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Stability in cognitive classification as a function of severity of impairment and ethnicity: A longitudinal analysis

Fernanda Arruda[a], Mónica Rosselli[a,b], Andrea Mejia Kurasz[c], David A. Loewenstein[b,d], Steven T. DeKosky[b,e], Merike K. Lang[a], Joshua Conniff[a], Idaly Vélez-Uribe[a,f], Emily Ahne[a], Layaly Shihadeh[a], Malek Adjouadi[b,g], Alicia Goytizolo[a], Warren W. Barker[b,f], Rosie E. Curiel[b,d], Glenn E. Smith[b,c], and Ranjan Duara[b,f]

[a]Department of Psychology, Charles E. Schmidt College of Science, Florida Atlantic University, Davie, FL; [b]1Florida Alzheimer's Disease Research Center, Miami Beach and Gainesville, FL, USA; [c]Department of Clinical and Health Psychology, University of Florida College of Public Health and Health Professions, Gainesville, FL, USA; [d]Department of Psychiatry and Behavioral Sciences and Center for Cognitive Neuroscience and Aging, Miller School of Medicine, University of Miami, Miami, FL, USA; [e]McKnight Brain Institute, University of Florida, Gainesville, FL, USA; [f]Wien Center for Alzheimer's Disease and Memory Disorders, Mount Sinai Medical Center, Miami Beach, FL, USA; [g]Center for Advanced Technology and Education, College of Engineering, Florida International University, Miami, FL, USA

ABSTRACT

Objective: The interaction of ethnicity, progression of cognitive impairment, and neuroimaging biomarkers of Alzheimer's Disease remains unclear. We investigated the stability in cognitive status classification (cognitively normal [CN] and mild cognitive impairment [MCI]) of 209 participants (124 Hispanics/Latinos and 85 European Americans).

Methods: Biomarkers (structural MRI and amyloid PET scans) were compared between Hispanic/Latino and European American individuals who presented a change in cognitive diagnosis during the second or third follow-up and those who remained stable over time.

Results: There were no significant differences in biomarkers between ethnic groups in any of the diagnostic categories. The frequency of CN and MCI participants who were progressors (progressed to a more severe cognitive diagnosis at follow-up) and non-progressors (either stable through follow-ups or unstable [progressed but later reverted to a diagnosis of CN]) did not significantly differ across ethnic groups. Progressors had greater atrophy in the hippocampus (HP) and entorhinal cortex (ERC) at baseline compared to unstable non-progressors (reverters) for both ethnic groups, and more significant ERC atrophy was observed among progressors of the Hispanic/Latino group. For European Americans diagnosed with MCI, there were 60% more progressors than reverters (reverted from MCI to CN), while among Hispanics/Latinos with MCI, there were 7% more reverters than progressors. Binomial logistic regressions predicting progression, including brain biomarkers, MMSE, and ethnicity, demonstrated that only MMSE was a predictor for CN participants at baseline. However, for MCI participants at baseline, HP atrophy, ERC atrophy, and MMSE predicted progression.

KEYWORDS
Alzheimer's disease; biomarkers; cognitive decline; cross-cultural; mild cognitive impairment; neuropsychology

Introduction

Detecting individuals at high risk of Alzheimer's Disease (AD) is critical for advancing the design of clinical trials and therapeutic interventions. As such, considerable attention has been placed on understanding pre-dementia states, such as Mild Cognitive Impairment (MCI), for those with this diagnosis have a higher likelihood of future cognitive decline (Loewenstein et al., 2012; Storandt et al., 2006).

Identifying the risk factors associated with the progression of pre-dementia states is challenging, given the evidence that some individuals with MCI revert to normal cognition or do not progress to further stages of AD, particularly in population-based samples compared to clinical cohorts (Malek-Ahmadi, 2016). The annual progression rate to dementia in patients with MCI ranges from 5% to 20% (Langa & Levine, 2014), while 5 to 10% will not progress to dementia even after ten years of follow-ups (Mitchell & Shiri-Feshki, 2009). Differences in recruitment strategies, study design, participant demographics (e.g., age, underlying etiology), follow-up visit length, and MCI diagnostic approaches adopted in each study influence these results and the stability of cognitive status (Ganguli et al., 2015, 2019; Oltra-Cucarella et al., 2018). Individual risk, protective factors, and some medications can also influence the stability of diagnosis and changes in cognition (Aiken-Morgan et al., 2018; Jak et al., 2009; Manly et al., 2008; Mitchell & Shiri-Feshki, 2008, 2009; Schinka et al., 2010; Ward et al., 2012).

The interaction of ethnicity and cognitive status stability still remains unclear. Most studies that examine cognitive status trajectory lack diverse ethnic/racial representation (Roberts et al., 2014). Perales-Puchalt et al. (2021) found that MCI risk among cognitively normal (CN) participants

CONTACT Mónica Rosselli mrossell@fau.edu Department of Psychology, Charles E. Schmidt College of Science, Florida Atlantic University, 3200 College Ave, Davie, FL 33314, USA.

was higher in Hispanics from Caribbean and South/Central American origins compared to non-Hispanic Whites, whereas Manly et al. (2008) demonstrated higher MCI and AD risk among African Americans and Caribbean Hispanics. Similarly, in a 14-year study with a large population-based sample ($N = 59{,}555$), a review of healthcare information showed dementia incidence rates were highest among African Americans relative to Latinos (mainly of Mexican descent) and Whites, despite controlling for demographic factors and comorbidities (Mayeda et al., 2016). In another diverse sample, MCI progressors were predominantly Caucasian when compared to Hispanics and African Americans (Mungas et al., 2010). Manly et al. (2008) did not observe ethnoracial differences in participants who were diagnosed with MCI at their initial visit and reverted to CN at subsequent visits. Overall, few studies have examined the stability of cognitive status for the US Hispanic population, despite data demonstrating that Hispanics are more likely to develop AD than non-Hispanic Whites and frequently present increased risk factors for MCI and dementia (Alzheimer Association, 2021). Notably, in the US., race, and ethnicity represent social constructs that reflect lived experiences and intersecting factors (e.g., systemic racism, access to healthcare, socio-environmental exposures, discrimination, and quality of education), driving AD-related health inequities among racially and ethnically minoritized communities. Accurately monitoring disease progression across racially and ethnically marginalized groups is critical for advancing science that investigates AD and related dementias (ADRD) (Babulal et al., 2019).

We investigated the stability in cognitive status classification for a sample of European American and Hispanic/Latino older adults from a geographical location with broad ethnic diversity (e.g., South Florida, Miami Dade County- United StatesCensus Bureau, 2015) who were classified as CN or MCI at baseline. A unique feature of this investigation was the inclusion of neuroimaging assessments such as MRI scans and the level of amyloid load from PET scans, which allowed for a comparison of biomarkers between groups of individuals who presented a change in cognitive diagnosis at follow-up and those who remained stable over time. We predicted that neuroimaging biomarkers (i.e., greater medial temporal lobe atrophy) would be associated with the progression of cognitive impairment (Bouwman et al., 2007). Due to limited data on the cognitive stability of the US. Hispanic/Latinos relative to European Americans, particularly among those residing in South Florida, the ethnic comparison of cognitive status change was considered exploratory.

Method

Participants

Participants were recruited from the 1Florida Alzheimer's Disease Research Center (1Florida ADRC) at Mount Sinai Medical Center (MSMC) in Miami, Florida, and were native English or Spanish speakers. Each participant was required to have a close family member or caregiver who was a trusted informant about the subject's cognitive and functional performance in daily activities. Exclusion criteria included the presence of significant motor or sensory deficits, no study partner (e.g., family member), psychiatric disorders, and less than seven years of education. For the current study, we also excluded participants who immigrated from countries other than Spanish-speaking Latin American countries and those who self-identified as an ethnicity other than Hispanic/Latino or European American. Because we analyzed the progression of cognitive diagnosis, participants diagnosed with dementia at baseline were excluded.

The baseline sample included 209 participants (134 [64.1%] females, 124 [59.3%] self-identified as Hispanic or Latino/a, and 85 [40.7%] as European Americans). The baseline demographic and clinical characteristics of each ethnic and diagnostic group are shown in Table 1. Among Hispanic/Latino participants, 75.8% ($n = 94$) chose to be tested in Spanish; the rest of the sample was tested in English. The majority of Hispanics were of Cuban descent (58%), Colombian descent (18%), and Argentinian descent (6%), and the remaining 18% were from Chile, Ecuador, Guatemala, Nicaragua, Peru, Puerto Rico, Uruguay, Venezuela, and the Dominican Republic combined. The average interval between baseline and follow-up visit 2 was 14.62 months ($SD = 3.81$, $Min = 10$, $Max = 33$) and 12.74 months ($SD = 4.12$, $Min = 3$, $Max = 33$) between visits 2 and 3. The mean interval between baseline and total follow-up time was 22.91 months ($SD = 7.14$, $Min = 10$, $Max = 48$). The average time interval between visits did not significantly differ across ethnic groups.

Materials

A geriatric psychiatrist administered a standard clinical assessment, which included the Clinical Dementia Staging Instrument (CDR®; Morris, 1993), the Mini-Mental Status Examination (MMSE; Folstein et al., 1975), and the Geriatric Depression Scale-15 (GDS-15; in Spanish .: Martínez de la Iglesia et al., 2002; Sheikh & Yesavage, 1986; Yesavage et al., 1983).

The CDR Scale (Morris, 1993) is a common measurement in dementia research (Hanninen et al., 2002; Huang et al., 2021; Li et al., 2006; Petersen, 2000) and has been used to diagnose MCI and dementia. (Huang et al., 2021).

The MMSE (Folstein et al., 1975) is a screening instrument to detect dementia and cognitive changes in geriatric populations (George et al., 1991; Lezak et al., 2004). It is highly sensitive (87%) and specific (82%) in the identification of dementia (Anthony et al., 1982; Crum et al., 1993), and has good interrater (.69–.95) and test-retest (.85–.99) reliability (Anthony et al., 1982; Dick et al., 1984; Folstein et al., 1975; Molloy et al., 1991).

The GDS-15 includes 15 items and is used to determine depressive symptomatology. It has high internal consistency in English ($\alpha = .80$; D'ath et al., 1994) and in Spanish ($\alpha = .81$; Fernández-San Martín et al., 2002; Lucas-Carrasco, 2012; Martínez de la Iglesia et al., 2002), as well as good validity in normal elderly populations (Kørner et al., 2006; Marc et al., 2008), in MCI (Debruyne et al., 2009), and in dementia (Lach et al., 2010; Lucas-Carrasco, 2012).

Table 1. Baseline demographic and clinical characteristics by ethnic group of the total sample and the subsample with biomarkers.

	EA M (SD) $n = 85$	H/L M (SD) $n = 124$	Total M (SD) $N = 209$	F	p	η_p^2	CN M (SD) $n = 89$	MCI M (SD) $n = 120$	F	p	η_p^2
Age	72.65 (8.61)	71.06 (6.74)	71.71 (7.58)	2.21	.138	.011	70.52 (6.19)	72.59 (8.38)	3.89	.050	0.018
Education	16.47 (2.90)	14.65 (3.71)	15.39 (3.51)	14.41	<.001	.065	15.82 (3.25)	15.08 (3.67)	2.32	.129	0.011
MMSE	28.33 (2.28)	28.02 (2.17)	28.15 (2.21)	0.96	.328	0.005	29.06 (1.27)	27.48 (2.51)	29.76	<.001	0.126
CDR	0.38 (0.23)	0.34 (0.26)	0.36 (0.25)	1.31	.254	0.006	0.17 (0.24)	0.50 (0.14)	150.00	<.001	0.420
GDS[a]	2.16 (2.47)	2.09 (2.19)	2.12 (2.30)	0.21	.844	0.000	1.64 (1.89)	2.49 (2.52)	6.95	.009	.034
Length of follow-up (months)	22.29 (6.74)	23.33 (7.41)	22.91 (7.14)	1.06	.304	0.005	23.80 (7.19)	22.25 (7.07)	2.42	.122	0.012
				X^2	p				X^2	p	
Female frequency	51 (60%)	83 (66.9%)	134 (64.1%)	1.05	.305		66 (74.2%)	68 (56.7%)	6.80	.009	
Subsample with biomarkers											
	EA M (SD) $n = 66$	H/L M (SD) $n = 94$	Total M (SD) $N = 160$	F	p	η_p^2	CN M (SD) $n = 63$	MCI M (SD) $n = 97$	F	p	η_p^2
Age	72.76 (8.96)	70.96 (7.21)	71.70 (7.99)	1.96	.162	0.012	70.22 (6.51)	72.66 (8.73)	3.61	.059	0.022
Education	16.20 (3.05)	14.48 (3.72)	15.19 (3.55)	9.56	.002	0.057	15.70 (3.38)	14.86 (3.64)	2.17	.143	0.014
MMSE	28.15 (2.50)	27.96 (2.26)	28.04 (2.35)	0.26	.609	0.002	29.10 (1.28)	27.35 (2.63)	24.06	<.001	0.132
CDR	0.39 (0.22)	0.36 (0.26)	0.37 (0.25)	0.90	.343	0.006	0.18 (.24)	0.50 (.14)	114.52	<.001	0.420
GDS[a]	2.36 (2.69)	2.21 (2.22)	2.27 (2.42)	0.13	.715	0.001	1.73 (1.96)	2.62 (2.63)	5.06	.026	0.032
HP atrophy	1.59 (1.55)	1.22 (1.22)	1.38 (1.37)	2.92	.089	0.018	0.68 (0.96)	1.83 (1.42)	31.77	<.011	0.167
ERC atrophy	1.58 (1.92)	1.10 (1.54)	1.30 (1.72)	3.08	.081	0.019	0.50 (1.00)	1.82 (1.89)	25.94	<.001	0.141
				X^2	p				X^2	p	
Female frequency	39 (59.0%)	66 (70.2%)	105 (65.6%)	2.13	.145		49 (77.8%)	56 (57.7%)	6.80	.009	
Positive Amyloid[b]	20 (31.7%)	28 (28.6%)	48 (29.8%)	0.19	.667		10 (14.3%)	38 (41.8%)	14.27	<.001	

EA: European Americans; H/L: Hispanic/Latinos; CDR: Clinical Dementia Rating Scale; MMSE: Mini Mental Status Examination; HP: Hippocampus; ERC: entorhinal cortex; CN: cognitively normal; MCI: mild cognitive impairment; GDS: Geriatric Depression Scale.

[a]GDS scores were missing for 7 cases, 5 were H/L and 2 were EA.

[b]Amyloid data was available for 161 participants (63 EA, 98 H/L), of which 70 were CN and 91 were MCI at baseline.

Neuropsychological assessment

Participants completed a neuropsychological battery that included the Hopkins Verbal Learning Test-Revised (HVLT-R; Brandt, 1991); the Logical Memory subtest of the Wechsler Memory Scale-Revised (WMS-R, Wechsler, 1987); Category and Phonemic Fluency (Benton & Hamsher, 1976); Block Design from the Wechsler Adult Intelligence Scale (WAIS-IV; Wechsler, 2014a); Trail-Making Test B (TMT-B; Reitan & Wolfson, 1986); Multilingual Naming Test (MINT; Gollan et al., 2012); and Stroop Test (Stroop, 1935; Trenerry et al., 1989). The Spanish evaluations used translated/adapted versions of the English tests with normative data for age, education, and language (Acevedo et al., 2009; Arango-Lasprilla, Rivera, Aguayo, et al., 2015; Arango-Lasprilla, Rivera, Garza, et al., 2015; Golden, 1999; Gollan et al., 2012; Peña-Casanova et al., 2009; Pereiro et al., 2017; Wechsler, 2014b).

Clinical diagnosis

Participants were classified as CN, MCI, or dementia using an algorithmic diagnosis (AlgDx) developed by Duara et al. (2010). The AlgDx combined cognitive information provided by an independent physician, who calculated the CDR Sum of Boxes score, and a neuropsychologist, who derived a neuropsychological diagnosis based on cognitive testing of impairment in several domains: memory, language, attention, executive function, and visuospatial abilities. The consensus team then determined the algorithmic diagnosis by combining the CDR Sum of Boxes score and the neuropsychological diagnosis. If there was disagreement between the CDR score and the neuropsychological diagnosis, a consensus conference with three neurologists and four neuropsychologists discussed the discrepancy. The AlgDx has been tested by Duara et al. (2010), demonstrating a high concordance with a consensus diagnosis (ConsDx). The physician's cognitive diagnosis (PhyDx) was based on the CDR (Morris, 1993) global score (CDR-GS) rating. The CDR-GS is derived from the analyses of 6 domains: Memory, Orientation, Judgement/problem solving, community affairs, home and hobbies, and personal care. It is rated on a 5-point scale as follows: 0 (no impairment), 0.5 (questionable/very mild impairment), 1 (mild impairment), 2 (moderate impairment), and 3 (severe impairment) (Julayanont & DeToledo, 2022). Participants with no subjective cognitive complaint or reported functional deficits, with a CDR of 0, and MMSE within the normal range, were classified as CN. Those with a CDR of .5, where the participant or informant reported memory deficits or cognitive decline or the physician observed it during the clinical assessment, were classified as MCI. Finally, participants with observed cognitive decline and a CDR of 1.0 or above were classified as dementia. The neuropsychologist's diagnosis (NPDx) was based on the neuropsychological assessment performed in the subject's preferred language (English or Spanish). Participants who performed within the expected mean (based on age and education norms) were classified as CN; those with scores 1.5 SDs below the mean on one or more cognitive measures were classified as MCI, and those who had scores of greater than 2.0 SDs below the mean on one or more cognitive measures were classified as dementia.

Procedure

This study was completed in accordance with the Declaration of Helsinki and was approved by the Institutional Revview Board (IRB) at Mount Sinai Medical Center (MSMC). Participants had an interview with the clinician as well as completed both a neuropsychological battery and physical examination at each visit. Some participants also underwent a brain MRI scan and were tested for brain amyloid load with a PET scan at baseline. The current study analyzed data obtained at the baseline visit and two follow-up evaluations.

MRI and atrophy

Participants underwent MRI scans with a Siemens Skyra 3 T MRI scanner at MSMC in Miami Beach, Florida. Brain images were obtained using a 3D T1-weighted sequence (MPRAGE) with 1.0 mm isotropic resolution. Free Surfer Version 6.1 software (http://surfer.nmr.mgh.harvard.edu) divided each regional volume of the left and right hemispheres by total intracranial volume to adjust for variation in head size. These data, plus visual reads of the images by a neurologist (R.D.), were employed to assess medial temporal lobe (MTL) atrophy, specifically hippocampal (HP) and entorhinal cortex (ERC) atrophy (Loewenstein et al., 2018) in both hemispheres combined. The following scale was used: 0 = no atrophy, 1–2 = mild atrophy, 3–4 = moderate atrophy, and 5–6 = severe atrophy.

Brain amyloid levels assessed with amyloid PET

Participants were scanned for 20 minutes on a Siemens Biograph 16 PET/CT scanner operating in 3-dimensional mode (55 slices per frame, 3-mm slice thickness, 128 × 128 matrices) using the following tracers: NeuraCeq ([F-18] Florbetaben; Piramal Imaging, Boston, MA) 300 MBq and Amyvid (Florbetapir; Eli Lilly, Indianapolis, IN). Images were obtained from the top of the head to the top of the neck, and CT data were used for initial attenuation correction and image reconstruction in the coronal, sagittal, and axial planes. As described in a previous paper from our group (Loewenstein et al., 2017), the Florbetaben PET/CT scan, including the skull outline, was linearly co-registered (i.e., trilinear interpolation) with 12 df onto the T1 image. This registration process ensured that MRI parcellation and segmentation were identical to the Florbetaben PET/CT image. An experienced neurologist (R.D.), blinded to the diagnosis, visually read and classified the level of amyloid for each scan dichotomously: amyloid positive or amyloid negative. This reader had shown high reliability (93.2% for amyloid positive, 100% for amyloid negative scans) with an independent neuroradiologist in rating amyloid scans of older adults (Loewenstein et al., 2016, 2018).

Statistical analyses

Individual univariate analyses of variance (ANOVAs) were used to compare the two ethnic groups and the two diagnostic groups (CN and MCI at baseline) on demographic variables (age and years of education), MMSE, CDR-GS, GDS total score, and length of follow-up. Chi-square tests compared the ethnic groups on the sex distribution. ANOVAs were also conducted to compare HP and ERC atrophy across ethnic and diagnostic groups, and chi-square tests compared the ethnic and diagnostic groups in the frequency of elevated amyloid on PET.

We controlled for demographic variables that were significantly different among ethnic groups in each diagnosis by including them as covariates, and therefore, ANCOVAS were subsequently performed for the CN and MCI groups.

Stability indices were calculated for each ethnic and diagnostic group, as well as the whole sample. The objective was to examine if the overall proportion trend was to progress or not within a diagnostic and ethnic group. The formula included the number of progressors in the numerator and the total number of participants in the group as the denominator. The progressors group included participants who progressed from either CN or MCI to a more severe diagnosis. This stability index reflects the proportion of participants that progressed to a more severe cognitive diagnosis within that diagnostic or ethnic group.

For MCI participants at baseline, another index score was calculated where the numerator was the frequency of progressors and the denominator was the frequency of progressors plus the frequency of reverters (those who reverted from MCI to CN). This index excluded stable participants and analyzed the proportion of progressors among participants who changed diagnosis throughout the follow-ups.

Progressors and non-progressors were compared on baseline demographic and characteristics, and total follow-up interval using one-way ANOVAs, and chi-square tests compared these groups on the frequency of females and Hispanic/Latinos. Progressors and unstable non-progressors (i.e., reverters) were compared on HP atrophy and ERC atrophy with one-way ANOVAs and on the frequency of positive amyloid with chi-square tests. These analyses were repeated for the whole sample and within each ethnic group. Neuropsychological tasks were also compared between progressors and non-progressors for CN, MCI, and the total sample using one-way ANOVAs. For multiple comparisons, *p*-values were corrected using false discovery rate (FDR) corrections (Benjamini & Hochberg, 1995).

Finally, a series of stepwise binomial logistic regressions were used to investigate whether ethnicity (European Americans coded as 0, Hispanic/Latinos coded as 1), MMSE, HP atrophy, ERC atrophy, and amyloid status (amyloid visual reads determined negative were coded as 0; those read as positive were coded as 1) were significant predictors in classifying participants as either progressors or non-progressors (progressors were coded as 1, and non-progressors were coded as 0) in the whole sample and for each diagnostic group. Collinearity was tested using each independent variable's variance inflation factor (VIF).

Results

Educational attainment significantly differed across ethnic groups (see Table 1), and there were no differences in age, MMSE, CDR, GDS, length of follow-up, and sex distribution, ($ps > .05$). Analyses were repeated for the subsample of participants with available biomarker data (160 participants with volumetric data and 161 with amyloid status information) and similar differences were observed (Table 1). For this subsample, we also compared the ethnic groups (with and without covariates) in terms of HP and ERC atrophy and they were not significantly different. The frequency of positive amyloid scans on PET also did not differ across ethnic groups, (31.7% of European Americans and 28.6% of Hispanics/Latinos had positive amyloid PET scans). No ethnic differences were observed in HP atrophy or ERC atrophy within the CN and MCI groups. Additionally, the percentage of participants with positive amyloid was not significantly different between ethnic groups in neither CN (Hispanic/Latino = 12.8%, European American = 16.1%), $p > .05$ nor the MCI group (Hispanic/Latino = 39.0%, European American = 46.9%), $p > .05$. HP and ERC atrophy differed significantly by the diagnostic group at baseline ($p < .001$; Table 1). The difference in frequency of positive amyloid PET scans was also significant across diagnostic groups ($p < .001$; Table 1).

We further investigated biomarker differences across ethnic groups for each diagnosis after controlling for education (Table 2). For the CN and MCI groups, the Hispanic/Latino and European American participants did not differ significantly in HP atrophy nor in the frequency of positive amyloid. Only ERC atrophy significantly differed across Hispanics/Latinos and European Americans diagnosed as CN.

The frequency of diagnoses for the whole sample and each ethnic group at baseline, follow-up 2, and follow-up 3 are presented in Table 3. A stability index (as described in the statistical analyses subsection) was calculated for baseline CN and MCI participants, combined for the whole sample and for each ethnic group to provide the ratio of progressors. For the whole sample, the stability index was 0.27 (57 progressors), among European Americans it was 0.29 (25 progressors), and for Hispanics/Latinos it was 0.26 (32 progressors), suggesting that most of the participants were non-progressors. The stability index calculated only for those

Table 2. Biomarkers across baseline diagnostic groups by ethnicity.

	Ethnic group comparison*				
	EA M (SD)	H/L M (SD)	*F*	*p*	η_p^2
HP atrophy	*n* = 66	*n* = 94			
CN (*n* = 63)	0.91 (1.19)	0.50 (0.69)	1.57	0.216	0.020
MCI (*n* = 97)	2.11 (1.61)	1.65 (1.26)	1.90	0.171	0.029
ERC atrophy					
CN (*n* = 63)	0.64 (1.28)	0.39 (0.71)	0.74	0.393	0.012
MCI (*n* = 97)	2.28 (2.04)	1.52 (1.74)	3.03	0.085	0.031
	EA %	H/L %	X^2	*p*	
Elevated amyloid	*n* = 63	*n* = 98			
CN (*n* = 70)	16.1	12.8	0.15	0.694	
MCI (*n* = 91)	46.9	39.0	0.53	0.466	

Table 3. Frequency of algorithmic diagnosis.

	Whole Sample				EA			H/L	
	Baseline ($N = 209$)	Follow-up 2 ($n = 209$)	Follow-up 3 ($n = 139$)	Baseline ($n = 85$)	Follow-up 2 ($n = 85$)	Follow-up 3 ($n = 53$)	Baseline ($n = 124$)	Follow-up 2 ($n = 124$)	Follow-up 3 ($n = 86$)
CN	89 (42.6%)	66 (31.6%)	66 (47.5%)	38 (44.7%)	23 (27%)	21 (39.6%)	51 (41.1%)	43 (34.7%)	45 (52.3%)
MCI	120 (57.4%)	125 (59.8%)	51 (36.7%)	47 (55.3%)	56 (65.9%)	21 (39.6%)	73 (58.9%)	69 (55.6%)	30 (34.9%)
Dementia	–	18 (8.6%)	22 (15.8%)	–	6 (7.1%)	11 (20.8%)	–	12 (9.7%)	11 (12.8%)

EA: European Americans; H/L: Hispanics/Latinos; CN: Cognitively Normal, MCI: Mild Cognitive Impairment.

diagnosed as CN at baseline was 0.30 (27 progressors) for the whole subsample, for CN European Americans, the index was 0.32 (12 progressors) and among CN Hispanics/Latinos, the stability index was 0.29 (15 progressors). The frequency of CN participants who progressed to MCI or dementia in visits 2 and/or 3 did not significantly differ across ethnic groups, $p > .05$.

The stability index calculated for those diagnosed as MCI at baseline was 0.25 (30 progressors), with a .28 index for European Americans (13 progressors) and a .23 value for Hispanics/Latinos (17 progressors). Frequencies of progressors and non-progressors among MCI at baseline did not differ between ethnic groups, $p > .05$.

For the whole MCI group, the stability index was 0.57 (30 progressors and 23 reverters), indicating that there were 14% more progressors than reverters among MCI participants. Within the European American group, the index was 0.72 (13 progressors and 5 reverters), and for the Hispanic/Latino group, it was 0.49 (17 progressors and 18 reverters). These findings indicate that there were 22% more progressors among European Americans and 1% more reverters than progressors for Hispanics/Latinos in the sample. The frequencies of progressors and reverters among European Americans and Hispanics/Latinos were not significantly different, $p > .05$. The frequency of MCI participants who remained stable also did not significantly differ across ethnic groups, $p > .05$; where 60.9% of European Americans and 51.4% of Hispanics/Latinos remained stable.

In the baseline demographic and clinical characteristics of progressors and non-progressors (CN and MCI at baseline), there were no differences in age, education, CDR, GDS, or total follow-up interval, but progressors had significantly lower MMSE scores (Table 4). The groups were similar in sex distribution and in ethnicity, $ps > .05$. Progressors had significantly more HP and ERC atrophy than non-progressors; however, the groups did not differ in the frequency of amyloid-positive cases (Table 4). Among CN, progressors and non-progressors differed in HP atrophy, $F\ (1, 61) = 4.54$, $p = .037$, $\eta_p^2 = .069$, but not in ERC atrophy ($p > .05$), nor in the frequency of positive amyloid scans, $p > .05$ (9.1% of progressors and 16.7% of non-progressors had positive scans). Among MCI, progressors had more HP atrophy $F\ (1, 95) = 9.06$, $p = .003$, $\eta_p^2 = .087$, ERC atrophy, $F\ (1, 95) = 11.52$, $p = .001$, $\eta_p^2 = .108$ and greater frequency of positive amyloid scans, $X^2\ (1, N = 91) = 5.98$, $p = .015$ (60.7% of progressors and 33.3% of non-progressors had positive scans) than non-progressors. Also, differences in the neuropsychological profiles were found between progressors and non-progressors for the whole sample and MCI. When analyzing the entire sample, better performance was observed for the non-progressors on total recall of the HVLT, Logical Memory Immediate and Delay, Total Semantic Verbal Fluency (Animals, Fruits, and Vegetables), and Trails B time (Table 5). No significant differences were observed for CN across progressors and non-progressors on the neuropsychological tasks (Table 6). In the MCI group, there were several significant differences between progressors and non-progressors (Table 7). Specifically, HVLT total recall, Logical Memory Immediate and Delay, Total Semantic Verbal

Table 4. Baseline demographic and clinical characteristics of progressors and non-progressors.

	Non-progressors M (SD)	Progressors M (SD)	Total M (SD)	*F*	*p*	η_p^2
	n = 152	*n* = 57	*N* = 209			
Age	71.318 (6.90)	73.11 (9.07)	71.71 (7.56)	2.69	.103	0.013
Education	15.46 (3.53)	15.21 (3.48)	15.39 (3.51)	0.21	.647	0.001
MMSE	28.61 (1.64)	26.91 (2.95)	28.15 (2.21)	27.64	<.001	0.118
CDR	0.35 (0.24)	0.39 (0.27)	0.36 (0.25)	0.95	.330	0.005
GDS[a]	1.96 (2.18)	2.57 (2.58)	2.13 (2.30)	2.89	.091	0.014
Total follow-up interval (months)	22.53 (6.97)	24.21 (7.47)	22.99 (7.13)	2.30	.131	0.011
HP atrophy[b]	1.168 (1.251)	1.883 (1.533)	1.378 (1.374)	9.46	.002	0.056
ERC atrophy[b]	1.018 (1.570)	1.979 (1.894)	1.300 (1.722)	10.99	.001	0.065
	n (%)	*n* (%)	*n* (%)	X^2	*P*	
Female frequency	95 (62.5%)	39 (68.4%)	134 (64.1%)	0.632	.427	
H/L frequency	92 (60.5%)	32 (56.1%)	124 (59.3%)	0.330	.565	
Positive amyloid[b]	89 (80.2%)	19 (38%)	48 (29.8%)	2.323	.128	

MMSE: Mini Mental Status Examination; CDR: Clinical Dementia Rating Scale; GDS: Geriatric Depression Scale, HP: Hippocampus, ERC: Entorhinal Cortex; H/L: Hispanics/Latinos.
[a]Only 146 non-progressors and 56 progressors had GDS scores; GDS was missing from 6 non-progressors and 1 progressor.
[b]Subsample of participants with biomarker data described in Table 1.

Table 5. Full sample of both CN and MCI progressors and non-progressors compared on neuropsychological scores.

	Non-progressors M (SD)	Progressors M (SD)	Total M (SD)	*F*	*p*	FDR *p*	η_p^2
	n = 129	*n* = 61	*N* = 190				
Total Recall: HVLT	22.23 (5.10)	20.00 (7.07)	21.51 (5.88)	6.09	.015	0.038	0.031
	n = 127	*n* = 61	*N* = 188				
Delayed Recall: HVLT	4.23 (4.25)	4.38 (4.25)	4.28 (4.24)	0.05	.823	0.944	0.000
	n = 125	*n* = 59	*N* = 184				
Retention: HVLT	41.46 (40.48)	42.54 (40.07)	41.81 (40.24)	0.03	.865	0.944	0.000
	n = 131	*n* = 59	*N* = 190				
Logical Memory Immediate	11.46 (4.29)	9.71 (5.23)	10.92 (4.66)	5.87	.016	0.038	0.030
	n = 121	*n* = 59	*N* = 180				
Logical Memory Delay	9.81 (4.28)	8.05 (4.99)	9.23 (4.59)	6.00	.015	0.038	0.033
	n = 133	*n* = 63	*N* = 196				
Semantic Verbal Fluency	42.52 (11.30)	37.73 (12.80)	40.98 (11.98)	7.04	.009	0.038	0.035
	n = 133	*n* = 60	*N* = 193				
FAS Verbal Fluency	35.34 (12.46)	34.95 (11.34)	35.22 (12.10)	0.04	.837	0.944	0.000
	n = 133	*n* = 60	*N* = 193				
FLAS Verbal Fluency	42.93 (16.73)	43.03 (14.77)	42.96 (16.11)	0.002	.966	0.966	0.000
	n = 128	*n* = 59	*N* = 187				
WAIS IV-Block Design	32.53 (9.76)	29.36 (10.54)	31.53 (10.09)	4.07	.045	0.09	0.021
	n = 129	*n* = 59	*N* = 188				
Trails B	109.64 (60.20)	152.39 (93.92)	123.05. (74.91)	14.11	<.001	0.012	0.071
	n = 132	*n* = 61	*N* = 193				
Stroop Color-Word (CW)	30.29 (8.97)	27.80 (10.74)	29.50 (9.61)	2.82	.095	0.143	0.015
	n = 81	*n* = 42	*N* = 123				
MINT Total	28.17 (3.63)	26.79 (4.59)	27.70 (4.02)	3.36	.069	0.118	0.027

HVLT: Hopkins Verbal Learning Test; WAIS-IV: Wechsler Adult Intelligence Scale; MINT: Multilingual Naming Test; FDR p: False Discovery Rate p-value. Tests of homogeneity of variance significant for HVLT total recall ($p = .003$), logical memory immediate recall ($p = .004$) and Trails B ($p < .001$). Welch's robust test for homogeneity of variance signicant for HVLT ($p = .030$), Trails B ($p = .002$), and logical memory immediate recall ($p = .027$).

Fluency, Block Design, Trails B Time, and Stroop Color-Word condition were significantly better for non-progressors compared to progressors. These differences remained significant after applying FDR corrections (see Figure 1 for plots of means across MCI progressors and non-progressors on significant neuropsychological tasks).

For the whole sample, progressors had significantly greater HP and ERC atrophy than unstable non-progressors. However, when examining each ethnic group separately, significant differences between progressors and unstable non-progressors were observed only in ERC atrophy for both ethnic groups, where progressors exhibited greater atrophy than unstable non-progressors (Table 8). Additionally, progressors had a higher frequency of positive amyloid for the whole sample and within Hispanics/Latinos, but not within the European Americans, $p > .05$. Furthermore, the frequency of unstable non-progressors and progressors across ethnic groups was not significantly different, with 71.1% of unstable non-progressors and 56.1% of progressors being Hispanics/Latinos, $p > .05$.

Finally, we used stepwise binomial logistic regressions predicting the classification of participants as progressors or non-progressors. The model, including ERC atrophy in step 1, MMSE in step 2, and ethnicity in step 3 for the whole sample (CN and MCI combined), was significant for step 1, X^2 (1) = 9.94, $p = .002$, step 2, X^2 (2) = 23.10, $p < .001$, and step 3, X^2 (3) = 23.40, $p < .001$. MMSE was the only predictor that significantly contributed to the model in steps 2 and 3. The model including HP atrophy in step 1, MMSE in step 2, and ethnicity in step 3 for the whole sample was

Table 6. Cognitively normal progressors and non-progressors compared on neuropsychological scores.

	Non-progressors M (SD)	Progressors M (SD)	Total M (SD)	*F*	*p*	FDR *p*	η_p^2
	n = 58	*n* = 23	*N* = 81				
Total Recall: HVLT	25.07 (3.97)	23.74 (6.00)	24.69 (4.64)	1.36	.247	0.329	0.017
	n = 57	*n* = 23	*N* = 80				
Delayed Recall: HVLT	7.33 (3.30)	6.78 (4.11)	7.18 (3.53)	0.400	.531	0.531	0.005
	n = 55	*n* = 23	*N* = 78				
Retention: HVLT	69.72 (30.63)	61.53 (38.85)	67.30 (33.22)	0.99	.324	0.389	0.013
	n = 58	*n* = 21	*N* = 79				
Logical Memory Immediate	13.84 (3.55)	12.29 (3.94)	13.43 (3.70)	2.80	.098	0.168	0.035
	n = 53	*n* = 23	*N* = 76				
Logical Memory Delay	11.72 (3.86)	11.00 (3.49)	11.50 (3.74)	0.59	.446	0.487	0.008
	n = 58	*n* = 25	*N* = 83				
Semantic Verbal Fluency	49.26 (9.53)	43.53 (9.93)	47.53 (9.95)	6.18	.015	0.060	0.071
	n = 58	*n* = 24	*N* = 82				
FAS Verbal Fluency	41.41 (11.10)	36.33 (10.27)	39.93 (11.05)	3.71	.058	0.161	0.044
	n = 58	*n* = 24	*N* = 82				
FLAS Verbal Fluency	50.31 (15.72)	45.08 (13.93)	48.78 (15.32)	2.00	.161	0.242	0.024
	n = 56	*n* = 23	*N* = 79				
WAIS IV-Block Design	35.04 (8.63)	30.91 (9.71)	33.84 (9.09)	3.46	.067	0.161	0.043
	n = 56	*n* = 25	*N* = 81				
Trails B	81.68 (31.99)	114.08 (70.43)	91.68 (49.17)	8.18	.005	0.060	0.094
	n = 58	*n* = 25	*N* = 83				
Stroop Color-Word (CW)	34.64 (8.12)	31.16 (8.86)	33.59 (8.45)	3.03	.085	0.168	0.036
	n = 37	*n* = 18	*N* = 55				
MINT Total	29.43 (2.58)	27.33 (3.14)	28.75 (2.92)	6.95	.011	0.060	0.116

HVLT: Hopkins Verbal Learning Test; WAIS-IV: Wechsler Adult Intelligence Scale; MINT: Multilingual Naming Test; FDR *p*: False Discovery Rate *p*-value.

Table 7. Mild Cognitive Impairment progressors and non-progressors compared on neuropsychological scores.

	Non-progressors M (SD)	Progressors M (SD)	Total M (SD)	*F*	*p*	FDR *p*	η_p^2
	n = 80	*n* = 26	*N* = 106				
Total Recall: HVLT	20.60 (4.72)	14.64 (5.40)	19.14 (5.52)	28.97	<.001	0.002	0.218
	n = 79	*n* = 26	*N* = 105				
Delayed Recall: HVLT	2.43 (3.54)	1.15 (2.57)	2.11 (3.36)	2.87	.093	0.112	0.027
	n = 79	*n* = 24	*N* = 103				
Retention: HVLT	26.15 (36.01)	12.45 (27.21)	22.96 (34.53)	2.95	.089	0.112	0.028
	n = 82	*n* = 26	*N* = 108				
Logical Memory Immediate	10.18 (3.90)	5.85 (4.40)	9.14 (4.42)	22.94	<.001	0.002	0.178
	n = 77	*n* = 25	*N* = 102				
Logical Memory Delay	8.64 (3.97)	4.12 (4.05)	7.53 (4.42)	24.20	<.001	0.002	0.195
	n = 84	*n* = 26	*N* = 110				
Semantic Verbal Fluency	38.74 (10.38)	27.54 (9.44)	36.09 (11.20)	24.07	<.001	0.002	0.182
	n = 84	*n* = 24	*N* = 108				
FAS Verbal Fluency	31.99 (11.95)	30.67 (11.06)	31.69 (11.72)	0.24	.628	0.685	0.002
	n = 84	*n* = 24	*N* = 108				
FLAS Verbal Fluency	38.89 (16.13)	37.46 (13.62)	38.57 (15.56)	0.16	.692	0.692	0.001
	n = 81	*n* = 25	*N* = 106				
WAIS IV-Block Design	31.22 (9.72)	25.08 (11.35)	29.77 (10.41)	7.03	.009	0.015	0.063
	n = 81	*n* = 23	*N* = 104				
Trails B	123.28 (66.95)	232.04 (78.74)	147.34 (82.84)	43.67	<.001	0.002	0.30
	n = 83	*n* = 24	*N* = 107				
Stroop Color-Word (CW)	28.25 (8.77)	20.42 (8.25)	26.50 (9.22)	15.24	<.001	0.002	0.127
	n = 50	*n* = 16	*N* = 66				
MINT Total	27.32 (4.01)	25.06 (5.95)	26.77 (4.61)	3.00	.088	0.112	0.045

HVLT: Hopkins Verbal Learning Test; WAIS-IV: Wechsler Adult Intelligence Scale; MINT: Multilingual Naming Test; FDR *p*: False Discovery Rate *p*-value.

significant in step 1, X^2 (1) = 8.71, p = .003, step 2, X^2 (2) = 23.48, $p < .001$, and step 3, X^2 (3) = 23.78, $p < .001$. MMSE was the only predictor that significantly contributed to the model in steps 2 and 3. Additionally, the model including amyloid status in step 1, MMSE in step 2, and ethnicity in step 3 for the whole sample was not significant for step 1, $p > .05$, but was significant for step 2, X^2 (2) = 19.71, $p < .001$, and for step 3, X^2 (3) = 23.05, $p < .001$. MMSE was the only significant predictor.

Stepwise binomial logistic regressions were also conducted for the CN and MCI diagnostic groups separately using progressors vs. non-progressors as dependent measures and HP, ERC, levels of amyloid, ethnicity, and MMSE as independent predictors (Tables 9 and 10). The model for CN including HP atrophy was significant in steps 1 and 2 with HP atrophy and MMSE as significant predictors, however, ethnicity was not a significant contributor (Table 9). The models having ERC atrophy and amyloid status in step

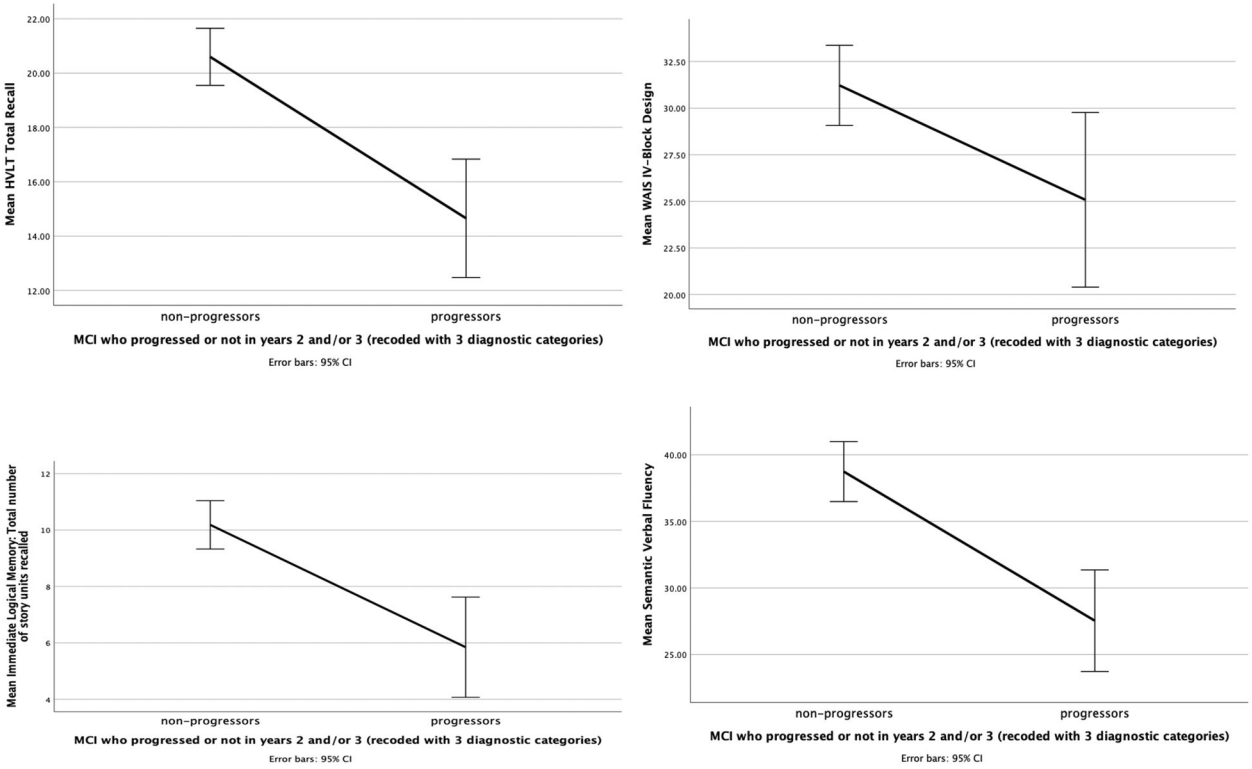

Figure 1. Neuropsychological score means across progressors and non-progressors in the MCI group. HVLT: Hopkins Verbal Learning Test; WAIS-IV: Wechsler Adult Intelligence Scale.

Table 8. ANOVAs - biomarkers of progressors vs. unastable non-progressors among Cognitively Normal and Mild Cognitive Impairment at baseline.

		Unstable non-progressors ($n = 35$) M (SD)	Progressors ($n = 47$) M (SD)	F	p	η_p^2
Whole Sample	HP atrophy	1.043 (1.067)	1.883 (1.533)	7.72	.007	0.088
	ERC atrophy	0.743 (1.190)	1.979 (1.894)	11.50	.001	0.126
		$n = 31$	$n = 50$	X^2	p	
	Positive amyloid	1 (3.2%)	19 (38.0%)	12.44	<.001	
		$n = 11$	$n = 21$			
EA	HP atrophy	1.227 (1.348)	2.381 (1.604)	4.14	.051	0.121
	ERC atrophy	0.727 (.984)	2.452 (2.109)	6.53	.016	0.179
		$n = 9$	$n = 22$	X^2	p	
	Positive Amyloid	0	7	3.70	.054	
		$n = 24$	$n = 26$			
H/L	HP atrophy	0.958 (.932)	1.481 (1.375)	2.43	.125	0.048
	ERC atrophy	0.750 (1.294)	1.596 (1.643)	4.05	.050	0.078
		$n = 22$	$n = 28$	X^2	p	
	Positive Amyloid	1 (4.5%)	12 (42.9%)	9.40	.002	

EA: European Americans; H/L: Hipanics/Latinos; HP: Hippocampus; ERC: entorhinal cortex; HA: Hispanic Americans for: H/L: Hispanics/Latinos.

1, were significant in step 2, but only due to MMSE driving the significance (Table 9). For the MCI group, all the biomarker models were significant contributors in Step 1 (Table 10). Additionally, HP and ERC atrophy were significant predictors in the models, together with global cognition as measured by the MMSE. Ethnicity was not significant a predictor in these models and amyloid status lost its significance as a predictor once MMSE was added to the model.

Because ERC atrophy and amyloid status were significant predictors of progression among MCI but not among CN, we ran two binomial logistic regressions for the whole sample including the interaction between ERC atrophy and diagnosis (ERC atrophy × diagnosis) or amyloid status and diagnosis (amyloid status × diagnosis) in step 1 and MMSE in step 2. Since ethnicity was never a significant predictor of progression, it was not included in these models. The model that included the interaction between amyloid status and diagnosis in step 1 and MMSE in step 2 was only significant for step 2, X^2 (2) = 21.94, $p < .001$, with MMSE as the only predictor that significantly contributed to the model. The model including the interaction between ERC atrophy and diagnosis in step 1 and MMSE in step 2 was significant for

Table 9. Binomial logistic regression analyses predicting "progressors vs. non-progressors" among CN participants at baseline ($n = 63$).

								Model	
		B	*SE B*	Wald	*p*	*OR*	*95% CI OR*	X^2	*p*
Step 1	HP atrophy	0.568	0.288	3.892	.049	1.765	1.004–3.103	4.154	.042
Step 2	HP atrophy	0.577	0.294	3.841	.050	1.781	1.000–3.171	5.335	.021
	MMSE	–0.551	0.283	3.789	.050	0.577	0.331–1.004		
Step 3	HP atrophy	0.601	0.305	3.887	.049	1.824	1.004–3.314	0.102	.750
	MMSE	–0.552	0.286	3.722	.054	0.576	0.329–1.009		
	Ethnicity	0.195	0.613	0.101	.751	1.215	0.366–4.038		
Step 1	ERC atrophy	0.494	0.281	3.107	.078	1.640	0.946–2.841	3.419	.064
Step 2	ERC atrophy	0.533	0.291	3.369	.066	1.705	0.964–3.013	5.776	.016
	MMSE	–0.580	0.287	4.073	.044	0.560	0.319–9.83		
Step 3	ERC atrophy	0.537	0.293	3.372	.066	1.712	0.964–3.037	0.012	.913
	MMSE	–0.582	0.289	4.045	.044	0.559	0.317–0.985		
	Ethnicity	0.065	0.594	0.012	.913	1.067	0.333–3.422		
Step 1	Amyloid status	–0.693	0.837	0.686	.407	0.500	0.097–2.577	0.758	.384
Step 2	Amyloid status	–0.897	0.880	1.040	.308	0.408	0.073–2.287	5.119	.024
	MMSE	–0.566	0.258	4.812	.028	0.568	0.343–0.941		
Step 3	Amyloid status	–0.898	0.872	1.060	.303	0.407	0.074–2.251	0.594	.441
	MMSE	–0.573	0.258	4.945	.026	0.564	0.340–0.934		
	Ethnicity	–0.418	0.543	0.593	.441	0.658	0.227–1.908		

MMSE: Mini Mental Status Examination; HP: Hippocampus; ERC: Entorhinal Cortex.

Table 10. Binomial logistic regression analyses predicting "progressors vs. non-progressors" among participants with MCI at baseline ($n = 97$).

								Model	
		B	*SE B*	Wald	*p*	*OR*	*95% CI OR*	X^2	*p*
Step 1	HP atrophy	0.462	0.167	7.625	.006	1.587	1.143–2.202	8.240	.004
Step 2	HP atrophy	0.396	0.182	4.715	.030	1.485	1.039–2.123	18.225	<.001
	MMSE	–0.416	0.114	13.299	<.001	0.659	0.527–0.825		
Step 3	HP atrophy	0.378	0.186	4.129	.042	1.460	1.013–2.103	0.175	.676
	MMSE	–0.421	0.116	13.232	<.001	0.656	0.523–0.823		
	Ethnicity	–0.234	0.557	0.176	.675	0.792	0.266–2.360		
Step 1	ERC atrophy	0.391	0.126	9.585	.002	1.478	1.154–1.893	10.341	.001
Step 2	ERC atrophy	0.283	0.139	4.113	.043	1.327	1.010–1.743	15.417	<.001
	MMSE	–0.399	0.115	11.975	<.001	0.671	0.536–0.841		
Step 3	ERC atrophy	0.270	0.144	3.494	.062	1.309	0.987–1.737	0.124	.725
	MMSE	–0.404	0.117	11.878	<.001	0.668	0.531–0.840		
	Ethnicity	–0.198	0.561	0.124	.725	0.821	0.273–2.464		
Step 1	Amyloid status	1.128	0.470	5.758	.016	3.091	1.230–7.769	5.948	.015
Step 2	Amyloid status	0.243	0.590	0.170	.680	1.275	0.401–4.050	17.424	<.001
	MMSE	–0.466	0.138	11.384	<.001	0.627	0.479–0.823		
Step 3	Amyloid status	0.228	0.592	0.148	.700	1.256	0.394–4.005	0.142	.706
	MMSE	–0.469	0.139	11.380	<.001	0.626	0.477–0.822		
	Ethnicity	–0.206	0.546	0.143	.706	0.814	0.279–2.374		

MMSE: Mini Mental Status Examination; HP: Hippocampus; ERC: entorhinal cortex.

step 1, X^2 (1) = 7.95, p = .005 and for step 2, X^2 (2) = 21.57, p < .001, however, with the addition of MMSE, the interaction between ERC atrophy and diagnosis lost its significance and MMSE remained the only significant predictor. No collinearity was detected among the predictors for any of the regression analyses. The VIFs were all below 4 (Ringle et al., 2015).

Discussion

We investigated stability in cognitive status classification among European American and Hispanic/Latino participants, evaluating possible differences as a function of ethnicity or baseline biomarkers (HP atrophy, ERC atrophy, and amyloid status). We also studied global cognition, ethnicity, MTL atrophy, and amyloid status as predictors of progression to a more severe clinical diagnosis. The frequency of CN and MCI participants who were progressors (progressed to a more severe cognitive diagnosis at follow-up) and non-progressors (those who were either stable throughout the follow-up or were unstable and progressed but later reverted to a diagnosis of CN) did not significantly differ across ethnic groups. Progressors had greater atrophy in the hippocampus (HP) and entorhinal cortex (ERC) at baseline compared to unstable non-progressors (reverters) for both ethnic groups, and more significant ERC atrophy was observed among progressors of the Hispanic/Latino group. For European Americans diagnosed with MCI, there were 60% more progressors than reverters (reverted from MCI to CN), while among Hispanics/Latinos with MCI, there were 7% more reverters than progressors. Binomial logistic regressions predicting progression, including brain biomarkers, MMSE, and ethnicity, demonstrated that only MMSE was a predictor for CN participants at baseline. The progressors from MCI to dementia had more HP and ERC atrophy than non-progressors as well as a higher frequency of positive amyloid. In stepwise binomial logistic regressions, ERC and HP atrophy remained significant predictors of

progression within MCI, even when controlling for global cognition. Additionally, this coincided with lower performance on neuropsychological tasks for progressors within the MCI diagnosis compared to non-progressors, particularly on measures of semantic memory, episodic memory, verbal fluency, executive function, and visuospatial abilities.

As anticipated, we found MTL atrophy, and the percentage of positive amyloid PET scans increased progressively across the diagnostic spectrum (MCI > CN), but the relationship between ethnicity and biomarkers was not significant. Previous findings from our group using a different South Florida sample of older adults classified into CN, amnestic MCI, and dementia found smaller hippocampal volumes for Non-Hispanic Whites compared to Hispanics (Burke et al., 2018); however, no diagnosis by ethnicity interaction was noted.

The proportion of MCI participants who progressed to dementia in our sample (25% in an average follow-up time of 22.25 months) was smaller than those reported in previous studies. For example, Bouwman et al. (2007) found that 56% of the 59 MCI patients progressed to dementia during a 19-month follow-up, and in Rosenberg et al. (2019), 38.1% (of 318 MCI participants) progressed to dementia with a mean follow-up period of 2.8 years ($SD = 1.9$, range 1–10 years). Notably, analyzing the percentage of progressors per year in our sample (11%) yields similar findings to Rosenberg et al.'s (2019) approximately 13% per year progression rate. The smaller percentage of progressors in our study compared to Bouwman et al.'s (2007) could be due, in part, to differences in the sample selection criteria. In the current study, participants with motor or sensory deficits and psychiatric disorders were excluded, whereas no exclusion criteria were described in Bouwman et al. (2007). Therefore, our sample may have had fewer comorbidities at a lower risk of dementia since baseline, while Bouwman's may represent a more heterogeneous sample (mixed neurodegenerative sample).

A unique aspect of the current study is the inclusion of a diverse sample. European Americans and Hispanics/Latinos 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. However, we observed that although the MCI group had 13% more progressors than reverters, the frequency of progressors was proportionately greater in the European American group, where there were 22% more progressors than reverters. In the Hispanic/Latino group, there were 1% more reverters than progressors. One possible explanation of this frequency distribution difference between ethnic groups is a potential cognitive inequality at baseline in the MCI European American and MCI Hispanic/Latino groups. However, this explanation is diminished by the lack of significant ethnic differences found in the MMSE, and the CDR between European Americans and Hispanics/Latinos with MCI.

Our results align with those of Mungas et al. (2010), who observed that MCI progressors were predominantly Caucasian (corresponds to our European American group) compared to Hispanics and African Americans. The greater number of reverters among Hispanics may indicate a need for a more careful assessment of this population to avoid false-positive diagnoses of MCI. This may involve test selection and/or a more careful assessment of other factors that could interfere with an individual's performance (e.g., depressive symptoms, anxiety, medication effects, or lack of sleep). Another potentially relevant variable in explaining the disparity of results between our ethnic groups is the equivalence in the level of difficulty between the Spanish and English tests. All tests used in this study were originally developed for English speakers and were translated and adapted to Spanish following the appropriate procedures. Although they have shown good reliability and validity within each language group, we are not aware of any comparison across languages on the level of difficulty of these tests.

When examining participants with CN and MCI diagnoses at baseline, the frequency of progressors and non-progressors did not differ across ethnic groups. Progressors and non-progressors who were CN at baseline had similar AD-biomarker profiles, but those diagnosed with MCI at baseline had greater HP and ERC atrophy among progressors. Similarly, MTL atrophy and amyloid status significantly differentiated progressors from unstable non-progressors across the entire sample. These results are not surprising, considering the large body of literature linking cognitive decline with MTL atrophy and amyloid status (Geroldi et al., 2006; Sperling et al., 2011). Here again, we can assume the influence of other factors on the diagnosis of MCI given to those who later were thought to have reverted to normal cognition. However, within ethnic groups, significant differences were only seen within Hispanics/Latinos, where progressors had greater ERC atrophy and a higher frequency of positive amyloid scans than the unstable non-progressors. It is important to note that these results may have been affected by the uneven distribution of Caucasian participants between progressors and unstable non-progressors. Hispanics also were the majority of unstable non-progressors (71.9% of the sample), meaning that Hispanics tended to be less stable and reverted to higher levels of cognition at follow-up. Future research should explore demographic and clinical factors that are associated with the instability of diagnosis.

When considering predictors of progression, a lower MMSE score was associated with a greater probability of classifying as a progressor in both European American and Hispanic/Latino samples, which is consistent with existing research (Loewenstein et al., 2012; Pozueta et al., 2011). Among MCI participants at baseline, greater HP and ERC atrophy were significant predictors of progression, together with MMSE. Amyloid status on PET and ethnicity were not significant predictors of progression among this group. Similarly, MTL volumes have been previously identified as a significant predictor of the progression from MCI to dementia by Bouwman et al., 2007. They also found amyloid status to be a significant predictor of progression, which was not the case in our sample. Furthermore, our results suggest that the use of MTL atrophy

and amyloid status among CN participants to identify individuals at risk of developing AD is not a strong enough predictor. Future research should explore other biomarkers and their capacity to identify individuals on the AD spectrum even before the appearance of clinical symptoms, which is critical for interventional research. There are several limitations of the current study. European Americans and Hispanics/Latinos had unequal sample sizes, and there was a small number of participants who were CN at baseline. Results may not be representative when participants are not followed throughout their entire disease trajectory, especially those in the earliest disease stage. However, ongoing data collection will facilitate examining the relationship between pre-dementia cognitive states and progression with a more extended follow-up period.

Additionally, we used a visual rating to create a 3-point ordinal scale to characterize the degree of atrophy, which has not been validated. We categorized groups based on self-reported ethnicity and treated Hispanics as a homogenous group, yet ethnicity may represent proxies for health-related (e.g., vascular health conditions) and sociocultural variables (e.g., immigration, quality of education) that impact late-life cognitive trajectories. Furthemore, exclusionary criteria (e.g., no study partner, $<$ 7 years of education) and potential recruitment differences between Hispanic/Latino and European American participants may have influenced our findings. Moreover, the sample included a large percentage of immigrants from Cuba and South America; therefore, the results cannot be generalized to other groups of Latinos/Hispanics living in the US. In this study, the neuropsychological diagnosis of MCI was based on one score below 1.5 SD below the mean that could lead to greater false positive errors, and this would be particularly true in a diverse sample. Despite these limitations, this study provided relevant information regarding cognitive status stability among Hispanics/Latinos, in contrast to European Americans, demonstrating a higher rate of those subjects that reverted from MCI to normal cognition, which calls for more investigation as to this reversion phenomenon in the Hispanic/Latino population. Moreover, the use of MTL atrophy as a predictor of future progression to dementia is shown to be effective among MCI but not in cognitively normal participants. Future research should include the predictive value of medications in association to brain biomarkers due to recent advancements in pharmacological treatments for AD (Atri, 2019; Khan et al., 2020). Finally, more research is also needed to understand what variables could drive the reversion diagnosis (i.e., CDR, MMSE, neuropsychological tests, or participant reports).

Disclosure statement

No potential conflict of interest was reported by the author(s).

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