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Authors

Hall, James R
Johnson, Leigh A
Zhang, Fan
et al.

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Using Fractional Anisotropy Imaging to Detect MCI and AD among Mexican Americans and non-Hispanic Whites: A HABLE study

James R. Hall[a,b,*], **Leigh A. Johnson**[a,b], **Fan Zhang**[a,c], **Melissa Petersen**[a,c], **Arthur W. Toga**[d], **Yonggang Shi**[d], **David Mason**[b], **Robert A Rissman**[e,f], **Kristine Yaffe**[g,h], **Sid E. O'Bryant**[a,b]
HABLE Study

[a]Institute for Translational Research, University of North Texas Health Science Center, Fort Worth, Texas, USA

[b]Department of Pharmacology and Neuroscience, University of North Texas Health Science Center, Fort Worth, Texas, USA

[c]Department of Family Medicine, University of North Texas Health Science Center, Fort Worth, Texas, USA

[d]Laboratory of Neuro Imaging, USC Stevens Neuroimaging and Informatics Institute, Keck School of Medicine of USC, University of Southern California, Los Angeles, CA, USA

[e]Department of Neurosciences, University of California, San Diego, La Jolla, CA, USA

[f]Veterans Affairs San Diego Healthcare System, San Diego, CA, USA

[g]Department of Psychiatry, Neurology, and Epidemology and Biostatistics, University of California, San Francisco, CA, USA

[h]San Francisco VA Medical Center, San Francisco, CA, USA

Abstract

[*]Corresponding Author: James R. Hall, Ph.D., University of North Texas Health Science Center, 3500 Camp Bowie Blvd, Fort Worth, Texas, 76107 USA; 1+817-735-2326, james.hall@unthsc.edu;.

Author Contributions All authors made substantial contributions to the creation and writing of this manuscript, agree with the findings and have given consent to include their names on this manuscript. JRH was involved in writing and revising the manuscript, LAJ reviewed and made substantial edits to the manuscript, FZ conducted the statistical analysis, MP was involved in the statistical analysis and revision of the manuscript, AWT was involved in designing the project and processing and analyzing the MRIs, YS was involved in processing and analyzing the MRIs, DM was involved in the revision of the manuscript, RAR was involved in designing the project and revision of the manuscript and KY was involved in the designing the project and revising the manuscript. SEO was primarily involved designing the project and writing the manuscript.

Conflicts of Interest

SEO has multiple patents on precision medicine for neurodegenerative diseases. None of the other authors report conflicts of interest.

Statement of Ethics

This project was approved by the University of North Texas Health Science Center IRB (IRB 2016-128 & 2017-165 Protocols) and is in accordance with Code of Ethics of the World Medical Association Declaration of Helsinki. Each participant (or his/her legal representative) signs written informed consent.

Data Availability

The HABLE database is publicly available through the UNTHSC Institute for Translational Research webpage and raw images available through LONI.

Introduction: Alzheimer's disease (AD) is the most frequently occurring neurodegenerative disease; however, little work has been conducted examining biomarkers of AD among Mexican Americans. Here we examined diffusion tensor MRI marker profiles for detecting MCI and dementia in a multi-ethnic cohort.

Methods: 3T MRI measures of fractional anisotropy (FA) were examined among n=1,636 participants of the ongoing community-based Health & Aging Brain among Latino Elders (HABLE) community-based study (Mexican American n=851; non-Hispanic white n=785).

Results: The FA-profile was highly accurate in detecting both MCI (AUC=0.99) and dementia (AUC=0.98). However, the FA-profile varied significantly not only between diagnostic groups but also between Mexican Americans and non-Hispanic whites.

Conclusion: Findings suggest that DTI markers may have a role in the neurodiagnostic process for detecting MCI and dementia among diverse populations.

Keywords

Alzheimer's disease; mild cognitive impairment; fractional anisotropy; diffusion tensor imaging; Mexican American

Introduction

Alzheimer's disease (AD) is the most common form of neurodegenerative disease effecting nearly 50 million older adults globally[1]. Having available valid, biologically based and readily available screening tools would facilitate early diagnosis and appropriate referrals. MRI is a diagnostic tool that has increased availability across a range of settings with a large literature documenting the utility of various MRI-based biomarkers for detecting MCI and AD. Despite this established literature, few studies have explicitly examined MRI-based measures for detecting MCI and AD among community-dwelling Mexican Americans.

Diffusion tensor imaging (DTI) of the brain is an advanced technique to examine structural connectivity that has been investigated as a putative diagnostic biomarker for MCI and AD [2]. Elevated diffusivity and decreased fractional anisotropy have been consistently found in prodromal AD and cognitively normal who develop MCI [3]. DTI has shown superficial white matter changes in both AD and MCI [4]. DTI measurements were able to distinguish normal controls, subcortical ischemic vascular disease patients and those with AD [5]. Kang et al [3] using the ADNI database found that a deep-learning algorithm of MRI-based biomarkers, including DTI, could accurately distinguish early MCI (EMCI) from normal controls with a 94% accuracy. Using advanced machine learning methods an MRI-based algorithm, including DTI measures, could discriminate AD from vascular dementia with 77% accuracy [6].

Despite the extant literature linking DTI measures to MCI and AD, the vast majority of this work has been conducted among dementia clinic-based non-Hispanic white participants. An emerging literature documents the impact of race and ethnicity on biomarkers of AD [7–10]; however, no prior studies have examined the potential diagnostic accuracy of DTI measures among community-dwelling Mexican Americans. Given that Hispanics are the largest ethnic

minority population in the U.S.[11], are expected to suffer the largest increase in AD and AD related dementias (ADRD) over the next several decades [12], and Mexican Americans make up 65% of the U.S. Hispanic community [13] it is important to understand biomarkers of AD among this population.

Our prior work has shown that there are significant differences in clinically diagnosed MCI and AD as compared to non-Hispanic whites in that: (1) the link between established clinical risk factors and MCI and AD are different among Mexican Americans [14] (2) ApoE4 genotype is lower among Mexican Americans [15] and (3) the blood-based biomarker profile of AD is different among Mexican Americans [16]. Our more recent work demonstrates that cerebral amyloid positivity rates are lower among Mexican Americans [17] and neurodegeneration begins at younger ages among this ethnic group. Given these prior findings, it is our hypothesis that DTI biomarker profiles will be different among Mexican Americans as compared to non-Hispanic whites.

The current study examined the diagnostic accuracy of DTI measures for detecting MCI and AD in a community-based cohort of Mexican Americans and non-Hispanic whites. We first focused on DTI-based measures of fractional anisotropy (FA) and then conducted follow-up models broadening the DTI-algorithm to include measures of FA, axial diffusivity (ADiff), mean diffusivity (MD) and radial diffusivity (RD).

Materials and Methods

Participants

The HABLE study is an ongoing, longitudinal, community-based project examining health disparities in MCI and AD among Mexican Americans as compared to non-Hispanic whites [17]. The HABLE study enrolls participants using our previously-published community-based participatory research (CBPR) approach [19–21], which has been demonstrated to be a successful method for engaging underserved populations into research [22, 23]. Our work has shown that our community-based approach yields a representative sample of the larger community [18]. The HABLE protocol takes place over multiple appointments all completed within a 4-month timeframe at the Institute for Translational Research (ITR) at the University of North Texas Health Science Center, Fort Worth, TX. The protocol includes an interview, functional exam, blood draw for clinical labs and biobanking, neuropsychological testing and 3T MRI of the brain. All aspects of the study protocol can be conducted in Spanish or English, depending on the participant's preference. An informant provides information regarding the participants daily functioning. Clinical dementia rating (CDR) scales are completed using these structured questions by a clinician with experience in dementia assessments. The UNT Health Science Center IRB has approved the HABLE protocols (2016–128 and 2017–165) and each participant (or his/her legal representative) signs written informed consent. The HABLE database is publicly available through the UNTHSC Institute for Translational Research webpage and raw images available through LONI.

Diagnostic Classification

Cognitive diagnoses are assigned algorithmically according to the following criteria: Normal Control (NC) = no cognitive complaints, CDR sum of boxes score of 0 and cognitive tests scores broadly within normal limits; Mild Cognitive Impairment (MCI): cognitive complaint (self or other), CDR sum of boxes score between 0.5–2.0[24] and at least one cognitive test score falling 1.5 standard deviation below normative ranges; Dementia: CDR sum of boxes score >=2.5 and at least two cognitive test scores 2 standard deviation below normative ranges. Those who have cognitive complaints and normal cognition are coded as subjective cognitive concerns (SCC). HABLE cohort z-score adjusted norms were created for all cognitive test scores stratified by education (0–7 years of education, 8–12 years of education, 13+ years of education), primary language (Spanish or English), age (age <=65 versus >=66).

Neuroimaging

Neuroimaging was conducted in Fort Worth, Texas for all participants. All HABLE neuroimaging scans are stored, managed, and processed by the USC Laboratory of Neuroimaging (LONI). The HABLE MRI protocol is based on that of ADNI3 using a 3T Siemens Magnetom SKYRA whole-body scanner. For this study, diffusion tensor MRI was examined. The DTI data was acquired from 64 gradient directions (b= 1000s/mm2) at a spatial resolution of 1.7mm×1.7mm×2.5mm. For the analysis of the DTI data, we first applied the eddy correct command from the FSL [25] to correct for distortions from eddy currents. After that, the DTI data was skull stripped with the BET tool from FSL and resampled to an isotropic resolution of 2mm. The FA was computed for each voxel in the DTI image. To measure the FA in major white matter regions, we used the nonlinear image registration tool from the ANTS software [26] to warp a publicly available white matter atlas [27] to each HABLE subject. For each hemisphere, the mean FA value of 13 white matter regions was finally computed for statistical analysis and machine learning classification (FA-algorithm). The mean values of axial diffusivity (ADiff), mean diffusivity (MD) and radial diffusivity (RD) of the same 13 white matter regions were used for follow-up analyses (DTI-algorithm).

Statistical Methods

Group comparisons for demographics were conducted using SPSS 24 (IBM). Support vector machine (SVM) analyses were conducted using R (V 3.3.3) statistical software. We used 10 times repeated 5-fold cross-validation to directly perform SVM parameter tuning and optimal cutoff determination using Grid Search, a traditional way of performing hyperparameter optimization [28]. Once the process is completed, the evaluation metrics are summarized using the mean. The advantage of 10 times repeated 5-fold cross-validation is that it can provide a more reliable estimate of out-of-sample performance by reducing the variance associated with a single trial of cross-validation. Diagnostic accuracy was calculated via receiver operating characteristic (ROC) curves. Diagnostic accuracy measures of sensitivity (SN), specificity (SP) as well as positive (PPV) and negative predictive value (NPV) were calculated. Analyses were conducted as follows: (1) detecting MCI versus normal control in the entire cohort, (2) detecting MCI versus normal control split by

ethnicity, (3) detecting dementia versus normal controls in the entire cohort and (4) detecting dementia versus normal control split by ethnicity. The SVM profile first examined FA (FA-profile) measures only then using FA, ADiff, MD and RD (DTI-profile).

Results

The characteristics of the HABLE cohort has been described in detail elsewhere [17]. The current study included n=1,636 participants: Mexican American n=851; normal control n=648, MCI n=145, dementia n=58; non-Hispanic White n=785; normal control n=654, MCI n=86, dementia n=45. To estimate positive (PPV) and negative predictive value (NPV), the base rates of diagnoses in the cohort were used. In the total cohort, the base rate of MCI was 14% and dementia was 6%. Among Mexican Americans, the base rate of MCI was 17% and dementia was 7%. Among non-Hispanic whites, the base rate of MCI was 11% and dementia 6%. Table 1 provides the demographic characteristics of the cohort. The Mexican American cohort was significantly younger ($p<0.001$) and obtained fewer years of education ($p<0.001$) than the non-Hispanic white cohort. The Mexican American cohort also had significantly higher rates of diabetes ($p<0.0001$) and were significantly less likely to have a primary care provider ($p<0.0003$).

With regards to detecting MCI in the entire cohort, the FA-profile (optimized cut-score=0.885) yielded an Area under the ROC curve (AUC) of 0.99, SN of 0.99, SP of 0.99 and, at 14% base rate, a PPV of 94% and NPV of 99%. See Figure 1 for classification accuracy, variable importance plot and ROC curve. The expanded DTI-profile (optimized cut-score =0.92) resulted in an AUC of 0.99, SN of 0.99, SP of 0.99 and PPV of 94% and NPV of 99%.

Examining the Mexican American cohort, the FA-profile (optimized cut-score = 0.964) yielded an AUC of 0.96, SN of 0.86, SP of 0.97 and, at a base rate of 17%, a PPV of 85% and NPV of 97%. See Figure 2 for classification accuracy, variable importance plot and ROC curve. The expanded DTI-profile yielded an AUC of 0.98, SN of 0.96, SP of 0.99 and a PPV of 95% and NPV of 99%. When examining the non-Hispanic White cohort, the FA-profile (optimized cut-score = 0.997) yielded an AUC of 0.89, SN of 0.74, SP of 0.94 and, at a base rate of 11%, a PPV of 60% and a NPV of 97%. See Figure 3 for classification accuracy, variable importance plot and ROC curve.

For detecting dementia in the entire cohort (optimized cut-score=0.976), the FA-profile yielded an AUC of 0.98, SN of 0.94, SP of 0.99 and, with a base rate of 6%, a PPV of 86% and NPV of 99% (Figure 4). The expanded DTI-based algorithm (optimized cut-score =0.92) yielded an AUC of 0.96, SN of 0.84, SP of 0.98 and PPV of 73% and NPV of 99%.

For Mexican Americans, the FA-profile (optimized cut-score = 0.903) yielded an AUC of 0.96, SN of 0.88 and SP of 0.99. At a base rate of 7%, the PPV was 87% and the NPV was 99%. See Figure 5 for classification accuracy, variable importance plot and ROC curve. The expanded DTI-profile yielded an AUC of 0.93, SN of 0.88, SP of 0.97, PPV of 69% and NPV of 99%. For the non-Hispanic White cohort, the FA-profile (optimized cut-score = 0.998) yielded an AUC of 1.0, SN of 1.0 and SP of 1.0. At a base rate of 7%, the PPV and

NPV were 100% (Figure 6). The expanded DTI-profile algorithm yielded an AUC of 0.93, SN of 0.73, SP of 0.98 and PPV of 70% and NPV of 98%.

Discussion

Our results support the application of a MRI based tool (FA-profile; DTI-profile) as a mechanism to detect MCI and Dementia cases in a multi-ethnic community-based sample. Our results suggest a 99% NPV for dementia and 97–100% for ruling out MCI and dementia across ethnic groups. The FA-profile for MCI and dementia were distinct as were the profiles within each category by ethnicity. The top five FA markers for dementia were anterior corona radiata, cingulum — hippocampus, superior longitudinal fasciculus, uncinate fasciculus and anterior limb of the internal capsule. The top five FA tracts for MCI were cingulum — cingulate gyrus, cingulum — hippocampus, splenium of the corpus callosum, anterior corona radiata and the inferior fronto — occipital fasciculus. However, within diagnostic classification, further differences were observed. The top five markers for dementia for Mexican Americans were anterior corona radiata, inferior fronto-occipital fasciculus, splenium of corpus callosum, cingulum of hippocampus, and superior corona radiata; Non-Hispanic Whites: posterior thalamic radiation, cingulum of hippocampus, cingulum cingulate gyrus, and genu and splenium of the corpus callosum. For Dementia cases, only two tracts overlapped across cohorts. Ongoing analysis is investigating these findings to determine the impact of these different tracts on cognitive processes as a function of ethnicity.

When the FA-profile was applied to detect MCI among the Mexican American cohort, the top tracts were the anterior limb internal capsule, posterior limb internal capsule, superior corona radiata, splenium and body of the corpus callosum. For the Non-Hispanic white cohort the top tracts were the posterior thalamic radiation, inferior fronto-occipital fasciculus, cingulum of hippocampus, anterior corona radiata, and superior longitudinal fasciculus. There was no overlap in white matter tracts across ethnic cohorts for the FA-profiles distinguishing MCI; however, there was overlap within ethnic group between MCI and Dementia profiles. For the FA-profile for the Mexican American cohort, two tracts overlapped across diagnostic groups (splenium of corpus callosum, superior corona radiate) while two different tracts overlapped (posterior thalamic radiation, cingulum of hippocampus) for the Non-Hispanic white cohort.

This provides valuable insight into the biological differences in disease profiles among a multi-ethic cohort and adds to the literature demonstrating the importance of understanding the biological mechanisms of MCI and dementia across racial and ethnic groups. Recent work has demonstrated that SES factors were significantly associated with MRI-based markers of neurodegeneration among African Americans [29. In the HABLE study, SES factors (i.e., acculturation, household income) were significantly related to MRI-based neurodegeneration among Mexican Americans, but not for non-Hispanic whites. This shows the importance of examining the AT(N) framework[30] biomarkers within the NIA Health Disparities Research Framework [31].

The FA-profile findings are consistent with prior work among Non-Hispanic white individuals with AD as compared to healthy older adults that showed a link between FA values in the corpus callosum, left internal capsule, corona radiate, posterior thalamic radiations, inferior longitudinal fasciculi, inferior fronto-occipital fasciculi, external capsule, cingulate gyri, right hippocampal cingulum, superior longitudinal fasciculi [2]. Further work is needed to examine longitudinal changes in FA values and association with AD among a multi-ethnic cohort to understand the utility of a FA-profile in diagnosing AD across all stages of the disease. Current work is ongoing in the HABLE study to explore longitudinal changes. We are adding an African American sample to our cohort to further clarify the impact of race and ethnicity on DTI profiles. The current findings provide evidence for the potential use of DTI-FA profiles in a neurodiagnostic process for screening out MCI and dementia among multi-ethnic populations.

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References

[1]. Dementia & Alzheimers Help | Global | Alzheimer’s Association n.d. https://alz.org/global/overview.asp (accessed December 13, 2020).

[2]. Mayo CD, Garcia-Barrera MA, Mazerolle EL, Ritchie LJ, Fisk JD, Gawryluk JR. Relationship between DTI metrics and cognitive function in Alzheimer’s disease. Front Aging Neurosci 2019. 10.3389/fnagi.2018.00436.

[3]. Kang L, Jiang J, Huang J, Zhang T. Identifying Early Mild Cognitive Impairment by Multi-Modality MRI-Based Deep Learning. Front Aging Neurosci 2020;12. 10.3389/fnagi.2020.00206.

[4]. Bigham B, Zamanpour SA, Zemorshidi F, Boroumand F, Zare H; Alzheimer’s Disease Neuroimaging Initiative. Identification of Superficial White Matter Abnormalities in Alzheimer's Disease and Mild Cognitive Impairment Using Diffusion Tensor Imaging. J Alzheimer’s Dis Rep. 2020 Feb 28;4(1):49–59. doi: 10.3233/ADR-190149. [PubMed: 32206757]

[5]. Tu MC, Lo CP, Huang CF, Hsu YH, Huang WH, Deng JF, Lee YC. Effectiveness of diffusion tensor imaging in differentiating early-stage subcortical ischemic vascular disease, Alzheimer's disease and normal ageing. PLoS One. 2017 Apr 7;12(4):e0175143. doi: 10.1371/journal.pone.0175143. [PubMed: 28388630]

[6]. Castellazzi G, Cuzzoni MG, Cotta Ramusino M, Martinelli D, Denaro F, Ricciardi A, et al. A Machine Learning Approach for the Differential Diagnosis of Alzheimer and Vascular Dementia Fed by MRI Selected Features. Front Neuroinform 2020;14. 10.3389/fninf.2020.00025.

[7]. Babulal GM, Quiroz YT, Albensi BC, Arenaza-Urquijo E, Astell AJ, Babiloni C, et al. Perspectives on ethnic and racial disparities in Alzheimer’s disease and related dementias: Update and areas of immediate need. Alzheimer’s Dement 2019;15:292–312. 10.1016/j.jalz.2018.09.009. [PubMed: 30555031]

[8]. O’Bryant SE, Xiao G, Edwards M, Devous M, Gupta VB, Martins R, et al. Biomarkers of Alzheimer’s disease among Mexican Americans. J Alzheimer’s Dis 2013. 10.3233/JAD-122074.

[9]. Morris JC, Schindler SE, McCue LM, Moulder KL, Benzinger TLS, Cruchaga C, et al. Assessment of Racial Disparities in Biomarkers for Alzheimer Disease. JAMA Neurol 2019. 10.1001/jamaneurol.2018.4249.

[10]. Howell JC, Watts KD, Parker MW, Wu J, Kollhoff A, Wingo TS, et al. Race modifies the relationship between cognition and Alzheimer's disease cerebrospinal fluid biomarkers. Alzheimer's Res Ther 2017. 10.1186/s13195-017-0315-1.

[11]. Pew Research Center [Internet]. How the Hispanic Population is Changing? [Cited 2020 March 10]. Available from: https://www.pewresearch.org/fact-tank/2017/09/18/how-the-us-hispanic-population-is-changing/

[12]. Matthews KA, Xu W, Gaglioti AH, Holt JB, Croft JB, Mack D, et al. Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015–2060) in adults aged ≥65 years. Alzheimer's Dement 2019. 10.1016/j.jalz.2018.06.3063.

[13]. Vespa J, Medina L, Armstrong DM. Demographic Turning Points for the United States: Population Projections for 2020 to 2060 Population Estimates and Projections Current Population Reports. n.d.

[14]. O'Bryant SE, Johnson L, Reisch J, Edwards M, Hall J, Barber R, Devous MD, Royall D, Singh M. Risk factors for mild cognitive impairment among Mexican Americans. Alzheimers Dement. 2013 Nov; 9 (6):622–631.e1. doi: 10.1016/j.jalz.2012.12.007. Epub 2013 May 2. [PubMed: 23643456]

[15]. O'Bryant SE, Johnson L, Balldin V, Edwards M, Barber R, Williams B, Devous M, Cushings B, Knebl J, Hall J. Characterization of Mexican Americans with mild cognitive impairment and Alzheimer's disease. J Alzheimers Dis. 2013;33(2):373–9. doi: 10.3233/JAD-2012-121420. [PubMed: 22976076]

[16]. O'Bryant SE, Xiao G, Edwards M, Devous M, Gupta VB, Martins R, Zhang F, Barber R; Texas Alzheimer's Research and Care Consortium (TARCC). Biomarkers of Alzheimer's disease among Mexican Americans. J Alzheimers Dis. 2013;34(4):841–9. doi: 10.3233/JAD-122074. [PubMed: 23313927]

[17]. O'Bryant SE, Johnson LA, Toga AW, Hall JR, Large S, Zhang F, Braskie M, Shi Y, Gavett B, Nandy R, Vintimilla R, King K, Palmer R, Petersen M, McColl R, Mason D, Christian B, Barber R, Philips N, Rissman R & Yaffe K for the HABLE Study Team. (2021, in press) The Health and Aging Brain among Latino Elders (HABLE) study Methods and Participant Characteristics. Alzheimer's & Dementia, Diagnosis, Assessment & Disease Monitoring

[18]. O'Bryant SE, Zhang F, Petersen M, Hall JR, Johnson LA, Yaffe K, Mason D, Braskie M, Barber RA, Rissman RA and Toga AW for the HABLE Study Team (in press) A Blood Screening Tool for Alzheimer's Disease Among Community-Dwelling Mexican Americans and non-Hispanic Whites: A Method for increasing Representation of Diverse Populations in Research and Trials. Alzheimer's & Dementia, Diagnosis, Assessment & Disease Monitoring

[19]. Johnson LA, Gamboa A, Vintimilla R, Cheatwood AJ, Grant A, Trivedi A, et al. Comorbid Depression and Diabetes as a Risk for Mild Cognitive Impairment and Alzheimer's Disease in Elderly Mexican Americans. J Alzheimer's Dis 2015. 10.3233/JAD-142907.

[20]. Szerlip HM, Edwards ML, Williams BJ, Johnson LA, Vintimilla RM, O'Bryant SE. Association between cognitive impairment and chronic kidney disease in Mexican Americans. J Am Geriatr Soc 2015. 10.1111/jgs.13665.

[21]. O'Bryant SE, Edwards M, Menon C V., Gong G, Barber R. Long-term low-level arsenic exposure is associated with poorer neuropsychological functioning: A project FRONTIER study. Int J Environ Res Public Health 2011. 10.3390/ijerph8030861.

[22]. O'Fallon LR, Dearry A. Community-based participatory research as a tool to advance environmental health sciences. Environ Health Perspect 2002. 10.1289/ehp.02110s2155.

[23]. Ravenell JE, Ogedegbe G. Community programs for hypertension: A means of identification and intervention in the highest-risk population. Hypertens. High Risk African Am. Curr. Concepts, Evidence-based Ther. Futur. Considerations, 2015. 10.1007/978-1-4939-2010-5_4.

[24]. O'Bryant Waring SC, Cullum CM, Hall JR, Lacritz L, Massman PJ, Lupo PJ, Reisch JS, Doody RSE. Staging dementia using Clinical Dementia Rating Scale sum of boxes scores. Arch Neurol 2008;65:1091–5. [PubMed: 18695059]

[25]. Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. FSL. Neuroimage. 2012 Aug 15;62 (2):782–90. doi: 10.1016/j.neuroimage.2011.09.015. Epub 2011 Sep 16. [PubMed: 21979382]

[26]. Avants BB, Epstein CL, Grossman M, Gee JC. Symmetric diffeomorphic image registration with cross-correlation: Evaluating automated labeling of elderly and neurodegenerative brain. Med Image Anal 2008;12:26–41. 10.1016/j.media.2007.06.004. [PubMed: 17659998]

[27]. Oishi K, Faria A, Jiang H, Li X, Akhter K, Zhang J, et al. Atlas-based whole brain white matter analysis using large deformation diffeomorphic metric mapping: Application to normal elderly and Alzheimer's disease participants. Neuroimage 2009;46:486–99. 10.1016/j.neuroimage.2009.01.002. [PubMed: 19385016]

[28]. LaValle SM, Branicky MS. On the relationship between classical grid search and probabilistic roadmaps. Springer Tracts Adv. Robot., 2004. 10.1007/978-3-540-45058-0_5.

[29]. Meeker KL, Wisch JK, Hudson D, Coble D, Xiong C, Babulal GM, Gordon BA, Schindler SE, Cruchaga C, Flores S, Dincer A, Benzinger TL, Morris JC, Ances BM. Socioeconomic Status Mediates Racial Differences Seen Using the AT(N) Framework. Ann Neurol. 2021 Feb;89 (2):254–265. doi: 10.1002/ana.25948. Epub 2020 Nov 7. [PubMed: 33111990]

[30]. Jr Jack, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018;14:535–62. 10.1016/j.jalz.2018.02.018. [PubMed: 29653606]

[31]. Hill CV, Pérez-Stable EJ, Anderson NA, Bernard MA. The National Institute on Aging Health Disparities Research Framework. Ethn Dis. 2015 Aug 7;25 (3):245–54. doi: 10.18865/ed.25.3.245. [PubMed: 26675362]

	Actual	
Predicted	MCI	NC
MCI	228	1
NC	3	1301
Sensitivity	99%	
Specificity	99%	
NPV	99%	
AUC	99%	

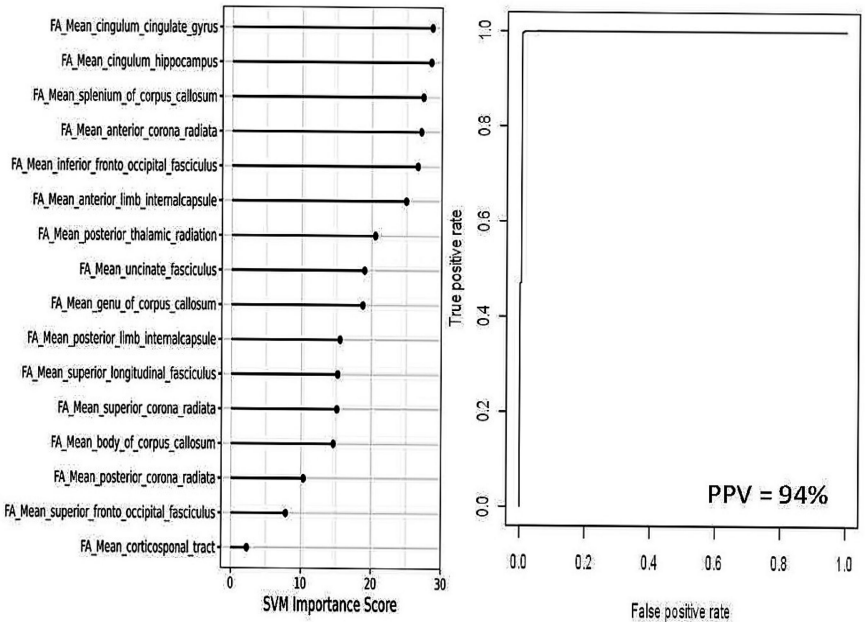
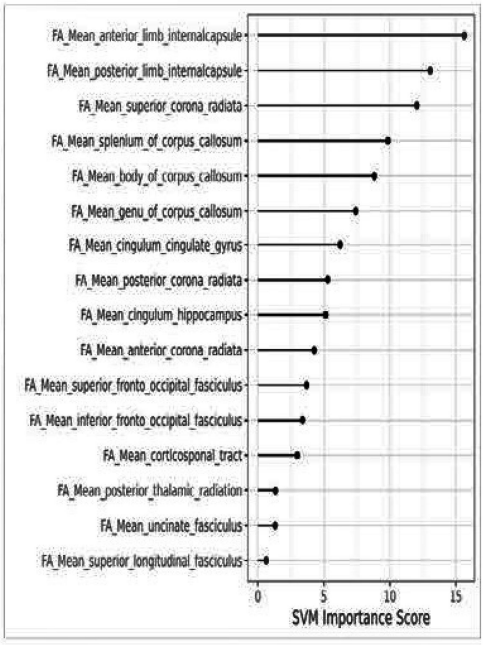


Figure 1:
Classifying MCI in the Cohort

	Actual	
Predicted	MCI	NC
MCI	124	20
NC	21	628
Sensitivity	86%	
Specificity	97%	
NPV	97%	
AUC	96%	



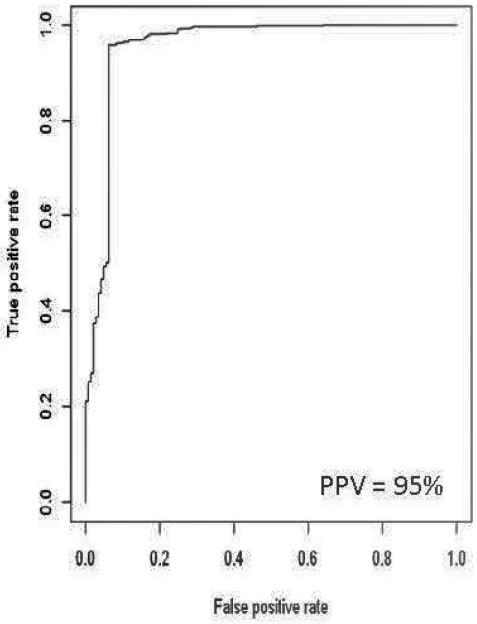
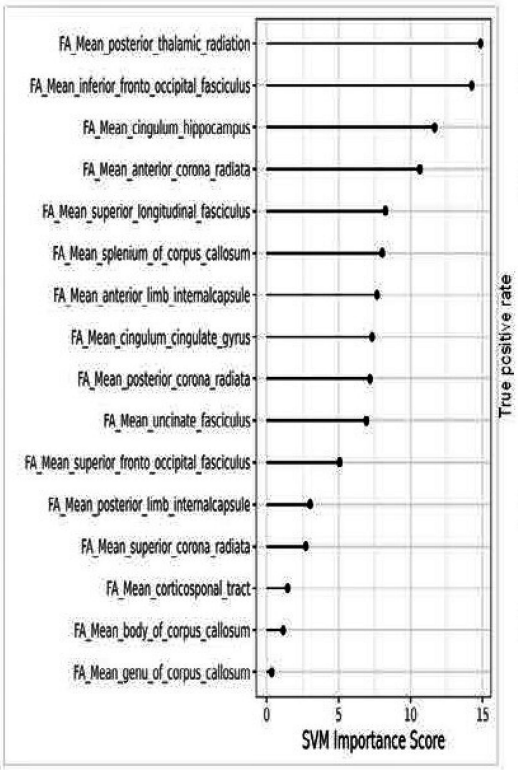


Figure 2:
Classifying MCI among the Mexican American Cohort

	Actual	
Predicted	MCI	NC
MCI	64	38
NC	22	616
Sensitivity	74%	
Specificity	94%	
NPV	97%	
AUC	89%	



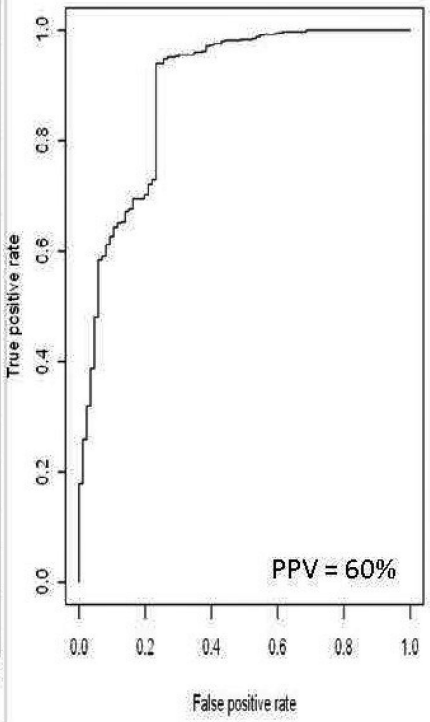


Figure 3:
Detecting MCI among the non-Hispanic White Cohort

	Actual	
Predicted	AD	NC
AD	97	5
NC	6	1297
Sensitivity	94%	
Specificity	99%	
NPV	99%	
AUC	98%	

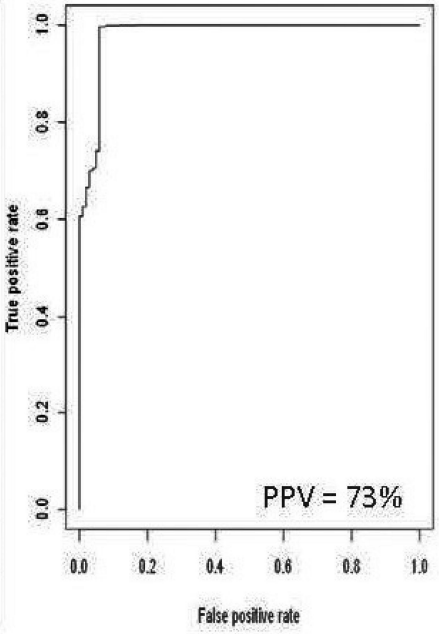
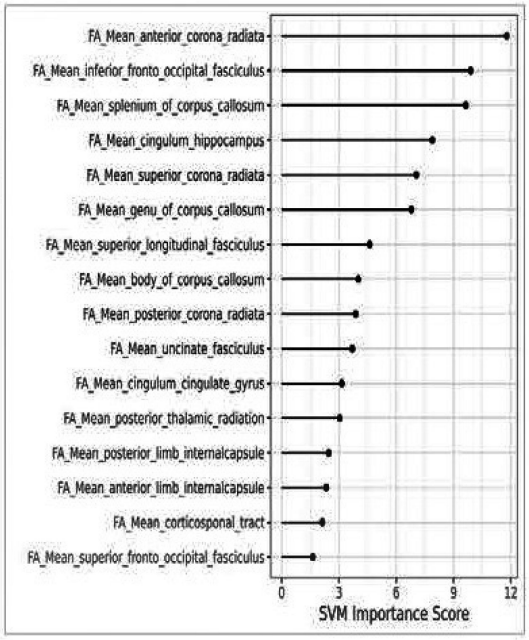


Figure 4:
Classifying Dementia among the Cohort

	Actual	
Predicted	AD	NC
AD	51	2
NC	7	646
Sensitivity	88%	
Specificity	99%	
NPV	99%	
AUC	96%	



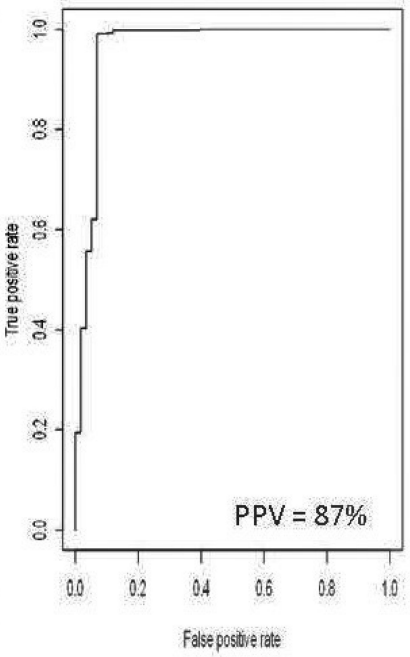
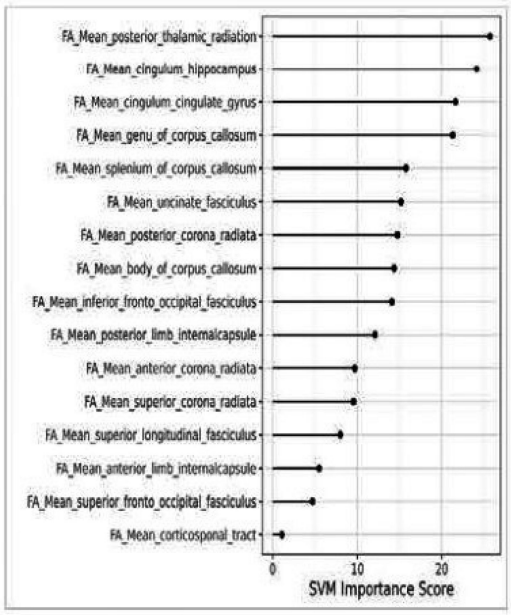


Figure 5:
Classifying Dementia among the Mexican American Cohort

	Actual	
Predicted	AD	NC
AD	45	0
NC	0	654
Sensitivity	100.00%	
Specificity	100.00%	
NPV	100.00%	
AUC	100.00%	



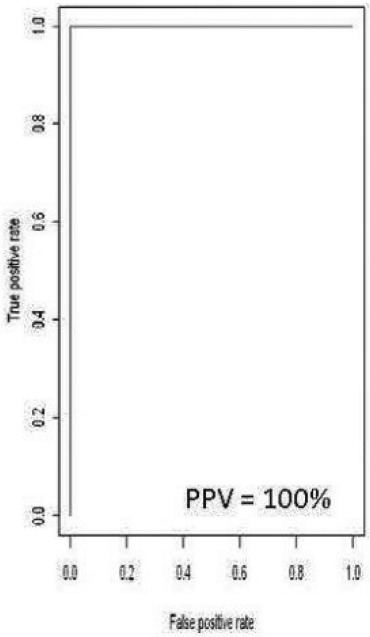


Figure 6:
Classifying Dementia among the non-Hispanic White Cohort

Table 1:

Baseline Cohort Characteristics

	Total Cohort N=1,636	**Mexican American N=850**	**Non-Hispanic White N=784**
Age	66.47 (8.78)	63.87 (7.99)	69.26 (8.75)
Gender (% female)	61%	67%	55%
Education	12.38 (4.81)	9.49 (4.59)	15.50 (2.57)
BMI	29.83 (5.88)	30.61 (5.66)	28.97 (6.00)
Diabetes (% yes)	25%	36%	13%
Dyslipidemia (% yes)	62%	64%	61%
Hypertension (% yes)	59%	63%	55%
Depression (% yes)	32%	33%	31%
Annual Income	$59,739.90 ($70,515.76)	$36,283.71 ($48,630.49)	$85,016.91 ($81,024.37)
Current Residence			
Own	76%	72%	79%
Rent	18%	19%	18%
Live Rent Free	5%	8%	2%
Insurance (% no)	86%	24%	4%
Have Primary Care Provider (% no)	13%	21%	4%
Control	80% (n=1302)	76% (n=647)	83% (n=653)
MCI	14% (n=231)	17% (n=145)	11% (n=86)
Dementia	6% (n=103)	7% (n=58)	6% (n=45)