across different populations, revealing both similarities and differences (13).

Among healthy older adults, high levels of physical activity are associated with enhanced cognitive performance, including faster information processing, improved attention (39), and better executive functions (EF) (40). Lifelong physical activity may lower the risk of dementia (41). Since physical activity also improves physical performance (e.g., muscle strength, walking speed, functional mobility, and balance) (42), it is unsurprising that there is a positive relationship between physical performance and cognition in healthy older adults (43). Specifically, older adults with higher levels of physical performance, such as mobility (44), balance (45), strength (44,46), and aerobic fitness (47), demonstrate better cognitive functions, including cognitive flexibility and overall cognition. Enhanced physical functioning, like balance (45) and strength (46,48), also decreases the risk of dementia (49), a relationship further strengthened in individuals with aMCI (50) or mild dementia (51). In individuals with aMCI, walking speed and Timed Up and Go (TUG) performance are associated with executive functions (EF) (50), which are higher cognitive functions supported by the prefrontal cortex (PFC) (52). It has been suggested that EF, rather than global cognition or memory, is essential for motor functions like balance and walking (53), and for performing activities of daily living (ADL) (54). This is supported by the positive relationship between walking and EF in a mixed group of cognitively healthy elderly and those with and without mild dementia (55).

	Rotated Factor Pattern			
Measures	Factor 1	Factor 2	Factor 3	Factor 4
Episodic Memory Eigenvalue= 2.92				
Logical Memory I	0.81	-0.21	0.10	0.34
Logical Memory II	0.80	-0.16	0.11	0.43
Buschke Delayed	0.75	-0.19	0.25	-0.03
Buschke Immediate	0.74	-0.24	0.27	0.17
Cognitive Speed Eigenvalue= 2.57				
TMT B	-0.28	0.85	-0.25	-0.23
TMT B-A	-0.28	0.84	-0.22	-0.18
TMT A	-0.16	0.63	-0.29	-0.27
Working Memory Eigenvalue= 2.04				
Digits Backward	0.19	-0.30	0.72	0.04
Letter-Number Rep.	0.16	-0.12	0.68	0.16
Digits Forward	0.17	-0.12	0.62	0.34
Executive Function Eigenvalue= 1.49				
Tower of London	0.23	-0.19	0.11	0.62
Letter-Number Man.	0.28	-0.37	0.24	0.49
One Back Accuracy	0.23	-0.40	0.26	0.46

Figure 2. Subdomains of WM/EF impairment. Rotated factor pattern of all cognitive measures extracted by VARIMAX rotation. Four factors were retained: episodic memory, cognitive speed, working memory, and executive function. Tests with a factor loading of 0.45 (or greater) were considered to load on a given factor (57).

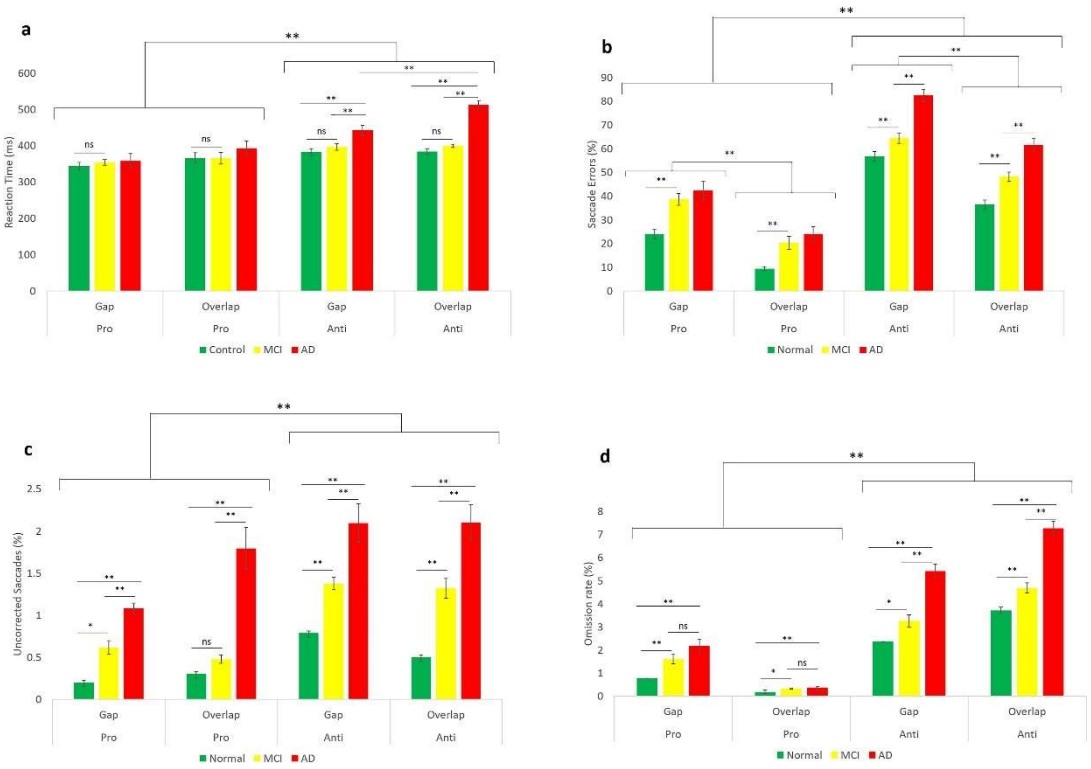

Figure 3. Bar graphs show the distribution of saccade reaction time (a), percentage of errors (b), uncorrected saccades (c) and saccade omission (d) in the gap and overlap conditions for all subjects in each group of participants. **p ≤ 0.001, *p ≤ 0.05, ns: not significant (58).

Hedayatjoo et al. (29) compared cognitive functions between individuals with MCI, AD, and healthy individuals, finding that impaired performance in new learning and recognition memory can indicate MCI and its progression to AD, while spatial working memory (SWM) assessment can be used to track MCI progression to AD (29). Warren et al. (56) investigated common neuropsychological tests for detecting cognitive and functional decline in the AD continuum. They focused on the ability of these tests to detect early stages of the disease, such as subjective memory complaints (SMC), finding that ADAS-13, RAVLT (learning), FAQs, ECog, and MoCA were predictors of AD progression, while TMT-B and RAVLT (immediate and forgetting) were not (56). Garcia-Alvarez et al. (57) examined WM and EF in MCI, linking them to frontal lobe morphometry and functional competence. They found that MCI patients performed worse on nearly all WM/EF tests, with EF impairments associated with reduced prefrontal cortical thickness. WM/EF accounted for over 50% of the variance in functional competence, with WM/EF impairments in MCI linked to specific frontal cortex circuitry compromises and associated with loss of daily functioning (57). Chehrehnegar et al. (58) reviewed executive performance deficits in MCI using saccade tasks, showing that eye-tracking technology, particularly the anti-saccade task, is a sensitive method for measuring cognitive impairment in dementia and MCI. This supports eye-tracking as a useful diagnostic biomarker for

Table 2. Structural brain correlates and cognitive functions involved in MMSE, ADAS-cog, and RAVLT (59).

Test	Cognitive functions	Relevant brain structures
MMSE	Temporo-spatial orientation	Precuneus Cortical gray matter
	Memory recall	Precuneus Intracranial arteries Hippocampus Cortical gray matter
	Concentration	Superior parietal lobule Cortical gray matter
	Language	Pars triangularis Hippocampus Caudal middle frontal gyrus Cortical gray matter
	Visuospatial function	Precuneus Superior parietal lobule Fusiform gyrus Caudal middle frontal gyrus Cortical gray matter
	Working memory	Precuneus Intracranial arteries Hippocampus Cortical gray matter
ADAS-cog	Temporo-spatial orientation	White matter lesions
	Memory and new learning: - Word recall - Orientation - Word recognition - Memorizing test instructions	Mesial temporal lobe White matter lesions Inferior lateral ventricles Hippocampus Putamen Amygdala Entorhinal cortex
	Language: - Commands - Spoken language ability - Naming objects / fingers - Word-finding difficulty - Comprehension	White matter lesions Inferior lateral ventricles Putamen Hippocampus
	Praxis: - Constructional praxis - Ideational praxis	White matter lesions
RAVLT	Episodic memory	White matter lesions Insula Inferior lateral ventricles Mesial temporal lobe Inferior parietal lobe Posterior cingulate cortex
	Attention	Putamen Inferior lateral ventricles Mesial temporal lobe Inferior parietal lobe Posterior cingulate cortex

assessing executive function in elderly individuals with cognitive impairment (58). Statsenko et al. (59) investigated the interplay between brain structure and function in normal aging and AD, employing machine learning to screen for MCI and dementia. They observed that global cognitive function undergoes slight changes with age in healthy individuals and generally remains stable in most disease cases (59). Volkers & Scherder (60) explored the correlation between physical performance and specific cognitive functions in older adults ranging from mild to severe cognitive impairment, highlighting a link between physical performance and WM in cognitively impaired older adults. The aim of this study was to examine the functioning of working memory, cognitive abilities, and behavioral and psychological symptoms in AD patients, MCI patients, and healthy individuals, aiming to better delineate differences and identify predictive factors for Alzheimer's disease and mild cognitive impairment (60).

Methodology

Hedayatjoo et al. (29) underscored the importance of predicting AD based on emerging neurocognitive dysfunction before clinical symptoms manifest. They focused on neuropathological changes in the mesial temporal lobe (MTL) and their impact on cognitive functions such as visual memory, working memory, and new learning. Their case-control study involved 15 patients with AD, 18 patients with MCI from Tehran University of Medical Sciences memory clinics, and 15 healthy controls. Participants underwent assessment using three subtests of the Cambridge Neuropsychological Test Automated Battery (CANTAB): spatial working memory (SWM), pattern recognition memory (PRM), and paired-associate learning (PAL) (29).

Warren et al. (56) evaluated the efficacy of common neuropsychological tests in detecting cognitive and functional decline across the AD spectrum. They utilized data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), recruiting participants via their website, media advertisements (newspaper, radio, social media), and healthcare providers. Their study encompassed 595 participants categorized as cognitively normal (CN), experiencing subjective memory complaints (SMC), early or late-stage MCI, or AD (56).

Garcia-Alvarez et al. (57) investigated impairments in WM and executive function (EF) among elderly healthy controls (EHCs), individuals with MCI, and those with AD. They compared 48 MCI patients, 124 EHCs, and 57 AD patients using various WM/EF measures, frontal lobe integrity indexes, and functional metrics. Sociodemographic, clinical status, cognitive variables, and MRI measures were compared between groups using chi-square and F tests (57).

Chehrehnegar et al. (58) utilized eye-tracking technology to explore saccade impairments, aiming to differentiate between a-MCI and other reference controls. They analyzed variables including executive function and MCI (58).

Statsenko et al. (59) examined age-related variability in cognitive and neuropsychological test scores in normal and accelerated aging. They developed regression models to predict functional performance in cognitive tests based on brain radiomics data. These models were trained on three ADNI cohorts—cognitively normal individuals, MCI patients, and dementia patients. They devised a method to classify examinees into cohorts of cognitively normal elderly, MCI patients, or dementia patients based on structure-function associations (59).

Finally, Volkers and Scherder (60) explored the relationship between physical performance and specific cognitive functions in older adults with mild to severe cognitive impairment. Their cross-sectional study involved 134 individuals with an average age of 82 years. Using multiple linear regression, they adjusted for covariates and global cognition levels to assess how mobility, strength, aerobic fitness, and balance affect working memory and episodic memory (60).

ADNI dataset

The data for this research were sourced from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). ADNI was initiated in 2003 as a collaborative effort between public and private entities, under the leadership of Principal Investigator Michael W. Weiner, MD. The primary aim of ADNI is to ascertain the efficacy of serial magnetic resonance imaging (MRI), alongside other biological markers and clinical and neuropsychological evaluations, in monitoring the progression of MCI and early Alzheimer's disease (AD).

In our study, we utilized both cross-sectional and longitudinal MRI data. Participants were selected from ADNI, encompassing ADNI2, ADNI3, and ADNIGO cohorts, provided they had PET data and MMSE score. Individuals with Subjective Memory Concerns (SMC) were excluded due to their low representation. The final sample included 390 healthy controls (HC), 931 individuals with MCI, and 289 individuals with AD.

All MCI participants were diagnosed with amnestic MCI based on the following criteria: Mini-Mental State Examination (MMSE) scores between 24 and 30, a self-reported memory complaint, objective memory impairment measured by education-adjusted scores on the Wechsler Memory Scale Logical Memory II, a Clinical Dementia Rating (CDR) of 0.5, no significant deficits in other cognitive domains, essentially preserved activities of daily living, and absence of dementia. The AD participants were diagnosed in accordance with the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD, with MMSE scores ranging from 20 to 26 (inclusive) and a CDR of 0.5 or 1.

Fluorodeoxyglucose positron emission tomography (FDG-PET) data were obtained in pre-processed form from the ADNI server. These FDG-PET images were acquired using various scanners, each adhering to platform-specific protocols. Dynamic 3D scans, consisting of six 5-minute frames, were collected 30-60 minutes post-injection of 185 MBq of 18F-FDG. To ensure consistency across different scanners, all original ADNI FDG-PET scans underwent standardized image pre-processing. Comprehensive details on FDG-PET acquisition and pre-processing can be found on the ADNI website (http://adni.loni.usc.edu/methods/documents/). For this study,

Table 3. Structural brain correlates and cognitive functions involved in DSST and TMT (59).

Test	Cognitive functions	Relevant brain structures
DSST	Motor speed	White matter lesions Caudate nucleus Cortical gray matter Inferior parietal cortex
	Working memory	White matter lesions Mesial temporal lobe Hippocampus Cortical gray matter Inferior parietal cortex Rostral middle frontal gyrus
	Attention	White matter lesions Mesial temporal lobe Hippocampus Caudate nucleus Cortical gray matter Inferior parietal cortex Rostral middle frontal gyrus
	Associative learning	White matter lesions Mesial temporal lobe Hippocampus Cortical gray matter
	Visuoperceptual abilities: - Scanning - Capacity to write/draw.	White matter lesions Mesial temporal lobe Hippocampus Fusiform gyrus Cortical gray matter Inferior parietal cortex
TMT	Visuoperceptual abilities: - Visual scanning - Visual-conceptual tracking - Visual-motor tracking	White matter lesions Mesial temporal lobe Inferior parietal cortex
	Information processing	White matter lesions Superior marginal cortex
	Attention	White matter lesions Mesial temporal lobe Inferior parietal cortex
	Motor speed	White matter lesions Inferior parietal cortex
	Memory: - Working memory - Rote memory	White matter lesions Mesial temporal lobe Inferior parietal cortex

the FDG-PET images were further spatially normalized to a custom FDG-PET standard space template and smoothed using a Gaussian smoothing kernel of 8 mm full-width at half maximum (FWHM) with SPM8.

We used a linear regression model to investigate the association between MMSE sub-scores and global FDG-PET SUVR adjusted for age, sex, and education.

Result and Discussion

Based on our analyses, there was a significant positive association between orientation, registration, and language with FDG-PET SUVR (Figure 4). Hedayatjoo et al. (29) conducted a study comparing three memory-based cognitive functions—spatial working memory (SWM), recognition memory, and new learning—across AD patients, MCI patients, and healthy individuals to detect early cognitive impairments associated with AD onset. They observed that SWM performance did not differ significantly between healthy individuals and those with MCI, while AD patients performed notably worse than both groups. In recognition memory tasks, healthy individuals achieved higher accuracy compared to both MCI and AD groups, with MCI patients outperforming AD patients. Regarding new learning abilities, healthy individuals exhibited superior performance compared to all groups, and MCI patients performed better than AD patients, as detailed in Table 1. These findings highlight that paired-associate learning (PAL) and pattern recognition memory (PRM) can effectively differentiate

Table 4. Results of multiple regression analysis with physical performances as predictors (Steps 3 and 4) of working memory and episodic memory after controlling for age, education, level of depression, number of comorbidities, medication, and MMSE (Steps 1 and 2) (60).

Dependent variable	Steps of analysis	Predictor	β	t	Cum $R2$	Incr $R2$
Working memory (n = 86)						
Step 1		Age	−0.23	2.12*		
		Education	0.26	2.50*		
		Depression	−0.22	2.13*		
		Comorbidity	−0.04	0.29		
		Medications	−0.13	1.1	0.17	0.17*
Step 2		MMSE	0.61	7.01**	0.49	0.32**
	Step 3	Mobility	0.08	0.77	0.49	0
	Step 4	MMSE ∗mobility	0.18	0.78	0.5	0
	Step 3	Balance	0.2	2.02*	0.51	0.03*
	Step 4	MMSE ∗ balance	0.15	0.39	0.52	0
	Step 3	Strength	0.31	3.43**	0.56	0.07**
	Step 4	MMSE ∗ strength	0. 81	1.79	0.57	0.01
	Step 3	Aerobic fitness	0.21	2.02*	0.51	0.03*
	Step 4	MMSE ∗ aerobic fitness	0.46	1.22	0.52	0.01
Episodic memory (n = 87)						
Step 1		Age	−0.29	2.60*		
		Education	0.19	1.82		
		Depression	0.07	0.62		
		Comorbidity	0.05	0.36		
		Medications	0.06	0.46	0.12	0.12
Step 2		MMSE	0.58	6.20**	0.4	0.29**
	Step 3	Mobility	−0.05	0.45	0.4	0
	Step 4	MMSE ∗mobility	−0.14	0.54	0.41	0
	Step 3	Balance	0.14	1.31	0.42	0.01
	Step 4	MMSE ∗ balance	−0.54	1.31	0.43	0.01
	Step 3	Strength	−0.07	0.72	0.41	0
	Step 4	MMSE ∗ strength	−0.40	0.76	0.41	0
	Step 3	Aerobic fitness	−0.00	0.02	0.4	0
	Step 4	MMSE ∗ aerobic fitness	−0.34	0.81	0.41	0.01

Notes: β: standardized beta coefficient; Cum: cumulative; Incr: increase; MMSE: Mini-Mental State Examination; t: t statistic. ∗ P value < 0.05; ∗∗ P value <0.01. (60).

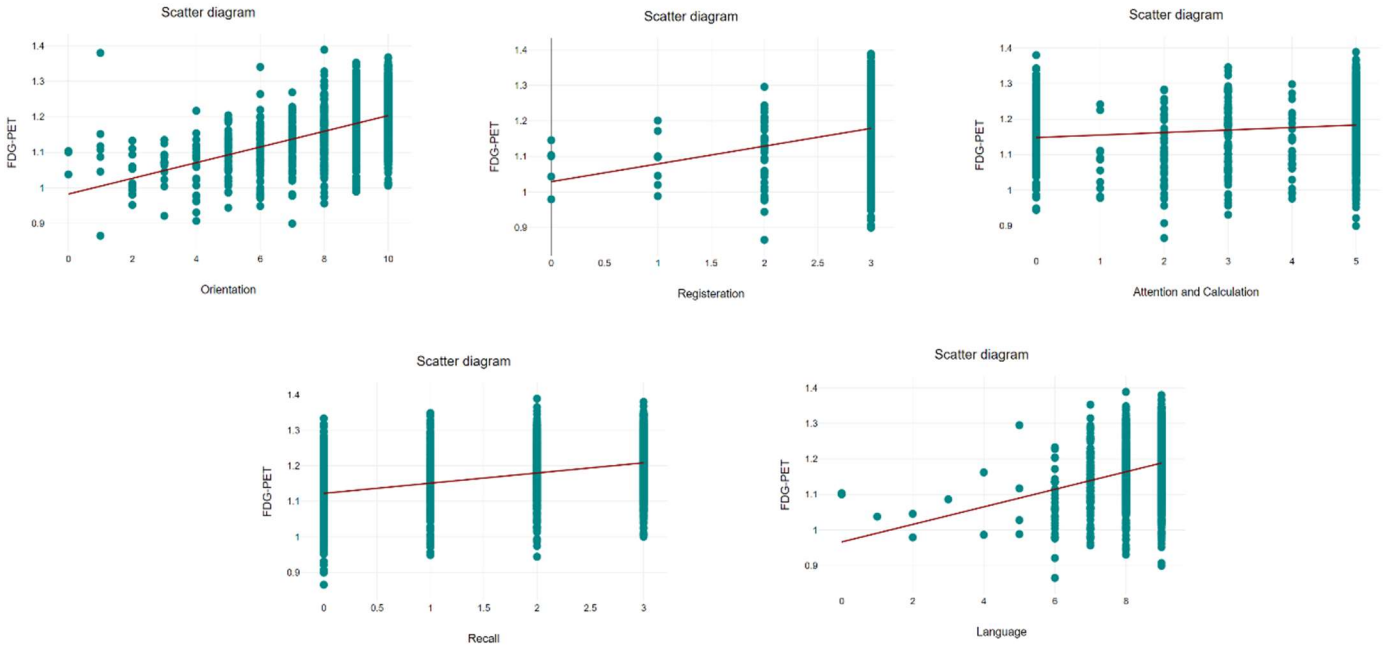

Figure 4. Scatter plot of association between MMSE score and FDG-PET among ADNI participants

healthy individuals from those with MCI and AD, and distinguish between MCI and AD patients. However, SWM alone may not sufficiently distinguish between healthy individuals and those with MCI, despite significant impairment observed in AD patients. Therefore, PRM and new learning capabilities could serve as valuable indicators for monitoring the progression from normal cognitive function to MCI and AD. Furthermore, the study suggests that assessing visual memory using CANTAB can aid in distinguishing various stages of MCI as it advances towards dementia (29).

Warren et al. (56) aimed to distinguish between groups categorized as cognitively normal (CN), those with subjective memory complaints (SMC), early mild cognitive impairment (EMCI), late mild cognitive impairment (LMCI), and AD using cognitive and functional tests. Their findings indicate that certain cognitive and functional assessments, such as ADAS-13, RAVLT (learning), FAQ, MoCA, and ECog, successfully predict different stages of the AD continuum. However, other neuropsychological tests, including RAVLT (immediate and forgetting) and TMT-B, were not predictive of AD stages (56).

García Alvarez et al. (57) compared 48 patients with MCI, 124 healthy individuals without cognitive impairment (EHC), and 57 patients diagnosed with AD across multiple measures of WM and executive function (EF), as well as indices of frontal lobe integrity and functional abilities. They observed differences in years of education between EHC and AD groups, and between MCI and AD groups (AD patients having fewer years of education), but no significant difference between EHC and MCI groups. Both MCI and AD groups showed higher scores on the Clinical Dementia Rating (CDR) sum of boxes compared to the EHC group, with the AD group scoring higher than the MCI group. Significant differences were also found in Mini-Mental State Examination (MMSE) scores among the groups. GLM analysis adjusted for age and education differences across groups, with gender considered as a covariate. Compared to AD patients, those with MCI performed better across all executive function measures (effect sizes ranging from 0.74 for one-back accuracy to 1.39 for TMT-A), except for zero-back accuracy where differences between MCI and AD were significant but equally impaired compared to EHC (see Figure 1). AD patients exhibited significant impairments across all measures compared to EHC. Their findings underscore that WM and EF deficits, associated with specific compromises in frontal brain circuits, are clinically relevant even at potentially preclinical stages of AD, as depicted in Figure 2 (57).

Chehrehnegar et al. (58) used eye-tracking technology to investigate saccade impairments to distinguish between a-MCI and a variety of reference controls, and based on Figure 3, it can be seen that their findings show that more errors, more omissions, and less corrections Characteristics of saccade behavior in the MCI group compared to the reference group. These eye tracking features can be considered as inhibitory control and working memory deficits in a-MCI subjects. Therefore, their results suggest the utility of the antisaccade task as a cognitive marker in a-MCI (58).

Statsenko et al. (59) designed an approach to classify subjects based on the pattern of structure-function relationship in groups of cognitively normal elderly (Table 2) and patients with MCI or dementia (Table 3) and found in the healthy population, the global cognitive function changes little with age. Also, in most cases, it remains stable during the course of the disease. In healthy adults and patients with MCI or dementia, the performance trends in the Digit Symbol Substitution Test and the Sequencing Test converge at the approximate point of 100 years of age (59).

Volkers & Scherder (60) found that strength, aerobic fitness and balance are significantly related to working memory. Physical functioning is not related to episodic memory in older adults with mild to severe cognitive impairment, but physical functioning is related to working memory in older adults with

cognitive impairment. Performance in balance, strength, and aerobic fitness is positively related to working memory performance, regardless of the level of cognitive impairment (see Table 4) (60).

Conclusion

In reviewing various studies, the following findings have been identified:

- Assessing new learning functions and recognition memory can serve as indicators of MCI and its progression to AD. However, spatial working memory assessment is only effective for evaluating MCI progression to AD. Visual memory evaluation through CANTAB could help differentiate between different stages of MCI as it progresses toward dementia.
- Certain cognitive and functional tests (such as ADAS-13, RAVLT learning, FAQ, MOCA, and ECog) can predict stages of the AD continuum. The ECog (both versions), RAVLT (learning), ADAS-13, and MoCA are recommended for screening all stages of the AD continuum.
- In MCI, WM/EF impairments are far from rare, based on specific compromises to frontal cortex circuitry, and are linked to a loss of everyday functioning. These impairments, even at the early stage of AD, have significant clinical consequences.
- The proportion of errors and uncorrected saccade movements can be markers for early diagnosis of a-MCI and mild AD. These indicators can help differentiate between a-MCI and healthy controls and have important implications for the early detection and monitoring of AD. Eye-tracking can be a valuable diagnostic tool for assessing executive function in aging individuals with cognitive impairments.
- In healthy individuals, global cognitive functioning changes slightly with age and remains stable across the disease course in most cases. Performance trends in the digit symbol substitution test and trail making test converge around the age of 100 years. In accelerated aging, neuronal loss varies among different cell groups and brain regions, with SFA potentially exhibiting pathology-specific features.
- For individuals with mild to severe cognitive impairment, performances in balance, strength, and aerobic fitness are significantly associated with working memory but not episodic memory.

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Declarations

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Conflict of interest

The authors have no conflicts of interest to disclose.

Availability of data

The datasets analyzed during the current study are available upon request with no restriction.

Code availability

Not applicable

Ethical approval

The data in this paper were obtained from the ADNI database (adni.loni.usc.edu). It does not include any examination of human or animal subjects.

Consent for publication

This manuscript has been approved for publication by all authors.

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