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REY AUDITORY VERBAL LEARNING TEST AS A TOOL FOR DIAGNOSIS OF MILD COGNITIVE IMPAIRMENT

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SUMMARY

Background. *Previous research suggests that patients with Alzheimer's disease (AD) manifest more "false alarm" (FA) responses in recognition memory tests than patients with Huntington disease (Delis et al., 1991), minimal cognitive impairment (MCI) or normal controls (Greenaway et al., 2006). It has been shown that 50% of patients with MCI develop dementia within 5 years (Gauthier et al., 2006). An early diagnosis of MCI when treatment is most effective is thus warranted. The objective of this study was to characterize recognition memory error patterns in patients with MCI in order to predict an incipient AD.*

Methods. *33 MCI patients whose MMSE scores were between 25 and 27 participated in the study and were compared to 97 TLE patients who underwent full neuropsychological evaluations. FA measure was applied to analyze the recognition memory errors on the Rey Auditory Verbal Learning Test (RAVLT).*

Results. *According to the independent sample t-test, MCI patients demonstrated significantly more FA errors than TLE patients (p=0.01). A significant negative correlation between the number of FA mistakes and the score on the MMSE was found in the MCI group (p=0.04).*

Conclusions: *The present findings suggest that a high number of FA errors, in a framework of a comprehensive neuropsychological evaluation, may be helpful in an early diagnosis of MCI.*

INTRODUCTION

Memory disorders are common in many neurological diseases, particularly those that involve medial temporal lobe dysfunction, for example, Temporal Lobe Epilepsy (TLE), Alzheimer disease (AD) and Korsakoff syndrome. The term "Mild Cognitive Impairment" (MCI) refers to a decline in memory and cognitive functions, more severe than what one might expect from normal aging, but not severe enough to warrant a diagnosis of dementia. MCI is commonly considered to be a transitional stage between normal aging and dementia. The deficits in MCI often interfere with the individual's everyday functioning and are a major cause for referrals to memory clinics. According to some reports, more than 50% of the individuals diagnosed with MCI, especially those of the amnestic type, will develop dementia, usually of the AD type, within 5 years (Gauthier et al., 2006).

There is considerable variability in the diagnostic criteria of MCI (Korczyn et al., 2006). Some classify patients as suffering from MCI if their scores on memory tests fall beyond the range of 1.5 standard deviations below the mean for their age (Arnaiziz et al., 2003). Others refer to aspects of cognition other than memory when trying to define the MCI population, for example, difficulty carrying out daily tasks (Chertkow, 2002). Thus different definitions and measures used among clinicians and researchers prevent a consensus on diagnostic criteria for MCI.

Epilepsy is a neurological disease in which memory complaints are a common symptom. A frequent form of epilepsy is temporal lobe epilepsy, the epileptogenic lesion of which is commonly hippocampal sclerosis. Since the hippocampus and the hippocampal formation are critical for consolidation of newly acquired information and for normal memory function, pathology in these structures is associated with memory impairments (Jefferys et al., 1999). Damage to the medial temporal lobes can lead to anterograde amnesia, i.e., difficulty in learning and retaining new information (Corkin et al., 1984; Kaut et al., 2001). Despite the differences in etiology and neuropathology, TLE and AD have one aspect in common: memory impairment in these two diseases results from temporal lobe dysfunction (Hodges et al., 1992; Jefferys et al., 1999; Dickerson et al., 2004).

There is also a difference in the course of memory impairment in these two diseases. Whereas in TLE patients the memory dysfunction is relatively stable over time, in MCI the memory dysfunction is in many cases progressive and may lead to dementia (Helmstaedter et al., 2003). In addition, some studies suggest that there may be differences in awareness for memory deficits in these populations (Cosentino & Stern, 2005). While patients with TLE usually complain about their memory problems, patients with AD are often unaware of their functional and memory difficulties, thus demonstrating lower meta-cognitive abilities.

Numerous memory tests exist to diagnose various aspects of memory and memory disorders. Most common of these are the auditory learning tests (e.g., the Rey Auditory Verbal Learning Test, RAVLT). This test is frequently used to examine the efficiency of the learning process, recall and recognition abilities, sensitivity to interference and forgetting. The RAVLT provides measures of immediate memory, efficiency of learning, short- and long-term recall, recognition, sensitivity to interference and forgetting (Rey, 1964; Van Der Elst & al, 2005).

Though recall and recognition are examined in the same test, they are different memory functions involving different brain structures. While the active recall ability has been linked to the hippocampal function, recognition has been associated with a sense of familiarity, implicating more widespread temporal brain areas (Viskontas et al., 2006). Auditory verbal recall measures have received ample attention in testing for epilepsy and dementia, while the pattern of recognition errors has received little attention, even though they might be important in characterizing different memory deficits.

In the past, there have been attempts to analyze recognition memory errors using signal detection theory (Snodgrass & Corwin, 1988). The signal detection model proposes that items presented for a recognition test lie along a continuum of familiarity. The response criterion is the decision boundary that the participant places on the continuum in order to categorize stimuli as either old or new. If the participant recognizes an old item, his answer is considered a "hit." If a new item is recognized as a non-familiar, the answer is considered as a "correct rejection" (CR). There are also two types of errors which can occur: if the participant recognizes erroneously a new item as familiar, the answer will be considered a "false-alarm" (FA), and if the participant does not recognize an old item as familiar, the answer is considered a "Miss."

Delis et al. (1991), who compared Huntington's disease patients and AD patients on the California Verbal Learning Test, suggested that AD patients may have difficulties with recognition discriminability. They found that AD patients recognize, incorrectly, many items from the recognition list as if they had appeared in the original list, while in fact they did not (many "FA"). In contrast, there is no evidence for a similar pattern in TLE patients. The recognition paradigm may reflect, among other tools used in memory assessment, the differential pattern of cognitive performances between the two populations and reflective of different brain structures and pathologies involved.

The objective of this study was to analyze and compare the results of the RAVLT recognition test in MCI and TLE patients, focusing on the differences in the pattern of correct ("hits") and incorrect ("FA") answers.

METHOD

Subjects

This was an archival study; the patients' data and diagnoses were taken from their medical records. All participants were seen at the Tel Aviv Sourasky Medical Center, between 1996 and 2006. The TLE patients underwent a neuropsychological evaluation as part of a comprehensive pre-surgical work-up. The MCI patients were examined as outpatients in the memory clinic.

The subject group consisted of 130 patients: 97 TLE patients who were candidates for epilepsy surgery (due to intractable seizures) and 33 MCI patients. Of the 112 patients admitted to the memory clinic with a complaint of memory problems, two patients who received a diagnosis of AD were excluded; the remaining 110 patients varied in their Mini-Mental Status Examination (MMSE) scores between 24 and 30. Patients whose MMSE scores were higher than 27 and lower than 25 were excluded, resulting in a reduced list of 33 patients defined as MCI.

Basic demographic information for the study population is given in Table 1.

Table 1. MCI & TLE patients

	N (males/females)	Age (years)	Education (years)
MCI	33 (20/13)	69.59 (10.25)	13.35 (3.93)
TLE	97 (49/48)	34.1 (10.06)	12.3 (2.39)

MATERIALS AND PROCEDURE

The battery of tests used with the MCI patients included the MMSE, a brief 30-item questionnaire commonly used as a screening tool for complaints of memory problems, or when a diagnosis of dementia is being considered (Folstein et al., 1975). There is an inverse relationship between MMSE scores and age, ranging from a median of 29 for those 18 to 24 years of age, to 25 for individuals 80 years of age and older. As mentioned above, MMSE scores were used also as cut off points (25-27) for creating a well defined group of MCI patients (Crum et al., 1993). Both TLE and MCI patients were administered the Hebrew version of RAVLT (Vakil et al., 1993).

The RAVLT consists of five presentations of a 15-word list (List A), with a free recall procedure following each presentation. Afterwards, a second 15 word list is presented (List B), followed by a recall phase, and then a sixth recall trial of list A (STM recall). Delayed recall is examined with a seventh

recall trial following a 20 minute delay. Recognition is tested by asking the respondent to indicate which of 50 words read aloud were from List A (15 possible hits) and which were not (35 possible FAs).

RESULTS

An overall comparison between the TLE and MCI groups on the different parameters of the RAVLT was performed, and the results are presented in Tables 2 and 3. The MCI patients performed better than the TLE patients on most age-standardized recall measures, whereas they did significantly worse on the recognition measures. An independent samples t-test was carried out to compare the raw number of FA errors of the recognition trial in the two patient groups. The MCI patients made significantly more FA errors (M=4.73, SD=5.67) than the TLE patients (M=2.45, SD=3.13) *($p<0.01$)*.

In addition, the different trials of the RAVLT have been correlated with the measures of general cognitive function in the two populations. The Pearson correlation coefficient test between MMSE results and RAVLT recall trials

Table 2. Mean Scores of RAVLT for 110 MCI and 97 TLE patients

Recall trial	Disease	N	T-test value	Mean and SD (raw scores)	Mean and SD (age standardized)	Sig. (2-tailed)
trial 5	MCI	110	3.96	10.54 (3.13)	-.64(1.53)	0.00
	TLE	97		10.74 (2.49)	-1.75(2.42)	
trial 7	MCI	110	4.40	8.17 (3.96)	-.50(1.43)	0.00
	TLE	97		8.48 (3.12)	-1.58(2.07)	
trial 8	MCI	110	5.04	8.24 (4.12)	-.58(1.49)	0.00
	TLE	97		7.59 (3.21)	-1.75(1.85)	

Table 3. Mean RAVLT scores for 33 MCI and 97 TLE patients

Recall trial	Disease	N	T-test value	Mean and SD (raw scores)	Mean and SD (standardized scores)	Sig. (2-tailed)
trial 5	MCI	33	1.743	9.48 (3.38)	-.99 (1.57)	.08
	TLE	97		10.74 (2.49)	-1.75 (2.41)	
trial 7	MCI	33	2.334	7.12 (4.36)	-.72 (1.48)	.02
	TLE	97		8.48 (3.12)	-1.58 (2.07)	
trial 8	MCI	33	2.713	7.09 (4.57)	-.80 (1.57)	.01
	TLE	97		7.59 (3.21)	-1.75 (1.85)	

was performed. A significant correlation was found between the MMSE scores and trial 5 of the RAVLT ($r=0.36$, $p<0.05$) in the MCI patient group.

The same t-test was done again with 33 MCI subjects. After age standardization of the memory scores, we found out that the MCI patients performed better than the TLE patients on RAVLT trials 7 and 8. The results are shown in Table 3.

DISCUSSION

The main finding of this research was a significant difference in the number of false alarm errors committed by MCI as compared to TLE patients on the recognition memory trial of the RAVLT, patients with MCI showing many more FA errors than patients with TLE. These results suggest that patients with MCI may be sensitive to confusion and interference on the learning and memory tasks.

By contrast, the TLE patients were significantly worse than the MCI patients on the active recall measures of the RAVLT. These measures, which were analyzed on a post-factum basis, suggest that patients with TLE may have a problem with active retrieval of newly learned information.

In addition to analyzing the strictly defined MCI patient group, we analyzed a larger sample of patients who arrived at the memory clinic. These patients were originally excluded form the MCI experimental group since they did not meet the strict criteria of the definition of MCI (MMSE 25-27). This patient group consisted of 110 patients complaining of memory problems, but they were not defined as MCI and were not diagnosed as suffering from dementia, either. An independent sample t-test was performed in order to compare the number of FA errors between TLE patients and this larger sample of patients that included the 33 patients who were characterized as MCI. We found that this larger patient group also made significantly more FA mistakes.

These results suggest that there may be a continuum in the time axis of memory decline. Individuals may suffer from memory problems, not meeting the diagnoses of either AD or MCI, but still showing a memory performance pattern that may be suggestive of these conditions. A significantly high number of FA on a recognition memory test, observed in our MCI patient sample, may be an early sign of possible further decline in memory abilities.

It should be mentioned that there was a large variance in FA error distribution in the MCI group, reflected by a large standard deviation (5.67, compared with the mean of 4.73). Some patients made many FA mistakes, and some made few or none at all. The purpose of future studies of this sample of patients will be to differentiate between those MCI patients who have many FA errors on a memory recognition test and those who have few or none, in terms of their risk of developing AD later. As mentioned before, earlier studies suggest that AD patients make many FA mistakes on recognition tests, suggesting that a process of confusion, decreased self-monitoring and

awareness, as well as sensitivity to interference may have taken place in these individuals (Petersen et al., 1999, 2001; Greenaway et al., 2006). Thus, if those MCI patients who had a high number of FA errors will indeed develop AD, while those MCI patients who did not have a significant number of FA errors will be less likely to develop AD, then our hypothesis will be supported. A high number of FA errors on a recognition memory test may be an early sign of dementia and an early predictor of incipient AD.

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