Original Article / Özgün Araştırma

A Practical Tool for the Detection of Limbic-type-memory Deficit: 5-Word-Test

Limbik Tipte Bellek Bozukluğunun Saptanması için Pratik Bir Aygıt: 5 Kelime Testi

● Gül Kayserili[1]*, ● Zerrin Yıldırım[2]*, ● Özgül Vupa Çilengiroğlu[3], ● Görsev G. Yener[4]

[1]Izmir Narlidere Nursing Home Elderly Care and Rehabilitation Center, Izmir, Turkey

[2]Bagcilar Training and Research Hospital, Clinic of Neurology; Istanbul University Aziz Sancar Experimental Medicine Research Institute, Department of Neuroscience, Istanbul, Turkey

[3]Dokuz Eylul University Faculty of Science, Department of Statistics, Izmir, Turkey

[4]Dokuz Eylul University Faculty of Medicine, Department of Neurology, Izmir, Turkey

*These authors contributed equally to this work.

Abstract

Objective: The 5-Word-Test (5WT) is a quick and practical verbal memory assessment tool that was developed by Dubois et al. The objective of this study was to establish the validity and reliability of its Turkish version with the purpose of acquiring a practical memory testing instrument that would discriminate the stages of the normal aging - mild cognitive impairment (MCI) - early Alzheimer-type dementia (ATD) continuum with high sensitivity and specificity.

Materials and Methods: One hundred six healthy participants (HP), 22 with MCI and, 39 patients with ATD consented to participate in the study. Participants were evaluated using the 5WT, Standardized Mini-Mental State Examination, verbal fluency and 3 Words-3 Shapes tests. The simultaneous validity tests of the 5WT with other cognitive tests and test-retest validity of the test were investigated using Spearman's rho correlation analysis. Parametric and non-parametric tests were used for group comparisons. For the discriminant ability of the 5WT, the Receiver Operating Characteristic (ROC) area under curve was measured.

Results: In 5WT cued recall score (CRS), all HPs, and in free recall score (FRS) 95.3% of them received 10 points. The 5WT score differences between HPs and the combined patient groups, and among MCI and ATD severity stage groups were significant (p<0.01). According to the ROC analysis, FRS and CRS had high sensitivity in discriminating HPs from patients, HPs from the MCI and MCI groups from the ATD. Inter-observer and test-retest correlations were quite high (r=0.85, r=0.95 respectively). The Cronbach alpha value of the test was found as 0.94.

Conclusion: In this study, we have shown that the Turkish version of 5WT is a valid and reliable test for HPs, and patients with ATD and MCI. Due to the ability of 5WT to discriminate among the stages of normal aging-ATD continuum, it may prove to be a practical tool to be used in specialized dementia out-patient clinics in our country.

Keywords: Five-Word-Test, Alzheimer's disease, mild cognitive impairment, verbal memory

Öz

Amaç: Dubois ve arkadaşları tarafından geliştirilen, hızlı ve pratik bir sözel bellek ölçeği olan 5 Kelime Testi'nin (5KT) Türkçe versiyonunun geçerlilik ve güvenilirliği oluşturularak normal yaşlanma, hafif kognitif bozukluk (HKB) ve Alzheimer tipi demans (ATD) sürekliliği evrelerini birbirlerinden yüksek duyarlılık ve özgüllükte ayıracak pratik bir enstrümanın elde edilmesi hedeflenmiştir.

Gereç ve Yöntem: Yüz altı sağlıklı katılımcı, 22 HKB ve 39 ATD'li birey olmak üzere toplam 167 katılımcı 5KT, Standardize Mini-Mental Durum Testi, Sözel Akıcılık [kategori akıcılığı (bir dakikadaki hayvan sayısı), bir dakikada meyve-insan ismi değişimli sayma, leksikal akıcılık (birer dakikada K-A-S ile başlayan kelime sayısı)], 3 Kelime 3 Şekil testleri ile değerlendirildi. 5KT'nin diğer kognitif testlerle eş zamanlı geçerlilik testleri ve test-tekrar test geçerliliği, Spearman rho testi ile testler arasındaki korelasyonlara bakılarak araştırıldı. Gruplar arası fark analizlerinde, veri dağılımına bakılarak parametrik ve non-parametrik testler kullanıldı. 5KT'nin ayırt ediciliği için "Receiver Operating Characteristic" (ROC) eğri altında kalan alana bakıldı.

Bulgular: 5KT ipuçlu hatırlama toplam puanında (İTP) sağlıklıların tümü, serbest hatırlama toplam puanında (STP) %95,3'ü 10 puan almıştır. Sağlıklı bireylerin ve hastaların, HKB ile farklı evrelerdeki ATD'lilerin, 5KT puanları arasındaki fark anlamlı bulunmuştur (p<0,01). ROC analizine göre STP [eğri

Öz

altında kalan alan (EAA): 0,99], sağlıklı bireyleri HKB ya da ATD tanılı bireylerden İTP'ye göre (EAA: 0,84) daha yüksek duyarlılıkla ayırt etmiştir. Sağlıklı bireyleri, HKB tanısı almış bireylerden ayırmada da STP (EAA: 0,98) İTP'ye (EAA: 0,64) göre daha yüksek duyarlılığa sahiptir. HKB'li bireyleri, ATD'li bireylerden ayırmada da STP (EAA: 0,96) İTP'ye (EAA: 0,92) göre daha yüksek duyarlılığa sahiptir. Uygulayıcılar arasında (r=0,80) ve aynı uygulayıcının farklı zamanlardaki uygulamaları arasında (r=0,95) test-tekrar test korelasyonu yüksektir. Testin güvenilirlik analizinde Cronbach alfa değeri 0,94 olarak bulunmuştur.

Sonuç: Bu çalışmada 5KT'nin Türkçe versiyonunun sağlıklı, ATD'li ve HKB'li bireylerde geçerli ve güvenilir bir test olduğu gösterilmiştir. 5KT normal yaşlanma-ATD sürekliliğini ayrıştırabildiği için özelleşmiş demans polikliniklerinde pratik bir enstrüman olarak kullanılabilir.

Anahtar Kelimeler: Beş Kelime Testi, Alzheimer hastalığı, hafif kognitif bozukluk, sözel bellek

Introduction

According to 2018 data, 50 million people worldwide have been diagnosed as having dementia. It is assumed that this number will reach 82 million people in 2030 and 152 million in 2050 (1). Alzheimer's disease (AD) has a 50-70% incidence among all dementia types, with its prevalence doubling every 5 years in the population aged over 65 years (2). Although it is known as a disease of elderly people, it is understood that its pathology begins 15-20 years before clinical symptoms appear (3). Studies on the treatment of the disease are increasing the importance of early diagnosis. Early diagnosis appears to be critical to provide treatments against the causes (4).

The core clinical feature for typical AD is that the free recall score (FRS) is low and patients do not benefit from cues in verbal episodic memory assessment (5). The recommended test for assessing this type of episodic memory impairment is the Free and Cued Selective Reminding Test (FCSRT) (6,7). Low total recall score in this test has 92% specificity in the recognition of patients with amnestic "mild cognitive impairment" (MCI) who may develop Alzheimer's-type dementia (ATD), and low total recall score and inability to benefit from cues are specific to ATD (8,9). Furthermore, impairment in FCSRT performance was associated with hippocampal atrophy, loss of gray matter in the medial temporal lobe, and presence of AD pathology in cerebrospinal fluid (10,11,12,13). In this sense, it is a very appropriate test to determine the diagnosis or risk of AD, but it is not considered suitable for use as a screening test due to the long time required for the application of the test.

There are neuropsychological tests in our country that are routinely used in dementia screening, for which the validity and reliability were shown (14,15,16). The most commonly used test is the Standardized Mini-Mental Test (SMMT). This test is evaluated over 30 points and free recall is evaluated over 3 points for 3 given words. Therefore, as mentioned above, it is insufficient to evaluate a hippocampal type of memory disorder, especially in the early stages, which is reflected in the clinic in the form of free recall difficulties and inability to benefit from cues (17). This test, which can evaluate the middle and advanced stage of ATD with high sensitivity, has low sensitivity in the early stages of ATD and in MCI.

Therefore, a screening test that can be relatively applied in a short time is needed to assess the episodic memory defect at an early stage. For this purpose, the 5-Word-Test (5WT) was developed in French in 1998 by Dubois et al. (18,19). This test provides an evaluation of verbal episodic memory through five words in different semantic categories. Learning of words is achieved with semantic cues. The patient is given a score out of 10 in total by testing instant free (IF) and cued recall, and delayed free (DF) and cued recall for five words. If delayed recall disorder is detected, the patient is given semantic cues and cued recall is evaluated. Thus, encoding, storage, and retrieval, which components of verbal episodic memory, are evaluated.

The 5WT, which tests the usage of semantic cues and which also tests instant and delayed recall was shown to be an appropriate test in determining ATD at an early stage (8,18,20). Therefore, it is predicted that the 5WT may catch individuals that will develop ATD in the MCI phase. This test, which has a cut-off value of 10, was shown to have 87% specificity and 91% sensitivity in distinguishing patients with ATD from the control group (CG) (18). In this study, individuals with MCI were also included.

In this study, the Turkish version of the 5WT was created and the validity and reliability of the Turkish form on healthy individuals and the distinguishing power of the test for MCI and ATD were evaluated.

Materials and Methods

The study was conducted in accordance with the Helsinki Declaration with the approval of the Ethics Committee of Izmir Dokuz Eylul University dated 22.08.2008/314.

Creation of the Turkish Version

Permission was obtained from Dubois to make the Turkish adaptation and validity-reliability study of the 5WT, which was developed by Dubois et al. (18), and was known as "Le Test de Cinq Mots" and the "Five-Word-Test" in the literature. In the literature, there were three different lists of words belonging to the 5WT. In order to determine the list of words from three different lists to prepare the Turkish version and to be used in the study, an evaluation was made considering its intelligibility by Turkish society and meeting the neuropsychological test development criteria. In this evaluation process, considering the frequency and intelligibility of the use of the Turkish equivalents of the French words in three separate lists in Turkish society, and the phonemic characteristics of the words in the list that do not resemble each other, the most appropriate list for Turkish society from among three different lists was determined. The scale, the original language of which was French, was translated into Turkish by two psychologists who knew French by staying true to the original. Its Turkish form was translated into French again

by another psychologist, ensuring conceptual consistency with the original.

First, the Turkish version of 5WT was performed to patients who were followed up in our neurology outpatient clinic with a diagnosis of dementia and MCI in the Neuropsychology Laboratory and to the healthy individuals over the age of 50 years in the field in the address of residence between May 2008 and January 2009 as a preliminary study, and then it was performed beginning from May 2019 for the purpose of the study.

Determination of Participants

The study was conducted between May 2009 and March 2010. Thirty-nine patients with ATD, 22 with MCI, and 106 healthy subjects (HS) were enrolled in the study. The ATD group was formed from participants aged over 50 years who were diagnosed as having AD according to the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-4) criteria, the diagnosis of possible AD criteria according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria and who had no accompanying psychiatric or neurologic disease. The MCI group was formed from participants who were diagnosed as having MCI according to the Petersen's criteria, were aged over 50 years, with a Clinical Dementia Rating (CDR) scale score of 0.5, and who had no accompanying psychiatric or neurologic disease. The HS group included participants aged over 50 years, who had an SMMT score of 24 and over, and who had a CDR score of 0, and who had no psychiatric or neurologic diseases. A consent form was obtained from all participants (AP) who all voluntarily agreed to participate in the study. Before the study was started, Geriatric Depression Scale (21) was applied to the candidates in order to exclude depression, and candidates with a score >11 were not enrolled in the study.

Method

A short sociodemographic data form was completed in which the sex, age, education, and professional status of the participants meeting the criteria were questioned. The 3 Words-3 Shapes (3W3S) test (22,23), counting words starting with K-A-S per minute for phonemic fluency (24,25), counting animal names per minute for categorical fluency, and counting fruit-human names alternately per minute (26), SMMT (27,28) and 5WT were then applied to the participants.

The 5-Word-Test

In this test developed by Dubois et al. (18), five words are taught to the participant and the IF and instant cued (IC) recall and after a steelmaking task, DF and delayed cued (DC) recall are scored (19). The total score of 5WT is evaluated out of 10 with the sum of IC and DC scores (see Appendix 1). In addition, FRS and cued recall total score (CRS) were calculated in our study.

Statistical Analysis

The Statistical Package for the Social Sciences Ver. 15.0 program was used for statistical analysis of the study. Cronbach alpha was used in internal consistency analysis and Pearson correlation analysis was used in test-retest reliability.

Two basic approaches were used to test the validity of the Turkish version of the 5WT:

1) Equivalent forms validity: Non-parametric correlations (Spearman rho) of the SMMT, 3W3S test and verbal categorical fluency tests, which were applied simultaneously to individuals, were performed.

2) Known-groups validity: In this study, the distribution of differences of diagnoses according to test scores were examined using the Levene test. In homogeneous groups, t-test for binary groups, ANOVA and post-hoc Tukey for multiple groups were used as parametric tests. In heterogeneous groups, the Mann-Whitney U test for binary groups and the Kruskal-Wallis and post hoc Mann-Whitney U tests for multiple groups were used as non-parametric tests. A "Receiver Operating Characteristic" (ROC) area under curve (AUC) was used in the statistical evaluation of the sensitivity and specificity of the test.

The CG, consisting of 61 participants, comprised 106 HS by matching them with 61 patients study group (SG) in terms of age, sex, education, and occupational status. AP in the CG and SG (n=122) were referred as the whole comparison subgroup (WCSG) in the article. AP (n=167) was used in the correlation tests, and WCSG was analyzed in the group comparison tests. For the measurement of homogeneity between CG and SG, Levene's test was used because of the lack of equal distribution between the groups in terms of age, and the chi-square test was used for the measurement of homogeneity of groups in terms of education, occupational status, and sex. P value of 0.05 was accepted as statistical significance. The Mann-Whitney U test, which is a non-parametric test that presents the mean scores and standard deviation as data and shows the significance of these data in terms of p values, was used in order to show the differentiability of the two groups by the test scores. The Spearman rho test, which is a non-parametric analysis method, was used to examine the relationship between the 5WT and other neuropsychological tests due to heterogeneous distribution, and the t-test and as non-parametric tests, the Mann-Whitney U test and the Kruskal-Wallis test were used to evaluate whether the test was affected by demographic data. The mean 5WT scores of CG and SG were analyzed using the one-sample t-test and the difference between the two groups in terms of mean test score was analyzed using the independent groups t-test.

Results

Sociodemographic Data

The sociodemographic characteristics of AP in the study are shown in Table 1.

Test-Retest Validity

Test-retest was performed with 40 HS and 30 patients in SG 4 months apart. The scores of the group retested by the same practitioner and the mean scores of the group retested by a different practitioner and the correlation between them are shown in Table 2. There was a positive correlation between test scores and retest scores in both groups.

The participants' 5WT subscores and standard deviations are shown in Table 3, and the chart of 5WT total score averages is

shown in Figure 1. It was observed that the test score tended to fall from healthy individuals to advanced stage ATD.

Parallel Forms Validity

The total score of 5WT in the HP group was 10 and due to the ceiling effect, no statistical calculation was made and the analyses were performed on the SG and AP (Table 4). When the SG and AP were evaluated, a positive relationship above expected moderate level between verbal categorical fluency tests, SMMT and 5WT. Athough no significant correlation was observed between test scores in the MCI group, a positive correlation was evident between test performances in advanced stages of ATD.

According to the ROC analysis applied to determine if 5WT could distinguish healthy individuals from patients and to determine the cut-off values where 5WT scores had high sensitivity and specificity for the disease, it was found that the 5WT total score distinguished healthy individuals (n=106) from patients (MCI and ATD) (n=61) with an 0.84 AUC with a "very good" manner, and the FRS of 5WT distinguished healthy individuals from patients (MCI and ATD) with a 0.99 AUC with a "very good" manner. The AUC belonging to the free and cued 5WT total scores, indicating that the difference with 0.000 p values (p<0.5) between HS and patients, is shown in Figure 2A.

Table 1. Sociodemographic features of the participants							
Demographic features		**Participants**					
		Healthy	All cases	MCI	ATD	Control group	Total
n (%)		106 (63.5%)	61 (36.5%)	22	39	61	167
Sex	Female	61 (57.5%)	37 (60.7%)	12	25	33 (54.1%)	98 (58.7%)
	Male	45 (42.5%)	24 (39.3%)	10	14	28 (45.9%)	69 (41.3%)
Age	Mean	73.5	81.5	79.3	82.7	80.3	76.5
	Standard deviation	9.8	6.2	4.8	6.6	6.5	9.5
Education	Non-literate	9 (8.5%)	4 (6.6%)	2	2	7 (11.5%)	13 (7.7%)
	Primary school	27 (25.5%)	17 (27.9%)	3	14	14 (23%)	44 (26.2%)
	Secondary school	17 (16%)	13 (21.3%)	6	7	11 (18%)	30 (17.9%)
	High school	26 (24.5%)	13 (21.3%)	6	7	18 (29.5%)	39 (23.2%)
	University	27 (25.5%)	14 (23%)	5	9	11 (18%)	41 (24.4%)
Occupational status	No work experience	21 (19.8%)	17 (27.9%)	3	14	10 (16.4%)	38 (22.8%)
	Have work experience	27 (25.5%)	13 (21.3%)	3	10	18 (29.5%)	40 (24%)
	Retired	58 (54.7%)	31 (50.8%)	16	15	33 (54.1%)	89 (53.3%)
Clinical stage (CDR)	0 (Healthy)	106	-	-	-	61	
	0.5 (MCI)	-	22 (36.1%)	22	-	-	
	1 (Early ATD)	-	16 (26.2%)	-	16	-	
	2 (Moderate ATD)	-	18 (29.5%)	-	18	-	
	3 (Advanced ATD)	-	5 (8.2%)	-	5	-	
CDR: Clinical Dementia Rating, MCI: Mild cognitive impairment, ATD: Alzheimer-type dementia							

Table 2. The correlation between mean free recall test score and cued recall test score in tests and retests performed by the same practitioner (intra) and different practitioners (inter)								
5WT mean score[a]		**Intra**				**Inter**		
		FRS		CRS		FRS		CRS	
		Test	RT	Test	RT	A Test	B RT	A Test	B RT
Control (n=20)		10	10	10	10	10	10	10	10
Patient (n=15)		4.3	3.9	7.9	7.8	4.8	4.1	8.8	8.5
R[b]	Healthy and patient	0.98		0.95		0.99		0.80	
	Patient	0.83		0.92		0.87		0.80	
5WT: 5-Word-Test, FRS: Free recall test score, CRS: Cued recall test score, RT: Retest, [a]ANOVA test, [b]Spearmen rho correlation analysis test								

It was found that the total score of 5WT distinguished healthy individuals (n=106) from patients with MCI (n=22) with a 0.64 AUC with a "moderate" manner, and a FRS of 5WT distinguished healthy individuals from patients with MCI with a 0.98 AUC with an "excellent" manner (Figure 2B). It was found that the total score of 5WT distinguished patients with MCI from patients with ATD with a 0.92 AUC with an "excellent" manner, and a FRS of 5WT distinguished patients with MCI from patients with ATD with a 0.96 AUC with an "excellent" manner (Figure 2C). The ROC AUC belonging to the FRS and CRS in 5WT, indicating the difference of .000 p values (p<0.5) between the two different study groups, is shown in Figure 2.

The ability of 5WT to distinguish individuals with MCI (n=106) from individuals with ATD (n=39) and its most sensitive threshold are shown in Table 5.

The ROC curve areas of 5WT FRS and CRS according to their strength to distinguish healthy individuals from individuals with ATD, individuals with MCI, and individuals with MCI and early-stage ATD are shown in Table 6.

Sensitivity and Specificity Analysis

According to sensitivity and specificity analysis, 5WT FRS was found to be more sensitive and specific than CRS. It was also
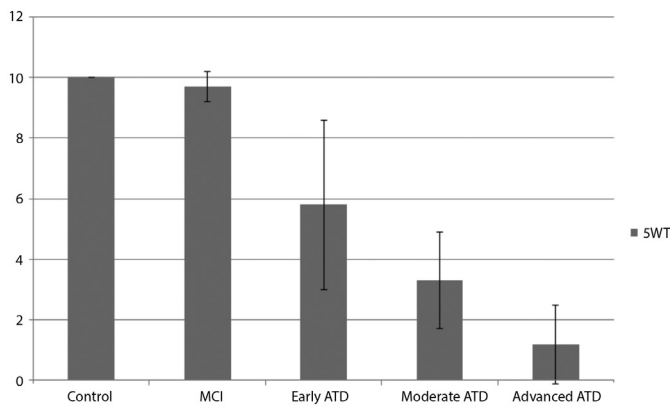

Figure 1. The chart of mean total 5-Word-Test score of the control and study groups

5WT: 5-Word-Test, MCI: Mild cognitive impairment, ATD: Alzheimer-type dementia

found that when the 5WT FRS threshold was set at 9 points, it was able to catch healthy people with 1.00 sensitivity and patients with early stage ATD with 0.88 specificity. 5WT FRS was found to have a sensitivity of 0.95 in indetifying healthy individuals and a specificity value of 1.00 in catching all cases, when the normal value of healthy individuals was taken as 10 points. However, when the normal value of 5WT CRS was taken as 10, it had high sensitivity in catching healthy people and had 0.81 specificity in catching patients with early stage ATD (Table 7, 8).

Internal Consistency of Test Items

In the reliability and internal consistency analyses on five different words in 5WT performed in the whole group (n=167), a high reliability coefficient was reached with a total Cronbach alpha value of 0.94. Each item assessed in the 5WT was understood by the participants and had a significant value in the measurement of the test. It was shown that when any item was removed the Cronbach alpha value lowered.

Discussion

It is thought that the 5WT developed by Dubois et al. (18) can be used as a screening test due to the fact that it is a practical test that can be applied in relatively short time and it is shown to have high sensitivity and specificity in separating patients with ATD from controls (8). Therefore, the Turkish version of 5WT and its validity and reliability were evaluated in Turkey. The reliability coefficient of the Turkish version of the test was found to be very high (0.94). It was also shown to distinguish patients with ATD from healthy individuals and patients with MCI. It was also found positively related with other neuropsychological tests used for the same purpose.

Early diagnosis of ATD is very important for the effectiveness of treatment and for the effectiveness of possible future treatment methods (29,30). It is known that MCI can also transform into dementia in the later period (29,31,32). In a standardization study of 5WT conducted by Croisile et al. (19,20) in 2007, 191 healthy elderly people, 76 of whom were male and 115 of whom were female, aged between 50 and 90 years, were taken as the sample group. In that study, the age range was divided into four groups (50-59 years, 60-69 years, 70-79 years, and ≥80 years). It was observed that 79.9% of the participants had 10 points (maximum value of total score), and did not require any

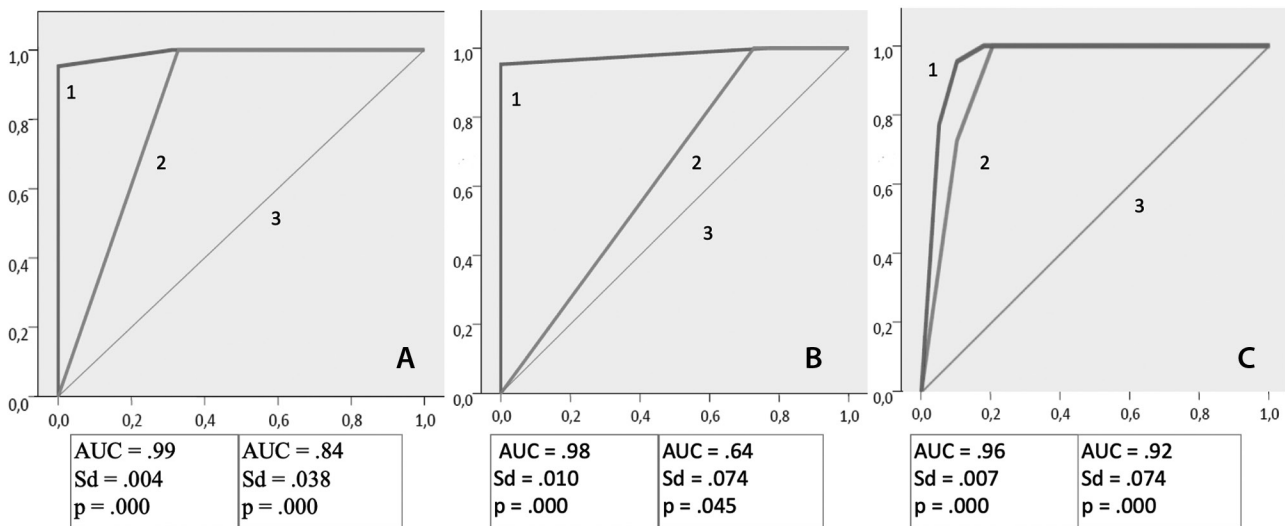| Table 3. Mean and standard deviations of the 5-Word-Test sub-score in the whole comparison subgroup												
5WT	**Control (n=61)**		**Patient (n=61)**		**MCI (n=22)**		**Early ATD (n=16)**		**Moderate ATD (n=18)**		**Advanced ATD (n=5)**	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
5WT _IS	5.0	0.0	3.8	1.6	5.0	0.0	3.8	1.5	3.1	1.3	1.2	1.3
5WT_IC	5.0	0.0	4.2	1.3	5.0	0.0	4.3	1.3	3.9	0.9	1.2	1.3
5WT_DS	4.9	0.2	1.7	1.8	3.7	0.5	1.2	1.5	0.1	0.4	0.0	0.0
5WT_DC	5.0	0.2	2.3	2.4	4.7	0.5	2.0	2.2	0.3	1.1	0.0	0.0
5WT_FRS	9.9	0.2	5.9	2.8	8.7	0.5	5.5	2.4	3.2	1.6	1.2	1.3
5WT_CRS	10.0	0.0	6.5	3.3	9.7	0.4	6.2	3.1	3.3	2.1	1.2	1.3
5WT: 5-Word-Test, IS: Instant spontaneous, IC: Instant cued, DS: Delayed spontaneous, DC: Delayed cued, FRS: Free recall total score, CRS: Cued recall total score, MCI: Mild cognitive impairment, ATD: Alzheimer-type dementia, SD: Standard deviation												

intervention and tending to remember the words in the order of delivery. In that study, the validity and reliability of 5WT in the French elderly population were evaluated. The 5WT was found to have 91% specificity and 63% sensitivity. When a more detailed assessment was performed by giving 2 points to each item in the free recall, a score of 20 was obtained. Its sensitivity increased to 84% when the overall score was below 18. In the same study, 5WT was observed to allow more objective assessment and determination of memory problems during memory health consultations (18,19).

Table 4. Correlation analysis by groups between 5-Word-Test and neuropsychological tests used in the study								
Health			MCI	Early ATD	Moderate+ Advanced ATD	All ATD	Study group	All participants
n		106	22	16	23	39	61	167
SMMT	r	-	0.211	0.141	500**	0.467**	0.697**	0.704**
	p	-	0.345	0.603	0.015	0.003	0.000	0.000
Animal list	r	-	0.174	0.204	0.320	0.362*	0.567**	0.632**
	p	-	0.440	0.449	0.137	0.024	0.000	0.000
F_H	r	-	-0.354	0.449	0.551**	0.572**	0.607**	0.612**
	p	-	0.106	0.081	0.006	0.000	0.000	0.000
KAS	r	-	-0.298	0.419	0.464**	0.420**	0.436**	0.406**
	p	-	0.178	0.106	0.026	0.008	0.000	0.000
3-Word	r	-	0.549**	-0.229	-	-0.015	0.653**	0.803**
	p	-	0.009	0.394	-	0.929	0.000	0.000
3-Shape	r	-	0.429*	-0.229	-	-0.015	0.654**	0.781**
	p	-	0.044	0.394	-	0.929	0.000	0.000
3W3S	r	-	0.521*	-0.229	-	-0.015	0.657**	0.785**
	p	-	0.013	0.394	-	0.929	0.000	0.000

*p<0.05, **p<0.01, r: Spearman rho test, 5WT: 5-Word-Test, MCI: Mild cognitive impairment, ATD: Alzheimer type dementia, SMMT: Standardized Mini-Mental State Test, F_H: Fruit-Human List, 3W3S: 3 Words-3 Shapes Test

(5WT applies to all rows — label shown at right margin)

A) AUC = .99, Sd = .004, p = .000 | AUC = .84, Sd = .038, p = .000

B) AUC = .98, Sd = .010, p = .000 | AUC = .64, Sd = .074, p = .045

C) AUC = .96, Sd = .007, p = .000 | AUC = .92, Sd = .074, p = .000

1: 5WT free recall total score
2: 5WT total score
3: Reference line

Figure 2. A) ROC curve for 5-Word-Test (5WT) cued and free total score in distinguishing healthy subjects from all patients. B) ROC curve for 5WT cued and free total score in distinguishing healthy subjects from mild cognitive impairment (MCI). C) ROC curve for 5WT cued and free total score in distinguishing MCI from Alzheimer-type dementia

AUC: Area under the curve, Sd: Standard deviation

In our study, the 5WT CRS was found to distinguish healthy individuals from patients at a very good level, and the 5WT FRS was found to distinguish perfectly. In addition, 5WT FRS was found to separate two different groups at "excellent" levels and better than other neuropsychological tests. This suggests that the 5WT has a very important feature as a reference point in determining diagnosis

Table 5. 5-Word-Test free recall total score and cued recall total score ROC curve areas and sensitive threshold values according to the power to distinguish mild cognitive impairment from Alzheimer-type dementia

MCI/ATD n=22/39	5WT-FRS	5WT-CRS
ROC curve area	0.96	0.92
The most sensitive threshold	8.5	9.5

5WT: 5-Word-Test, FRS: Free recall total score, CRS: Cued recall total score, MCI: Mild cognitive impairment, ATD: Alzheimer-type dementia

Table 6. 5-Word-Test free recall total score and cued recall total score ROC curve areas according to the power to distinguish healthy subjects from mild cognitive impairment, Alzheimer type dementia and study group

		5WT FRS	5WT CRS
Area under the ROC curve	HS/ATD n=106/39	0.99	0.84
	HS/MCI+early ATD n=106/38	0.99	0.75
	HS/MCI n=106/22	0.98	0.64

HS: Healthy subjects, 5WT: 5-Word-Test, FRS: Free recall total score, CRS: Cued recall total score, MCI: Mild cognitive impairment, ATD: Alzheimer-type dementia

in terms of the practitioner, along with its advantageous features such as being very short, having low cost, and being performed in a short time. At the same time, in sensitivity and specificity calculations, the 5WT FRS was found to have higher selectivity in identifying patients, and higher sensitivity in determining healthy subjects than the 5WT CRS. We believe that the lower distinguishing power of CRS compared with FRS in separating MCI from healthy individuals can be explained by two reasons. The first is that not all individuals diagnosed as having MCI will develop dementia, and the second is that in the MCI stage, the person is able to capture the healthy individual in CRS by recognizing words with clues, that is, through familiarity compensation. In patients with ATD, the drop in FRS and CRS clearly indicates that this test is able to detect the typical primary type of memory impairment. When the threshold value of FRS was determined as 9, it was found that it was able to catch healthy individuals with 1.00 sensitivity and patients with early stage ATD with 0.88 specificity. When the threshold value of FRS was determined as 10, it was found to have 0.95 sensitivity in determining healthy individuals and 1.00 specificity for identifying all patients. In this respect, we believe that 5WT is a useful screening test for predicting a primary type of memory impairment when the FRS score is 9 or below and the CRS score is below 10.

Limitation of the Study

Most of the individuals with MCI included in the study showed a different performance from HS and patients with ATD in the 5WT and other neuropsychological tests. However, to suggest that poor performance in 5WT is an early diagnostic finding for diagnosis of ATD, a longitudinal study should be conducted with individuals with MCI. It is considered a remarkable finding that individuals with MCI in our study showed slightly lower performance than healthy individuals; however, there was no definitive information that they would later be diagnosed as having ATD.

Table 7. Sensitivity and specificity levels of 5-Word-Test (5WT) cued and free total scores in catching patients and healthy subjects according to the threshold scores set for 5WT

Sensitivity and specificity calculations[a]

	Healthy subjects	Study group	MCI	Early ATD	Moderate-Advanced ATD	5WT total score	
Sensitivity	106/106 1.00	-	-	-	-	Threshold 10	CUED
Specificity	-	41/61 0.67	6/22 0.27	13/16 0.81	22/23 0.96		
Sensitivity	101/106 0.95	-	-	-	-	Threshold 10	FREE
Specificity	-	61/61 1.00	22/22 1.00	16/16 1.00	23/23 1.00		
Sensitivity	106/106 1.00	-	-	-	-	Threshold 9	
Specificity	-	42/61 0.69	5/22 0.23	14/16 0.88	23/23 1.00		

[a]Calculation based on formula

5WT: 5-Word-Test, MCI: Mild cognitive impairment, ATD: Alzheimer-type dementia

Table 8. Distribution of the healthy group and the study group by the Clinical Dementia Rating clinical stage according to 5-Word-Test (10 and 9) and Standardized Mini-Mental State Test cut-off value (24)

Diagnosis		SMMT >24	SMMT ≤24	5WT: 10	5WT <10	5WT FRS: 10	5WT FRS: 9	5WT FRS <9	n
n		120	47	126	41	101	24	42	167
Healthy CDR 0		106	0	106	0	101	5	0	106
Patient	CDR 0.5	12	10	16	6	0	17	5	22
	CDR 1	1	15	3	13	0	2	14	16
	CDR 2	1	17	1	17	0	0	18	18
	CDR 3	0	5	0	5	0	0	5	5

5WT: 5-Word-Test, FRS: Free recall total score, SMMT: Standardized Mini-Mental State Test, CDR: Clinical Dementia Rating

Conclusion

5WT is an easy-to-implement and useful test that assesses verbal memory performance with semantic cues. It was concluded that the Turkish version of the test might be appropriate for use as a screening test for ATD in the clinics of related units in the Turkish community with a reliability coefficient of 0.94.

References

1. World Alzheimer Report 2018. Alzheimer's Disease International. Erişim Tarihi: 20.01.2019. Available from: https://www.alz.co.uk/research/world-report-2018

2. Prince M, Albanese E, Guerchet M, et al. World Alzheimer Report 2014. Dementia and risk reduction. An analysis of protective and modifiable factors. Alzheimer's Disease International (ADI), London, September 2014.

3. Jack CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9:119-128.

4. Sahin HA, Gurvit IH, Emre M, et al. The attitude of elderly lay people towards the symptoms of dementia. Int Psychogeriatr 2006;18:251-258.

5. Jack CR, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:257-262.

6. Buschke H. Cued recall in amnesia. J Clin Neuropsychol 1984;6:433-440.

7. Grober E, Buschke H. Genuine memory deficits in dementia. Developmental Neuropsychology 1987;3:13-36.

8. Van Harten AC, Smits LL, Teunissen CE, et al. Preclinical AD predicts decline in memory and executive functions in subjective complaints. Neurology 2013;81:1409-1416.

9. Vos SJB, Xiong C, Visser PJ, et al. Preclinical Alzheimer's disease and its outcome: A longitudinal cohort study. Lancet Neurol 2013;12:957-965.

10. Benzinger TLS, Blazey T, Jack CR, et al. Regional variability of imaging biomarkers in autosomal dominant Alzheimer's disease. Proc Natl Acad Sci USA 2013;110:E4502-4509.

11. Ikonomovic M, Abrahamson E, Kofler J, et al. Neuropathology and biochemical correlations of [F-18]AV-1451 and [C-11]PiB PET imaging in a subject with Alzheimer's disease. In: Johnson KA, Jagust WJ, Klunk WE, Mathis CA, eds. 11th Human Amyloid Imaging. Miami, Florida 2017;157.

12. Burnham SC, Bourgeat P, Doré V, et al. Clinical and cognitive trajectories in cognitively healthy elderly individuals with suspected non-Alzheimer's disease pathophysiology (SNAP) or Alzheimer's disease pathology: a longitudinal study. Lancet Neurol 2016;15:1044-1053.

13. Mormino EC, Papp KV, Rentz DM, et al. Heterogeneity in suspected non-Alzheimer disease pathophysiology among clinically normal older individuals. JAMA Neurol 2016;73:1185-1191.

14. Erkal B. Nöropsikolojik testlerin klinik psikolojide -tanı ve tedavide- kullanımı. Kriz Dergisi 1995;3:155-158.

15. Can H, İrkeç C, Karakas S. Alzheimer tipi demansın farklı evrelerinin nöropsikolojik profili. Yeni Sempozyum Dergisi 2006;44:115-135.

16. Gürvit IH, Baran B. Demanslar ve kognitif bozukluklarda ölçekler. Nöropsikiyatri Arşivi 2007;44:58-65.

17. Mormont E, Jamart J, Robaye L. Validity of the five-word test for the evaluation of verbal episodic memory and dementia in a memory clinic setting. J Geriatr Psychiatry Neurol 2012;25:78-84.

18. Dubois B, Touchon J, Portet F, et al. "Les 5 mots", épreuve simple et sensible pour le diagnostic de la maladie d'Alzheimer. Presse Med 2002;31:1696-1699.

19. Croisile B, Astier JL, Beaumont C. Étalonnage du test des cinq mots dans une population de sujets sains. Revue Neurologique 2007;163:323-333.

20. Croisile B, Astier JL, Beaumont C, Mollion H. Le Test des cinq mots dans les formes légres de maladie d'Alzheimer: comparaison du score total, du Score Total Pondéré, du Score d'apprentissage et du Score de mémoire dans trois classes d'âge (60 ans, 70 ans, 80 ans). Revue Neurologique 2010:711-720.

21. Ertan T, Eker E. Reliability, validity, and factor structure of the geriatric depression scale in Turkish elderly: Are there different factor structures for different cultures? Int Psychogeriatr 2000;12:163-172.

22. Weintraub S, Mesulam MM (1985). Mental state assessment of young and elderly adults in behavioural neurology. In Mesulam MM (ed.). Principles of

behavioral neurology. 4th ed. Philadelphia: FA Davis, 1985:71-123.

23. Kudiaki C, Aslan A. The Three Words-Three Shapes test: Normative data for the Turkish elderly. Arch Clin Neuropsychol 2007;22:637-645.

24. Lezak MD. Neuropsychological Assessment. 3rd ed. Oxford University Press, New York;1995.

25. Tumaç A. Normal deneklerde frontal hasarlara duyarlı bazı testlerde penformansa yaş ve eğitimin etkisi (Yüksek Lisans Tezi). İstanbul: İstanbul Üniversitesi, Sosyal Bilimler Enstitüsü;1997.

26. Benton AL, Hamsher K deS, Sivan AB. Multilingual Aphasia Examination. 3rd ed. San Antonio, TX: Psychological Corporation;1994.

27. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.

28. Güngen C, Ertan T, Eker E, Yaşar R, Engin F. Standardize Mini Mental Test'in Türk toplumunda hafif demans tanısında geçerlik ve güvenilirliği. Türk Psikiyatri Dergisi 2002;13:273.

29. İnan L. Alzheimer Hastalığında Histopatoloji. Demans Dizisi 1999;1:52-61.

30. İşeri P, Efendi H. Demanslı Hastaya Klinik Yaklaşım ve Tedavi. Sted 2003;12:458.

31. Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: Clinical characterization and outcome. Arch Neurol 1999;56:303-308.

32. Amieva H, Jacqmin-Gadda H, Orgogozo JM, et al. The 9 year cognitive decline before dementia of the Alzheimer type: A prospective population-based study.Brain 2005;128:1093-1101.

Appendix 1. 5-Word-Test

MUSEUM
LEMONADE
GRASSHOPPER
STRAINER
TRUCK

Dubois B. (1998)
Adapted to Turkish by Gül Kayserili (2008)

Date: .... / .... / 20.............

Name:..

Surname:..

Gender:...

Birth date:...

Telephone:..

Education status:...

Address:...

Occupation:..

Hand dominance:...

His/her physician:...

Diagnosis:...

	Learning (Instant Memory)		Recall (Long Term Memory)	
	Instant Free Recall	**Instant Cued Recall**	**Delayed Free Recall**	**Delayed Cued Recall**
Drink - Lemonade				
Kitchenware - Strainer				
Vehicle - Truck				
Building - Museum				
Animal - Grasshopper				
Score				
Total Score				

INSTRUCTIONS

1. Learning Phase (Instant Memory)

a. Presentation of the list

The person is asked to read the 5-word list aloud. *"Read this list of words out loud and try to keep those words in mind. I'll ask you all this again later."*

The word list, which is taught only once, is continued to be shown to the person and the categorical cues are taught verbally. These categories are never shown visually to the person

"From all the words here, can you tell which one is a building? Which one is a drink? Which one is an animal? Which one is a kitchenware? Which one is a vehicle?"

b. Control of coding

The page on which the words are written is kept from the person and the person is asked for instant recall. *"Can you tell me what's in your mind from the words you've learned?"*

The number of words he/she can remember is recorded as an instant free recall score. If he/she is unable to remember all of the words, he/she is given categorical cues only for the words he/she has forgotten, allowing him/her to remember. *"There was a building name, what was it?, Which drink name did I say?, Which animal name did I say?, Which kitchenware name did I say?, Which vehicle name did I say?"*

The number of words he/she remembers using categorical cues is recorded as an instant cued recall score. The sum of the instant free recall and instant cued recall score is recorded. If the total score is 5, the words are assumed to have been learned and recorded. In this case, the memory is tested. If the score is <5, the word list is shown again and the words and categories that he/she has forgotten are reminded. *"Which of these words is a building name? Which is the name of a drink? Which one is an animal name? Which is the name of a kitchenware? Which is the name of a vehicle?"* This stage is repeated until all the words are learned.

2. Attention Activity

The purpose of this intervening attention activity is to divert one's attention away for 3-5 minutes. In the meantime, tests that evaluate the patient's attention activity, visual-spatial construction skill, or time-space orientation may be performed.

3. Memory Phase (Delayed Recall)

a. Long term free recall

"Can you tell me again the words you have just learned?" The number of words he/she remembers is recorded as a delayed free recall score. If he/she cannot remember all of the words you move on to the next stage.

b. Long term cued recall

By uttering categorical cues for forgotten words, one is allowed to remember. *"There was a building name, what was it?, Which drink name did I say?, Which animal name did I say?, Which kitchenware name did I say?, Which vehicle name did I say?"*

The number of words he/she remembers using cues is recorded as a delayed cued recall score.

The total score is calculated by summing up the instant cued recall and delayed cued recall scores.