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Stephanie L. Garrett, MD, CHPE Date

Is executive function impairment an Alzheimer's disease variant in African Americans or a separate and distinct dementia phenotype?

By

Stephanie L. Garrett, MD CHPE
Master of Science

Clinical Research

Ihab Hajjar, MD MS
Advisor

Felicia C. Goldstein, PhD
Committee Member

Matthew Magee, MPH PhD
Committee Member

Shakira Suglia, ScD
Committee Member

Accepted:

Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

Date

Is executive function impairment an Alzheimer's disease variant in African Americans or a separate and distinct dementia phenotype?

By

Stephanie L. Garrett
MD, Wright State University
School of Medicine, 1998

Advisor: Ihab Hajjar, MD MS

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Abstract

Is executive function impairment an Alzheimer's Disease variant in African Americans or a separate and distinct dementia phenotype?

By Stephanie L. Garrett, MD CHPE

Problem/Relevance: African Americans (AA) are at increased risk of developing Alzheimer's disease (AD) yet are less likely to be diagnosed. It is unclear if this is due to health seeking practices, cultural views and misperceptions regarding cognitive decline and dementia, or more clinical reasons. Waiting for memory impairment, a key requirement in the clinical diagnosis of dementia, may be too late for early detection of cognitive impairment in AA. Rather, we postulate that executive function may be a better domain to assess as it is vulnerable to the effects of hypertension, a highly prevalent condition in AA. Furthermore, we hypothesize that executive function impairment is an AD nonamnestic variant associated with AD cerebral spinal fluid (CSF) biomarkers.

Design/Analysis: The current investigation is a cross-sectional analysis of data from a cohort study, Brain Stress Hypertension and Aging Research Program (BSHARP), a study that oversampled AA to permit studies regarding racial disparities. Statistical tests of comparison between AA and Whites were completed to assess for group differences, and regression analyses conducted to assess potential associations between executive function impairment and AD CSF biomarkers.

Findings: Baseline data from 366 participants are reported here. AA (41.8% of the total sample) were younger (mean age 63.2 ± 6.7) than Whites (67.4 ± 8.2), possessed less formal education, and had higher proportions of hypertension, and obesity. Executive function impairment, defined as difficulty in higher-order cognitive skills involved in coordination and regulation, occurred in 20% of the sample- 26% of AA and 15% of Whites. Risk factors associated with impaired executive function were AA race (OR= 2.46 [1.11, 5.50]), and 10-year increase in age (OR= 1.80 [1.04, 3.10]). We found no association between impaired executive function and AD CSF biomarkers (OR 1.0 AB1-42, OR 0.99 Tau, OR 0.96 pTau), when analyzed by cognitive status, when adjusted for age, sex, education in years, and family history of AD, or when race interaction was included. There was an association between Tau to amyloid ratio, or TAR (OR 1.16 SE1.64) and impaired executive function but this OR significantly increased to 7.45 for the adjusted analysis, likely indicating lack of power.

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INTRODUCTION

African Americans (AA) are more likely to have higher rates of Alzheimer's dementia (AD) and AD combined with multiple comorbid conditions (1). AA are also two times more likely to develop late-onset AD than whites and less likely to be diagnosed (2). It is unclear if this is mostly due to issues surrounding health seeking practices, cultural views and misperceptions regarding cognitive decline and dementia, or poorly understood clinical mechanisms. Currently not even dementia screening is recommended in primary care (3). Even if it were, a key question we must ask is, given the above disparity in AD prevalence and diagnosis, "Are the current dementia screening tools, which are typically memory -based, the most effective for AA?"

We postulate that waiting for memory impairment, a key requirement in the clinical diagnosis of any type of dementia, may be too late for early detection in AA. Memory is only one of several key cognitive domains (language, learning and memory, social cognition, complex attention, executive function, and perceptual motor function) (4) and falls below executive function in the hierarchical ladder of control (5). Furthermore, executive function may be a better cognitive domain to assess as it is vulnerable to the effects of hypertension, a highly prevalent condition in AA (6). *The purpose of this research is to describe the frequency of executive function impairment in adults in an urban environment, with focus on African Americans in particular; and to assess whether African American / Black race confers a greater risk of executive function impairment.*

Finally, this research seeks to ask the question, "Is executive function impairment a non-amnestic AD variant or is it a distinct dementia phenotype?" A recent working group, a joint endeavor between the National Institute on Aging (NIA) and the Alzheimer's Association recommended a fundamental shift in AD research diagnosis from an amnestic clinical neurodegenerative syndrome to a biomarker-based categorization. However, within this new

framework the group recognized the existence of a non-amnestic AD variant that required more investigation (7).

We hypothesize that, for African Americans, executive function impairment is more prevalent than in Whites with MCI and shows stronger associations with AD cerebral spinal fluid (CSF) biomarkers. Our study aims are as follows: 1) To determine the frequency rate of executive function impairment in a convenience sample of adults, White and Black / African American, with normal cognition and mild cognitive impairment (MCI); 2) To assess whether executive function impairment is associated with AD CSF biomarkers in African Americans and, if present, whether this association differs from Whites. This second aim, will answer the question if executive function impairment is a non-amnestic AD variant based on the presence of biomarkers known to predict development of AD.

These hypotheses will be tested using cross-sectional analyses of secondary data generated from a prospective observational cohort study.

BACKGROUND

A fundamental shift is occurring in how dementia diagnoses are established. This shift is taking place not only in the research domain but also in the setting of expert clinical practice. The call for this shift comes from the National Institute on Aging (NIA) and the Alzheimer's Association who recommend moving away from diagnosing Alzheimer's Disease, for example, as a nonspecific "multidomain amnestic dementia" phenotype, toward a 'biological definition' based on specific biomarkers that indicate future development of Alzheimer's dementia (7, pg. 5).

This issue of 'dementia specificity'- or the ability to determine the specific type of dementia is somewhat problematic. For many patients, their doctors believe that such a task is too problematic leading to delay in recognition and diagnosis resulting in poor outcomes for patients and their caregivers (8).

Early detection of significant cognitive impairment and dementia, defined as impairment which negatively impacts day-to-day function, is contingent on early identification of functional impairments. While there has been limited investigation into screens that may achieve this (9), not much is known regarding how best to assess complex daily function in older AA, particularly as rates of dementia and AD are higher for this group. Relying on self-reported difficulty in daily function may be too late when trying to detect the earliest of functional decline. Furthermore, previous studies have shown that, in AA, executive function impairment distinguishes a global phenotype of dementia distinct from Whites that may be mediated by hypertension (HTN) (10).

Executive function is a cognitive domain involved in planning, organizing, and differentiation (11) that may be less prone to cultural factors and therefore a "purer" measure of cognitive status for diverse populations. It is a key cognitive domain integral to complex daily tasks like driving, managing finances, and managing medications. These higher complexed daily functions tend to be the first to deteriorate in dementia and signal a need for assessment.

The Role of AD CSF Biomarkers

There are key biomarkers in cerebral spinal fluid (CSF) obtained via lumbar puncture that indicate eventual development of AD. For example, AB1-42 (beta amyloid) is deposited in the brain of persons who eventually develop AD. The corresponding decreased amount in CSF, per a certain cutoff, indicates this deposition and a cognitive classification of prodromal AD. Additionally, a lower concentration of AB1-42 in the CSF predicts future cognitive decline (12). A second AD biomarker, Tau, directly reflects the level of neurodegeneration occurring in the brain- a directly proportional relationship. Tau seems to be more prevalent in AD lesions in younger individuals as compared to AB1-42. Finally, a third biomarker, a ratio of tau to AB1-42, designated as 'TAR', has been found to be a superior predictor of future cognitive impairment (12).

Finally, despite the reality that African Americans are at increased risk of AD, the majority of AD biomarker studies have included few African Americans. It is therefore unclear if AD biomarkers have similar diagnostic utility for AA with cognitive impairment. Although emerging evidence suggests racial variability in cerebrospinal fluid (CSF) levels of Tau (13).

However, while executive function as a measure of complex cognitive function may pose an inviting tool for the early assessment of cognitive function, its relation to Alzheimer's disease development is not understood. The NIA and the Alzheimer's Association also acknowledge the existence of non-amnestic variant phenotypes of AD, one of which consists mainly of a decline in executive function. Therefore, a study to assess if this could be a different AD phenotype in African Americans is warranted.

The potential link between African American/ Black race, HTN, impaired executive function, and AD CSF biomarkers could indicate an HTN-mediated mechanism of progressive global cognitive decline either impacting or competing with the accepted amyloid cascade pathway of AD in African Americans.

METHODS

Study Design

The current investigation is a cross-sectional analysis of baseline data from a cohort study, Brain Stress Hypertension and Aging Research Program (BSHARP) (PI, Hajjar- AG051633), a study oversampled for inclusion of African Americans to permit studies regarding racial disparities. BSHARP includes in its baseline assessment an extensive array of cognitive testing, sampling of cerebrospinal fluid to measure AD biomarkers, and neuroimaging with brain magnetic resonance imaging (MRI).

Study Population

The study population was comprised of adults 50 years or older who were either recruited to participate in BSHARP, or sought to participate in an Emory research study, and who were referred from the Emory Goizueta Alzheimer's Disease Research Center (ADRC) as well as from strategic community partnerships. Inclusion criteria for study participants in general included having a study informant and being willing and able to undergo lumbar puncture and brain MRI. Additional inclusion criteria for study participants categorized as having normal cognition required the following: Montreal cognitive assessment testing score (MoCA) (14) of 26/30 or higher, clinical dementia rater score of 0.0, an absence of subjective memory complaints, and an education-adjusted normal score on Logical Memory delayed recall subscale of the Wechsler Memory Scale (≥ 11/25 for 16 or more years of education, ≥ 9 for 8-15 years of education, and ≥ 6 for < 7 years of education).

Conversely, inclusion criteria for study participants with MCI include report of subjective memory complaints, MoCA score of <26, CDR (15) memory sum of boxes score of 0.5, abnormal function as indicated by delayed recall subscale of the Wechsler Memory Scale (<11

for 16 or more years of education; <9 for 8-15 years of education,; and < 6 for <7 years of education), and a Functional Assessment Questionnaire (FAQ) <9 (16).

Exclusion criteria included a history of stroke in the past three years, unwillingness or inability to complete a lumbar puncture and/or brain MRI, not having a study informant, a clinical diagnosis of dementia of any type, and any study participant having abnormal serum thyroid stimulating hormone levels (>10 mU/mL) or vitamin B12 (< 250 pg/mL) as these values indicate a "reversible" cause for dementia.

Disagreements regarding classification of cognition status for study participants were first reviewed by study physician and neuropsychiatrist to achieve a consensus diagnosis. If disagreement persisted, a third independent cognitive neurologist from Emory, who was blinded regarding the initial evaluation diagnosis, was consulted and this assessment broke the tie.

Measurements

Data reported in this report was drawn from the baseline assessment of study participants of the Emory University Brain Stress Hypertension and Aging Research Program (BSHARP), an infrastructure of observational longitudinal cohort studies of vascular contributors to prodromal AD (17). The Emory University Institutional Review Board approved the study protocol prior to recruitment.

This analysis used CLOX 1 to assess executive function. CLOX 1 provides a quick and observable measure of executive function (i.e. planning and coordinating) and involves a clock drawing task which is easily implemented and therefore relevant as a tool for use in busy healthcare environments. The CLOX task is performed by instructing the participant to draw a clock "that says 1:45; set the hands and numbers on the face so that even a child could read them." CLOX includes a fifteen- item scoring process. The highest score attainable is 15 points. A score indicative of cognitive impairment is less than or equal to 10. Normative performance data of the CLOX task for similarly powered racial / ethnic cognition studies for diverse populations in the south have been published previously and these cut offs were used to

determine executive function impairment in the current analysis (10). *For this analysis, executive function was the defined outcome.*

The exposure, or predictors, in the current analysis are defined as presence of AD biomarkers in a study participant's cerebrospinal fluid (CSF). The four predictors included three single biomarkers- AB1-42 a biomarker that reflects B amyloid deposition, Tau and pTau markers of neurodegeneration, and a ratio of two biomarkers called TAR for Tau to B-amyloid ratio. Levels of CSF biomarkers Aβ1-42, tau, and pTau181 were measured using a multiplex platform (xMAP; Luminex Corp) with immunoassay kit–based reagents (INNO-BIA AlzBio3; Innogenetics; for research use–only reagents). Cutoff points were not used in order to maximize power.

Covariates included customary factors that have significant impact on potential cognitive impairment and other chronic diseases. These included age, sex, education in years, and family history of Alzheimer's disease. Presence of these covariates was determined per self-report.

All analyses in the current project were conducted only for study participants with complete data, resulting at times in some diminished power during particularly specified analyses. For the 'parent' observational cohort study BSHARP, a weekly data query report, including missing, out of range, and logic checks, was generated by the study statistician. Additionally, timeliness and completeness of responses to data queries was routinely monitored.

Sample Size and Power Considerations

Again, the study sample for this current investigation is a convenience sample. Therefore, power considerations do not apply.

Analytic Plan

Study participant characteristics, or summary statistics, were compared between the two racial groups (AA vs. Whites) using t-tests or chi-square statistics. Frequency, or proportion, of

executive impairment was calculated for the total sample and by race; proportions were plotted via bar graph.

Multivariable logistic regression was utilized to assess potential risk factors for executive function impairment. Regression analysis was used to determine whether CSF biomarkers are associated with executive function impairment as measured by CLOX1, adjusted for key risk factors, and affected by race interaction. CSF biomarkers (Aβ, Tau, p-tau, the tau to Aβ ratio and p-Tau to Aβ ratio) were used as continuous variables in all regression analyses. Measures of association are expressed as odds ratios.

Regression Model and SAS 9.4 Code

The unadjusted model to assess for any association between executive function impairment and AD CSF biomarkers for the total sample in those with executive dysfunction (study participants with normal cognition and MCI) is as follows:

```
proc reg data=import1;
model clx_1=ab42*;
where clx_1<=10;
run;
```

**all other biomarkers would be substituted here*

Where clx_1 = total CLOX1 score; clx_1<=10 indicates executive function impairment.

The adjusted model to assess for any association between executive function impairment and AD CSF biomarkers for the total sample is as follows:

```
proc reg data=import1;
model clx_1=Tau* age male educationyrs fhxalzheimer;
where clx_1<=10;
run;
```

**all other biomarkers would be substituted here*

Where educationyrs= education in years; and fhxalzheimer= family history of AD.

The adjusted model to assess for any association between executive function impairment and AD CSF biomarkers for the total sample *with race interaction*:

```
proc reg data=import1;
model clx_1=ptau* age male educationyrs fhxalzheimer  ;
by subject_race;
where clx_1<=10;
run;
```

**all other biomarkers would be substituted here*

RESULTS

Demographic Results

This analysis includes baseline data for 366 study participants, 153 AA (41.8%) and 213 W (58.2%). Demographic results are reported in Table 1. AA were younger (mean age 63.2 ± 6.7) than Whites (67.4 ± 8.2). Only 44% of AA attained a minimum bachelor's degree or higher vs. 72.3% for W. Nearly 70% of AA were hypertensive vs. 36.9% for W. Additionally, 44% of AA were obese or morbidly obese vs. 24% for W. Regarding a family history of AD, Whites had 61% participants with this history vs. only 42% of AA. Finally, nearly 51% of AA had a MoCA score of < 26, indicating cognitive impairment vs. 34.9% of W.

Demographic data also show significant differences by race regarding executive function impairment where 26% of AA demonstrated impairment vs. 15% of W as measured by CLOX1.

Prevalence of impaired executive function for the total sample and by race is displayed in Figure 1. *So nearly 2:1 AA to W have impaired executive function in our sample.*

Risk Factors for Executive Function

Multivariable logistic regression analyzing predictors for impaired executive function include black/AA race, OR 2.46 ([1.11, 5.50] p=0.028), and age per 10-year increase, 1.80 ([1.04, 3.10] p=0.035). *So, after adjusting for age, black/AA race was associated with increased risk of impaired executive function as well as a 10-year increase in age, after adjusting for race.*

Relationship between executive function impairment and AD CSF biomarkers

The association between impaired executive function and AD CSF biomarkers is displayed in Table 3. This analysis included participants with normal cognition as well as participants with MCI. Analyses included three single biomarkers, AB1-42, Tau, and pTau and also included the Tau to AB1-42 ratio, or TAR. The unadjusted analysis did not demonstrate an association for

AB1-42 OR 1.00 SE (0.00), Tau OR 0.99 (0.01), or pTau OR 0.96 (0.05). The odds ratio for TAR did demonstrate an association, which was 1.16 (1.64).

The adjusted analysis mirrored the unadjusted analysis, failing to demonstrate any association between impaired executive function and AD CSF biomarkers. In this analysis the model was adjusted for age, sex, education in years, and family history of AD. Results include OR, SE for AB1-42 of 0.99 (0.01), Tau 1.00 (0.01), and pTau 0.98 (0.06). There was a significant increase in the OR for TAR in the adjusted analysis, OR 7.45 (2.17) but was concerning that this value indicated a lack of power in the analysis as there were only 30 participants who had completed data.

Interaction with Race

Regression analysis of impaired executive function and AD CSF biomarkers by race interaction is highlighted in Table 4. Again, there was not demonstrated an association between executive function impairment and any single AD CSF biomarker in either the unadjusted or the adjusted analysis; for AA adjusted analysis showed for AB1-42 OR 1.00 (0.01), Tau OR 0.99 (0.02), pTau OR 0.96 (0.10). For W (adjusted analysis), AB1-42 OR 0.99 ((0.01), Tau OR 1.01 (0.04), and pTau 0.95 (0.14). Odds ratio for the TAR biomarker was different with race interaction. For AA, there was no association for unadjusted or adjusted analyses. The OR for TAR for AA in the unadjusted analysis was 0.00 (5.31) and for the adjusted analysis was 0.00 (5.92). For W, the unadjusted analysis showed an OR of 3.27 (2.49) and was essentially 0 for the adjusted analyses, again concerning for indicating a lack of power.

Analysis by cognitive status

Odds ratios remained unchanged after regression analysis by cognitive classification was completed.

Analysis accounting for systolic blood pressure

Adding systolic blood pressure into the model, to adjust for systolic blood pressure did not change the finding of a lack of association. Also, in the current analysis, there was found no association between systolic blood pressure and executive function impairment using regression analysis.

Results Summary

Therefore, while race was a risk factor for executive function impairment, analyses did not indicate that this increased risk of executive function impairment in AA was associated with CSF biomarkers of AD.

DISCUSSION/CONCLUSIONS

We hypothesized that, for African Americans, executive function impairment was an AD nonamnestic variant associated with AD cerebral spinal fluid (CSF) biomarkers. Based on our results we must reject this hypothesis and conclude that executive function impairment is a distinct neurocognitive phenotype more frequent in presentation for middle-aged African Americans.

We also aimed to determine the rate of executive function impairment in African Americans and did determine this to be nearly 30%, almost twice that as for Whites. We also determined that African American/Black race increased one's risk of executive function impairment.

That our analyses and data demonstrate that age is associated with executive function impairment is consistent with the association of increasing age with most major chronic diseases (18). Increasing age would also potentially be a proxy for advancing vascular disease, highly prevalent in African Americans, and a potential explanation for this disparity in executive function performance (19).

Our findings confirm earlier results of a study using CLOX1 as a measure of executive function impairment in a southeastern community of independent older adults (10). CLOX was used to measure executive function as well as visuo- construction ability and distinguished a global dementia phenotype seen in different proportions among African American and White study participants. Characterizing a global dementia as type 1 involving both executive function impairment and posterior cortical impairment vs. a type 2 dementia with executive impairment alone. African Americans were 2.5 times as likely to have the type 1 dementia phenotype vs. type 2. But impaired executive function was common to both phenotypes.

Limitations for this study include no within group diversity. Race was given as self-report from study participants and there was no objective verification of within group diversity. Additionally, there was no assessment of genetic diversity to further assess racial/ethnic variability. The current investigation may have been somewhat underpowered to identify a

significant association (if one were to exist) with presence of AD CSF biomarkers. Finally, because this is a cross-sectional study, temporality cannot be established.

Strengths of this study include the very diverse study population and large presence of under-represented African Americans who, as an overall group, have not enjoyed a high degree of inclusion in historic cognition studies and clinical trials.

Race is a likely risk factor for executive function impairment. While high prevalence of vascular disease may account for these findings, confirmation requires further investigation.

Next steps for study should focus on executive function impairment as a separate and distinct dementia phenotype with higher risk for development in African Americans and whether vascular risk factors are associated and, if aggressively treated, could temper severity of presentation or speed of decline.

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TABLES / FIGURES

Table 1. Baseline Sample Characteristics of Study Participants

Sample Characteristic N= 366	African American N= 156 (41.8%)	White N= 213 (58.2%)	p-value
Age, years	63.2 ± 6.86	67.4 ± 8.23	< 0.001
Sex:			0.809
Female	99 (64.7%)	134 (62.9%)	
Male	54 (35.3%)	79 (37.1%)	
Education:			< 0.001
Some high school	3 (1.96%)	3 (1.41%)	
High School Diploma or GED	25 (16.3%)	18 (8.45%)	
Associate degree/some college/vocational school	57 (37.3%)	38 (17.8%)	
Bachelor's/ college degree	32 (20.9%)	68 (31.9%)	
Some post-graduate+	36 (23.5%)	86 (40.4%)	
BMI:			< 0.001
Normal or Healthy weight	29 (19.5%)	92 (44.0%)	
Obese	52 (34.9%)	42 (20.1%)	
Morbid Obesity	14 (9.4%)	8 (3.83%)	
Hypertension	101(68.7%)	76(36.9%)	< 0.001
MOCA:			0.003
≥26	75 (49%)	138(65.1%)	
<26	78 (51.0%)	74 (34.9%)	
Family History of Dementia	64 (42.1%)	127 (61.1%)	0.001
Comorbidity Score (± *SD*)	4.22 (2.82)	3.38 (2.22)	0.003
CLOX1:			0 .062
>10	44 (66.7%)	59 (81.9%)	
≤10	22 (33.3%)	13 (18.1%)	

GED- General Educational Development; BMI- Body Mass Index; CLOX1- Executive Function measure
MoCA- Montreal Cognitive Assessment- < 26 Mild Cognitive Impairment

Figure 1. Prevalence of Executive Function Impairment Overall & by Race
(Generated in R version 3.4.3 by Chen, Y)

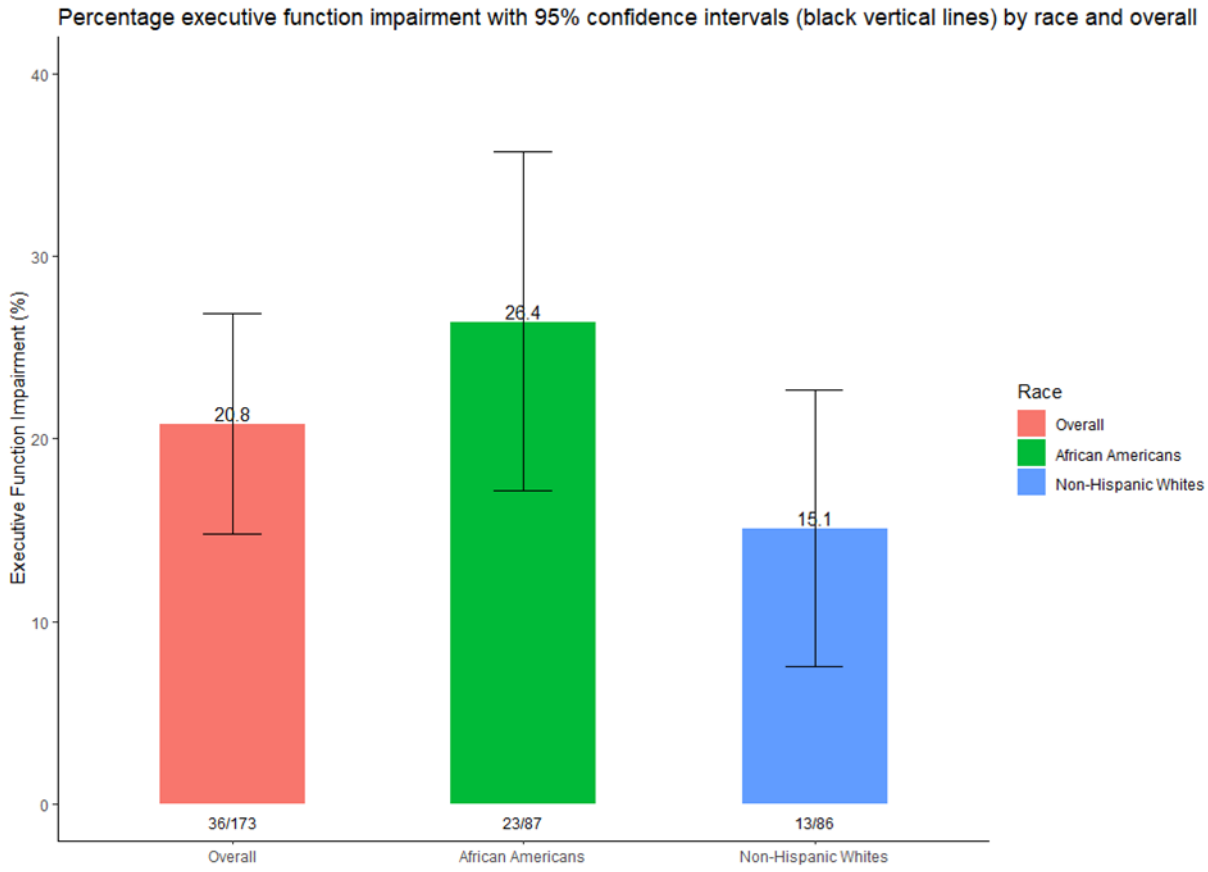

Table 2. Multivariable analysis of risk factors potentially associated with executive function impairment (CLOX1) (n = 172 patients)

Risk Factor		Executive function impairment (CLOX1 <= 10) Yes n / N (%)	No n / N (%)	Estimate ± SE	Odds Ratio	Model P-value
Race†	Black or African American	23/87 (26.4%)	64/87 (73.6%)	0.90 ± 0.41	2.46 [1.11, 5.50]	0.028
	White	13/85 (15.3%)	72/85 (84.7 %)		Reference	.
Age ††	Per 10-year increase	34/130 (26.2%)	96/130 (73.8%)	0.06 ± 0.03	1.80 [1.04, 3.10]	0.035

† after adjusting for age

†† after adjusting for race

Table 3. Odds of executive function impairment for AD CSF Biomarkers

N=30	Odds Ratio, SE	*Adjusted Odds Ratio, SE
Biomarker CSF Present		
AB1-42	1.00 (0.00)	0.99 (0.01)
Tau	0.99 (0.01)	1.00 (0.01)
pTau	0.96 (0.05)	0.98 (0.06)
TAR	1.16 (1.64)	7.45 (2.17)

*Adjusted for age, sex, education in years, and family history of Alzheimer disease

AD- Alzheimer's Disease, CSF- Cerebral Spinal Fluid, TAR- Tau to Amyloid ratio

Table 4. Odds of executive function impairment for AD CSF Biomarkers with race interaction

	N=17	**Odds ratio, SE**	***Adjust OR, SE**
African Americans	CSF Biomarker Present		
	AB1-42	1.00 (0.01)	1.00 (0.01)
	Tau	0.98 (0.02)	0.99 (0.02)
	pTau	0.98 (0.10)	0.96 (0.10)
	TAR	0.00 (5.31)	0.00 (5.92)
	N=13		
Whites	CSF Biomarker Present		
	AB1-42	0.99 (0.01)	0.99 (0.01)
	Tau	1.00 (0.02)	1.01 (0.04)
	pTau	0.96 (0.09)	0.95 (0.14)
	TAR	3.27 (2.49)	- (>20)

* Adjusted for age, sex, education in years, and family history of Alzheimer disease

CSF- Cerebrospinal Fluid, TAR- Tau to Amyloid ratio