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Neuropsychological Deficit Profiles, Vascular Risk Factors, and Neuropathological Findings in Hispanic Older Adults with Autopsy-Confirmed Alzheimer's Disease

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Abstract

This study aimed to determine if patterns of neuropsychological deficits, vascular risk factors, and neuropathology differ in Hispanic and Non-Hispanic patients with autopsy-confirmed Alzheimer's disease (AD). Participants were enrolled in a longitudinal study at the Shiley-Marcos AD Research Center at the University of California, San Diego. Hispanic (n = 14) and Non-Hispanic (n = 20) patients with autopsy-confirmed AD who scored ≥95 on the Dementia Rating Scale (DRS) were included. Patient groups were matched on age, education, global mental status, and severity of functional decline; they were compared to Hispanic (n = 14) or Non-Hispanic (n = 20) cognitively-normal controls of similar age and education. Ethnicity (Hispanic, Non-Hispanic) by disease state (autopsy-confirmed AD or cognitively normal) comparisons were made for cognitive test performance and vascular risk factors. Patient groups were further compared on measures of AD (Braak stage, neuritic plaques, neurofibrillary tangles), vascular neuropathology, and performance across cognitive domains of memory, language, attention, executive functions, and visuospatial abilities after scores were z-transformed based on respective culturally-appropriate control groups. Patient groups had similar overall AD pathology burden, whereas Hispanics with AD had more small parenchymal arteriolar disease and amyloid angiopathy than Non-Hispanics with AD. Despite largely similar pathology, Hispanics with AD were less cognitively impaired (relative to respective NC groups) than Non-Hispanics with AD, and exhibited a different pattern of deficits across cognitive domains. Findings suggest that cognitive deficits that are usually prominent in

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AD may be less salient in Hispanic patients and this may adversely impact the ability to clinically detect the disease in mild to moderate stages.

Keywords

Alzheimer's disease; autopsy; bilingualism; Hispanics; neuropsychology

INTRODUCTION

Alzheimer's disease (AD) currently affects approximately 5.2 million Americans and is one of the leading causes of death in the United States. The prevalence of AD is expected to increase to 13.8 million Americans by the year 2050 [1]. The growing prevalence of AD in the United States is occurring in conjunction with a growing elderly Hispanic population [2], and some studies suggest that the prevalence of dementia may be higher among Hispanics than Non-Hispanic Whites [3]. As AD increases in the U.S. Hispanic population, consideration must be given to how culturally-related demographic (e.g., bilingualism and education) and health (e.g., high vascular risk) factors impact current clinical and neuropsychological procedures used to detect AD. This requires an examination of the relationship between these factors, cognitive deficit profiles (relative to demographically- and culturally-appropriate healthy comparison groups), and brain pathology in Hispanic patients with autopsy-confirmed AD. Unfortunately, studies with autopsy-confirmation of AD in Hispanic patients who were prospectively examined with comprehensive cognitive and clinical assessment have not been reported. Here we report the clinical features and neuropsychological deficit profiles of 14 Hispanic patients with autopsy-confirmed AD when they were first evaluated at a stage of mild to moderate dementia. Their performance was compared to that of a group of Non-Hispanic White patients with autopsy-confirmed AD who were similar in stage of global dementia, age, and education level at time of their first evaluation. Brain pathology, vascular risk factors, and cognitive performance were compared between the two groups.

MATERIALS AND METHODS

Participants

From 1989 to 2016, fifty-five Hispanic patients with dementia died and were autopsied during their participation in the longitudinal study of the Shiley-Marcos Alzheimer's Disease Research Center (ADRC) at the University of California, San Diego (UCSD). Twenty-six of these 55 received a neuropathological diagnosis of AD. Sixteen of these 26 autopsy-confirmed AD patients were diagnosed with dementia and scored above 95 on the Dementia Rating Scale (DRS) [4] at their first ADRC evaluation and were therefore capable of completing a full battery of neuropsychological tests. Two of these 16 patients had presenilin 1 mutations with early age of onset (age 33 and 46 years, respectively, at time of death) and were not included in our analyses. Thus, 14 patients were included in our detailed study of neuropsychological test performance, cardiovascular risk factors, and neuropathologic features.

The Hispanic patients with autopsy-confirmed AD were compared to 20 Non-Hispanic White patients with autopsy-confirmed AD who were also diagnosed with dementia and scored ≥95 on the DRS at their first ADRC evaluation. The Non-Hispanic patient group was drawn from a larger pool in the ADRC cohort to form a comparison group that was similar to the Hispanic patient group in average age, education, level of dementia as measured by the DRS, and degree of functional impairment. The Non-Hispanic patient pool consisted of 335 Non-Hispanic patients with dementia who died and received a neuropathological diagnosis of AD between 1989 and 2016 (n = 529 out of 875 autopsies), and had a DRS score ≥95 (n = 335 out of 529 with a neuropathological diagnosis of AD) at their first ADRC evaluation. Separate culturally-appropriate healthy comparison groups were drawn from larger pools to be similar to their respective patient groups on age and education. All individuals in the normal comparison groups were judged to be cognitively normal at their first ADRC evaluation and for all subsequent years of their participation in the ADRC longitudinal study (Hispanic: M = 7.3 years, SD = 3.9; Non-Hispanic: M = 6.2 years; SD = 5.3; p = 0.55). Because of the low education level of the Hispanic sample, we were forced to draw the matching Non-Hispanic samples from a very restricted set of individuals. Therefore, there were very few instances where a choice between two or more Non-Hispanic patients or controls had to be made. In those instances, the decision was made randomly.

Written informed consent to participate in the study was obtained prior to testing from all participants or their caregivers consistent with California State law. Informed consent for autopsy was obtained at the time of death from the next of kin. The research protocol was reviewed and approved by the human subjects review board at UCSD.

Clinical and neuropsychological procedures

Neurologic, neuropsychiatric, and neuropsychological evaluations were carried out as part of the initial UCSD ADRC research study protocol [5]. The neurologic/medical evaluation included a review of history with the participant or informant (in the case of patients), a modified Hachinski ischemia score [6], clinical mental status testing, and a physical neurological examination. Blood pressure, glucose, cholesterol, triglyceride, and body mass index (BMI) were measured. Presence or absence of a historical diagnosis of hypertension, diabetes, atrial fibrillation, congestive heart failure, angina, and intermittent claudication, as well as history of stroke and transient ischemic attacks, were obtained from the participant or informant (in the case of patients) and a review of medical records. The neuropsychiatric evaluation consisted of interviews of the participant or informant (in the case of patients) using the Diagnostic Interview Schedules [7] for psychosis, depression, and substance dependence, and the Neuropsychiatric Inventory [8].

A battery of neuropsychological tests was administered by a trained psychometrist (see Table 6). Detailed descriptions of the tests have been published [9]. Translation of test materials was performed by bilingual psychologists, nurses, and physicians in consultation with a certified translator. Back translation was performed for all materials that were shown or read to the participant during testing. The psychometrists who tested Hispanic participants were bilingual and bicultural, and had Mexican-American, Central American, or Puerto

Rican heritage. Testing was conducted individually in a quiet well-lit room. Language of testing was determined based on the participant's self-reported preferred language.

Neuropathologic procedures

Autopsy was performed within 12 hours of death. In accordance with the Terry et al. [10] protocol, the left hemibrain was fixed by immersion in 10% formalin for 5–7 days. Paraffin-embedded blocks from midfrontal, rostral superior temporal and inferior parietal neocortex, hippocampus, entorhinal cortex, basal ganglia/substantia innominata, mesencephalon, and pons were cut at 7-μm thickness for hematoxylineosin (H & E) and thioflavin-S staining and counts. Neuritic plaque and neurofibrillary tangle (NFT) counts (and the absence of Lewy bodies in the locus coeruleus, substantia nigra, nucleus basalis, and neocortex) were determined by a single examiner (L.A.H.). In compliance with acceptable methods according to current NIA-AA criteria for the neuropathologic assessment of AD [11], lesions were evaluated visually in 10-μm-thick sections stained with thioflavin-S and viewed with ultraviolet illumination and a 440-μm bandpass wavelength excitation filter. Neuritic plaques were brightly stained and contained filamentous amyloid and swollen or dystrophic neurites either with (mature neuritic plaque) or without (immature neuritic plaque) compact amyloid cores. Entire cortical sections were surveyed to find areas with the heaviest pathologic burden, and these were selectively chosen for lesion enumeration. Three low magnification fields (×100; 1.76 mm^2) were used for count of neuritic plaques, and three high magnification fields (×500; 0.1 mm^2) were used for count of NFTs. The results were then averaged to provide a single neuritic plaque and NFT count for each of four brain regions (midfrontal cortex, inferior parietal cortex, superior temporal cortex, and hippocampus) from each case.

A modified Braak stage was obtained for each case using methods described by Hansen and Terry [12]. Briefly, the modified Braak stage for AD pathology involves counting the number of NFT in at least five neuron clusters in layer two of the entorhinal cortex and then averaging the results. Cases with modified Braak Stage I to IV have fewer than 18 tangles, on average, in layer two of the entorhinal cortex and sparse neocortical tangles. Modified Braak Stage V cases have moderate numbers of tangles in at least two neocortical sections. In modified Braak Stage VI, all neocortical areas assessed have at least moderate numbers of tangles. NIA-Reagan Institute criteria based on the number of plaques and tangles in the neocortex, limbic, and paralimbic regions were applied [13, 14]. All patients were classified as having a "high" or "intermediate" likelihood of dementia due to AD by NIA-Reagan Institute criteria, except one Hispanic patient who met CERAD neuropathological criteria for probable AD.

All autopsied brains were examined for ceresbral amyloid angiopathy (CAA) and cerebrovascular disease (i.e., hemorrhage, large artery infarction, lacunes, cortical microinfarcts, arteriosclerosis, and atherosclerosis in the Circle of Willis). The severity of CAA was semi-quantitatively measured as mild, moderate, or severe on thioflavin-S stained prepasrations of the midfrontal cortex, superior temporal gyrus, inferior parietal cortex, and posterior hippocampus using a method described previously [15]. Capillary CAA was not

calculated. Cerebrovascular disease, arteriosclerosis, and atherosclerosis were also semi-quantitatively measured as mild, moderate, or severe [16].

Statistical analyses

Groups were compared on demographic, neuropathological, and health variables using between-group Analysis of Variance (ANOVA) for continuous variables and Chi-Square or Fisher's exact test of independence for categorical variables. Patterns of cognitive deficits exhibited by patients with AD were compared across ethnicities by first creating composite domain scores that were the average of z-scores (relative to the respective ethnically-appropriate NC group) for each test within each of five cognitive domains: memory, language, attention, executive functioning, and visuospatial abilities. When necessary, scores were modified so that negative z-scores reflected poorer performance. The tests included in each cognitive domain were based on a previously reported factor analysis [17]. The domain scores were then submitted to a Group (Hispanic AD versus Non-Hispanic AD) by Cognitive Domain ANOVA. When the Group main effect was significant, follow-up *t*-tests were conducted to compare Hispanic AD and Non-Hispanic AD patients within each cognitive domain. Significance levels were adjusted using Bonferroni correction (p of 0.05/5 domains = $p < 0.01$). If the Group by Cognitive Domain interaction effect was significant, separate one-way repeated-measures ANOVAs of domain scores for Hispanic and Non-Hispanic patients with AD were conducted to determine each group's profile of impairment across domains.

Group differences on specific cognitive tests within each domain were explored through a series of Group (AD versus NC) by Ethnicity (Hispanic versus Non-Hispanic) ANOVAs. Planned pairwise group comparisons were carried out to determine if significant interaction effects were due to differences between patient groups, control groups, or both. This allowed exploration of the possible impact of differences in control group performance in the two ethnicities on measurement of impairment in the respective patient groups. In these exploratory analyses the significance level was set at $p = 0.05$.

RESULTS

Participant demographics

Participant demographics are presented in Table 1. The four participant groups did not differ significantly in age, education, sex distribution, or reported rates of depression (all ps≥ 0.30). As expected, patients with AD scored worse than NC participants on the DRS in both the Hispanic ($F(1,26) = 26.45$, MSE = 64.76, $p < 0.001$, $\eta^2 = 0.50$) and Non-Hispanic cohorts ($F(1,37) = 90.58$, $MSE = 51.54$, $p < 0.001$, $\eta^2 = 0.71$). Hispanic and Non-Hispanic patients with AD did not differ on DRS scores ($p = 0.33$), nor did the Hispanic and Non-Hispanic NC participants ($p = 0.11$). Patients with AD were rated worse than NC participants on the Pfeffer Outpatient Disabilities Scale (PODS) [17], a measure of activities of daily living, in both the Hispanic ($F(1,26) = 73.43$, MSE = 14.22, $p < 0.001$, $\eta^2 = 0.74$) and Non-Hispanic cohorts ($F(1,38) = 164.82$, MSE = 8.52, $p < 0.001$, $\eta^2 = 0.81$). There was no difference on the PODS for Hispanic versus Non-Hispanic patients with AD ($p = 0.89$) or NC participants ($p = 0.33$). The Hispanic and Non-Hispanic patients with AD did not differ

significantly in the interval between initial evaluation and death ($p = 0.24$). There was no significant difference in the percentages of Hispanic patients with AD (21%) and Hispanic NC participants (29%) tested in Spanish versus in English (Fisher's Exact Test, $p = 1.00$). Countries of origin for the Hispanic NC participants are as follows: Mexican ($n = 12$), Chilean ($n = 1$), and unknown ($n = 1$). Countries of origin for the Hispanic patients with AD are: Mexican ($n = 12$), Peruvian ($n = 1$), and Colombian ($n = 1$).

Cardiovascular disease risk factors in Hispanic versus Non-Hispanic patients with AD

Hispanic patients with AD had higher rates of diabetes (Fisher's exact test $p = 0.007$), but lower systolic blood pressure ($F(1,32) = 11.77$, $MSE = 193.46$, $p = 0.002$, $\eta^2 = 0.27$), pulse pressure (systolic – diastolic; $F(1,32) = 10.53$, $MSE = 124.02$, $p = 0.003$, $\eta^2 = 0.25$), and cholesterol ($F(1,32) = 17.80$, $MSE = 1370.09$, $p < 0.001$. $\eta^2 = 0.38$) than Non-Hispanic patients with AD (see Table 2). Hispanic and Non-Hispanic NC participants did not differ across these risk factors. The Hispanic NC participants had a significantly higher BMI ($F(1,32) = 4.11$, $MSE = 24.18$, $p = 0.05$, $\eta^2 = 0.11$), and a greater rate of hypertension (Fisher's exact test, $p = 0.04$), than the Non-Hispanic NC participants.

Neuropathology in Hispanic versus Non-Hispanic patients with AD

Hispanic and Non-Hispanic patients with AD did not differ in total brain weight or Braak staging (see Table 3; both ps ≥ 0.15). Groups were similar in neuritic plaque and tangle counts across midfrontal, superior temporal, inferior parietal, and hippocampal cortical regions, with the exception of fewer neuritic plaques in the midfrontal region ($F(1,29) = 5.15$, $MSE = 240.34$, $p = 0.031$, $\eta^2 = 0.15$) and the inferior parietal region ($F(1,29) = 6.28$, $MSE = 195.811$, $p = 0.018$, $\eta^2_p = 0.18$), in Hispanic than Non-Hispanic patients. Hispanics and Non-Hispanics did not differ in tangle counts across any of the four cortical regions ($p \geq 0.19$).

Hispanic patients had a higher frequency of small parenchymal arteriolar disease than Non-Hispanic patients ($\chi^2 = 14.67$, $p = 0.002$; see Table 4), and a greater rate of moderate to severe amyloid angiopathy (62% versus 55%; $\chi^2 = 8.42$; $p = 0.038$). The groups did not differ in burden of other aspects of vascular brain pathology, including large infarcts, hemorrhages (agonal infarcts and hemorrhages were excluded), microinfarcts, lacunar infarcts, subcortical arteriosclerosis, cortical necrosis, medial temporal lobe sclerosis, hippocampal sclerosis, or atherosclerosis (all ps ≥ 0.12).

Neuropsychological test performance

Cognitive profile analysis—The mean cognitive domain scores for Hispanic and Non-Hispanic patients with AD are shown in Fig. 1. A Group (Hispanic AD versus Non-Hispanic AD) by Domain Score repeated measures ANOVA revealed significant main effects of Group ($F(1,32) = 13.75$, $MSE = 2.11$, $p = 0.001$, $\eta^2 = 0.30$) and Cognitive Domain ($F(2.88,92.06) = 5.31$, $MSE = 4.06$, $p = 0.002$, $\eta^2 = 0.14$), and a significant Group by Cognitive Domain interaction ($F(2.9, 92.1) = 3.40$, $MSE = 0.77$, $p = 0.023$, $\eta^2 = 0.09$). Mauchly's test of sphericity indicated that the assumption of sphericity had been violated, $\chi^2(9) = 21.93$, $p = 0.009$, therefore degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = 0.72$). Follow-up analyses were carried out to understand

the significant Group by Cognitive Domain interaction effect. Separate one-way repeated-measures ANOVAs for Hispanic and Non-Hispanic patients with AD showed a statistically significant difference between domains for the Hispanic patients ($F(4,52) = 7.01$, $MSE = 0.43$, $p < .001$, $\eta^2 = 0.11$), and a marginal difference between domains for the Non-Hispanic patients ($F(4,76) = 2.34$, $MSE = 0.63$, $p = 0.06$, $\eta^2 = 0.35$). Pair-wise differences between domain scores within each group were examined with *post-hoc* Fisher's LSD tests (see Table 5). Pairwise comparisons in the Hispanic group showed that performance in the Memory domain was significantly worse than performance in the Language ($p = 0.04$), Attention ($p < 0.001$), Executive Functioning ($p = 0.008$), or Visuospatial ($p = 0.05$) domains. Performance in the Attention domain was significantly less impaired than performance in the Language ($p = 0.05$) and Executive Functioning domains ($p = 0.02$). Pairwise comparisons in the Non-Hispanic group showed that performance in the Visuospatial domain was less impaired than performance in the Memory ($p = 0.004$), Attention ($p = 0.035$), or Executive Functioning ($p = 0.006$) domains (degree of impairment in the latter domains did not differ).

Separate group comparisons for each cognitive domain showed that Hispanic patients with AD were less impaired than Non-Hispanic patients with AD in the Memory ($F(1,32) = 12.30$, $MSE = 0.11$, $p = 0.001$, $\eta^2 = 0.28$), Attention ($F(1,32) = 12.50$, $MSE = 1.78$, $p = 0.001$, $\eta^2 = 0.28$), and Executive Functioning ($F(1,32) = 8.59$, $MSE = 0.68$, $p = 0.006$, $\eta^2 = 0.21$) domains. Differences between Hispanic and Non-Hispanic patients with AD in the Language ($F(1,32) = 4.28$, $MSE = 0.77$, $p = 0.047$) and Visuospatial domains ($F(1,32) = 3.88$, $MSE = 0.98$, $p = 0.058$, $\eta^2 = 0.11$) were marginal.

We repeated these analyses with domain scores for the Hispanic AD patients that were based on z-scores derived from a larger Hispanic normative reference group developed by the ADRC (published normative data for Hispanic elderly with relatively low education do not exist for the specific tests we used). The ADRC norms are based on 98 cognitively normal Hispanic elderly adults who have no cognitive complaints, no evidence of functional decline, a normal neurological examination with normal mental status testing, and no change in diagnostic status over at least one additional annual evaluation (mean age = 66.6 ± 9.3; mean education = 11.2 ± 4.5). When we used these norms to generate z-scores for the 14 autopsy-confirmed Hispanic patients with AD, the pattern of results we obtained was the same as with the smaller, matched NC sample. The Memory domain score changed from −1.50 to −1.69, Language changed from −1.10 to −1.04, Attention changed from −0.35 to −0.64, Executive Function changed from −0.95 to −0.77, and Visuospatial changed from −0.55 to −0.56. These small differences may reflect the younger mean age of the larger normative sample.

Performance on individual cognitive tests—The mean scores achieved by Hispanic and Non-Hispanic patients with AD and NC participants on individual cognitive tests are presented by cognitive domain in Table 6. Scores from each test were submitted to Group (AD versus NC) by Ethnicity (Hispanic versus Non-Hispanic) ANOVA. Since these analyses were exploratory, only the results of the interaction effect are reported (see Table 6), and the *p*-value for significance was set at 0.05. Planned pairwise group comparisons were carried out to determine if significant interaction effects were due to differences between patient

groups, control groups, or both. Group by Ethnicity interaction effects were significant for immediate recall on the WMS Visual Reproduction test (Memory domain; $F(1,61) = 5.05$, $MSE = 10.26$, $p = 0.03$, $\eta^2_p = 0.08$), the WAIS-R Vocabulary subtest (Language domain; $F(1,61) = 5.62$, $MSE = 115.34$ $p = 0.02$, $\eta^2_p = 0.08$), the forward condition of WAIS-R Digit Span test (Attention domain; $F(1,64) = 10.06$, $MSE = 1.26$, $p = 0.037$, $\eta^2_p = 0.07$), the Trail Making Test Part B (Executive Function domain; $F(1,59) = 6.59$, $MSE = 3361.07$, $p = 0.01$, $\eta^2_p = 0.10$), and the WAIS-R Digit Symbol Substitution test (Executive Function domain; $F(1,63) = 5.41$, $MSE = 116.15$, $p = 0.023$, $\eta^2_p = 0.08$). Follow-up tests of simple contrasts revealed that Hispanic patients with AD outperformed Non-Hispanics patients with AD on immediate recall of the WMS Visual Reproduction test ($F(1,31) = 10.06$, $MSE = 4.83$, $p = 0.003$, $\eta^2 = 0.25$), while the NC groups did not differ ($p = 0.42$). In contrast, Hispanic NC participants obtained significantly lower scores than Non-Hispanic NC participants on the WAIS-R Vocabulary subtest ($F(1,30) = 11.13$, $MSE = 100.59$ $p = 0.002$, $\eta^2 = 0.27$), forward condition of WAIS-R Digit Span ($F(1,32) = 10.05$, $MSE = 1.36$, $p = 0.003$, $\eta^2 = 0.24$), Trail Making Test Part B ($F(1,32) = 5.01$, $MSE = 1476.68$ $p = 0.03$, $\eta^2 = 0.14$) and WAIS-R Digit Symbol Substitution test ($F(1,32) = 5.41$, $MSE = 116.15$, $p = 0.023$, $\eta^2_p = 0.08$), but the Hispanic and Non-Hispanic patients with AD did not differ on any of these measures (all p's > 0.11).

DISCUSSION

Despite similar age, education, global mental status, and severity of functional decline, mildly-to-moderately demented Hispanic patients with autopsy-proven AD were significantly less impaired than Non-Hispanic patients with AD across domains of Memory, Attention, and Executive Functioning when scores were z-transformed based on respective culturally-appropriate normal control groups. The patient groups also differed in the profile of cognitive deficits they exhibited across domains with Hispanic patients having larger deficits in Memory, and smaller deficits in Attention, relative to other domains—a profile typical of early AD [19, 20]. Conversely, Non-Hispanic patients had smaller deficits in the Visuospatial domain than in all other domains (which did not differ from each other)—a profile typical of more moderate disease stages when other domains of functioning beyond episodic memory become significantly affected [20]. It is notable that with the exception of Memory, average domain scores of Hispanic patients with AD were less than or equal to 1 SD below normal performance, a level that would not be considered clinically impaired. In contrast, the average Memory, Language, Attention, and Executive Functioning domain scores of Non-Hispanic patients were more than 1.5 SD below normal performance. These differences in severity and profiles of neuropsychological impairment occurred despite comparable global markers of disease severity (global mental status, functional decline, test-death interval) at the time of testing and similar levels of AD pathology at time of death.

The reduced salience of neuropsychological impairment in Hispanic patients with AD (compared to Non-Hispanics) may be related to poorer performance of the cognitively healthy elderly individuals to whom the patients with AD were compared. Our exploratory analyses of performance on individual neuropsychological tests within the various cognitive domains showed that the Hispanic NC group performed significantly worse than the Non-Hispanic NC group on key measures from several cognitive domains, including the WAIS-R

Vocabulary test (Language), the WAIS-R Digit Symbol Substitution test (Executive Functioning), the Trail Making Test part B (Executive Functioning), and the WAIS-R Digit Span subtest (Attention). In contrast, the Hispanic and Non-Hispanic patients with AD performed comparably on these and all other measures except immediate recall on the WMS Visual Reproduction test (Memory). Thus, higher (i.e., less impaired) z-scores and cognitive domain-scores in Hispanic than Non-Hispanic patients with AD is not due to better performance in the Hispanic patients, but to worse performance in the Hispanic than the Non-Hispanic NC group despite equivalent age, education, and gender distribution. The difference in the control groups is consistent with previous findings of disadvantages on neuropsychological tests in non-cognitively impaired Hispanic older adults [21–23] and could be due to a number of factors including differences in the quality of the educational experience (e.g., [24]) or incomplete and inappropriate cultural and linguistic adaptation of the cognitive tests [25–27]. In addition, a higher prevalence of risk factors associated with cognitive impairment, such as high BMI and hypertension, in Hispanic than Non-Hispanic controls could contribute to the observed differences in cognitive performance [28–30].

Even though similar cognitive scores were achieved by the two patient groups at the initial evaluation, lower scores would have been expected in Hispanic than Non-Hispanic patients with AD given that Hispanic normal control participants performed worse than Non-Hispanic control participants. This suggests that there may have been a slower rate of cognitive decline in the Hispanic than Non-Hispanic patients. This possibility is consistent with recent research that suggests bilingualism may confer a degree of cognitive reserve that attenuates the cognitive manifestations of AD [23, 31, 32]. Participants in the Hispanic cohort at the UCSD ADRC all report some degree of bilingualism with varying degrees of proficiency [33]. Picture naming scores, first in their dominant language and then in the non-dominant language, were available for 50% of the Hispanic participants in the current study. On average, these participants correctly named 72% (SD = 21%) of 68 items in their dominant language and 39% (SD = 19%) in their non-dominant language, for an average bilingual index score (non-dominant/dominant; see [33]) of 55% (SD = 21%). Although we did not have naming scores for all Hispanic participants, all were drawn from the same population and would likely have similar objectively measured degrees of bilingualism. Prospective longitudinal research is needed to confirm our speculation that bilingualism may confer a degree of cognitive reserve that might slow the rate of cognitive decline in Hispanic patients with autopsy-confirmed AD.

It is also possible that the Hispanic NC group was more likely than the Non-Hispanic NC group to contain individuals with undiagnosed or preclinical AD and this lowered the group’s performance and made it more difficult to detect impairment in the Hispanic patients with AD. Although it is difficult to rule out this possibility without autopsy confirmation or AD biomarkers, we used rigorous clinical criteria to identify NC in both Hispanic and Non-Hispanic samples, including requiring no complaints about cognition (i.e., all NC considered themselves “cognitively normal” for their age), no evidence of functional decline, a normal neurological examination with normal mental status testing, and no change in diagnostic status over an average of 6 subsequent annual evaluations. Nevertheless, future studies are needed in which the absence of AD or other neuropathology is demonstrated by biomarkers or eventual autopsy confirmation.

Although the Hispanic patients with AD appeared less impaired than Non-Hispanic patients with AD in most cognitive domains, the two groups had comparable levels of AD pathology at the time of death. The patient groups did not differ significantly in Braak stage or in counts of neuritic or diffuse plaques or NFTs in the hippocampus and most cortical regions. The only exceptions were that Hispanic patients had fewer neuritic plaques in mid-frontal and inferior parietal cortex than Non-Hispanic patients. It is possible that lower neuritic plaque pathology in these two cortical regions partially accounts for the less impaired cognitive performance of Hispanic than Non-Hispanic patients with AD.

Hispanics with AD had a greater degree of small parenchymal arteriolar disease and amyloid angiopathy, than Non-Hispanics with AD. A potential shift in balance between neurovascular and AD pathology may alter specific aspects of cognition [34] so that the profile of cognitive impairment that typifies the mild-to-moderate stage of AD (i.e., prominent impairment in episodic memory, semantic memory and executive functioning) [35] becomes less salient in Hispanics with AD. It should be noted, however, that although some research suggests an additive effect of vascular and AD pathology on generating cognitive impairment and dementia [36, 37], Reed and colleagues [38] found that concomitant subcortical neurovascular pathology had little effect on the severity of memory, language, or executive function deficits in Non-Hispanic patients with autopsy-confirmed AD. Thus, the slight over-representation of neurovascular pathology we observed in the Hispanic patients with AD may have had little effect on the profile of cognitive deficits they exhibited.

Given the increased prevalence of some aspects of vascular pathology in Hispanic than Non-Hispanic patients with AD, it is somewhat surprising that a number of vascular risk factors such as cholesterol levels, systolic blood pressure, and pulse pressure (a measure of arterial stiffness) were lower in Hispanic than Non-Hispanic patients (although diabetes showed the opposite pattern). Both higher pulse pressure [39–41] and increased cholesterol [42, 43] are associated with increased AD pathology and worse cognition in domains affected in early AD. However, recent research suggests that vascular risk factors in mid-life have a stronger relationship to dementia than vascular risk factors in late-life [44, 45]. Therefore, the late-life vascular risk factors we measured may not reveal the true contribution of these factors to the development of dementia and vascular pathology at the time of death.

Several caveats should be considered. First, the sample of Hispanic patients with both comprehensive cognitive testing in the mild-to-moderate stage of dementia and autopsy-confirmed AD is small and the results need to be replicated. However, results from the cognitive profile analysis and individual test comparisons are relatively robust with medium to large effect sizes. Furthermore, the results are relatively unique in that few previous studies of prospectively evaluated Hispanic patients with AD have autopsy confirmation of the disease. Second, the present study focused primarily on patients of Mexican descent from the southwestern United States so findings may not generalize to Hispanic-American older adults in other areas of the United States. Replication of our study in a larger and more heterogeneous group of Hispanic-American patients with AD would broaden the implications of the results and might identify other factors that impact the profile of cognitive deficits in Hispanic and Non-Hispanic patients with AD. Finally, a sample of

Hispanic patients with AD and NC participants who volunteer for research at an ADRC may not be especially representative of the general population of Hispanics. We do not have detailed socioeconomic status data on our sample, but can compare education level and preference for Spanish language use with data from the US Census Bureau's 2016 American Community Survey for the San Diego area. The American Community Survey showed that in the San Diego area approximately 60% of Hispanics over the age of 60 do not speak English "very well", and approximately 40% of Hispanics over the age of 65 have less than High School education. In our small sample, 42.8% of Hispanics chose to be tested in Spanish, and 42.9% had less than High School education. Thus, at least on these measures, our sample is quite similar to the San Diego area elderly Hispanic population at large. There may, however, be other factors related to a research sample that selectively impacted the pattern of results we obtained.

In conclusion, our results suggest that profiles of neuropsychological deficits in Hispanic patients with AD diverge in severity and pattern from age and education matched white, Non-Hispanic patients. Differences between ethnicities with regard to level of performance in culturally and linguistically matched healthy control participants, vascular contributions to neuropathology, and potential protective factors such as bilingualism may alter the profile of cognitive deficits observed *in vivo*, ultimately impacting the sensitivity and specificity of cognitive tests in diagnosing AD in Hispanic older adults. These factors can influence the severity and profile of cognitive deficits seen in AD making it harder to differentiate the disease from normal aging or other dementing disorders. Further characterization of the pattern of neuropsychological deficits associated with AD in elderly Hispanic patients is necessary to improve the ability to effectively detect subtle cognitive impairment in this population.

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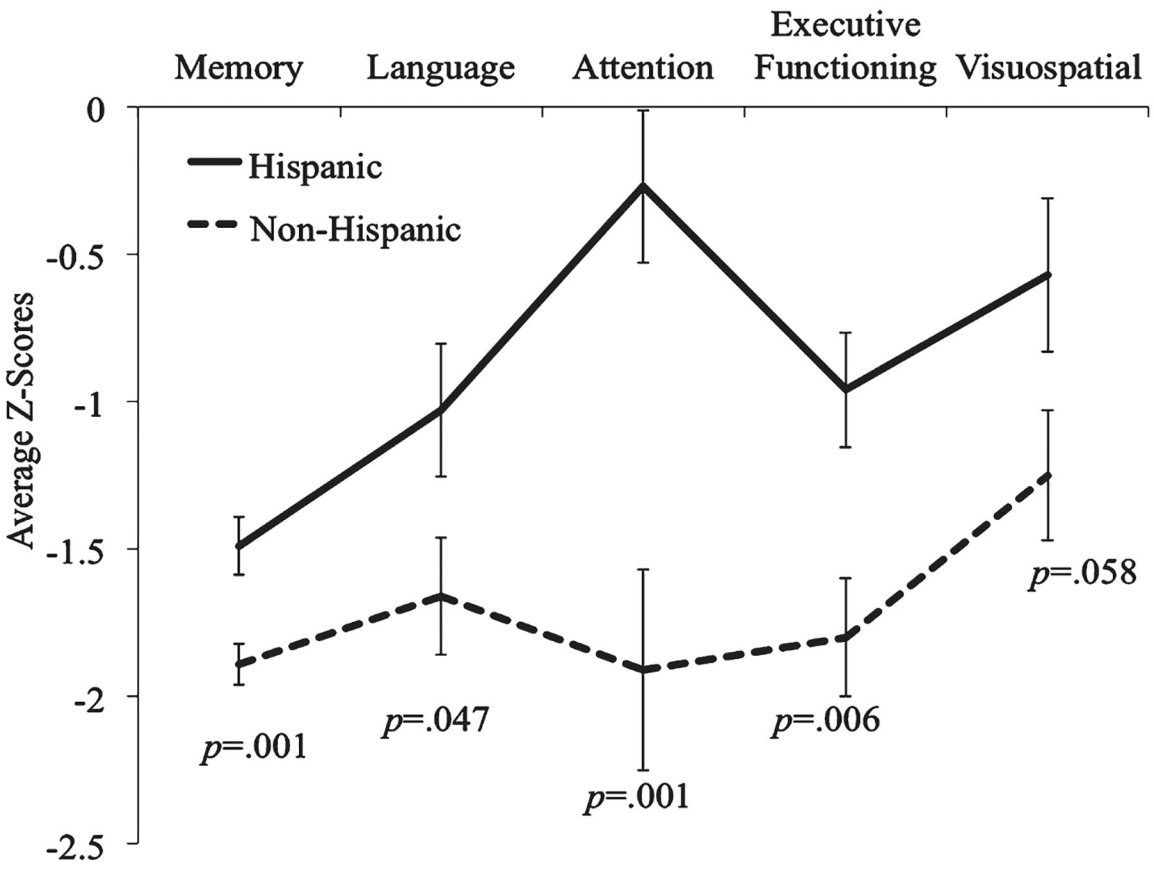

Fig. 1.

Average normalized (i.e., z-scores) of Hispanic and Non-Hispanic patients with Alzheimer's disease across cognitive domains. Error bars reflect standard error of the mean. Reported *p*-values reflect Hispanic versus Non-Hispanic one-way ANOVAs.

Table 1

Demographic information and measures of cognitive and functional ability for Hispanic and Non-Hispanic normal control participants and patients with Alzheimer's disease

	Hispanic				Non-Hispanic			
	AD (*n* =14)		NC (*n* =14)		AD (*n* = 20)		NC (*n* = 20)	
	M	***SD***	***M***	***SD***	***M***	***SD***	***M***	***SD***
Age at Year 1	78.50	5.6	76.36	5.3	77.45	5.4	77.20	6.5
Education	10.50	5.2	11.29	4.5	10.50	2.1	11.10	2.2
% Female	64%	–	71%	–	65%	–	70%	–
Test-Death Interval (months)	100.21	36.8	–	–	85.65	34.1	–	–
Dementia Rating Scale	118.07	9.0	133.71	6.9	114.90	9.3	136.79	3.8
Clinical Dementia Rating: Global[1]	1.18	0.4	0	0.0	0.90	0.2	0	0.0
Pfeffer Outpatient Disability Scale	12.43	5.3	0.21	0.8	12.20	4.1	0.35	0.6
% with Symptoms of Depression[2]	29%	–	25%	–	31%	–	20%	–

AD, Alzheimer's disease; NC, normal controls; *M*, mean; *SD*, standard deviation.

[1] *n* = 2 Non-Hispanic and *n* = 3 Hispanic NCs had CDR data available; *n* = 5 Non-Hispanic and *n* = 11 Hispanic patients with AD had CDR data available.

[2] *n* = 8 Hispanic NCs and *n* = 16.

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Table 2

Cardiovascular health measures for Hispanic and Non-Hispanic Alzheimer's disease and normal control participants at time of initial neuropsychological testing

	Hispanic AD N = 14		Non-Hispanic AD N = 20		*p*-value[1]	Hispanic NC N = 14		Non-Hispanic NC N = 20		*p*-value[1]
	M	***SD***	***M***	***SD***		***M***	***SD***	***M***	***SD***	
BP Systolic	133.57	(12.6)	150.20	(14.7)	<0.01	143.71	(12.7)	137.15	(21.9)	0.32
BP Diastolic	76.71	(6.4)	80.75	(8.9)	0.16	82.07	(9.5)	75.80	(12.0)	0.11
Pulse Pressure	56.86	(11.4)	69.45	(11.0)	<.01	61.64	(10.0)	61.35	(16.4)	0.95
Glucose	122.93	(52.8)	96.83	(24.9)	0.07	107.42	(47.7)	111.05	(32.6)	0.80
Cholesterol	206.93	(46.2)	263.29	(27.4)	<0.001	225.25	(31.0)	231.79	(33.4)	0.59
Triglycerides	178.79	(141.0)	145.59	(56.2)	0.38	204.50	(146.9)	180.58	(105.1)	0.60
BMI	26.75	(4.7)	23.96	(4.3)	0.09	29.54	(6.0)	26.06	(4.0)	0.05

	% Yes	*% Yes*	*p*-value[2]	*% Yes*	*% Yes*	*p*-value[2]
Hypertension	36%	30%	1.00	57%	20%	0.04
Diabetes	36%	0%	<0.01	14%	5%	0.56
History of Stroke	0%	10%	0.50	0%	0%	NA
History of TIA	14%	5%	0.56	0%	5%	1.00
History of Heart Attack	7%	5%	1.00	7%	10%	1.00
Atrial Fibrillation	7%	5%	1.00	14%	5%	0.56
Congestive Heart Failure	14%	0%	0.16	0%	10%	0.50
Angina	28%	5%	0.14	7%	15%	0.63
Intermittent Claudication	7%	0%	0.41	0%	5%	1.00

AD, Alzheimer's disease; NC, normal controls; *M*, mean; *SD*, standard deviation; BP, blood pressure; BMI, body mass index; TIA, transient ischemic attack.

[1]One-way ANOVAs comparing Hispanic and Non-Hispanic participants in AD group and in NC group;

[2]Fisher's Exact Test.

Table 3

Brain weight, Braak stage, and number of neuritic plaques, and neurofibrillary tangles (per high powered field) in several cortical regions and the hippocampus for Hispanics and Non-Hispanics with autopsy-confirmed Alzheimer's disease

		Hispanic			Non-Hispanic			*p*-value
		***n*[1]**	***M***	***SD***	***n*[1]**	***M***	***SD***	
	Brain Weight	13	1063.38	(115.5)	20	1069.75	(170.4)	0.907
	Braak Stage	13	4.77	(1.4)	19	5.32	(0.7)	0.154
Cortical Region								
Midfrontal	Neuritic Plaques	12	22.08	(17.1)	19	35.05	(14.5)	0.031
	Tangles	12	2.92	(4.9)	19	5.21	(9.1)	0.432
Superior Temporal	Neuritic Plaques	11	18.55	(14.1)	19	24.26	(14.1)	0.293
	Tangles	11	5.00	(5.55)	19	7.26	(5.2)	0.271
Inferior Parietal	Neuritic Plaques	12	20.33	(14.5)	19	33.26	(13.7)	0.018
	Tangles	12	3.50	(5.4)	19	5.11	(3.7)	0.334
Hippocampus	Neuritic Plaques	12	9.83	(6.6)	19	13.26	(5.8)	0.140
	Tangles	12	16.50	(10.3)	19	22.74	(14.0)	0.193

M, mean; *SD*, standard deviation; *p*-values reflect one-way ANOVAs comparing Hispanic and Non-Hispanic participants in AD group.

[1]For two Hispanic participants and one Non-Hispanic participant, AD pathology data were not available but all three participants were diagnosed with AD upon autopsy.

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Table 4

Frequency of vascular neuropathology in Hispanics and Non-Hispanics with autopsy-confirmed Alzheimer's Disease

	Hispanic (n = 10)	Non-Hispanic (n = 19)[1]	p-value[2]
	#Yes	*#Yes*	
Large Infarcts	0	4[†]	0.119
Microinfarcts	0	2	0.496
Lacunar Infarcts	2	4	1.000
Hemorrhages	0	1	1.000
Cortical Necrosis	0	0	1.000
Medial Temporal Lobe Sclerosis	2	1	0.561

	None	*Mild*	*Moderate*	*Severe*	*None*	*Mild*	*Moderate*	*Severe*	p-value[3]
Atherosclerosis (circle of Willis)	4	3	5	2	4	7	3	5	0.442
Small Parenchymal Arteriolar Disease[4]	2	3	4	0	15	0	1	1	0.002
Amyloid Angiopathy[5]	4	1	3	5	3	5	10	1	0.038

[1] Data for all vascular neuropathology variables are missing for one Non-Hispanic participant.

[2] p-value reflects Fisher's exact test of independence.

[3] p-value reflects chi-squared test of independence.

[4] n = 5 Hispanics and n = 3 Non-Hispanics missing data regarding small parenchymal arteriolar disease.

[†] infarcts occurred at time of death.

Table 5

Mean pair-wise differences (standard error) between Cognitive Domains Scores presented separately for Hispanic and Non-Hispanic patients. Significant differences reflect results of Fisher's LSD

Non-Hispanic Patients					
	Memory	**Language**	**Attention**	**Executive Functioning**	**Visuospatial**
Memory	–	–	–	–	–
Language	0.23 (0.20)	–	–	–	–
Attention	−0.02 (0.33)	−0.25 (0.33)	–	–	–
Executive Functioning	0.09 (0.19)	−0.14 (0.24)	0.11 (0.26)	–	–
Visuospatial	0.64 (0.20) **	0.41 (0.25)	0.66 (0.29) *	0.55 (0.18) **	–
Hispanic Patients					
	Memory	**Language**	**Attention**	**Executive Functioning**	**Visuospatial**
Memory	–	–	–	–	–
Language	0.46 (0.20) *	–	–	–	–
Attention	1.22 (0.23) ***	0.77 (0.36) *	–	–	–
Executive Functioning	0.53 (0.17) **	0.07 (0.20)	−0.70 (0.26) *	–	–
Visuospatial	0.92 (0.26) **	0.46 (0.27)	−0.31 (0.29)	0.39 (0.19)	–

* $p < 0.05$;

** $p < 0.01$,

*** $p < 0.001$.

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Table 6

Raw neuropsychological test-scores for Hispanic and Non-Hispanic groups

	Hispanic				Non-Hispanic				*p*-values*
	AD		NC		AD		NC		
	M	***SD***	***M***	***SD***	***M***	***SD***	***M***	***SD***	
Memory									
WMS Visual Reproduction Test (Immediate)	6.93	2.46	10.07	3.65	4.47	1.98	11.22	4.22	0.028
WMS Visual Reproduction Test (Delay)	1.00	1.71	7.00	3.70	0.89	1.24	7.61	5.15	0.673
Derived Verbal Memory Test	−2.51	0.57	−0.14	1.26	−2.61	0.64	0.07	1.03	0.490
Language									
Boston Naming Test-30 item	19.36	6.33	24.86	3.61	20.25	6.27	26.80	2.67	0.669
Letter Fluency Test (FAS)	25.14	9.77	33.71	14.90	27.25	13.75	38.95	16.06	0.653
Category Fluency Test	28.43	8.36	46.29	9.29	23.75	6.46	48.00	10.92	0.151
WAIS-R Vocabulary Subtest	41.77	9.58	40.33	11.20	41.00	12.39	52.55	9.28	0.021
Attention									
WAIS-R Digit Span Forward	5.64	1.15	5.21	1.05	5.75	1.02	6.50	1.24	0.037
Trail Making Test A	83.00	35.22	51.64	23.08	90.05	42.80	42.75	13.54	0.313
Executive Functioning									
Clock Setting Test	8.64	3.57	10.27	2.45	6.26	3.80	9.75	3.54	0.303
Modified Wisconsin Card Sorting Test	2.85	1.57	4.36	1.99	2.53	1.77	4.70	1.56	0.452
WAIS-R Digit Span Backward	5.00	1.88	5.71	1.68	5.30	1.53	6.10	2.17	0.925
WAIS-R Digit Symbol Substitution Test	26.92	5.99	35.93	11.51	21.30	13.97	42.80	8.76	0.023
Trail Making Test B	204.23	70.35	131.93	40.53	250.25	78.17	101.95	36.91	0.013
Visuospatial Abilities									
WISC-R Block Design Test	23.21	11.70	37.71	10.39	19.65	11.39	40.65	11.17	0.243
Clock Drawing Test - Command	2.29	0.73	2.57	0.51	1.95	0.76	2.65	0.59	0.207
Copy a Cube Test	11.14	2.63	11.08	1.73	9.75	3.13	11.40	1.88	0.174
WMS-R Visual Reproduction Test (Copy)	14.50	2.47	15.36	3.05	13.95	2.55	16.44	2.26	0.208

M, mean; *SD*, standard deviation; AD, Alzheimer's disease; NC, normal control; WAIS-R, Wechsler Adult Intelligence Scale Revised; WMS-R = Wechsler Memory Scale Revised.

**p*-values reflect group by ethnicity interaction effect.