The Relationship of Plasma Biomarkers of Alzheimer's Disease and Neuropsychological Test Performance in Older Adults with Unimpaired Cognition: The Impact of Ethnicity

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Article

The Relationship of Plasma Biomarkers of Alzheimer's Disease and Neuropsychological Test Performance in Older Adults with Unimpaired Cognition: The Impact of Ethnicity

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Abstract: There has been significant increase of studies investigating plasma biomarkers of Alzheimer's and their relationship to cognitive functioning. The impact of ethnicity on this relationship has not been extensively studied. The current research investigated the relationship between the plasma biomarkers of total tau, $A\beta_{40}$, $A\beta_{42}$ and NfL and neuropsychological test performance in a bi-ethnic sample of cognitively unimpaired, older community dwelling adults. The 1326 cognitively unimpaired participants drawn from The Health & Aging Brain Study – Health Disparities (HABS-HD) study included 765 Mexican American participants and 860 non-Hispanic White participants with complete plasma biomarkers and neuropsychological testing. Plasma samples were assayed using Simoa technology. Significant differences in concentrations were found for all of the plasma biomarkers. NHWs had significantly higher levels of each of the biomarkers with a lower $A\beta_{42}$/ $A\beta_{40}$. With none of the biomarkers related to performance on any of the neuropsychological tests. For MAs, $A\beta_{40}$ was the only biomarker that was significantly related to neuropsychological test performance. $A\beta_{40}$ levels were negatively related to performance on Trails A, Trails B and Digit Symbol Substitution. Results suggest that the relationship of these biomarkers to cognitive functioning is impacted by ethnicity and may be domain specific.

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1. Introduction

The AT(N) framework[1] provides a biologically based approach to understanding the nature of Alzheimer's and its diagnosis and progression. Initially the AT(N) framework emphasized imaging and CSF biomarkers as reflecting the nature of the pathological processes underlying AD. Subsequently there has been an increased interest in blood-based biomarkers of these processes due to the cost-effective, minimally invasive and highly scalable nature of these biofluids[2–6]. The advent of single molecule array technology has made the reliable assessment of plasma biomarkers of amyloid ($A\beta_{40}$ & $A\beta_{42}$), tau (total tau) and neurodegeneration (NfL) possible.

High levels of baseline $A\beta_{42}$ has been shown to predictive of cognitive decline in cognitively unimpaired[7] and higher levels of $A\beta_{42}$ and total tau were predictive of cognitive decline in healthy older adults.[8]. Studies of the relationship of $A\beta_{40}$ and cognitive decline have generally failed to show a strong relationship although the ratio of $A\beta_{42}$ to $A\beta_{40}$ ($A\beta_{42}$/ $A\beta_{40}$) has been related to cognitive

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decline[9] and conversion from MCI to dementia[10]. In studies of cognitively unimpaired individuals, the ratio has been shown to significantly predict brain amyloidosis in in a multinational study[11] and to predict cognitive changes in non-demented study participants[12]. Lower plasma $A\beta_{42}$/ $A\beta_{40}$ has been associated with cognitive decline over time in a community-based cohort[14]. Lower plasma $A\beta_{42}$/ $A\beta_{40}$ has also been found to predict cognitive decline in healthy individuals with subjective cognitive complaints[13] and is associated with a steeper rate of decline on test scores of attention, memory and executive functions in cognitively normal elderly[4].

Total tau has been associated with increased declines in neuropsychological performance on measures of attention, memory and visuospatial and the risk for developing MCI[15]. Pase et al.[16] found total tau was related to measures of memory, attention and executive functioning and increased risk for dementia in the Framingham Dementia study.

Neurofilament Light (NfL), a marker of neurodegeneration that has been related to a number of neurological diseases, has been shown to be related to memory, language and executive functions in non-dementia elders and MCI[17]. Marks et al.[18] in a longitudinal study of cognitive decline found baseline plasma NfL to be associated with decline in global cognition and the combination of elevated NfL and elevated plasma total tau was associated with declines in global cognition and memory.

Even with the significant increase in research investigating the utility of plasma biomarkers there are a number of gaps in our understanding of the factors influencing the level of these biomarkers and their relationship to measures of cognitive impairment. One of the gaps in understanding is the impact of ethnicity on plasma biomarkers. Little of the research on plasma biomarkers has focused on diverse United States populations in community settings. Among those studies that have been conducted on plasma biomarkers of AD and ethnicity, the vast majority have been biethnic/bi-racial studies comparing Hispanics or African Americans (AA) to Non-Hispanic Whites (NHW) across diagnostic groups or research on one of the ethnoracial groups comparing diagnostic groups. A cross-sectional study of elderly Mexican Americans (MA) found NfL having a negative impact on performance on neurocognitive testing for both cognitively unimpaired and MCI[19]. Gonzales et al.[20] found that total tau and NfL discriminated between diagnostic groups for both Hispanics (predominately Mexican Americans) and NHWs. The same study found no difference in NfL levels in a demographically matched subset of the two ethnic groups. O'Bryant et al.[21] in a bi-ethnic study of Mexican Americans (MAs) and NHWs found NfL significantly associated with diagnostic groups for both ethnic groups. A study of a diverse Florida sample found no effect for Hispanic ethnicity (predominately Caribbean background) on NfL levels[22].

A study of plasma biomarkers in African Americans including tau and $A\beta_{42}$ comparing cognitively normal controls with Alzheimer's patients found that tau was significantly higher in the AD group and $A\beta_{42}$ level was not associated with Alzheimer's[23]. A WHICAP community-based study of plasma biomarkers found no significant differences across Hispanic, Black and Non-Hispanic Whites in concentrations of t tau, $A\beta_{40}$, $A\beta_{42}$ or NfL[24]. A study of ADNI participants comparing matched samples of African Americans, Non-Hispanic Whites and Hispanics found no significant difference in plasma p-tau 181 and NfL across the racial/ethnic groups[25]. Whereas, a community based study of MAs, AAs and NHWs found significant differences between the groups on these biomarkers in both cognitively unimpaired and those with MCI[26].

These mixed findings suggest the need for further investigations to assess the effect of ethnicity on plasma biomarkers. The current research investigated the relationship between the plasma biomarkers of total tau, $A\beta_{40}$, $A\beta_{42}$ and NfL and neuropsychological test performance in a bi-ethnic sample of cognitively unimpaired, older community dwelling adults.

2. Methods

Participants & Assessment

The current study included 1326 participants with unimpaired cognition drawn from The Health & Aging Brain Study – Health Disparities (HABS-HD) study. The HABS-HD study is an ongoing, longitudinal, project examining health disparities in cognitive aging among community dwelling

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older Mexican Americans. The study cohort is composed of Mexican Americans (MA) and non-Hispanic whites (NHW) and was recently expanded to include African Americans[27]. The HABS-HD methods have been described in detail elsewhere[28]. Recruitment utilizes a community-based participatory research (CBPR) approach .which has been used successfully as a recruitment modality for reaching underserved and minority populations. This approach involves collaborating with local communities through outreach (holding community events, seminars), word of mouth, marketing modalities (newspaper, television, radio). Feedback related to clinical lab work, MRI clinical reads, and neuropsychological test results is provided to the participants and their health care providers.

Criteria for inclusion in the study include 1) self-reported ethnicity of African American (AA), Mexican American (MA) or Non-Hispanic White (NHW), 2) willingness to provide blood samples, 3) capable of undergoing neuroimaging studies, 4) age 50 and above, and 5) fluent in English or Spanish. Study exclusion criteria include 1) Type 1 diabetes, 2) presence of active infection, 3) current/recent (12 month) cancer (other than skin cancer), 4) current severe mental illness that could impact cognition (other than depression), 5) recent (12 months) traumatic brain injury with loss of consciousness, 6) current/recent alcohol/substance abuse, 7) active severe medical condition that could impact cognition such as end stage renal failure, chronic heart failure or chronic obstructive pulmonary disease and 8) current diagnosis of non-Alzheimer's related dementia.

The HABS-HD protocol includes an interview, functional exam, blood draw for clinical labs and biobanking, neuropsychological testing and 3T MRI of the brain. Amyloid and tau PET scans are ongoing for the full cohort. All aspects of the study protocol can be conducted in Spanish or English based on the preference of the participant. The HABS-HD study is conducted under IRB approved protocols and each participant (or his/her legal representative) signs written informed consent. The data included in this study includes only Mexican American and non-Hispanic white participants since the recruitment of the African American participants is ongoing. The data is available through the UNTHSC Institute for Translational Research (ITR) website[29].

Neuropsychological Assessment

The neuropsychological test battery includes: Mini Mental Status Exam[30] (MMSE); Wechsler Memory Scale- Third Edition (WMS-III)[31]; Digit Span, Logical Memory, Digit Symbol Substitution; Trail Making Test Parts A and B[32] ; Spanish-English Verbal Learning Test (SEVLT)[33] ; Animal Naming (semantic fluency)[34], FAS (phonemic fluency)[35] as well as the American National Adult Reading Test (English-speakers)[36], Word Accentuation Test (Spanish-speakers)[37], and depression (30-item Geriatric Depression Scale[38]). Norms specific to the study population were utilized where available[39]. A study partner with knowledge of the participant is interviewed for clinician completion of the Clinical Dementia Rating (CDR) Scale[40].

Diagnostic Classification

Cognitive diagnoses are assigned using an algorithm (decision tree) that is verified at consensus review. Unimpaired Cognition (UC) = no cognitive complaints, CDR sum of boxes score of 0 and cognitive test scores broadly within normal limits (i.e. performance no more than 1.5 standard deviations below the mean of the normative range on any test]); Mild Cognitive Impairment (MCI): cognitive complaint (self or other), CDR sum of boxes score between 0.5- 2.0 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. For the current study, only those meeting criteria for unimpaired cognition were included.

Assays

Blood Collection & Processing Procedures

Samples were assayed by the Institute for Translational Research (ITR) Biomarker Core in the University of North Texas Health Science Center ITR Laboratory. Fasting blood collection and processing followed the international guidelines for AD biomarker studies[41]. The ITR laboratory

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utilized the Hamilton Robotics EasyBlood for blood processing, aliquoting and re-aliquoting and a custom Hamilton Robotics StarPlus system was utilized for preparation of all plates. Proteomic assays for this study were processed on a multi-plex biomarker assay platform using electrochemiluminescence (ECL) using commercially available kits (Quanterix, Lexington, MA, USA).

Samples

A total of 500µl of plasma was utilized to measure biomarker levels using the Single Molecule Array (Simoa) technology from Quanterix. The NfL calibration range was 0-500pg/mL with the dynamic range of 0-2000pg/mL. CV for NFL was 0.038 and LLOD was 0.038pg/mL.

Multiplexed detection of $A\beta_{42}$, $A\beta_{40}$ and Total Tau was conducted using Simoa technology. Calibration ranges for $A\beta_{42}$, $A\beta_{40}$ and Total Tau were 0-60pg/mL, 0-140pg/mL, 0-100pg/mL and dynamic ranges of 0-240pg/mL, 0-560pg/mL, 0-400pg/mL, respectively. CVs for $A\beta_{42}$, $A\beta_{40}$ and Total Tau were reported at 0.043, 0.043 and 0.061 respectively. LLODs for $A\beta_{42}$, $A\beta_{40}$ and Total Tau were reported at 0.045pg/mL, 0.196pg/mL, and 0.019pg/mL, respectively. Interplate CVs were derived for high and low pooled controls from the Quanterix automated system: NFL (high control CV= 0.035, Low control CV= 0.092); $A\beta_{42}$ (High control CV= 0.051, Low control CV=0.040); $A\beta_{40}$ (High control CV=0.050, Low control CV= 0.042); Total Tau (High control CV=0.040, Low control CV= 0.047).

Statistical Analysis

The relationship between the biomarkers and neuropsychological tests was assessed using SPSS-25 (IBM). Neuropsychological test scores were transformed to z scores .For MMSE raw scores were used. Demographic data were analyzed using independent group t tests and chi squared. ANOVAs co-varying sex and age assessed differences between the two ethnic groups. Regression models including age and sex were created to examine the link between the blood-based biomarkers of $A\beta_{40}$, $A\beta_{42}$, Total Tau, NfL and neuropsychological test performance. Regression models were created for Mexican Americans and Non-Hispanic Whites separately. Statistical significant was set at $p<0.05$.

3. Results

Table 1 presents the characteristics of the sample which included 765 Mexican Americans (Males N= 245, Females N= 520) and 860 Non-Hispanic Whites (Males N=378, Females N= 482) with unimpaired cognition. The MAs were significantly younger than the NHW and had significantly fewer years of education. The MA group was composed of a significantly higher percent of females. Although the MMSE scores fell within the normal range for both groups, the NHWs scored significantly higher than the MAs did. Significant differences in concentrations were found for all of the plasma biomarkers co-varying sex, age, education and APOEε4 status. NHWs had significantly higher levels of each of the biomarkers with a lower $A\beta_{42}$/ $A\beta_{40}$.

Table 1. Characteristics of the Sample.

	Mexican American N= 765	**Non-Hispanic White N= 860**	
Age	M= 62.88 SD= 7.690	M=68.29 SD= 8.335	t= 13.543 df= 1623 p= .000*
Education	M= 9.96 SD= 4.509	M= 15.75 SD= 2.645	t= 31.977 df= 1623 p= .000*
Gender % Female	68%	56%	X^2 = 13.924 p= .000*
MMSE	M= 27.353 SD= 2.033	M= 29.77 SD= 1.042	F= 530.36 df= 1, 1623

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			p= .000*
$A\beta_{40}$	M= 2.635 SD= .6209	M= 2.795 SD= .6825	F= 24.215 df= 1, 1623 p= .000*
$A\beta_{42}$	M=1.552 SD= 1.108	M= 1.798 SD= 1.267	F= 17.630 df= 1, 1623 p= .000*
NfL	M= 1.645 SD= 1.099	M=1.931 SD= 1.200	F= 24.886 df= 1, 1623 p= .000*
t-Tau	M= .9896 SD= 1.356	M= 1.252 SD= 1.581	F= 12.738 df= 1, 1623 p= .000*
$A\beta_{42}$/ $A\beta_{40}$	M= .5790 SD= .2402	M= .5402 SD= .2139	F= 11.864 df= 1, 1623 p= .000*

*p= ≤.05.

On neuropsychological testing NHWs scored significantly higher on Trails A (F(1, 1, 1623)= 99.457, p= .000), Trails B (F(1, 1623)= 58.22, p= .000 along with MMSE (F(1, 1623)= 530.36, p= .000). No statistically significant difference between the two groups was found for Digit Symbol Substitution (F(1, 1623)= .076, p= .783), FAS (F(1, 1623)= ..229, p= .632), Animal Naming (F(1, 1623)= .386, p= .533) , Digit Span (F(1, 1623)= .436, p= .509), Logical Memory 1 (F(1, 1623)= .007, p= .935), Logical Memory 2 (F(1, 1623)= .047, p= .892) SVELT Immediate Memory (F(1, 1288)= .135, p= .714) or SVELT Delayed (F(1, 1623)= .099, p= .5753).

Table 2 presents the relationship of the plasma biomarkers to the neuropsychological test performance. The regression models reveal that none of the biomarkers was related to performance on any of the neuropsychological tests for the NHW participants. For the MA participants, $A\beta_{40}$ was a significant predictor of performance on Trails A and B and Digit Symbol Substitution. The $A\beta_{42}/A\beta_{40}$ ratio was negatively related to performance on Digit Symbol Substitution. Neither $A\beta_{42,}$ Total Tau nor NfL were significantly related to performance on any of the neuropsychological measures.

Table 2. Regression of Plasma Biomarkers and Neuropsychological Tests by Ethnicity.

	Mexican Americans N= 765	**Non-Hispanic Whites N= 860**
Digit Span	NS	NS
Trails A	$A\beta_{40}$ t= -2.612 p= .009*	NS
Trails B	$A\beta_{40}$ t= -2.290 p= .022*	NS
Digit Symbol Substitution	$A\beta_{40}$ t= -2.265 p= .024* $A\beta_{42}/A\beta_{40}$ ratio t= -1.961 p=.050*	NS
FAS	NS	NS
Animals	NS	NS
SEVLT Immediate Memory	NS	NS
SEVLT Delayed Memory	NS	NS
Logical Memory Immediate	NS	NS
Logical Memory Delayed	NS	NS
MMSE	NS	NS

*p= ≤.05 NS= Not Significant.

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4. Discussion

The findings of the current research show that the relationship of select plasma biomarkers of AD to neuropsychological performance in cognitively normal participants is different for the two ethnic groups under study. For MA participants, $A\beta_{40}$ was related in the expected direction to attention, processing speed and executive functions but neither $A\beta_{42}$ the other biomarker of amyloid nor t tau or NfL were related to any of the cognitive domains assessed. Although the NHW participants had significantly higher levels of each of the biomarkers and lower levels of the amyloid ratio, there was no relationship to test performance. Scores on measures of language were not related to any of the plasma biomarkers in either group.

Possible explanations for the relationship of $A\beta_{40}$ to specific domains of cognitive functioning for the Mexican American sample may be related to the nature of the neuropsychological tests, the characteristics of $A\beta_{40}$ and the level of vascular risks in our cohort. The Trail Making Tests (A&B) and Digit Symbol Substitution Test as measures of attention, processing speed and executive functioning have been shown to activate the prefrontal cortex[42,43], an area of the brain significantly impacted by vascular disease. $A\beta_{40}$ deposition has been related to cerebrovascular impairment involved in cognitive impairment and Alzheimer's[44] . Mexican American participants in the current study had significantly higher rates of hypertension and diabetes, two vascular-related risks related to cognitive decline[45,46].

Although the current study has relatively large, well-characterized samples of two distinct ethnic groups from a community-based cohort, there are limitations that may affect the generalizability of our results. The diagnostic assignment was based on clinical rather than imaging-based criteria. The issue of diagnostic validity will be resolved in the ongoing study as the entire HABS-HD cohort is undergoing brain amyloid imaging. The study population was limited to MA and NHW participants and our knowledge of the effect of diverse ethnoracial groups on these biomarkers will be greatly enhanced as we add 1000 African Americans to our cohort. Medical co-morbidities such as chronic kidney disease, which have been shown to effect the level of plasma biomarkers of amyloid and neurodegeneration[47–49] were not considered in our analyses. Other research has shown that the plasma biomarkers of $A\beta_{42}$/ $A\beta_{40}$ and NfL when added to demographic data are useful in the prediction of cognitive decline in cognitively unimpaired[50]. Given that our data was cross-sectional, we cannot assess the ability of our baseline levels to predict cognitive decline for either MA or NHW participants. As longitudinal data becomes available for our cohort the meaningfulness of our baseline measures as predictors of cognitive change will be assessed. The current study indicates that in cognitively unimpaired, ethnic factors significantly affect the relationship of select blood based biomarkers to neuropsychological test performance. In light of these findings, ethnicity needs to be considered when evaluating the impact of these biomarkers on cognition.

Author Contributions: JRH = conceptualization and design of study; acquisition and interpretation of data; drafting and revising manuscript; final approval of version to be published; agreement to be accountable for the accuracy and integrity of the work. MP = design of study; acquisition and interpretation of data; drafting and revising manuscript; final approval of version to be published; agreement to be accountable for the accuracy and integrity of the work. SEO = conceptualization and design of study; acquisition, analysis and interpretation of data; drafting and revising manuscript; final approval of version to be published; agreement to be accountable for the accuracy and integrity of the work.

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Institutional Review Board Statement: All participants (or his/her legal representative) signed written informed consent before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki and the protocol was reviewed and approved by the UNTHSC IRB protocols UNTHSC 2016–128 & 2020–125.

Data Availability: Data is available by contacting the University of North Texas Health Science Center Institute for Translational Research https://apps.unthsc.edu/itr/.

Conflicts of Interest Disclosures: SEO has multiple patents on precision medicine for neurodegenerative diseases and is the founding scientist of Cx Precision Medicine. No other authors reported any potential conflicts of interest.

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