Received: 12 July 2023 | Revised: 22 December 2023 | Accepted: 30 December 2023

DOI: 10.1002/trc2.12448

Alzheimer's & Dementia
Translational Research & Clinical Interventions

RESEARCH ARTICLE

Differentiating MCI from depression through verbal memory scores

Seyda Cankaya[1] | **Betul Yalciner**[2] | **Melek Kandemir Yilmaz**[3] | **Burak Yulug**[1]

[1]Alaaddin Keykubat University, Faculty of Medicine, Department of Neurology and Neuroscience, Alanya, Turkey

[2]Okan University, Faculty of Medicine, Department of Neurology, Istanbul, Turkey

[3]American Hospital, Department of Neurology, Bodrum, Turkey

Correspondence
Burak Yulug, Alaaddin Keykubat University, Faculty of Medicine, Department of Neurology, PC: 07400, Alanya, Turkey.
Email: burak.yulug@alanya.edu.tr

Abstract

INTRODUCTION: The present study aims to assess the differences between major depressive disorder (MDD) and mild cognitive impairment (MCI) in terms of verbal learning profile together with structural changes in the brain on magnetic resonance imaging (MRI) and to reveal predictive factors for MCI.

METHODS: Fifty-six patients with MDD and 31 MCI subjects were assessed using the Turkish Verbal Memory Processes Test (VMPT). Brain MRI was used to evaluate sulcal atrophy (SA), ventricular atrophy, periventricular white matter hyperintensity (WMH), subcortical WMH, basal ganglia infarct, medial temporal lobe atrophy, and infratentorial infarct scores based on the Modified Visual MRI Rating Scale (MVMRS). The symptoms of depression were evaluated with the Beck Depression Inventory in both groups. Demographic factors, VMPT scores, and MVMRS scores between MDD and MCI groups were compared. Also, potential predictors of MCI were analyzed by binary logistic regression analyses.

RESULTS: The total scores of VMPT and the scores of VMPT subgroups, including immediate memory, highest learning, total learning, and delayed recall, were significantly higher in the MDD groups compared to MCI patients (Mann-Whitney *U*, Student's *t*-test, $p < 0.05$), indicating that higher scores were associated with better memory. The total MVMRS score and a subgroup of MVMRS, the SA score, were significantly higher in MCI patients compared to the MDD group, suggesting more atrophic changes and a higher burden of infarction in MCI patients. In our statistical analyses, impaired immediate memory ($p < 0.001$; OR = 6.002; 95% CI: 1.996–18.042), increased SA ($p = 0.008$; OR = 1.522; 95% CI: 1.118–2.073), and education ($p = 0.028$; OR = 0.84; 95% CI: 0.719–0.981) were significant predictive values obtained through backward Wald elimination in the binary logistic regression model for detecting MCI.

CONCLUSION: Our findings suggest that VMPT may potentially represent a novel neuropsychiatric test that might be combined with MRI-based morphometric evaluation methods, such as MVMRS.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
© 2024 The Authors. Alzheimer's & Dementia: Translational Research & Clinical Interventions published by Wiley Periodicals LLC on behalf of Alzheimer's Association.

KEYWORDS
depression, MCI, MRI, VMPT

1 | INTRODUCTION

Although depressive symptoms occur in a significant proportion of individuals with mild cognitive impairment (MCI), the mechanisms underlying the association between depression and cognitive decline have not yet been elucidated. Among the various mechanisms proposed for the common pathophysiology between depression and MCI,[1] a special role has been attributed to structural and functional hippocampal integrity, a strong indicator of immediate memory performance in both healthy and depressive patients.[2]

Based on the evidence of these structural and functional data, it is not unreasonable to assume that the presence of depression has been increasingly identified as a risk factor for dementia.[3] However, subsyndromal depressive symptoms can also be observed during the prodromal phases of dementia, making not only a clear-cut diagnosis in this intermediate zone challenging,[4] but also appearing to increase the risk of progression of dementia, which prompted us to evaluate the impact of both factors on MCI.

The situation is also complicated by the fact that even some cerebrovascular risk factors, as well as cerebrovascular disease itself, play a critical role in contributing to the development of MCI, dementia, and depression late in life.[5] This accords with a recent meta-analysis suggesting that the incidence of not only MCI but also major depressive disorder (MDD) increases significantly with age.[6] However, as briefly mentioned above, there are challenges in differentiating between depression and MCI, given the existing body of data that supports the presence of a subgroup with depression within MCI. This includes considerable meta-analyses indicating the prevalence of depression within MCI is 32%, suggesting that it is essential to consider that depressed symptoms might also serve as early indicators or markers of dementia.[7] Another main reason contributing to the diagnostic difficulties between MCI and MDD is that cognitive impairment in MCI is often less pronounced than in dementia. Additionally, there are some overlapping critical brain regions responsible for emotions and cognition which present a strong rationale for the increased risk of dementia in the MDD population.

Especially worthy of mention here is that MDD patients with cognitive impairment are also at a greater risk of developing dementia compared to those without MDD.[8] This, in turn, indicates the importance of accurately identifying these patients by recommending regular cognitive follow-up examinations.

However, such a clear-cut identification of these specific groups of patients can be challenging, and a more comprehensive and specific assessment is urgently required. In addition to well-known conventional screening tools such as the Mini-Mental State Examination (MMSE), we also need a more specific approach for these particular groups of neurological and psychiatric diseases.

The Turkish Verbal Memory Process Test (VMPT)[9] is one of the most frequently used memory tests for this purpose due to its ability to elicit verbal information in several ways, focusing especially on normal and interfered prefrontal executive functions.[10,11] The VMPT, an adapted and validated form of the Rey Auditory Verbal Learning Test (RAVLT) for the Turkish population, has been extensively used in various cognition studies and it has been shown that the VMPT is a very useful test for assessing neurodegenerative and non-degenerative cognitive disorders, and MCI.[10–12] Although the VMPT is a valuable tool for detecting executive functions in patients with cognitive impairment, there is still insufficient data available regarding the radiological correlates of these test scores. To fill this gap, we used a combination of the VMPT and the Modified Visual MRI (magnetic resonance imaging) Rating Scale (MVMRS) in this present study. The MVMRS has been developed by Yalciner et al. as a scale that evaluates the atrophy, white matter hyperintensities (WMHs), basal ganglia infarct (BGI), and infratentorial infarct (ITI) together for proposing a practical and standardized MRI for the clinicians to be used in daily practice.[13] In this study, we used the MVMRS for detecting levels of WMHs, ventricular atrophy (VA), and parahippocampal atrophy, which were applied to differentiate MDD from MCI in the study population.

In this context, we have collected real-world data from patients who applied for a non-specific memory clinic, making our findings valuable and relevant for the general neurology population.

Our main aim was to show the utility of the MVMRS and cognitive tests in distinguishing MDD from MCI and to evaluate the predictive role of the existence of MDD and/or depressive symptoms in MCI based on our previous work that indicated the value of the MVMRS for patients with forgetfulness. Our hypothesis was suggested by Yalcin et al.'s observation that the MVMRS is a useful scale for discriminating patients with Alzheimer's dementia and depressive patients.[13]

2 | MATERIALS AND METHODS

2.1 | Participants

Participants diagnosed with MDD and MCI were recruited from the general neurology clinic at the Bayindir Hospital Icerenkoy. Individuals who completed evaluations of their neuropsychological and depressive complaints were included in this analysis ($n = 87$). Fifty-six pure MDD patients and 31 with pure MCI constituted the study group.

Depression and MCI were diagnosed based on all available clinical and neuropsychological information by consensus of a panel of neurologists, neuropsychologists, and psychiatrists in line with international guidelines. All participants underwent a comprehensive clinical assessment, including the Structured Clinical Interview for

DSM Disorders (SCID) for the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V)[14] to establish a history of MDD. Also, MCI subjects were identified according to the criteria for MCI,[15] which included (1) a memory complaint, preferably confirmed by an informant; (2) objective memory impairment, adjusted for age and education; (3) normal or near-normal performance on general cognitive functioning and no or minimum impairment of daily life activities; and (4) not meeting the criteria for dementia according to the DSM-V.

Using the Beck Depression Inventory (BDI; categorized as 0 to 9: minimal depression, 10 to 18: mild depression, 19 to 29: moderate depression, 30 to 63: severe depression) and the DSM-V, we included patients who were either MCI or MDD, while excluding patients who fell into the overlapping category between these two diseases, as well as those with acute stages of depression and severe dementia that might potentially bias the cognitive results.

Following neuropsychological assessments, the results were discussed in order to exclude other potential causes, such as acute neurological diseases (eg, stroke, Parkinson's disease, normal pressure hydrocephalus), severe or unstable medical diseases (eg, cardiac disease, hypertension, current infection, neoplasia, and clinically significant hepatic, renal, pulmonary, metabolic, or endocrine disturbances), or the presence of comorbid diseases, including delirium, alcohol or drug dependency, and schizophrenia. The study was conducted in a retrospective and double-blinded manner. Within that context, we have excluded potential causes that can mimic a degenerative cognitive status.

This retrospective study of clinical data was approved by the Bayindir Hospital Icerenkoy Ethics Committee (2010/826). Due to the retrospective nature of the study, no informed consent was required or obtained.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (PubMed, Cochrane) sources, meeting abstracts, and presentations. There are several studies for differentiating mild cognitive impairment (MCI) from depression but lacked data-driven support that Verbal Memory Processes Test (VMPT) adapted from Rey Auditory Verbal Learning Test (RAVLT) and Modified Visual Magnetic Resonance Imaging Rating Scale (MVMRS) could be utilized as a novel screening tool for MCI.
2. **Interpretation**: Our findings demonstrated that the predictive value of VMPT and MVMRS in differentiating MCI from depression suggesting that a combination of both approaches might be beneficial in clinical contexts when it is challenging to determine whether an individual has mild cognitive impairment (MCI) or major depressive disorder (MDD).
3. **Future directions**: The manuscript proposes that VMPT may support the radiological findings in the differential diagnosis of MCI from depression in clinic routine. Our findings may shed light on MCI and MDD pathophysiology with further fMRI studies.

2.2 | Modified Visual MRI Rating Scale (MVMRS)

The MVMRS was created by Yalciner et al. based on the combined measurement of atrophy, WMH, BGI, and ITI,[13] with a high ability to discriminate MDD from MCI and high interrater reliability in the Turkish population, making this multi-modal tool a strong candidate to provide a practical and standardized MRI for clinicians in daily practice.[13] It is also worth noting that evaluating the interrater reliability of magnetic resonance visual assessment using the MVMRS between two neurologists and a radiologist has resulted in results ranging from good to excellent.[16] The details of the MVMRS are shown in Table 1.

In this scale, SA, VA, medial temporal lobe atrophy (MTA), periventricular WMH (PWMH), subcortical WMH (SCWMH), BGI, and ITI are scored separately on the scale.

SA was graded from 0 to 9 based on the widths of the central sulci, interhemispheric fissure, and other cortical sulci on the axial T1 (repetition time [TR] = 673 ms, echo time [TE] = 12 ms, 3 or 5 mm slice thickness, 0.6 mm gap) image corresponding to the slice level where the central sulci are best viewed (most similar to the shape of an inverted omega). VA was graded on a 0 to 9 range on the axial T1 (TR = 673 ms, TE = 12 ms, 3 or 5 mm slice thickness, 0.6 mm gap) slice showing the frontal and occipital horns of the lateral ventricles together with the third ventricle.

Periventricular WMH was graded on a 0 to 4 range based on the WMH identified as continuous, confluent areas of high signal intensity adjacent to anterior or posterior horns of the lateral ventricles and along the ventricular system on fluid-attenuated inversion recovery (FLAIR; TR = 8000 ms, TE = 80 ms, 3 or 5 mm slice thickness, 0.6 mm gap) images.

Subcortical WMH was graded on a 0 to 4 range based on the WMH identified as lesions located in the white matter but not touching the periventricular area on FLAIR (TR = 8000 ms, TE = 80 ms, 3 or 5 mm slice thickness, 0.6 mm gap) images.

BGIs were graded on a 0 to 2 range from FLAIR (TR = 8000 ms, TE = 80 ms, 3 or 5 mm slice thickness, 0.6 mm gap) images, based on the hyperintensities in the caudate nucleus, putamen, globus pallidus, and thalamus regions.

ITIs were graded in a 0 to 2 range from FLAIR (TR = 8000 ms, TE = 80 ms, 3 or 5 mm slice thickness, 0.6 mm gap) images, based on the hyperintensities in the brainstem and cerebellum.

2.3 | The Turkish VMPT

The VMPT is a word-list learning test developed, adapted, and validated by Öktem based on the RAVLT with high test-retest and interrater reliability.[9,17]

TABLE 1 Details of the MVMRS.

Atrophy	Sulcal	0–9	
	Ventricular	0–9	
MTA	Width of choroid fissure	Width of temporal horn	Height of hippocampal formation
0	N	N	N
1	↑	N	N
2	↑↑	↑	↓
3	↑↑↑	↑↑	↓↓
4	↑↑↑	↑↑↑	↓↓↓
WMH	Periventricular	Subcortical	
	0: No lesion	0: No lesion	
	1: Caps	1: <5 small focal and/or <2 large focal lesions	
	2: Thin line	2: 5–12 small focal and/or 2–4 large focal lesions	
	3: Halo	3: >12 small focal and/or >4 large focal or confluent lesions	
	4: Irregular, extending to the deep white matter	4: Predominantly confluent lesions	
Infarcts	Basal ganglia	Infratentorial	
	0: No lesion	0: No lesion	
	1: Few lesions (1–3)	1: Few Lesions (1-3)	
	2: Many lesions (>4)	2: Many lesions (>4)	
Other	Tumor etc.		

Abbreviations: MVMRS, Modified Visual MRI (magnetic resonance imaging) Rating Scale; MTA, medial temporal lobe atrophy; WMH, white matter hyperintensities.

The VMPT differs from the RAVLT in terms of the cognitive processes targeted for assessment and the application processes of the verbal material.[18] The VMPT permits the evaluation of the processes of working memory, learning or acquiring knowledge, retention of information, and recalling. It differs in some respects from the traditional RAVLT, which prioritizes the measurement of normal and interfered prefrontal executive functions. The Turkish version of RAVLT, like the original version, consists of several word lists (Lists A and B) measuring learning, free recall, free recall under proactive interference, recall after a very long time, and recognition over recall (RR), as follows. The immediate memory score (number of responses given by the subject in the initial pronunciation of the words), complete learning points (number of attempts ensuring complete learning = "access to criteria" score), total learning score (total number of words recalled in each trial), the highest learning point (the maximum number of words the subject was capable of remembering in trials), and long-term recall scores are determined in a two-step process. In the first step, 15 words are read out 10 times. After each reading, the patient is asked to repeat what he can remember (total learning). In the second step, the patient is asked to repeat the same 15 words after 45 minutes (delayed free recall).[9,18]

Immediate memory is categorized as 0 = normal (5 to 10 points), or 1 = impaired (0 to 4 points); highest learning is categorized as 0 = normal (14 or 15 points), 1 = moderate (10 to 13 points), or 2 = severe (10> points); total learning is categorized as 0 = normal (100 to 140 points), 1 = moderate (80 to 99 points), or 2 = severe (80> points); delayed recall is categorized as 0 = normal (11 to 15 points), 1 = moderate (7 to 10 points), or 2 = severe (7> points); the VMPT total score is categorized as 0 = normal (14 to 15 points), 1 = moderate (10 to 13 points), or 2 = severe (10> points) in the VMPT.[17]

2.4 | Statistical analysis

Patient characteristics of MDD and MCI were compared using the respective two-sample tests (*t*-test, Mann-Whitney *U* test, or chi-square test for normally distributed variables, non-normally distributed metric variables, and nominal variables, respectively).

To identify predictors of MCI, in a binary logistic regression model, all potential predictors were considered singly (univariate analysis) in the first step. Variables included sociodemographics (age, education), verbal process (VMPT), and radiologic findings (MVMRS). The potential predictors were analyzed in the second step with multivariable logistic regression analysis (enter method). Finally, a binary logistic regression model was built using a backward Wald approach in the third step, with variables retained at a *p*-value of <0.05. In addition, odds ratios (ORs) were determined to measure effect sizes.

TABLE 2 Clinical and demographic characteristics of the patients and group comparison of MCI and MDD.

	MDD ($n = 56$)	MCI ($n = 31$)	p
Education (years), median (IQR)	11 (3.5)	11 (3)	0.097
Age, median (IQR)	61 (18.5)	70 (23)	0.057
Sex (female), *N* (%)	30 (54%)	19 (61%)	χ^2: 0.639, p: 0.508
Severity of MDD with BDI			
Minimal (0–9 points), *N* (%)	7 (38.9)	5 (41.7)	χ^2:0.035, p:0.983
Mild (10–18 points), *N* (%)	6 (33.3)	4 (33.3)	
Moderate (19–29 points), *N* (%)	5 (27.8)	3 (25)	
BDI total score (mean ± SD)	14.05±8.74	13.29±7.74	0.946
MVMRS subscores			
Sulcal atrophy, median (IQR)	3 (2)	5 (3.5)	**0.013***
Ventricular atrophy, median (IQR)	3 (2.5)	3 (2.5)	0.634
Periventricular WMH, median (IQR)	1 (1)	0.5 (2)	0.763
Other, median (IQR, min-max)	1 (2)	1.5 (1)	0.145
Basal ganglia infarcts, median (IQR, min-max)	0 (0, 0-2)	0 (0, 0-2)	0.901
Infratentorial infarcts, median (IQR, min-max)	0 (0, 0-1)	0 (0, 0-1)	0.944
MTA, median (IQR)	1 (1)	1 (1)	$\chi^2 = 1.106$, p = 0.575
MVMRS total score, median (IQR)	10 (7)	12 (8)	**0.047***
VMPT subscores			
Immediate memory, median (IQR)	5 (2)	4 (2)	<**0.001***
Highest learning, median (IQR)	10 (3)	9 (2)	**0.007***
Total learning (mean ± SD)	90.5 ± 22.9	75.2 ± 22.1	**0.003***
Delayed recall (mean ± SD)	8.7 ± 3.1	6.9 ± 3.7	**0.02***
Recognition, median (IQR)	3 (3)	3 (2)	0.297
VMPT total score, median (IQR)	10 (5)	10 (3)	**0.034***

Note: Normally distributed data were analyzed with Student's *t*-test (data presented as mean ± SD); non-normally distributed data were analyzed with a Mann-Whitney *U* test (data presented as median-IQR), and categorical variables were analyzed with Pearson chi-Square test (χ^2).
Abbreviations: BDI, Beck Depression Inventory; IQR, interquartile range; MCI, mild cognitive impairment; MDD, major depressive disorder; MTA, medial temporal lobe atrophy; MVMRS: Modified Visual MRI Rating Scale, N, number of cases; VMPT, Verbal Memory Processes Test; WMH, white matter hyperintensities.
*$p < 0.05$.

3 | RESULTS

Completed data on the MRI and neurocognitive tests were available for 87 individuals, and these were included in the study. There was no significant difference in terms of age, sex, and years of education between groups ($p > 0.05$) (Table 2). Also, the severity of the BDI score ($\chi^2 = 0.035$, $p = 0.983$) and the mean of BDI total score (Student's t-test, $p = 0.946$) showed no difference between depressive and MCI patients (Table 2).

The median VMPT total score (Mann-Whitney *U* test, $p = 0.034$) and selected subscores of the VMPT (immediate memory, highest learning, total learning, delayed recall) were significantly higher in depressive patients than in the MCI group (higher scores indicating greater memory) ($p < 0.05$) (Table 2).

We detected that not only the MVMRS total score (Mann-Whitney *U* test, $p = 0.047$), but also the SA score (Mann-Whitney *U* test, $p = 0.013$), which is a subgroup of the MVMRS scale, were higher in the MCI group, indicating a high burden of infarct and larger atrophy (Table 2).

In univariate logistic regression analyses, we observed that impaired immediate memory, low highest learning score, low total learning score, increased SA, delayed recall, and aging were significant predictors for MCI. Multivariable logistic regression analysis adjusted for age and education showed that impaired immediate memory and atrophic findings (SA and VA) remained as significant predictive values. In our statistical analyses, impaired immediate memory ($p = 0.001$; OR = 6.002; 95% confidence interval [CI]: 1.996–18.042), increased SA ($p = 0.008$; OR = 1.522; 95% CI: 1.118–2.073), and education ($p = 0.028$; OR = 0.84; 95% CI: 0.719–0.981) were predictive values obtained through backward Wald elimination in the binary logistic regression model for detecting MCI (Table 3). Our findings of the logistic regression analyses for the identification of predictors of MCI are shown in Table 3.

TABLE 3 Binary logistic regression model for MCI by variables (categorical values presented with cut points).

Variables	Category	*N* (%)	Univariate OR (% 95 CI)	*p*	Multivariable Adjusted OR (% 95 CI)	*p*	Multivariable (BW-WALD) Adjusted OR (% 95 CI)	*p*
VMPT scores								
Immediate memory	5-10: Normal (ref)	49 (56.3)						
	5>: Impaired	38 (43.7)	4.818 (1.87– 12.39)	**0.001***	5.061 (1.32–19.47)	**0.018***	6.002 (1.996–18.042)	**0.001***
Highest learning	14–15: Normal (ref)	18 (20.7)					–	
	10–13: Moderate	43 (49.4)	0.79 (0.23–2.75)	0.709	0.369 (0.03–5.03)	0.454		
	10>: Severe	26 (29.9)	4.16 (1.13–15.25)	**0.032***	0.798 (0.04–16.96)	0.885		
Total learning	100–140: Normal (ref)	24 (27.6)			–		–	
	80–99: Moderate	27 (31)	1.6 (0.44–5.79)	0.474				
	80>: Severe	36 (41.4)	3.8 (1.17–12.39)	**0.027***				
Delayed-recall	11–15: Normal (ref)	22 (25.3)					–	
	7–10: Moderate	38 (43.7)	1.481 (0.52–4.18)	0.494	0.244 (0.05–1.34)	0.105		
	7>: Severe	27 (31)	3.094 (0.89– 10.8)	0.100	0.485 (0.05–5.12)	0.548		
Recognition			1.137 (0.91– 1.42)	0.254	1.095 (0.78–1.54)	0.604	–	
VMPT-Total score	14–15: Normal (ref)	30 (34.5)			–		–	
	10–13: moderate	40 (46)	1.09 (0.99–1.2)	0.458				
	10>: Severe	17 (19.5)	3.094 (0.89–10.8)	0.077				
MVMRS scores								
Sulcal atrophy			1.292 (1.054–1.583)	**0.013***	1.549 (1.084–2.214)	**0.016***	1.522 (1.118–2.073)	**0.008***
Ventricular atrophy			1.074 (0.835–1.379)	0.579	0.616 (0.38–0.997)	**0.049***	0.707 (0.482–1.039)	0.077
Periventricular WMH			0.931 (0.579–1.498)	0.769	0.667 (0.322–1.384)	0.277	–	
Basal ganglia infarcts			1.156 (0.379–3.528)	0.800	0.964 (0.176–5.268)	0.966	–	
Infratentorial infarcts			0.9 (0.078–10.342)	0.933	0.652 (0.032–13.169)	0.780	–	
Total score			1.09 (0.99–1.2)	0.072	–		–	
MTA	0	16 (18.5)					–	
	1	44 (50.5)	1.714 (0.473–6.212)	0.412	1,769 (0.312–10.032)	0.520	–	
	2	27 (31)	2.062 (0.525–8.096)	0.299	0.54 (0.056–5.186)	0.594	–	
BDI score			0.988 (0.909–1.075)	0.786	0.972 (0.774–1.221)	0.807	–	
Age (years)			1.041 (1–1.08)	**0.035***	1.045 (0.98–1.11)	0.171	–	
Education (years)			0.898 (0.79– 1.02)	0.1	0.84 (0.71–1)	0.056	0.84 (0.719–0.981)	**0.028***

Note: Analysis of the effect of VMPT, MVMRS, and demographical characteristics on the dependent variable MCI, which was assessed by univariate logistic regression, multivariable logistic regression, and backward Wald method.

Abbreviations: BDI, Beck Depression Inventory; BW-WALD, backward Wald; MCI, mild cognitive impairment; MTA, medial temporal lobe atrophy; N, number of cases; OR, odds ratio; MVMRS: Modified Visual MRI Rating Scale; Ref, reference category; VMPT, Verbal Memory Processes Test; WMH, white matter hyperintensity.

*$p < 0.05$.

4 | DISCUSSION

The results of this study revealed significant differences in VMPT sub-scores and morphometric scores of the MVMRS assessment between the MCI and depression groups. Furthermore, impaired immediate memory scores and increased SA were associated with a sixfold and a one and one half-fold greater diagnosis rate with MCI, respectively. The risk of dementia decreased by 0.84 times as the years of education increased.

VMPT sub-scores also changed, suggesting impaired executive functions in the MCI group compared to the MDD group.

Although there is sizable literature on the association of late-life depressive symptoms with incident MCI and dementia,[3] we revealed that neither the levels of depression nor its existence might significantly contribute to the development of MCI, suggesting that parameters such as altered morphology and impaired cognitive scores might be an independent risk factor for MCI. A good example is seen in the study by Rosenberg et al.,[8] indicating that neuropsychiatric symptoms observed in the early phases of preclinical Alzheimer's disease (AD) in individuals with MCI are strongly linked to a higher likelihood of developing dementia and AD.

Herein, our binary logistic regression analysis showed no significant impact of BDI severity on being MCI while backward Wald regression showed that only SA and impaired immediate memory were significant in predicting MCI along with education (Table 3).

Several studies have shown that the RAVLT is an important test for differentiating dementia from pseudo-dementia, as well as cognitively normal individuals from those with MCI.[19] Additionally, Estévez-González et al. found that the RAVLT is a powerful tool for discriminating individuals with subjective memory complaints from those with MCI.[20]

Powell et al. found that particularly seven RAVLT recall trials and the total of Trials I-V were more sensitive in discriminating a group of normal individuals from a mixed cognitive impairment group.[21]

Furthermore, performance on the RAVLT is affected by a variety of neurological conditions,[22] including hydrocephalus,[23] vertebrobasilar insufficiency,[24] and early Alzheimer-type dementia.[25]

However given the undeniable overlapping of depressive states and degenerative dementia,[8] it is worth mentioning that not only depressive states but even some subtle depressive symptoms might be prominent signs of MCI. For instance, Smith et al. have recently highlighted this issue by showing that MCI patients might be initially presented with some subtle depressive neuropsychiatric symptoms related to a concomitant degeneration of serotonergic and dopaminergic neurons before the cognitive degenerative stage is apparent.[26] This is clinically evident in a recent work by Ebrahim et al., showing that affective dysregulation and apolipoprotein (*APOE*) ε4 carrier status in the context of mild behavioral impairment is associated with a considerable risk of developing dementia and amnestic MCI,[27] fitting well with a novel study by Smith et al. indicating a possible link between serotonergic degeneration and amyloid beta accumulation in the pathogenesis of late-life depression.[28] In a reversed pattern, the role of serotonergic and dopaminergic polymorphism in behavioral symptoms of dementia has already been observed,[29] which has been suggested by several studies indicating that depressive patients might show some cognitive dysfunctional patterns resembling a cognitive profile in MCI, making it difficult to make a clear-cut discrimination between these two diseased conditions.[8,30,31] Considering all these diagnostic difficulties, we evaluated only pure MCI patients and patients with the diagnosis of only MDD to prevent any bias related to overlapped symptoms and diseased states reported in both conditions.

In the backward Wald binary logistic regression analysis, we observed that immediate memory was the only variable as a predictive factor of MCI that survived among other VMPT parameters. A recent study from Turkey using the adapted Turkish-language version of the RAVLT, in other words, the VMPT, showed that the subtests of the verbal memory processes, including short-term memory recall (total learning) and long-term memory recall (delayed free recall), were capable of differentiating MCI from mild dementia.[32] Our findings indirectly suggest recent functional data indicating that impaired connectivity between the right amygdala, occipital and parietal lobe, and left hippocampus is accompanied by a greater decrease in the RAVLT and immediate recall in MCI than in MDD-MCI and controls.[2]

To summarize, these findings suggest that the VMPT may potentially represent a novel neuropsychometric test that sufficiently differentiates MCI from MDD. Further studies with additional imaging tools, particularly those considering the relevant brain regions, should be used to differentiate patients with MDD from those in the early stages of dementia, such as MCI.

5 | CONCLUSION

Despite some minor limitations, such as the small sample size and lack of a control group, this study is clinically significant in showing that practical and powerful cognitive tests are essential in identifying subtle cognitive impairments in both MDD and MCI patients. Such a purely clinical approach can be reinforced with practical morphological assessment tools, of which the MVMRS total score assessment seems to be a particularly suitable candidate.

ACKNOWLEDGMENTS

There are no acknowledgments to make. Sponsorship/Grants: No sponsorship or grants were involved in the conduct of this study.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

The ethics committee at Bayindir Hospital Icerenkoy, Istanbul, Turkey, approved the study protocol. Written informed consent was obtained from all participants or, in the case of cognitively impaired persons, from a proxy (usually a guardian or a family member).

REFERENCES

1. Zihl J, Reppermund S, Thum S, Unger K. Neuropsychological profiles in MCI and in depression: differential cognitive dysfunction patterns or similar final common pathway disorder? *J Psychiatr Res*. 2010;44(10):647-654. doi:10.1016/j.jpsychires.2009.12.002
2. Zheng LJ, Yang GF, Zhang XY, et al. Altered amygdala and hippocampus effective connectivity in mild cognitive impairment patients with depression: a resting-state functional MR imaging study with granger causality analysis. *Oncotarget*. 2017;8(15):25021. doi:10.18632/oncotarget.15335
3. Han FF, Wang HX, Wu JJ, Yao W, Hao CF, Pei J. Depressive symptoms and cognitive impairment: a 10-year follow-up study from the Survey of Health, Ageing and Retirement in Europe. *Eur Psychiatry*. 2021;64(1):e55. doi:10.1192/j.eurpsy.2021.2230
4. Byers AL, Yaffe K. Depression and risk of developing dementia. *Nat Rev Neurol*. 2011;7(6):323-331. doi:10.1038/nrneurol.2011.60
5. Duman RS, Voleti B. Signaling pathways underlying the pathophysiology and treatment of depression: novel mechanisms for rapid-acting agents. *Trends Neurosci*. 2012;35(1):47-56. doi:10.1016/j.tins.2011.11.004
6. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia–meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr Scand* . 2009;119(4):252-265. doi:10.1111/j.1600-0447.2008.01326.x
7. Wong B, Ismail Z, Goodarzi Z. Detecting depression in persons living with mild cognitive impairment: a systematic review. *Int Psychogeriatr* . 2022;34(5):453-465. doi:10.1017/S1041610222000175
8. Rosenberg PB, Mielke MM, Appleby BS, Oh ES, Geda YE, Lyketsos CG. The association of neuropsychiatric symptoms in MCI with incident dementia and Alzheimer disease. *Am J Geriatr Psychiatry* . 2013;21(7):685-695. doi:10.1016/j.jagp.2013.01.006
9. Tanör ÖÖ. *Öktem sözel bellek süreçleri testi.(Öktem-SBST) el kitabı*. Türk Psikologlar Derneği; 2011.
10. Hanoğlu L, Ercan FB, Mantar N, et al. Accelerated forgetting and verbal memory consolidation process in idiopathic nondement Parkinson's disease. *J Clin Neurosci* . 2019;70:208-213. doi:10.1016/j.jocn.2019.08.012
11. Yildiz T, Oğuzhanoğlu NK, Topak OZ. Cognitive outcomes of transcranial magnetic stimulation in treatment-resistant depression: a randomized controlled study. *Turk J Med Sci* . 2023;53(1):253-263. doi:10.55730/1300-0144.5580
12. Kurt P, Emek-Savaş DD, Batum K, et al. Patients with mild cognitive impairment display reduced auditory event-related delta oscillatory responses. *Behav Neurol* . 2014. 2014:268967. doi:10.1155/2014/268967
13. Yalciner BZ, Kandemir M, Taskale S, Tepe SM, Unay D. Modified visual magnetic resonance rating scale for evaluation of patients with forgetfulness. *Can J Neurol Sci* . 2019;46(1):71-78. doi:10.1017/cjn.2018.333
14. First MB. Structured clinical interview for DSM-IV-TR axis I disorders. *(No Title)*. 2005.
15. Petersen RC. *Mild cognitive impairment: aging to Alzheimer's disease*. Oxford University Press; 2003.
16. Kandemir Yilmaz M, Yalciner ZB, Tepe MS. Interrater reliability of modified visual MRI rating scale assessing atrophy and white matter changes. *Ideggyogy Sz*. 2023;76(1-2):19-24. doi: 10.18071/isz.76.0019
17. Oktem O. Sozel Bellek Surecleri Testi (SBST). *Noropsikiyatri Arsivi (Turkish)*. 1992;29:196-206.
18. Can H, Doğutepe E, Yazıhan NT, Korkman H, Erdoğan Bakar E. Construct validity of auditory verbal learning test. *Turkish Journal of Psychiatry*. Fall 2016;27(3):195-203. https://www.ncbi.nlm.nih.gov/pubmed/27711940
19. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4(6):561-571. doi:10.1001/archpsyc.1961.01710120031004
20. Estévez-González A, Kulisevsky J, Boltes A, Otermín P, García-Sánchez C. Rey verbal learning test is a useful tool for differential diagnosis in the preclinical phase of Alzheimer's disease: comparison with mild cognitive impairment and normal aging. *Int J Geriatr Psychiatry* . 2003;18(11):1021-1028. doi: 10.1002/gps.1010
21. Powell JB, Cripe LI, Dodrill CB. Assessment of brain impairment with the Rey Auditory Verbal Learning Test: a comparison with other neuropsychological measures. *Arch Clin Neuropsychol* . 1991;6(4):241-249. https://www.ncbi.nlm.nih.gov/pubmed/14589516
22. Goldstein G, Hersen M. *Handbook of psychological assessment. Specialized Neuropsychological Assessment Methods*. Elsevier. 2000.
23. Ogden JA. Neuropsychological and psychological sequelae of shunt surgery in young adults with hydrocephalus. *J Clin Exp Neuropsychol* . 1986;8(6):657-679. doi:10.1080/01688638608405186
24. Ponsford JL, Donnan GA, Walsh KW. Disorders of memory in vertebrobasilar disease. *J Clin Exp Neuropsychol* . 1980;2(4):267-276.
25. Mitrushina M, Satz P, Van Gorp W. Some putative cognitive precursors in subjects hypothesized to be at-risk for dementia. *Arch Clin Neuropsychol* . 1989;4(4):323-333.
26. Smith GS, Barrett FS, Joo JH, et al. Molecular imaging of serotonin degeneration in mild cognitive impairment. *Neurobiol Dis* . 2017;105:33-41. doi:10.1016/j.nbd.2017.05.007
27. Ebrahim IM, Ghahremani M, Camicioli R, Smith EE, Ismail Z. Effects of race, baseline cognition, and APOE on the association of affective dysregulation with incident dementia: a longitudinal study of dementia-free older adults. *J Affect Disord* . 2023;332:9-18. doi:10.1016/j.jad.2023.03.074
28. Smith GS, Kuwabara H, Nandi A, et al. Molecular imaging of beta-amyloid deposition in late-life depression. *Neurobiol Aging* . 2021;101:85-93. doi:10.1016/j.neurobiolaging.2021.01.002
29. Proitsi P, Lupton MK, Reeves SJ, et al. Association of serotonin and dopamine gene pathways with behavioral subphenotypes in dementia. *Neurobiol Aging*. 2012;33(4):791-803. doi:10.1016/j.neurobiolaging.2010.06.011
30. Rosenberg PB, Mielke MM, Appleby B, Oh E, Leoutsakos JM, Lyketsos CG. Neuropsychiatric symptoms in MCI subtypes: the importance of executive dysfunction. *Int J Geriatr Psychiatry* . 2011;26(4):364-372. doi:10.1002/gps.2535
31. Ismail Z, Elbayoumi H, Fischer CE, et al. Prevalence of depression in patients with mild cognitive impairment: a systematic review and meta-analysis. *JAMA Psychiat*. 2017;74(1):58-67. doi:10.1001/jamapsychiatry.2016.3162
32. Şair A, Şair YB, Ayar S. Differentiating mild forms of cognitive impairment and dementia: where other tests fail, verbal memory assessment may prove critical. *Meandros Med Dental J*. 2021;22(2):18753824. doi:https://doi.org/10.4274/meandros.galenos.2021

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Cankaya S, Yalciner B, Yilmaz MK, Yulug B. Differentiating MCI from depression through verbal memory scores. *Alzheimer's Dement*. 2024;10:e12448. https://doi.org/10.1002/trc2.12448