Original
ISSN 2413-0516

The role of Neuropsychological Assessment in the Differential Diagnoses of Late-Onset Depression, Dementia, and Mild Cognitive Impairment

Gulin Morkavuk[1*], Gokce Sirvanli[1]

[1]Department of Neurology, Faculty of Medicine, Ufuk University, Ankara, Turkey.
*Correspondence to: Morkavuk Gulin (E-mail: drgcmor@yahoo.com)
(Submitted: 26 October 2022 – Revised version received: 20 November 2022 – Accepted: 12 December 2022 – Published online: 26 June 2023)

Abstract

Objective: The present study aimed to compare the neuropsychological test parameters of dementia, depression, and MCI patients and determine the disease-specific test characteristics and their relationship with electroencephalography.

Methods: Ninety-one patients who were admitted to the neurology outpatient clinic with forgetfulness complaints between October 2019 and March 2022 and whose neuropsychological tests were performed were included in the study. The files of these 91 patients were reviewed retrospectively and their sociodemographic data were recorded. Furthermore, the EEG results which were taken during the patients' evaluation period due to forgetfulness were evaluated. Neuropsychological tests were compared between patients with dementia, MCI and depression. It was also investigated whether there was a relationship between NPT test parameters and EEG in patients with EEG results.

Results: The study was completed with 87 patients. Of these 87 patients, 54 were female and 33 were male. Twenty-four patients had depression, 16 MCI, and 47 dementia. All of the dementia patients had Alzheimer's type dementia. When dementia, depression, and MCI groups were compared, the age difference was statistically significant ($P = 0.001$). The mean age of the depression group was 66.5, the MCI group was 73.5, and the dementia group was 77. WMS-I, WMS-II, WMS-III, WMS-IV, similarities test, clock drawing test, trail making test, shape copying, language, and mood evaluation tests were statistically significantly different between the groups. There was no statistically significant difference between the groups regarding gender, education level, dominant hand, and occupation. EEG background activity frequencies were also examined between the groups, and there was no statistically significant difference.

Conclusion: In conclusion, when evaluating patients who present with the complaint of forgetfulness, a detailed neuropsychological evaluation must be performed in addition to other diagnostic tests. Sensitive tests should be included to confirm the diagnosis, especially in cases where being in between for the differential diagnosis. Thus, further studies are needed on this subject.

Keywords: Neuropsychological assessment, dementia, depression, mild cognitive impairment

Introduction

Dementia is a common cognitive disorder that significantly affects the patient's quality of life. Mild cognitive impairment (MCI) is a clinical condition with a high risk of progression to dementia. MCI is considered a prodrome of dementia that includes more forgetfulness than expected for a person's age, but almost all of the daily functionality is preserved and does not meet clinically probable dementia criteria.[1] It is known that about half of the patients diagnosed with MCI develop dementia within 3 years,[1] and estimated that in the 75–79 age group, the incidence of MCI is 22.5 per 1000 people per year and the number rises to 60.1 in the 85 and over age group.[2] MCI is associated with a significant risk of developing dementia, but approximately 18% of MCI patients do not spontaneously revert to normal cognition and progress to dementia.[3] Due to the lack of effective disease-modifying treatments for advanced dementia, diagnosis and disease intervention at an early stage, particularly at the MCI stage, is recognized as a critical strategy in disease management that can potentially affect long-term outcomes. However, there is currently no consensus on guidelines for routine screening of MCI, resulting in a significant number of undiagnosed MCI patients in the community.[4] Therefore, there is a need to develop reliable tools that can be used from screening to diagnosis.

Another condition that is mistaken with dementia is depression in older adults. This condition, called late-onset depression (LOD), appears for the first time after the age of 50–65 and differs from early-onset depression in many areas. It is known that some of these patients have cognitive disorders.[5-7] Moreover, depression is common during dementia and may even appear as the first symptom of dementia.[8]

Today, Mini Mental Test (MMT) is generally used to support the diagnosis of dementia in neurology outpatient clinics. However, this test is insufficient to detect MCI status. In this case, a detailed neuropsychological evaluation may be guiding. The present study aimed to compare the neuropsychological test parameters of dementia, depression, and MCI patients and determine the disease-specific test characteristics and their relationship with electroencephalography (EEG).

Material and Method

Ninety-one patients who were admitted to the neurology outpatient clinic with forgetfulness complaints between October 2019 and March 2022 and whose neuropsychological tests were performed were included in the study. The files of these 91 patients were reviewed retrospectively and their sociodemographic data were recorded. Furthermore, the EEG results which were taken during the patients' evaluation period due to forgetfulness were evaluated. The WMS (Wechsler Memory Scale) (I-II) personal-actual information and orientation subtest was performed within the scope of the neuropsychological assessment battery. WMS-R (III) mental control, WMS (IV) logical story test, WMS-R (V) number range subtest, WAIS-R (Wechsler Adult Intelligence Scale-Revised) binary similarity

subtest, Verbal Fluency test, Clock Drawing test, Luria Alternan Sequences Test, Stroop test, and Trail Making test assessed attention and executive functions. Öktem Verbal Memory Processes test (Ö-VMPT) and WMS (VI) visual production subtest were used as memory tests. Line Direction Determination test, Benton Face Recognition test, and Shape Copying test were performed for visual-spatial evaluation. Boston Naming test was used for language skills, and Geriatric Depression Scale or Depression, Anxiety, Stress Scale (DASS) tests were applied for mood assessment. If the patients were clinically evaluated and able to reach a diagnosis, they were included in one of the depression, dementia, and MCI groups. The diagnosis of MCI was made according to the Peterson criteria.[9] Four patients whose diagnoses could not be clarified were excluded. The remaining 87 patients were compared in terms of MMT, Montreal Cognitive Assessment (MoCA), and neuropsychological assessment battery tests. First, the tests were compared between the 3 groups together, then between the MCI and depression and MCI and dementia groups. It was also investigated whether there was a relationship between NPT test parameters and EEG in patients with EEG results. This study was performed as per the Declaration of Helsinki and with the approval of University Faculty of Medicine Ethics Committee.

Tests performed within the scope of neuropsychological assessment battery:

1. **WMS (I-II) information and orientation :** It is a subtest in which the person is evaluated regarding age, date of birth, follow-up of current events, place, and time information.
2. **Attention and Executive Function Tests**
   - 2.1. **WMS-R mental control subtest (WMS III):** It is a test applied regarding the ability to maintain attention, which is one of the frontal functions.
   - 2.2. **WMS Logical memory (WMS-IV):** It is a test that measures the reproducibility of the verbally given story in the short and long-term recall.
   - 2.3. **WMS-R Digit span test (WMS-V):** The digit span test is divided further into two subtests. Straight number range is used for 'short-term memory' evaluation, while inverse number range is used for 'complex attention' evaluation as it requires tracking skills.
   - 2.4. **WAIS-R similarities test :** It is a subtest given for the evaluation of abstraction skills.
   - 2.5. **Verbal fluency test:** It includes lexical verbal fluency tests (with letters K, A, S -in Turkish version-) sensitive to frontal lobe lesions and semantic verbal fluency tests (animal counting, fruit-name counting) sensitive to temporal lobe lesions and used to measure fronto-temporal entorhinal cortex functions.
   - 2.6. **Clock Drawing Test:** It is a short-term practical screening test that provides information on intellectual and perceptual skills. It provides an assessment of skills such as auditory comprehension, motor planning and management, visual memory and restructuring, numerical knowledge, abstract thinking, focusing and tolerance to frustration, inhibition of physical properties of stimuli.
   - 2.7. **Luria Alternan Sequences Test:** It is one of the bedside tests that evaluate sequencing, planning, and ability to cope with distractors.
   - 2.8. **Stroop Test (Çapa version):** It is a test that measures complex attention. As the duration of interference increases, the patient's difficulty in maintaining attention and suppressing distracting stimuli emerges. It requires literacy.
   - 2.9. **Trail Making test:** It is a complex attention level-determining test sensitive to motor speed and visual scanning, assessing focused attention (A-form) and category switching skills (B-form). It requires literacy.
3. **Memory Tests**
   - 3.1. **Öktem Verbal Memory Processes Test (Ö-VMPT):** It evaluates memory in areas such as primacy effect and recency effect, creating a certain learning strategy, recalling information, and recognizing information. It helps to confirm the diagnosis by distinguishing the secondary and primary types of memory impairment.
   - 3.2. **WMS visual reproduction (WMS-VI):** It is a test used in the clinical measurement of visual memory. Instant and long-term recall values are checked.
4. **Visual-Spatial Skill Tests**
   - 4.1. **Benton Face Recognition Test:** It is sensitive to damage to the "what" pathway in the visual association cortex. It is used for the evaluation of occipito-temporal region functions in visual-spatial skills.
   - 4.2. **Judgement of line orientation test:** The occipitoparietal region is used to evaluate the "where" pathway functions. Complex visual perception is measured.
   - 4.3. **Shape Copy Test:** It is a practical short-term test used to evaluate visuospatial restructuring ability.
5. **Language Skill**
   - 5.1. **Boston Naming Test:** This test, which contains items of varying difficulty, is used to measure the ability to name the seen object.
6. **Mood Assessment**
   - 6.1. **The Geriatric Depression Scale (GDS):** It evaluates change of effect, restlessness, inactivity, disturbing thoughts, withdrawal from life, negative judgments about the past, present, and future.
   - 6.2. **The Depression, Anxiety, Stress Scale (DASS):** It is a test that evaluates stress, anxiety, and depression based on self-report in 14 items.

Statistical Analysis

Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) 22.0 (IBM, Chicago, Illinois, USA). Kolmogorov Smirnov and Shapiro-Wilk tests were performed to test the homogeneity and normality of the scaled data. Pearson chi square and fischer were used for evaluation of monimal data of each groups, student's T for scale parametric data, Mann Whitney-U for scale nonparametric data. Ona way-ANOVA, Kruskal Wallis, posthoc multiple comparison (Bonferroni) tests were used for analysis of multiple groups. Univariate multinomial logistic regression test was performed in multivariate analysis. A p-value of <0.05 was considered statistically significant.

Results

Ninety-one patients who underwent neuropsychological tests were included. However, 4 patients whose diagnosis could not be clarified were excluded. The study was completed with 87 patients. Of these 87 patients, 54 were female and 33 were male. Twenty-four (27.6%) patients had depression, 16 (18.4%)

MCI, and 47 (54%) dementia. All of the dementia patients had Alzheimer's type dementia. The sociodemographic characteristics of the patients are presented in Table 1 in detail.

All patients were planned to be applied to the same tests. Nevertheless, tests that could not be completed by the patients were not included in the study. Among the applied neuropsychological tests, WMS-I was applied to 77 patients, WMS-II to 80, WMS-III to 64, WMS-IV to 50, WMS-V to 76, WMS-VI 68, similarities test to 78, clock drawing test to 79, Luria Alternan Sequences Test to 76, verbal fluency test to 70, Stroop test to 13, face recognition to 61, line direction determination to 66, shape copying to 71, language to 75, trail making test to 23, SBST to 37, and mood tests to 68 patients (Table 2).

When dementia, depression, and MCI groups were compared, the age difference was statistically significant ($P = 0.001$). The mean age of the depression group was 66.5, the MCI group was 73.5, and the dementia group was 77. There was no statistically significant difference between the groups regarding gender, education level, dominant hand, and occupation. WMS-I, WMS-II, WMS-III, WMS-IV, similarities test, clock drawing test, trail making test, shape copying, language, and mood evaluation tests were statistically significantly different between the groups. In correlation with neuropsychological tests, MMT was also statistically significantly different between groups. While the MMT score was similar in the depression and MCI groups, it was significantly lower in the dementia group. Moreover, as expected, mood tests had statistically significantly higher scores in the depression group. EEG background activity frequencies were also examined between the groups, and there was no statistically significant difference (Table 3).

When dementia and MCI groups were compared in terms of sociodemographic characteristics, there was a statistically significant difference in terms of gender ($P = 0.022$). While the MCI group consisted of 10 male and 6 female patients, the dementia group had 14 male and 33 female patients. Male patients were more in the MCI group, and female dominance was observed in the dementia group. When the 2 groups were compared in terms of occupations, it was determined that the number of retired soldiers/policemen was higher in the MCI group, and the number of housewives and retired teachers in the dementia group was higher, and the difference was statistically significant ($P = 0.047$). There was no significant difference between the groups in terms of education level. When neuropsychological battery tests were examined separately between dementia and MCI groups, a statistically significant difference was observed between WMS-II, WMS-IV, WMS-V, similarity test, clock drawing test, trail making test, shape copying, and SBST ($P = 0.02$, $P = 0.015$, $P = 0.038$, $P = 0.015$, $P = 0.01$, $P = 0.026$, $P = 0.02$, $P = 0.029$, respectively)

When the depression and MCI groups were examined separately, no difference was observed between sociodemographic data. Similarly, no statistically significant difference was determined in any of the NPT subtests when examined separately. As expected, mood test scores were statistically significantly higher in the depression group ($P = 0.008$).

Besides, when neuropsychological test parameters and EEG background activity frequencies were examined in terms of correlation, there was no statistically significant correlation in any group.

The univariant multinomial regression analysis of the factors found in Table 3 is summarized in Table 4. When we considered the depression group as the reference category, one unit increase in the age variable increased the probability of being diagnosed with dementia 1.129 times and the probability of MCI being 1.091 times. The impaired WMS1 test increases the probability of patients having dementia 6.697 times compared to depression but does not cause a significant difference between MCI and depression diagnoses. Similarly, defective WMS2, WMS3, and WMS4 tests increase the probability of patients having dementia compared to the probability of having depression. In mood tests (DASS, GDS), a negative correlation was determined between diagnoses. Accordingly, a disordered mood test increases the probability of dementia by 0.200 units and the probability of MCI by 0.107 units. In other words, the fact that this test had pathological results increased the likelihood of patients having depression. A detailed review of the Univariate multinomial regression analysis is presented in Table 4.

Table 1. **The Sociodemographic Characteristics of the Patients**

Age, year, mean ± SD,range	71,83 ± 9,69 (42–86)
Diagnosis, n(%)	
Depression	24 (%27,6)
MCI	16 (%18,4)
Dementia	47 (%54)
Gender, n(%)	
Male	33 (%37,9)
Female	54 (%62,1)
Dominant hand, n(%)	
Right	83 (%95,4)
Left	2 (%2,3)
Education, n(%)	
Uneducated	2 (%2,3)
Primary school	29 (%33,3)
Junior high school	9 (%10,3)
High school	25 (%28,7)
University	20 (%23)
Occupation, n(%)	
Housewife	26 (%29,9)
Tailor	4 (%4,6)
Soldiers/policemen	5 (%6,9)
Engineer	4 (%4,6)
Doctor	2 (%2,3)
Official	14 (%16,1)
Teacher	9 (%10,3)
Driver	3 (%3,4)
Other	10 (11,5)

Discussion

Alzheimer's dementia (AD) is a type of dementia with insidious onset and memory impairment. However, sometimes mood disorders may occur in the early stages of the disease.[10] Whether late-onset depression is a pre-stage of dementia or a risk factor for dementia is still controversial. Most studies report that 30-50% of individuals with AD present with symptoms of depression such as low mood, apathy, and social withdrawal.[11] These depressive disorders that occur in dementia cause increased deficits in functioning, increased problem behaviors, increased nursing home placement, caregiver stress, and increased mortality.[12,13]

Furthermore, a study has demonstrated that antidepressant treatment stimulates neurogenesis and tropism, and

Table 2. **Neuropsychological Test Parameters of All Patients**

WMS-I, n(%)	
Abnormal	54
Normal	23
WMS-II, n(%)	
Abnormal	39
Normal	41
WMS-III, n(%)	
Abnormal	57
Normal	7
WMS-IV, n(%)	
Abnormal	25
Normal	25
WMS-V, n(%)	
Abnormal	43
Normal	33
WMS-VI, n(%)	
Abnormal	21
Normal	32
STM: Normal, LTM: Abnormal	11
STM: Abnormal, LTM: Normal	4
Similarities test, n(%)	
Abnormal	62
Normal	16
Clock drawing test, n(%)	
Abnormal	51
Normal	28
Luria Alternan Sequences Test, n(%)	
Abnormal	41
Normal	35
Verbal fluency test, n(%)	
Both abnormal	29
Both normal	24
SVF: abnormal, LVF: normal	12
SVF: normal, LVF: abnormal	5
Stroop test, n(%)	
Abnormal	9
Normal	4
Trail making test, n(%)	
Abnormal	11
Normal	8
A form: Normal, B form: Abnormal	4
Face Recognition Test, n(%)	
Abnormal	21
Normal	40
Judgement of line orientation test, n(%)	
Abnormal	52
Normal	14
Shape Copy Test, n(%)	
Abnormal	25
Normal	46
Language Skill, n(%)	
Abnormal	26
Normal	49
Mood Evaluation, n(%)	
Abnormal	26
Normal	42
Verbal Memory Processes Test, n(%)	
All abnormal	7
All normal	12
LS:low	6
TRS and LS: low	2
IMS, LS: low	9
IMS: low	1
EEG, mean±SD,range	8,58 ± 0,86 (6–10)
MMT, mean±SD,range	24,35 ± 4,13 (11–30)
MoCA, mean±SD,range	14,20 ± 5,63 (6–23)

STM: Short term memory, LTM:Long term memory, SVF: semantic verbal fluency, LVF: lexical verbal fluency, LS: learning score, TRS: total recall score, IMS: instant memory score, EEG: electroencephalogram, MMT: mini mental test, MoCA: Montreal Cognitive Assessment.

improves learning properties and differentiation and proliferation of new neurons.[14] Therefore, strategies that promote the prevention, early diagnosis, and adequate treatment of depression can potentially prevent or delay dementia in older adults[15] We can interpret this situation as depression as a modifiable risk factor for dementia.

Documented cognitive difficulties in elderly depressed patients without dementia have been indicated to be within memory, attention, naming, verbal fluency, visuospatial abilities, processing speed, and executive functions.[8,16-18] Findings from studies that specifically evaluated the differences in memory profiles among AD patients when compared to depressed patients show that although both groups exhibited impaired performance on immediate and delayed recall tasks, patients with depression generally retained the learned information.[8] Studies have generally compared AD and depression or AD and MCI patients in terms of NPTs. We wanted to compare the NPT results by including all 3 groups in our study and aimed to determine the specific tests specific to each group by examining the pairwise combinations in addition to the triple group. However, when MCI and dementia groups were compared, although we could detect differences between NPT results, we could not determine any difference between MCI and depression groups.

Long-term memory can be divided into two groups: declarative memory and procedural memory.[19] Declarative memory is an open process, conscious, and controlled. With this process, visual or verbal information emerges at the end of a conscious recall. Declarative memory consists of two parts, episodic and semantic memory. Semantic memory refers to general information about the world. Knowing the capital city of Germany or mathematical formula is all about semantic memory. It is not linked to a specific time frame. Semantic memory is not sensitive to loss or change of information.[20] On the contrary, episodic memory is related to time and context. It is based on specific events in the person's past. What we ate for dinner and where we last went for vacation are related to episodic memory. Episodic memory is more sensitive to information change and loss. With this information, we can say that semantic memory is known, and episodic memory is remembered.[20] Episodic memory impairment is typically the first presenting symptom in AD. The region that modulates episodic memory is the medial temporal lobe structure. As we know, prominent medial temporal lobe atrophy develops in AD.[21] Of the six main memory systems, episodic memory is the most clinically relevant observed in AD.[22] Robust episodic

Table 3. **Comparison of Neuropsychological Test Parameters and Sociodemographic Characteristics of Patients with Dementia, Mild Cognitive İmpairment and Depression**

Clinicopathological Factors	No. Of Patients (%)			*P*-value
	Depression (24 patients)	MCI (16 patients)	Dementia (47 patients)	
Age, year, median, range	66,50 (42–86)	73,50 (63–83)	77 (52–85)	$P < 0{,}001^{H}$
Gender, n				
Male	9	10	14	
Female	15	6	33	$P = 0.066^{‡}$
Dominant hand, n				$P = 0.441^{‡}$
Right	24	15	44	
Left	0	1	1	
Education, n				$P = 0{,}123^{‡}$
Uneducated	1	0	1	
Primary school	5	3	21	
Junior high school	1	4	4	
High school	9	4	12	
University	8	5	7	
Occupation, n				$P = 0{,}099^{‡}$
Housewife	10	1	15	
Tailor	0	1	3	
Soldiers/policemen	3	3	0	
Engineer	2	0	2	
Doctor	0	1	1	
Official	5	4	5	
Teacher	1	2	6	
Driver	0	0	3	
Other	1	3	6	
WMS-I, n				$P = 0{,}004^{‡}$
Abnormal	11	9	34	
Normal	13	4	6	
WMS-II, n				$P = 0{,}001^{‡}$
Abnormal	7	3	29	
Normal	17	11	13	
WMS-III, n				$P = 0{,}009^{‡}$
Abnormal	14	9	34	
Normal	5	2	0	
WMS-IV, n				$P = 0{,}001^{‡}$
Abnormal	4	2	19	
Normal	13	6	6	
WMS-V, n				$P = 0{,}082^{‡}$
Abnormal	12	4	27	
Normal	12	8	13	
WMS-VI, n				$P = 0{,}066^{‡}$
Abnormal	5	3	13	
Normal	14	9	9	
STM: Normal, LTM: Abnormal	4	1	6	
STM: Abnormal, LTM: Normal	0	0	4	
Similarities test, n				$P = 0{,}009^{‡}$
Abnormal	16	8	38	
Normal	8	5	3	
Clock drawing test, n				$p < 0{,}001^{‡}$
Abnormal	7	8	36	
Normal	16	7	5	
Luria Alternan Sequences Test, n				$P = 0{,}115^{‡}$
Abnormal	10	6	25	
Normal	13	9	13	
Verbal fluency test, n				$P = 0{,}071^{‡}$
Both abnormal	4	4	21	
Both normal	12	5	7	
SVF: abnormal, LVF: normal	3	3	6	
SVF: normal, LVF: abnormal	2	1	2	

Stroop test, n				$P = 0{,}146^{‡}$
Abnormal	2	3	4	
Normal	3	1	0	
Trail making test, n				$P = 0{,}002^{‡}$
Abnormal	0	3	8	
Normal	4	4	0	
A form: N, B form: B	3	1	0	
Face Recognition Test, n				$P = 0{,}313^{‡}$
Abnormal	5	4	12	
Normal	16	9	15	
Judgement of line orientation test, n				
Abnormal	14	10	28	$P = 0{,}099^{‡}$
Normal	8	2	4	
Shape Copy Test, n				$P = 0{,}007^{‡}$
Abnormal	4	2	19	
Normal	18	11	17	
Language Skill, n				$P = 0{,}042^{‡}$
Abnormal	4	3	19	
Normal	18	10	21	
Mood Evaluation, n				$P = 0{,}004^{‡}$
Abnormal	15	2	9	
Normal	8	10	24	
Verbal Memory Processes Test, n				$P = 0{,}060^{‡}$
All abnormal	1	1	5	
All normal	8	4	0	
LS:low	2	0	4	
TRS and LS: low	0	1	1	
IMS, LS: low	2	2	5	
IMS: low	1	0	0	
EEG, median, range	9 (7–10)	9 (8–9)	9 (6–10)	$P = 0{,}827^{H}$
MMT, mean ± SD, range	27,07 ± 2,15 (23–30)	27,25 ± 2,5 (24–30)	21,86 ± 3,91 (11–28)	$P < 0.001^{F}$
MoCA, mean ± SD, range	–	17 ± 5,25(10–23)	10 ± 3,16(6–13)	$P = 0{,}087^{F}$

STM: Short term memory, LTM:Long term memory, SVF: semantic verbal fluency, LVF: lexical verbal fluency, LS: learning score, TRS: total recall score, IMS: instant memory score, EEG: electroencephalogram, MMT: mini mental test, MoCA: Montreal Cognitive Assessment, SD: standart deviation; Min:minimum; Max:maximum;
[F]Anova test;
[‡]χ^2 tests;
[H]Kruskal Wallis test

memory is required to remember to turn off the stove, take medicine, pay bills, and not get lost while driving. Deficiencies in these functional areas are initially unclear and can often be attributed to normal aging by the patient. During this period, NPTs are guiding the detection of episodic memory disorders. SBST is an important test that can distinguish many memory-related parameters from each other. In our study, SBST was statistically significantly different, especially in the comparison of AD and MCI groups. SBST test was applied to 15 AD and 8 MCI patients in total, and this test was abnormal in all dementia patients, while it was normal in half of MCI patients. This situation suggests how valuable the SBST test is in differential diagnosis and that it should be applied in NPT. Another distinguishing test in our study is considered WMS-V. WMS-V was defective in 50% of depressed patients, 67.5% of dementia patients, and only 33% of MCI patients. This result indicates that this test may not be very helpful in the differential diagnosis of patients with depression, but might be a guide when distinguishing between dementia and MCI. Of course, making a differential diagnosis with one or two tests will not be the right method. However, trying to apply these tests while performing NPT can make our work easier. The tests used in the NP battery are not standard everywhere. However, if it is determined which tests are more sensitive through studies, these tests may become standard in the coming years.

Studies have shown that performance-based measures that evaluate functional status in addition to NPT are more successful than NPT alone in distinguishing clinically normal elderly people from MCI. With the Harvard Automated Phone Task developed in this regard, patients are asked to perform tasks such as bank transfers or selecting a new primary care family physician using the voice response system. It was reported that with this task assessment, clinically normal elderly, MCI and young normal participants can be distinguished.[23-26] However, since our study was designed retrospectively, functional status evaluation could not be performed.

Cognitive evaluation is especially crucial in MCI patients. The separation of cognitively healthy elderly people with MCI with NPTs not only provides early diagnosis but also allows pharmacological and non-pharmacological treatments to be started as early as possible, thus preventing cognitive decline. Studies have reported that neuropsychological evaluation is more sensitive than some neuroimaging and cerebrospinal fluid (CSF) biomarkers for the distinction of MCI and AD.[27] Some studies argue that standard NPTs can be used to distinguish preclinical AS from healthy elderly, while some studies argue that standard NPTs are not sensitive[27,28] and that special tests should be used.[29-31] Contrary to AD, it has been reported that semantic memory is more affected in MCI.[32,33] Figurative language comprehension assessments also show promise as

Table 4. **Univariate multinomial logistic regression analysis of characteristics factors for Patients with Dementia, Mild Cognitive Impairment and Depression**

Characteristics	Univariate analysis	
	OR (95% CI)	*P*-value
Age		
MCI	1,091 (1,013–1,174)	0,021
Dementia	1,129 (1,060–1,203)	< 0,001
WMS1		
MCI	2,659 (0,639–11,06)	0,179
Dementia	6,697 (2,053–21,84)	0,002
WMS2		
MCI	0,662 (0,140–3,123)	0,603
Dementia	5,418 (1,809–16,22)	0,003
WMS3		
MCI	1,607 (0,255–10,13)	0,614
Dementia	150367587	<0,001
WMS4		
MCI	1,083 (0,154–7,642)	0,936
Dementia	10,29 (2,418–43,81)	0,002
Similarities test		
MCI	0,800 (0,197–3,254)	0,755
Dementia	6,333 (1,486–26,99)	0,013
Clock drawing test		
MCI	2,612 (0,678–10,05)	0,163
Dementia	16,45 (4,531–59,78)	< 0,001
Shape Copy Test		
MCI	0,818 (0,128–5,233)	0832
Dementia	5,029 (1,419–17,83)	0,012
Language Skill		
MCI	1,350 (0,250–7,278)	0,727
Dementia	4,071 (1,168–14,19)	0,028
Mood Evaluation		
MCI	0,107 (0,19–0,610)	0,012
Dementia	0,200 (0,063–0,632)	0,006
MMT		
MCI	1,043 (0,611–1,782)	0,876
Dementia	0,459 (0,283–0,744)	0,002

*The reference category is: depresyon.

precise measures of cognition. Figurative language skills may be impaired especially in early AD[34] and MCI.[35] A study published in 2022 in which neuropsychological evaluations of 35 MCI and 56 healthy volunteers were performed reported that MCI patients had worse performance in MoCA and semantic memory tests.[36] In this study, it was revealed that especially semantic memory and figurative language skills tests are more sensitive than standard psychometric tests in distinguishing MCI patients from healthy volunteers. In this case, we can conclude that episodic memory is more prominently affected in AD patients, and semantic memory is more prominently affected in MCI and preclinical AD.

Another study concluded that patients with amnestic mild cognitive impairment (aMCI) had an 8.6-fold higher risk of conversion to AD when compared to patients reporting memory problems without objective deterioration in neuropsychological tests.[37] In a study published in 2018, GBD, aMCI, and healthy controls were monitored for AD conversion for 4 years. At the end of 4 years, 41 of 60 aMCI patients and 57 of 115 LLD patients had converted to AD. None of the 66 healthy volunteers who were followed up did transform to AD. Crude risks for developing AD at 4 years from baseline were 68.33% and 49.57% for the aMCI and GBD groups, respectively.[15] The gender difference observed in our study also supports the hypothesis that not every MCI patient progresses to dementia. Because in our study, there was a male predominance in the MCI group and a female predominance in the dementia group. If each MCI had progressed to dementia, we would expect more male patients to be seen in the dementia group.

There are also studies comparing NPTs of patients with MCI and depression. A study by Benson et al. on depression subjects determined that MMSE scores were not significantly different from aMCI subjects.[38] Our study determined no statistical difference between neuropsychological tests between MCI and depression patients, and only mood tests had higher scores in depression patients.

The limitations of the study can be listed as the inability to apply the same tests to all patients, to perform tests to evaluate the functionality of the patients, the low number of MCI patients, and the retrospective design of the study.

Conclusion

In conclusion, when evaluating patients who present with the complaint of forgetfulness, a detailed neuropsychological evaluation must be performed in addition to other diagnostic tests. Sensitive tests should be included to confirm the diagnosis, especially in cases where being in between for the differential diagnosis. Thus, further studies are needed on this subject.

Conflicts of Interest Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia–meta-analysis of 41 robust inception cohort studies. *Acta psychiatrica scandinavica.* 2009;119(4):252–265.
2. Gillis C, Mirzaei F, Potashman M, Ikram MA, Maserejian N. The incidence of mild cognitive impairment: A systematic review and data synthesis. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring.* 2019;11:248–256.
3. Canevelli M, Grande G, Lacorte E, et al. Spontaneous reversion of mild cognitive impairment to normal cognition: A systematic review of literature and meta-analysis. *Journal of the American Medical Directors Association.* 2016;17(10):943–948.
4. Zhuang L, Yang Y, Gao J. Cognitive assessment tools for mild cognitive impairment screening. *Journal of neurology.* 2021;268(5):1615–1622.
5. Kliegel M, Zimprich D. Predictors of cognitive complaints in older adults: A mixture regression approach. *European Journal of Ageing.* 2005;2(1):13–23.
6. Mahapatra A, Sharma P, Khandelwal SK. Late onset depression: A recent update. *Journal of Mental Health and Human Behaviour.* 2015;20(1):4.
7. Koenig AM, Bhalla RK, Butters MA. Cognitive functioning and late-life depression. *Journal of the International Neuropsychological Society.* 2014;20(5):461–467.

8. Wright SL, Persad C. Distinguishing between depression and dementia in older persons: Neuropsychological and neuropathological correlates. *Journal of geriatric psychiatry and neurology.* 2007;20(4):189–198.
9. Petersen RC. Mild cognitive impairment as a diagnostic entity. *Journal of internal medicine.* 2004;256(3):183–194.
10. Salami O, Lyketsos CG. Clinical Features of Alzheimer's Disease: Cognitive and Non-Cognitive. *Principles and Practice of Geriatric Psychiatry.* 2010:226–231.
11. Zubenko GS, Zubenko WN, McPherson S, et al. A collaborative study of the emergence and clinical features of the major depressive syndrome of Alzheimer's disease. *American Journal of Psychiatry.* 2003;160(5):857–866.
12. Gilley DW, Bienias J, Wilson R, Bennett D, Beck T, Evans D. Influence of behavioral symptoms on rates of institutionalization for persons with Alzheimer's disease. *Psychological Medicine.* 2004;34(6):1129–1135.
13. Suh GH, Kil Yeon B, Shah A, Lee JY. Mortality in Alzheimer's disease: A comparative prospective Korean study in the community and nursing homes. *International Journal of Geriatric Psychiatry: A journal of the psychiatry of late life and allied sciences.* 2005;20(1):26–34.
14. Boldrini M, Underwood MD, Hen R, et al. Antidepressants increase neural progenitor cells in the human hippocampus. *Neuropsychopharmacology.* 2009;34(11):2376–2389.
15. Lauriola M, Mangiacotti A, D'Onofrio G, et al. Late-life depression versus amnestic mild cognitive impairment: Alzheimer's disease incidence in 4 years of follow-up. *Dementia and Geriatric Cognitive Disorders.* 2018;46(3-4):140–153.
16. Ganguli M, Du Y, Dodge HH, Ratcliff GG, Chang C-CH. Depressive symptoms and cognitive decline in late life: A prospective epidemiological study. *Archives of general psychiatry.* 2006;63(2):153–160.
17. Elderkin-Thompson V, Kumar A, Mintz J, Boone K, Bahng E, Lavretsky H. Executive dysfunction and visuospatial ability among depressed elders in a community setting. *Archives of Clinical Neuropsychology.* 2004;19(5):597–611.
18. Butters MA, Whyte EM, Nebes RD, et al. The nature and determinants of neuropsychological functioning in late-lifedepression. *Archives of general psychiatry.* 2004;61(6):587–595.
19. Squire LR. Memory systems of the brain: A brief history and current perspective. *Neurobiology of learning and memory.* 2004;82(3):171-177.
20. Mesulam M-M. *Principles of behavioral and cognitive neurology:* Oxford University Press; 2000.
21. Ashendorf L, Alosco ML, Bing-Canar H, et al. Clinical utility of select neuropsychological assessment battery tests in predicting functional abilities in dementia. *Archives of Clinical Neuropsychology.* 2018;33(5):530–540.
22. Gold DA. An examination of instrumental activities of daily living assessment in older adults and mild cognitive impairment. *Journal of clinical and experimental neuropsychology.* 2012;34(1):11–34.
23. Goldberg TE, Koppel J, Keehlisen L, et al. Performance-based measures of everyday function in mild cognitive impairment. *American Journal of Psychiatry.* 2010;167(7):845–853.
24. Sadek JR, Stricker N, Adair JC, Haaland KY. Performance-based everyday functioning after stroke: Relationship with IADL questionnaire and neurocognitive performance. *Journal of the International Neuropsychological Society.* 2011;17(5):832–840.
25. Marshall GA, Amariglio RE, Sperling RA, Rentz DM. Activities of daily living: where do they fit in the diagnosis of Alzheimer's disease? *Neurodegenerative disease management.* 2012;2(5):483–491.
26. Marshall GA, Dekhtyar M, Bruno JM, et al. The Harvard Automated Phone Task: New performance-based activities of daily living tests for early Alzheimer's disease. *The journal of prevention of Alzheimer's disease.* 2015;2(4):242.
27. Bondi MW, Jak AJ, Delano-Wood L, Jacobson MW, Delis DC, Salmon DP. Neuropsychological contributions to the early identification of Alzheimer's disease. *Neuropsychology review.* 2008;18(1):73–90.
28. Thomas KR, Edmonds EC, Eppig J, Salmon DP, Bondi MW, Initiative AsDN. Using neuropsychological process scores to identify subtle cognitive decline and predict progression to mild cognitive impairment. *Journal of Alzheimer's Disease.* 2018;64(1):195–204.
29. Rentz DM, Parra Rodriguez MA, Amariglio R, Stern Y, Sperling R, Ferris S. Promising developments in neuropsychological approaches for the detection of preclinical Alzheimer's disease: A selective review. *Alzheimer's research & therapy.* 2013;5(6):1–10.
30. Loewenstein DA, Curiel RE, Duara R, Buschke H. Novel cognitive paradigms for the detection of memory impairment in preclinical Alzheimer's disease. *Assessment.* 2018;25(3):348–359.
31. Xie L, Wisse LE, Das SR, et al. Longitudinal atrophy in early Braak regions in preclinical Alzheimer's disease. *Human brain mapping.* 2020;41(16):4704–4717.
32. Papp KV, Rentz DM, Orlovsky I, Sperling RA, Mormino EC. Optimizing the preclinical Alzheimer's cognitive composite with semantic processing: The PACC5. *Alzheimer's & Dementia: Translational Research & Clinical Interventions.* 2017;3(4):668–677.
33. Vonk JM, Flores RJ, Rosado D, et al. Semantic network function captured by word frequency in nondemented APOE ε4 carriers. *Neuropsychology.* 2019;33(2):256.
34. Papagno C, Lucchelli F, Muggia S, Rizzo S. Idiom comprehension in Alzheimer's disease: The role of the central executive. *Brain.* 2003;126(11):2419–2430.
35. Cardoso S, Silva D, Maroco J, De Mendonça A, Guerreiro M. Non-literal language deficits in mild cognitive impairment. *Psychogeriatrics.* 2014;14(4):222–228.
36. Klooster N, Humphries S, Cardillo E, et al. Sensitive Measures of Cognition in Mild Cognitive Impairment. *Journal of Alzheimer's Disease.* 2021;82(3):1123–1136.
37. Lehrner J, Gufler R, Guttmann G, et al. Annual conversion to Alzheimer disease among patients with memory complaints attending an outpatient memory clinic: The influence of amnestic mild cognitive impairment and the predictive value of neuropsychological testing. *Wiener Klinische Wochenschrift.* 2005;117(18):629–635.
38. Benson AD, Slavin MJ, Tran T-T, Petrella JR, Doraiswamy PM. Screening for early Alzheimer's disease: Is there still a role for the mini-mental state examination. *Prim Care Companion J Clin Psychiatry.* 2005;7(2):62–69.

This work is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported License which allows users to read, copy, distribute and make derivative works for non-commercial purposes from the material, as long as the author of the original work is cited properly.