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The Association Between Functional Assessment and Structural Brain Biomarkers in an Ethnically Diverse Sample With Normal Cognition, Mild Cognitive Impairment, or Dementia

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Abstract

Objective: To investigate the association between the functional activities questionnaire (FAQ) and brain biomarkers (bilateral hippocampal volume [HV], bilateral entorhinal volume [ERV], and entorhinal cortical thickness [ERT]) in cognitively normal (CN) individuals, mild cognitive impairment (MCI), or dementia.
Method: In total, 226 participants (137 females; mean age = 71.76, *SD* = 7.93; Hispanic Americans = 137; European Americans = 89) were assessed with a comprehensive clinical examination, a neuropsychological battery, a structural magnetic resonance imaging, and were classified as CN or diagnosed with MCI or dementia. Linear regression analyses examined the association between functional activities as measured by the FAQ on brain biomarkers, including HV, ERV, and ERT, controlling for age, education, global cognition, gender, and ethnicity.
Results: The FAQ significantly predicted HV, ERV, and ERT for the entire sample. However, this association was not significant for ERV and ERT when excluding the dementia group. The FAQ score remained a significant predictor of HV for the non-dementia group. Age, education, gender, ethnicity, Montreal Cognitive Assessment score, and FAQ were also significant predictors of HV for the overall sample, suggesting that younger Hispanic females with fewer years of education, higher global mental status, and better functioning, were more likely to have larger HV.
Conclusion: FAQ scores were related to HV in older adults across clinical groups (CN, MCI, and dementia), but its association with the entorhinal cortex was driven by individuals with dementia. Demographic variables, including ethnicity, additionally influenced these associations.

Keywords: Functional Activities Questionnaire; Alzheimer 's disease; Mild cognitive impairment; Functional assessment; Entorhinal volume; Hippocampal volume; Aβ load; Brain biomarkers

The diagnostic criteria of major neurocognitive disorder (dementia), according to the "Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition" (DSM-5; American Psychiatric Association, 2013), includes significant cognitive and functional decline, indicating that independence in everyday activities (i.e., personal hygiene, meal preparation, housework, managing finances, etc.) are compromised. Functional decline is also part of the diagnostic criteria for mild neurocognitive disorder (mild cognitive impairment or MCI), and in these cases, the individual may be generally independent, but employs

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compensatory strategies, receives some assistance or applies more effort to execute complex instrumental activities of daily living (IADLs; e.g., paying bills, preparing a meal) (American Psychiatric Association, 2013; Albert et al., 2011; Loewenstein & Mogosky, 1999).

The functional activities questionnaire (FAQ) (Pfeffer, Kurosaki, Harrah, Chance & Filos, 1982) is a commonly used measure for diagnostic purposes, and, in combination with cognitive tests, can accurately discriminate between cognitively normal (CN) individuals, and those diagnosed with MCI or dementia (Steenland et al., 2008; Brown et al. 2011; Devanand, Liu, & Brown, 2017). The FAQ is a sensitive tool for detecting functional impairment in patients with MCI, who generally report mild deficits in one or more items, and this is an important indicator for early diagnosis and prognosis (Brown et al., 2011).

Biological markers, such as brain volume and the abnormal accumulation of amyloid and tau proteins, can aid in the diagnostic classification of abnormal aging and in determining etiology. The National Institute on Aging and the Alzheimer's Association have proposed the use of these biomarkers as additional criteria for the clinical research diagnosis of Alzheimer's disease (AD) (McKhann et al., 2011) and more recently, a "research framework" was published including three groups of biomarkers: those with β-amyloid (Aβ) deposition, pathologic tau, and neurodegeneration [AT(N)] (Jack Jr et al., 2018). Neurodegeneration biomarkers are reflected in lower volume of the cerebral cortex. In the early stages of AD, this atrophy is mainly observed in the entorhinal cortex and the hippocampus (deToledo-Morrell et al., 2004). Hampel and colleagues (2008) reviewed neuroimaging and neurochemical biomarkers, determining that reduced hippocampal volume (HV) is considered an established structural biomarker for early AD diagnosis, and is also a good predictor of conversion from MCI to AD (Hampel et al., 2008; Frisoni, Fox, Jack, Scheltens, & Thompson, 2010). The entorhinal cortex is additionally sensitive to cognitive decline in abnormal aging (Hampel et al., 2008; Olsen et al., 2017).

The association between neuropsychological measures and brain volumetric biomarkers has been investigated, demonstrating a relationship between decreased performance on cognitive tests and reduced volume in the hippocampus and entorhinal cortex (Choi et al., 2016; Nathan et al., 2017; Olsen et al., 2017). Specifically, lower scores on measures of general cognition have been associated with lower entorhinal cortical volume (Olsen et al., 2017), and deficits in confrontation naming and memory tests have been related to decreased HV (Choi et al., 2016).

The link between daily functioning and AD biomarkers is relatively unknown, especially within CN individuals and in those diagnosed with MCI who are at risk of developing AD. Jutten and colleagues (2019) found an association between normalized total gray matter volume in magnetic resonance imaging (MRI) scans and IADL functioning across the AD spectrum (CN, MCI, and AD), but not within each diagnostic group (subjective cognitive decline, MCI, or AD). Also, a relationship was found between the volumes of the left medial temporal lobe, precuneus, and IADLs among Aβ positive participants (Jutten et al., 2019). Additionally, in mild AD, an association between lower inferior temporal cortical thickness as measured with structural MRI and greater IADL impairment at baseline has been described (Marshall et al., 2014). Longitudinally across the AD spectrum, lower supramarginal, as well as inferior temporal cortical thickness, less Aβ present in the cerebrospinal fluid (CSF), and greater total tau levels have been shown to be concomitant with worsening impairment in IADLs (Marshall et al., 2014). Rueda and colleagues (2015) reported that functional impairment was associated with decreased HV, Aβ deposition, and levels of phosphorylated tau from CSF for the entire sample (CN, MCI, and AD) and in only the MCI group, but no association was found for CN or AD participants. In sum, previous research has reported a strong relationship between daily functioning and multiple biomarkers across the AD spectrum (CN, MCI, and AD).

Two studies analyzed the relationship between the FAQ and severity of functional impairment as well as neurodegeneration in the medial temporal lobes (Brown et al., 2011; Vassilaki et al., 2018). In Brown and colleagues (2011), the total number of functional deficits was associated with lower hippocampal and entorhinal volumes (ERVs) in participants diagnosed with aMCI and AD. Individuals with aMCI reported more significant functional deficits and exhibited smaller HV than functionally intact aMCI individuals (Brown et al., 2011). Higher FAQ scores have also been associated with a greater likelihood of presenting neurodegeneration, as well as a composite cortical thickness measure (bilateral entorhinal, inferior temporal, middle temporal, and fusiform cortex) and Aβ load for the whole sample (CN and MCI; Vassilaki et al., 2018).

Vassilaki and colleagues (2018) did not provide information regarding the association between FAQ scores and cortical thickness of specific brain structures included in the composite measure. Important limitations to these studies include small sample sizes (Jutten et al., 2019), lack of ethnic diversity (88% Caucasian; Rueda et al., 2015), no report of ethnic breakdown (Brown et al., 2011; Vassilaki et al., 2018), the use of only partial correlations describing the association between functional impairment and biomarkers (Rueda et al., 2015), and the exclusion of CN participants from neuroimaging analyses (Brown et al., 2011).

The current study attempted to overcome these limitations by investigating the association between the total FAQ score and structural MRI brain biomarkers (HV, ERV, and entorhinal thickness [ERT]) in an ethnically diverse sample (European Americans and Hispanic Americans; EAs and HAs) of older adults. We included CN, MCI, and AD participants allowing for the investigation of brain biomarkers across the AD spectrum from participants who were suffering from no, subtle, mild, or

severe functional deficits. Additionally, we investigated the relationship between FAQ and biomarkers within a subsample of non-dementia participants (CN and MCI) to explore whether this association is present early in disease progression before the detection of significant cognitive decline.

Previous research on the association between the FAQ and structures that are sensitive to AD (e.g., hippocampus and entorhinal cortex) generally use functional measures such as the FAQ as outcomes or dependent variables (Vassilaki et al., 2019) with biomarkers entered as predictors or independent variables. The current study is distinct from preceding investigations because here we explored the association between FAQ and biomarkers using the FAQ as a predictor in regression analyses and structural brain biomarkers as outcome measures. With the FAQ as a predictor instead of an outcome measure, this corresponds to the most frequent order of events in clinical practice, in which clinicians first collect medical information about a patient, including functional assessment, and later have access to neuroimaging results. Therefore, the goal of this study was to analyze whether higher impairment in daily functioning, as measured by the FAQ, is associated with variation in the volumes of specific brain regions (i.e., the hippocampus and the entorhinal cortex) as well as variation in the ERT, while controlling for a global level of cognition and demographic variables. Brain atrophy is a hallmark in the diagnosis of AD; therefore, it is relevant to know the extent to which variance in the individual's functional status relates to brain atrophy in specific areas recognized as sensitive to early manifestations of AD.

We hypothesized that the total FAQ score would be a significant predictor of HV, ERV, and ERT, with higher FAQ scores predicting lower HV, ERV, and ERT for the whole sample of older adults and in a subsample of participants without dementia. We predicted that the association between FAQ scores and brain volumes or thickness would be significant, even after controlling for general cognition and important demographic variables such as age, education, ethnicity, and sex.

Method

Participants

Participants were recruited from the 1Florida's Alzheimer's Disease Research Center (1Florida ADRC) at Mount Sinai Medical Center in Miami Beach, Florida. Participants were required to have an informant who could provide accurate information about the participant's cognitive and functional performance on daily activities (e.g., close relative or caregiver), were native English or Spanish speakers, and were evaluated using the National Alzheimer's Coordinating Center (NACC) uniform data set (UDS) forms and questionnaires, which included the clinical dementia rating (CDR) scale (Morris, 1993) and the FAQ (Pfeffer et al. 1982), as well as a neuropsychological test battery. MRI scans were done for eligible participants. Among the 226 participants in this study, 137 (60.6%) were female, 137 (60.6%) were HA, and 89 were EA. All EA participants were tested in English and 70% of the HA were tested in Spanish ($n = 97$). The remaining HA participants preferred to be tested in English. Spanish tests were translated versions of the English tests with appropriate age, education, and language normative data (Acevedo et al., 2009; Arango-Lasprilla, Rivera, Aguayo et al., 2015a; Arango-Lasprilla et al., 2015b; Gollan et al., 2012; Golden, 1999; Peña-Casanova et al., 2009; Pereiro et al., 2017; Wechsler, 2014b).

Participants were classified into three groups based on the following diagnostic criteria of CN, MCI, and dementia. The CN group included individuals without self-report or informant report of memory complaints, cognitive decline, or functional deficits, with scores on cognitive tests that were within the expected range for age, education as well as language-related norms, and a Global CDR scale (Morris, 1993) of zero. The MCI group consisted of participants who had memory complaints reported by the patient and/or informant or the patient had presented evidence of cognitive decline observed during clinical assessment, with a Global CDR of.5. They also presented scores that were 1.5 SD below the mean for age, education, and language-matched norms on one or more cognitive measures: Delayed Recall of the Hopkins Verbal Learning Test-Revised (Brandt, 1991); logical memory subtest of the Wechsler Memory Scale-Revised (Wechsler, 1987); category and phonemic fluency (Benton & Hamsher, 1976); block design from the Wechsler Adult Intelligence Scale (WAIS-IV; Wechsler, 2014a); Trail-Making Test B (Reitan, 1986); Multilingual Naming Test (Gollan, Weissberger, Runnqvist, Montoya, & Cera, 2012); and Stroop Test (Stroop, 1935; Trenerry, Crosson, DeBoe, & Leber, 1989). MCI participants met the criteria for mild neurocognitive disorder diagnosis, according to the DSM-5 (American Psychiatric Association, 2013). Participants diagnosed with the major neurocognitive disorder (dementia; American Psychiatric Association, 2013) had scores of more than 1.5 SD below the mean for age, education, and language-matched norms on cognitive measures in addition to a CDR score of 1.0 or above.

The diagnosis of MCI or dementia was established using the criteria outlined above and was confirmed by a consensus between a neurologist, and a neuropsychologist. The FAQ score was not used to diagnose participants. Patients with dementia matched the clinical profile of probable AD (McKhann, Drachman, Folstein, Katzman, Price, & Stadlan, 1984). An etiological diagnosis could only be established for 95% of the sample ($n = 40$): 35 were considered primary AD, 2 had frontotemporal degeneration, 1 had primary vascular brain injury (secondary AD), and 2 had suspected non-Alzheimer's disease pathology.

Table 1. Frequency and percentage of "not applicable" and 'unknown' FAQ items

FAQ item	1	2	3	4	5	6	7	8	9	10
Percentage of missing	5.75	13.71	1.33	17.26	1.77	4.87	1.77	1.77	1.77	2.21
N/A	12	30	1	32	4	11	3	2	0	4
Unknown	1	1	2	7	0	0	1	2	4	1

Note: FAQ = functional activities questionnaire.

Participants were excluded if they reported motor or sensory deficits, psychiatric disorders, low literacy levels (sixth grade or below), or the use of medications such as antipsychotics or acetylcholinesterase inhibitors.

This study was approved by the Mount Sinai Medical Center Institutional Review Board.

Materials and Procedure

Functional Activities Questionnaire (FAQ)

The FAQ (Pfeffer et al., 1982) was not part of the initial neuropsychological battery and was administered by a clinician to an informant (a family member or caregiver who maintained a close relationship with the participant). The FAQ is a 10-item questionnaire that includes questions about the individual's performance on instrumental activities of daily living and should be answered according to the participant's performance over the previous 4 weeks. It includes the following items: writing checks, paying bills, balancing a checkbook, assembling tax records, business affairs, or papers, shopping alone for clothes, household needs, or groceries, playing a game of skill, working on a hobby, heating water, making a cup of coffee, and turning off the stove after use, preparing a balanced meal, keeping track of current events, paying attention to, understanding, discussing TV, books, or magazines, remembering appointments, family occasions, holidays, and medications, and traveling out of neighborhood, driving, and arranging to take buses. The informant rated the participant on a 4-point scale, 0: they are considered normal, 1: they have difficulty but can do it alone, 2: they require assistance, and 3: they are dependent. The informant can also rate an item as "not applicable" in case the participant had never done the task.

The Spanish version of the FAQ was translated and adapted by the Spanish Translation and Adaptation Work Group, composed of investigators from Alzheimer's Disease Centers across the USA, to account for variations among Spanish speaking individuals from different countries and socio-cultural backgrounds (Acevedo et al., 2009).

FAQ total scores ranging from 0 to 3 are considered normal, scores greater than 3 indicate the presence of functional impairment, and scores greater than 12 indicate dementia (Tappen et al., 2010). As this instrument was not used for diagnostic purposes, these cutoffs were not used. If three or more items were reported as "not applicable" or "unknown," the participant was excluded from the analyses ($n = 13$; 12 HA, of which 9 were females, and one EA female). Eighty-eight participants had 1 or 2 items rated as "not applicable" or "unknown." Among them, no significant differences were found between HA ($n = 56$) and EA ($n = 32$) participants, or across gender (54 females). However, there was a significant difference in the frequency of not applicable/unknown items across diagnoses, with 46% of MCI participants, 52.4% of those with dementia, and only 19.7% of CN participants identifying 1 or 2 items as "not applicable" or "unknown," X^2 $(2, N = 226) = 16.61$, $p < .001$.

The items that were most frequently "not applicable" included item 4 (playing a game of skill, working on a hobby; $n = 39$), item 2 (assembling tax records, business affairs, or papers; $n = 31$), and item 1 (writing checks, paying bills, balancing a checkbook; $n = 13$). Most of the items without scores were "not applicable,", or "never done" (96.8% in item 2, 82.1% in item 4, and 92.3% in item 1; Table 1), with only a small number of cases reported as "unknown."

Geriatric Depression Scale (GDS)—Short Form

The GDS (Sheikh & Yesavage, 1986) is a widely used instrument to assess depression. The GDS-Short Form (GDS-15) is a 15-item questionnaire in which participants respond "yes" or "no," based on how they have felt during the past week. Items include questions such as: "Are you basically satisfied with your life?" "Do you feel that your life is empty?" and "Do you feel helpless?". A score greater than or equal to 5 is suggestive of clinical depression. This measure was used to describe the mood characteristics of the sample.

Clinical Dementia Rating (CDR)

The CDR (Morris, 1993) is a global rating scale used for its ability to distinguish between CN, MCI, and dementia. This scale has good clinical validity predicting functional changes and dementia (Woolf et al., 2016). It can also differentiate between AD participants and normal controls in a sample of Spanish-speaking and English-speaking individuals, supporting the use of this instrument with Spanish-speaking populations (Sano et al., 2006). The CDR includes questions regarding the patient's cognition and functionality divided into six domains: memory, orientation, judgment and problem solving, community affairs, home, and hobbies, and personal care. The level of impairment for each domain is rated on a 5-point scale including: 0 = normal, 0.5 = questionable, 1 = mild, 2 = moderate, and 3 = severe. The overall CDR score corresponds to 0 = normal, 0.5 = MCI, 1 = mild dementia, 2 = moderate dementia, and 3 = severe dementia. This scale was used for diagnostic purposes for the current study.

Magnetic resonance imaging (MRI)

Participants underwent MRI scanning using a Siemens Skyra 3 T MRI scanner at Mount Sinai Medical Center in Miami Beach, Florida. Brain images were obtained using a 3D T1-weighted sequence (MPRAGE) with 1.0 mm isotropic resolution. Free Surfer Version 6.1 software (http://surfer.nmr.mgh.harvard.edu) was employed to assess hippocampal (HV) and entorhinal cortex volumes (ERV) as well as entorhinal cortical thickness (ERT). We combined homologous regions in the left and right hemispheres. All volumetric measurements were adjusted for each participant's total intracranial volume, and values were expressed as a percent of total intracranial volume.

Statistical Analyses

Univariate analyses of variance (ANOVAs) were used to compare the two ethnic and three diagnostic groups on demographic variables (age and years of education), symptoms of depression (GDS-15), Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) scores, FAQ scores, HV, ERV, and ERT. Additionally, chi-square tests were used to compare the ethnic groups in terms of gender and frequency of diagnosis.

Using linear regression analyses, we examined the contribution of the FAQ to the variance in HV, ERV, and ERT, including age, years of education, general cognition (MoCA scores), gender, and ethnicity as covariates. Gender and ethnicity were entered as categorical variables; females were coded as 1 and males were coded as 0 for gender, and Hispanics were coded as 1, and EAs were coded as 0 for ethnicity. These analyses were performed for the whole sample and for a subsample of non-dementia participants (MCI and CN).

Results

The two ethnic groups were compared in terms of demographic variables (age and years of education), MoCA, GDS, FAQ total scores, and brain biomarkers (HV, ERV, and ERT) using ANOVAs (see Table 2). The two groups were similar in age, GDS total, FAQ total, ERV, and ERT. EA participants reported higher education and had higher MoCA scores, whereas HA had higher HV compared to EA. Inferential statistics for between-group comparisons are shown in Table 2. In addition, the ethnic groups did not differ in their gender distribution, X^2 (1, N = 226) = .68, p = .411 (62.77% of HA and 57.30% of EA were female), or in frequency of diagnosis, X^2 (2, N = 226) = 1.20, p = .549 (with 40 [29%] CN, 69 [50%] MCI, and 28 [21%] participants with dementia in the HA sample; 31 [35%] CN, 44 [49%] MCI, and 14 [16%] dementia participants in the EA sample). For the subsample of non-dementia (CN and MCI) participants, the ethnic groups only differed in years of education, MoCA scores, HV, and ERV (see Table 3).

The diagnostic groups were also compared on demographic variables (age and years of education), MoCA, GDS, FAQ total scores, HV, ERV, and ERT using ANOVAs (Table 2). There were significant differences between the groups in education, GDS, MoCA, FAQ, HV, ERV, and ERT. Bonferroni post-hoc tests revealed that CN participants had more years of education than the MCI and dementia groups, but MCI and dementia had similar education levels. Also, post-hoc tests indicated that CN participants reported significantly lower GDS scores than MCI and dementia, with similar total GDS among those groups. CN had significantly higher MoCA scores than MCI and dementia, and MCI had higher scores than the dementia group. FAQ scores were significantly lower among CN participants when compared to MCI and dementia, with the highest scores and lowest functionality reported in the dementia group. Additionally, there were significant differences in brain biomarkers between the three groups; CN presented significantly larger values for HV, ERV, and ERT relative to MCI and dementia, while MCI participants presented greater HV, ERV, and ERT when compared to the dementia group.

Table 2. Demographic and clinical characteristics of the whole sample. Means and (standard deviations) are presented

	HA	EA	Total	*F*	*p*	η_p^2	CN	MCI	Dementia	*F*	*p*	η_p^2
	n = 137	*n* = 89	*N* = 226				n = 71	n = 113	n = 42			
Age	71.07 (7.62)	72.82 (8.30)	71.76 (7.93)	2.664	.104	.012	70.75 (6.15)	71.88 (7.88)	73.14 (10.34)	1.24	.293	.011
Education	14.23 (3.45)	16.30 (2.77)	15.04 (3.35)	22.721	<.001	.092	16.20 (2.89)	14.85 (3.31)	13.62 (3.61)	8.75	<.001	.073
MoCA	20.77 (5.54)	22.94 (4.22)	21.63 (5.16)	9.931	.002	.042	25.15 (2.95)	21.94 (3.35)	14.83 (5.61)	100.23	<.001	.473
GDS	2.57 (2.47)	2.34 (2.66)	2.48 (2.55)	.448	.504	.002	1.61 (1.89)	2.73 (2.65)	3.29 (2.87)	7.19	.001	.061
FAQ	4.76 (7.06)	4.24 (5.93)	4.55 (6.63)	.335	.563	.001	.72 (1.33)	3.15 (3.47)	14.81 (8.16)	150.58	<.001	.575
HV	.00487 (.00069)	.00466 (.00067)	.00479 (.00069)	5.171	.024	<.001	.00519 (.00057)	.00472 (.00062)	.00429 (.00070)	28.82	<.001	<.001
ERV	.00231 (.00049)	.00223 (.00047)	.00228 (.00048)	1.664	.198	<.001	.002492 (.00034)	.00228 (.00049)	.00191 (.00043)	23.14	<.001	<.001
ERT	6.16 (.81)	6.15 (.88)	6.16 (.84)	.019	.892	<.001	6.59 (.53)	6.18 (.81)	5.34 (.76)	39.46	<.001	.261

Notes: Data are presented as mean (standard deviation); MoCA = Montreal Cognitive Assessment; GDS = Geriatric Depression Scale; FAQ = Functional Activities Questionnaire; HV = bilateral hippocampal volume; ERV = bilateral entorhinal volume; ERT = entorhinal thickness.

Table 3. Demographic and clinical characteristics of the non-dementia sample

	HA	EA	Total	*F*	*p*	η_p^2
	M(SD)	*M(SD)*	*M(SD)*			
	n = 109	*n* = 75	*N* = 184	–	–	–
Age	70.85(6.85)	72.29(7.79)	71.44(7.26)	1.75	.187	.010
Education	14.63(3.27)	16.44(2.82)	15.37(3.21)	15.14	<.001	.077
MoCA	22.66(3.68)	23.93(3.26)	23.18(3.56)	5.84	.017	.031
GDS	2.38(2.26)	2.17(2.69)	2.29(2.44)	.306	.581	.002
FAQ	2.10(2.95)	2.37(3.27)	2.21(3.08)	.347	.557	.002
HV	.00502(.00061)	.00473(.00065)	.00490(.00064)	9.391	.003	<.001
ERV	.00242(.00045)	.00228(.00044)	.00236(.00045)	4.124	.044	<.001
ERT	6.37(.68)	6.29(.82)	6.34(.74)	.526	.469	.003

Notes: MoCA = Montreal Cognitive Assessment; GDS = Geriatric Depression Scale; FAQ = Functional Activities Questionnaire; HV = bilateral hippocampal volume; ERV = bilateral entorhinal volume; ERT = entorhinal thickness.

Linear regression analyses with simultaneous entry investigated the contribution of the FAQ, age, years of education, MoCA scores, gender, and ethnicity to explaining the variance of HV, ERV, and ERT for the whole sample and the non-dementia subsample (Tables 4– 6). The models predicting HV are displayed in Table 4. The significant model predicted 42% of the variance in HV for the whole sample and 34% of the variance in HV for the non-dementia subsample. All variables were significant predictors in this model. Age, years of education, and FAQ presented negative β coefficients predicting HV, while ethnicity, gender, and MoCA presented positive associations with HV. This suggests that younger female HA participants with fewer years of education, higher MoCA scores, and lower FAQ scores had a higher chance of presenting larger HV.

As for ERV (Table 5), the linear regression model for the whole sample significantly predicted 23% of the variance in ERV, and the only three predictors that significantly contributed to this variance were ethnicity, MoCA score, and FAQ. This model suggests that HA participants, with higher MoCA and lower FAQ scores, had an increased likelihood of larger ERV. Age, education, and gender did not significantly contribute to this model ($ps > .05$). Within the non-dementia subsample, the model predicted 11% of the variance in ERV ($p < .001$). The only significant predictors were ethnicity and MoCA scores ($p < .05$), suggesting that HA with higher MoCA scores were more likely to have greater ERV. Age, education, gender, and FAQ did not significantly contribute to the ERV model for non-dementia participants.

For the regression analyses predicting ERT (Table 6), the model significantly predicted 36% of the variance ($p < .001$) for the whole sample, where age, MoCA score, and FAQ score were all significant predictors ($p < .05$). The model for non-dementia participants significantly predicted 18% of the variance in ERT, where age and MoCA were the only significant predictors. These results suggest that, for the whole sample, older participants with lower MoCA scores and higher FAQ scores had smaller ERT values. Among non-dementia participants, older participants with lower MoCA scores had smaller ERT.

Table 4. Linear Regression Analyses predicting Hippocampal volume

Predictors	Whole Sample (N = 226)						Predictors	Non-dementia (n = 184)					
	B	*SE B*	*β*	*t*	*p*	ΔR^2		*B*	*SE B*	*β*	*t*	*p*	ΔR^2
Age	−3.03E-5	.00	−.35	−6.59	<.001	.11	Age	−3.13E-5	.00	−.36	−5.44	<.001	.11
Education	−2.45E-5	.00	−.12	−2.08	.039	.01	Education	−2.93E-5	.00	−.15	−2.25	.026	.02
Ethnicity	.00	.00	.12	2.22	.027	.01	Ethnicity	.00	.00	.16	2.48	.014	.02
Gender	.00	.00	.24	4.54	<.001	.05	Gender	.00	.00	.25	4.04	<.001	.06
MoCA	3.17E-5	.00	.24	3.33	.001	.03	MoCA	2.85E-5	.00	.16	2.19	.030	.02
FAQ	−2.47E-5	.00	−.24	−3.48	.001	.03	FAQ	−3.54E-5	.00	−.17	−2.58	.011	.03
Adjusted R^2	.42						Adjusted R^2	.34					
F	28.19						*F*	16.76					
p	<.001						*p*	<.001					

Notes: MoCA = Montreal Cognitive Assessment; FAQ = Functional Activities Questionnaire; ΔR^2 = squared semi-partial correlations.

Table 5. Linear regression analyses predicting entorhinal volume

Predictors	Whole sample (N = 226)						Predictors	Non-dementia (n = 184)					
	B	*SE B*	*β*	*t*	*p*	ΔR^2		*B*	*SE B*	*β*	*t*	*p*	ΔR^2
Age	−5.03E-6	.00	−.08	−1.4	.171	.01	Age	−3.84E-6	.00	−.06	−.82	.416	<.01
Education	1.29E-6	.00	.01	.14	.891	<.01	Education	−4.29E-6	.00	−.03	−.40	.688	<.01
Ethnicity	.000	.00	.13	2.10	.037	.02	Ethnicity	.00	.00	.18	2.45	.015	.03
Gender	.000	.00	.12	1.94	.053	.01	Gender	.00	.00	.11	1.59	.113	.01
MoCA	2.20E-5	.00	.24	2.90	.004	.03	MoCA	3.78E-5	.00	.30	3.54	.001	.06
FAQ	−1.91E-5	.00	−.26	−3.36	.001	.04	FAQ	3.35E-7	.00	.002	.03	.976	<.01
Adjusted R^2	.23						Adjusted R^2	.11					
F	12.41						*F*	4.62					
p	<.001						*p*	<.001					

Notes: MoCA = Montreal Cognitive Assessment; FAQ = Functional Activities Questionnaire; ΔR^2= squared semi-partial correlations.

Table 6. Linear regression analyses predicting entorhinal thickness

Predictors	Whole sample (N = 226)						Predictors	Non-dementia (n = 184)					
	B	*SE B*	*β*	*t*	*p*	ΔR^2		*B*	*SE B*	*β*	*t*	*p*	ΔR^2
Age	−.02	.01	−.16	−2.85	.005	.02	Age	−.02	.01	−.16	−2.15	.033	.02
Education	−.02	.02	−.07	−1.09	.275	<.01	Education	−.02	.02	−.09	−1.22	.22	<.01
Ethnicity	.10	.10	.06	.96	.338	<.01	Ethnicity	.11	.11	.07	1.02	.31	<.01
Gender	.06	.09	.03	.61	.54	<.01	Gender	.07	.10	.05	.72	.47	<.01
MoCA	.06	.01	.36	4.85	<.001	.07	MoCA	.08	.02	.36	4.48	<.001	.09
FAQ	−.03	.01	−.27	−3.79	<.001	.04	FAQ	−.01	.02	−.06	−.75	.452	<.01
Adjusted R^2	.36						Adjusted R^2	.18					
F	21.74						*F*	7.59					
p	<.001						*p*	<.001					

Notes: MoCA = Montreal Cognitive Assessment; FAQ = Functional Activities Questionnaire; ΔR^2= squared semi-partial correlations.

The squared semi-partial correlations (ΔR^2) in which the FAQ was a significant volumetric predictor indicate a small contribution to the total variance, ranging from 3 to 4% (Tables 4–6). The variance contribution of other significant predictors ranged between 2% and 11%, 1% and 2%, 1% and 3%, 1% and 5%, and 2% and 9% for age, education, ethnicity, gender, and MoCA, respectively.

Discussion

We aimed to explore the predictive validity of functional abilities, as measured by the FAQ, to HV, ERV, and ERT in HA and EA participants diagnosed as CN, MCI, or dementia. Age, education, gender, ethnicity, and general cognition (MoCA scores) were included with the FAQ as predictors and with outcomes of structural brain biomarkers for all regression models. Results indicated significant associations of FAQ scores, age, ethnicity, gender, and MoCA scores with HV. HA participants who were female, reporting superior functionality in daily life activities (i.e., lower FAQ scores), better general cognitive function, younger

age, and fewer years of education were more likely to exhibit larger hippocampi, even among participants without dementia. The volume of the entorhinal cortex was also predicted by FAQ scores, MoCA, and ethnicity for the whole sample, suggesting that Hispanic individuals with less functional impairment and higher general cognition were more likely to exhibit greater ERV. ERT was also significantly predicted by FAQ, age, and MoCA scores. Younger participants with higher MoCA and lower FAQ scores were more likely to have larger ERT across the AD spectrum. However, FAQ was not associated with ERV and ERT in individuals without dementia, indicating that this relationship was being driven by the dementia sample only.

The current study was unique in exploring the effects of ethnicity on brain atrophy. In addition to supporting previous findings demonstrating the association between the FAQ and volumetric biomarkers, our results provide new information regarding the predictive value of the FAQ on the variance of structural biomarkers relevant to AD. Results from this study are in line with previous findings in which functional impairment was associated with HV in both MCI and dementia (Rueda et al., 2015; Brown et al., 2011), as well as a composite cortical thickness measure (bilateral entorhinal, inferior temporal, middle temporal, and fusiform cortex) among CN and MCI (Vassilaki et al., 2018). Our results also support previous reports describing a relationship between cognitive abilities (e.g., confrontation naming and memory) and HV and ERV (Choi et al., 2016; Olsen et al., 2017), as well as functional impairment and decreased ERV for aMCI and dementia (Brown et al., 2011). The variance explained by the FAQ was between 3% and 4% and was similar to the percentage explained by the MoCA, suggesting that functional and cognitive screening measures have modest but similar predictive values in explaining the variance of the volume for these vulnerable temporal lobe regions in the aging brain.

Few studies have investigated the association between brain biomarkers and measures of functional assessment, particularly among groups without dementia. In the present investigation, the FAQ-HV association remained in individuals without a clinical diagnosis of dementia, indicating that functional decline is reflected in decreased HV early in the aging process. On the other hand, neither the FAQ-ERV nor the FAQ-ERT associations were significant when the dementia group was excluded. This finding suggests that the entorhinal cortex may become more compromised as the disease progresses.

Demographic variables significantly influenced the relationship between functional impairment and brain volumetric measures. For example, ethnicity was a significant contributor to the association between FAQ and HV, indicating that HA participants with lower FAQ scores were more likely to have larger HV than EA participants. Our results, like previous research, highlight the importance of considering ethnicity to improve our understanding of cognitive aging in culturally diverse populations. Gavett and colleagues (2018) found that cognitive decline in African Americans and Hispanics was related to global gray matter change and baseline white matter hyperintensities, while AD pathology appeared to be a more important contributor to cognitive decline for Whites compared to Hispanics. Similarly, Caribbean Hispanics and African Americans without dementia exhibited larger relative brain volumes than White non-Hispanics (Brickman et al., 2008). Future research should replicate the current study in other ethnic groups.

Furthermore, older participants were more likely to exhibit reduced HV. This finding is in line with the literature showing age-related changes in atrophy for participants diagnosed with MCI and AD (Holland et al., 2012; Fiford et al., 2018). Previous research described a decline in HV with age in CN individuals and, to a greater extent, in patients with probable AD (Jack et al., 1997).

Our findings also indicated that female participants with higher cognitive functioning and lower functional impairment were more likely to exhibit higher HV. However, gender was not predictive of ERT and ERV. Previous findings have shown contradictory results regarding sex differences and biomarkers. Cavedo and colleagues (2018) reported a lack of sex differences in hippocampal and basal forebrain volumes for older CN adults with subjective memory complaints. However, in a sample with MCI, Burke et al. (2019) reported that HV affected the progression to dementia only in females.

Education was included in the regression models as a way of controlling for the differences observed between ethnic and diagnostic groups. Interestingly, in our sample, education contributed to the HV model in an unexpected direction; those with less years of schooling, better cognition and higher functional abilities were more likely to have larger HV. Prior research shows inconclusive results regarding the relationship between education and HV. Legdeur and colleagues (2019) found that among CN individuals, low educational level was associated with abnormal HV between the ages of 64.2 and 74.7 years, but this association was less common in older individuals (above 89 years). However, no significant relationship between education and hippocampal atrophy was observed among CN adults (18–65 years; Pira, Cherubini, Caltagirone, & Spalletta, 2011), and education did not alter the rate of hippocampal atrophy across the AD spectrum (Lo & Jagust, 2013).

The present results support the evidence that the FAQ is a useful instrument for the detection of early signs of functional decline by associating it with underlying brain pathology (e.g., HV loss), even at the stage when individuals do not present a dementia syndrome (among CN and MCI). This suggests that patients with normal cognition and mild functional deficits should be followed more closely than those without functional deficits. Nonetheless, longitudinal studies should determine whether CN participants with mild FAQ deficits are at an elevated risk of undergoing abnormal aging compared to those with normal FAQ scores.

Limitations of our study include an overrepresentation of MCI in the sample, and an unequal gender distribution, although this was controlled for by including gender as a predictor in the regression models. A large majority of the participants at the 1Florida ADRC are females, who have been reported to volunteer for clinical studies at a higher rate than males (Harris et al., 2012). Another limitation includes the frequency of "not-applicable" or "unknown" FAQ responses among participants. To lessen the impact of this issue, we only included participants that had at least 80% of the FAQ completed, with most of the "missing" items reported as "not applicable." Moreover, the percentages of participants with missing items were equivalent across the ethnic and gender groups. Another shortcoming is that information regarding the informant's demographic characteristics and the nature of the relationship with the participant was not collected. Previous literature has demonstrated that cohabitation status, relationship to the participant, informant level of education, and race/ethnic group influence the accuracy of the informant report on IADL performance (Hackett, Mis, Drabick, & Giovannetti, 2020). However, all participants were accompanied by a reliable informant (e.g., close relative or caregiver) who could provide accurate information about the patient's cognitive and functional performance on daily activities.

Future studies should investigate the external validity of the FAQ by exploring its association with other biomarkers in larger ethnically diverse samples of older adults, including individuals with normal cognition, and follow them using a longitudinal analysis to determine if these associations could be examined as a function of disease progression. As the results of this study indicate a complex relationship between FAQ and structural biomarkers, the association of additional demographic and functional variables with volumetric biomarkers of AD should be further explored using structural equation modeling. Additionally, FAQ items can be correlated with ERV and HV as well as other disease-related regions beyond the medial temporal areas in order to determine the functional abilities that may become more compromised as the disease progresses. Finally, because the FAQ assesses perceived functional ability, future research should corroborate the current findings using additional objective measures of functional ability, which do not rely on informant report.

Conflict of Interest

None declared.

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