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Detection of visuoperceptual deficits in preclinical and mild Alzheimer's disease

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Abstract

Exhaustive neuropsychological assessment of mild cognitive impairment (MCI) subjects frequently identifies cognitive deficits other than memory. However, visuoperception has rarely been investigated in MCI. The 15-Objects Test (15-OT), a visual discrimination task based on the Poppelreuter Test, consists of 15 overlapping objects. Poppelreuter-type tests are frequently used to detect visual agnosia. However, more complex tests, such as the 15-OT, are required to detect visuoperceptual signs in those patients who perform correctly on simple tests. The aim of the present study was to investigate visuoperceptual deficits in MCI patients and to assess the usefulness of the 15-OT to discriminate Alzheimer's disease (AD) and MCI patients from controls. The 15-OT, and a neuropsychological battery included in the diagnostic assessment, was administered to 44 healthy controls, 44 MCI patients, and 44 mild AD patients. Performance on the 15-OT was significantly different between groups. MCI scored between AD and controls. When MCI and AD patients had relatively normal performance on simple tests (Poppelreuter), increased significant abnormalities were found by a more difficult visuoperceptual test (15-OT). Regression analyses showed that the 15-OT was a significant predictor of group membership, but the Poppelreuter Test did not significantly contribute to the models. Visuoperceptual processing is impaired early in the clinical course of AD. The 15-OT allows detection of visuoperceptual deficits in the preclinical and mild AD stages, when classical tests are still unable to detect subtle deficits. So, its inclusion in neuropsychological batteries that are nowadays used in the clinical practice would allow increasing their diagnostic potential.

Keywords

Visual discrimination; Visuoperceptual; Mild cognitive impairment; Alzheimer's disease

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INTRODUCTION

Alzheimer's disease (AD) is a major cause of disability in the elderly and one for which there is currently no effective treatment that significantly alters the course of the disease. To date, the most effective pharmacological and nonpharmacological therapies can only extend the time before an individual patient enters the most severe and debilitating stage of the dementia (Becker, Tarraga, Scott, & Lopez, 2007; Sitzer, Twamley, & Jeste, 2006). Furthermore, it appears likely that neuroprotective disease-modifying therapies, directed at the fundamental biological process of AD, will become available in the future. When that happens, it will be critical to be able to detect the disease at its earliest stages, in an effort to reduce the pathological damage and possibly prevent the onset of the dementia.

The search for a biomarker of the preclinical stages of AD has focused on functional and structural brain imaging studies (Dubois & Albert, 2004). However, these methodologies are costly and cannot be used in all cases due to contraindications. In contrast, neuropsychological testing is more cost effective and may be the most sensitive method to assess the early impaired brain functions in a diagnostic unit. Efforts to identify neuropsychological tests that can detect a prodromal or preclinical Alzheimer's disease stage have focused on episodic memory (Perri, Serra, Carlesimo, Caltagirone, & Early Diagnosis Group of the Italian Interdisciplinary Network on Alzheimer's Disease, 2007; Sarazin et al., 2007), which makes sense given that the presence of memory deficits is a requirement for a diagnosis of dementia or MCI in many nomenclatures (e.g., DSM-IV; *Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition*; American Psychiatric Association, 1994). However, there is consistent evidence that dementia syndromes, including AD, do not universally begin with memory deficits (Huff et al., 1987), and there are patients with atypical presentations (Small et al., 1997).

Due to the heterogeneity in AD, there is a need for sensitive tools that measure domains other than memory. Individual tests that assess functions other than memory, such as visuospatial processing, may have a high sensitivity to neurodegenerative disease. One such measure, the 15-Objects Test (15-OT), is primarily a test of visuospatial function, but it also requires the ability to disentangle a simple visual form from a complex figure, as well as recognizing the whole of the figure and not confusing "parts." In order to successfully complete this task, individual patients must be able to perform visual attentional functions, have executive abilities, and to recognize the objects as objects.

In 1989, the 15-OT was developed by Pillon and coworkers (1989) to assess the slowing of cognitive processing (measuring the time needed to complete the task) in Parkinson's disease (PD), and it has only been used in patients with PD (Alegret et al., 2000; Leroy et al., 1996; Pillon et al., 1989) and Huntington's disease (Gómez-Ansón et al., 2008; Gómez-Ansón et al., 2007). However, it has not been administered as a visuospatial test measuring the correct answers.

It is well known that AD involves damage to visual association cortex. So, visual object perception, as other cognitive abilities, suffers a progressive deterioration in AD from the early stages of the disease (Laatu, Revonsuo, Jäykkä, Portin, & Rinne, 2003). Apperceptive visual agnosia has been associated to bilateral cortical atrophy in occipital and inferior temporal cortex (Hof & Bouras, 1991; Lueschow, Miller, & Desimone, 1994). Although the medial temporal areas are the first brain regions to deteriorate in AD, bilateral temporo-parietal and temporo-occipital hypoperfusion on single photon emission computed tomography (SPECT) and hypometabolism on positron emission tomography (PET) may be detected before the onset of dementia (Devous, 2002; Encinas et al., 2003; Kogure et al., 2000; Matsuda et al., 2002). Since similar changes can be demonstrated in those subjects with MCI and in those genetically at

risk of developing AD, it is expected that visuoperceptual abnormalities would be found in such patients.

Although global cognitive status and daily living activities are relatively preserved in patients diagnosed with MCI (Petersen & Morris, 2005; Petersen et al., 1999), when they are exhaustively assessed memory and other cognitive impairments can be found (Nordlund et al., 2005; Tales, Haworth, Nelson, Snowden, & Wilcock, 2005), such as visuoperceptual deficits (Nordlund et al., 2005). Poppelreuter-type tests are the most frequently included in neuropsychological batteries to detect visual agnosia. In the clinical practice, however, their extremely simplicity (i.e., the Poppelreuter Test has only five overlapping figures) makes it difficult to identify the incipient visuoperceptual deficits. More complex tests are required to detect the first visual discrimination signs in those patients that perform correctly on simple visual gnosis tests. So, the 15-OT could be useful to assess visuoperceptual deficits in MCI and mild AD patients. It would increase the diagnosis value of the neuropsychological batteries most frequently used nowadays in clinical practice.

The aim of the present study was to investigate the presence of visuoperceptual deficits in MCI patients and to assess the usefulness of the 15-OT to discriminate AD patients and MCI from controls.

METHOD

Participants

A sample of 132 individuals participated in this study: 44 mild AD patients, 44 participants with MCI (9 amnesic single domain and 35 amnesic multiple domain), and 44 healthy elderly controls (EC). Cognitively normal individuals were recruited from local centers for the elderly, as well as from Fundacio ACE in Barcelona (Spain). Patients with MCI and AD were also recruited from the diagnostic unit of Fundacio ACE, and they underwent neurological examination and neuropsychological testing as part of a diagnostic evaluation.

The three study groups were statistically similar in terms of age, gender, and educational level. Mean age was 76.98 years (± 3.84 , range 69–85) for AD patients, 76.50 (± 5.11 , range 65–85) for MCI participants, and 75.09 (± 6.54 , range 65–93) for EC. All groups comprised 22 men and 22 women. Most patients (56.8%) had middle- or elementary-school education (EC, 45.5%; MCI, 59.1%; AD, 65.9%), 21.2% had high-school education or Associate's degrees (EC, 31.8%; MCI, 22.7%; AD, 9.1%), 19% had a Bachelor's degree (EC, 20.5%; MCI, 15.9%; AD, 20.5%), and only 3% were literate with fewer than 3 years of formal education (EC, 2.3%; MCI, 2.3%; AD, 4.5%).

The EC participants were considered to be cognitively normal by a neurologist and a neuropsychologist. That is, there were no cognitive complaints by participant or informant, no evidence by history of functional impairment due to declining cognition, a Mini-Mental State Examination (MMSE) score of ≥ 27 , and no cognitive impairment as measured by the neuropsychological battery detailed below.

The AD patients met criteria for probable AD from the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984). The MMSE (Folstein, Folstein, & McHugh, 1975) for participants with AD ranged from 18 and 26, and all had a clinical dementia rating (CDR) staging of 1, indicating a mild degree of impairment.

Patients with MCI fulfilled Petersen's diagnostic criteria (Petersen et al., 1999), including subjective memory complaint, normal general cognition, preserved performance in activities

of daily living, absence of dementia, and a measurable impairment in memory function, with or without deficit in other cognitive domains (MCI amnesic single domain or MCI amnesic multiple domain; Petersen & Morris, 2005); all had a CDR rating of 0.5.

No participants were entered into the present study if they were younger than 65 years, were illiterate, were currently suffering from significant depressive symptoms, major depression or other DSM-IV Axis I psychiatric disorder (except for dementia syndrome), had a neurological disease (other than dementia or MCI), had a structural lesion on computed tomography/magnetic resonance imaging (CT/MRI) imaging, had a history of alcohol or other substance abuse, had severe visual abnormalities including glaucoma or cataracts, or had severe dysarthria or anomia.

The Ethics Research Committee of our center approved this study, and all participants gave written, informed consent prior to participating in the procedures described below.

Neuropsychological assessment

The 15-OT (Pillon et al., 1989) was evaluated in the present study. Additional neuropsychological tests were administered as part of the diagnostic assessment. All of the neuropsychological tests, except for the 15-OT, were used in the diagnostic process to classify participants as EC, MCI, or AD.

For the 15-OT, the participants were shown a card (either Form A or Form B: EC, 20 A and 24 B; MCI, 22 A and 22 B; AD, 24 A and 20 B) on which were drawn 15 overlapping line drawings of common objects (Figure 1). They were simply asked to say aloud the names of all of the objects that they could see on the sheet. The number of correct responses was recorded, and the participants were allowed to take as much time as they needed to identify all of the objects that they could see on the page. Incorrect identifications were also recorded (that is, the incorrect naming or interpretation of an object, or the incorrect interpretation of a part of an object). To limit the influence of impaired naming, if participants were unable to name an object that they had identified, credit for correct response was given if they were able to define or describe the object that they had identified.

The Poppelreuter Test, which is similar in many ways to the 15-OT, also requires the participants to name aloud the 5 objects that they could see in each one of the two figures. Both correct responses (without penalties for describing in spite of naming) and errors were registered.

The neuropsychological battery administered in the diagnostic procedure included tests sensitive to attention, verbal learning and memory, language, visual gnosis, praxis, and executive functions including: Temporal, Spatial, and Personal Orientation, Digit Spans (forwards and backwards), Block Design, and Similarities subtests of the Wechsler Adult Intelligence Scale–Third Edition (WAIS–III); The Word List Learning from the Wechsler Memory Scale–Third Edition (WMS–III); The 15-item abbreviated Boston Naming Test; Poppelreuter's Test and Luria's Clocks Test; ideomotor and imitation praxis; the Automatic Inhibition subtest of the Syndrom Kurtz Test (SKT); phonetic verbal fluency (words beginning with "p" during one minute); semantic verbal fluency ("animals" during one minute); and the Spanish version of the Clock Test. The MMSE (Folstein et al., 1975) was administered as a measure of global cognition. Neuropsychological scores are summarized in Table 1.

Statistical analysis

Statistical analysis was performed using commercially available software (SPSS-PC, Version 15.0; SPSS Inc, Chicago, IL). The primary analysis was a between-group analysis of variance on the 15-OT. Additionally, logistic regression models were used to assess the overall

discriminative value of the 15-OT. Each one of the three logistic regression models analyzed the ability of the 15-OT to correctly classify each pair of groups (AD vs. MCI, AD vs. EC, and MCI vs. EC). To adjust the model and to check the overall discriminative value of the 15-OT, cutoff scores for the 15-OT were proposed, which were the values that required the most optimal ability to classify. Measures of sensitivity/specificity and positive/negative prediction rates were calculated. The area under the receiver-operating characteristic (ROC) curve was also reported (AUC). The AUC curve represents the ability of a test to identify a particular case (i.e., affected participants). A value of 1 indicates a perfect diagnostic accuracy, whereas a value of 0.5 indicates an inaccurate diagnostic. Pearson's correlation analyses, with Bonferroni's corrections, were used to relate performances on the 15-OT to the other cognitive test scores. All statistical analyses were performed using two-tailed probability.

RESULTS

The scores of the MCI patients on cognitive tests were generally between those of the AD patients and those of the controls, although in some cases (e.g., repetition, ideomotor praxis) their scores were similar to those of the AD patients.

The evaluation of the 15-OT proceeded independently of the analysis of the main neuropsychological test battery, to avoid the problem of circularity. That is, this measure was not used as part of the decision process for participant classification and thus could be tested for its ability to predict the results of that classification.

As shown in Table 2, the mean number of correct responses on the 15-OT was significantly different between groups; the scores of MCI and AD patients were significantly lower than those of controls. MCI patients performed significantly better than patients with AD, and, as expected, patients with AD also performed significantly more poorly than EC (Table 2). Performance on the 15-OT did not depend on the form administered, because there were no statistically significant differences between A and B forms in any group.

The performance of the three participant groups on the 15-OT is shown in Figure 2. Median scores of the groups were progressively lower from controls to MCI and AD patients. While the range of the scores was also greatest in the AD patients, the control participants performed near the test ceiling (i.e., 13.7/15). The 95% confidence interval (CI) around the mean of the control participants was 13.4–14.1, so we established the lower limit of normal performance as 13 correct responses. When we dichotomized the groups on the 15-OT using this cutoff, we found that 16.0% of the control participants, 64.6% of the MCI participants, and 84.4% of the AD patients performed abnormally (see Figure 2). A cutoff score of 13 correct answers would separate MCI and EC with a sensitivity of 86% and a specificity of 66%.

Concerning the logistic regression analysis, the 15-OT was chosen as a predictor, and the diagnosis was taken as a dichotomic variable. The first logistic regression model resulted in a statistically significant classification of AD versus EC groups, $\chi^2(1) = 76.16$, $p = .0005$; 86.4% (95% CI 73.33–93.6) of AD patients and 86.4% (95% CI 73.3–93.6) of EC were correctly classified by the model. The AUC value was 0.95 (95% CI 0.92–0.99). Using a cutoff score of 12 as determined in that model, participants who identified a minimum of 13 objects were more than 4.5 times as likely to belong to the EC group as to the AD group.

The second logistic regression model, to classify AD versus MCI groups, was statistically significant, $\chi^2(1) = 16.38$, $p = .0005$, with 63.6% (95% CI 48.9–76.2) of AD patients and 79.5% (95% CI 65.5–88.8) of MCI participants correctly classified. The AUC value was 0.75 (95% CI 0.64–0.85), using a score of 10 on the 15-OT as the cutoff in that model. Participants who identified a minimum of 11 objects were more than 1.5 times as likely to belong to the MCI group.

The third logistic regression model, obtained to classify MCI versus EC groups, was also statistically significant, $\chi^2(1) = 40.91, p = .0005$, with 63.6% (95% CI 48.9–76.2) of MCI patients and 86.4% (95% CI 73.3–93.6) of EC correctly classified by the model. The AUC value was 0.85 (95% CI 0.78–0.93), using a cutoff score of 12. Participants who identified a minimum of 12 objects were more than 3 times as likely to belong to the EC group.

When errors and correct answers were introduced in the logistic regression analysis, using the stepwise method, only the correct answers entered in the analysis. So, although the number of errors and correct answers in the 15-OT did significantly and inversely correlate ($r = -.78$), the variable “errors” did not add discriminative value to the logistic regression model.

We compared the ability of the 15-OT to discriminate the three groups with that of the Poppelreuter Test. We repeated all of the regression analyses and found that in each case the 15-OT was a significant predictor of group membership, but the Poppelreuter Test did not significantly contribute to the models.

The mean correct answers in the 15-OT for the control group was 13.82, with a standard deviation of 1.08. We took the cutoff as a 1.5 standard deviations below the mean (12.19). So, taking the 15-OT cutoff of 12.19 correct answers, 63.6% of MCI and 86.4% of AD group participants obtained an impaired performance. Concerning the Poppelreuter Test, taking a normal performance at 10 correct answers, 38.63% of MCI participants and 52.27% of AD participants obtained an impaired performance. So, the 15-OT is more sensitive to detecting visuoperceptual abnormalities than is the Poppelreuter Test in AD.

If we take Petersen and Morris (2005) subtypes of MCI, we found that 68.6% of MCI amnesic multiple domain patients had a poor performance on the 15-OT, while only 44.4% of MCI amnesic single domain patients had abnormal scores.

Taking the whole sample, statistically significant correlations were found between a better performance on the 15-OT and a better performance on the two screening tests used in the neuropsychological assessment, the MMSE ($r = .59, p < .001$) and the Clock test ($r = .55, p < .001$).

DISCUSSION

The 15-OT is a very sensitive tool to detect visuoperceptual deficits in the early stages of AD. Patients with MCI also have impaired performance on this test compared to controls, but performed significantly better than the AD patients. Taken together, these findings indicate that the 15-OT test is sensitive to the clinical progression of the visuoperceptual impairment associated with AD.

In spite of the fact that our MCI and mild AD patients had relatively normal performance on measures of simple visual perception (i.e., the Poppelreuter), there were nevertheless significant abnormalities on this more difficult test of visual gnosis, the 15-OT. This is important for several reasons. First, this demonstrates that even in relatively mild stages of the degenerative process, there are abnormalities of visual information processing that can be detected with appropriately complex tasks. Second, by increasing the difficulty of an apparently simple visual task that contains numerous subroutines and goals, including attentional and executive functions, it is possible to increase the sensitivity of the task to the more subtle cognitive deficits of MCI. This suggests that measures such as the 15-OT may be useful for the detection of AD before it becomes a clinical dementia (i.e., MCI). This would be extremely important in the context of pharmacological and nonpharmacological interventions that may potentially delay the onset of clinical dementia, or to retard the inevitable progression of the disease, in that earlier intervention should provide maximum benefit.

Alteration of the temporo-parietal cortex and posterior cingulate gyrus are strong predictors of conversion to AD from MCI (Bell-McGinty et al., 2005; Chetelat et al., 2003, 2005). Visual object identification, associated to bilateral cortical atrophy in occipital and inferior temporal cortex (Hof & Bouras, 1991; Lueschow et al., 1994), is impaired in the incipient stages of AD (Done & Hajilou, 2005; Rami, Serradell, Bosch, Villar, & Molinuevo, 2007; Viggiano et al., 2007). For example, mild AD patients, compared to controls, need significantly more visually complete information to accurately recognize visually degraded images of familiar objects (Done & Hajilou, 2005; Viggiano et al., 2007). Using a test with distorted images, Rami et al. (2007) also found visuoperceptual impairment in a group of 27 participants with mild AD. Other studies have demonstrated visual agnosia in mild-to-moderate AD patients by means of overlapping figure identification tests (Mendez, Mendez, Martin, Smyth, & Whitehouse, 1990) and visual form discrimination tests (Fujimori, Imamura, Yamashita, Hirano, & Mori, 1997).

Although it is clear that visual gnosis is frequently impaired from the first stages of AD, little information is available about visuoperceptual performance in participants with MCI. In a sample of 112 MCI participants and 35 controls, Nordlund et al. (2005) reported that when a comprehensive neuropsychological battery is used, impairment in domains other than memory may be detected in most of MCI participants. They found visuoperceptual deficits (measured by the Visual Object and Space Perception Battery, Silhouettes subtest) in approximately 40% of their MCI patients. We also found a high proportion (63.6%) of MCI patients with visuoperceptual deficits. Moreover, 44.4% of the MCI patients who were initially classified as “amnesic single domain” were in fact “amnesic multiple domain” based on their poor 15-OT performance. Among our patients with MCI initially classified as amnesic multiple domain, visuoperceptual deficits were detected in up to 68.6% of cases. Such a progression, probably the cause of the higher risk of developing dementia in MCI amnesic multiple domain patients than in MCI amnesic single domain patients, is also the cause of the more diffuse cognitive impairment showed by MCI multiple domain participants (Bozoki, Giordani, Heidebrink, Berent, & Foster, 2001).

As shown in the present study, traditional cognitive tests, such as the Poppelreuter Test, which includes only five easily recognizable objects, are not sensitive enough to detect visuoperceptual abnormalities in MCI and mild AD patients because of its simplicity. Since the 15-OT allows the detection of those subtle deficits, its inclusion in the neuropsychological batteries would increase their diagnostic potential in the clinical practice. Moreover, performances on the 15-OT and other screening tools, such as the MMSE and the Clock Test, have been found to be directly related in the present study.

It is increasingly important to identify AD in the presymptomatic state due to the potential availability of neuroprotective agents for degenerative brain disorders. The 15-OT in combination with other neuropsychological tests provides such a way of identifying early AD. Because the data reported here were obtained from participants who had been evaluated in a referral clinic, it will be important to see how well these tests perform in the context of community-based studies that are able to capture participants with disease before significant symptoms are recognized by the patients or their families. Our data reported is an important first step in the process of validating the utility of these screening measures.

Further longitudinal studies are needed to determine whether those MCI participants with lower performances on the 15-OT have an increased risk of conversion to AD.

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Figure 1.
The 15-Objects Test: Forms A and B.

Figure 2.
Performance of controls, MCI patients, and mild AD patients on the 15-Objects Test.
Notes: MCI: mild cognitive impairment. AD: Alzheimer's disease.

TABLE 1

Performance (mean scores) on the neuropsychological battery and MMSE

	Normal controls	MCI	AD	F(2, 131)
Orientation				
Temporal	4.98 (0.15)	3.82 (1.32)	2.89 (1.56)	34.61 ^{a,b,c}
Spatial	5.00 (0.00)	4.98 (0.15)	4.84 (0.43)	4.74 ^c
Personal	5.00 (0.00)	4.89 (0.39)	4.41 (0.79)	16.87 ^{b,c}
Learning				
Trial 1	4.23 (1.44)	2.95 (1.29)	2.70 (1.65)	13.58 ^{a,c}
Trial 4	9.73 (1.86)	5.95 (1.79)	4.64 (1.67)	97.41 ^{a,b,c}
Delayed Recall	7.61 (2.50)	1.75 (2.05)	0.32 (0.74)	179.60 ^{a,b,c}
Digit Span				
Forward	7.59 (1.73)	7.25 (1.56)	6.48 (1.32)	6.00 ^c
Backward	4.84 (1.41)	3.93 (1.39)	3.55 (1.39)	9.98 ^{a,c}
Praxis				
Ideomotor	4.00 (0.00)	3.98 (0.15)	3.98 (0.15)	0.50
Construction	3.91 (0.29)	3.16 (1.16)	2.30 (1.47)	23.93 ^{a,b,c}
Imitation	3.93 (0.25)	3.50 (0.76)	2.52 (1.25)	31.21 ^{b,c}
Comprehension	5.98 (0.15)	5.82 (0.39)	5.77 (0.48)	3.80 ^c
Repetition	4.00 (0.00)	4.00 (0.00)	3.98 (0.15)	1.00
SKT errors	0.64 (0.84)	1.23 (2.30)	3.55 (5.25)	9.29 ^{b,c}
Visual Naming	14.80 (0.59)	13.95 (1.46)	12.09 (2.23)	33.91 ^{a,b,c}
Fluency				
Phonetic	14.59 (3.96)	11.16 (4.77)	9.11 (4.09)	18.31 ^{a,c}
Semantic	17.16 (4.00)	13.75 (4.61)	9.73 (3.62)	36.25 ^{a,b,c}
Abstract reasoning	11.86 (1.59)	9.41 (2.61)	7.82 (3.72)	23.61 ^{a,b,c}
Luria's Clocks	3.64 (0.49)	3.11 (0.89)	2.16 (1.29)	27.34 ^{a,b,c}
Clock Test	6.91 (0.29)	5.93 (1.21)	4.23 (2.12)	39.80 ^{a,b,c}
MMSE	29.29 (0.86)	25.95 (2.27)	23.25 (2.35)	79.90 ^{a,b,c}

Note. MCI: mild cognitive impairment. AD: Alzheimer's disease. SKT: Syndrom Kurtz Test. MMSE: Mini-Mental State Examination. Mean scores (standard deviations in parentheses).

^aControls differed from MCI.

^bMCI differed from AD.

^cControls differed from AD.

TABLE 2

Performance on measures of visual perception

	Control group		MCI group		AD group		F(2, 131)
	M	SD	M	SD	M	SD	
15-Objects	13.82	1.08	11.57	1.97	9.68	2.19	57.56*** ^{a,b,c}
Poppelreuter	9.89	0.39	9.50	0.76	9.05	1.27	9.92*** ^c

Note. MCI: mild cognitive impairment. AD: Alzheimer's disease. M: mean. SD: standard deviation.

^aControls differed from MCI.

^bMCI differed from AD.

^cControls differed from AD.

***
p < .0005.