COGNITIVE MARKERS OF PROGRESSION FROM NORMAL COGNITION TO MCI AND FROM MCI TO DEMENTIA ACROSS EUROPEAN AND HISPANIC AMERICANS

by

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This dissertation was prepared under the direction of the candidate's dissertation advisor, Dr. Monica Rosselli, Department of Psychology, and has been approved by all members of the supervisory committee. It was submitted to the faculty of the Charles E. Schmidt College of Science and was accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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ABSTRACT

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Objective: Our main objectives were to identify cognitive markers of progression to a more severe cognitive diagnosis, explore possible differences between ethnic groups and to correlate cognitive markers of progression with biomarkers of AD (hippocampal and entorhinal volumes) and frontal volumes (lateral orbitofrontal, medial orbitofrontal, superior frontal, and rostral middle frontal volumes). Method: 207 participants (M_{age} = 71.79, *SD* = 7.48, 123 Hispanic Americans [HA]) were followed for an average of 23 months. Participants were classified into 3 diagnostic groups (Cognitively normal [CN], mild cognitive impairment [MCI], or dementia) based on the CDR global score and the neuropsychological baseline data was used as predictors of progression status. For the CN group, the Benson Figure delayed recall was a predictor of cognitive decline, and within the MCI group, the Benson delayed recall, the HVLT immediate recall, the TMT-B, category fluency, and three measures of the LASSI-L (A1 cued recall, A2 cued recall, and delayed recall) were significant predictors of progression to dementia and are

suggested as cognitive markers of progression for MCI individuals. Memory cognitive markers and category fluency correlated with medial temporal lobe volumes, and the TMT-B correlated with superior frontal volume. We did not observe significant differences in cognitive markers across ethnic groups. Conclusion: we identified cognitive markers of progression for CN and for MCI diagnoses which were not different across ethnic groups. These findings contribute to literature on the early identification of individuals at risk of progression to a more severe cognitive status even within asymptomatic individuals which can facilitate a more time- and cost-effective practice that is essential to the provision of the appropriate treatment to those at higher risk of progression.

Keywords: mild cognitive impairment, abnormal aging, Alzheimer's disease, cognitive markers, progression, aging, cognitive decline, Hispanics.

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About 11 percent of the American population that are age 65 and older has Alzheimer's dementia and this number is expected to increase every year ("2021 Alzheimer's disease facts and figures," 2021). Since the pathophysiological changes of Alzheimer's disease (AD) start decades before the onset of clinical symptoms, current research has placed considerable attention to the early identification of individuals at high risk for developing dementia due to AD. This is critical for interventional research and clinical practice and is specifically important considering the suggestion that pharmacological treatment will be most effective if administered in the earliest stages of brain disease before the appearance of clinical symptoms (Loewenstein, Curiel, Duara & Buschke, 2018). Research on mild cognitive impairment (MCI) has aimed at the detection and characterization of those at greater risk of further decline (Storandt, Grant, Miller & Morris, 2006; Loewenstein et al., 2012). Nonetheless, it is important to also focus on the identification of asymptomatic individuals who have a greater risk for future cognitive decline.

The diagnosis of MCI is not enough to characterize those who will or not progress to dementia given that some MCI individuals revert to normal cognition or do not progress to further stages of AD (Malek-Ahmadi, 2016). Clinical and population-based samples suggest that the annual progression rate to dementia in patients with MCI ranges

from 5% to 20% (Langa et al., 2014); a meta-analysis suggested that this progression rate ranges from 5 to 10% and that most people with MCI will not progress to dementia even after 10 years of follow-up (Mitchell & Shiri-Feshki, 2009). Because of this difference in progression rates, the fact that most MCI do not progress to dementia, and that many revert to normal cognition, some authors even question the validity of MCI as a diagnostic entity (e.g., Klekociuk, Saunders & Summers, 2016; Edmonds, Delano-Wood, Jack, Galasko, Salmon & Bondi., 2016). Spontaneous recovery does not align with the definition of MCI as a prodrome of a neurodegenerative disease (Klekociuk et al., 2016) and are most likely due to a diagnostic error (false positive diagnosis) (Klekociuk & Summers, 2014). This highlights the importance of examining potential cognitive markers that differentiate stable/progressive MCI and unstable MCI or those who revert to normal cognition (Klekociuk & Summers, 2014). Determining cognitive markers that could differentiate between stable MCI, progressive MCI, and MCI who recover to normal cognition with a single time-point assessment with a high degree of sensitivity and specificity will lower the cost and time consumption of assessment and benefit research and clinical practice (Klekociuk & Summers, 2014).

Most studies that examine the stability of cognitive status do not include a sample that is diverse in ethnic/racial representation (Roberts et al., 2014) and, therefore, the relationship between the stability of cognitive diagnosis and ethnicity, and its related social and behavioral factors, remains unclear. Some studies have demonstrated a higher risk of progression to MCI and/or dementia across some minority groups in the USA. Hispanics from the Caribbean and South/Central America have shown a greater risk of progression from normal cognition to MCI than non-Hispanic Whites, while Hispanics of

Mexican descent, non-Hispanic Whites, and African Americans had similar MCI risk (Perales-Puchalt et al., 2020). Dementia incidence rates were highest among African Americans relative to Latinos (largely of Mexican descent) and Whites in a population-based sample followed for 14 years (Mayeda, Glymour, Quesenberry, & Whitmer, 2016). Conversely, Mungas et al. (2010) demonstrated that MCI progressors were predominantly Caucasian compared to Hispanics and African Americans but participants with stable MCI and those who reverted to normal were distributed across groups. Manly and colleagues (2008) also demonstrated no ethno-racial differences among MCI who reverted to normal cognition.

The current recommendations from the National Institute of Aging-Alzheimer's Association for the diagnosis of MCI due to AD include the use of biomarkers for clinical research diagnosis (Albert et al., 2011). One of the categories of biomarkers that have been most studied includes biomarkers of neuronal injury (e.g. CSF tau/p-tau, hippocampal or medial temporal lobe atrophy on MRI; Albert et al., 2011). Hippocampal (HP) volume and Entorhinal cortex (ERC) volume are progressively smaller in the AD spectrum, with CN individuals presenting greater volume than MCI, and MCI presenting greater volume than individuals with dementia (Frisoni, Fox, Jack, Scheltens, & Thompson, 2010; Vemuri et al., 2008).

In a previous study (Arruda et al., submitted) we investigated the stability in cognitive status classification in a sample of European Americans (EA) and Hispanic Americans (HA) including longitudinal data of participants classified as cognitively normal (CN) and MCI at baseline, investigating possible differences as a function of ethnicity and baseline brain biomarkers. EA and HA were not significantly different in

progression rate nor in the frequency of reverters, and HP and ERC atrophy were significant predictors of future progression to dementia, regardless of ethnicity, among MCI but not among CN participants.

The current study has the objective of incorporating three important aspects potentially related to risk of future cognitive decline: cognitive markers of progression, ethnicity, and biomarkers of neurodegeneration related to AD.

Neuropsychological profile of progressors

In a cohort of cognitively normal (CN) older adults (N = 253), mostly Hispanics and White Americans, that were followed for an average of 4.5 years, Chen et al. (2017) found that worse executive function (EF) at baseline was associated with increased risk for progression to MCI. This research, however, used composite scores from the Spanish English Neuropsychological Assessment Scales battery (SENAS) in which only one aspect of memory (episodic memory with a list learning test) was investigated, and EF was assessed with only verbal fluency (category and phonemic fluencies) and a working memory task. Conversely, Garcia-Herranz, Diaz-Mardormingo & Peraita (2016) found that long delay recall from a Spanish version of the California Verbal Learning Test (CVLT) was the most sensitive measure and had the greatest capacity to predict progression from MCI to AD. They also observed that impairment in multiple domains was associated with higher risk of progression. This study analyzed the predictive value of cognitive tests from multiple cognitive domains (episodic memory, EF, attention, language, visuospatial constructional skill, and praxis), sociodemographic variables, follow-up time (average of 3.22 years, SD = 1.38), and emotional state on progression. Among sociodemographic variables, only gender was a significant predictor of

progression (men had higher risk of progression, which is different from other studies that suggest women are at a higher risk). Limitations of this study include the use of only one test of memory (list learning) with multiple scores (e.g. immediate free recall, long delay free recall, long delay cued recall), and the use of the same tests for diagnostic purposes which constitutes a circularity problem. Additionally, their sample was limited including 105 MCI participants of which 24 progressed to dementia during the follow-up and they did not include a control group.

Many of the studies that examine the neuropsychological profile of progressors classify their participants based on their subtype of MCI. Amnestic MCI (aMCI) present a memory deficit that may be associated with other cognitive deficits (aMCI multidomain) or not (aMCI single domain). Dysexecutive MCI (dMCI) are those that present an executive function deficit which may also be associated with other deficits.

Crocco et al. (2021) examined percentage of semantic intrusion errors (PIE) on the subscales that measure proactive semantic interference of the Loewenstein-Acevedo Scales for Semantic Interference and Learning (LASSI-L), a cognitive stress test, as a predictor of progression among Pre-MCI and (aMCI) participants in a 26-month period. Pre-MCI participants are those that are not CN but do not meet full criteria for MCI. The PIE was able to distinguish between Pre-MCI who progressed to MCI and Pre-MCI who reverted to normal cognition and predicted 83.3% of aMCI participants who progressed to dementia. Limitations of this study include small sample sizes (51 stable CN, 25 PreMCI non-progressors, 22 MCI progressors to aMCI, and 18 MCI progressors to dementia) and lack of neuroimaging.

Some studies compare stability of cognitive status across MCI subtypes. Perri, Serra, Carlessimo and Caltagirone (2007) examined differences in the cognitive profile of stable aMCI (*n* = 111) and aMCI who progressed to AD after 2 years (*n* = 79). aMCI presented preservation of short-term and implicit memory but extensive impairment of episodic long-term memory, with progressors being more severely impaired than stable aMCI. They further suggest that tests that involve free delayed recall of verbal material (word list and story recall) had the greatest sensitivity to the memory deficits presented by aMCI that progressed to AD. Additionally, progressors presented more impaired learning curve across the word list trials than non-progressors. Huey et al. (2013) compared aMCI (*n* = 98), dMCI (*n* = 33), and multiple-domain MCI (*n* = 154) in rate of progression to dementia from a community ethnic diverse sample of 1167 participants followed for an average of 4.5 years (*SD* = .8). They observed that dMCI were less likely to progress to dementia. Additionally, the presence of executive dysfunction, measured by category fluency, phonemic fluency and the Similarities subtest of the Wechsler Adult Intelligence Scale-revised (WAIS-R), in multiple domain MCI did not increase the risk of progression to dementia.

Cerbone, Massman, Kulesz, Woods and York (2020) examined predictors of rate of cognitive decline among single and multi-domain aMCI participants (*N* = 151) in an average follow-up of 1.61 years. Worse EF (measured by the Trail Making Test- Part B, the Stroop Color and Word Test, Color-word inhibition condition, Letter fluency, and the Digit Span backwards and Similarities Subtest of the WAIS) and greater memory impairment at baseline predicted a faster rate of decline. Memory performance (tested by the Logical Memory and the Visual Reproduction I and II of the Wechsler Memory

Scale- revised) itself was not predictive of rate of cognitive decline, but greater number of impaired memory scores was. There are several limitations to this study including that the sample was 94% non-Hispanic Caucasians, which limits the generalizability of their results to minority ethnic groups, and most of the participants only had one follow-up visit, which limits the identification of progressors who might take longer to present detectable decline.

A study that examined cross-sectional data of the learning curve on the Rey Auditory Verbal Learning Test (RAVLT) across stable aMCI (n = 15), stable non-amnestic MCI (n-aMCI, n = 36), healthy controls (n = 29), and recovered MCI (n = 29) observed that stable aMCI was associated with a reduced learning curve (Klekociuk & Summers, 2014).

Ganguli et al. (2018) in a community sample (N = 1603, ages 65 and older) 5-year longitudinal study investigated what baseline characteristics distinguished the MCI subgroups (stable, reverters, and progressors) from one another and from those who remained consistently normal, by comparing demographic, health, and cognitive characteristics. Baseline cognitive diagnosis was based on the Global CDR diagnosis, and cognitive data were used as predictors of MCI outcome. Progressors had memory impairment and APOE4 genotype consistent with a typical prodromal AD profile. The memory composite included scores from the Logical Memory and the Visual Reproduction subtests of the WMS-R, and the Fuld Object Memory Test. The cognitive deficits observed in stable MCI and those who reverted to normal cognition were hypothesized to be caused by diabetes and heart failure and, therefore, the cognitive

impairments may not be progressive if the underlying conditions are adequately controlled.

In summary, the literature is not conclusive as to which neuropsychological measures are the most predictive of future cognitive decline among CN and MCI individuals. There are contradictory results regarding the predictive capacity of list learning tests with some studies observing that some measures of this type of test are the most predictive of progression (e.g., long delay recall [Garcia-Herranz et al., 2016; Perri et al., 2007], impaired learning curve [Perri et al., 2007]) and others suggesting they are not able to detect risk of progression (e.g., Chen et al., 2017). Additionally, research is not conclusive about the contribution of EF deficits to the risk of progression to a more severe cognitive status. Some studies have observed that worse EF was associated with a higher risk for progression (e.g., Chen et al., 2017; Cerbone et al., 2020), while others suggested that the presence of this deficit was not related to progression (e.g., Huey et al., 2013).The use of category fluency and phonemic fluency as measures of EF have yielded contradictory results across studies (e.g., Chen et al., 2017; Huey et al., 2013). Moreover, among CN participants, the literature is yet more restricted, with Chen et al. (2017) suggesting that worse EF is associated with increased progression risk and Crocco et al. (2021) observing that semantic intrusion errors on a word-list recall test identifies CN at higher risk of progression. These and other inconsistencies support the need for further studies investigating cognitive markers of progression among CN and MCI individuals.

A study that investigated which neuropsychological tests predicted progression to AD in Hispanics and non-Hispanics found that the Boston Naming Test and time to complete the Trail Making Test A (TMT-A) and TMT-B significantly predicted

progression from CN to AD in both ethnic groups (Weissberger, Salmon, Bondi and Gollan, 2013). Cognitive measures that were sensitive to progression only among Hispanics were related to error scores and included the number of errors on TMT-A and TMT-B and the non-perseverative errors on the Wisconsin Card Sorting Test (WCST). Among non-Hispanics the Vocabulary subtest of the WAIS-R and Semantic fluency were sensitive to progression, which was not observed for Hispanics. One major limitation of this study was the small sample size (e.g., only included 11 Hispanic-progressors, and 11 non-Hispanic progressors).

Despite growing attention to ethnicity and race in AD research (Barnes, 2022), there is still a need for a further characterization of the cognitive markers associated with cognitive status stability across ethnic groups. This is important considering that Hispanics are more likely to develop AD than non-Hispanic European Americans and are more likely to experience risk factors for MCI and dementia ("2021 Alzheimer's disease facts and figures," 2021).

Biomarkers of progression within the AD spectrum

Volumetric biomarkers of neurodegeneration associated with AD, such as the medial temporal regions (e.g., hippocampus and entorhinal cortex), have been related to memory impairment and overall cognitive performance (Brooks & Loewenstein, 2010; Duara et al., 2008). Moreover, somestudies have observed ethnic differences in these regions' volumes, with non-Hispanic presenting smaller volumes than Hispanics for the same level of cognitive performance (DeCarli et al., 2008; Zahodne et al., 2015; Burke et al., 2018).

Additionally, frontal lobe volume has been related to cognitive decline associated with AD. Frontal lobe function, as assessed by the Frontal Assessment Battery (FAB), has been associated with the volume of the left dorsolateral prefrontal cortex (Matsuoka et al., 2017). Lerch et al. (2004) investigated cortical thickness across the entire brain comparing controls and participants with probable AD and observed cortical thickness decline in temporal, frontal, and inferior parietal regions, with more pronounced cortical thinning in the medial temporal lobes. In the frontal lobes, the greatest differences between controls and AD participants were in the left anterior cingulate, the dorsolateral prefrontal cortex, and the orbitofrontal cortex.

Study Aims

The present study aimed to (1) identify cognitive markers of progression, (2) explore possible differences in cognitive markers of progression between ethnic groups, and (3) to investigate whether the identified cognitive markers are associated with biomarkers of AD. To that extent, we investigated multiple cognitive domains, namely executive functions (EF), attention, memory, working memory (WM), and visuospatial abilities, including 2 or more tests in each domain, to overcome some of the limitations of previous studies. We explored the baseline neuropsychological characteristics of CN and MCI progressors and non-progressors and expected that memory and executive function domains would be the best predictors of progression (Chen et al., 2016; Garcia-Herranz et al., 2016; Huey et al., 2013). Additionally, to stablish the cognitive markers of progression, we explored, post hoc, which neuropsychological tests from the significant cognitive composites could predict cognitive classification (progressors and non-progressors). We did not make specific predictions about which tests would be identified

as cognitive markers of progression considering that the literature provides contradictory results from previous studies. Regarding ethnicity, we expected that category fluency would be a predictor of progression only among EA based on the findings of Weissberger et al. (2013). Finally, we predicted that there would be significant correlations between the cognitive markers of progression and two brain biomarkers of Alzheimer's Disease, Hippocampal (HP) volume and Entorhinal cortex (ERC) volume, as well as frontal lobe volume (lateral orbitofrontal, medial orbitofrontal, superior frontal, and rostral middle frontal volumes).

One important aspect of this study includes the investigation of cognitive markers of progression not only among MCI but also among CN individuals. This will contribute to the literature on the identification of those in the preclinical stages of AD and facilitate for a more objective assessment that can be both time and cost effective. Moreover, the investigation of two ethnic groups will contribute to the understanding of how ethnic differences, and their related social and behavioral factors, are related to cognitive decline and whether it is necessary to consider to use of different instruments in the assessment of minority groups. The inclusion of a large battery of tests in the analyses is also a strength of this study which allowed us to investigate multiple cognitive domains and increased the chance of identifying significant cognitive markers. Finally, we included the use of brain biomarkers which can support the relationship between the identified cognitive markers and Alzheimer's disease.

METHOD

Participants

Participants were recruited from the 1Florida Alzheimer's Disease Research Center (1Florida ADRC) at Mount Sinai Medical Center in Miami Beach, Florida and were native English or Spanish speakers. Each participant was required to have a close relative or caregiver that could participate as an informant, providing information about the subject's cognitive and functional performance in daily activities. Exclusion criteria included the presence of motor or sensory deficits, psychiatric disorders, low literacy levels (sixth grade or below), or those who were immigrants from countries other than Spanish-speaking Latin American countries, or whose ethnicity is not European American (EA) or Hispanic American (HA).

Participants who identified themselves as EA (n=XX) and HA (N=XX) were classified into 3 clinical groups (cognitively normal [CN], MCI, or dementia) based on the Clinical Dementia Rating Scale (CDR- Morris, 1993) global score (Global CDR score), following the procedure from Ganguli et al. (2018) so that we could use the neuropsychological baseline data as predictors of cognitive status trajectory. The Global CDR is based on the scores from 6 categories (memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care), where memory is considered the primary category. Each domain is independently rated on a 5-point scale. A global CDR score of 0 indicates normal cognition, a score of 0.5 indicates MCI, a score of 1 mild dementia, 2 moderate dementia, and 3 severe dementia (Ganguli

et al., 2018). Saxton et al. (2009) has found that the CDR diagnosis of MCI can be influenced by demographic (age and education), cognitive and clinical factors (diabetes and heart conditions). Therefore, for validity purposes, to assure that the groups differed in general cognition and daily functional abilities, which are the core aspects of the diagnosis of MCI and of dementia, we compared the 3 diagnostic groups (63 CN, 144 MCI, 45 dementia) on the Mini-mental State Examination (MMSE) score and the Functional Activities Questionnaire (FAQ) score after controlling for demographic variables that were significantly different between the groups. The three groups differed significantly on both the MMSE, F (2, 248) = 89.41, $p < .001$, $\eta_p^2 = .446$ and the FAQ, F (2, 240) = 83.71, $p < .001$, $\eta_p^2 = .418$. The dementia group had lower scores on the MMSE (M = 21.16, SE = .48) than the MCI group (M = 27.78, SE = .26) and the MCI group performed worse than the CN group (M = 28.96, SE = .40). FAQ scores were higher (worse performance) for the dementia group (M = 18.38, SE = 1.08) than the MCI group (M = 3.74, SE = .59), and the MCI group had greater scores than the CN group (M = 1.33, SE = .91). These findings confirmed the validity of the diagnostic categories because as expected the dementia group presented worse performance on the MMSE and the FAQ than the MCI group and the MCI group performed worse than the CN group. The dementia group was not included in our analyses of progression.

The baseline sample included 207 participants (63 CN, 144 MCI, 59.4% HA, 64.3% females). Baseline demographic and clinical characteristics of each ethnic and diagnostic group are shown in Table 1. As expected, diagnostic groups differed in global cognition (MMSE scores), with CN participants presenting a better performance than MCI participants, $p < .001$. The MCI group presented higher GDS scores than the CN

group, $p = .047$. The two ethnic groups were similar in age, MMSE, CDR scores, GDS scores, follow-up time, and female frequency. EA presented more years of education than HA, $p < .001$, but the ethnic groups did not differ in the other demographical and clinical characteristics. Among HA participants, 88 were bilinguals and 91 chose to the tested in Spanish, while the rest of the sample was tested in English. 75% ($n = 63$) of the EA sample and 66% ($n = 81$) of the HA sample received a diagnosis of MCI. The same analyses were repeated for the subsample of participants for which we have volumetric biomarkers. This subsample demonstrated the same pattern of results for the demographical and clinical variables (Table 1). Additionally, EA had significantly smaller HP, lateral OFC, and medial OFC volumes than HA and MCI participants had smaller HP, ERC and medial OFC volumes, $ps < .05$.

Materials

Participants completed a comprehensive neuropsychological battery which evaluated attention, memory, confrontation naming, visuospatial abilities, executive function, verbal fluency, and overall cognition. Cognitive tests included the Hopkins Verbal Learning Test-Revised (HVLT-R; Brandt, 1991); Logical Memory subtest of the Wechsler Memory Scale-Revised (WMS-R, Wechsler, 1987); Digit Span subtest from the Wechsler Adult Intelligence Scale (WAIS-IV; Wechsler, 2014a); Benson complex figure (delayed recall; Possin, Luluz, Alcantar, Miller, & Kramer, 2011); Category (animals, fruits, and vegetables) and Phonemic Fluency (F, A, and S; Benton & Hamsher, 1976); Block Design from the WAIS-IV (Wechsler, 2014a); Trail-Making Test B (TMT-B; Reitan & Wolfson, 1993); the Stroop Test (Stroop, 1935; Trenerry, Crosson, DeBoe, & Leber, 1989); and the Loewenstein-Acevedo Scales for Semantic Interference and

Learning (LASSI-L; Curiel et al, 2013). The Spanish evaluations used translated versions of the English tests and adapted with appropriate age, education, and language normative data (Acevedo et al., 2009; Arango-Lasprilla, Rivera, Aguayo, et al., 2015; Arango-Lasprilla, Rivera, Garza, et al., 2015; Gollan et al., 2012; Golden, 1999; Peña-Casanova et al., 2009; Pereiro et al., 2017; Wechsler, 2014b).

Hopkins Verbal Learning Test- HVLT

The HVLT (Brandt, 1991) consists of a 12-item word list, from which there are four words from each of three semantic categories (precious stones, 'human shelter', animals). The list is read to the participant and immediately the subject's free recall is recorded. This procedure is repeated for two more trials. The first three trial scores are averaged to form an immediate score. Then, after a delay period of 10 minutes, the participant is asked to freely recall the list of words one more time. Finally, a list of 24 words (12 from the original list, 6 related distractors, and 6 unrelated distractors) is read to the participant which is asked to identify is the word was or not on the original list by saying "yes" or "no". The HVLT-R has good test-retest reliability (Benedict et al., 1998) and demonstrated construct validity (Shapiro, Benedict, Schretlen, & Brandt, 1999). Additionally, it has been shown to have 87% sensitivity and 98% specificity for dementia (Hogervorst et al., 2002).

Logical Memory subtest of the WMS-R

The Logical Memory subset of the WMS-R (Wechsler, 1987) is designed to measure episodic memory for verbal material. Two short stories are read to participants, and they are asked to retell each story from memory immediately after hearing it. After a delay period of 20 to 30 minutes, participants are asked to freely recall the stories and

respond “yes” or “no” to questions about both stories. This subtest has been shown to have high interrater reliability (McGuire & Batchelor, 2007).

Digit span subtest of the WAIS-IV

During the administration of the Digit Span subtest of the WAIS-IV (Wechsler, 2014a) participants are read a sequence of one-digit numbers (from 1 to 9; e.g., 7 – 4 - 9) and asked to repeat the sequence in the same order (digit span forward). Then, they are read a sequence of numbers and asked to repeat them in the reverse order (Digit Span Backwards). Two trials are administered for each span (sequence length ranging from 2 to 8) and two errors in a given span prompts the interruption of the task. This subtest has been shown to have high reliability for the digit span forward and low reliability for the digit span backward (de Paula, Malloy-Diniz & Romano-Silva, 2016).

Benson Complex Figure

The Benson Complex Figure test (Possin, Luluz, Alcantar, Miller, & Kramer, 2011) is a simplified version of the Rey-Osterrieth Complex Figure. The participant is asked to copy the complex figure to the best of their ability. When they are done, they are instructed to look at the figure for another 5 seconds to try to remember the design because they will be asked to draw it from memory later. After a delay period of 10 to 15 minutes, the participant is asked to draw the figure from memory. Eight elements of the figure are scored for accuracy and placement.

Category Fluency

Participants are instructed to name as many animals, fruits, and vegetables in 60 seconds per category. Incorrect words include proper names, numbers, repetitions, or words sharing similar roots. The sum of all 3 categories was used.

Phonemic Fluency

Participants were told to produce as many words as possible that started with the letters F, A, and S and were given 60 seconds to complete each task. They were instructed not to use proper names, numbers, and repetitions. The sum of all letters was used.

Block Design

This subtest of the WAIS-IV (Wechsler, 2014a) requires the participant to use blocks, which have two sides that are solid red, two sides that are solid white, and two sides that are half red and half white, to form figures like the pictures that are given to them in a stimulus book. The stimuli progressively increase in level of difficulty. Scoring takes into consideration accuracy and time to complete the task. There are time limits for each item and there are item for which the participant gets bonus points when able to conclude faster.

Trail Making Test (TMT)

During the TMT part A, participants are instructed to draw a line connecting 25 circles numbered from 1 to 25 as quickly as possible. In Part B, participants receive a paper with numbers and letters in circles and are asked to draw lines connecting the circles alternating between numbers and letters while maintaining numerical and alphabetic order (Reitan & Wolfson, 1986). Participants are allowed 150 s for part A and 300 s for part B and the score is based on time to complete the task. Studies have demonstrated high test-retest reliability for the TMT with intervals of 1 day or 1 month between assessments (Woods, Wyma, Herron, & Yund, 2015).

Stroop Color-Word Interference Test

The Stroop test (Stroop, 1935; Trenerry et al., 1989) is a measure of inhibitory control and interference and requires participants to inhibit reading a word (a color) while correctly identifying the ink color of the text. Participants completed color (C), word (W), and color-word conditions (CW) and were allowed 45 seconds for each task. Predicted CW scores were calculated with the following formula: (WxC)/(W+C). Subsequently, this value was subtracted from the CW score. Interference scores indicate the degree to which the participant can control interference. The Stroop CW has been widely used and is believed to have reasonable reliability and validity (MacLeod et al., 1991).

Loewenstein-Acevedo Scales for Semantic Interference and Learning (LASSI-L)

There are two lists of 15 words each, all of which are fruits, musical instruments, or articles of clothing which the participants are instructed to try to remember. The words are presented one at a time on cards and are read by the participants. Participants are made aware of the semantic categories, which helps facilitate and guide their learning. After the participant has read aloud all 15 words from the first list (List A), there is a free recall trial (A1 recall), followed by cued recall trials (A1 cued recall) for each of the three categories (i.e., fruits, musical instruments, and articles of clothing). List A is presented again, and an additional cued recall trial (A2 cued recall) for each category is conducted. Then, a second list (List B) from the same semantic categories is presented and is followed by a free recall trial (B1 recall) and one cued recall trial by category (B1 cued recall). Finally, List B is presented for a second time, followed by cued recall trials (B2 cued recall). Then, free recall (A2 recall) and cued recall trials of List A (A3 cued recall) are conducted. For each free recall trial, the participants are given 60 seconds, and are

allowed 20 seconds for each semantic category during cued recall trials. After 20 min, there is a delayed free recall of both lists. The LASSI-L has high sensitivity (87.9%) and specificity (91.5%) in determining aMCI (Crocco, Curiel, Acevedo, Czaia, & Loewenstein, 2014) in addition to high test–retest reliability (Loewenstein & Acevedo, 2005).

Procedure

Participants went through a clinician interview, a comprehensive neuropsychological battery, blood tests, and a short physical examination at each study visit. Some participants also underwent a brain MRI scanning at baseline. The current study will use data obtained during baseline and two follow-up evaluations.

MRI and volume

MRI scanning was done using a Siemens Skyra 3T MRI scanner. Brain parcellation was obtained utilizing a 3D T1-weighted sequence (MPRAGE) with 1.0 mm isotropic resolution. FreeSurfer Version 5.3 software (http://surfer.nmr.mgh.harvard.edu) was used (Loewenstein et al., 2017). Bilateral brain regions from MRI scans that are associated with AD (hippocampi and entorhinal cortex; Henneman et al., 2009; Leandrou et al., 2018) and frontal lobe volume that has been associated with EF and cognitive decline, namely the lateral and medial orbitofrontal cortex (OFC; Bryden & Roesch, 2015, Lerch et al., 2004). Additionally, as an exploratory analysis we included bilateral superior frontal and rostral middle frontal volumes. GMV measurements were corrected for total individual intracranial volume.

Data analyses.

All analyses were done using 2020 IBM® SPSS Statistics software (IBM Corp., Armonk, N.Y., USA) . We ran individual univariate analyses of variance (ANOVAs) to compare the diagnostic groups (CN and MCI) and the two ethnic groups on demographic variables (age and years of education), MMSE, global CDR, GDS total scores, and length of follow-up time, and a chi-square test to compare the groups on sex distribution.

To investigate the cognitive markers of progressors and non-progressors, we ran a factor analysis with the cognitive measures to determine if the measures could be grouped as cognitive composite scores to be examined in subsequent analyses. First, we standardized to Z-scores each individual test score. Because the scores of TMT-A and TMT-B are the time taken to complete the tasks and greater scores reflect worse performance, these scores had to be corrected by multiplying them by -1. The factor analysis was conducted using the principal axis factoring selection with oblimin rotation including 13 cognitive measures, which yielded 3 composite scores. The decision on the number of factors was directly obtained from SPSS based on Eigenvalue greater than 1. Another factor was extracted separately from the LASSI-L recall measures. Since this is a new instrument that was developed based on the framework of a cognitive stress test, we decided to treat it separately from the other cognitive tests so we can examine its value in predicting cognitive status trajectory. Therefore, another factor analysis was performed including the LASSI-L's 9 recall measures, which yielded one composite score. The dementia group was included in the calculation of Z-scores and on the factor analyses to account for all of the variation in scores but was excluded from the remaining analyses which had the objective of analyzing progression.

Subsequently, we created a standardized composite score for each cognitive domain/factor by calculating the mean of all test scores within each domain.

Based on the stability of cognitive diagnosis throughout the follow-up, participants were classified as *CN non-progressors* or *MCI non-progressors* if they did not present a change in diagnosis between the first and the last visit. They were classified as *CN progressors* if they moved to MCI and/or dementia, and *MCI progressors* if they progressed to dementia. We compared progressors and non-progressors within each diagnostic group in baseline demographic and clinical characteristics using individual ANOVAs.

We also compared the stability/diagnosis groups (*CN progressors* and *CN non-progressors*, *MCI progressors* and *MCI non-progressors*) in the four cognitive composite scores using 2X2 ANCOVAs (2 ethnic groups and 2 stability/diagnosis groups) for CN and for MCI, controlling for age, education, sex, and length of follow-up time, if these were significantly different between the groups. Within the CN group, we did not have to control for any of these variables, but for the MCI group, we controlled for age and follow-up interval. Bonferroni corrections for multiple comparisons were done and the *p*-value was set to .006 (8 comparisons).

To establish the cognitive markers of progression, as a post hoc analysis, we ran a Binomial Logistic Regression entering as predictors each of the neuropsychological test scores from the cognitive composites that were significantly different between progressors and non-progressors in the previous analyses. The neuropsychological test scores were the independent variables and the classification as progressors or non-

progressors was the dependent variable. We ran separate regressions for each cognitive domain to limit the number of predictors entered.

Finally, we ran partial correlations between the significant cognitive markers of progression and brain biomarkers related to Alzheimer's disease (HP volume and ERC volume) and frontal lobe volumes (lateral OFC, medial OFC, superior frontal, and rostral middle frontal) controlling for the effects of age, gender, and education.

RESULTS

The Principal Axis Factor analysis of the cognitive measures yielded 3 factors with Eigenvalue greater than 1, explaining a total of 62.07% of the variance for the entire set of variables (structure matrix shown in Table 2; correlations between all tests are presented in Appendix A). Factor 1 was labeled executive functions due to the high loadings of the following tests : TMT-A, TMT-B, Stroop CW, Block design, category fluency, and phonemic fluency (FAS). This factor explained 44.61% of the variance. The second factor was labeled working memory due to the high loadings by the digit span forward, and the digit span backward tests, and explained 11.76% of the variance. The third factor, labeled immediate and delayed memory, had high loadings of the Benson figure delayed recall, logical memory immediate recall, logical memory delayed recall, HVLT immediate recall, and HVLT delayed recall. This factor explained 5.71% of the variance. Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy was .876 and Barlett's Test of Sphericity X^2 (78) = 1594.54, $p < .001$.

The second principal axis factor analysis included the 9 recall measures of the LASSI-L (correlations between all LASSI-L recall measures are presented in Appendix B). All the measures factored together (1 factor) and predicted 71.03% of the variance with factor loadings ranging from 0.77 to 0.89. Extraction communalities ranged from 0.59 to 0.80. Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy was .933 and Barlett's Test of Sphericity X^2 (36) = 2193.09, $p < .001$.

Means and standard deviations of the Z-scores from all cognitive measures are presented in Appendix C.

Univariate analyses of variance (ANOVAs) compared progressors and non-progressors among CN and MCI participants on demographic and clinical characteristics (Table 3). Within CN, the only variable that was significantly different across groups was the MMSE, which was higher for non-progressors than for progressors. Within MCI, age, MMSE, and length of follow-up were significantly different, where MCI progressors were older, had lower MMSE scores, and had a longer interval between the first and the last visit. Therefore, we entered age and follow-up interval as covariates in the next analyses for the MCI group. We did not enter the MMSE as a covariate considering that the cognitive composites under investigation are also affected by the cognitive deficits influencing performance in the MMSE.

2x2 ANOVAs were conducted to evaluate the effect of ethnicity and progression status on each of the composite scores, within CN participants (Table 4). The ANOVA with the EF composite as the dependent variable showed a significant main effect of ethnicity, F (1, 59) = 9.43, p = .003, but the main effect of progression status was not significant, p > .050. HA (M = .38, SD = .52) performed worse than EA (M = .68, SD = .42) in the EF composite. There was also a significant interaction between ethnicity and progression status, F (1, 59) = 4.41, p = .040, but this significance did not survive Bonferroni corrections for multiple comparisons (p-value = .006).

The ANOVA evaluating the effect of ethnicity and progression status on the WM composite score in the CN group yielded a significant main effect of ethnicity, F (1, 59) = 33.63, p < .001, but no significant main effect of progression status, p > .050.

Additionally, the interaction was not significant, $p > .050$. HA performed worse on WM ($M = -.25$, $SE = .12$) than EA ($M = 1.02$, $SE = .18$) regardless of progression status. The ANOVA with the immediate and delayed memory composite as the dependent variable showed a significant main effect of progression status, F (1, 59) = 9.25, $p = .004$, but no main effect of ethnicity, $p > .050$. The interaction between ethnicity and progression status was also not significant, $p > .05$. Progressors ($M = .40$, $SE = .14$) performed worse than non-progressors ($M = .90$, $SE = .08$) on their immediate and delayed memory composite scores, regardless of ethnicity. Finally, the ANOVA with the LASSI-L recall composite as the DV showed no significant main effect of ethnicity nor progression status, and no significant interaction between ethnicity and progression status, $ps > .050$, within the CN group.

Since within MCI participants, progressors and non-progressors differed in age and follow-up interval, those variables were entered as covariates in the ANCOVAs. Therefore, we ran 2x2 ANCOVAs with ethnicity and progression status as the IVs and each of the cognitive composite scores as the DV (Table 5). The ANCOVA with the EF composite as the DV showed a significant main effect of ethnicity, F (1, 138) = 6.64, $p = .011$, which however did not survive Bonferroni corrections for multiple comparisons with the p-value set to .006. There was a significant main effect of progression status, F (1, 138) = 29.11, $p < .001$. Progressors ($M = -.45$, $SE = .09$) had worse scores than non-progressors ($M = .16$, $SE = .04$) in executive function tasks. The interaction between ethnicity and progression status was not significant, $p > .050$.

The ANCOVA with the WM composite as the DV demonstrated a significant main effect of ethnicity, F (1, 137) = 28.80, $p < .001$, but no significant main effect of

progression status, $p > .050$. The interaction between ethnicity and progression status was also not significant, $p > .050$. HA ($M = -.36$, $SE = .11$) performed worse than EA ($M = .60$, $SE = .14$) regardless of progression status. Additionally, the ANCOVA with the immediate and delayed memory composite as the outcome variable had a significant main effect of progression status, F (1, 138) = 46.54, $p < .001$, but no significant main effect of ethnicity, $p > .050$. The interaction between ethnicity and progression status was also not significant, $p > .050$. Progressors ($M = -.73$, $SE = .19$) performed worse than non-progressors ($M = .17$, $SE = .05$) on immediate and delayed memory tasks independent from ethnicity. Finally, the ANCOVA with the LASSI-L recall composite as the DV demonstrated a significant main effect of progression status, F (1, 136) = 35.72, $p < .001$, but no significant main effect of ethnicity, $p > .050$. The interaction between ethnicity and progression status was not significant, $p > .050$. Progressors ($M = .49$, $SE = .16$) performed worse than non-progressors ($M = .79$, $SE = .09$) on the LASSI-L composite regardless of ethnicity.

To establish the cognitive markers of progression, as a post hoc analysis, we ran a Binomial Logistic Regression entering the tests from the immediate and delayed memory composite as predictors of the classification as a progressor or non-progressor within the CN group. Additionally, we ran HierarchicalBinomial Logistic Regressions entering the tests from the immediate and delayed memory composite, the EF tests, and the LASSI-L recall measures as predictors of progression in step 1 and entering age and length of follow-up time in step 2, within the MCI group (Table 6). Age and follow-up time were entered into the models with the MCI group because these variables were significantly different between progressors and non-progressors with this diagnosis (Table 3) and

because these variables are important for cognitive decline. We wanted to see if, after adding these variables to the model, the contributions of the cognitive tests would remain. The binomial logistic regression within the CN group was significant, X^2 (5) = 15.49, p = .008, and the model was able to correctly classify 80.7% of the participants. Its classification accuracy was better for non-progressors (90.5% correct) than for progressors (53.3% correct), but the classification of both groups was better than chance. The only predictor that significantly added to accuracy to this model was the Benson figure delayed recall, p = .035. Upon consideration that the full model -2 log-likelihood was 50.22 no model difficulties were seen. The model with the immediate and delayed memory tests as predictors of progression within MCI was significant for step 1, X^2 (5) = 52.32, p < .001, and the Benson figure delayed recall and the HVLT total immediate recall were the only predictors that added accuracy to the model, *ps* < .050. This model was able to correctly classify 82.6% of participants. After adding age and follow-up interval in step 2, the model was still significant, X^2 (2) = 59.03, p < .001, and its classification accuracy for the whole model increased by about two percent (84.8%); 91.4% of non-progressors were correctly classified and 59.3% of progressors were correctly classified. The classification accuracy for both groups was better than chance. The full model -2 log likelihood was 74.73, therefore, no model difficulties were observed. The Benson Figure delayed recall, the HVLT immediate recall, and follow-up interval were the predictors that added accuracy to the model. The model with the EF tests as predictors of progression within MCI participants was significant in step 1, X^2 (6) = 42.00, p < .001, and the TMT- B, the Block design test, and the category fluency predictors that added accuracy to the model, *ps* < .050. This model correctly classified

86.3% of participants. After the inclusion of age and follow-up time in step 2, however, the model remained significant, X^2 (8) = 44.08, p < .001, and TMT-B and category fluency remained as predictors that added accuracy to the model. Block design was no longer a significant predictor in step 2, and the classification accuracy of the model was 87% (about the same as in step1); correctly classifying 95.4% of non-progressors and 47.8% of progressors (significantly less than chance). No model difficulties were observed given that the full model -2 log-likelihood was 77.65. Finally, the model with the LASSI-L recall measures as the predictors of progression was significant, X^2 (9) = 63.84, p < .001, and the only significant predictor was the LASSI delayed recall, p = .002. This model was able to correctly classify 87.3% of participants. After the inclusion of age and follow-up interval in step 2, the model remained significant, X^2 (11) = 76.90, p < .001, and three recall measures of the LASSI were significant predictors (A1 cued recall, A2 cued recall, and delayed recall). The full model -2 log-likelihood was 74.30, therefore, no model difficulties were seen. The model in step 2 was able to correctly classify 91.5% of participants, an improvement of about 5%; correctly classifying 96.5% of non-progressors, and 70.4% of progressors (classification of both groups is better than chance).

We ran partial correlations between the cognitive markers of progression within each baseline diagnostic group and brain volumetric biomarkers, controlling for age, education, and sex. Within the CN group we examined the Benson delayed recall and observed that it was not significantly correlated with ERC volume, r (51) = .14, p = .336, HP volume, r (51) = -.01, p = .973, lateral orbitofrontal r (51) = .07, p = .646, medial orbitofrontal volume, r (51) = .14, p = .317, superior frontal volume, r (51) = .19, p =

.164, and rostral middle frontal volume, r (51) = .05, p = .733. Within the MCI group, the Benson delayed recall was significantly positively correlated with HP and ERC volumes but did not correlate with frontal volumes (Table 7). The HVLT immediate recall was significantly positively correlated with HP, ERC and superior frontal volumes. TMT-B was significantly positively correlated with the superior frontal volume and the category fluency test was significantly positively correlated with the HP and ERC volumes. The LASSI A1 cued recall was positively correlated with ERC volume, while the LASSI A2 cured recall was positively correlated with HP, ERC and superior frontal volumes. Lastly, the LASSI delayed recall was positively correlated with HP volume (Table 7).

DISCUSSION

The major goal of this study was to identify cognitive markers of progression to dementia among CN and MCI participants. For this, we investigated four cognitive composite scores (executive function, working memory, immediate and delayed memory, and the LASSI-L recall composite) and further explored the predictive capacity of individual tests within the domains that were significantly different between progressors and non-progressors. Based on previous findings, we expected that the memory and the EF domains would be the best predictors of progression (Chen et al., 2016; Garcia-Herranz et al., 2016; Huey et al., 2013), however, we did not make predictions regarding specific tests because of the contradictory findings presented in the literature, especially regarding list learning tests (Garcia-Herranz et al., 2016; Perri et al., 2007; Chen et al., 2017) and category and phonemic fluencies (Chen et al., 2017; Huey et al., 2013). We further explored whether the cognitive markers of progression would be the same across the two studied ethnic groups, European Americans and Hispanic Americans. Finally, we anticipated that the cognitive markers of progression would be correlated with biomarkers of AD (HP and ERC volumes) and frontal volumes (lateral OFC, medial OFC, superior frontal, and rostral middle frontal volumes).

Our sample included CN and MCI individuals at baseline that were followed for an average of 23.5 months (*SD* = 7.09). The diagnostic groups presented differences in MMSE scores and GDS scores where MCI participants were more impaired on overall cognition and presented more symptoms of depression. Additionally, MCI participants

presented smaller volumes in the HP, ERC, and medial OFC. The EA group was more highly educated and, congruent with previous studies, presented smaller HP (DeCarli et al., 2008; Zahodne et al., 2015; Burke et al., 2018), lateral OFC, and medial OFC volumes. Furthermore, the comparison between progressors and non-progressors demonstrated that progressors had worse performance on the MMSE, and within MCI, progressors were older and had a longer follow-up interval. Among CN individuals, the EA group performed better than HA on the EF composite and on the WM composite, but no ethnic differences were observed on the immediate and delayed memory composite and on the LASSI-L recall composite.

CN progressors performed worse on the immediate and delayed memory composite than non-progressors. More specifically, the Benson delayed recall the only test that added to the accuracy in the identification of progressors classifying about 81% of CN participants as progressors or not and is suggested as a cognitive marker within this diagnostic group. The model was better at classifying non-progressors, although the classification of progressors was better than chance. This result contradicts the findings of Chen et al. (2017) whofound memory as a predictor of progression to MCI in CN individuals, but different from our study they only included verbal memory measures in their analyses. Additionally, in contrast with our results, they observed their EF composite to be predictive of cognitive decline. However, the neuropsychological tests used in the EF composite scores were different across studies. Category and phonemic fluencies were part of the EF composite in both studies, but Chen et al. (2017) also included one working memory task, while we included the TMT-A, TMT-B, Stroop CW, and block design. Moreover, although the Benson delayed recall was a good measure to

identify those who will not present cognitive decline among individuals with normal cognition, we did not observe correlations with brain biomarkers of AD. We had anticipated that these correlations would be significant, however, this result is in line with the findings from our previous study (Arruda et al., submitted) in which HP and ERC atrophy were not significant predictors of progression within CN participants, only within MCI individuals.

MCI progressors presented worse performance in the EF composite, the immediate and delayed memory composite, and the LASSI-L composite but did not differ from non-progressors in the working memory composite. The Benson delayed recall, the HVLT immediate recall, the TMT-B, category fluency, and three measures of the LASSI-L (A1 cued recall, A2 cued recall, and delayed recall) were the predictors that added accuracy to the identification of progressors s to dementia and are suggested as cognitive markers of progression for MCI individuals.

In our study, the Benson delayed recall was a significant predictor of progression among CN and MCI individuals. Most studies do not include a measure of visual memory however, Cerbone et al. (2020) utilized the visual reproduction I and II subtests and the logical memory subtest of the WMS-R and found that the greater the number of impaired memory tests the greater the risk for progression among MCI individuals. Their study, however, investigated the predictive capacity of their memory composite and not each test individually.

Some studies have investigated the learning curve in list-learning tests and found that MCI progressors had more impaired learning curve than non-progressors (Perri et al., 2007) and that stable aMCI had a reduced learning curve compared to stable non-

amnestic MCI and recovered MCI (Klekociuk & Summers, 2014). The HVLT immediate recall, which was a significant predictor of progression in our study, is an average of three learning trials, which can be interpreted as being similar to a learning curve. Therefore, our result regarding the HVLT is congruent with the literature. Moreover, while most list learning tests are extensive and complex, the HVLT is a brief, reliable, and easy to administer memory test (Hogervorst et al., 2002).

Additionally, the EF cognitive markers of progression (TMT-B and category fluency) were able to correctly classify 87% of MCI participants. This model however was only significant for the classification of non-progressors (95% accuracy). Previous studies have yielded inconclusive results regarding the contribution of EF deficits to progression among MCI individuals. Worse performance on an EF composite score including category fluency, phonemic fluency, and the Similarities subtest of the WAIS-R among MCI without memory deficits (dMCI) was not found to increase the risk of progression to dementia (Huey et al., 2013). However, Cerbone et al. (2020) observed that worse EF performance, as measured by the TMT-B, the Stroop CW, the Stroop color inhibition condition, phonemic fluency, digit span backwards, and Similarities in aMCI, was associated with a higher risk of further cognitive decline. Therefore, the difference in results observed in these previous studies might be related to the presence or absence of a memory deficit in conjunction with the EF deficit. Because we diagnosed participants based on the CDR global score we did not classify participants based on MCI subtypes and it is possible that most of our MCI sample is, in fact, aMCI, in which case our results would corroborate the findings from Cerbone et al. (2020).

The A1 cued recall, A2 cued recall, and the delayed recall measures of the LASSI-L were cognitive markers of progression among MCI participants. Previously, the LASSI-L's percentage of intrusion errors has been found to be a good predictor of pre-MCI, which is a subset of cognitively normal participants, who progressed to dementia (Crocco et al., 2021). Therefore, our results add to the literature demonstrating the contribution of this memory test in distinguishing those at higher risk of progression not only among CN but also among MCI individuals. The three LASSI-L markers, together with follow-up interval, were able to correctly classify 91.5% of MCI participants as progressors or not, compared to 84.8% classification accuracy of the Benson delayed and the HVLT immediate recall with follow-up time. Moreover, The LASSI-L model had a high classification accuracy of non-progressors (97%) and of progressors (70%).

Among the MCI cognitive markers of progression, the Benson delayed and the HVLT immediate recall were significantly correlated with HP and ERC volumes, which is consistent with the literature considering the role of the medial temporal lobes in memory (Choi et al., 2016; Olsen et al., 2017). Moreover, the LASSI A2 cued recall marker correlated with both measures of volume in the medial temporal lobe and with the superior frontal volume, which can be understood considering that during this task the participant is required to recall the list of words according to the categories that are given, which requires inhibition of the words from the remaining categories (an executive function component of the task). Additionally, category fluency also correlated with HP and ERC volumes suggesting the importance of memory for the execution of this task. Finally, TMT-B, which is a measure of executive function, namely set shifting, was correlated with superior frontal volume.

Although we observed some performance differences across ethnic groups (e.g., within CN participants, EA performed better in the EF composite and in the WM composite; within MCI, EA performed better in the WM composite), we did not identify significant interactions between ethnicity and progression status. Therefore, we did not observe the need to investigate different cognitive markers of progression across ethnic groups. Weissberger et al. (2013) identified common cognitive markers of progression between Hispanics and non-Hispanics and specific markers for each ethnic group. For Hispanics, they observed that the cognitive markers were the number of errors on the TMT-A and TMT-B and the non-perseverative errors on the WCST, which were measures that we did not analyze in this study. Among non-Hispanics they found the vocabulary subtest of the WAIS-R (not included in our study) and the category fluency to be predictive of progression. It is possible that the tests used in our neuropsychological battery are more adequate for both ethnic groups studied, however there were major differences between our study and Weissbeger et al's regarding sample and methodology. They had a smaller CN sample of which all progressed to dementia while we had a larger sample and were able to compare progressors and non-progressors.

In our sample, EA performed better than HA on digit span forward and backwards, category fluency, and on phonemic fluency. These are all verbal measures that have been previously documented to suffer from the influence of bilingualism (and the majority of the HA sample is bilingual), which has been associated with disadvantages on verbal tests (e.g., fluency tests; Gollan, Montoya, & Werner, 2002; Lehtonen et al., 2018). This effect may be due to increased linguistic interference between languages (Rosselli et al., 2000).

Some limitations should be taken into consideration when examining our results. First, the diagnosis was given based on the CDR-global score alone to allow for us to utilize the neuropsychological data as predictors of progression. Additionally, some of our subgroups consisted of a small number of participants (e.g., 17 CN progressors, 27 MCI progressors) which signals that we should examine our results with caution and pushes for further studies which can replicate and expand on our current findings. Furthermore, since this is an on-going longitudinal study, it will be important to replicate this study once we have data with a longer follow-up interval considering that some of non-progressors in our sample might still progress in the long run.

In summary, the findings from this study contribute to literature on the early identification of individuals at risk of progression to a more severe cognitive status among CN and MCI participants. We identified one cognitive marker of non-progressors among CN participants (Benson delayed recall). Although our aim was to identify cognitive markers of progression, being able to identify individuals who will likely not progress to a more severe cognitive diagnosis is also important. . We further identified 7 cognitive markers of progression (Benson delayed recall, HVLT delayed recall, TMT-B, category fluency, LASSI A1 cued recall, LASSI A2 cued recall, and LASSI delayed recall) within the MCI group. These results are very promising given the high classification accuracy of the models tested (using combinations of these measures). The MCI group is very heterogenous among which part of the individuals revert to normal cognition, some progress to dementia, and the majority remains stable (Malek-Ahmadi, 2016; Mitchell & Shiri-Feshki, 2009). Therefore, being able to distinguish between MCI progressors and non-progressors with a single time-point assessment contributes to a

more time- and cost-effective practice which will benefit both research and clinical practice (Klekociuk & Summers, 2014), being essential to the provision of the appropriate treatment to those at higher risk of progression to dementia.

TABLES

Table 1

Baseline demographic and clinical characteristics by ethnic group of the total sample and the subsample with biomarkers

H	EA M (SD)	HA M (SD)	Total M (SD)	*F*	*p*	η_p^2	CN M (SD)	MCI M (SD)	*F*	*p*	η_p^2
	n = 84	*n* = 123	*N* = 207				*n* = 63	*n* = 144			
Age	72.8 (8.46)	71.07 (6.67)	71.79 (7.48)	2.83	.094	.014	70.33 (6.34)	72.43 (7.86)	3.49	.063	.017
Education	16.50 (2.90)	14.72 (3.68)	15.44 (3.49)	13.73	<.001	.063	16.05 (3.19)	15.18 (3.62)	2.73	.100	.013
MMSE	28.43 (2.10)	28.00 (2.27)	28.17 (2.21)	1.89	.171	.009	29.05 (1.34)	27.79 (2.40)	15.16	<.001	.069
CDR	.38 (.22)	.33 (.24)	.35 (.23)	1.97	.162	.010	.00 (.00)	.50 (.00)	-	-	-
GDS*	2.10 (2.42)	2.14 (2.22)	2.13 (2.30)	.020	.888	.000	1.64 (2.04)	2.34 (2.38)	3.98	.047	.020
Length of follow-up (months)	22.44 (6.46)	23.46 (7.49)	23.05 (7.09)	1.04	.309	.005	24.51 (7.38)	22.41 (6.89)	3.89	.050	.019
				X^2	*p*				X^2	*p*	
Female frequency	50 (59.5%)	83 (67.5%)	133 (64.3%)	1.38	.241		45 (71.4%)	88 (61.1%)	2.03	.154	

Subsample with volumetric biomarkers

	EA M (SD)	HA M (SD)	Total M (SD)	*F*	*p*	η_p^2	CN M (SD)	MCI M (SD)	*F*	*p*	η_p^2
	n = 78	*n* = 114	*N* = 192				*n* = 61	*n* = 131			
Age	72.17 (7.96)	71.13 (6.70)	71.55 (7.24)	.947	.332	.005	70.39 (6.38)	72.09 (7.57)	2.31	.131	.012
Education	16.71 (2.87)	14.77 (3.55)	15.56 (3.42)	16.01	< .001	.078	16.08 (3.12)	15.31 (3.53)	2.12	.147	.011
MMSE	28.42 (2.16)	28.05 (2.28)	28.20 (2.23)	1.28	.260	.007	29.05 (1.35)	27.81 (2.45)	13.68	<.001	.067
CDR	.37 (.22)	.33 (.24)	.34 (.23)	1.42	.235	.007	.00 (.00)	.50 (.00)	-	-	-

GDS*	2.16 (2.48)	2.18 (2.23)	2.17 (2.33)	.005	.942	.000	1.59 (1.98)	2.44 (2.44)	5.50	.020	.029
HP volume	.0047	.0050	.0049	11.23	<.001	.056	.0052	.0048	14.79	<.001	.072
	(.0006)	(.0006)	(.0006)				(.0006)	(.0006)			
ERC volume	.0023	.0024	.0024	2.61	.108	.014	.0025	.0023	4.97	.027	.025
	(.0004)	(.0005)	(.0004)				(.0004)	(.0004)			
Lateral OFC volume	.0092	.0095	.0094	7.08	.008	.036	.0095	.0093	1.99	.160	.010
	(.0010)	(.0009)	(.0010)				(.0010)	(.0010)			
Medial OFC volume	.0064	.0066	.0065	4.12	.004	.021	.0067	.0064	4.37	.038	.022
	(.0008)	(.0007)	(.0007)				(.0007)	(.0007)			
Superior Frontal	.0244	.0251	.0248	2.73	.100	.014	.0250	.0248	.40	.528	.002
Volume	(.0029)	(.0025)	(.0027)				(.0025)	(.0028)			
Rostral middlefrontal	.0171	.0173	.0173	.60	.439	.003	.0177	.0171	3.82	.052	.020
volume	(.0022)	(.0019)	(.0020)				(.0020)	(.0020)			
Female frequency	47 (60.3%)	78 (68.4%)	125 (65.1%)	1.36	.244		45 (73.8%)	80 (61.1%)	2.96	.086	

Note. EA = European Americans; HA = Hispanic Americans; CDR = Clinical Dementia Rating Scale; GDS = Geriatric Depression Scale; MMSE = Mini Mental Status Examination; HP = Hippocampus; ERC = entorhinal cortex; OFC = orbitofrontal cortex; *GDS scores were missing for 7 cases, 5 were HA and 2 were EA.

Table 2

Principal Axis Factoring: Obtained Factors and Variable Loadings (Structure Matrix)

	Composites			
	Executive Function	Working Memory	Immediate and delayed Memory	Extraction Communalities
Trail Making Test- A	0.78	0.31	-0.47	0.61
Trail Making Test- B	0.83	0.38	-0.54	0.69
Stroop Color-word	0.73	-0.27	0.36	0.55
Block Design	0.60	-0.36	0.36	0.38
Category Fluency	0.74	-0.30	0.65	0.63
Phonemic Fluency	0.62	-0.44	0.35	0.43
Digit Span Forward	0.30	-0.90	0.08	0.82
Digit Span Backward	0.48	-0.74	0.24	0.58
Benson Figure Recall	0.51	-0.22	0.72	0.54
Logical Memory Immediate	0.49	-0.08	0.89	0.80
Logical Memory Delay	0.45	-0.14	0.96	0.94
HVLT Immediate Recall	0.72	-0.22	0.75	0.69
HVLT Delayed Recall	0.52	-0.14	0.61	0.42

Table 3

Baseline demographic and clinical characteristics of cognitively normal (CN) and MCI progressors and non-progressors

		Non-progressors M (SD)	Progressors M (SD)	Total M (SD)	*F*	*p*	η_p^2
		n = 46	*n* = 17	*N* = 63			
	Age	70.30 (7.00)	70.41 (4.37)	70.33 (6.34)	.004	.953	.000
	Education	16.35 (2.86)	15.24 (3.70)	16.05 (3.12)	1.60	.211	.025
	MMSE	29.30 (.94)	28.35 (1.94)	29.05 (1.34)	6.88	.011	.101
Cognitively Normal	CDR	.00 (.00)	.00 (.00)	.00 (.00)	-	-	-
	GDS*	1.50 (2.11)	2.00 (1.87)	1.64 (2.04)	.732	.396	.012
	Length of follow-up (months)	24.41 (7.48)	24.76 (7.31)	24.51 (7.38)	.028	.868	.000
					X^2	*p*	
	Female frequency	32 (69.6%)	13 (76.5%)	45 (71.4%)	.29	.590	
	HA frequency	30 (65.2%)	12 (70.6%)	42 (66.7%)	.16	.688	

		Non-progressors M (SD)	Progressors M (SD)	Total M (SD)	*F*	*p*	η_p^2
		n = 117	*n* = 27	*N* = 144			
	Age	71.64 (7.25)	75.85 (9.49)	72.43 (7.86)	6.54	.012	.044
	Education	15.26 (3.62)	14.81 (3.67)	15.18 (3.62)	.34	.562	.002

MCI	MMSE	28.37 (1.77)	25.30 (3.11)	27.79 (2.40)	47.64	<.001	.251
	CDR	.50 (.00)	.50 (.00)	.50 (.00)	-	-	-
	GDS*	2.19 (2.21)	2.96 (2.93)	2.34 (3.38)	2.34	.128	.017
	Length of follow-up (months)	21.70 (6.62)	25.48 (7.33)	22.41 (6.89)	6.87	.010	.046
					X^2	p	
	Female frequency	71 (60.7%)	17 (63.0%)	88 (61.1%)	.48	.827	
	HA frequency	65 (55.6%)	16 (59.3%)	81 (56.3%)	.12	.727	

Note. EA = European Americans; HA = Hispanic Americans; CDR = Clinical Dementia Rating Scale; GDS = Geriatric Depression Scale; MMSE = Mini Mental Status Examination; MCI = mild cognitive impairment

Table 4

Means, Standard deviations, and Univariate Analyses of Variance for differences in each cognitive composite scores by Ethnicity and Progression status among CN participants.

		EA *n* = 21	HA *n* = 42	Total *N* = 63					
		Mean (SD)	Mean (SD)	Mean (SD)		*F*	*df*	*p*	η_p^2
EF composite	Progressors (*n* = 17)	.79 (.46)	.05 (.73)	.26 (.74)	Ethnicity	9.43	1, 59	.003	.138
	Non-progressors (*n* = 46)	.65 (.42)	.51 (.34)	.56 (.37)	Progression status	1.29	1, 59	.260	.021
	Total	.68 (.42)	.38 (.52)	.48 (.51)	Ethnicity*Progression Status	4.41	1, 59	.040	.070
WM composite	Progressors (*n* = 17)	1.08 (.81)	.09 (.85)	.19 (.90)	Ethnicity	33.63	1, 59	<.001	.363
	Non-progressors (*n* = 46)	.97 (.91)	-.16 (.66)	.23 (.93)	Progression status	.01	1, 59	.911	.000
	Total	.99 (.87)	-.21 (.60)	.19 (.90)	Ethnicity*Progression Status	.39	1, 59	.535	.007
Immediate and delayed Memory composite	Progressors (*n* = 17)	.41 (.54)	. 39 (.64)	.40 (.60)	Ethnicity	1.45	1, 59	.233	.024
	Non-progressors (*n* = 46)	1.09 (.47)	.71 (.52)	.84 (.53)	Progression status	9.25	1, 59	.004	.135
	Total	.94 (.56)	.62 (.57)	.72 (.58)	Ethnicity*Progression Status	1.27	1, 59	.265	.021
LASSI-L	Progressors (*n* = 17)	.61 (.70)	.37 (.62)	.44 (.63)	Ethnicity	2.53	1, 59	.117	.041
	Non-progressors	.96 (.67)	.61 (.52)	.73 (.59)	Progression status	2.62	1, 59	.111	.042

composite	(*n* = 46) Total	.88 (.68)	.54 (.55)	.65 (.61)	Ethnicity*Progression Status	.09	1, 59	.763	.002

Note. CN = cognitively normal, EA = European Americans; HA = Hispanic Americans; EF = executive function; WM = working memory; LASSI-L = Loewenstein-Acevedo Scales for Semantic Interference and Learning.

Table 5

Means, Standard deviations, and Univariate Analyses of Covariance for differences in each cognitive composite scores by Ethnicity and Progression status among MCI participants.

		EA *n* = 63	HA *n* = 81	Total *N* = 144					
		Mean (SD)	Mean (SD)	Mean (SD)		*F*	*df*	*p*	η_p^2
EF composite	Progressors (*n* = 27)	-.39 (.56)	-.49 (.44)	-.45 (.48)	Age	17.99	1, 138	<.001	.115
					Follow-up interval	2.95	1, 138	.088	.021
					Ethnicity	6.64	1, 138	.011	.046
	Non-progressors (*n* = 117)	.32 (.46)	.04 (.48)	.16 (.49)	Progression status	29.11	1, 138	<.001	.174
	Total	.19 (.55)	-.06 (.52)	.05 (.54)	Ethnicity*Progression Status	.099	1, 138	.753	.001
WM composite	Progressors (*n* = 27)	.49 (1.01)	-.56 (.89)	-.13 (1.06)	Age	9.22	1, 137	.003	.063
					Follow-up interval	.016	1, 137	.899	.000
					Ethnicity	28.80	1, 137	<.001	.174
	Non-progressors (*n* = 117)	.50 (.82)	-.15 (.78)	.14 (.86)	Progression status	.152	1, 137	.698	.001
	Total	.50 (.85)	-.23 (.82)	.09 (.91)	Ethnicity*Progression Status	2.71	1, 137	.102	.019
Immediate and delayed Memory	Progressors (*n* = 27)	-.58 (.68)	-.90 (.56)	-.77 (.62)	Age	4.90	1, 138	.028	.034
					Follow-up interval	3.83	1, 138	.052	.027
					Ethnicity	1.88	1, 138	.173	.013
	Non-progressors (*n* = 117)	.15 (.70)	.18 (.48)	.17 (.58)	Progression status	46.54	1, 138	<.001	.252

composite	Total	.03 (.74)	-.03 (.65)	-.01 (.69)	Ethnicity*Progression Status	2.17	1, 138	.143	.015
	Progressors (n = 27)	-.79 (.56)	-.77 (.70)	-.78 (.63)	Age	12.73	1, 136	<.001	.086
					Follow-up interval	.11	1, 136	.746	.001
LASSI-L	Non-				Ethnicity	1.48	1, 136	.226	.011
recall	progressors	.27 (.75)	.11 (.57)	.18 (.66)	Progression status	35.72	1, 136	<.001	.208
composite	(n = 117)								
	Total	.08 (.82)	-.07 (.69)	-.01 (.75)	Ethnicity*Progression Status	.002	1, 136	.968	.000

Note. MCI = mild cognitive impairment; EA = European Americans; HA = Hispanic Americans; EF = executive function; WM = working memory; LASSI-L = Loewenstein-Acevedo Scales for Semantic Interference and Learning.

Table 6

Binomial logistic regression analyses with cognitive tests predicting "progressors vs. non-progressors"

			B	*SE B*	Wald	*p*	*OR*	95% CI *OR*	*Model* X^2	*p*
CN (n = 57)*		Benson delayed recall	-1.27	.60	4.43	.035	.28	.087 –.916	15.49	.008
		Logical Memory Immediate	1.26	1.17	1.18	.277	3.54	.362 – 34.741		
Immediate and delayed Memory tests		Logical Memory delayed	-1.01	1.19	.71	.400	.37	.035 – 3.796		
		HVLT immediate	-.99	.66	2.26	.132	.37	.104 – 1.347		
		HVLT delayed	-.25	.54	.21	.647	.78	.272 – 2.244		
MCI (n = 132)**	Step 1	Benson delayed recall	-1.01	.46	4.85	.028	.37	.150 –.896	52.32	< .001
		Logical Memory Immediate	-.30	.69	.19	.660	.74	.191 – 2.85		
		Logical Memory delayed	-.18	.79	.05	.816	.83	.178 – 3.892		
		HVLT immediate	-1.56	.64	5.93	.015	.21	.060 –.738		
		HVLT delayed	.60	.48	1.56	.212	1.81	.712 – 4.622		
Immediate and delayed Memory Tests	Step 2	Benson delayed recall	-1.21	.51	5.60	.018	.30	.109 - .812	59.03	<.001
		Logical Memory Immediate	-.62	.75	.70	.40	.54	.124 – 2.310		
		Logical Memory delayed	.13	.83	.03	.87	1.14	.225 – 5.786		
		HVLT immediate	-1.37	.65	4.47	.03	.25	.07 - .90		
		HVLT delayed	.46	.50	.84	.36	1.58	.59 – 4.22		
		Age	.01	.04	.08	.78	1.01	.94 – 1.10		

		Follow-up interval	.11	.05	5.21	.02	1.12	1.02 – 1.24		
MCI (n = 131)*** Executive Function tests	Step 1	TMT- A	-.65	1.02	.41	.524	.52	.070 – 3.864	42.00	<.001
		TMT-B	-1.19	.49	5.97	.015	.30	.116 –.790		
		Stroop CW	-.65	.45	2.04	.153	.52	.216 – 1.271		
		Block design	.86	.42	4.25	.039	2.36	1.043 – 5.342		
		Category Fluency	-1.24	.43	8.23	.004	.29	.125 –.676		
		Phonemic Fluency	.38	.39	.943	.332	1.46	.682 – 3.115		
	Step 2	TMT- A	-.338	1.09	.10	.756	.71	.085 – 6.010	44.08	<.001
		TMT-B	-1.25	.51	6.09	.014	.29	.107 - .774		
		Stroop CW	-.71	.47	2.27	.132	.49	.197 – 1.236		
		Block design	.83	.43	3.67	.055	2.29	.981 – 5.359		
		Category Fluency	-1.21	.44	7.51	.006	.30	.125 - .708		
		Phonemic Fluency	.30	.40	.55	.457	1.34	.617 – 2.924		
		Age	.01	.04	.11	.744	1.01	.935 – 1.099		
		Follow-up interval	.06	.04	1.71	.191	1.06	.972 – 1.151		
MCI (n = 142)*** LASSI-I Recall	Step 1	A1 recall	-.79	.56	1.98	.160	.46	.153 – 1.361	63.84	<.001
		A1 cued recall	.80	.63	1.61	.206	2.23	.645 – 7.680		
		A2 cued recall	-1.01	.75	1.79	.181	.37	.084 – 1.598		
		B1 recall	-.73	.61	1.46	.23	.48	.146 – 1.579		
		B1 cued recall	.93	.69	1.81	.179	2.53	.653 – 9.783		
		B2 cued recall	-.83	.67	1.57	.211	.43	.118 – 1.603		
		A2 recall	-.26	.51	.26	.610	.77	.286 – 2.086		
		A3 cued recall	.69	.57	1.48	.223	2.00	.656 – 6.071		
		Delayed recall	-1.43	.47	9.48	.002	.238	.096 –.594		
	Step 2	A1 recall	-.81	.71	1.31	.253	.45	.111 – 1.784	76.90	<.001
		A1 cued recall	1.87	.88	4.50	.034	6.48	1.154 – 36.397		

measures		A2 cued recall	-2.10	.97	4.70	.030	.12	.018 - .818
		B1 recall	-.63	.65	.94	.333	.53	.149 – 1.904
		B1 cued recall	1.40	.81	3.03	.082	4.06	.837 – 19.642
	Step2	B2 cued recall	-1.39	.75	3.42	.064	.25	.058 – 1.086
		A2 recall	-.79	.58	1.85	.173	.45	.146 – 1.415
		A3 cued recall	1.19	.67	3.13	.077	3.29	.880 – 12.324
		Delayed recall	-1.77	.60	8.84	.003	.17	.053 - .546
		Age	.01	.05	.08	.780	1.01	.921 – 1.116
		Follow-up interval	.22	.08	8.25	.004	1.25	1.073 – 1.450

Note. CN = cognitively normal; MCI = mild cognitive impairment; HVLT = Hopkins Verbal Learning Test; TMT = trail making test; LASSI-L = Loewenstein-Acevedo Scales for Semantic Interference and Learning; * 6 participants were missing test scores; ** 12 participants were missing test scores; *** 13 participants missing test scores; **** 2 cases missing test scores.

Table 7

Partial correlations between cognitive markers of progression and volumetric biomarkers, controlling for age, education, and sex for the MCI group (n = 117).

	Benson delayed recall	HVLT immediate recall	TMT-B	Category Fluency	LASSI A1 cued recall	LASSI A2 cued recall	LASSI delayed recall	HP volume	ERC volume	Lateral OFC volume	Medial OFC volume	Superior Frontal volume	Rostral middlefrontal volume
Benson delayed recall	1	.52****	.35****	.41****	.39****	.58****	.55****	.34****	.37****	-.01	.11	.13	.04
HVLT immediate recall	-	1	.42****	.52****	.58****	.64****	.62****	.28***	.28***	.06	.18	.22*	.14
TMT-B	-	-	1	.45****	.35****	.45****	.50****	.13	.18	.01	.08	.28***	.12
Category Fluency	-	-	-	1	.50****	.65****	.53****	.36****	.31****	.11	.12	.14	.12
LASSI A1 cued recall	-	-	-	-	1	.80****	.64****	.08	.20*	-.04	.10	.20	.03
LASSI A2 cued recall	-	-	-	-	-	1	.73****	.33****	.31****	.09	.17	.33****	.07
LASSI-L delayed recall	-	-	-	-	-	-	1	.22*	.10	-.04	.04	.17	.13
HP volume	-	-	-	-	-	-	-	1	.43****	.39****	.40****	.33****	.09

ERC volume	-	-	-	-	-	-	-	-	1	.26**	.39****	.32****	.16
Lateral OFC volume	-	-	-	-	-	-	-	-	-	1	.54****	.46****	.34****
Medial OFC volume	-	-	-	-	-	-	-	-	-	-	1	.55****	.41****
Superior Frontal volume	-	-	-	-	-	-	-	-	-	-	-	1	.42****
Rostral middlefrontal volume	-	-	-	-	-	-	-	-	-	-	-	-	1

Note. MCI = mild cognitive impairment; HVLT = Hopkins Verbal Learning Test; TMT = trail making test; LASSI-L = Loewenstein-Acevedo Scales for Semantic Interference and Learning; HP = Hippocampus; ERC = entorhinal cortex; OFC = orbitofrontal cortex; ****p < .001, *** p < .005, **p < .010, *p < .050

APPENDICES

Appendix A

Correlations and confidence intervals among all standardized neuropsychological measures included in the factor analysis

	Benson delay	Digit span F	Digit span B	TMT-A	TMT-B	LM-I	LM-D	HVLT I	HVLT D	Stroop CW	BD	CF	PF
Benson delay	1	.14	.24** [.10,.37]	.29** [.16,.42]	.40** [.27,.51]	.57** [.47,.66]	.66** [.57,.73]	.54** [.43,.63]	.38** [.25,.50]	.30** [.16,.42]	.38** [.25,.49]	.49** [.38,.59]	.15* [.01,.29]
Digit span F	-	1	.66** [.57,.73]	.21** [.07,.34]	.26** [.13,.39]	-.04	.04	.08	.04	.16* [.02,.29]	.27** [.14,.40]	.17* [.03,.30]	.35** [.22,.47]
Digit span B	-	-	1	.33** [.21,.45]	.38** [.26,.50]	.11	.16* [.03,.29]	.22** [.08,.35]	.16* [.03,.30]	.28** [.15,.40]	.30** [.17,.42]	.27** [.14,.40]	.36** [.23,.47]
TMT-A	-	-	-	1	.66** [.57,.73]	.29** [.16,.41]	.30** [.17,.42]	.46** [.34,.56]	.31** [.18,.43]	.49** [.37,.59]	.39** [.26,.50]	.44** [.32,.54]	.36** [.23,.47]
TMT-B	-	-	-	-	1	.37** [.24,.48]	.37** [.24,.48]	.46** [.35,.57]	.38** [.25,.49]	.54** [.43,.63]	.49** [.38,.59]	.49** [.38,.59]	.46** [.34,.56]
LM-I	-	-	-	-	-	1	.89** [.86,.91]	.61** [.51,.69]	.46** [.35,.57]	.25** [.12,.38]	.16* [.02,.29]	.48** [.37,.58]	.22** [.09,.35]
LM-D	-	-	-	-	-	-	1	.61** [.51,.69]	.45** [.33,.55]	.23** [.09,.35]	.22** [.09,.35]	.49** [.38,.59]	.23** [.10,.36]
HVLT I	-	-	-	-	-	-	-	1	.61** [.52,.69]	.41** [.28,.52]	.35** [.22,.47]	.57** [.47,.66]	.35** [.23,.47]

HVLT D	-	-	-	-	-	-	-	-	1	.31** [.18,.43]	.22** [.08,.35]	.55** [.44,.64]	.36** [.23,.47]
Stroop CW	-	-	-	-	-	-	-	-	-	1	.34** [.21,.46]	.38** [.25,.49]	.35** [.23,.47]
BD	-	-	-	-	-	-	-	-	-	-	1	.36** [.23,.47]	.21** [.07,.34]
CF	-	-	-	-	-	-	-	-	-	-	-	1	.52** [.41,.61]
PF	-	-	-	-	-	-	-	-	-	-	-	-	1

Note. R / [CI LL, CI UL]. ** $p < .01$, * $p < .05$

Digit Span F = digit span forward; Digit Span B = digit span backwards; TMT = trail making test; LM-I = logical memory immediate; LM-D = logical memory delay; HVLT I= Hopkins verbal learning test immediate recall; HVLT D = HVLT delay; BD = block design; CF = category fluency; PF = phonemic fluency.

Appendix B

Correlations between the LASSI-L recall measures

	A1 recall	A1 cued recall	A2 cued recall	B1 recall	B1 cued recall	B2 cued recall	A2 recall	A3 cued recall	Delayed recall
A1 recall	1	.81** [.76,.86]	.73** [.66,.79]	.64** [.55,.71]	.63** [.54,.71]	.63** [.54,.71]	.61** [.51,.69]	.61** [.52,.69]	.60** [.50,.68]
A1 cued recall	-	1	.78** [.72,.83]	.63** [.54,.71]	.66** [.58,74]	.66** [.57,.73]	.64** [.55,.71]	.68** [.60,.75]	.64** [.55,.72]
A2 cued recall	-	-	1	.63** [.54,.71]	.65** [.56,.72]	.69** [.61,.75]	.61** [.52,.69]	.65** [.56,.72]	.70** [.63,.77]
B1 recall	-	-	-	1	.79** [.74,.84]	.74** [.67,.80]	.52** [.41,.61]	.55** [.44,.63]	.60** [.50,.68]
B1 cued recall	-	-	-	-	1	.76** [.69,.81]	.55** [.45,.64]	.60** [.51,.68]	.67** [.59,.74]
B2 cued recall	-	-	-	-	-	1	.51** [.40,.61]	.57** [.47,.76]	.69** [.61,.76]
A2 recall	-	-	-	-	-	-	1	.74** [.68,.80]	.61** [.51,.69]
A3 cued recall	-	-	-	-	-	-	-	1	.59** [.49,.67]
Delayed recall	-	-	-	-	-	-	-	-	1

Note. R / [CI LL, CI UL]. ** $p < .001$

Appendix C

Means and Standard Deviations of all test measures by ethnic groups and by diagnostic groups.

	EA M (SD)	HA M (SD)	Total M (SD)	*F*	*p*	η_p^2	CN M (SD)	MCI M (SD)	Total M (SD)	*F*	*p*	η_p^2
Benson delayed recall	.17 (.87) *n* = 84	.23 (.95) *n* = 112	.21 (.91) *n* = 196	.20	.657	.001	.66 (.74) *n* = 57	.02 (.91) *n* = 139	.21 (.91) *n* = 196	22.15	<.001	.102
Digit span forward	.57 (1.07) *n* = 84	-.24 (.81) *n* = 122	.09 (1.00) *n* = 206	38.31	<.001	.158	.14 (.99) *n* = 63	.07 (1.01) *n* = 143	.09 (1.00) *n* = 206	.16	.686	.001
Digit span backwards	.68 (.88) *n* = 84	-.21 (.88) *n* = 122	.15 (.98) *n* = 206	51.34	<.001	.201	.25 (.93) *n* = 63	.11 (1.00) *n* = 143	.15 (.98) *n* = 206	.91	.342	.004
TMT-A	.25 (.32) *n* = 84	.12 (.34) *n* = 122	.17 (.34) *n* = 206	7.96	.005	.038	.27 (.28) *n* = 63	.13 (.36) *n* = 143	.17 (.34) *n* = 206	6.84	.010	.032
TMT-B	.39 (.54) *n* = 84	.08 (.80) *n* = 119	.21 (.72) *n* = 203	10.11	.002	.048	.47 (.54) *n* = 63	.09 (.76) *n* = 140	.21 (.72) *n* = 203	13.33	<.001	.062
Logical Memory immediate recall	.30 (.91) *n* = 82	.20 (.87) *n* = 123	.24 (.89) *n* = 205	.66	.418	.003	.68 (.72) *n* = 63	.04 (.88) *n* = 142	.24 (.89) *n* = 205	25.46	<.001	.111
Logical memory delayed recall	.30 (.95) *n* = 82	.21 (.86) *n* = 121	.25 (.89) *n* = 201	.53	.468	.003	.73 (.72) *n* = 63	.03 (.88) *n* = 142	.25 (.89) *n* = 205	29.83	<.001	.128
HVLT immediate recall	.32 (.87) *n* = 80	.18 (.83) *n* = 121	.23 (.85) *n* = 201	1.38	.241	.007	.70 (.75) *n* = 63	.02 (.81) *n* = 138	.23 (.85) *n* = 201	31.28	<.001	.136
HVLT delayed recall	.30 (1.07) *n* = 79	.09 (.97) *n* = 120	.17 (1.01) *n* = 199	2.10	.148	.011	.83 (.85) *n* = 63	-.13 (.94) *n* = 136	.17 (.94) *n* = 199	47.08	<.001	.193
Stroop CW	.13 (.88)	.20 (.92)	.17 (.91)	.24	.628	.001	.58 (.86)	-.01 (.87)	.17 (.91)	20.30	<.001	.092

	n = 82	*n* = 120	*n* = 202				*n* = 62	*n* = 140	*n* = 201			
Block	.22 (.83)	.17 (.91)	.19 (.87)	.14	.713	.001	.44 (.90)	.08 (.85)	.19 (.87)	7.25	.008	.035
Design	*n* = 82	*n* = 119	*n* = 201				*n* = 61	*n* = 140	*n* = 201			
Category	.39 (1.01)	.08 (.76)	.20 (.88)	6.51	.011	.032	.68 (.77)	-.01 (.84)	.20 (.88)	29.75	<.001	.129
fluency	*n* = 80	*n* = 122	*n* = 202				*n* = 62	*n* = 140	*n* = 202			
Phonemic	.48 (1.03)	-.09 (.81)	.14 (.95)	19.35	<.001	.087	.46 (.81)	-.004 (.97)	.14 (.95)	10.92	.001	.051
fluency	*n* = 83	*n* = 122	*n* = 205				*n* = 63	*n* = 142	*n* = 205			
LASSI A1	.28 (1.00)	.12 (.90)	.18 (.94)	1.54	.216	.008	.70 (.75)	-.05 (.92)	.18 (.94)	31.69	<.001	.135
recall	*n* = 82	*n* = 123	*n* = 205				*n* = 63	*n* = 142	*n* = 205			
LASSI A1	.30 (.99)	.10 (.88)	.18 (.93)	2.39	.124	.012	.70 (.72)	-.06 (.92)	.18 (.93)	34.17	<.001	.144
cued recall	*n* = 82	*n* = 123	*n* = 205				*n* = 63	*n* = 142	*n* = 205			
LASSI A2	.28 (.87)	.24 (.78)	.26 (.82)	.10	.75	.001	.67 (.52)	.73 (.86)	.26 (.82)	26.26	<.001	.115
cued recall	*n* = 82	*n* = 123	*n* = 205				*n* = 63	*n* = 142	*n* = 205			
LASSI B1	.24 (1.07)	.13 (.96)	.17 (1.00)	.62	.431	.003	.75 (.94)	-.09 (.92)	.17	36.05	<.001	.151
recall	*n* = 82	*n* = 123	*n* = 205				*n* = 63	*n* = 142	(1.00)			
									n = 205			
LASSI B1	.29 (1.14)	.12 (.84)	.19 (.97)	1.43	.234	.007	.65 (.89)	-.01 (.94)	.19 (.97)	22.32	<.001	.099
cued recall	*n* = 82	*n* = 123	*n* = 205				*n* = 63	*n* = 142	*n* = 205			
LASSI B2	.27 (.97)	.24 (.84)	.25 (.89)	.030	.863	.000	.72 (.70)	.04 (.89)	.25 (.89)	28.60	<.001	.123
cued recall	*n* = 82	*n* = 123	*n* = 205				*n* = 63	*n* = 142	*n* = 205			
LASSI A2	.36 (1.06)	.09 (.94)	.20 (1.00)	3.85	.051	.019	.54 (1.02)	.05 (.95)	.20	11.27	<.001	.053
Recall	*n* = 82	*n* = 123	*n* = 205				*n* = 63	*n* = 142	(1.00)			
									n = 205			
LASSI A3	.17 (1.08)	.09 (.86)	.12 (.95)	.38	.540	.002	.49 (.99)	-.04 (.89)	.12 (.95)	14.60	<.001	.067
cued recall	*n* = 82	*n* = 123	*n* = 205				*n* = 63	*n* = 142	*n* = 205			
LASSI	.34 (.90)	.15 (.90)	.23 (.90)	2.04	.155	.010	.66 (.70)	.03 (.91)	.23 (.90)	23.75	<.001	.105
delayed	*n* = 82	*n* = 123	*n* = 205				*n* = 63	*n* = 142	*n* = 205			
recall												

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