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The association of depression and apathy with Alzheimer's disease biomarkers in a cross-cultural sample

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ABSTRACT

Cross-cultural differences in the association between neuropsychiatric symptoms and Alzheimer's disease (AD) biomarkers are not well understood. This study aimed to (1) compare depressive symptoms and frequency of reported apathy across diagnostic groups of participants with normal cognition (CN), mild cognitive impairment (MCI), and dementia, as well as ethnic groups of Hispanic Americans (HA) and European Americans (EA); (2) evaluate the relationship between depression and apathy with Aβ deposition and brain atrophy. Statistical analyses included ANCOVAs, chi-squared, nonparametric tests, correlations, and logistic regressions. Higher scores on the Geriatric Depression Scale (GDS-15) were reported in the MCI and dementia cohorts, while older age corresponded with lower GDS-15 scores. The frequency of apathy differed across diagnoses within each ethnicity, but not when comparing ethnic groups. Reduced volume in the rostral anterior cingulate cortex (ACC) significantly correlated with and predicted apathy for the total sample after applying false discovery rate corrections (FDR), controlling for covariates. The EA group separately demonstrated a significant negative relationship between apathy and superior frontal volume, while for HA, there was a relationship between rostral ACC volume and apathy. Apathy corresponded with higher Aβ levels for the total sample and for the CN and HA groups.

KEYWORDS

Aging; Alzheimer's disease; apathy; biomarkers; dementia; depression; mild cognitive impairment

In 2011, the National Institute on Aging and the Alzheimer's Association (NIA-AA) consensus recommendations for all-cause dementia modified its core diagnostic criteria to include "changes in personality, behavior or comportment" (McKhann et al., 2011). Neuropsychiatric symptoms (NPS) accompany cognitive decline almost universally, being experienced by approximately 90% of patients with Alzheimer's Disease (AD) (Guimarães et al., 2008). These disturbances in perception, thought content, mood, and behavior have also been described as Behavioral and Psychological Symptoms of Dementia (BPSD) that accompany cognitive and functional decline as the illness progresses (Furneri et al., 2021) and are associated with a higher burden of neuropathologic markers of dementia (Dam et al., 2016; David et al., 2016; Edwards et al., 2009; Gauthier et al., 2010).

The most common BPSD symptoms are apathy and depression. Apathy is described by Nobis and Husain (2018) as a multi-dimensional concept, with diagnosis criteria based on a loss of motivation in two of three dimensions such as goal-directed behavior/cognition, emotion, and social interaction, corresponding functional impairments, and no presence of reduced consciousness, impairment or distress, lasting more than four weeks (Landes et al., 2001; Robert et al., 2009, 2018; Theleritis et al., 2014). Teixeira et al. (2021) also indicated that apathy might differ from depression in lacking subjective feelings of sadness and negative thoughts. In contrast, depression in AD has been described by significant mood reactivity and two or more symptoms of weight gain, increase in appetite, paralysis, hypersomnia, and interpersonal sensitivity to rejection with impairment in social or occupational domains (as defined by Lojko & Rybakowski, 2017 and the Diagnostic and Statistical Manual of Mental Disorders or DSM-5; American Psychiatric Association, 2013).

The prevalence of apathy and depression in normal cognition, MCI, and dementia

Apathy is increasingly prevalent among older adults with Mild Cognitive Impairment (MCI) and dementia. Manera et al. (2019) reported that apathy was experienced by 25% of

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participants diagnosed with MCI, and 77% of those with major neurocognitive disorder also experienced this symptom. It was less prevalent for older adults with normal cognition (Sherman et al., 2018), ranging from 1.4% to 6% using the Neuropsychiatric Inventory (NPI) among those cognitively unimpaired.

Depression has been reported in 5–10% of older individuals without dementia (Skoog, 2011) and in 11–30% of older adults (Ma, 2020). In MCI, depressive symptom prevalence has ranged between 16.9% and 55% across several studies (Ismail et al., 2017; Ma, 2020). Depression rates range between 30% and 50% in AD patients, which are observed as a symptom of prodromal AD (i.e., MCI) and decrease in more severe stages of dementia (Mortby et al., 2012; Teixeira et al., 2021).

The relationship of depression and apathy with cognitive decline

Depressive symptoms are considered a significant predictor or "prodrome" of MCI and AD (Enache et al., 2011; Geda et al., 2014; Mosoiu, 2016) and have been associated with an increased rate of progression to dementia (Moon et al., 2017; Sugarman et al., 2018). Late-life depression (LLD), defined as the first major depressive episode in an older individual (i.e., someone who has not had major depression previously), is also associated with an increased likelihood of a vascular dementia diagnosis compared to AD (Diniz et al., 2013). Apathy is also significantly associated with cognitive decline in MCI (Delrieu et al., 2015; Ma, 2020), even independently of depression (Palmer et al., 2010; Starkstein et al., 2001). Furthermore, the symptoms combined have been shown to strongly predict a greater risk of illness progression in MCI and dementia (Donovan et al., 2014; Geda et al., 2014; Pink et al., 2015; Rosenberg et al., 2013; Ruthirakuhan et al., 2019; Saczynski et al., 2010; Snowden et al., 2015). These two neuropsychiatric conditions are difficult to differentiate due to overlap in symptomatology, including reduced volition, psychomotor retardation, fatigue, hypersomnia, lack of insight, and pessimism (Ishii et al., 2009; Tagariello et al., 2009). However, they remain two separate clinical syndromes (Mortby et al., 2012) and are associated with different deficits in cognitive function, suggesting distinct frontal lobe pathologies in amnestic MCI (Zahodne & Tremont, 2013).

Neuroanatomical/neuropathological correlates of depression and apathy in MCI and AD

A unique brain circuitry mediating the relationship between apathy and depression in MCI and AD suggests that they are different nosological conditions (Stella et al., 2014). Depression corresponds with frontal-limbic regions in MCI and AD (Teixeira et al., 2021), particularly the serotonergic neurons (Stella et al., 2014). Depression persistence in Major Depressive Disorder (MDD) correlated with atrophy in the hippocampus (McKinnon et al., 2009; Taylor et al., 2014) as well as the parahippocampal gyrus, amygdala, and orbitofrontal (OFC) and anterior cingulate (ACC) cortices in late-life depression (LLD), similar to the pathology observed in AD (Bora et al., 2012; Shimoda et al., 2015). Another study found depressive symptoms associated with gray matter volume reduction over time in the left temporal lobe and advancing age in the cingulate gyrus and OFC, but not the hippocampus (Dotson et al., 2009). In MCI, depression has been shown to associate with a higher rate of atrophy in the frontal lobe and the ACC (Sacuiu et al., 2016; Zahodne et al., 2013). Atrophy in the hippocampus and medial temporal lobes has been similarly associated with depression in MCI and AD (Dhikav et al., 2014; Wu et al., 2018); while decreased volumes have also been found in the parahippocampal gyrus and cerebellum in early AD (Capogna et al., 2019).

Apathy in MCI and AD has been found to correspond with increased vulnerability in the frontostriatal circuits (Nobis & Husain, 2018), particularly in dopaminergic and cholinergic networks (Stella et al., 2014). While negative associations were observed between apathy and volumes of the ventromedial, ventrolateral, and dorsolateral prefrontal cortex (PFC), the posterior cingulate cortex (PCC), adjacent lateral cortex, superior temporal sulcus, ACC, medial frontal cortex, OFC, bilateral putamen, and the left caudate nucleus in MCI and AD (Banning et al., 2019; Nobis & Husain, 2018; Teixeira et al., 2021; Theleritis et al., 2014), Stella et al. (2014) indicated that the ACC and the OFC were the core regions associated with apathy; the OFC is involved in sensory, affective, and motivational processes contributing to feedback for decision-making, goal-directed cognition, and affective reactions, whereas the ACC is associated with reward-based decision-making and motivation. Furthermore, Sherman et al. (2018) described decreased volumes in the ACC and frontal lobes (structures involved in motivation) for MCI compared to controls. In addition, atrophy in the ventromedial and ventrolateral PFC, the PCC and adjacent lateral cortex, and the bank of the superior temporal sulcus, have been independently found to be associated with apathy in mild AD (Huey et al., 2017).

Amyloid beta ($A\beta$), a well-established AD biomarker measured with Positron Emission Tomography (PET; Herrup, 2010; Pimplikar et al., 2010), is implicated in some types of depression (Palop & Mucke, 2010). Most studies have not found a consistent association between depressive symptoms and $A\beta$ biomarkers (Banning et al., 2019). An analysis of 371 MCI participants included in the Alzheimer Disease Neuroimaging Initiative (ADNI) cohort showed more extensive clusters of $A\beta$ deposition in the frontotemporal and insular regions of $A\beta$ positive ($A\beta+$), depressed participants compared to nondepressed individuals. Depressive symptoms in participants with a higher $A\beta$ load also shortened AD's progression time (Brendel et al., 2015). In older individuals with normal cognition, a positive correlation was observed between depressive symptoms and higher $A\beta$ deposition (Krell-Roesch et al., 2018), particularly in regions of the precuneus, PCC (Yasuno et al., 2016), and parietal cortex in those who had a lifetime history of MDD and in those with LLD (Smith et al., 2021; Wu et al., 2014).

However, this relationship has been inconsistently reported, finding either no significant association between these variables (De Winter et al., 2017) or lower Aβ pathology in the context of LLD (Mackin et al., 2021; Pomara & Imbimbo, 2021).

The relationship between Aβ levels and apathy has also been inconsistently reported. The results of two small studies using PET with Pittsburgh compound B (PiB) demonstrated a positive relationship between Aβ deposition and apathy in AD, indicating that further research is needed to comprehend this association better (Banning et al., 2019). Nobis and Husain (2018) reported a positive correlation between apathy severity measured with the Neuropsychiatric Inventory (NPI; Kaufer et al., 2000) and Aβ deposition, specifically in the medial frontal and orbitofrontal areas, insula, and right ACC in AD participants. Among AD patients with apathy, greater Aβ deposition has been found within the bilateral frontal and right anterior cingulate regions (Mori et al., 2014). Similarly, Marshall et al. (2013) found that Aβ burden, rather than regional hypometabolism, was associated with greater apathy in MCI.

More recently, Banning et al. (2020) investigated the association between AD biomarkers and neuropsychiatric symptoms using the Neuropsychiatric Inventory Questionnaire (NPI-Q; Kaufer et al., 2000), finding that lower CSF levels of Aβ_{42} and smaller hippocampal volumes were associated with apathy, but not with depression across the AD spectrum.

Culture, demographic variables, and neuropsychiatric symptoms

Hispanic populations in the U.S. develop symptoms of probable AD or vascular dementia at an earlier age (approximately 4 years younger) even after controlling for demographic variables (Fitten et al., 2014), and are approximately 1.5–2 times more likely to be diagnosed with AD (Fargo & Bleiler, 2014; Tang et al., 2001). It has been reported that depression and apathy correspond with disease severity (Donovan et al., 2014; Geda et al., 2014; Lyketsos et al., 2002; Mortby et al., 2012; Onyike et al., 2007; Pink et al., 2015; Rosenberg et al., 2013; Ruthirakuhan et al., 2019; Saczynski et al., 2010; Snowden et al., 2015; Wilson et al., 2011), but few studies have analyzed these neuropsychiatric symptoms cross-culturally.

Salazar et al. (2017) found differences in neuropsychiatric symptoms between Hispanic and non-Hispanic White groups in AD, where depression, among other symptoms such as agitation, anxiety, irritability, hallucinations, nighttime disturbances, and elation, was more commonly found in the Hispanic group. However, apathy, agitation, irritability, depression, and anxiety were more commonly reported in the non-Hispanic group. Additionally, Ortiz et al. (2006) found the highest scores (using the NPI) for the Hispanic AD group were for apathy and anxiety, but apathy and depression were highest for the non-Hispanic White group. Significantly higher total NPI scores were also reported in the Hispanic group compared to the non-Hispanic White group.

Other research has indicated ethnic differences in neuropsychiatric symptoms for those diagnosed with AD or mixed dementia. The risk of apathy in mixed dementia was 80% lower for Hispanics when compared to White patients, and Hispanics with AD had a 50% lower reported risk of depressed mood than White patients (Hargrave et al., 2000). However, this study analyzed small groups of Hispanics compared to the White subsample. Another study compared Hispanics and non-Hispanics on progression to MCI using clusters of neuropsychiatric symptoms from the NPI-Q and found that among the non-Hispanic participants, early conversion to MCI was predicted by higher psychomotor apathy scores. In contrast, for the Hispanic cohort, early disease progression was identified by physical behavior symptom scores (Thakur et al., 2021).

Additional research has reported higher levels of depression in older Hispanic individuals of pre-retirement age compared to White non-Hispanic participants (González et al., 2010; Rodriguez-Galan & Falcón, 2009; Russell & Taylor, 2009). Factors associated with depression among Hispanics include lower education and socioeconomic status (Mungas et al., 2005; Williams et al., 2010). In addition, depression, diabetes, age, and level of education have predicted an increased risk of MCI for Mexican Americans (Johnson et al., 2015). Some reports including community-dwelling older adults found that lower acculturation levels, particularly in females and immigrants, may affect performance on neuropsychological tests, influence symptoms of depression, and worsen health outcomes (Arnold et al., 1994; González et al., 2001; Torres, 2010).

Current study

Given the high prevalence and association of neuropsychiatric symptoms with known AD biomarkers, further investigation is warranted to analyze if these findings occur among Hispanic individuals at risk for AD. The present study compared two distinct ethnic groups, Hispanic Americans (HA) and European Americans (EA), to (1) determine if any differences exist in depressive symptoms (Geriatric Depression Scale—GDS-15) across ethnic groups and diagnostic categories (cognitively normal [CN], MCI, and dementia); (2) compare frequencies of reported apathy (NPI-Q) across ethnicities and diagnoses, and (3) examine the association between depression and apathy with Aβ deposition observed in PET scans, and brain volumes measured through Magnetic Resonance Imaging (MRI) among HA and EA.

It was hypothesized that, because of their high co-occurrence, the frequency of apathy and severity of depressive symptoms would increase for dementia and MCI groups compared to the CN cohort (Ismail et al., 2017; Lang et al., 2021; Ma, 2020; Sherman et al., 2018). The presence of apathy, and greater severity of depressive symptoms, were expected among the HA participants compared with the EA group, using both self and informant reports (Fargo & Bleiler, 2014; Ortiz et al., 2006; Tang et al., 2001). Finally,

consistent with previous research (Banning et al., 2019; Bora et al., 2012; Dhikav et al., 2014; McKinnon et al., 2009; Mori et al., 2014; Shimoda et al., 2015; Taylor et al., 2014; Teixeira et al., 2021; Wu et al., 2018), it was hypothesized that a negative correlation would exist between the number of depressive symptoms and cortical brain volume (greater atrophy would correspond with more symptoms of depression) in medial temporal and frontal regions. A negative association was also expected between apathy and cortical volume in the frontal-striatal brain regions (Banning et al., 2019; Nobis & Husain, 2018; Sherman et al., 2018; Stella et al., 2014; Teixeira et al., 2021; Theleritis et al., 2014). No association between Aβ deposition and depression was expected due to inconsistent reports about the association between these variables (De Winter et al., 2017; Krell-Roesch et al., 2018; Mackin et al., 2021). However, a positive correlation between Aβ deposition and the presence of apathy was expected within the MCI and dementia groups (Donovan et al., 2014; Marshall et al., 2013).

Method

Participants

The initial sample comprised 341 participants enrolled at the Wien Center (Mount Sinai Medical Center), the Miami Beach site of the 1Florida Alzheimer's Disease Research Center, between September 2015 and September 2019. We excluded 57 participants for the analyses (18 participants who were subsequently judged to have cognitive impairment related entirely to a psychiatric diagnosis such as post-traumatic stress disorder, bipolar disorder, and schizophrenia, and 39 participants whose ethnicities were not reported or differed from EA and HA). Participants were excluded if they were immigrants from countries other than Spanish-speaking Latin-American countries and if their primary language was not English or Spanish.

The final sample included baseline data (year 1) from 284 participants (175 HA and 109 EA), with 63.4% females ($n = 180$), 40.8% born in the U.S ($n = 116$), and 49.6% raised in the U.S ($n = 141$). The mean age was 71.80 ($SD = 7.91$), with a mean of 14.99 ($SD = 3.59$) years of education (see Table 1 for characteristics of the sample across diagnostic and ethnic groups). HA participants were assessed in Spanish or English, depending on the participant's language of preference. There were 129 (73.7%) HA participants tested in Spanish and 46 (26.3%) tested in English. All EA participants were tested in English. Spanish language evaluations with equivalent standardized neuropsychological tests were administered, and age, education, and cultural/language normative data were used for these translated versions (Arango-Lasprilla, Rivera, Aguayo, et al., 2015; Arango-Lasprilla, Rivera, Garza, et al., 2015; Benson et al., 2014; Golden, 1999; Gollan et al., 2012; Ostrosky-Solís et al., 2000; Peña-Casanova, Quiñones-Ubeda, Gramunt-Fombuena, Quintana-Aparicio, Aguilar, Badenes, et al., 2009; Peña-Casanova, Quiñones-Ubeda, Gramunt-Fombuena, Quintana-Aparicio, Aguilar, Molinuevo, et al., 2009; Wechsler, 2014). Proficient Spanish/English bilingual psychometricians

Table 1. Characteristics of the sample using percentages and means (SD) by diagnostic and ethnic groups.

	Hispanic American (HA)				European American (EA)			
							Dementia Total	
Variables	CN $n = 55$	MCI $n = 92$	Dementia $n = 28$	Total $n = 175$	CN $n = 41$	MCI $n = 56$	$n = 12$	$n = 109$
% (*n*)	31.4% (55)	52.6% (92)	16.0% (28)	100.0% (175)	37.6% (41)	51.4% (56)	11.0% (12)	100.0% (109)
Sex (female)	80.0% (44)	58.7% (54)	67.9% (19)	66.9% (117)	65.9% (27)	53.6% (30)	50.0 % (6)	57.8% (63)
Born in US	1.8% (1)	4.3% (4)	7.1% (2)	4.0% (7)	100.0% (41)	100.0% (56)	100% (12)	100.0% (109)
Raised in US	20.0% (11)	18.5% (17)	14.3% (4)	18.3% (32)	100.0% (41)	100.0% (56)	100% (12)	100.0% (109)
Handedness (right)	94.5% (52)	94.6% (87)	92.9% (26)	94.3% (165)	78.0% (32)	80.4% (45)	83.3% (10)	79.8% (87)
Diabetes	18.2% (10)	21.7% (20)	14.3% (4)	19.4% (34)	7.3% (3)	16.1% (9)	41.7% (5)	15.6% (17)
Hypertension	52.7% (29)	55.4% (51)	67.9% (19)	56.6% (99)	34.1% (14)	41.1% (23)	66.7% (8)	41.3% (45)
Hypercholesterolemia	52.7% (29)	70.7% (65)	46.4% (13)	61.1% (107)	46.3% (19)	62.5% (35)	66.7% (8)	56.9% (62)
Apathy from NPI-Q (yes)	14.5% (8)	26.1% (24)	53.6% (15)	26.9% (47)	2.4% (1)	19.6% (11)	66.7% (8)	18.3% (20)
Descriptive mean (SD)								
Age	69.93 (5.85)	71.21 (7.17)	71.75 (9.67)	70.89 (7.25)	70.49 (6.38)	74.66 (9.67)	76.25 (8.99)	73.27 (8.71)
Years of education	15.15 (3.23)	14.16 (3.75)	12.57 (4.66)	14.22 (3.83)	17.10 (2.57)	15.80 (2.88)	15.33 (2.27)	16.24 (2.77)
MMSE total	28.89 (1.61)	27.22 (2.35)	20.32 (5.62)	26.64 (4.10)	29.32 (0.91)	27.46 (2.80)	24.08 (2.81)	27.79 (2.75)
GDS-15 total	1.87 (2.32)	2.58 (2.69)	2.93 (2.67)	2.41 (2.59)	1.44 (1.69)	2.77 (2.95)	3.08 (2.31)	2.30 (2.55)

Note. CN (Cognitively Normal) $n = 96$; MCI (Mild Cognitive Impairment) $n = 148$; Dementia $n = 40$; NPI-Q: Neuropsychiatric Inventory-Questionnaire; MMSE: Mini-Mental State Examination; GDS-15: Geriatric Depression Scale-15 (Short Form).

administered neuropsychological testing in Spanish. The majority of the participants were born in the U.S. ($n = 115$) or Cuba ($n = 105$) followed by Colombia ($n = 28$) and Argentina ($n = 10$). Other countries of birth included Chile ($n = 4$), Dominican Republic ($n = 2$), Ecuador ($n = 2$), Guatemala ($n = 1$), Nicaragua ($n = 3$), Peru ($n = 4$), Puerto Rico ($n = 4$), Uruguay ($n = 2$), and Venezuela ($n = 4$).

The study was approved by the Institutional Review Board at Mount Sinai Medical Center in Miami Beach. Either the participant or a legal representative provided informed consent. The analytic sample completed a clinical interview, physical examination, and a comprehensive neuropsychological battery. A subsample of 251 participants completed a brain MRI scan, and 160 participants received a PET scan.

For this sample, 47.9% ($n = 136$) were on antidepressant medication, and 32 participants (11.3%) were taking other anxiolytic, antipsychotic, or opioid medications. For the normal control group, 38 participants (39.6%) were taking antidepressant medication, and 10 (10.4%) were prescribed other anxiolytic, antipsychotic, and opioid medications. In the MCI cohort, 70 participants (47.3%) took antidepressants, and 15 (10.1%) were on other medications (anxiolytic, antipsychotic, and opioid). Finally, 28 participants (70.0%) in the dementia group were taking antidepressant medications, and 7 (17.5%) were on other medications such as anxiolytics, antipsychotics, and opioids.

Diagnostic determination

Using clinical history, neuropsychological data, and Clinical Dementia Rating (CDR® Dementia Staging Instrument; Hughes et al., 1982; Morris, 1993) scores, participants were classified as cognitively normal (CN; $n = 96$), MCI ($n = 148$), or dementia ($n = 40$). The diagnosis was based on a physical examination, and participant and study partner interviews conducted by an experienced geriatric psychiatrist who also administered the CDR. Additionally, a neuropsychological battery was administered to all EA participants in English and to the HA group in the language of preference (English or Spanish).

The neuropsychological diagnosis included a neuropsychological test battery from the National Alzheimer's Coordinating Center (NACC) and additional neuropsychological tests as described below. Global cognition was measured using the MMSE (Folstein et al., 1975) as part of the neuropsychological battery of tests that assessed various cognitive domains.

The CN group had no memory complaints, cognitive or functional decline, and a CDR-Global Score (CDR-GS) of 0. Participants received a diagnosis of MCI at the baseline assessment if they met Petersen's criteria for MCI (Petersen et al., 2014) and demonstrated all of the following: (a) subjective cognitive complaints by the participant and/or collateral informant; (b) evidence by clinical evaluation, or history of memory or other cognitive decline; (c) a CDR-GS of 0.5, and (d) task performance of 1.5 SD below the means of matched norms for participants of the same age, education, and language on one or more cognitive measures such as the immediate and delayed recall of the Hopkins Verbal Learning Test-Revised (HVLT-R; Benedict et al., 1998) and the Logical Memory delayed story passage (Beekly et al., 2007), or on non-memory cognitive function tasks such as confrontation naming (MINT; Gollan et al., 2012), inhibitory control (Stroop Task; Golden & Freshwater, 2002; Stroop, 1935; Trenerry et al., 1989), and visual attention (Trail Making Test A and B [TMT A and B]; Corrigan & Hinkeldey, 1987; Reitan, 1958; Reitan & Wolfson, 1993). Finally, criteria for dementia included neuropsychological task performance of at least 2 SD below the mean in two cognitive domains (one memory and one non-memory task) using age, education, and language-matched normative data and a CDR-GS score of 1.0 or greater. These participants also met DSM-5 criteria for Major Neurocognitive Disorder, including functional impairment sufficient to interfere with the performance of instrumental activities of daily living (IADLs).

Materials and procedure

Depression

As part of the clinical interview, the participant's depression was determined using the self-report measure of the Geriatric Depression Scale 15-item short form (GDS-15 in English: Sheikh & Yesavage, 1986; Yesavage et al., 1982; GDS-VE in Spanish: Martínez de la Iglesia et al., 2002) and reported symptoms above a raw score of 5 were considered clinical depression. This scale includes 15 items such as "Do you feel that your life is empty?" and "Do you often feel helpless?" with "yes" or "no" responses coded as 0 or 1 to determine depressive symptomatology. This scale has been previously used for measuring symptoms of depression in CN, MCI, and dementia (Sugarman et al., 2018) and has high internal consistency in English ($\alpha = .80$; D'ath et al., 1994) and in Spanish ($\alpha = .81$; Fernández-San Martín et al., 2002; Lucas-Carrasco, 2012; Martínez de la Iglesia et al., 2002). It also has good validity in cognitively normal older populations (Kørner et al., 2006; Marc et al., 2008), MCI (Debruyne et al., 2009), and dementia (Lach et al., 2010; Lucas-Carrasco, 2012).

Neuropsychiatric symptoms

An informant for the participant completed the NPI-Q (Cummings et al., 1994; Kaufer et al., 2000) during a clinical interview with an experienced psychiatrist in English (Kaufer et al., 2000) or in Spanish, translated by the Spanish Translation and Adaptation Work Group (STAWG) from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS; Acevedo et al., 2009; Salazar et al., 2017), to evaluate the presence of apathy/indifference (0 for no, 1 for yes). This is one of the most frequent scales to measure apathy in MCI, and it has been validated in dementia populations (Sherman et al., 2018). This measure is similar to Hispanic and non-Hispanic Whites, indicating it can be meaningfully interpreted in both ethnic groups (Sayegh & Knight, 2014). It includes questions about apathy symptoms, such as: "Does the patient seem less interested in his/her usual activities or in the

activities and plans of others?". Severity of each symptom was also recorded (1 = mild, 2 = moderate, and 3 = severe). Test-retest reliability ($r = 0.80$ and 0.94 for the total symptom scale and distress scale, respectively) and convergent validity ($r = .91$ between NPI total score and NPI-Q severity total) for this measure are adequate in English (Kaufer et al., 2000), and are considered good in Spanish (for the total symptom and distress scales respectively, test-retest reliability, $r = .89$ and .90, and convergent validity, $r = .88$ and .92; Boada et al., 2002).

MRI and cortical volumetric data

Normalized values (using the regional volume divided by the intracranial volume) were acquired for the hippocampus (HP), entorhinal cortex (EC), lateral and medial OFC, ACC, and superior frontal volumes measured in cubic millimeters (mm^3). These brain structures were selected based on the demonstrated sensitivity of these regions to both AD, and apathy and depression (Banning et al., 2019; Bora et al., 2012; Dhikav et al., 2014; McKinnon et al., 2009; Mori et al., 2014; Nobis & Husain, 2018; Sherman et al., 2018; Shimoda et al., 2015; Stella et al., 2014; Taylor et al., 2014; Teixeira et al., 2021; Theleritis et al., 2014; Wu et al., 2018). The images were obtained from a Siemens Skyra 3 T MRI scanner at Mount Sinai Medical Center in Miami Beach, Florida, with a 3-D T1-weighted sequence (MPRAGE) and a 1.0 mm isotropic resolution. Free Surfer Version 6.0 software was used (http://surfer.nmr.mgh.harvard.edu), dividing each regional volume of the left and right hemispheres by total intracranial volume to adjust for variation in head size. Total volumes were calculated by summing each region's left and right hemisphere volumes.

PET and amyloid (Aβ) levels

PET scans were acquired using Florbetaben tracer binding to Aβ plaques. The FMRIB Software Library (FSL) was used to co-register the PET image to the MRI T1 image. Florbetaben PET scans were co-registered linearly with trilinear interpolation of 12 degrees of freedom onto the MRI T1 image. Therefore, the segmentation and parcellation were consistent across both scans. The FreeSurfer-calculated ROI volumes were then used in calculating the global standard uptake value ratios (SUVRs), averaging cortical uptake in the frontal, parietal, lateral temporal, occipital, and anterior/posterior cingulate areas with normalized mean gray matter counts in the cerebellum. Therefore, SUVRs are quantified using the cerebellar cortex as a reference region. Atrophy correction was not used in the calculations of SUVR and centiloid values. Subsequently, global Aβ was expressed in centiloid units, using the whole cerebellum as a reference region and a conversion formula reported by Rowe et al. (2017).

Statistical analyses

All analyses were conducted using SPSS Version 28. A series of frequency distribution analyses were performed for demographic and clinical variables among the diagnostic (CN, MCI, and dementia) and ethnic groups (HA and EA) to identify the necessary covariates. Two ANOVAs were conducted to investigate differences in age and education across diagnoses with Mann–Whitney U tests as pairwise comparisons. Also, two additional ANOVAs compared ethnic groups on education and age.

For the first study aim of determining differences in depressive symptoms as measured by the GDS-15 across ethnic groups and diagnostic categories, a 2 (ethnicities, HA and EA) × 3 (diagnoses, CN, MCI, and dementia) univariate ANCOVA investigated differences in depressive symptoms as measured with the GDS-15 total, and the interaction between diagnostic and ethnic groups, controlling for age, sex, and education. Three Tukey HSD post-hoc analyses measured differences in GDS-15 total score between CN and MCI, MCI and dementia, and CN and dementia. False Discovery Rate (FDR; Benjamini & Hochberg, 1995) corrections were applied to the p-values from the ANCOVAs and post-hoc tests.

For the second aim to compare frequencies of apathy across ethnicities and diagnoses, two chi-squared tests and two nonparametric tests (for two and K independent samples) analyzed differences in ethnicities and diagnoses on frequencies reporting apathy as measured by NPI-Q for the whole sample. Also, a chi-squared and a nonparametric test (for K independent samples) were conducted comparing frequencies of the apathy item separately within each ethnicity across the three diagnostic groups.

To satisfy the third aim of examining the association between depression and apathy with Aβ deposition and brain atrophy among HA and EA, ANOVAs, correlations, and regression analyses were performed. Seven ANOVAs compared volumetric variables of the total HP, EC, lateral OFC, medial OFC, rostral ACC, superior frontal cortex, and global Aβ load in Centiloid between ethnicities. Partial correlations determined the association of the GDS-15 total and the NPI-Q symptom of apathy with these normalized volumetric variables of the total HP, EC, lateral OFC, medial OFC, rostral ACC, and superior frontal cortex, controlling for age, sex, education, and diagnosis. FDR corrections were used for multiple comparisons in these analyses.

A binomial logistic regression was also performed for the whole sample to determine the predictive accuracy of the significant volumetric variables from the correlations (block 1) and demographic variables of age, sex, education, MMSE total, and ethnicity (block 2) in predicting the presence of apathy. The same analyses were also conducted separately for each ethnicity (EA and HA).

Global Aβ load in centiloid was also analyzed using partial correlations for GDS-15 total and apathy (controlling for age, sex and education) within the entire sample and in each ethnicity and diagnosis. FDR corrections for multiple comparisons (Benjamini & Hochberg, 1995) were applied to the correlation analyses. All analyses had a p-value set to $< .05$.

Results

Demographic variable analyses across diagnostic and ethnic groups

Table 1 shows the means and the distribution of demographic variables across the diagnoses and ethnicities.

Table 2. Univariate analysis of covariance for differences in the Geriatric Depression Scale (GDS-15) by Ethnicity and Diagnostic Group ($N = 284$) including covariates (age, sex, and education).

Variables	*F*	*df*	*p*	η_p^2	*FDR p*
Ethnicity	0.35	1, 275	.556	.001	.579
Diagnosis	7.28	2, 275	<.001	.050	.006
Ethnicity*Diagnosis	0.75	2, 275	.473	.005	.579
Age	9.61	1, 275	.002	.034	.006
Sex	0.50	1, 275	.479	.002	.579
Education	0.31	1, 275	.579	.001	.579

Note. HA = Hispanic Americans: Cognitively Normal (CN) = 55, Mild Cognitive Impairment (MCI) = 92, Dementia = 28; EA = European Americans: Cognitively Normal (CN) = 41, Mild Cognitive Impairment (MCI) = 56, Dementia = 12; Total Hispanic American (HA) $n = 175$; Total European American (EA) $n = 109$; FDR p = False Discovery Rate *p*-value (Benjamini–Hochberg *p*-value). According to pairwise comparisons, differences between normal and MCI were significant ($p = .012$) and normal and dementia were also significant ($p = .021$), remaining significant after applying FDR corrections (Benjamini–Hochberg $ps = .032$ for both comparisons).

Pearson's chi-squared tests determined the differences in categorical demographic and clinical variables across the groups. No significant chi-squared tests were observed across ethnicity in sex, hypercholesterolemia, or diabetes.

Sex distribution was significantly different across diagnostic groups, χ^2 (2, $N = 284$) = 7.44, $p = .024$, with more females in all three groups. No differences were observed in ethnic groups' handedness, born or raised in the US across diagnoses. No differences were found in the language of evaluation, hypertension, or diabetes across diagnostic groups.

ANOVAs examined the relationship between age and education across the diagnostic and ethnic groups. Age, F (2, 281) = 3.24, $p = .041$, $\eta_p^2 = .02$, and years of education, F (2, 281) = 8.19, $p < .001$, $\eta_p^2 = .06$, differed across diagnostic groups. The lowest age and highest education were reported in the CN group. Levene's test for homogeneity of variance was significant for age, $p < .001$. According to Kruskal–Wallis nonparametric tests for K independent samples, age, $p = .021$, and years of education, $p < .001$, significantly differed across groups. For pairwise comparisons using individual Mann–Whitney U tests, CN and MCI groups differed in years of education, $p = .003$, and age, $p = .015$; this was also found between the CN and dementia groups for education, $p < .001$, and age, $p = .027$, with lower age and higher education reported in CN. No significant differences were found between MCI and dementia on these variables.

Age, F (1, 282) = 6.17, $p = .014$, $\eta_p^2 = .02$, and education, F (1, 282) = 22.89, $p < .001$, $\eta_p^2 = .08$, also differed significantly across ethnic groups, with the EA group being older and having higher education. Levene's test for homogeneity of variance was significant for age, $p = .013$, and number of years of education, $p = .004$. Mann–Whitney U Tests revealed that age, $p = .041$, and education, $p < .001$, significantly differed across ethnicities.

Univariate ANCOVAs of GDS-15 differences across diagnostic and ethnic groups

Univariate ANCOVAs (see Table 2) analyzed the differences in depressive symptoms as measured by the GDS-15 across diagnosis, ethnicity, and the interaction between diagnosis and ethnicity, controlling for sex, education, and age covariates. After applying FDR corrections (Benjamini & Hochberg, 1995), only age and diagnostic groups were significant, with higher depressive symptoms reported in dementia participants compared to the other two diagnostic groups, and older age was associated with lower GDS-15 total scores. GDS totals significantly differed between CN and MCI and CN and dementia on Tukey HSD post hoc analyses even after FDR corrections (Benjamini & Hochberg, 1995).

Frequency analyses of NPI-Q apathy symptoms across diagnostic and ethnic groups

Chi-squared and nonparametric tests analyzed differences in ethnicity and diagnostic groups on reporting apathy. There were no significant differences between HA and EA in reporting apathy. However, there were significant differences across diagnostic groups in reported apathy, χ^2 (2, $N = 284$) = 36.28, Kruskal–Wallis $H = 36.15$, $p < .001$, with more cases reported in MCI (35/148) and dementia (23/40) compared to normal cognition (9/96).

Within each ethnic group, there were significant differences in apathy across diagnoses. For the HA cohort, there were more cases proportionally reporting apathy in MCI (24/92) and dementia (15/28), χ^2 (2, $N = 175$) = 14.44, Kruskal–Wallis $H = 14.36$, $p < .001$, compared to normal cognition (8/55). For the EA group, there was also a higher frequency of apathy reported in MCI (11/56) and dementia (8/12) compared to normal cognition (1/41), χ^2 (2, $N = 109$) = 25.69, Kruskal–Wallis $H = 25.45$, $p < .001$.

Differences in biomarkers across ethnicities

Tables 3 and 4 show mean total volumes and volumes divided by hemisphere, as well as Aβ levels across diagnostic and ethnic groups. Table 5 depicts differences in these biomarker variables across ethnicities. After FDR corrections, the lateral OFC and rostral ACC differed across ethnic groups, with larger volumes in HA participants compared to EA. The total HP, lateral OFC, medial OFC, superior frontal, and rostral ACC were significant prior to corrections. No differences were observed across ethnic groups in Aβ level.

Correlations of volumetric variables with depressive symptoms across ethnicities

Table 6 shows the partial correlations of GDS total with volumetric data of the total HP, EC, lateral OFC, medial OFC, superior frontal cortex, and rostral ACC for the entire sample controlling for age, education, sex, and diagnosis. There were no significant associations between depression and total cortical volumes for the total sample after applying FDR corrections. Both the medial OFC and the rostral ACC were significantly negatively correlated with depressive symptoms before the corrections. When dividing the sample

Table 3. Descriptive statistics: total volumetric variables by diagnostic and ethnic groups.

	HA ($n = 153$)				EA ($n = 98$)			
Variable mean (SD)	CN $n = 46$	MCI $n = 80$	Dementia $n = 27$	Total $n = 153$	CN $n = 39$	MCI $n = 47$	Dementia $n = 12$	Total $n = 98$
Total hippocampus	.00519 (.000571)	.00481 (.000570)	.00430 (.000655)	.00483 (.000654)	.00499 (.000540)	.00446 (.000653)	.00427 (.000663)	.00465 (.000670)
Total entorhinal cortex	.00249 (.000381)	.00229 (.000437)	.00188 (.000412)	.00228 (.000462)	.00240 (.000317)	.00217 (.000480)	.00182 (.000383)	.00222 (.000446)
Total lateral OFC	.00967 (.000912)	.00938 (.000967)	.00891 (.001191)	.00938 (.001020)	.00923 (.001029)	.00910 (.000852)	.00815 (.001550)	.00903 (.001071)
Total medial OFC	.00682 (.000643)	.00640 (.000650)	.00622 (.000799)	.00650 (.000708)	.00650 (.000672)	.00632 (.000795)	.00556 (.001117)	.00630 (.000838)
Total superior frontal	.02553 (.002523)	.02472 (.002181)	.02374 (.002749)	.02479 (.002453)	.02516 (.002867)	.02363 (.002730)	.02236 (.003411)	.02408 (.003000)
Total rostral ACC	.00291 (.000316)	.00287 (.000390)	.00267 (.000535)	.00285 (.000405)	.00276 (.000499)	.00270 (.000443)	.00248 (.000487)	.00269 (.000474)
	CN $n = 28$	MCI $n = 47$	Dementia $n = 20$	Total $n = 95$	CN $n = 23$	MCI $n = 32$	Dementia $n = 10$	Total $n = 65$
Amyloid level in centiloid	10.11 (24.81)	33.78 (38.69)	57.14 (29.58)	31.72 (36.94)	9.47 (21.00)	40.08 (44.92)	74.90 (75.62)	34.60 (49.28)

Note. OFC: Orbitofrontal Cortex; ACC: Anterior Cingulate Cortex; CN: Cognitively Normal; MCI: Mild Cognitive Impairment; HA: Hispanic Americans; EA: European Americans.

Table 4. Descriptive statistics: brain volumetric variables across diagnostic and ethnic groups.

	HA ($n = 153$)				EA ($n = 98$)			
Variable mean (SD)	CN $n = 46$	MCI $n = 80$	Dementia $n = 27$	Total $n = 153$	CN $n = 39$	MCI $n = 47$	Dementia $n = 12$	Total $n = 98$
Right hippocampus	.00266 (.000313)	.00245 (.000317)	.00223 (.000367)	.00247 (.000354)	.00256 (.000295)	.00226 (.000324)	.00218 (.000322)	.00237 (.000347)
Left hippocampus	.00253 (.000274)	.00236 (.000282)	.00207 (.000330)	.00236 (.000326)	.00243 (.000266)	.00220 (.000368)	.00209 (.000359)	.00228 (.000352)
Left entorhinal cortex	.00129 (.000215)	.00118 (.000241)	.00096 (.000231)	.00118 (.000255)	.00123 (.000161)	.00109 (.000261)	.00094 (.000229)	.00113 (.000240)
Right entorhinal cortex	.00120 (.000212)	.00111 (.000242)	.00092 (.000241)	.00110 (.000250)	.00117 (.000230)	.00108 (.000288)	.00088 (.000275)	.00109 (.000277)
Left medial OFC	.00334 (.000346)	.00312 (.000403)	.00301 (.000428)	.00317 (.000407)	.00318 (.000398)	.00312 (.000445)	.00272 (.000599)	.00310 (.000467)
Right medial OFC	.00348 (.000365)	.00328 (.000343)	.00321 (.000445)	.00333 (.000381)	.00331 (.000347)	.00320 (.000424)	.00285 (.000530)	.00320 (.000430)
Left lateral OFC	.00491 (.000475)	.00472 (.000534)	.00446 (.000618)	.00473 (.000550)	.00466 (.000570)	.00462 (.000441)	.00413 (.000727)	.00458 (.000555)
Right lateral OFC	.00476 (.000474)	.00466 (.000486)	.00444 (.000636)	.00465 (.000519)	.00456 (.000508)	.00448 (.000467)	.00402 (.000858)	.00446 (.000562)
Right superior frontal	.01263 (.001221)	.01205 (.001178)	.01165 (.001452)	.01215 (.001281)	.01242 (.001516)	.01155 (.001378)	.01091 (.001905)	.01181 (.001580)
Left superior frontal	.01290 (.001467)	.01267 (.001185)	.01209 (.001591)	.01264 (.001369)	.01274 (.001502)	.01209 (.001467)	.01145 (.001612)	.01227 (.001545)
Left rostral ACC	.00167 (.000254)	.00163 (.000218).	.00146 (.000323)	.00161 (.000260)	.00159 (.000283)	.00157 (.000317)	.00135 (.000261)	.00155 (.000304)
Right rostral ACC	.00124 (.000198)	.00124 (.000248)	.00122 (.000289)	.00123 (.000240)	.00117 (.000303)	.00113 (.000194)	.00113 (.000278)	.00114 (.000251)

Note. OFC: Orbitofrontal Cortex; ACC: Anterior Cingulate Cortex; Cognitively Normal: CN; Mild Cognitive Impairment: MCI; HA: Hispanic Americans; EA: European Americans.

Table 5. ANOVAs comparing volumes of the memory and frontal regions across ethnicities.

Variables [$N = 251$; HA ($n = 153$), EA ($n = 98$)]	F	df	p	η_p^2	FDR p
Total HP volume	4.52	1, 249	.034	.018	.054
Total EC volume	1.02	1, 249	.313	.004	.313
Total lateral OFC volume	6.78	1, 249	.010	.027	.030
Total medial OFC volume	4.07	1, 249	.045	.016	.054
Total superior frontal volume	4.17	1, 249	.042	.016	.054
Total rostral ACC	7.33	1, 249	.007	.029	.030
[$N = 160$; HA ($n = 95$), EA ($n = 65$)]	F	df	p	η_p^2	
Global amyloid in CL	0.18	1, 158	.673	.001	

Note. HA: Hispanic Americans; EA: European Americans; HP: Hippocampus; EC: Entorhinal Cortex; OFC: Orbitofrontal Cortex; ACC: Anterior Cingulate Cortex; CL: Centiloid; FDR p: False Discovery Rate p-value (Benjamini–Hochberg p-value). Levene's test was significant for the medial OFC, $p = .034$, and the superior frontal volume, $p = .018$. Also, it was significant for amyloid level, $p = .035$. According to Mann–Whitney U tests, there were significant differences between groups only for the medial OFC volume, $p = .046$.

by ethnicity, including only the significant areas of the medial OFC and the rostral ACC, there were no significant associations for EA ($n = 98$). Prior to FDR corrections, the rostral ACC volume was significantly negatively correlated with depressive symptoms, $r(92) = -.227$, $p = .028$, for EA participants. There were also no significant associations between these regions and the GDS-15 score for the HA group ($n = 153$).

Correlations of volumetric variables with apathy

We performed partial correlations analyzing the entire sample using Pearson r, which is mathematically equivalent to the point-biserial correlation (Linacre & Rasch, 2008), for

Table 6. Partial correlations of GDS-15 and apathy with volumetric data with total volumes for total sample ($N = 251$, $df = 245$).

Control variables Age, education, sex, and diagnosis	GDS-15 correlation Pearson *r*	*p*	*FDR p*	Apathy/ indifference correlation Pearson *r*	*p*	*FDR p*
Total HP	−.049	.443	.532	−.083	.193	.290
Total EC	−.039	.540	.540	−.030	.639	.639
Total lateral OFC	−.101	.114	.171	−.074	.249	.299
Total medial OFC	−.130	.042	.124	−.103	.106	.212
Total superior frontal	−.119	.062	.124	−.141	.027	.081
Total rostral ACC	−.148	.020	.120	−.188	.003	.018

Note. HP: Hippocampus; EC: Entorhinal Cortex; OFC: Orbitofrontal Cortex; ACC: Anterior Cingulate Cortex; GDS-15 = Geriatric Depression Scale-15; *FDR p*: False Discovery Rate *p*-value (Benjamini–Hochberg *p*-value).

Table 7. Summary of hierarchical logistic regression analyses of demographic and volumetric variables in predicting apathy.

EA group ($n = 98$)	*B*	*SE B*	Wald χ^2	*p*	Exp(*B*)
Block 1: Significant variables in equation					
Total sup. frontal volume	−271.62	110.93	6.00	.014	1.084E-118
Block 2: Significant variables in equation					
Total sup. frontal volume	−301.34	141.08	4.56	.033	1.355E-131
MMSE total	−.24	0.10	6.07	.014	.788
HA group ($n = 153$)					
Block 1: Significant variables in equation					
Total rostral ACC	−1408.63	503.66	7.82	.005	0.0E0
Block 2: Significant variables in equation					
Total rostral ACC	−1618.70	567.61	8.13	.004	0.0E0
MMSE total	−.13	.05	6.44	.011	.878
Sex	−.88	.44	4.12	.042	.413

Note. HA: Hispanic American; EA: European American; MMSE: Mini-Mental State Examination; ACC: Anterior Cingulate Cortex; Variables that were not significant for Block 1: rostral ACC for EA, and superior frontal volume for HA. For Block 2: age, sex, and education.

apathy, and volumetric variables of total HP, EC, lateral OFC, medial OFC, superior frontal, and rostral ACC controlling for age, sex, education, and diagnosis (see Table 6). The total rostral ACC volume remained significantly associated with apathy after applying FDR corrections; prior to correcting for multiple comparisons, the superior frontal volume was also significant.

We also ran partial correlations controlling for covariates in the HA ($n = 153$) and the EA ($n = 98$) groups separately, analyzing the association between the significant brain regions (total rostral ACC and the superior frontal volume) with apathy. The total rostral ACC was negatively correlated with apathy, $r(147) = -.257$, $p = .002$ for HA, which remained ($p = .004$) after FDR corrections. For the EA group, there was a significant correlation between the superior frontal volume and apathy, $r(92) = -.246$, $p = .017$, which remained ($p = .034$) after FDR corrections.

Demographic and volumetric logistic regressions predicting apathy

We conducted a logistic regression analysis including two blocks: the first block contained variables of total rostral ACC and superior frontal volumes since both were significant with apathy in the correlations, and the second block incorporated age, sex, years of education, MMSE total, and ethnicity. In block 1, only including the total rostral ACC and superior frontal volumes, the overall model was significant, χ^2 (2, N = 251) = 15.24, $p < .001$, and had a prediction accuracy of 76.9%. Both the total rostral ACC, $B = -842.84$, $\chi^2 = 5.41$, $p = .020$, as well as the total superior frontal volume, $B = -130.28$, $\chi^2 = 4.44$, $p = .035$, were significant in predicting apathy.

In block 2, the model remained significant, χ^2 ($df = 7$) = 45.11, $p < .001$, with prediction accuracy increasing to 80.5%. The total rostral ACC was still significant, $B = -1139.78$, $\chi^2 = 7.37$, $p = .007$. Additionally, MMSE, $B = -.153$, $\chi^2 = 10.86$, $p < .001$, and Ethnicity, $B = -.842$, $\chi^2 = 4.68$, $p = .031$, were significant. The total superior frontal volume lost significance upon introducing covariates into the model. This indicated that HA participants with smaller rostral ACC and lower global cognition were more likely to report apathy.

Logistic regression analyses were also used separately for each ethnicity, including two blocks, with the first block examining volumetric variables and the second block containing age, sex, years of education, and MMSE total (see Table 7).

Dividing the sample by ethnicity for HA in block 1, including predictors of rostral ACC and superior frontal volumes, the overall model was significant, χ^2 (2, $N = 153$) = 12.81, $p = .002$, and had 73.2% accuracy. The only significant predictor of the volumes model was the total rostral ACC. At block 2, including covariates and volumes, the overall model remained significant, χ^2 (6, $N = 153$) = 27.28, $p < .001$, and had 77.1% accuracy. The only significant predictors in the volumes model, including covariates, were the total rostral ACC, the MMSE, and sex. Therefore, this

suggests that male HA participants with smaller rostral ACC and lower MMSE had a higher likelihood of reporting apathy.

For EA, in block 1, with just total rostral ACC and superior frontal volumes as predictors, the overall model was significant, χ^2 (2, $N = 98$) = 10.13, p = .006, and had 82.7% accuracy. Only the total superior frontal volume was significant, and the rostral ACC was not significant in predicting apathy for EA. In block 2, including volumes and demographic variables, the overall model remained significant, χ^2 (6, $N = 98$) = 21.87, p = .001, and increased to 85.7% accuracy. The superior frontal volume, and MMSE total, were negatively associated with reporting apathy. EA participants with smaller superior frontal volume and lower MMSE were more likely to report apathy.

Correlations of Aβ level in centiloid with depression and apathy

We also analyzed whether depressive symptoms as measured by the GDS-15 were significantly correlated with Aβ level using partial correlations controlling for age, education, and sex. There were no significant associations between GDS-15 and Aβ levels for the whole sample. Upon splitting the sample by diagnostic group, there were no significant associations between Aβ and depressive symptoms controlling for age, education, and sex in CN or MCI groups, but there was a significant association between depressive symptoms and Aβ level for participants diagnosed with dementia, $r(25)$ = −.405, p = .036. We also analyzed correlations between Aβ and GDS-15 across the two ethnic groups and found no significant associations in EA or HA separately.

Finally, we evaluated whether apathy from the NPI-Q was significantly correlated with Aβ using partial correlations controlling for age, education, and sex. There was a significant association between apathy and Aβ level for the entire sample, $r(155)$ = .185, p = .020.

For HA ($n = 95$) and EA ($n = 65$) separately, there was a significant association between global Aβ in centiloid and apathy only for HA participants, $r(90)$ = .236, p = .023, but there was no significant association between these variables for the EA group. Also, correlating Aβ level and apathy for CN ($n = 51$), MCI ($n = 79$), and dementia ($n = 30$) separately, Aβ level was significant with apathy only in the CN diagnostic group, $r(46)$ = .356, p = .013.

Discussion

This study investigated depressive and neuropsychiatric symptoms across diagnostic groups of CN, MCI, and dementia, as well as ethnicities of HA and EA. Differences in GDS total were found between diagnostic groups in which dementia and MCI participants reported higher depressive symptoms than the CN cohort, and the frequency of neuropsychiatric symptoms of apathy differed across diagnostic groups for HA and EA, but not when comparing ethnicities.

Larger volumes in the lateral OFC and rostral ACC were found in the HA group compared to EA. Depressive symptoms did not significantly correlate with cortical volumes for the whole sample or within each ethnicity; apathy, however, negatively correlated with the volumetric values of the rostral ACC after FDR corrections. The EA group demonstrated a negative association between superior frontal volume and apathy, whereas HA participants had a significant negative association between apathy and the rostral ACC. Aβ load was positively correlated with apathy for the whole sample and only for the CN group. An unexpected finding was that GDS total score was negatively associated with Aβ load in the dementia subgroup supporting previous findings of lower Aβ pathology in the context of LLD (Mackin et al., 2021; Pomara & Imbimbo, 2021). This finding may have occurred because atrophy correction was not used in the current study while calculating quantitative values for Aβ load and because the dementia group is most likely to have sufficient global atrophy to reduce global SUVR and centiloid values.

The obtained results additionally demonstrated that the severity of depressive symptoms increased with cognitive decline. Higher scores were reported on the GDS total for MCI and dementia diagnoses compared to CN. These groups tended to be older and had lower education, which is consistent with previous research findings that depressive symptoms increase with the prevalence of MCI (Ismail et al., 2017), and that late-life depression is often associated with a higher likelihood of MCI and dementia (Diniz et al., 2013; Enache et al., 2011; Geda et al., 2014; Mosoiu, 2016). Other research has also demonstrated depression to be associated with a higher rate of progression to dementia (Moon et al., 2017; Sugarman et al., 2018). Age was a significant covariate and had an inverse relationship with GDS total (i.e. younger participants in this cohort were overall more depressed), consistent with previous findings of depressive symptoms having an inverse relationship with age (Gilley et al., 2004).

Apathy has been independently associated with a decline in cognitive function (Delrieu et al. 2015; Ma, 2020; Palmer et al., 2010; Starkstein et al., 2001). Higher symptoms reported on the NPI-Q predicted more than a 40% risk of incident dementia and AD, while higher GDS scores corresponded to a 30% risk (Rosenberg et al., 2013), with the presence of any neuropsychiatric or depressive symptom significantly increasing the risk of incident dementia and AD. We found significant differences in apathy across diagnostic groups and within each ethnicity, but not when comparing ethnic groups in the whole sample. There was a higher frequency of apathy in MCI and dementia for both HA and EA individuals. They both had similar apathy frequency that increased with the severity of the diagnosis.

Additional studies have found that neuropsychiatric symptoms corresponded to an increased risk of disease progression but have not analyzed differences across ethnicities (Donovan et al., 2014; Geda et al., 2014; Pink et al., 2015; Wilson et al., 2011). In one recent cross-sectional study, differences were observed in neuropsychiatric symptoms

between Hispanic and non-Hispanic White ethnic groups diagnosed with AD (Salazar et al., 2017), and their results were somewhat consistent with those from the current study. They found that apathy was more frequently reported in the non-Hispanic white group within the AD diagnosis, and the Hispanic ethnicity was associated with most of the other symptoms on the NPI for both the control and AD groups but not in MCI. They measured all of the symptoms and reported differences between the two ethnic groups, where symptoms such as agitation/aggression, depression, anxiety, irritability, hallucinations, nighttime behavioral disturbances, and elation were found to be more common among Hispanics. In contrast, non-Hispanic Whites more commonly reported apathy, agitation, depression, anxiety, and irritability. These findings support discrepancies in the behavioral and emotional expression of dementia between these two ethnic populations.

We also found larger cortical volumes in the HA group when comparing ethnicities, particularly for the lateral OFC and the rostral ACC; this might suggest that the HA group has more brain reserve, reflected in some frontal lobe functions such as the inhibitory control demanded by bilingualism, or dual culture experiences and migration-related factors. Previous research from our group demonstrated more gray matter volume in language and EF regions for bilinguals compared to monolinguals participants in this sample (Torres et al., 2022). Disinhibition can be predicted by OFC region volume in dementia, and also the ACC, OFC, IFG, and temporal lobes correlated with disinhibition, demonstrating the critical role of these brain regions with inhibitory functions (Krueger et al., 2011).

There were no significant associations between depressive symptoms and volumetric variables for the whole sample after FDR corrections. Prior to the corrections, the medial OFC and the rostral ACC were significant. No significant associations were found between GDS-15 and the significant volumes of medial OFC and rostral ACC after FDR corrections within the EA group. Before the correction, the medial OFC and rostral ACC were significantly related to GDS-15. There were no significant associations between GDS-15 and cortical volumes within the HA group. Previous research found associations with depression between the ACC and frontal lobe structures such as the OFC (Bora et al., 2012; Dotson et al., 2009; Shimoda et al., 2015) in cognitively normal and MCI participants, although, for dementia, depression was associated with atrophy in medial temporal regions (Capogna et al., 2019; Dhikav et al., 2014; Wu et al., 2018).

Reported associations between depression and cortical thinning in the cingulate gyrus, specifically for MCI and AD, have also been demonstrated. However, no associations with medial temporal regions, including the hippocampus, have been described (Banning et al., 2019). These findings are consistent with the current study identifying no relationship between volumetric variables within the medial temporal regions and depression. Moreover, Banning et al. (2020) reported no significant association between depression and biomarkers in MCI across the AD spectrum.

For apathy, using partial correlations between this symptom and volumes controlling for covariates, we found significant associations between apathy and cortical volumes of rostral ACC after FDR corrections, although prior to corrections, the superior frontal volume was also significant. Interestingly, this finding partially agreed with that of Stella et al. (2014), who indicated that the ACC and OFC were the main cortical regions related to apathy. Although, Sherman et al. (2018) found similar results, where decreased ACC and frontal lobe volumes were associated with MCI, which are involved with motivation. Banning et al. (2019) reported that apathy was negatively associated with volumes in ventromedial and ventrolateral PFC regions, the posterior cingulate cortex, the lateral cortex, superior temporal sulcus, and anterior cingulate cortex.

We found that lower general cognitive function measured by the MMSE and lower superior frontal volumes predicted apathy in EA, while for the HA group, lower rostral ACC volume and lower MMSE predicted apathy. These results are somewhat consistent with findings reported in the review by Banning et al. (2019) where the severity of apathy was negatively associated with volumes of regions for the dorsolateral PFC and the OFC, which was not found in the current study. Although, the superior frontal volume was negatively correlated with apathy for only EA in the current study. Similarly, this variable served as a significant predictor for apathy within this ethnic group, further confirming discrepancies of ethnicity in the relationship between apathy and volumetric variables.

Within-group analyses by ethnic group demonstrated that for EA, the superior frontal volume predicted apathy, along with the MMSE scores, suggesting EA participants with smaller frontal volumes and lower global cognition have a higher risk to report apathy. The HA group showed a significant relationship between rostral ACC and predicting apathy. Also, the male sex was found to predict apathy and lower global cognition. Therefore, male HA participants with lower rostral ACC volume and lesser global cognition were more likely to report apathy. These results suggest different possible mechanisms of apathy across these ethnicities, with cortical structures more involved with apathy in EA participants; the same was observed for medial and limbic structures in HA individuals.

Investigations of ethnic differences in neuropsychiatric symptoms, as well as in volumetric brain variables, are relatively rare. In another study from our research group with the same cross-cultural sample, depressive symptoms significantly predicted cognitive dysfunction in semantic memory and confrontation naming only for the EA group (Lang et al., 2021). This relationship was not observed for the HA group, indicating a differential influence of neuropsychiatric symptoms on cognitive dysfunction across cultural groups. Moreover, cultural differences in the correlations of brain volume and cognition have been reported (Rosselli et al., 2022); the strongest predictor of cognitive decline for African American and Caucasian groups was global gray matter change, while baseline white matter hyperintensity

volumes served as the strongest predictor of cognitive decline for Hispanics (Gavett et al., 2018).

In the current study, Aβ correlated with apathy in the HA cohort but not for EA participants. Previous research has observed a relationship between Aβ and apathy in AD dementia (Donovan et al., 2014; Marshall et al., 2013; Mori et al., 2014). However, not many studies have investigated this relationship in the context of ethnicity due to the low numbers of Hispanic and nonwhite participants included in this type of research (Miao et al., 2021).

There were no correlations between GDS-15 and Aβ within each ethnicity or the overall sample, consistent with research that indicated no significant association between these variables (De Winter et al., 2017). However, we found a significant association between GDS-15 scores and Aβ in the dementia group, with lower depression corresponding to higher Aβ. Others have found no relationship between these two variables (Brendel et al., 2015; Chung et al., 2016). Our study's lack of atrophy correction when calculating Aβ load may have contributed to these contradictory findings. Previous research used Aβ visual reads considering brain Aβ load in specifically frontotemporal and insular cortices of depressed participants and corresponding hypermetabolism in nondepressed individuals, categorized with positive and negative Aβ scans (Aβ -negative or Aβ -positive; Brendel et al., 2015). Other studies found lower Aβ pathology in the context of LLD (Mackin et al., 2021; Osorio et al., 2014).

Limitations of the present study are an overrepresentation of HA participants in the sample compared to EA and a larger MCI group relative to dementia and CN. The dementia sample was relatively small, limiting the power of the statistical analyses. We also only analyzed apathy as a dichotomous instead of a continuous variable, as was used in Onyike et al. (2007), although the NPI is one of the most commonly used measures of apathy in MCI and is validated for the assessment of neuropsychiatric symptoms in dementia; however, there is still a need to improve apathy assessment for the pre-dementia population (Sherman et al., 2018). Also, this measure has been shown to operate similarly in both ethnicities (Sayegh & Knight, 2014). Additionally, we could not distinguish between the early and late onset of depression, which may differentially impact the risk of diagnosis (Li et al., 2011). Different types of depression and severity of symptoms were also not considered for the current study.

Future directions should include using an apathy scale measuring severity rather than a dichotomous variable to investigate its association with volumetric loss in the frontal regions. Mild, moderate, and severe levels of depression and the frequency of episodes (single episode, recurrent, partial, and complete remission) should also be considered. Additionally, other neuropsychiatric symptoms such as hallucinations, delusions, agitation/aggression, disinhibition, and motor disturbances could be investigated further to determine the influence of behavioral disturbances on neuropsychological dysfunction, AD biomarkers, and cognitive decline. Other biomarkers such as cortical thickness, tau pathology, inflammation, and conditions related to cardiovascular health could also be analyzed to determine their contribution to neuropsychiatric variables in MCI and dementia for a cross-cultural sample. In future studies, we aim to use a longitudinal design to analyze whether depression and apathy are significant predictors of the progression from CN to MCI and from MCI to dementia.

Disclosure statement

None of the authors have conflict of interest involving this manuscript.

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