Revista Iberoamericana de Neuropsicología, Vol. 6, No. 1: 68-87, enero-junio, 2023.

Family history of dementia associated with lower phonemic fluency on the Spanish version of the CERAD

Hjalmar Zambrana-Bonaparte, PsyD* y Youssef Ahmad-Pereira, PhD

Abstract

Objective: *Dementia prevalence in Latin America is becoming a significant public health problem, especially in the Caribbean. Family history of dementia (FHD) is a risk factor for dementia and appears to be associated with poorer neuropsychological test performance among non-demented individuals. The purpose of this preliminary study was to examine the relationship between FHD and test performance among cognitively healthy Puerto Ricans.*

Method: *Fifty Spanish-speakers (age 55-74 years) were administered an online version of the CERAD battery and were divided among two groups based on self-reported FHD. A Principal Component Analysis generated five factors: non-contextual memory, phonemic fluency, contextual memory, semantic and recognition memory, and working memory, accounting for 73.82% of the overall variance in the 16 original variables.*

Results: *Multivariate analysis of covariance showed a main effect of FHD on the combined dependent variables after controlling for covariates age and education with large effect size ($\eta_p^2 = .233$). Subsequent analyses of covariance only revealed a main effect of FHD on phonemic fluency after controlling for covariates with moderate effect size ($\eta_p^2 = .124$). Except for contextual memory, the dementia history group (+DH) generally performed lower than the non-dementia history group (-DH).*

Conclusions: *Data suggest that FHD can be negatively associated with neuropsychological test performance among cognitively healthy Puerto Ricans. FHD as a covariate in normal cognitive aging studies should be considered, even among the young-old adult range. Further exploration of the relationship between +DH and test performance, specifically phonemic fluency among Puerto Ricans, is warranted.*

Keywords:

CERAD, Spanish-speakers, history of dementia, neuropsychological performance, phonemic fluency, teleneuropsychology

* Albizu University, Mayagüez University Center, Mayagüez, Puerto Rico
Carr. 64 Esquina Calle #3, Urb. Industrial Algarrobos, Mayagüez, P.R. 00680
(787) 481-0511
hzambrana474@sju.albizu.edu

Introduction

The proportion and the total number of older adults in most populations around the world are increasing dramatically. According to this phenomenon, known as population aging, one in five people around the globe will be 60 years or older by the year 2050.[1] A concerning fraction, considering that advancing age is a risk factor for cognitive decline and late-onset dementia, including Alzheimer's disease (AD).[2,3] Another risk factor for cognitive decline and late-onset dementia in adults is having a family history of dementia (FHD), even independently of known genetic risk factors such as apolipoprotein E (APOE) e4 allele.[4-8]

The relationship between first line (biological parent) FHD and neuropsychological test performance in non-demented middle-aged and older adults has been documented in several studies, revealing diverse findings, which might be attributable to differences in study designs, sample size, unique sociodemographic characteristics, as well as measured constructs and testing procedures. For instance, La Rue et al.[9] found that relatives of AD patients (N = 40) were more likely than healthy controls (N = 24) to show cognitive decline. Similarly, Locke et al.[10] reported that FHD might be a significant individual predictor of developing cognitive impairment, predicting clinical diagnoses on average 3.6 years later as measured by a verbal learning test. Another study found that baseline scores in processing speed, executive functioning, memory encoding, and delayed memory among 39 participants with a family history of AD were lower than 33 participants without AD history. Whereas AD family history did not influence the degree of cognitive decline over time, and baseline cognitive performance did not vary according to APOE e4 carrier status.[11] Talboom and colleagues[12] reported lower verbal learning performance throughout four decades before the typical onset of AD with a sample of 59, 571 individuals between 18 and 85 years old.

A study involving 1500 participants (50 years and older) aimed to address the extent to which Amyloid/Tau/Neurodegeneration biomarker status can be predicted by known Alzheimer's Disease (AD) risk factors such as FHD. The results found that a non-AD pathology group was notable for having the lowest frequency of FHD. In contrast, FHD was further positively associated with tau biomarkers (OR = 1.55, 95% CI 1.04-2.32, p = 0.03). The authors suggested that the family history of dementia risk factor was predictive of AD's pathology (RR = 4.12, 95% CI 1.93-8.77, p = 0.001) in cognitively healthy adults.[13] Moreover, it appears that a family history of AD beyond the parents does not change the risk of AD in their offspring.[5]

Additional studies have not found a significant impact of family history of dementia on cognition as an independent factor, but it has been suggested that FHD has an additive negative effect on cognition, interacting with other risk factors, such as APOE e4, HIV, and medical comorbidities.[14-16] Similarly, Ritchie et al.[17] found that parental dementia history was not associated with overall poorer cognitive performance at an early age (40-59) among 210 participants, although results showed that individuals with dementia history had lower visual working memory test scores when time progressed towards dementia onset. Meanwhile, Mackin et al.[18] found that FHD was not significantly associated with processing speed, visual attention, visual memory, or working memory tasks as measured with a computerized cognitive assessment battery in a sample of 3,011 cognitively normal participants.

Individuals experience an accelerated decline in neuropsychological testing scores five to seven years before a dementia diagnosis.[19,20] Therefore, neuropsychological testing is crucial in the early detection and monitoring of cognitive and behavioral function changes in AD and other dementias. The CERAD[21] (Consortium to Establish a Register for Alzheimer's Disease) neuropsychological battery it's an alternative that was developed to better screen for memory (Word List Memory Trials, Word List Recall, and Recognition), language (Modified Boston Naming Test and Animal Fluency), praxis (Constructional Praxis), and general status (Mini-Mental State). It has been translated to approximately 20 languages and is currently used to gather information on cognitively

impaired and cognitively normal individuals.[22] Since then, various alternative and extended versions such as including additional neuropsychological testing variables (e.g., Clock Drawing Test, Trail Making Test) have been used to accommodate different research and clinical objectives.[23-26]

Dementia prevalence is higher in most Latin American countries compared to North America, Europe, and Asia, and is becoming a significant public health problem, especially in the Caribbean.[27-29] It is also relevant to indicate that the Latino community is estimated to be 1.5 times more prone to develop AD than White Non-Hispanics.[30] This is partly due to ethnoracial factors, which can influence biological biomarkers, cardiovascular and neuropsychiatric risk factors, and lifestyle behaviors, resulting in differences in epidemiology, clinical presentation, and course of AD among these ethnoracial groups.[31] Meantime, Puerto Rico may have one of the highest dementia prevalence (11.7%) among Latin American countries.[32] Puerto Ricans also represent the second-largest Latin group in the United States (5.8 million), which is higher than the Island population.[33] During the past years, a massive out-migration of productive Puerto Rican adults to the United States occurred in part secondary to Hurricane Maria.[34] However, information among Puerto Ricans and other Latinos about normal cognitive aging, AD, its diagnosis, and psychosocial interventions is insufficient due to the under-representation of this population in research studies.[31] Other contributing reasons for this need for information among Latinos are the lack of clinical training opportunities, normative data, and culturally-relevant neuropsychological instruments for Puerto Ricans and other Latin Americans.[35,36]

Lastly, emerging literature suggests that culture and language has more influence than age or education of neuropsychological testing,[37-39] which limits its interpretation,[40,41] highlighting the need for more culturally sensitive measures. In summary, population aging, dementia prevalence, Puerto Rican representation in the US, in conjunction with neuropsychological testing practicality, and its known impact by language and culture, emphasizes the need for a more comprehensive understanding of age-related cognitive decline within the Puerto Rican population and any impact that familial history of dementia may have. Furthermore, this relationship has not been thoroughly examined among cognitively healthy Puerto Rican adults. Therefore, this preliminary cross-sectional study could be considered foundational in evaluating the relationship between parental history of dementia and neuropsychological test performance among a sample of cognitively healthy Puerto Rican adults. It was hypothesized that neuropsychological test performance would be significantly lower among participants with a parental history of dementia. The impact of age, education, and sex on neuropsychological test performance was also examined.

Method

Participants

The sample of this study consisted of 50 cognitively healthy, community-dwelling Puerto Rican adults aged 55 to 74 years old, currently living in Puerto Rico. The inclusion criteria were the following: (1) participants with five or more years of education since certain tasks required basics reading and writing abilities, (2) self-reported basic computer literacy skills, (3) having access to a computer with a camera and microphone within their household to carry out a contact-free study due to the declared COVID-19 worldwide pandemic, and (4) all participants were screened using the Mini-Mental State Exam Spanish version. As the objective of this study was to obtain a relatively cognitive healthy sample, participants with a score value of 25 or higher were to be included.[42] The following exclusion criteria for the study were considered: dementia diagnosis, stroke, moderate to severe traumatic brain injury, epilepsy, Parkinson's disease, or other central nervous system diseases to reduce potential confounding variables with known cognitive effects, and impact on test performance.

Materials and Instruments

Health questionnaire

This instrument consists of a brief questionnaire developed to obtain a social and medical profile from the participants in the study. It contains information regarding gender, age, years of education,

medical conditions, activities of daily living, and dementia history (parents and siblings). The entire questionnaire was verbally administered through an audio-video conference call. Family history of dementia was obtained from participants based on their response to the following two yes/no questions: "Please indicate if your mother had or has AD or other forms of dementia" and "Please indicate if your father had or has AD or other forms of dementia." Participants who answered "yes" to any of these two questions were assigned to the dementia history group (+DH), and those who responded "no" to both questions were assigned to the non-dementia history group. Consequently, the terms family history of dementia, parental history of dementia, and dementia history group are used interchangeably throughout this article.

Neuropsychological testing

The present study's authors collaborated to adapt tests from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery[21] to an online format to accommodate the study to the physical distancing preventive measures that were present during the COVID-19 pandemic. The CERAD Spanish version used for this investigation was previously adapted for Puerto Rican culture and developed to analyze cognitive performance among Spanish-speaking non-demented nonagenarians residents of Puerto Rico by senior scientists from Mount Sinai School of Medicine.[23,24] This aforementioned version included complex paper-pencil tests (i.e., Constructional Praxis and Trail Making Test) that were excluded for the present study primarily due to anticipated challenges in monitoring the participants through a computer screen. Furthermore, it included additional measures (i.e., Logical Memory, Letter Fluency, Clothing Fluency, and Digit Span) not found in the original CERAD battery[21] and other published studies.[23-26] The selected tests are similar to those recommended for videoconference testing due to their strong teleneuropsychology validity, including multi-ethnic and diagnostically diverse samples.[43,44] The adapted battery included the following tests that were administered in the presented order by the principal investigator (PI):

1. *Mini-Mental State Exam*:[42] This test was used as a brief screening tool of cognitive function, in which spelling WORLD (MUNDO) backward was used in preference to subtraction of serial sevens; it was not used for further assessment or analyses other than as an inclusion criterion. Scoring range, 0-30.
2. *10-item Word List Learning task*:[45] ten words with roughly the same meaning and extension to the English version, while adapted to the Puerto Rican lexicon were presented consecutively on the participant's computer screen and were read aloud by the participant, with a different order used on each of three successive occasions. Following each presentation, the participant was asked to recall the nouns that were read. The scoring range is 0-10 for each presentation or 0-30 for all three presentations combined.
3. *Logical Memory (LM) I*: The LM subtest within this battery was equivalent to the original story B standard English version of the LM in the WMS-IV.[46] The basic storyline follows the original version, but in the Puerto Rican version, the person, city, and street names are replaced with more suitable Puerto Rican substitutes. LM I consist of immediate recall of story events following auditory presentation by the examiner.[47] The scoring range is 0-25.
4. *30-item Boston Naming Test*:[48] participants are asked to identify 30 drawings of increasing complexity, with a maximum of 20 seconds for each drawing. One point is awarded for each correct response, with a total possible score of 30 points.
5. *Word List Recall*: delayed recall of the nouns of the 10-item Word List Learning task after a 10-to-12-minute delay. A maximum of 90 seconds is allowed. Scoring range, 0-10.
6. *Word List Recognition*: the 10 original nouns of the Word List Learning task interspersed with 10 new nouns were presented one at a time at the participant's computer screen. The participant was asked to indicate for each noun whether it had been presented

previously or not. Original and new nouns were scored separately. The scoring range for each is 0-10, and the total score is 0-20.

7. *Logical Memory II*: free recall of presented story (LM I) was elicited after a 10-to-12-minute delay. Each correct detail was awarded one score point. The scoring range is 0-25.
8. *Logical Memory Recognition*: The 15 recognition questions (either yes or no) about the story (LM I) are subsequently given to LM II to assess the recognition ability. The scoring range, 0-15.
9. *Letter Fluency*: the participant must produce orally as many words possible for a specific letter,[47] except proper names or derivatives (diminutives, etc.), which in the case of the CERAD Spanish-language version, included letters are "P", "A", and "N" instead of the traditional "F", "A", and "S", since it has been suggested that the last letters occur with greater frequency in English than in the Spanish language.[49,50] The score is the number of correct words said by a participant in 90 seconds.
10. *Semantic Fluency*: This test measures impairment in verbal production, semantic memory, and language. Participants are asked to name as many animals as possible in 90 seconds. The score is the total number of different animals named. The same procedure was carried out again with the total number of clothes named.
11. *Digit Span Forward (DSF) and Backwards (DSB)*: This test within the battery is from the Wechsler Adult Intelligence Scale, 3rd Edition (WAIS-III)[51] equivalent to Puerto Rican culture (EIWA-III-PR),[52] the latest version in the Island. It consists of several pairs of random number sequences that the examiner reads aloud at a rate of one per second and then asks for immediate recall. Scoring range, 0-9 (DSF) and 0-8 (DSB).
12. *Geriatric Depression Scale*:[53] developed considering both content and design to assess depressive symptoms and screen for depression among older people. This version consists of a 30-item questionnaire that was presented as an interview. The questions are presented in a yes or no format. Scoring range, 0-30.

Study Procedures

Participants included in this study were cognitively healthy community-dwelling adults. They were recruited through published announcements and messages through social media, which explained the inclusion and exclusion criteria that individuals must have met if interested. Those willing to participate and met the criteria completed and electronically signed an informed consent form. After consenting, they were given a link for a virtual appointment and asked to be in a distraction-free room with two pencils, an eraser, and three letter-size white paper sheets. If they agreed, they could benefit from a family member's (i.e., usually a younger or more tech-friendly individual) help to start the audio-video conference call. Then, the family member would have kindly been asked to leave the room after everything was set up (e.g., chair and camera position, audio) and if the participant had no further questions about the upcoming procedure. Next, the principal investigator would continue a private audio-video conference call where the participant would firstly be screened for cognitive deterioration using the Mini-Mental State Exam (MMSE). The MMSE items were read aloud to the participant. Before reading the temporal orientation items (i.e., date, year, month), the PI would ask the participant to not look at their wristwatch (if they had one) or any clock in the room (on a wall) or on the computer screen. Two stimuli were individually presented on the screen (i.e., one slide stating "cierre los ojos," Spanish for "close your eyes," and the double-pentagon copy design). Of note, the MMSE items: "write a sentence" and copy design were the only ones requiring paper and pencil throughout the entire procedure. All interested individuals met screening criteria for inclusion, and no participant was excluded. After the screening phase, the participant underwent an interview (health questionnaire) in which all questions were read aloud. Lastly, standardized neuropsychological testing was conducted (described in detail under instru-

ments). The entire procedure was carried out in Spanish for approximately 90 minutes. The Albizu University Institutional Review Board approved the study. The research was completed in accordance with the Helsinki Declaration.

Statistical Analyses

Between-group comparison of sociodemographic variables between the non-dementia history group (-DH) and the dementia history group (+DH) was carried out using chi-square for categorical and *t*-test for numeric variables. Descriptive statistics were performed for sociodemographic characteristics. Descriptive statistics were also obtained for raw performance on all CERAD tests and the additional tests. The impact of age and education on neuropsychological test performance was explored through Pearson correlation analyses, and point biserial correlation was used for sex.

All CERAD's subtest scores were converted to z-scores (calculated with the mean and standard deviation of the respective subtest scores within the sample) since the verbal fluency tasks do not have a maximum score. As mentioned, the CERAD battery was adapted to an online format, resulting in the exclusion of paper-pencil tests to accommodate testing to the established physical restrictions due to the COVID-19 pandemic. In addition, it included additional tests besides the ones within the original version of the CERAD battery.[21] Therefore, the factor structure within this version was expected to be somewhat different. The *Standards for Educational and Psychological Testing*[54] states that authors should document any adaptation to the standardized testing procedure and provide evidence of the validity of the testing data since the intended measured constructs could have been modified secondary to the adaptation. Consequently, to explore, identify, and document the factor structure of the new adapted online battery and reduce the number of tests of significance comparing group membership (-DH & +DH) within the sample, the neuropsychological assessment variables (neuropsychological test performance) were aggregated by factor analysis, using principal component analysis (PCA) and oblique (Oblimin) rotation. Oblique rotation was selected as it was clearly expected that the resulting factors from the neuropsychological variables should be related, resulting in the broader domains of cognition assessed by the battery. These identified cognitive domains were also converted to a mean z-score, and a global cognitive z-score (mean of the five domains) was created.

Data distribution was verified using skewness and kurtosis and through the Kolmogorov-Smirnov test of all variables, following Mertler & Vannatta's[55] recommendations. After the resulting cognitive factors were identified and interpreted, their comparison between familial dementia history membership was conducted using a multivariate analysis of covariance (MANCOVA) with familial dementia history status (-DH and +DH) as the independent variable, education level and age as the covariates, and simultaneously, the neuropsychological performance resulting factors as the dependent variables. Sex was not included due to a lack of linearity with the dependent variables when data was examined for the fulfillment of MANCOVA assumptions.

Subsequent analysis of covariance was performed for each cognitive factor for descriptive purposes. Bonferroni correction was applied to conservatively control for error rate and reduce the chances of a Type 1 error. The effect sizes for such comparison between groups were computed using partial-eta squared for multivariate analyses.

These procedures were performed using the General Linear Model feature of version 27.0 of the IBM SPSS Statistics (SPSS®; SPSS, Inc. Chicago, Illinois), also used for all statistical analyses.

Results

Demographics

The participants had a mean score value of 29.12 (SD = 1.09) on the Mini-Mental Status Examination (MMSE), which was the study's screening measure for cognitive impairment within the sample. MMSE scores ranged from 26 to a perfect score of 30, and 48 participants scored 27 or higher. This screening measure excluded no individual since the range of

values falls within the "normal" range scores for the MMSE, including for the Spanish-speaking population.[56-58] Therefore, suggesting that the participants were not demented or in the early stages of a dementing process when they were evaluated.

Among the sample, 20 participants (40%) had one or more first-degree relatives (parents) with dementia. Of those with dementia history, 5 participants (25%) had one or more siblings with dementia, 14 participants (70%) reported a positive dementia history on their mother's side of the family, and 6 participants (30%) reported it by their father's side. One participant reported a family history of dementia from both his father and mother's sides. Of the participants with dementia history, 60% were male, and 40% were females. Between-group comparison of sociodemographic variables between the dementia history group (+DH) and the non-dementia history group (-DH) showed no statistically significant differences for gender and education level. Age was also not significant (p = .313). The +DH (N = 20) had a mean age of 63.85 (SD = 6.31) and the -DH (N = 30) had a mean age of 62.20 (SD = 5.08). Table 1 shows all the sociodemographic characteristics and cardiovascular risk factors among the sample.

Factor Analysis

The Principal Component Analysis (PCA) with the Direct Oblimin rotation method generated

Table 1. Demographics of Study Groups and Full Sample

Characteristic	-DH	+DH	*p*-value*	Full sample
Total number	30	20	-	50
Age in years	62.20 (5.08)	63.85 (6.31)	.313	62.86 (5.60)
Education *n* (%)			.157	
<High School	1 (3.3)	0 (0)		1(2)
High School	2 (6.7)	2 (10)		4 (8)
Some College	7 (23.3)	3 (15)		10 (20)
Undergraduate	7 (23.3)	5 (25)		12 (24)
Graduate	13 (43.3)	10 (50)		23 (46)
Female, *n* (%)	19 (63.3)	8 (40)	.105	27 (54)
Right-handed, *n* (%)	27 (90)	19 (95)	.523	46 (92)
Mother DH, *n* (%)	-	14 (70)	-	14 (28)
Father DH, *n* (%)	-	7 (35)	-	7 (14)
Sibling DH, *n* (%)	-	5 (25)	-	5 (25)
Sedentary behavior	5.63 (2.26)	5.50 (2.80)	.854	5.58 (2.46)
Cardiovascular risk factors *n* (%)				
Hypertension	16 (53.3)	10 (50)	.817	26 (52)
High cholesterol	10 (33.3)	7 (35)	.903	17 (34)
Diabetes mellitus	3 (10)	3 (15)	.594	6 (12)
BMI, (kg/m2)	25.86 (4.14)	25.55 (3.41)	.784	25.74 (3.83)
Arthritis	7 (23.3)	6 (30)	.599	13 (26)

Note: Data are presented as frequencies (percentage) and as means (standard deviation) for these variables: age, sedentary behavior = hours/day, and body mass index (BMI). *p-value from chi-squared test for education, gender, handedness, hypertension, cholesterol, and diabetes; p-value from t-test for age, sedentary behavior, and BMI

Table 2. Total Variance Explained and Eigenvalues for the Principal Component Analysis Solution

	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings[a]
Component	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total
1	6.151	38.446	38.446	6.151	38.446	38.446	3.831
2	2.079	12.993	51.439	2.079	12.993	51.439	3.314
3	1.335	8.342	59.781	1.335	8.342	59.781	3.507
4	1.199	7.496	67.277	1.199	7.496	67.277	3.452
5	1.047	6.544	73.821	1.047	6.544	73.821	2.389
6	.907	5.670	79.491				
7	.663	4.142	83.632				
8	.599	3.743	87.375				
9	.471	2.945	90.321				
10	.415	2.593	92.913				
11	.326	2.035	94.949				
12	.270	1.686	96.634				
13	.210	1.310	97.944				
14	.170	1.060	99.004				
15	.103	.645	99.649				
16	.056	.351	100.000				

Note: When components are correlated, sums of squared loadings cannot be added to obtain a total variance.

a five-factor solution with eigenvalues > 1, which accounted for 73.82% of the variance in cognitive test performance (see Table 2). The rotated solution converged in 14 interactions, and loadings above .650 were selected from the resulting components (see Table 3). The first factor, interpreted as non-contextual memory (NCM), received high loadings from measures of word list delayed recall and word list learning trials 1–3, and accounted for 38.44% of the variance in overall test performance. The second factor, identified as phonemic fluency (PF), had high loadings from the letter fluency task (P, A, N) and accounted for a further 12.99% of the variance in test scores. The logical memory measures (immediate, delayed, and recognition) loaded on the third factor, which accounted for another 8.34% of the variance and was denominated contextual memory (CM.) The fourth factor, identified as semantic and recognition memory (SRM), received high loadings from the category fluency task (animals, clothing), the Boston Naming Test, and the word list recognition trial, accounting for 7.50% of the variance in the test scores. Finally, with high loadings from the digit span forward/backward sub-tests, the fifth factor was identified as working memory (WM) and accounted for another 6.54% of the test performance.

Familial Dementia History and Neuropsychological Test Performance

All raw performance on CERAD subtests and additional tests for both groups and the full sample was provided for reference on Table 4. Multivariate analysis of covariance (MANCOVA) was conducted to determine the effect of familial dementia history on neuropsychological test performance as measured by the PCA's resulting factors (NCM, PF, CM, SRM, and WM) while controlling for age and education level. The Box's Test revealed that equal variances could be assumed, $F(15, 6625.227) = .369$, $p = .987$; therefore, Wilk's Lambda was used as the test statistic.[55]

Table 3. Factor Loadings of the CERAD Neuropsychological Variables Resulting from a Principal Component Analysis (Rotation Method: Oblimin with Kaiser Normalization)

	Factor loadings				
CERAD variable	**1**	**2**	**3**	**4**	**5**
WLL Trial 2	.825				
WLL Trial 3	.797				
WLL Delayed Recall	.791				
WLL Trial 1	.781				
Letter Fluency (P)		-.874			
Letter Fluency (A)		-.838			
Letter Fluency (N)		-.837			
LM II Delayed Recall			.892		
LM I Immediate Recall			.874		
LM Recognition			.829		
Category Fluency (clothing)				-.800	
WLL Recognition				-.777	
Category Fluency (animals)				-.762	
Modified Boston Naming test				-.695	
Digit Span Forward					.860
Digit Span Backward					.755

Note: Absolute values below .650 are suppressed. NCM (1) = non-contextual memory, PF (2) = phonemic fluency, CM (3) = contextual memory, SRM (4) = semantic and recognition memory, WM (5) = working memory. Domains obtained from CERAD=Consortium to Establish a Registry for Alzheimer's Disease. We also tested for general cognition (total MMSE score), but it was not included in the principal component analysis.

The MANCOVA revealed a statistically significant main effect of familial dementia history on the combined dependent variables (NCM, PF, CM, SRM, and WM) after controlling for covariates (age and education), Wilk's Λ=.767, $F(5, 42) = 2.554$, $p = 0.042$, $\eta_p^2 = .233$, with an observed power of .736. The covariates of age and education significantly influenced the combined dependent variable, Wilk's Λ=.589, $F(5, 42) = 5.853$, $p = <.001$, $\eta_p^2 = .411$; Wilk's Λ=.717, $F(5, 42) = 3.316$, $p = .013$, $\eta_p^2 = .283$, respectively. Before conducting the MANCOVA, data was screened for missing data and outliers. Boxplots showed indication of two outliers on WM for the -DH and one outlier on CM for the +DH. These three outliers were retained to capture the reality of the sample. No indication of outliers was found on NCM, PF, and SRM. All dependent variables met normality (values for Skewness and Kurtosis between -1 and +1) across dementia history groups; only WM for the -DH obtained a Kurtosis value of 1.469 and a Skewness value of 1.121, which could be considered acceptable.[59] A preliminary MANCOVA was carried out to test the assumptions of homogeneity of variance-covariance and homogeneity of regression slopes, and assumptions were met.

Subsequent analysis of covariance (ANCOVA) was performed on each dependent variable (individual cognitive domain *z*-score) and with the global cognitive z-score (mean of the five domains) for descriptive purposes (see Table 5). The +DH generally performed lower compared to the -DH, except for CM. These analyses indicated that only the dependent variable (DV) of phonemic fluency was significantly affected ($P < 0.05$) by familial dementia history membership with a moderate effect size, $F(1, 46) = 6.494$, $p = .014$, $\eta_p^2 = .124$, by the covariate of age $F(1, 46) = 4.527$, $p = .039$, $\eta_p^2 = .90$, and by education level

Table 4. Tests Raw Scores across Study Groups and Full Sample, and Relationships of Age, Education, and Sex with Test Scores in the Puerto Rican Sample

CERAD subtests	-DH (*N* = 30)	+DH (*N* = 20)	Whole sample	Age	Education	Sex
MMSE	29.16 (0.91, 27-30)	29.05 (1.35, 26-30)	29.12 (1.09, 26-30)	-.414**	.243	-.065
WLL Trial 1	5.06 (1.43, 2-8)	4.35 (1.26, 2-6)	4.78 (1.40, 2-8)	-.458**	.248	-.200
WLL Trial 2	7.00 (1.28, 5-9)	6.60 (1.56, 4-10)	6.84 (1.40, 4-10)	-.474**	.242	-.009
WLL Trial 3	8.23 (1.19, 6-10)	7.55 (1.23, 5-9)	7.96 (1.24, 5-10)	-.381**	.332*	-.003
WLL D.R.	6.30 (1.89, 3-9)	5.50 (2.25, 0-9)	5.98 (2.06, 0-9)	-.416**	.192	.009
WLL R.	19.33 (1.21, 15-20)	19.35 (1.03, 16-20)	19.34 (1.13, 15-20)	-.422**	.131	.221
BNT (30)	23.73 (4.37, 15-29)	24.30 (3.96, 14-29)	23.96 (4.18, 14-29)	-.441**	.367**	.174
LM I	12.43 (2.68, 7-17)	12.45 (2.92, 8-19)	12.44 (2.75, 9-19)	-.084	.397**	.248
LM II	11.30 (3.16, 5-17)	11.35 (3.64, 6-18)	11.32 (3.32, 5-18)	-.214	.426**	.166
LM R.	12.40 (1.52, 10-15)	12.65 (1.03, 11-15)	12.50 (1.34, 10-15)	-.039	.258	.075
P	19.96 (5.58, 10-30)	16.20 (5.87, 3-25)	18.46 (5.93, 3-30)	-.374**	.296*	-.072
A	17.26 (5.36, 7-27)	14.00 (5.37, 6-24)	15.96 (5.55, 6-27)	-.433**	.332*	-.154
N	11.60 (5.18, 3-21)	9.10 (3.98, 2-17)	10.60 (4.85, 2-21)	-.324*	.324*	-.015
Animals	25.16 (5.50, 18-38)	22.80 (5.83, 11-35)	24.22 (5.70, 11-38)	-.394**	.363**	.284*
Clothing	18.83 (5.54, 6-28)	16.25 (3.61, 11-23)	17.80 (4.98, 6-28)	-392**	.351*	.127
DSF	5.96 (1.37, 4-9)	5.65 (1.08, 4-8)	5.84 (1.26, 4-9)	-.239	.218	.054
DSB	4.50 (1.54, 2-8)	4.40 (1.09, 3-7)	4.46 (1.37, 2-8)	-291*	.312*	.042

Note: Data are presented as mean (standard deviation, range). WLL, word list learning. LM, logical memory. D.R., delayed recall. R., recall. BNT, Boston Naming Test. Phonemic fluency task, 90 seconds for each letter (P, A, N). DSF, Digit Span Forward. DSB, Digit Span Backward. GDS-30, Geriatric Depression Scale. Pearson correlation for age and years of education is significant at the $*p < 0.05$; $**p = <0.01$. Point biserial correlation is significant at the $*p < 0.05$.

Table 5. Means, Standard Deviations, and Analyses of Covariance in Parental History of Dementia and Neuropsychological Test Performance

	-DH	+DH	Sign. covariates	*F*(1,46)	η_p^2
NCM	.17 (.76)	-.26 (.83)	Age, $p = .001$	3.35	.068
PF	.23 (.88)	-.35 (.80)	Age, $p = .039$ Ed., $p = .012$	6.49*	.124
CM	-.02 (.89)	.04 (.87)	Ed., $p = .001$	.001	.000
SRM	.07 (.83)	-.12 (.70)	Age, $p = .002$	.447	.010
WM	.06 (.96)	-.09 (.66)	Ed., $p = .010$	.559	.012
GC	.10 (.64)	-.16 (.55)	Age, $p = .004$ Ed., $p < .001$	3.33	.068

Note: Data are presented as mean (standard deviation). Ed. = education; GC = global cognition; $*p < .05$.

Table 6. Letter Fluency Trials Z-Scores Across Familial Dementia History Groups

	-DH z-score	+DH z-score	η_p^2	-DH Raw M (SD) for 90 sec.	+DH Raw M (SD) for 90 sec.	-DH Raw M (SD) for 60 sec.	+DH Raw M (SD) for 60 sec.
P	.25	-.38	.099*	19.97 (5.58)	16.20 (5.87)	15.20 (4.28)	12.80 (4.62)
A	.24	-.35	.098*	17.27 (5.37)	14.00 (5.37)	13.30 (4.45)	10.35 (3.73)
N	.21	-.31	.080	11.60 (5.18)	9.10 (3.99)	9.26 (3.94)	7.20 (3.30)
PAN (mean)	.23	-.35	.124*	48.80 (14.39)	39.30 (13.23)	37.76 (11.27)	30.35 (10.25)

Note: Analyses of covariance (covariates: age and education). *$p < .05$. Letter fluency task, 90 seconds for each letter (P, A, N). Raw scores for 90 and 60 second trials (mean, standard deviation) provided for reference.

$F(1, 46) = 6.820$, $p = .012$, $\eta_p^2 = .129$. No statistical significance was present when applying Bonferroni correction ($P < 0.01$). The remaining DV's did not show a main effect by the IV. Effect sizes were considered small effects across CM, SRM, and WM with non-significant ANCOVAs. The effect size for NCM and on the global cognitive score was considered moderate, although not statistically significant.

As phonemic fluency was the only domain to be significantly impacted by the independent variable at an alpha value of 0.05, for descriptive purposes, similar ANCOVA's were performed on the z-scores of each letter fluency 90-seconds trial that composed the PF factor. The average raw score of the sum of these trials and the raw scores for each trial (90 and 60 seconds) was also provided (see Table 6).

The Geriatric Depression Scale (GDS-30) was used to assess depressive symptomatology; it was not used in any prior analyses. The mean scores across the +DH and -DH groups were considered normal and not clinically at risk for depression, $\bar{x} = 3.70$ and $\bar{x} = 3.06$, respectively. Therefore, no significant impact from this variable on neuropsychological test performance was expected.

Age, Education, Sex and Neuropsychological Test Performance

The relationship between individual subtests performance with age, years of education, and sex was included in Table 4. Overall, results revealed negative and statistically significant relationships between age and 12 out of the 16 test variables used in the PCA. Years of education correlated significantly and positively with 10 of them. Sex only correlated with one testing variable. In addition, only age significantly correlated (negatively) with the MMSE.

Discussion

This study evaluated the relationship between parental history of dementia and neuropsychological test performance with an adapted online Spanish version of the CERAD. To date, limited research exists assessing the relationship of these variables among Puerto Ricans living on the Island.

The results of this study provide initial support of an impact from a parental history of dementia on neuropsychological test performance among a cognitively healthy and young-old Puerto Rican sample. Specifically, FHD significantly impacted the combined dependent variables (5 factors) while controlling for age and education level. In addition, the +DH group performed lower than the -DH group on four out of five cognitive factors while having an independent effect only on phonemic fluency (PF). The effect on PF was significant ($p = .014$) at an alpha value of .05 while more of a statistical trend when implementing Bonferroni correction. These preliminary findings contribute to the available literature describing the relationship of dementia history with performance on measures of neuropsychological functioning in non-demented middle-aged and older adults.[9-12,15,16] Additionally, it adds to the literature on this topic by obtaining data on an

underrepresented population in research studies (i.e., Puerto Ricans).

Morrow et al.[16] reported an interaction between a high number of medical problems and a family history of dementia with overall poorer test performance and an independent statistically significant effect on executive function, which contained phonemic and semantic fluency tasks, and digit span backward. The current study showed an independent main effect of FHD on phonemic fluency ($P < 0.05$). In contrast, there was no significant impact from FHD on the factor loaded with semantic fluency tasks or the working memory factor, composed of both digit span forward and backward. These discrepancies may be explained by the difference in tests/domains factor constructs. Also, their total sample's mean age (73.1) was approximately ten years older than the present study; therefore, a lower cognitive performance could be expected.

Another similar finding was previously demonstrated with cognitively healthy middle-aged and older adults with comparable demographics (age and education) to the current study's sample. Donix et al.[11] reported that having a family history of dementia, specifically Alzheimer's disease (AD), was associated with poorer baseline scores in executive functioning, which included a measure of letter fluency. However, their findings also showed lower baseline scores in processing speed, memory encoding, and delayed memory. Additionally, other studies have also suggested an association between +DH and memory abilities such as encoding and delayed memory.[9,10,12] Although not statistically significant ($p = .074$), there was a trend for an association of family history of dementia with poorer test performance in the obtained non-contextual memory domain (NCM), such that results showed a moderate effect size ($\eta_p^2 = .068$) and an observed power of .434.

Although the underlying mechanism for this relationship is still unknown, some studies suggest it may have a negative additive effect on cognition when in the presence of other risk factors such as APOE e4, HIV positive, and medical comorbidities.[14-16] This could be clinically important considering Puerto Rican's adverse cardiometabolic profile among older adults, characterized by a high prevalence of hypertension (70.2%), lipid metabolism disorder (62.2%), diabetes (53,6%), obesity (37.6%), and metabolic syndrome (38.2%).[60,61]

Within executive function's subdomains, cognitive flexibility, inhibition, and processing speed have shown to be strong predictors for verbal fluency in cognitively healthy participants.[62] Furthermore, literature suggests that preserved executive function is required to properly perform letter fluency tasks.[63,64] On the other hand, first-line history of AD has been associated with lower cerebral perfusion, a higher burden of white matter lesions and microbleeds, and microstructural white matter differences in cognitively healthy late middle-aged and young-old adults.[8,65] These white matter changes have been shown to be associated with lower executive function and processing speed in cognitively healthy older adults.[66] Considering that the covariates of age and education were controlled for, a possible explanation is that dementia history could have accounted for lower phonemic fluency performance among this sample.

Among this sample, no differences were found in the semantic and recognition memory domain (SRM), composed of semantic fluency tasks (animals, clothing), naming (Boston Naming Test), and word list recognition. As mentioned, the word list recognition trial was presented one word at a time on the participant's computer screen, making the forced-choice recognition trial visual in nature. Also, the addition of another semantic fluency task (clothing fluency) followed the factor structure tendency as the original CERAD version, loading with the BNT and animal fluency.[21] Nonetheless, the phonemic fluency task (PAN) generated an additional factor that explained the second most variation in the neuropsychological variables among the sample. This could partly be explained by the evidence showing that different neural networks are active during these tasks, semantic fluency and visual confrontation naming requiring more temporal-lobe involvement, while phonemic

fluency shows more frontal-lobe involvement.[67-69] These findings support the idea that lower scores on the PF domain by the +DH group are likely due to difficulties with the executive components of the task (e.g., switching to a new strategy when the current one is exhausted), rather than language and semantic memory skills. However, further studies with more tasks measuring executive functioning and processing speed could clarify since evidence suggests that language processing is a critical component for phonemic fluency, showing factor loadings from semantic and phonemic fluency in conjunction with the BNT.[70]

Recognizing the need for better knowledge of the preclinical phase of AD and other dementias among Puerto Ricans, the relation between +DH and phonemic fluency as a possible prodromal stage for cognitive impairment could be considered in future studies and in clinical settings. Of note, it is relevant to consider that phonemic fluency differences have been reported among Spanish speakers from different countries (i.e., Puerto Rico, Chile, Dominican Republic, and Spain), providing preliminary evidence that not all Spanish speakers perform similarly, and that ethnicity, language, and culture should be addressed by the discipline of Clinical Neuropsychology.[71]

96% of the sample scored 27 or higher on the MMSE, which is considered a better indicator of normal cognitive function than 25 or higher.[57,72] Considering the significantly lower phonemic fluency performance by the +DH group, results support the use of cognitive screeners that incorporate phonemic fluency tasks in Puerto Rico, which is not the case of the MMSE, even though it is one of the most commonly administered screeners. This could favor an appropriate referral to the neuropsychology specialty and reduce the probability of a false negative diagnosis among this Puerto Rican population. This should be encouraged within the psychology and neuropsychology practice, as well as other medical institutions within the Island.

These preliminary findings suggest that researchers may consider family history of dementia as a covariate in studies of normal cognitive aging, even among the late middle-aged and young-old adult range. La Rue et al.[9] also made a similar suggestion upon a Northern American sample. Additionally, the possible sensitivity of phonemic fluency tasks and its relationship with a family history of dementia could strengthen clinical practice with non-demented young-old Puerto Ricans with dementia history. Lastly, although limited, this study provides initial data on 50 Puerto Ricans' neuropsychological test performance for commonly used tests, contributing to the need for information on the second-largest Latin group in the United States.

Factor Structure

A principal component analysis (PCA) was carried out to explore the factor structure of the study's CERAD battery due to its adaptation to an online format, the exclusion of tests found in the original CERAD, and the inclusion of additional tests not found in the earliest version. Although the authors acknowledge the limitations of conducting a PCA with a sample size of 50, the present study's ratio of subjects to variables meets the minimum for PCA.[73] The inclusion and exclusion of tests might partially explain the additional two factors that were generated in the present study for a total of five factors compared to the three traditional factors that have been documented in the literature across different languages.[21,26,74,75] However, similar tendencies to previous CERAD's factor structure include: 1) Word List Tasks weighted heavily on Factor 1 while accounting for the most variance in overall test performance, and 2) Animal Fluency and Boston Naming Test loaded within the same factor.[21,23,26,74,75] Compared to the original CERAD, no Praxis factor was generated due to the exclusion of the Constructional Praxis Test. Lastly, the three new factors generated in this study can be explained by the following additional tests: 1) Letter Fluency (Phonemic Fluency); 2) Logical Memory (Contextual Memory), and Digit Span (Working Memory).

Interestingly, the PF factor explained the second most variance (12.99%) in test performance among this sample, even more than the factor with loadings from the Boston Naming Test and Animal Fluency, which typically loads as the second,[21,26] or third

factor.[74,75] Further exploration and validation of this battery might be beneficial since it could shed light on other explanations for neurocognitive changes among Puerto Ricans apart from Alzheimer's disease, which the original CERAD was designed for.

Age, Education, Sex and Neuropsychological Test Performance

The current study revealed a significant influence of age and education on the linear composite of the five cognitive domains/neuropsychological performance with large effect sizes. Age had a larger effect size compared to education level. Overall test performance was not significantly influenced by sex. Subsequent analysis of covariance also indicated that age and education were significant covariates when examining the impact of FHD on the global cognitive z-score (mean of the five domains) while not showing a main effect by dementia history.

However, contextual memory (CM) and working memory (WM) were not independently significantly impacted by age, while education level did not independently influence the NCM and SRM domain. It is well established that educational attainment and age impact neuropsychological test performance, including the CERAD battery.[25,76-78] More extended formal education is associated with superior performance on letter fluency, category fluency, naming, logical memory, and digit span.[25,79-81]

Consequently, high educational attainment among this sample could have substantially accounted for the results on the obtained domains, composed of verbal fluency tests, naming, digit span, and logical memory. Also, the whole sample's age range (55-74) and size could have partly contributed. Future studies should aim to collect data from Puerto Ricans with lower educational levels while utilizing the CERAD for a more comprehensive analysis and further developing the adapted version of the battery.

Limitations and Research Perspectives

The applied cross-sectional design does not detect changes over time, and therefore a follow-up was not performed. Previous longitudinal studies investigating the impact of family history of dementia on cognition have shown evidence of more significant cognitive decline over time among relatives compared to controls,[9,10] while contradictory results have also been reported.[11] Therefore, a longitudinal approach could certainly provide valuable information on possible cognitive decline among this cognitively healthy relative's population.

Second, familial history of dementia was based on self-reported data. However, the applied data collection method was a structured and detailed interview. This method has been successfully used previously and found reliable.[82] As carried out within this study, future researchers addressing this variable should consider asking for senile dementia and not only Alzheimer's Disease or related dementias. Among the current study, participants would respond that a parent did not have AD or dementia but would provide an affirmative response to having a diagnosis of senile dementia. Clinical neuropsychologists and future researchers should be aware of this phenomenon when interviewing Puerto Ricans in both clinical and research settings.

Third, the full sample is not representative of the Puerto Rican population concerning education. Under-representation of low-educated individuals is an unfortunate but common circumstance in many research studies. The fourth limit of this study is the small sample size, which could have reduced statistical power and potentially reduced the generalization of results, further supported when Bonferroni correction was implemented. Thus, this study's findings are preliminary.

Future studies with a larger and more diverse sample in terms of broader years of education, age range, and individuals from different regions of the Island are needed to explore and describe the relationship among these variables more in-depth. It would also be beneficial to have participants divided by early-onset relatives and late-onset relatives since prodromal effects can vary.[8] The current sample did not show a statistically significant difference among the groups' cardiovascular risk factors,

which can be considered a statistical control measure. However, future studies among Puerto Ricans should control for medical and cardiovascular conditions since it has been reported that combined with dementia history, it may have an accumulative negative effect on cognition.[16]

Statistical controls were carried out for confounding variables that research has shown to impact cognition[83] and CERAD performances,[25,78] especially age and education.[76,77] To the author's knowledge, this study may be considered one of the few that might have documented the impact of having a family history of dementia on neuropsychological test performance among a cognitively healthy Puerto Rican sample.

A novel element is the development and use of an online adapted version of the CERAD Spanish version by the authors. This topic is considered clinically important since there is a lack of studies on implementing tele-testing in Puerto Rico. Tele-testing might be a useful alternative tool when patients have challenges reaching the clinician for face-to-face testing. Therefore, this line of research should be perused in the Island. On the current study, the PCA's results support that the measured constructs (i.e., non-contextual memory, phonemic fluency, contextual memory, and working memory) among this study were not altered due to the online adaptation and was simply an accommodation due to the COVID-19 circumstances.[54] Thus, a future study with a larger sample should aim to carry out validity analysis with this adapted online version.

As mentioned, neuropsychological testing was performed online; for this reason, testing conditions may have differed from one individual to another. The investigators attempted to limit this variability through interviewer training and detailed and standardized testing protocols. Research has documented that there is currently limited evidence validating the use of teleneuropsychology in the under-represented population due to a lack of participation, partly due to having less internet access and comfort using technology.[43,44,84,85] Hence, this phenomenon may explain the highly educated sample that reached out and agreed to participate in the current study, which probably had better internet and computer access and felt more comfortable using technology during the COVID-19 global pandemic. Also, due to the online format, paper and pencil tests that would have been used to assess attention, processing speed, visuospatial ability, and visual memory were taken out of the Spanish version CERAD battery—leaving the investigators with a battery that assesses more partially lateralized functions of the left hemisphere. Nevertheless, similar tests used for the study have been proposed for cognitive assessment in older adults and were useful and studied in TeleNP dementia evaluations and older adults.[43,44] Future studies addressing the impact of FHD on neuropsychological test performance among Puerto Ricans should consider implementing visual memory, visual-constructive, and processing speed tasks for a more comprehensive measure and understanding of any association.

Disclosure statement

The authors do not have conflicts of interest regarding this research study.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Acknowledgments

We want to thank the Puerto Rican Psychological Association and AARP Puerto Rico for their support, as well as James Tyler Rosier's scientific advice and valuable comments. We are also grateful to the participants of this study for taking their valuable time in taking part in this research.

REFERENCES

1. World Health Organization. Global strategy and action plan on ageing and health. Geneva, Switzerland. World Health Organization. 2017.
2. Braak H, Thal DR, Ghebremedhin E, Tredici KD. Stages of the Pathologic Process in Alzheimer Disease: Age Categories From 1 to 100 Years. J Neuropathol Exp Neurol. 2011;70(11):10.
3. Deary IJ, Corley J, Gow AJ, Harris SE, Houlihan LM, Marioni RE, et al. Age-associated cognitive decline. British Medical Bulletin. 2009 Dec 1;92(1):135–52.
4. Green RC, Cupples LA, Go R, Benke KS, Edeki T, Griffith PA, et al. Risk of Dementia Among White and African American Relatives of Patients with Alzheimer Disease. JAMA. 2002;287(3):329–36.
5. Jayadev S, Steinbart EJ, Chi Y-Y, Kukull WA, Schellenberg GD, Bird TD. Conjugal Alzheimer Disease: Risk in Children When Both Parents Have Alzheimer Disease. Arch Neurol [Internet]. 2008 Mar 1 [cited 2021 Aug 8];65(3). Available from: http://archneur.jamanetwork.com/article.aspx?doi=10.1001/archneurol.2007.61
6. Scarabino D, Gambina G, Broggio E, Pelliccia F, Corbo RM. Influence of family history of dementia in the development and progression of late-onset Alzheimer's disease. Am J Med Genet. 2016 Mar;171(2):250–6.
7. Sleegers K, Bettens K, De Roeck A, Van Cauwenberghe C, Cuyvers E, Verheijen J, et al. A 22-single nucleotide polymorphism Alzheimer's disease risk score correlates with family history, onset age, and cerebrospinal fluid Aβ Alzheimer's & Dementia. 2015 Dec;11(12):1452–60.
8. Wolters FJ, van der Lee SJ, Koudstaal PJ, van Duijn CM, Hofman A, Ikram MK, et al. Parental family history of dementia in relation to subclinical brain disease and dementia risk. Neurology. 2017 Apr 25;88(17):1642–9.
9. La Rue A, O'hara R, Matsuyama SS, Jarvik LF. Cognitive changes in young-old adults: Effect of family history of dementia. Journal of Clinical and Experimental Neuropsychology. 1995 Feb;17(1):65–70.
10. Locke DEC, Ivnik RJ, Cha RH, Knopman DS, Tangalos EG, Boeve BF, et al. Age, family history, and memory and future risk for cognitive impairment. Journal of Clinical and Experimental Neuropsychology. 2009 Jan;31(1):111–6.
11. Donix M, Ercoli LM, Siddarth P, Brown JA, Martin-Harris L, Burggren AC, et al. Influence of alzheimer disease family history and genetic risk on cognitive performance in healthy middle-aged and older people. The American Journal of Geriatric Psychiatry. 2012;20(7):565–73.
12. Talboom JS, Ha A, Schrauwen I, Lewis CR, Bertinelli SF, Hammersland C, et al. Family history of Alzheimer's disease alters cognition and is modified by medical and genetic factors. eLife. 2019;16.
13. Calvin CM, de Boer C, Raymont V, Gallacher J, Koychev I, The European Prevention of Alzheimer's Dementia (EPAD) Consortium. Prediction of Alzheimer's disease biomarker status defined by the 'ATN framework' among cognitively healthy individuals: results from the EPAD longitudinal cohort study. Alz Res Therapy. 2020 Dec;12(1):143.
14. Hayden KM, Zandi PP, West NA, Tschanz JT, Norton MC, Corcoran C, et al. Effects of Family History and Apolipoprotein E4 Status on Cognitive Decline in the Absence of Alzheimer Dementia. ARCH NEUROL. 2009;66(11):1378–83.
15. Moore DJ, Arce M, Moseley S, McCutchan JA, Marquie-Beck J, Franklin DR, et al. Family History of Dementia Predicts Worse Neuropsychological Functioning Among HIV-Infected Persons. JNP. 2011 Jan;23(3):316–23.
16. Morrow LA, Snitz BE, Rodriquez EG, Huber KA, Saxton JA. High medical co-morbidity and family history of dementia is associated with lower cognitive function in older patients. Family Practice. 2009 Oct 1;26(5):339–43.
17. Ritchie K, Carrière I, Su L, O'Brien JT, Lovestone S, Wells K, et al. The midlife cognitive profiles of adults at high risk of late-onset Alzheimer's disease: The PREVENT study. Alzheimer's & Dementia. 2017 Oct;13(10):1089–97.

18. Mackin RS, Insel PS, Truran D, Finley S, Flenniken D, Nosheny R, et al. Unsupervised online neuropsychological test performance for individuals with mild cognitive impairment and dementia: Results from the Brain Health Registry. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2018 Jan;10(1):573–82.
19. Grober E, Hall CB, Lipton RB, Zonderman AB, Resnick SM, Kawas C. Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease. J Inter Neuropsych Soc [Internet]. 2008 Mar [cited 2021 Oct 9];14(02). Available from: http://www.journals.cambridge.org/abstract_S1355617708080302
20. Jungwirth S, Zehetmayer S, Bauer P, Weissgram S, Tragl KH, Fischer P. Prediction of Alzheimer dementia with short neuropsychological instruments. J Neural Transm. 2009 Nov;116(11):1513–21.
21. Morris JC, Heyman A, Mohs RC, Hughes JP, van Belle G, Fillenbaum G, Mellits ED, & Clark C. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology. 1989 39(9): 1159–1165. https://doi.org/10.1212/wnl.39.9.1159
22. Duke Aging Center. Assessments Instruments. 2021. Available from: https://sites.duke.edu/centerforaging/cerad/assessments/
23. Carrión-Baralt JR, Meléndez-Cabrero J, Rodríguez-Ubiñas H, Schmeidler J, Beeri MS, Angelo G, et al. Impact of APOE β4 on the Cognitive Performance of a Sample of Non-Demented Puerto Rican Nonagenarians. Journal of Alzheimer's disease. 2009;18(3):533–40.
24. Carrión-Baralt JR, Meléndez-Cabrero J, Schnaider Beeri M, Sano, M, & Silverman JM. The neuropsychological performance of nondemented Puerto Rican nonagenarians. Dementia and geriatric cognitive disorders. 2009;27(4):353–360.
25. Karrasch M, Laine M. Age, education, and test performance on the Finnish CERAD. Acta Neurologica Scandinavica. 2003 Aug;108(2):97–101.
26. Lee JH, Lee KU, Lee DY, Kim KW, Jhoo JH, Kim JH, et al. Development of the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K). The journals of gerontology. Series B, Psychological sciences, and social sciences. 2002; 57(1), P47–P53.
27. Nitrini R, Bottino CMC, Albala C, Custodio Capuñay NS, Ketzoian C, Llibre Rodriguez JJ, et al. Prevalence of dementia in Latin America: a collaborative study of population-based cohorts. Int Psychogeriatr. 2009 Aug;21(4):622–30.
28. Prince M, Wimo A, Guerchet M. World Alzheimer Report 2015- The global impact of dementia. 2015. Alzheimer's Disease International. Available at: http://www.worldalzreport2015.org
29. Rodriguez JJL, Ferri CP, Acosta D, Guerra M, Huang Y, Jacob K, et al. Prevalence of dementia in Latin America, India, and China: a population-based cross-sectional survey. The Lancet. 2008 Aug;372(9637):464–74.
30. Vega IE, Cabrera LY, Wygant CM, Velez-Ortiz D, Counts SE. Alzheimer's Disease in the Latino Community: Intersection of Genetics and Social Determinants of Health. Abisambra J, editor. JAD. 2017 Jun 23;58(4):979–92.
31. 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 & Dementia. 2019 Feb;15(2):292–312.
32. Prina AM, Acosta D, Acostas I, Guerra M, Huang Y, Jotheeswaran AT, et al. Cohort Profile: The 10/66 study. Int J Epidemiol. 2016 May 6;1-10.
33. US Census Bureau. International Data Base: Hispanic or Latino origin by specific origin. 2019. Retrieved November 28, 2021.
34. Kishore N, Marqués D, Mahmud A, Kiang MV, Rodriguez I, Fuller A, et al. Mortality in Puerto Rico after Hurricane Maria. N Engl J Med. 2018 Jul 12;379(2):162–70.
35. Rodríguez-Irizarry W, Oliveras-Rentas R, Olabarrieta-Landa L, Arango-Lasprilla JC. La práctica de la neuropsicología en Puerto Rico: implicaciones para la certificación de la especialidad. Revista Iberoamericana de Neuropsicologia. 2018;1(1):18.

36. Arango-Lasprilla JC, Stevens L, Morlett Paredes A, Ardila A, Rivera D. Profession of neuropsychology in Latin America. Applied Neuropsychology: Adult. 2017 Jul 4;24(4):318–30.
37. Ardila A. Cultural Values Underlying Psychometric Cognitive Testing. Neuropsychol Rev. 2005 Dec;15(4):185.
38. Judd T, Capetillo D, Carrion-Baralt J, Marmol LM, Miguel-Montes LS, Navarrete MG, et al. Professional Considerations for Improving the Neuropsychological Evaluation of Hispanics: A National Academy of Neuropsychology Education Paper. Archives of Clinical Neuropsychology. 2009 Mar 1;24(2):127–35.
39. Puente AE, & Agranovich AV. The Cultural in Cross-Cultural Neuropsychology. In G. Goldstein, S. R. Beers, & M. Hersen (Eds.), Comprehensive handbook of psychological assessment, Vol. 1. Intellectual and neuropsychological assessment. John Wiley & Sons; 2004. p.321–332.
40. Ardila A. The impact of culture on neuropsychological test performance. In Uzzell, B., Pontón, M.O., & Ardila, A. (Eds.), International Handbook of Cross-Cultural Neuropsychology. New York: Psychology Press; 2013. p. 23-44.
41. Ardila A. Cross-Cultural Neuropsychology: History and Prospects. RUDN Journal of Psychology and Pedagogics. 2020 Dec 15;17(1):64–78.
42. Folstein MF, Folstein SE, & McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. 1975;12(3):189-198.
43. Marra DE, Hamlet KM, Bauer RM, Bowers D. Validity of teleneuropsychology for older adults in response to COVID-19: A systematic and critical review. The Clinical Neuropsychologist. 2020 Nov 16;34(7–8):1411–52.
44. Kitaigorodsky M, Loewenstein D, Curiel Cid R, Crocco E, Gorman K, González-Jiménez C. A Teleneuropsychology Protocol for the Cognitive Assessment of Older Adults During COVID-19. Front Psychol. 2021 May 13;12:651136.
45. Rosen WG, Mohs RC, & Davis KL. A new rating scale for Alzheimer's disease. American Journal of Psychiatry. 1984;141(11):1356-1364.
46. Drozdick LW, Wahlstrom D, Zhu J, Weiss LG. The Wechsler Adult Intelligence Scale—Fourth Edition and the Wechsler Memory Scale—Fourth Edition. In: Contemporary intellectual assessment: Theories, tests, and issues, 3rd ed. New York, NY, US: The Guilford Press; 2012. p. 197–223.
47. Lezak MD, editor. Neuropsychological assessment. 5th ed. Oxford; New York: Oxford University Press; 2012.
48. Kaplan EF, Goodglass H, and Weintraub S. The Boston Naming Test. 2nd Edition, Lea & Febiger, Philadelphia; 1983.
49. Puente AE, & Ardila A. Neuropsychological assessment of Hispanics. In E. Fletcher-Janzen, T. L. Strickland, & C. R. Reynolds (Eds.), Handbook of cross-cultural neuropsychology. Kluwer Academic Publishers; 2000. p.87–104.
50. Puente AE, Perez-Garcia M, Lopez RV, Hidalgo-Ruzzante NA, & Fasfous AF. Neuropsychological assessment of culturally and educationally dissimilar individuals. In F. A. Paniagua & A.-M. Yamada (Eds.), Handbook of multicultural mental health: Assessment and treatment of diverse populations. Elsevier Academic Press; 2013. p. 225–241.
51. Wechsler D. The Wechsler Adult Intelligence Scale (3rd ed.). San Antonio, TX: The Psychological Corporation; 1997.
52. Wechsler D.Escala de Inteligencia Wechsler para Adultos – Tercera Edicion (EIWA-III). San Antonio, TX: Pearson; 2008.
53. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: A preliminary report. Journal of Psychiatric Research. 1983;17(1):37–49.
54. American Educational Research Association, American Psychological Association, & National Council on Measurement in Education (Eds.). Standards for educational and psychological testing. American Educational Research Association. 2014.

55. Mertler CA, & Vannatta RA. Advanced and multivariate statistical methods: Practical application and interpretation (4th ed.). Pyrczak; 2010.
56. Blesa R, Pujol M, Aguilar M, Santacruz P, Bertran-Serra I, Hernández G, et al. Clinical validity of the 'mini-mental state' for Spanish speaking communities. Neuropsychologia. 2001 Jan;39(11):1150–7.
57. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-Based Norms for the Mini-Mental State Examination by Age and Educational Level. JAMA. 1993;269(18):2386–91.
58. Ostrosky-Solís F, López-Arango G, Ardila A. Sensitivity and Specificity of the Mini-Mental State Examination in a Spanish-Speaking Population. Applied Neuropsychology. 2000 Mar;7(1):25–31.
59. George D & Mallery M. SPSS for Windows step by step: A simple guide and reference, 17.0 update (10th ed.) Boston: Pearson; 2010.
60. Armendáriz A. Informe de la Salud en Puerto Rico. 2016. Retrieved from: http://www.salud.gov.pr/Estadisticas-Registros-y-Publicaciones/Estadisticas Vitales/Informe de la Salud en Puerto Rico 2016.pdf
61. Pérez CM, Sánchez H, Ortiz AP. Prevalence of Overweight and Obesity and Their Cardiometabolic Comorbidities in Hispanic Adults Living in Puerto Rico. J Community Health. 2013 Dec;38(6):1140–6.
62. Amunts J, Camilleri JA, Eickhoff SB, Heim S, Weis S. Executive functions predict verbal fluency scores in healthy participants. Sci Rep. 2020 Dec;10(1):1–11.
63. Henry JD, Crawford JR. A Meta-Analytic Review of Verbal Fluency Performance Following Focal Cortical Lesions. Neuropsychology. 2004;18(2):284–95.
64. Ruff RM, Light RH, Parker SB, Levin HS. The Psychological Construct of Word Fluency. Brain and Language. 1997 May;57(3):394–405.
65. Adluru N, Destiche DJ, Lu SY-F, Doran ST, Birdsill AC, Melah KE, et al. White matter microstructure in late middle-age: Effects of apolipoprotein E4 and parental family history of Alzheimer's disease. NeuroImage: Clinical. 2014;4:730–42.
66. Jacobs HIL, Leritz EC, Williams VJ, Van Boxtel MPJ, Elst W van der, Jolles J, et al. Association between white matter microstructure, executive functions, and processing speed in older adults: The impact of vascular health. Hum Brain Mapp. 2013 Jan;34(1):77–95.
67. Baldo JV, Shimamura AP. Letter and Category Fluency in Patients with Frontal Lobe Lesions. Neuropsychology. 1998;12(2):259–67.
68. Melrose RJ, Campa OM, Harwood DG, Osato S, Mandelkern MA, Sultzer DL. The neural correlates of naming and fluency deficits in Alzheimer's disease: an FDG-PET study. Int J Geriat Psychiatry. 2009 Aug;24(8):885–93.
69. Stuss DT, Alexander MP, Hamer L, Palumbo C, Dempster R, Binns M, et al. The effects of focal anterior and posterior brain lesions on verbal fluency. J Int Neuropsychol Soc. 1998 May;4(3):265–78.
70. Whiteside DM, Kealey T, Semla M, Luu H, Rice L, Basso MR, et al. Verbal Fluency: Language or Executive Function Measure? Applied Neuropsychology: Adult. 2016 Jan 2;23(1):29–34.
71. Buré-Reyes A, Hidalgo-Ruzzante N, Vilar-López R, Gontier J, Sánchez L, Pérez-García M, et al. Neuropsychological test performance of Spanish speakers: Is performance different across different Spanish-speaking subgroups? null. 2013 Apr 1;35(4):404–12.
72. O'Bryant SE, Humphreys JD, Smith GE, Ivnik RJ, Graff-Radford NR, Petersen RC, et al. Detecting Dementia with the Mini-Mental State Examination in Highly Educated Individuals. Arch Neurol [Internet]. 2008 Jul 1 [cited 2022 Jan 22];65(7).
73. Kline, P. An easy guide to Factor Analysis. London, Routledge; 1994.
74. Aguirre Acevedo DC, Gómez RD, Moreno Másmela S, Henao Arboleda E, Motta Artunduaga M, Muñoz C, et al. Validez y fiabilidad de la batería neuropsicológica CERAD-Col. RevNeurol. 2007;45(11):655.
75. Ehrensperger M, Berres M, Taylor K, Monsch A. Early detection of Alzheimer's disease with a total score of the German CERAD. Journal of the International Neuropsychological Society. Cambridge University Press; 2010;16(5):910–20.

76. Ardila A, Rosselli M, & Ostrosky-Solis F. Sociocultural factors in neuropsychological assessment. In Puente, A. E., & McCaffrey, R. J. (Eds.), Handbook of Neuropsychological assessment: A biopsychosocial perspective. Springer Science & Business Media; 1992. p. 181-192.
77. Ardila A, Ostrosky-Solis F, Rosselli M, Gómez C. Age-Related Cognitive Decline During Normal Aging: The Complex Effect of Education. Archives of Clinical Neuropsychology. 2000;15(6):495–513.
78. Welsh KA, Butters N, Mohs RC, Beekly D, Edland S, Fillenbaum G, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery. Neurology. 1994;44(4):609–14.
79. Ahn YD, Yi D, Joung H, Seo EH, Lee YH, Byun MS, et al. Normative Data for the Logical Memory Subtest of the Wechsler Memory Scale-IV in Middle-Aged and Elderly Korean People. Psychiatry Investig. 2019 Nov 25;16(11):793–9.
80. Bolla KI, Gray S, Resnick SM, Galante R, Kawas C. Category and Letter Fluency in Highly Educated Older Adults. The Clinical Neuropsychologist. 1998 Aug;12(3):330–8.
81. Ostrosky-Solís F, Lozano A. Digit Span: Effect of education and culture. International Journal of Psychology. 2006 Oct;41(5):333–41.
82. Silverman JM, Breitner JC, Mohs RC, & Davis KL. Reliability of the family history method in genetic studies of alzheimer's disease and related dementias. The American Journal of Psychiatry. 1986;143(10):1279-1282.
83. Craik FIM, Salthouse TA. The Handbook of Aging and Cognition. 3rd ed. New York: Psychology Press; 2008.
84. Bilder RM, Postal KS, Barisa M, Aase DM, Cullum CM, Gillaspy SR, et al. InterOrganizational practice committee recommendations/guidance for teleneuropsychology (TeleNP) in response to the COVID-19 pandemic. The Clinical Neuropsychologist. 2020 Nov 16;34(7–8):1314–34.
85. Scott TM, Marton KM, Madore MR. A detailed analysis of ethical considerations for three specific models of teleneuropsychology during and beyond the COVID-19 pandemic. The Clinical Neuropsychologist. 2021 Mar 24;1–21.