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Memory for Unfamiliar Faces Differentiates Mild Cognitive Impairment from Normal Aging

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Abstract

Memory for unfamiliar faces has received little attention in the effort to identify neuropsychological measures that could differentiate mild cognitive impairment (MCI) from normal aging and/or predict conversion from MCI to dementia. We used the Wechsler Memory Scale-III Faces test to investigate facial memory in normal aging (n = 58), MCI (n = 74) and mild Alzheimer's disease (n = 22). After adjustment for age, gender, and years of education, MCI patients demonstrated significantly poorer memory for unfamiliar faces than their healthy peers. Lower scores were also associated with worsening cognition and functional abilities but not an increased risk of dementia.

Keywords

mild cognitive impairment; Alzheimer's disease; facial memory; conversion

Introduction

Memory for facial information has long been regarded as a special type of visuospatial memory, different from memory for drawings, objects, or scenes (Farah, Wilson, Drain, & Tanaka, 1998). For instance, infants show a differential response to faces as compared to other types of perceptual stimuli (Goren, Sarty, & Wu, 1975) and healthy adults across a wide range of ages can easily recognize many more faces after a single exposure than they can words (McCarthy & Warrington, 1990). The ability to identify and remember faces is also of great relevance to everyday life, particularly an individual's ability to stay engaged with others as well as accomplish a myriad of routine tasks. Face identification deficits are fairly common in the latter stages of Alzheimer's disease (AD), and, in some of the young-onset dementias related to frontotemporal lobar degeneration, these impairments can be especially severe. Despite the everyday importance and special nature of facial memory, the study of this ability in individuals with mild cognitive impairment (MCI) has clearly lagged behind that of memory for other forms of information.

Mild cognitive impairment is now widely considered an interim state between normal aging and dementia during which an individual complains of forgetfulness and typically performs

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poorly on objective tests of episodic memory but does not fully meet diagnostic criteria for dementia. Initially, the individual with MCI and/or others (e.g., relatives, co-workers, and friends) notice lapses of memory that are significant but insufficient to interfere with activities of daily living. Persons with MCI are at significantly greater risk for progressing to dementia than their healthy age-matched peers. Average conversion rates to AD range from 10–15% annually among individuals with MCI as compared to 1–2% in cognitively normal older adults (Petersen, 2004). With recognition of MCI as a high risk pre-dementia state, researchers have aggressively sought to identify ways of accurately separating those individuals who will experience ongoing cognitive decline from those who will not.

Cognitive profiling has proven an important tool among others researchers are investigating, to predict the conversion from MCI to dementia. For the most part, efforts to identify neuropsychological markers of conversion have focused primarily on the learning and retention of verbal information. Multiple studies have shown that measures of episodic memory are not only sensitive to the effects of MCI and AD (Brooks, Weaver, & Scialfa, 2006; Petersen, Smith, Warings, Ivink, Tangalos, & Kokmen, 1999; Rabin, Pare, Saykin, Brown, Wishart, Flashman, & Santulli, 2009; Tremont, Miele, Smith, &Westervelt, 2010), but also strong predictors of progression from the former to the latter (Albert, Blacker, Moss, Tanzi, & McArdle, 2007; Chapman, Mapstone, McCracy, Gardner, Porsteinsson, Sandoval, … Reilly, 2011; Rabin et al., 2009). Not all measures of episodic memory, however, perform equally as predictors of conversion. For example, tasks assessing list-learning ability and memory for stories are both sensitive to MCI and AD but differ in predictive power. As a case in point, the total learning score on the 16-item California Verbal Learning Test was not only better than the score on the Wechsler Memory Scale – Third Edition (WMS-III) Logical Memory (LM) test for distinguishing normals from MCI, but also a stronger predictor of conversion to dementia over a 4-year period (Rabin et al., 2009). Expanding research into the neuropsychological differences between MCI and AD is particularly important as the distinction between these two conditions has become increasingly difficult given the heterogeneous nature of MCI. In particular, patients with multiple domain amnestic MCI can demonstrate subtle deficits in numerous areas of cognitive functioning in addition to recent memory, making it difficult to differentiate these individuals from those with mild AD. Despite a fervent interest in identifying which MCI patients are at high risk of developing AD, there are currently no clinical, neuroimaging, or biological markers that predict conversion to AD with certainty or reliably distinguish MCI patients who will progress from those who will remain stable or revert back to normal. Cognitive testing offers a relatively inexpensive and noninvasive means of not only monitoring, but potentially predicting, the conversion from MCI to AD.

Both the nature and predictive power of verbal and visual-spatial impairments in MCI have received considerable attention from researchers, yet little is known about how MCI affects episodic memory for unfamiliar faces and whether impairment of this particular form of visual memory could differentiate normal cognition, MCI, and AD. Assessing visual memory via recognition of unfamiliar faces is advantageous, given the limitations of measures involving the retention of abstract designs or identification of famous faces commonly used for this purpose in MCI. First, a subject may use verbal as well as visual strategies to encode the stimuli in the WAIS-R Visual Reproductions test (Wechsler, 1987)

and the Complex Figure Test (Osterrieth, 1944; Rey, 1941) , thereby confounding interpretation of the results. For example, one of the to-be-remembered designs in the Visual Reproductions test could be verbally described and encoded by the subject as “a large square-shaped window with four dots located in the center of each quadrant.” Secondly, performance of some subjects may be affected by subtle motor impairments, such as increasing difficulty with handwriting (Yan, Rountree, Massman, Doody, & Li, 2008) and execution of goal-directed movements (Yan & Dick, 2006), known to emerge in MCI . Finally, the use of abstract patterns as stimuli limits the real-world applicability of testing results. In light of these drawbacks, the objective of the current study is to quantify visual memory in cognitively normal individuals and those with MCI or AD using the WMS-III Faces test (Wechsler, 1997), which measures recognition of unfamiliar faces. The WMS is one of the most widely used measures of memory among clinicians and researchers alike (Tulsky, Chiaravalloti, Palmer, & Chelune, 2003) and has undergone numerous revisions since its original publication in 1945. The WMS-III Faces test offers a potentially purer measure of visual memory than other tests in that it (1) lessens the possibility of verbal mediation through short stimuli exposure times, (2) does not require a motor response or intact visuospatial drawing abilities, and (3) has greater ecological validity given the importance of remembering facial information to daily life.

Interestingly, little attention has been given to the learning and retention of unfamiliar faces in MCI although identification of famous faces has been repeatedly investigated. Several studies (e.g., Ahmed, Arnold, Thompson, Graham, & Hodges, 2008; Estévez-Gonzalez, Garcia-Sánchez, Boles, Otermin, Pascual-Sedano, Gironell, & Kulisevsky, 2004) have found that individuals with MCI are less able to identify famous faces than their cognitively healthy peers. Anatomically distinct regions of the brain appear to be involved in the identification of famous faces versus the encoding and retention of unfamiliar faces. More specifically, identification of famous faces and landmarks has been localized to the left temporal lobe (Gorno-Tempini & Price, 2001; Grabowski, Damasio, Tranel, Ponto, Hichwa, & Damasio, 2001) while learning and retention of unfamiliar faces has been linked to the right temporal lobe (Dade & Jones-Gotman, 2001; Doss, Chelune & Naugle, 2004; Schiltz, Dricot, Goebel, & Rossion, 2010). In addition to tapping separate areas of the brain, tests of memory for famous versus unfamiliar faces differ in that performance on the former, but not the latter, is reliant on prior knowledge about the stimuli. As compared to the WMS-III Faces test, which assesses the ability to recognize which of several unfamiliar faces was encountered a few seconds or minutes ago, measures of memory for famous faces evaluate the capacity to recall a specific name that goes with a well-known face. Consequently, tests of memory for famous faces really assess the ability to access and retrieve information that an individual has accumulated in long-term memory over many years or even decades. To its advantage, the WMS-III Faces test does not require any particular knowledge about the stimuli prior to exposure, and, as a result, performance is less likely to be affected by age, cultural background, and level of education/literacy.

To our knowledge, only one study has investigated how persons with MCI process and retain unfamiliar facial information. Recently, Seelye, Howieson, Wild, Moore, and Kaye (2009) explored differences in visual and verbal memory among normal controls (NC), MCI, and early AD subjects using the WMS-III Faces test and two measures of verbal memory, the

WMS-III Logical Memory test and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List task (Morris, Heyman & Mohs, 1989). As expected, the MCI and AD patients exhibited significant impairments on both measures of verbal memory relative to NC. Interestingly, while AD patients scored significantly worse than NC on the WMS-III Faces test, individuals with MCI performed as well as their healthy peers. Based on the results, the authors hypothesized that the brain regions involved in facial memory may be less affected in MCI than early AD, while areas involved in recent verbal memory are compromised in both conditions.

Although intriguing, the conjecture that individuals with MCI are able to recognize unfamiliar faces as well as cognitively normal peers requires independent validation with an adequately powered study. The Seelye et al. (2009) study included only 24 MCI, 47 AD, and 98 NC subjects. Consequently, the study's inability to detect a difference on the WMS-III Faces test between MCI and NC could have stemmed from an underpowered test resulting from a small MCI sample.

To address the small MCI sample limitation of the Seelye et al. (2009) study and further our knowledge of facial memory in MCI, the current manuscript (1) compares performance on the WMS-III Faces and CERAD Word List recognition tests in a sample of 74 MCI, 22 AD, and 58 NC subjects; (2) investigates if performance on the WMS-III Faces test predicts conversion from MCI to dementia; and (3) explores the relationship of WMS-III Faces test scores to measures of functional abilities, executive functioning, and disease severity. In a post hoc analysis, we also investigate how the WMS-III Faces test scores differ by MCI subtype, that is, in the amnestic single versus multiple domain form of the disorder.

Methods

Participants

One-hundred-and fifty-one community-dwelling older adults participated in this study. All subjects were recruited from a specialized, university-based memory clinic, namely the Alzheimer's Disease Research Center (ADRC) at the University of California, Irvine (UCI). Each subject completed a clinical evaluation that included a detailed medical history, neurological examination, and neuropsychological assessment. A study partner or knowledgeable informant, usually the spouse or an adult child, provided information about the participant's functional abilities, current affective state, and behavioral symptoms via a standardized clinical interview. Subjects with a diagnosis of MCI and AD underwent brain imaging, typically an MRI or CT scan, plus blood tests, including a complete blood count, metabolic panel, serum B12, folate, TSH, and RPR. Subjects were excluded if they had evidence of a stroke or cortical infarction either from the neurological examination or brain imaging, extensive subcortical vascular disease, a space-occupying lesion, or a history of alcohol/substance abuse, major neurological (e.g., traumatic brain injury, normal pressure hydrocephalus) disorder or psychiatric (e.g., schizophrenia, bipolar disorder) illness. A team of professionals representing neurology, neuropsychology, and nursing at the UCI ADRC reviewed all data and then classified each participant into one of the three diagnostic groups (i.e., NC, MCI, or AD) based on a consensus of their expert opinions.

Of the 58 NC participating in this project, 38 (64%) had completed at least 1 and up to 6 annual reassessments (M = 2.7) following an initial baseline evaluation as part of the longitudinal follow up in the ADRC. All of the NC had a global Clinical Dementia Rating (CDR/ Morris, 1993) scale score of 0, CDR Memory Box score of 0, and Mini-Mental State Examination (MMSE/ Folstein, Folstein, & McHugh, 1975) score in the normal range of 25 to 30 points inclusive at entry into the study. NC had no significant cognitive complaints and scored above an objective cutoff of 1.5 standard deviations below the mean for their age on tests from a comprehensive neuropsychological test battery. In addition to recent episodic memory, the cognitive domains assessed during the neuropsychological evaluation included attention, working memory, psychomotor speed, language, visual-spatial functioning, and executive abilities. Additionally, NC were free of any significant deficits in their instrumental activities of daily living as indicated by intact scores on the Functional Activities Questionnaire (FAQ/Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982) and Bristol Activities of Daily Living Scale (BADLS/ Bucks, Ashworth, Wilcock, & Siegfried, 1996).

Of the 74 MCI subjects sampled, 54 (76%) had been followed for 1 to 6 years (M = 2.0) after the baseline visit. All had amnestic MCI, with a greater number fulfilling the modified Petersen (2004) criteria for the multiple domain (n = 55; 74%) than single domain (n = 19; 26%) subtype of the disorder. Each subject and/or study partner reported a noticeable decline in one or more cognitive domains, resulting in a global CDR score of 0.5. None of the MCI subjects met the standard NINCDS-ADRDA clinical criteria (McKhann, Drachmann, Folstein, Katzman, Price, & Stadian, 1984) for either probable or possible AD at the entry visit or showed a significant impairment in social or occupational functioning.

Subjects with single domain amnestic MCI reported only a memory problem and typically scored at or below 1.5 standard deviations from the mean for their age on the 30-minute delayed recall measures of the WMS-III Logical Memory test. As well as scoring at or below 1.5 standard deviations from the mean on the these delayed recall measures, subjects with multiple domain amnestic MCI showed a similar level of impairment on one or more other tests of cognitive functioning. As the likely neurodegenerative etiology of single and multiple domain amnestic MCI is AD (Petersen, 2004), all of the MCI subjects in this study were at high risk for conversion.

Finally, of the 22 AD patients participating in this project, 18 (82%) had completed from 1 to 6 annual reassessments (M = 1.9). All AD participants met the standard criteria (McKhann et al., 1984) for probable or possible AD at entry into the study. That is, they demonstrated significant deficits in memory and two or more other cognitive domains with impaired activities of daily living. Additionally, at entry, all AD patients had a CDR global score of 0.5 or 1.0, suggesting a “mild dementia,” and scored above 19 out of 30 points on the MMSE.

The diagnostic process used to classify participants as NC, MCI, or mild AD in this study was similar to that employed by Seelye et al (2009). For example, in both studies, CDR scores were based on the results of structured interviews with knowledgeable informants regarding the participant’s memory and other cognitive abilities as well as his/her performance on a wide variety of activities of daily living. In addition, when assigning CDR

scores, the clinical teams in both studies had access to scores on measures of overall mental status (e.g., MMSE) and selected neuropsychological tests. While all of the participants in this study were administered the WMS-III Faces test as part of the standard neuropsychological evaluation, scores were not used for diagnostic classification.

Materials and procedures

Each participant completed the three measures utilized in this study as part of a comprehensive battery of neuropsychological tests administered routinely at the UCI ADRC. More specifically, the WMS-III Faces test (Wechsler, 1997) and the CERAD Word List task (Morris, Heyman, & Mohs, 1989), which both assess recent memory, plus the Trail Making Test-Part B (TMT-B; Reitan, 1958), a measure of executive functioning, were utilized in this study. Unlike Seelye et al. (2009), who utilized the WMS-III Logical Memory test, we did not include scores from this measure, although available for all participants in the analysis. Only scores on the CERAD Word List task were compared to those on the WMS-III Faces test as these two measures, while involving different domains (i.e., words and unfamiliar faces) share the same process, namely recognition memory. Additionally, the WMS-III Faces test and CERAD Word List task both use a 'Yes-No' recognition paradigm, in which chance performance is 50% correct, as well as include a 30-minute delayed retention measure.

Briefly, WMS-III Faces is a three-step test of recognition memory. First, the examiner asks the subject to remember 24 color photographs of different faces, presented one at a time at a pace of 2 seconds per face. Wechsler (1997), the test's developer, selected faces of children and adults that reflected the racial composition of the U.S. population at the time. Each picture is tightly cropped to show only the face, and none of the individuals have heavy make-up, full mustaches, or beards that would disguise their features. Next, immediately after showing the last face in the series, the examiner presents 48 faces – the original 24 intermixed with 24 distractors or foils – one at a time and asks the subject to identify which were seen previously. The 24 foils are similar to the targets in age, gender, and ethnic background. At the end of the immediate recognition test, the examiner forewarns the subject of the upcoming 30-minute retention test. Finally, after the delay, the examiner presents another set of 48 faces, including 24 new foils with the original images, one at a time and again asks the subject to identify those seen previously. Every correct response, that is saying 'yes' if the face was part of the original 24 and 'no' if it was not, earns 1 point. As a result, raw scores on the immediate (i.e., Faces 1) and delayed (i.e., Faces 2) recognition tests, respectively, can range from 48 to 0 points correct. If none of the faces presented initially are stored in memory, or if the subject responds in a completely random fashion (i.e., guessing) during the immediate and delayed recognition tests, the probability of generating a correct response in each trial is 0.5, resulting in a total score of 24 (± 7) points (Holdnack & Delis, 2004).

When a subject was unsure of how to respond, the examiner provided encouragement to "make the best choice," and a reminder to say "yes" if the face was familiar and "no" if it was unfamiliar. To avoid a potential response bias, any subject who answered "yes" or "no" repeatedly 5–6 times was reminded that some of the faces were shown previously and some

were new. If a subject reported not knowing the answer or just guessing, the examiner would discontinue the test if the subject scored at chance or below for the first 24 items and was frustrated or reluctant to continue. If, however, the subject reported guessing but was willing to continue, all items were administered as even healthy older adults report guessing on this test. Among our subjects, 2 with MCI and 3 with AD received a raw score of 24 on the delayed retention test (i.e., Faces 2) after reporting that they could not remember seeing the faces or were simply guessing.

Examiners administered and scored the CERAD Word List task (Morris, Heyman, & Mohs, 1989), which involves remembering a list of 10 unrelated words across three learning/study trials, according to standard procedures with tests of immediate free recall and 5-minute delayed recall and recognition. In addition, the UCI ADRC routinely administers 30-minute delayed recall and recognition tests to increase diagnostic utility of the CERAD Word List task. In this study, availability of the 30-minute delayed recognition scores enhanced comparability with the WMS-III Faces test, allowing comparison of how well the to-be-remembered verbal (i.e., words) and visual (i.e., faces) information was maintained over an extended interval.

To administer the CERAD Word List task the examiner initially presents the 10 words on cards, one at a time for 2 seconds each, for the subject to read aloud. Immediately after each trial, the examiner administers a test of free recall. Five and 30 minutes after and three learning trials, the examiner administers delayed recall and recognition memory tests. On each ‘Yes-No’ recognition test (i.e., CERAD Recog1 at 5 minutes and CERAD Recog2 at 30 minutes), the examiner presents a set of 20 words one at a time and asks the subject to distinguish the 10 target words from 10 foils/distracters. In CERAD Recog2, the UCI ADRC uses 10 distractor words that are similar in length and frequency of occurrence to the foils in CERAD Recog1. Raw scores on the 5- and 30-minute recognition tests can range from 0 to 20 correct. Finally, examiners administered TMT-B using standardized instructions with the maximum allowed completion time of 300 seconds.

All subjects underwent the same battery of neuropsychological tests during their initial and annual follow-up evaluations. The order in which the tests were administered was the same across subjects with the TMT-B coming rather early in the 2-hour session and the CERAD Word List and WMS-III Faces tests later. None of the tests intervening between Faces 1 and 2 were likely to produce interference as they assessed constructional skills (e.g., WAIS-III Block Design), abstract verbal reasoning (e.g., WAIS-III Similarities), general knowledge (e.g., WAIS-R Information), everyday problem solving, and psychomotor speed (e.g., Kendrick Digit Copy).

Endpoints

The co-primary endpoints of interest were raw scores for each subject at his/her baseline evaluation on the delayed recognition measures of the WMS-III Faces test (i.e., Faces 2) and CERAD Word List (i.e., CERAD Recog2) task.

Among the subgroup of MCI patients, secondary endpoints included the time to dementia conversion (i.e., a change in the clinical diagnosis from MCI to dementia) and scores on

functional ability as measured by the FAQ, executive functioning as measured by the TMT-B, and dementia severity as measured by the CDR Sum of Boxes (CDR-SB). Briefly, the FAQ is administered to the informant of each subject and is comprised of 10 items that assess a variety of instrumental activities of daily living and complex cognitive/social functions. Items include writing checks, paying bills, and keeping track of financial records; assembling tax or business records; driving and traveling out of the neighborhood; shopping alone; playing games of skill; keeping track of current events; paying attention and understanding while reading or watching a TV show; remembering appointments, family occasions, and to take medications; making coffee or tea; and preparing a balanced meal. As the individual's level of impairment on each item is rated along a 4-point scale extending from '0' (completely independent) to '3' (totally dependent), FAQ total scores can range from 0 to 30 points with higher scores indicating worse performance. The CDR-SB is derived from the CDR, a well-known clinician-completed scale for staging the subject's level of impairment across six areas of functioning (i.e., recent memory, orientation, judgment and problem-solving, home and hobbies, community affairs, and personal care). Scores in each of the six areas can range from '0' (normal or unimpaired) to '0.5' (very mild impairment), '1' (mild), '2' (moderate), or '3' (severe). The CDR-SB score represents the sum of the six domain scores and can range from a low of '0' to a high of '18,' with higher scores indicating greater impairment.

Statistical Analysis.

Demographic characteristics of the selected sample were summarized by group using mean and interquartile range for continuous variables, and by counts and proportions for categorical variables. Two-sample t tests assuming unequal variance were used to describe differences in demographic variables and test scores for the three groups. For the primary analysis, we used linear regression to compare pairwise mean differences for the three groups on the Faces 2 and CERAD Recog2 test scores. Adjustments for age, gender, and years of education were *a priori* specified as they could potentially confound the comparisons of interest. We used robust standard errors (White, 1980) to obtain asymptotically valid standard error estimates in the presence of potential heteroscedasticity and the Holm's procedure (Holm, 1979) to account for multiple comparisons in the form of adjusted p-values. A test was declared statistically significant at the family-wise 0.05 error level if the adjusted p-value was less than 0.05. Reported 95% confidence intervals (CI) were not corrected for multiple comparisons.

The secondary analysis, which included only MCI subjects, investigated the association of scores on the WMS-III Faces 2 test at baseline with the time to conversion using a Cox proportional hazards model, adjusting for age, gender, years of education, and baseline MMSE score. This allowed an estimate of the effect of the baseline WMS-III Faces 2 test score with the time to dementia conversion while controlling for the adjustment variables. Robust standard errors were used for inference regarding model parameters (Lin & Wei, 1989). A similar analysis was also conducted to assess the association of the CERAD2 recognition score with risk of conversion to dementia. Additional analyses examined the association of the time-varying WMS-III Faces 2 test score with three longitudinal endpoints, namely scores on the FAQ, TMT-B, and CDR-SB. Generalized estimating

equations (GEE) along with robust standard errors applied to account for within-subject correlation in repeated measurements (Liang & Zeger, 1986). All longitudinal analyses adjusted for age, gender, years of education, and baseline MMSE score. For this set of analyses, we scaled scores on the WMS-Faces 2 test, MMSE, FAQ, TMT-B, and CDR-SB by the standard deviation of each baseline score among the NC subjects (i.e., 4.26, 1.07, 0.46, 29.28, and 0.13, respectively) to yield estimates on a meaningful scale. We did not account for multiple comparisons in this set of analyses due to their secondary nature.

Results

Tables 1 and 2 detail the demographic characteristics and scores of NC, MCI, and AD subjects on the neuropsychological test battery. As shown in Table 1, the three groups were comparable in gender, ethnicity, and years of education. MCI patients, however, were significantly older than the normal controls but not their peers with AD. Subsequent analyses controlled for this age difference. Most subjects were in their late 60s to early 70s and had completed at least a high school education (> 12 years). Across groups, there were more females (n = 90) than males (n = 61). Of the total sample, 103 (68%) participants self-identified as Caucasian, 36 (24%) as Asian American, 12 (8%) as Hispanic, and 3 (2%) as African American. All of the cognitive tests and interviews were administered in English as this was the participants' preferred or primary language. Although a majority of the participants have undergone multiple annual evaluations since joining the UCI ADRC, only the data and diagnoses from their initial or baseline assessment were used to classify subjects into one of the three groups.

As might be expected, MCI patients performed significantly worse than NC, but better than their peers with AD, on the MMSE, a measure of global cognitive functioning. The average MMSE score of AD patients fell in the mildly demented range. Analyses revealed that MCI patients also scored significantly below NC on measures of acquisition or learning ability (i.e., CERAD Learning Trials), delayed retention of words (i.e., CERAD 5- and 30-minute recall and recognition) and stories (i.e., WMS III Logical Memory 1 and 2), information-processing speed (i.e., Symbol Digit Modality Test), verbal fluency (i.e., category and letter fluency), visuospatial constructional skills (i.e., WAIS-III Block Design), mental flexibility (i.e., Trail-Making Test, Parts A & B), abstract verbal reasoning (i.e., WAIS-III Similarities), and psychomotor speed (i.e., Kendrick Digit Copy). Scores of MCI patients were, however, comparable to those of NC on measures of general knowledge (i.e., WAIS-R Information), attention (i.e., WAIS-III Digit Span), confrontational object naming (i.e., Boston Naming Test), and drawing ability (i.e., CERAD Drawing). Finally, AD patients scored significantly below the MCI patients and NC on all tests except category fluency (i.e., CERAD Animal Naming). On this test of word-finding ability, AD patients performed comparably to their peers with MCI but significantly worse than NC.

Findings from the primary analyses comparing the performance of the NC, MCI, and AD participants on the WMS-III Faces 2 and CERAD Recog2 tests are illustrated in Figures 1 and 2, respectively, using box plots. Data from all participants, including the 2 with MCI and 3 with AD who scored at chance levels on Faces 2 were included in the analyses, as excluding them was found to have no significant impact. Controlling for age, gender, and

education, MCI participants scored 3.18 points below the NC (95% CI: −4.93, −1.43; p = 0.0008) on the WMS-III Faces 2 test. Subjects with AD scored 6.46 points less on the WMS-III Faces 2 test than NC (95% CI: −8.86, −4.06; $p < 0.0001$) and 3.28 points less on average than their peers with MCI (95% CI: −5.68, −0.89; $p = 0.0073$). A similar pattern of deficits by group was observed for the CERAD Recog2 endpoint. That is, after controlling for age, gender, and years of education, MCI participants scored an average 2.20 points below their healthy peers on the CERAD Recog2 test (95% CI: −2.81, −1.58; $p = 0.0000$). In comparison, subjects with AD scored an average 4.86 points below the NC (95% CI: −6.05, −3.67; $p = 0.0000$) and 2.66 points below those with MCI (95% CI: −3.94, −1.38; p = 0.0001). All comparisons were statistically significant at the family-wise 0.05 error.

While all 58 NC subjects remained ‘cognitively healthy’ during the course of the six- year follow-up period, 22 of the 74 MCI patients (30%) converted to dementia. Of the 22, all but one developed AD. The remaining one was diagnosed with a combination of AD and Dementia with Lewy bodies. Among MCI participants with the same age, gender, education level, and entry MMSE score, a 1-standard deviation (*SD*) reduction in the WMS-III Faces 2 test score at baseline was associated with a 1.39-fold increase in the risk for conversion to dementia (95% CI: 0.94, 2.08; $p = 0.1020$). Although this hazard ratio was not statistically different from 1 at the 0.05 level, it suggests that MCI participants with lower scores on the WMS-III Faces 2 test at entry were at a higher risk of conversion to dementia. In assessing the association of the CERAD2 recognition test score with risk for conversion to dementia, the hazard ratio was estimated to be 1 (i.e., not statistically significant). In repeated measures analyses (Table 3), a 1-*SD* reduction in the WMS-III Faces 2 test score was associated with a 1.51-*SD* increase in the FAQ (95% CI: 0.08, 2.94; $p = 0.0380$), a 0.34-*SD* increase in the TMT-B score (95% CI: 0.08, 0.60; $p = 0.0105$), and a 2.09-*SD* increase in the CDR-SB (95% CI: 0.74, 3.44; $p = 0.0024$). These findings indicate that MCI participants with lower scores on the WMS-III Faces 2 test at entry were more likely to experience a decline in their cognitive and functional abilities.

Finally, a post hoc analysis explored the differences WMS-III Faces 2 test scores by MCI subtype. After controlling for age and MMSE score, participants diagnosed with the single domain form of amnestic MCI scored 3.86 points higher on average than their peers with the multiple domain subtype (95% CI:1.39, 6.34; $p = 0.0022$).

Discussion

Our study had three major strengths which enabled us to further clarify the extent to which facial recognition memory is affected by MCI, as compared to healthy aging and AD. First, our finding that facial recognition memory as measured by the WMS-III Faces test is impaired in MCI when scores are adjusted for age, gender and education was based on data from three times as many patients as included in the Seeyle et al. (2009) study (i.e.,74 vs. 24). Secondly, all participants underwent a comprehensive evaluation process on an annual basis. Thirdly, participants were followed longitudinally for up to six years. Availability of accurate longitudinal diagnostic data made it possible to assess the potential increased risk for conversion associated with impairments in facial recognition memory and the association between facial recognition and change in activities of daily living.

Our finding that facial recognition memory is impaired in MCI suggests that the WMS-III Faces test may have clinical utility both for differentiating MCI patients from cognitively normal older adults and potentially foreshadowing future conversion from MCI to AD. The latter claim would need to be confirmed in an independent study with a larger sample size as we failed to reach statistical significance in our analysis. Other findings from this study are generally consistent with our expectations. Specifically, NC significantly outperformed AD patients on tests of recognition memory for both unfamiliar faces and words. Also consistent with prior research (Holdnack & Delis, 2004; Seelye et al. 2009), patients with mild AD performed worse than their peers who had MCI or were cognitively normal on both the WMS-III Faces test and the CERAD Word List tasks.

Our finding that memory for unfamiliar faces is not preserved in MCI was not previously observed in Seelye et al. (2009). This could be accounted for in a number of ways. First, in our opinion, the most likely explanation is that the higher number of MCI patients participating in our (n = 74) than Seelye's (n = 24) study yielded greater statistical precision, thereby increasing the likelihood of detecting a meaningful difference between the MCI and NC subjects on the WMS-III Faces test. Second, the conflicting findings could have resulted from MCI patients in our study being more cognitively impaired than those participating in Seelye et al. (2009). Although this explanation is feasible, as the majority of individuals with single and multiple domain amnestic MCI progressively decline to dementia, a comparison of the neuropsychological test scores of the MCI patients in the two studies suggests otherwise. For instance the mean (± *SD*) scores on the MMSE of the MCI patients involved in Seelye's and our study were 26.9 (2.4) and 27.2 (2.4) points, respectively. In addition, the total number of words recalled on the CERAD Word List task across the three learning trials was also similar: 16.4 (4.3) in Seelye et al. versus 16.3 (3.4) in our study. After a 5-minute delay, the MCI patients involved in Seelye's study could recall an average of 3.6 (2.9) words on the CERAD Word List task, compared to 3.7 (1.9) words in our study. As scores of the MCI patients on measures of verbal memory and overall mental status were almost identical in the two studies, the lack of association observed in Seelye et al. is unlikely attributable to differences in level of cognitive impairment. Finally, it may be postulated that the MCI patients in our study have performed poorly on the WMS-III Faces 2 test because of decreased attention to the stimuli or by failing to comprehend the nuances of the task which only became clear after the study trial was over and the first recognition test started. However, this explanation appears unlikely for a number of reasons. First, the neuropsychological tests were administered by well-trained clinicians who would have corrected any misunderstanding of the instructions by the subject and/or redirected the subject's attention to the task if they saw evidence of poor concentration or problems with distractibility. Additionally, the subject's attention is focused on the target faces when first presented by the examiner's verbal instructions to "remember this one" as each of the 24 photographs is shown. Lastly, it is unlikely that the MCI patients participating in this study failed to attend to the to-be-remembered faces because they scored similarly to their healthy peers on standard measures of attention, namely the forward and backward versions of the WAIS-III Digit Span (see Table 2).

As facial memory involves the recognition of the individual features of each face and the configuration of these features into a whole image (Sergent, 1984), difficulties with

perceptually discriminating the targets from foils could have contributed to the impaired performance of the MCI patients in our sample. To investigate this possibility, it would have been helpful to include a discrimination or visual-matching task, in which subjects are shown a series of two faces at a time (i.e., identical target-target pairs and different target-foil pairs) and asked to state whether the faces are the 'same' or 'different,' following completion of the WMS-III Faces 2 test. While we did not include such a discrimination task in this study, it seems unlikely that the NC and MCI participants differed in how they processed the visual stimuli. That is, while the faces used as the targets and foils in the WMS-III Faces test are similar in terms of age, gender, and ethnicity, each face is novel and consequently can be easily distinguished from the others. Moreover, the MCI patients and NC performed similarly on other tests involving visual discrimination, such as the CERAD Drawing test which entails copying a series of line drawings of different geometric shapes. Presumably, if the MCI patients were perceiving the to-be-copied shapes differently from their healthy peers, the two groups would not have earned similar scores (i.e., 10.4 and 10.6 points, respectively) on this particular test.

Although basic perceptional abilities needed to perform the WMS-III Faces test appeared intact among MCI patients in our study, higher level perceptual difficulties could have affected their performance (Barense, Groen, Lee, Yeung, Brady, Gregori, … Henson, 2012; Newsome, Duarte, & Barense, 2012). Impaired performance on memory tests is usually attributed to a deficit in the medial temporal lobe (MTL) "memory systems" which include the, hippocampus, a structure responsible for consolidation of new episodic memories. Alternatively, Barense et al. (2012) has suggested that overload in perceptual processing of multiple stimuli, as presented in the WMS-III Faces test, can produce impoverished representations in the perirhinal cortex (PRC) of the MTL, producing interference that impairs memory. Representational-hierarchical theory proposes that (a) the PRC plays a role in perceptual as well as mnemonic functions, and (b) perceptional information flows from the posterior to anterior regions of the brain, with representations growing in complexity as they reach the PRC. For example, the image of a face flows from the posterior regions, where simple features (e.g., shape of the head, eyes, and nose) are represented, forward anteriorly, with unique features being integrated into a whole enroute to the PRC. A constant stream of visual input (e.g., viewing multiple faces one after another as in the WMS-III Faces test) can create interference downstream, thereby disrupting memory for the unified images. More specifically, in the WMS-III Faces test, it is the stream of overlapping basic features from the various faces that produces interference. If this is the case, perhaps focusing an individual on the key features of a face (e.g., eyebrows, dimples, shape of the lips) rather than the face as a whole could support memory for the image. While interesting, the representation-hierarchal theory and its implications were not focus of this study.

Our secondary goal was to explore the relationship between WMS Faces test scores at the initial or baseline visit in MCI patients and subsequent progression to AD or another dementia. Consistent with published rates of conversion (Petersen et al., 1999; Petersen, 2004), 22 MCI subjects (i.e., 11 or 15% per year) actually converted to dementia during the average two-year follow-up period. Low scores on the WMS-III delayed retention test (i.e., Faces 2) did increase the risk for dementia, but not significantly. That being said, the current study was underpowered to address this particular question, with only 22 of 74 MCI subjects

progressing in diagnosis. Such a question should be considered in future research that includes large numbers of MCI participants with longer follow-up periods to estimate progression rates.

While the relationship of WMS-III Faces 2 test scores and conversion did not reach statistical significance, poor performance was associated with a significant worsening on measures of cognitive and functional abilities. In other words, low scores did not predict a shift from one (i.e., MCI) diagnostic category to another (i.e., AD or another dementia) but were a harbinger of subtle and significant progressive decline in severity of cognitive impairment as reflected in CDR-SB scores, functional abilities as measured by the FAQ, and executive functioning as assessed by the TMT-B. Notably, a strong relationship between conversion and deficits in executive and functional abilities has been repeatedly reported in the literature (Schimitter-Edgecombe, Woo & Greeley, 2009; Tabert, Albert, Borukhova-Milov, Camacho, Pelton, Liu, … Devanand, 2002).

In addition to the size of the sample for assessing differences in the rates of dementia progression, the current study does suffer from other potential limitations., First, we used the WMS-III Faces test to assess facial memory The WMS-III Faces test was not included in the WMS-IV (Wechsler, 2009) due to a low correlation with other nonverbal memory tests within the same battery (r = .26) (Holdnack & Delis, 2004; Wechsler, 1997). While the WMS-III Faces test did not load heavily with other measures representing the general domain of visual memory, multiple studies suggest memory for faces is a unique and specific ability (Hildebrandt, Wilhelm, Schmiedek, Herzmann, & Sommer, 2011; Wilmer, Germine, Chabris, Chatterjee, Gerbasi, & Nakayama, 2012). Despite its exclusion from the WMS-IV, we chose to use the WMS-III Faces test, which was modeled and developed after Warrington's original Recognition Memory Test (Warrington, 1984) due to its common use in both research and clinical practice.

Two final potential limitations involve the scoring approach utilized in our study and the overall generalizability of our findings. This study, like Seelye et al. (2009), used the standard approach to scoring the WMS-III Faces test. Some, however, have criticized the scoring procedure (i.e., 1 point for each correctly recognized target and foil), as older individuals performing at almost chance levels can fall in the average range when raw scores are converted to age-adjusted scale scores (Levy, 2010). To address this issue, Holdnack and Delis (2004) proposed an alternate scoring procedure for the elderly in which the number of false positives (i.e., foils identified as having been shown) are subtracted from the total number of correct hits (i.e., targets correctly identified). Nevertheless, we used the standard scoring procedures, despite its potential weakness, to maintain comparability with Seelye et al. and as recommended by Wechsler (1997). Lastly, generalizability of the results may be limited by the study sample, a group of well-educated individuals who self-selected to participate in longitudinal follow up as part of the UCI ADRC. Despite this potential limitation, the sample was representative of the diverse population living in Southern California, with 24% of subjects being Asian, 8% Hispanic, 2% African-American, and 68% Caucasian.

In conclusion, this study supports the clinical utility of the WMS-III Faces test for differentiating MCI from normal aging and potentially identifying risk for decline. Additionally, recognizing that memory for unfamiliar faces is actually impaired in MCI increases appreciation for how early this disorder compromises the ability to relate to others. Further research in the utility of the WMS-III Faces test for predicting long-term dementia risk is warranted.

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References

Ahmed S, Arnold R, Thompson SA, Graham KS, & Hodges JR (2008). Naming of objects, faces, and buildings in mild cognitive impairment. Cortex, 44(6), 746–752. doi:10.1016/j.cortex.2007.02.002 [PubMed: 18472044]

Albert MS, Blacker D, Moss MB, Tanzi R, & McArdle JJ (2007).Longitudinal change in cognitive performance among individuals with mild cognitive impairment. Neuropsychology, 21, 158–169. doi: 10.1037/0894-4105.21.2.158 [PubMed: 17402816]

Benton AL, & Hamsher K. deS. (1978). Multilingual Aphasia Examination: Manual. Iowa City: University of Iowa Press.

Barense MD, Groen IIA, Lee ACH, Yeung L-K, Brady SM, Gregori M, Kapur N, Bussey TJ, Saksida LM, & Henson RNA (2012). Intact memory for irrelevant information impairs perception in amnesia. Neuron, 75, 157–167. doi:10.1016/j.neuron.2012.05.014 [PubMed: 22794269]

Brooks BL, Weaver LE, & Scialfa CT (2006). Does impaired executive functioning differentially impact verbal memory measures in older adults with suspected dementia? The Clinical Neuropsychologist, 20, 230–242. doi:10.1080/13854040590947461 [PubMed: 16690544]

Bucks RS, Ashworth DL, Wilcock GK, & Siegfried K. (1996). Assessment of activities of daily living in dementia: Development of the Bristol Activities of Daily Living Scale. Age Ageing, 25, 113–120. [PubMed: 8670538]

Chapman RM, Mapstone M, McCrary JW, Gardner MN, Porsteinsson A, Sandoval TC, Guillily MD, DeGrush E, & Reilly LA (2011). Predicting conversion from mild cognitive impairment to Alzheimer's disease using neuropsychological tests and multivariate methods. Journal of Clinical and Experimental Neuropsychology, 33(2), 187–199. doi: 10.1080/13803395.2010.499356 [PubMed: 20711906]

Dade LA, & Jones-Gotman M. (2001). Face learning and memory: The Twins test. Neuropsychology, 15(4), 525–534. doi:10.1037//0894-4105.15.4.525 [PubMed: 11761042]

Doss RC, Chelune GJ, & Naugle RI (2004).WMS-III performance in epilepsy patients following temporal lobectomy. Journal of the International Neuropsychological Society, 10, 173–179. doi:10.1017/S1355617704102026 [PubMed: 15012837]

Estévez-González A, Garcia-Sánchez C, Boles A, Otermin P, Pascual-Sedano B, Gironell A, & Kulisevsky J. (2004). Semantic knowledge of famous people in mild cognitive impairment and progression to Alzheimer's disease. Dementia and Geriatric Cognitive Disorders, 17(3), 188–95. doi: 10.1159/000076355 [PubMed: 14739543]

Farah MJ, Wilson KD, Drain M, & Tanaka JN (1998). What is "special" about face perception? Psychological Review, 105, 482–498. [PubMed: 9697428]

Folstein MF, Folstein SE, & McHugh PR (1975). 'Mini-mental state.' A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research, 12, 189–198. [PubMed: 1202204]

Gibson AJ, & Kendrick DC (1979). The Kendrick Battery for the Detection of Dementia in the Elderly. Windsor, UK: NFER Publishing Co.

Goren CC, Sarty M, & Wu RWK (1975).Visual following and pattern discrimination of face-like stimuli by newborn infants. Pediatrics, 65, 544–549.

Gorno-Tempini ML & Price CJ (2001). Identification of famous faces and buildings: A functional neuroimaging study of semantically unique items. Brain, 124(10), 2087–2097. doi: 10.1093/brain/124.10.2087 [PubMed: 11571224]

Grabowski TJ, Damasio H, Tranel D, Ponto LL, Hichwa RD, & Damasio AR (2001). Human Brain Mapping, 13(4), 199–212. doi:10.1002/hbm.1033 [PubMed: 11410949]

Hildebrandt A, Wilhelm O, Schmiedek F, Herzmann G, & Sommer W. (2011). On the specificity of face cognition compared with general cognitive functioning across adult age. Psychology and Aging, 26, 701–715. doi: 10.1037/a0023056 [PubMed: 21480718]

Holdnack JA & Delis DC (2004). Parsing the recognition memory components of the WMS-III face memory subtest: Normative data and clinical findings in dementia groups. Journal of Clinical and Experimental Neuropsychology, 26, 459–483. doi:10.1080/13803390490496687 [PubMed: 15512935]

Holm S. (1979). A simple sequentially rejective multiple test procedure. Sandinavian Journal of Staistics, 6, 65–70.

Kaplan E, Goodglass H, & Weintraub S. (1983). The Boston Naming Test. Philadelphia: Lea and Febiger.

Levy B. (2003). About the power for detecting severe impairment in older adults with the Faces test from Wechsler Memory Scale-III: Simply guess and save face. Journal of Clinical and Experimental Neuropsychology, 25(3), 376–381. doi:10.1076/jcen.25.3.376.13804 [PubMed: 12916650]

Lin DY, & Wei LJ (1989). The robust inference for the Cox Proportional Hazards Model. Journal of the American Statistical Association, 84(408), 1074–1078.

McCarthy RA, & Warrington EK (1990). Cognitive neuropsychology. San Diego: Academic Press.

McKhann G, Drachmann D, Folstein M, Katzman R, Price D. & Stadian EM (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Service Task Force on Alzheimer's disease. Neurology, 34, 939–944. [PubMed: 6610841]

Morris JC, (1993). The Clinical Dementia Rating (CDR): Current version and scoring rules. Neurology, 43, 2412–2414.

Morris JC, Heyman A, & Mohs RC (1989). The consortium to establish a registry for Alzheimer's disease (CERAD): Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology, 39, 1159–1165. [PubMed: 2771064]

Newsome RN, Duarte A, & Barense MD (2012). Reducing perceptual interference improves visual discrimination in mild cognitive impairment: Implications for a model of perirhinal cortex function. Hippocampus, 22, 1990–1999. doi: 10.1002/hipo.22071 [PubMed: 22987677]

Osterrieth PA (1944). The test for copying a complex figure. Archives de Psychologie, 30, 206–356.

Petersen RC, (2004). Mild cognitive impairment as a diagnostic entity. Journal of Internal Medicine, 256, 183–194. doi: 10.1111/j.1365-2796.2004.01388.x [PubMed: 15324362]

Petersen RC, Smith GE, Warings SC, Ivink RJ, Tangalos EG, & Kokmen E. (1999). Mild cognitive impairment: Clinical characterization and outcome. Archives of Neurology, 56, 303–308. [PubMed: 10190820]

Pfeffer RI, Kurosaki TT, Harrah CH Jr., Chance JM, & Filos S. (1982). Measurement of functional activities in older adults in the community. Journals of Gerontology, 37, 323–329. [PubMed: 7069156]

Rabin IA, Pare N, Saykin AJ, Brown MJ, Wishart HA, Flashman LA, & Santulli RB (2009). Differential memory test sensitivity for diagnosing amnestic mild cognitive impairment and predicting conversion to Alzheimer's disease. Aging, Neuropsychology, and Cognition, 16, 357–376. doi:10.1080/13825580902825220

Reitan RM (1958). Validity of the trail making test as an indicator of organic brain damage. Perceptual and Motor Skills, 8, 271–276.

Rey A. (1941). Psychological testing in the case of traumatic encephalopathy. Archives de Psychologie, 28, 286–340.

Schiltz C, Dricot L, Goebel R, & Rossion B. (2010). Holistic perception of individual faces in the right middle fusiform gyrus as evidenced by the composite face illusion. Journal of Vision, 10(2):25, 1–16. doi 10.1167/10.2.25

Schmitter-Edgecombe M, Woo E, & Greeley DR (2009). Characterizing multiple memory deficits and their relation to everyday functioning in individuals with mild cognitive impairment. Neuropsychology, 23(2), 168–177. doi:10.1037/a0014186oi [PubMed: 19254090]

Seelye AM, Howieson DB, Wild KV, Moore MM, & Kaye JA (2009). Wechsler Memory Scale-III Faces test performance in patients with mild cognitive impairment and mild Alzheimer's disease. Journal of Clinical and Experimental Neuropsychology, 31(6), 682–688. doi:10.1080/13803390802484763 [PubMed: 19037811]

Sergent J. (1984). An investigation into component and configural processes underlying face perception. British Journal of Psychology, 75, 221–242. [PubMed: 6733396]

Smith A. (1973). Symbol Digits Modality Test: Manual. Los Angeles: Western Psychological Services.

Tabert MH, Albert SM, Borukhova-Milov L, Camacho Y, Pelton G, Liu X, Stern Y, & Devanand DP (2002). Neurology, 58, 758–764. [PubMed: 11889240]

Tremont G, Miele A, Smith MM, & Westervelt HJ (2010). Comparison of verbal memory impairment rates in mild cognitive impairment. Journal of Clinical and Experimental Neuropsychology, 32(6), 630–636. doi 10.1080/13803390903401328 [PubMed: 20603742]

Tulsky DS, Chiaravalloti ND, Palmer BW, & Chelune GJ (2003). The Wechsler Memory Scale – Third Edition: A new perspective. In Tulsky DS, Saklofske DH, Chelune GJ, Heaton RK, Ivnik RJ, Bornstein R, Prifitera A, & Ledbetter M. (Eds.), Clinical Interpretation of the WAIS-III and WMS-III (pp.93–139). San Diego: Academic Press.

Warrington EK, (1984). Recognition Memory Test: Manual. Windsor, U.K.: NFER-NELSON Publishing Company.

Wechsler D. (1981). Manual for the Wechsler Adult Intelligence Scale-Revised. New York: Psychological Corporation.

Wechsler D. (1981). Wechsler Memory Scale-Revised Edition: Administration and Scoring Manual. San Antonio: The Psychological Corporation.

Wechsler D. (1997). The Wechsler Adult Intelligence Scale – III Manual. San Antonio: The Psychological Corporation.

Wechsler D. (1997). Wechsler Memory Scale – Third Edition: Administration and Scoring Manual. San Antonio: The Psychological Corporation.

Wechsler D. (2009). Wechsler Memory Scale – Fourth Edition. San Antonio: The Psychological Corporation.

Wilmer JB, Germine L, Chabris CF, Chatterjee G, Gerbasi M, & Nakayama K. (2012). Capturing specific abilities as a window into human individuality: The example of face recognition. Cognitive Neuropsychology, 29(5–6), 360–392. doi:10.1080/02643294.2012.753433 [PubMed: 23428079]

White H. (1980). A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity. Econometrica, 48, 817–830.

Yan JH, Rountree S, Massman P, Doody RS, & Li H. (2008). Alzheimer's disease and mild cognitive impairment deteriorate fine motor control. Journal of Psychiatric Research, 42, 1203–1212. doi:10.1016/j.psychires.2008.01.006 [PubMed: 18280503]

Yan JH, & Dick MB (2006). Practice effects on motor control in healthy seniors and patients with mild cognitive impairment or mild Alzheimer's disease. Aging, Neuropsychology, and Cognition, 13, 385–410. doi:10.1080/138255890969609oi

Zeger SL, & Liang KY (1986). Longitudinal data analysis for discrete and continuous outcomes. Biometrics, 42, 121–130. [PubMed: 3719049]

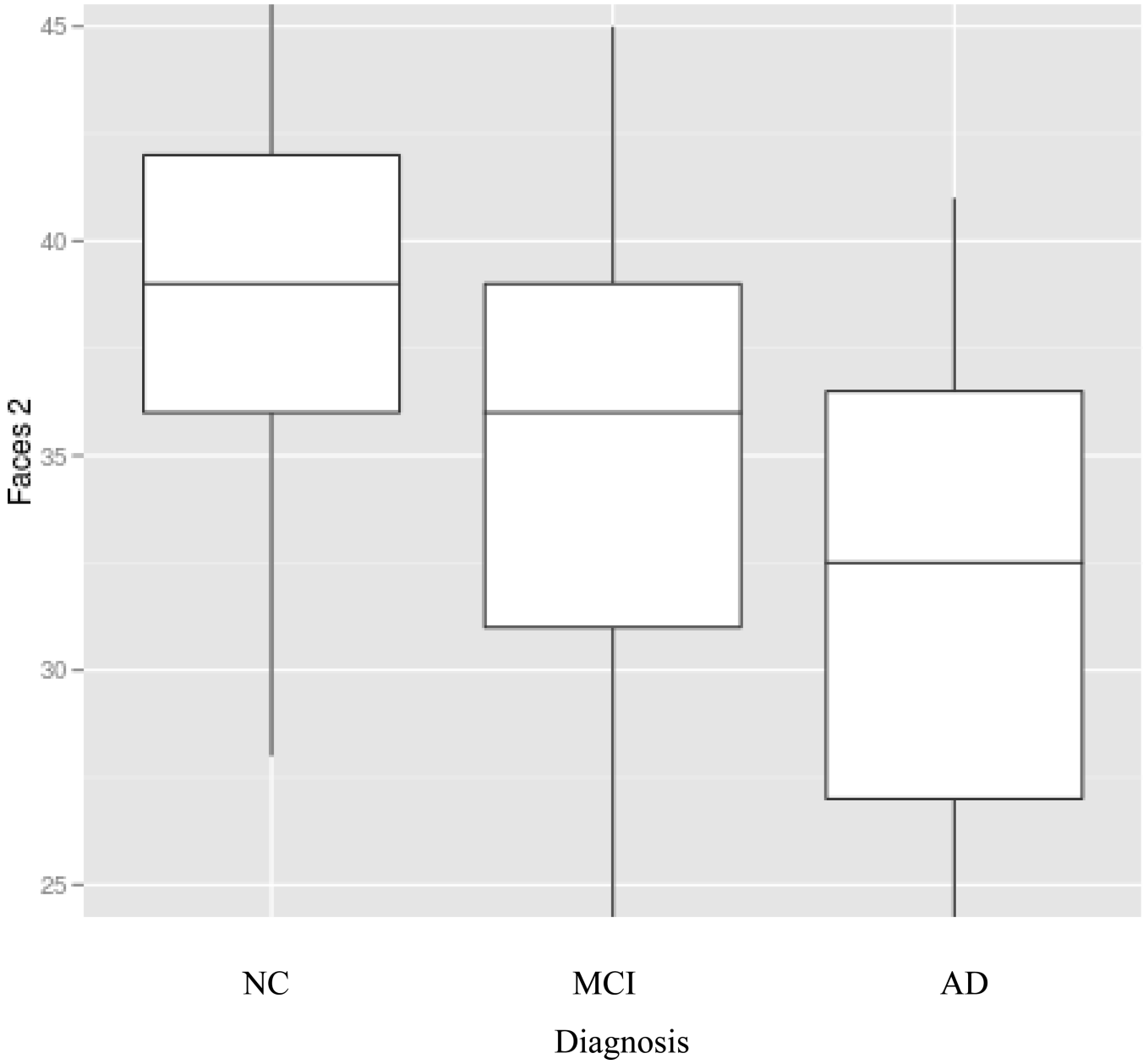

Figure 1.
Box plot showcasing the distribution of the Faces 2 scores for the three groups.

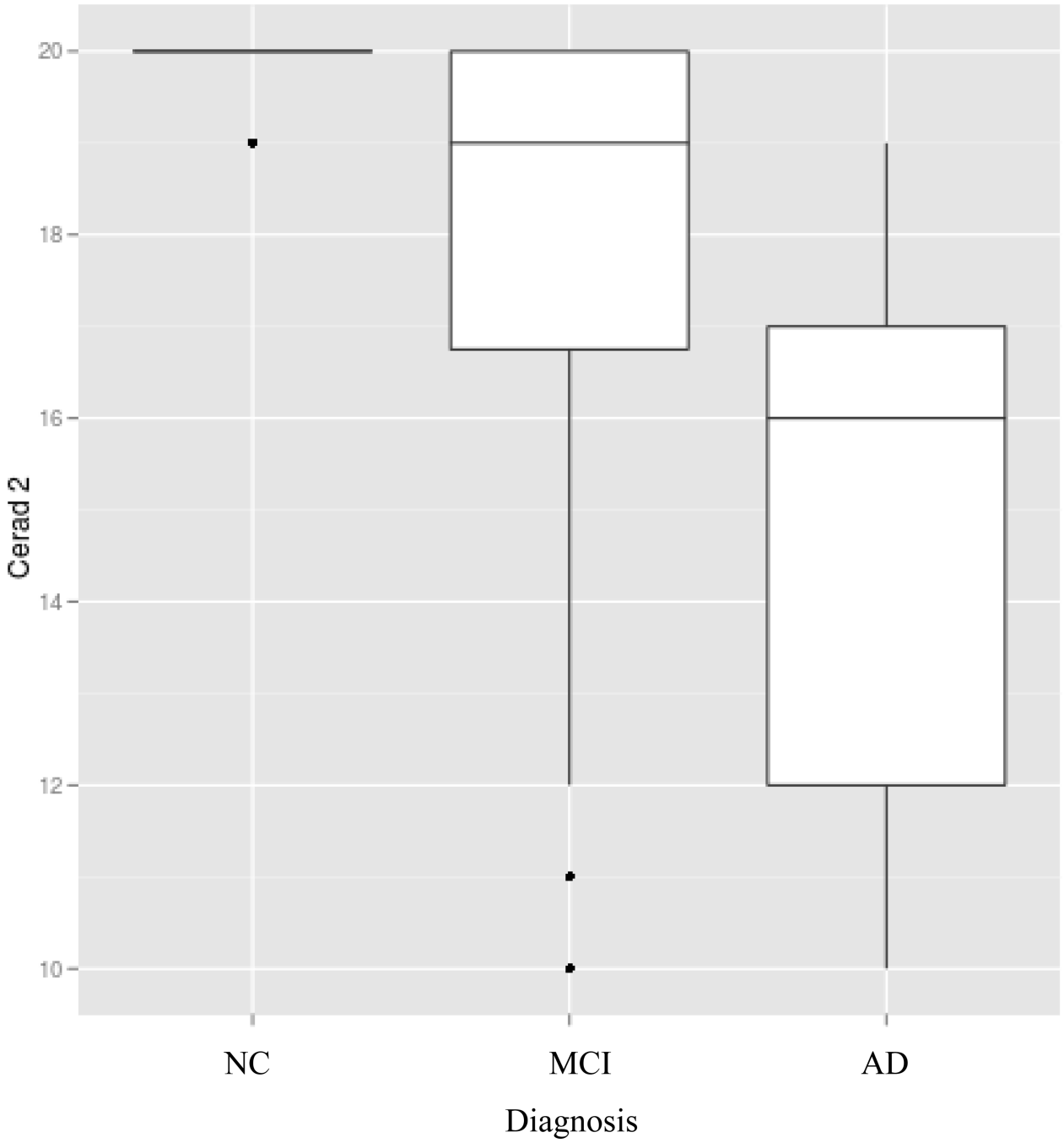

Figure 2.
Box plot showcasing the distribution of the CERAD Recogn2 scores for the three groups.

Table 1

Demographic Characteristics

Variable	Normal (*n* = 58)	MCI (*n* = 74)	Dementia (*n* = 22)
Age (in years)	68 (63–74)	74 * (69–80)	72 (63–83)
Gender			
M	18 (31.0%)	35 (47.3%)	9 (40.9)
F	40 (69.0%)	39 (52.7%)	13 (59.1)
Education (in years)	17 (15–18)	16 (14–18)	16 (13–18)
Years followed			
0	20 (34.5%)	19 (25.7%)	4 (18.2%)
1	9 (15.5%)	12 (16.2%)	7 (31.8%)
2	2 (3.5%)	14 (18.9%)	5 (22.7%)
3	2 (3.5%)	10 (13.5%)	2 (9.1%)
4	11 (18.9%)	15 (20.3%)	2 (9.1%)
5	11 (18.9%)	3 (4.0%)	2 (9.1%)
6	6 (5.2%)	1 (1.4%)	0 (0.0%)

Note: Continuous variables are reported as mean and range; categorical variables are reported as counts and proportions.

* denotes statistically different than Normal at the 0.05 level.

Table 2

Neuropsychological Test Scores in Normal, MCI, and AD Groups

Test	Normal		MCI		AD	
	M	*SD*	*M*	*SD*	*M*	*SD*
Mini-Mental State Exam	29.15	1.07	27.21 *	2.38	23.63 *†	2.93
CERAD Learning Trials	24.0	2.82	16.33 *	3.43	12.52 *†	3.37
CERAD Word List: 5-minute recall	8.38	1.55	3.73 *	1.93	1.61 *†	1.74
CERAD Word List: 30-minute recall	8.71	1.47	3.58 *	2.29	1.28 *†	1.84
CERAD Word List: 5-minute Recog1 total	19.98	0.13	18.55 *	1.89	16.47 *†	2.76
CERAD Word List: 30-minute Recog2 total	19.91	0.28	17.65 *	2.54	14.9 *†	2.87
WMS-III Logical Memory 1: Total raw score	45.33	8.56	28.79 *	11.04	14.40 *†	9.26
WMS-III Logical Memory 2: Total raw score	29.11	6.63	13.28 *	9.29	5.0 *†	6.22
WMS-III Faces 1: Total raw score	38.0	4.24	33.73 *	4.89	30.40 *†	4.55
WMS-III Faces 2: Total raw score	38.92	4.25	35.13 *	4.97	33.0 *	4.55
WAIS-R Information: Raw score	24.38	5.07	24.13	4.08	20.04 *†	4.84
WAIS-III Digit Span Forward: Raw score	9.44	2.30	9.71	2.15	8.31 *†	1.88
WAIS-III Digit Span Backwards: Raw score	6.96	2.45	6.32	1.91	4.95 *†	1.73
Symbol Digit Modality Test: Number written	49.43	6.56	35.10 *	9.69	21.57 *†	10.71
30-item Boston Naming Test: Total correct	24.98	4.01	24.06	4.98	21.54 *†	4.14
CERAD Animal Naming: Total in 60 seconds	19.20	4.99	15.60 *	4.60	13.04 *	5.93
COWAT (Letter Fluency): Words in 3 min.	41.54	12.86	34.39 *	13.09	25.0 *†	15.70
CERAD Drawing	10.64	0.66	10.41	0.86	8.54 *†	2.04
WAIS-III Block Design: Raw score	36.59	10.40	29.13 *	9.90	19.14 *†	10.55
Trail Making Test, Part A: Time in sec.	30.10	9.29	45.10 *	16.77	71.45 *†	41.30
Trail Making Test, Part B: Time in sec.	84.16	40.91	156.01 *	83.21	262.95 *†	59.02
WAIS-III Similarities: Raw score	25.52	3.56	21.51 *	5.6	17.19 *†	7.03
Kendrick Digit Copy: Time in sec.	57.45	10.07	75.25 *	20.96	91.85 *†	36.80

Notes:

* denotes statistically different than Normal at the 0.05 level.

† denotes statistically different than MCI at the 0.05 level.

Mini-Mental State Examination (MMSE: Folstein, Folstein, & McHugh, 1975); Word List, Animal Fluency, and Constructional Praxis (i.e., Drawing) subtests from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD: Morris, Heyman, & Mohs, 1989); Logical Memory tests, immediate and delayed recall, and Faces tests, immediate and delayed recognition, from the Wechsler Memory Scale 3rd Edition (WMS-III: Wechsler, 1997); Information subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R: Wechsler, 1981); Digit Span Forward, Digit Span Backwards, Block Design, and Similarities subtests from the Wechsler Adult Intelligence Scale 3rd Edition (WAIS-III: Wechsler, 1997);

Symbol Digit Modality Test (Smith, 1968); Boston Naming Test, 30-item version (Kaplan, Goodglass & Weintraub, 1983); Controlled Oral Word Association Test (COWAT: Benton & Hamsher, 1976); Trail Making Test A and B (Reitan, 1958); and Kendrick Digit Copy test (Gibson & Kendrick, 1979).

Table 3

Adjusted Mean Difference Scores for FAQ, TMT-B, and CDR-SB in the Longitudinal Model for MCI Subjects

Variable	Adjusted MeanDifference	95% CI	p-value
FAQ TS (per 1 SD Norm)			
Faces 2 (per 1 SD Norm)	−1.51	−2.94, −0.08	0.038
Age	0.38	0.38, 0.74	0.034
MMSE	−2.16	−2.57, −1.75	0.000
Female	−0.73	−6.44, 4.98	0.803
Education (years)	0.36	−0.63, 1.36	0.474
TMT-B (per 1 SD Norm)			
Faces 2 (per 1 SD Norm)	−0.34	−0.60, −0.08	0.010
Age	0.02	−0.04, 0.08	0.539
MMSE	−0.21	−0.27, −0.14	0.000
Female	−0.12	−1.15, 0.90	0.812
Education (years)	−0.22	−0.37, −0.07	0.004
CDR-SB (per 1 SD Norm)			
Faces 2 (per 1 SD Norm)	−2.09	−3.44, −0.74	0.002
Age	0.03	−0.26, 0.33	0.818
MMSE	−3.07	−3.72, −2.42	0.000
Female	−2.61	−7.40, 2.17	0.284
Education (years)	0.12	−0.77, 1.02	0.786

Note: Estimated regression coefficients for the 3 longitudinal endpoints using Generalized Estimating Equations. Each estimated coefficient represents the average mean difference of the endpoint (e.g., FAQ-TS SD) associated with a 1 unit change in the covariate.