Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.ajgponline.org

Regular Research Article

Structural Brain Differences Between Cognitively Impaired Patients With and Without Apathy

Nathan K. Chan, H.B.Sc., Philip Gerretsen, M.D., Ph.D., M. Mallar Chakravarty, Ph.D., Daniel M. Blumberger, M.D., M.Sc., Fernando Caravaggio, Ph.D., Eric Brown, M.D., M.Sc., Ariel Graff-Guerrero, M.D., Ph.D., for the Alzheimer's Disease Neuroimaging Initiative *

ARTICLE INFO

Article history:
Received February, 20 2020
Revised November, 21 2020
Accepted December, 6 2020

ABSTRACT

Objective: *Since apathy increases in prevalence with severity of dementia pathology, we sought to distinguish concomitant neurodegenerative processes from brain differences associated with apathy in persons with mild cognitive impairment (MCI) and Alzheimer's Disease (AD). We examined relative structural brain differences between case-control matched cognitively impaired*

From the Centre for Addiction and Mental Health (CAMH), Toronto, Ontario, Canada; Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada; Geriatric Mental Health Division, CAMH, University of Toronto, Toronto, Ontario, Canada; Campbell Family Mental Health Research Institute, CAMH, University of Toronto, Toronto, Ontario, Canada; Douglas Mental Health University Institute, Montreal, Quebec, Canada; Department of Psychiatry, McGill University, Montreal, Quebec, Canada; and the Department of Biological and Biomedical Engineering, McGill University, Montreal, Quebec, Canada. Send correspondence and reprint requests to Ariel Graff-Guerrero M.D., MSc, Ph.D., Multimodal Imaging Group, Research Imaging Centre, Centre for Addiction and Mental Health., 250 College Street, Toronto, Ontario, M5T 1R8, Canada. e-mail: ariel_graff@yahoo.com.mx

This work was funded by Canadian Institutes of Health Research (CIHR) Grant MOP-142493 and MOP-141968. N.K.C. was funded by a CIHR Canada Graduate Scholarships-Masters Program. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

* Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

https://doi.org/10.1016/j.jagp.2020.12.008

Key Words:
Structural MRI
Alzheimer's Disease
mild cognitive impairment
cognitively normal
apathy
dementia
cortical thickness
case-control
matching
ADNI
frontostriatal circuits
frontotemporal association areas
region of interest analysis
mixed models
healthy controls

patients with and without apathy. ***Design:*** *Cross-sectional case-control study.* ***Setting:*** *Fifty-eight clinical sites in phase 2 of the AD Neuroimaging Initiative across the United States and Canada.* ***Participants:*** *The ≥ 55 years of age with MCI or AD dementia and no major neurological disorders aside from suspected incipient AD dementia. Participants with apathy ($n = 69$) were age-, sex-, apolipoprotein E ε4 allele carrier status-, Mini-Mental State Exam score-, and MCI or AD dementia diagnosis-matched to participants without apathy ($n = 149$).* ***Interventions:*** *The 3-tesla T1-weighted MRI scan and neurocognitive assessments. Using the Neuropsychiatric Inventory apathy domain scores, participants were dichotomized into a with-apathy group (score ≥ 1) and a without-apathy group (score = 0).* ***Measurements:*** *Cortical thicknesses from 24* a priori *regions of interest involved in frontostriatal circuits and frontotemporal association areas.* ***Results:*** *False-discovery rate adjusted within-group comparisons between participants with apathy and participants without apathy showed thinner right medial orbitofrontal (mOFC; mean difference (MD) ± standard error of MD (SE) = −0.0879 ± 0.0257 mm; standardized MD (d) = −0.4456) and left rostral anterior cingulate (rACC; MD ± SE = −0.0905 ± 0.0325 mm; d = −0.3574) cortices and thicker left middle temporal cortices (MTC; MD ± SE = 0.0688 ± 0.0239 mm; d = 0.3311) in those with apathy.* ***Conclusion:*** *Atrophy of the right mOFC and left rACC and sparing of atrophy in the left MTC are associated with apathy in cognitively impaired persons.* (Am J Geriatr Psychiatry 2020; ■■:■■–■■)

OBJECTIVE

Alzheimer's Disease (AD), an age-related neurodegenerative illness characterized by progressive cognitive decline and brain atrophy, accounts for 60%–80% of dementias.[1] Apathy, a neuropsychiatric symptom as associated with deficits in goal-directed behaviour, is present in 39% of individuals with mild cognitive impairment (MCI) and 72% of patients with AD.[2] In those with subjective cognitive concerns or MCI, apathy is associated with a twofold increased risk of dementia.[3,4] Clarifying the specific structural correlates of apathy may support the development of therapeutic approaches and improve outcomes.

Le Heron et al.[5,6] hypothesize that frontostriatal circuits including brain regions such as the ventromedial prefrontal cortex, anterior cingulate cortex, striatum, and supplementary motor area/posterior midcingulate cortex are involved in the generation of goal-directed behaviours, while deficits in these regions may manifest as apathy. Several studies across neuroimaging modalities support the link between frontostriatal deficits and apathy, both as a transdiagnostic feature across brain disorders[7] and specifically in AD.[8] Cortical grey matter (GM) atrophy in frontotemporal association areas such as the dorsolateral prefrontal cortex,[9–11] ventrolateral prefrontal cortex,[10,12] and areas within the temporal cortex[11,13,14] has also been associated with apathy in AD. With that said, degeneration in these regions is a core feature of AD pathology, especially as the disease enters more advanced stages.[15] Given that the prevalence of apathy increases with dementia severity,[2] the average cognitively impaired patient with apathy is likely at a more advanced stage of AD compared to one that does not experience apathy; thus, disease stage could confound which brain regions are associated with apathy in AD, especially if such differences are not accounted for in inferential analyses. This could explain the wide heterogeneity of brain regions associated with apathy in AD, whereas a nuanced approach toward controlling disease stage may help de-obfuscate the specific brain regions associated with apathy.

In light of this, we sought to clarify which previously reported region-wise GM differences are associated specifically with apathy across the spectrum of cognitive impairment using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Differences were assessed by measuring GM thickness for cortical regions of interest (ROIs). To account for potential confounding due to differences in

disease stage, within-strata comparisons were performed between participants with and without apathy matched for age, sex, apolipoprotein E epsilon 4 (APOE4) allele carrier status, Mini-Mental State Exam (MMSE) score, and MCI or AD diagnosis. We hypothesized that apathy would be associated with discrete patterns of regional brain atrophy in frontostriatal circuits and frontotemporal association areas amongst persons with cognitive impairment due to no neurological diseases other than suspected incipient AD.

METHODS

Participants

Data from participants in the ADNI database were extracted.[16] ADNI was launched in 2003 to test whether neuroimaging, biological, and clinical markers can be combined to measure the progression of AD. Only participants from ADNI phase 2 (ADNI2) were examined. ADNI2 inclusion criteria specified participants that were between 55 and 90 years of age at time of enrolment (inclusive) with Modified Hachinski[17] scores < 5 and Geriatric Depression Scale (GDS)[18] scores < 6. Participants were excluded from ADNI2 if they exhibited any significant neurologic disease other than suspected incipient AD.

Data from the most recent visit of each ADNI2 participant that completed both the Neuropsychiatric Inventory and a 3T T_1-weighted magnetic resonance imaging (MRI) scan on the same date was selected. Of 610 participants identified, 203 were cognitively normal (CN), 266 had MCI, and 141 had AD dementia. Herein, these data are described as the "original data." As we sought to examine GM differences associated with apathy across cognitively impaired (CI) participants, CN participants were excluded from the main analysis. However, comparisons with CN participants were performed in supplementary analyses and are described in Supplemental Digital Content. Since ADNI screened participants for neurologic diseases other than suspected incipient AD, we reasoned that MCI and AD dementia participants likely exhibited cognitive impairment due to AD pathology. We were also interested in effect of apathy from a transdiagnostic perspective, so we combined the MCI and AD dementia groups, leaving 407 CI participants in the original data. Nevertheless, subsequent inferential analyses accounted for differences in diagnosis via match strata or directly as fixed effects.

Clinical Assessments

Participants from ADNI2 completed several assessments, including the MMSE, (measures global cognitive impairment, scored from 0 [worst] to 30 [best]);[19] the Montreal Cognitive Assessment (MoCA, measures cognitive impairment, scored from 0 [worst] to 30 [best]);[20] the Clinical Dementia Rating scale (CDR, measures cognitive and functional impairment due to dementia across 6 subscales, each scored on a 5-point scale from 0 [best] to 3 [worst]);[21] the Functional Activities Questionnaire (FAQ, measures functional impairment, scored from 0 [best] to 30 [worst]);[22] and the Neuropsychiatric Inventory (NPI).[23] For the CDR, cognitive and functional subsums of boxes (range from 0 [best] to 9 [worst])[24] were also computed, as well as the CDR sum of boxes (CDR-SB, sum of all 6 subscales, scored from 0 [best] to 18 [worst]).[21] The NPI is a clinical assessment that examines 12 behavioural domains, and each domain is scored for symptom frequency (0 [none] to 4 [very frequently]) and severity (0 [none] to 3 [severe]). The product of these scores provides a total domain score (0 [best] to 12 [worst]). The NPI apathy domain score was used to dichotomize participants into two categories: with apathy (NPI-Apathy $\geq$ 1) or without apathy (NPI-Apathy = 0).

Neuroimaging Analysis

Preprocessed T_1-weighted MRI scans were retrieved from ADNI for each participant. MRI acquisition and preprocessing for ADNI2 have previously been described.[25]

The recon-all pipeline from FreeSurfer version 6.0 was performed on preprocessed scans using the FreeSurfer recon-all Brain Imaging Data Structure App software on two high-performance computing clusters: the Niagara Supercomputer from SciNet at the University of Toronto (Toronto, Canada)[26, 27] and Scientific Computing Cluster at the Centre of Addition and Mental Health (Toronto, Canada). FreeSurfer methods and documentation have previously been described and can be found online (see http://surfer.nmr.mgh.harvard.edu). Cortical thicknesses by

regions defined in the Desikan-Killiany atlas[28] were computed from reconstructed surface parcellations. Quality control (QC) checks were performed on MRI scans and their respective reconstructed surfaces using VisualQC[29] for visualization and Qoala-T[30] for assisted, semi-automated assessments; QC methods are described further in the Supplemental Digital Content (see Supplementary Methods).

Cortical thicknesses were examined from 24 bilateral *a priori* regions of interest (ROIs). ROIs were selected based on reported findings from previous studies that investigated apathy in cognitively impaired participants. Frontostriatal circuits included the following ROIs: superior frontal cortex, medial orbitofrontal cortex (mOFC), rostral anterior cingulate cortex (rACC), and caudal anterior cingulate cortex. Frontotemporal association areas included the following ROIs: in the frontal lobe, rostral middle frontal cortex, lateral orbitofrontal cortex, pars orbitalis, and pars triangularis; in the parietal lobe, supramarginal areas; and in the temporal lobe, superior temporal cortex (STC), middle temporal cortex (MTC), and inferior temporal cortex. A schematic of a priori ROIs is provided in the Supplemental Digital Content (see Supplementary Figure 1). Cortical thicknesses were not spatially normalized as previous studies have indicated that doing so may introduce confounds and statistical noise.[31-33]

Case-Control Matching

Coarsened Exact Matching (CEM)[34] was applied to match participants with apathy ("cases") to participants without apathy ("controls") within strata formed from unique combinations of match variable bins. The match variables selected were age, sex, APOE4 carrier status, MMSE score, and diagnostic status. The selection of match variables is discussed in greater detail in the Supplemental Digital Content (see Supplementary Methods). Age was divided into 8 5-year bins (55−59, 60-64, . . ., 85−89, 90−94). Sex was divided into 2 bins (male or female). APOE4 allele number was divided into two bins (0 alleles or ≥ 1 allele; i.e., APOE4 carrier status). MMSE score was divided into 5 4-point bins (≤ 14, 15−18, 19−22, 23−26, 27−30). Diagnostic status was divided into two bins (MCI or AD dementia). Each stratum was assigned weights to normalize the distribution of controls to the distribution of cases. CEM weighting is discussed further in the Supplementary Methods. Matching was implemented with the ***MatchIt***[35] version 3.0.2 package for R version 3.5.1.

Inferential Statistics

Demographics and clinical assessment scores between participants with and without apathy in the original data were compared with, for (pseudo-)continuous variables, Welch's t test for differences in means; for nominal categorical variables, Pearson's chi-squared test for independence in frequencies; and for ordinal categorical variables, the Cochran-Armitage test for trend.

For comparisons in the matched samples, strata-wise mean differences between participants with or without apathy amongst (pseudo-)continuous variables were tested using linear mixed-effects models, with CEM strata entered as random factors (random intercepts model) and CEM weights entered as weights. The unstructured variance-covariance structure was used to model the random effects, and models were fitted with the restricted maximum likelihood (REML) criteria. Models were implemented with ***lme4***[36] version 1.1-21 and ***lmerTest***[37] version 3.0-1 for R version 3.5.1. For nominal categorical variables, tests for strata-wise independence (i.e., conditional independence) of apathy and the respective variable were performed with the generalized Cochran-Mantel-Haenszel (CMH) test using CEM weights as frequencies. For ordinal categorical variables, tests for strata-wise trend were also performed with the generalized CMH test using CEM weights as frequencies. The CMH statistic for general association was reported for tests of independence, and the CMH statistic for differences in row mean scores was reported for tests of trend where participants with or without apathy were represented as rows. CMH tests were implemented with ***vcdExtra***[38] version 0.7-1 for R version 3.5.1.

A mixed-effects analysis of variance (ANOVA) was designed to test whether cortical thicknesses differed by ROIs between participants with and without apathy. The dependent variable was cortical thickness. Fixed effects were the ROIs, the presence or absence of apathy, and the apathy x ROIs interaction. CEM match strata were included as random factors (random intercepts model) to adjust for within-strata variation, serving as a pseudovariable for the match variables of age, sex, APOE4 carrier status, MMSE score, and diagnostic status. Participant IDs were

included as random factors to adjust for within-subject variation across ROI thicknesses. The unstructured variance-covariance structure was used to model the random effects. The models were adjusted with CEM weights and fitted with the REML criteria. Satterthwaite's method was used to estimate residual degrees of freedom.[39] The apathy x ROIs interaction was the effect of interest, and the null hypothesis for the interaction (that there are no ROI-wise differences in cortical thicknesses between participants with and without apathy) was rejected if p was less than $\alpha = 0.05$. Effect sizes in the form of partial coefficients of determination (partial R^2) were estimated with the Nakagawa and Schielzeth approach using the ***r2glmm***[40] version 0.1.2 package for R version 3.5.1.

If the apathy x ROIs interaction was significant in the above analysis, then each ROI would be examined in separate *post-hoc* mixed-effects univariate ANOVAs to investigate which specific ROIs were associated with apathy. The dependent variable was the ROI-specific cortical thickness. The fixed effect of interest was the presence or absence of apathy, and CEM match strata were included as random factors (random intercepts model). The unstructured variance-covariance structure was used to model the random effects. The models were adjusted by CEM weights and fitted with the REML criteria. To adjust for multiple comparisons, only findings that survived the false discovery rate (FDR) correction at $q = 0.05$ were considered significant. However, findings that reported unadjusted $p < 0.05$ were also reported for completeness. Estimated Marginal Means (EMMs) were computed from *post-hoc* models to estimate ROI thicknesses for each group when applicable. Effect sizes in the form of standardized mean differences were also computed by standardizing ROI-wise cortical thickness measurements and re-running the models.[41]

All models were checked for homogeneity of within strata variance via Fligner-Killeen test and normality of residuals via Q-Q plots.

RESULTS

Participants and Matching

Prior to matching, 407 CI participants were identified from ADNI. 23.6% of the participants exhibited apathy ($n = 96$). There were no significant differences in mean age, sex, or number of APOE4 alleles between participants with and without apathy. Participants with apathy had lower MMSE and MoCA scores, greater FAQ and CDR scores, and were more frequently diagnosed with AD dementia rather than MCI compared to participants without apathy. Comparisons between the original set of CI participants with apathy to the matched CI participants with apathy are summarized in Supplemental Digital Content (see Supplementary Results and Supplementary Table 1).

After CEM, 36 strata containing at least 1 participant with apathy and at least 1 participant without apathy were identified. Within these strata, 69 participants with apathy were matched to 149 participants without apathy. Comparing the matched participants with apathy to the matched participants without apathy, there were no significant strata-wise differences in mean age, sex, number of APOE4 alleles, MMSE scores, and diagnosis. Matched participants with apathy had significantly greater FAQ scores and CDR subscores for measures related to functional impairment. The CDR orientation subscore was also greater amongst matched participants with apathy.

CI participant demographics for the original and matched data are summarized in **Table 1** and **Table 2**. Balance statistics for match variables show that CEM was effective at minimizing differences in match variable means and frequencies between CI participants with apathy matched to those without apathy; these results are summarized in Supplemental Digital Content (see Supplementary Results and Supplementary Table 2).

Cortical Regions of Interest Analysis

ROI differences are with respect to a participant with apathy relative to an age-, sex-, APOE4 carrier status-, MMSE score-, and MCI or AD diagnosis-matched participant without apathy. No mixed-effects models showed gross violations of strata-wise homoscedasticity or deviations from normality. **Figure 1** describes results from *post-hoc* univariate models for ROIs that showed uncorrected $p < 0.05$.

As indicated by the apathy x ROIs interaction in the mixed-effects analysis, relative ROI-wise differences in cortical thicknesses between CI participants with and without apathy were detected

TABLE 1. Demographics of Cognitively Impaired Participants from the Original Data

	All CI Participants		CI With Apathy		CI Without Apathy		Statistic[a]	df	p
N	407		96		311				
Age (SD), years	74.84	(7.57)	75.76	(6.40)	74.56	(7.89)	t = -1.514	191.89	0.1317
Sex							χ^2 = 2.406	1	0.1209
Female (%)	172	(42.3)	34	(35.4)	138	(44.4)			
Male (%)	235	(57.7)	62	(64.6)	173	(55.6)			
Education (SD), years	16.12	(2.69)	15.72	(2.78)	16.24	(2.66)	t = 1.637	152.45	0.1037
APOE4							χ^2 = 3.490	2	0.1746
Non-carrier (%)	195	(47.9)	38	(39.6)	157	(50.5)			
Heterozygous carrier (%)	160	(39.3)	44	(45.8)	116	(37.3)			
Homozygous carrier (%)	52	(12.8)	14	(14.6)	38	(12.2)			
MMSE (SD)	25.61	(4.41)	23.66	(4.53)	26.22	(4.19)	t = 4.929	148.67	**<0.0001**
CDR									
Sum of Functional Subscales (SD)	1.07	(1.38)	2.06	(1.45)	0.76	(1.20)	χ^2 = 64.315	1	**<0.0001**
Personal Care (SD)	0.18	(0.42)	0.38	(0.57)	0.12	(0.34)	χ^2 = 28.331	1	**<0.0001**
Community Affairs (SD)	0.41	(0.51)	0.78	(0.51)	0.30	(0.46)	χ^2 = 63.893	1	**<0.0001**
Home & Hobbies (SD)	0.48	(0.61)	0.91	(0.61)	0.35	(0.54)	χ^2 = 60.251	1	**<0.0001**
Sum of Cognitive Subscales (SD)	1.82	(1.39)	2.67	(1.28)	1.55	(1.32)	χ^2 = 46.588	1	**<0.0001**
Judgement & Problem Solving (SD)	0.55	(0.48)	0.83	(0.43)	0.47	(0.46)	χ^2 = 42.364	1	**<0.0001**
Memory (SD)	0.76	(0.49)	1.01	(0.47)	0.68	(0.46)	χ^2 = 32.469	1	**<0.0001**
Orientation (SD)	0.50	(0.56)	0.83	(0.55)	0.40	(0.52)	χ^2 = 42.370	1	**<0.0001**
Sum of Boxes (SD)	2.89	(2.66)	4.73	(2.52)	2.31	(2.43)	χ^2 = 59.844	1	**<0.0001**
MoCA (SD)	21.45	(5.45)	19.04	(5.29)	22.17	(5.30)	t = 4.952	148.01	**<0.0001**
FAQ (SD)	7.48	(8.51)	13.24	(8.22)	5.70	(7.80)	t = -7.944	151.48	**<0.0001**
Diagnosis							χ^2 = 46.223	1	**<0.0001**
MCI (%)	266	(65.4)	35	(36.5)	231	(74.3)			
Dementia (%)	141	(34.6)	61	(63.5)	80	(25.7)			
NPI Apathy							t = -15.384	95.00	**<0.0001**
Mean score (SD)	1.02	(2.26)	4.31	(2.75)	0.00	(0.00)			
Score = 0 (%)	311	(76.4)	0	(0.0)	311	(100.0)			
Score ≥ 1 (%)	96	(23.6)	96	(100.0)	0	(0.0)			

p-values below 0.05 are bolded and are considered significant findings.

APOE4 = apolipoprotein E, epsilon 4 allele; CDR = Clinical Dementia Rating Scale; CI = cognitive impairment; df = degrees of freedom; FAQ = Functional Activities Questionnaire; MCI = mild cognitive impairment; MMSE = Mini-Mental State Exam; MoCA = Montreal Cognitive Assessment; NPI = Neuropsychiatric Inventory; p = p-value; SD = standard deviation; t = t-statistic; χ^2 = chi-square statistic.

[a] Tests were performed with Welch's t-test for means, Pearson's chi-squared test for independence of frequencies/counts, and the Cochran-Armitage test for trend for CDR scores and related subscales.

($F_{23,4,975.73} = 3.16$, $p < 0.0001$). FDR-adjusted *post-hoc* analyses showed that the right mOFC and left rACC were thinner in participants with apathy, whereas the left MTC was thicker in participants with apathy. For ROIs that showed uncorrected $p < 0.05$, **Table 3** lists results for *post-hoc* univariate ANOVAs, and **Table 4** lists EMMs for cortical thicknesses by ROI.

Additional analyses and their respective methods and results are described in the Supplemental Digital Content. This includes (1) results from *post-hoc* univariate ANOVAs, EMMs, and descriptive statistics for all ROIs considered in the main analysis (see Supplementary Tables 3 to 5), provided for completeness; (2) results from mixed-effects ANOVAs for all ROIs in the main analysis comparing the effect size of apathy by MCI or AD dementia diagnosis (see Supplementary Table 6), performed to clarify whether differences in ROI-wise cortical thickness between persons with and without apathy differ amongst persons with MCI or AD dementia; (3) comparisons across all CI participants from the original data (i.e., unmatched) for ROIs that showed unadjusted p0.05 (see Supplementary Table 7), performed to confirm whether these ROI-wise differences could be generalized to unmatched participants in ADNI2, and (4) comparisons between CI participants with apathy matched to both CI participants without apathy and CN participants for ROIs that showed unadjusted $p < 0.05$ (see Supplementary Tables 8 to 13), performed to contextualize relative differences in these ROIs with respect to healthy brains.

TABLE 2. Demographics of Cognitively Impaired Participants from the Matched Data

	All Matched CI[b]		Matched CI With Apathy		Matched CI Without Apathy[b]		Statistic[a]	df	p
N	218		69		149				
Age (SD), years	75.95	(6.06)	75.99	(6.07)	75.93	(6.07)	t = 0.282	180.85	0.7779
Sex							χ^2 = 0.000	1	1.0000
Female (%)	88.46	(40.6)	28	(40.6)	60.46	(40.6)			
Male (%)	129.54	(59.4)	41	(59.4)	88.54	(59.4)			
Education (SD), years	15.89	(2.89)	15.97	(2.81)	15.86	(2.94)	t = 0.312	181.91	0.7553
APOE4							χ^2 = 1.490	2	0.4746
Non-carrier (%)	85.30	(39.1)	27	(39.1)	58.30	(39.1)			
Heterozygous carrier (%)	102.72	(47.1)	35	(50.7)	67.72	(45.4)			
Homozygous carrier (%)	29.98	(13.8)	7	(10.1)	22.98	(15.4)			
MMSE (SD)	24.96	(3.97)	25.07	(3.86)	24.91	(4.04)	t = 1.087	180.84	0.2786
CDR									
Sum of Functional Subscales (SD)	1.45	(1.39)	1.91	(1.56)	1.24	(1.25)	χ^2 = 23.451	1	**<0.0001**
Personal Care (SD)	0.26	(0.50)	0.36	(0.59)	0.22	(0.44)	χ^2 = 6.491	1	**0.0108**
Community Affairs (SD)	0.56	(0.49)	0.69	(0.52)	0.50	(0.46)	χ^2 = 16.975	1	**<0.0001**
Home & Hobbies (SD)	0.63	(0.61)	0.86	(0.65)	0.52	(0.57)	χ^2 = 26.923	1	**<0.0001**
Sum of Cognitive Subscales (SD)	2.24	(1.30)	2.36	(1.18)	2.18	(1.36)	χ^2 = 3.715	1	0.0539
Judgement & Problem Solving (SD)	0.71	(0.46)	0.75	(0.42)	0.69	(0.48)	χ^2 = 2.369	1	0.1238
Memory (SD)	0.88	(0.47)	0.90	(0.43)	0.88	(0.49)	χ^2 = 0.290	1	0.5899
Orientation (SD)	0.64	(0.52)	0.71	(0.52)	0.61	(0.51)	χ^2 = 4.888	1	**0.0270**
Sum of Boxes (SD)	3.69	(2.54)	4.27	(2.55)	3.42	(2.50)	χ^2 = 16.888	1	**<0.0001**
MoCA (SD)	19.91	(5.30)	20.06	(5.06)	19.84	(5.43)	t = 0.541	174.27	0.5890
FAQ (SD)	10.22	(8.09)	11.87	(8.31)	9.46	(7.90)	t = 3.399	179.92	**0.0008**
Diagnosis							χ^2 = 0.000	1	1.0000
MCI (%)	98	(44.9)	31	(44.9)	66.94	(44.9)			
Dementia (%)	120	(55.1)	38	(55.1)	82.06	(55.1)			
NPI Apathy							t = 19.041	194.61	**<0.0001**
Mean score (SD)	1.32	(2.47)	4.16	(2.73)	0.00	(0.00)			
Score = 0 (%)	149.00	(68.3)	0	(0.0)	149.00	(100.0)			
Score ≥ 1 (%)	69.00	(31.7)	69	(100.0)	0.00	(0.00)			

p-values below 0.05 are bolded and are considered significant findings.

APOE4 = apolipoprotein E, epsilon 4 allele; CDR = Clinical Dementia Rating Scale; CEM = coarsened exact matching; CI = cognitive impairment; CMH = Cochran-Mantel-Haenszel; df = degrees of freedom; FAQ = Functional Activities Questionnaire; MCI = mild cognitive impairment; MMSE = Mini-Mental State Exam; MoCA = Montreal Cognitive Assessment; NPI = Neuropsychiatric Inventory; SD = standard deviation; p = p-value; t = t-statistic; χ^2 = chi-square statistic.

[a] Tests for stata-wise differences in means were performed with linear mixed-effects models adjusted by CEM weights, using CEM strata as a random effect. This approach generalizes the dependent samples t-test for paired data to stratified data. Tests for strata-wise independence (i.e. conditional independence) or trend (for CDR only) were performed with the generalized CMH test, using CEM weights as frequencies. The CMH statistic for general association is reported for tests of independence, whereas the CMH statistic for differences in row mean scores is reported for tests of trend where matched CI participants with or without apathy were represented as rows. This approach similarly generalizes McNemar's test for paired data to stratified data.

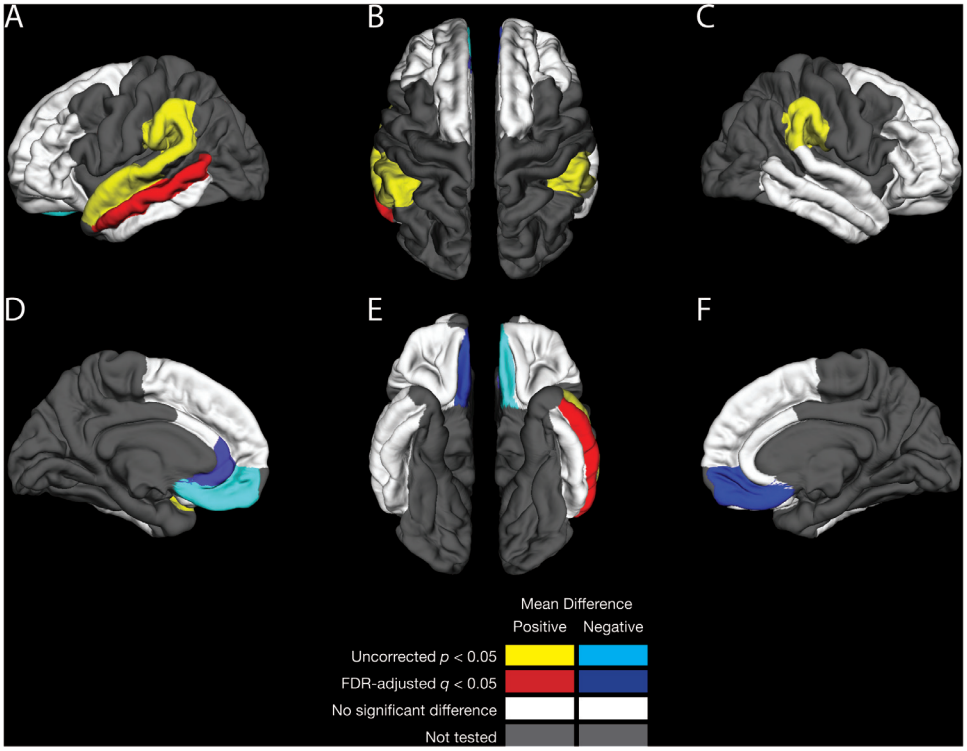
[b] Weighted means and counts were computed using CEM weights.

DISCUSSION

This study investigated the relative structural brain differences between CI participants with and without apathy from the ADNI2 database. We observed that cortical GM was thinner in the right mOFC and left rACC and thicker in the left MTC in CI participants with apathy relative to CI participants without apathy.

A strength of this study is the ability to detect relative differences between participants with and without apathy that share demographic and genetic characteristics, as well as levels of global cognitive impairment (i.e. within-strata differences). Previous studies have shown that measures of global cognitive impairment such as MMSE are correlated with whole-brain GM atrophy in AD.[42] However, since apathy is also associated with brain atrophy and cognitive impairment,[43] cognitive impairment is an important confounder when considering which brain regions mediate apathy across varying severities of neurodegenerative disease. Similar rationale applies

FIGURE 1. Cortical Regions of Interest Associated with Apathy in Cognitively Impaired Participants. ROIs that reported uncorrected $p < 0.05$ between participants with and without apathy on the fsaverage brain from FreeSurfer. Yellow- and cyan-coloured regions indicate uncorrected $p < 0.05$. Red- and blue-coloured regions indicate significant differences (FDR-adjusted $q < 0.05$). White regions indicate no significant difference (uncorrected $p > 0.05$), and grey regions were not tested. Positive mean differences (red and yellow regions) indicate that the ROI was thicker while negative mean differences (blue and cyan regions) indicate that the ROI was thinner in CI persons with apathy relative to matched CI persons without apathy. Estimated marginal means and mean differences between participants with and without apathy are reported in Table 4, and ROI-wise descriptive statistics are reported in Supplementary Table 5. (A) Left lateral perspective. (B) Superior perspective. (C) Right lateral perspective. (D) Left medial perspective. (E) Inferior perspective. (F) Right medial perspective. CI = cognitive impairment; FDR = false discovery rate; ROI = region of interest.



for the use of MCI or AD diagnosis as a match variable and motivates its inclusion. Additionally, the reported link between APOE4 carrier status, risk of incident dementia, and apathy motivates the use of APOE4 as a match variable.[44] Other match variables, like age and sex, are also associated with differences in GM and could also contribute to confounding.[31] Thus, the use of match strata as a pseudovariable for match variables in this study, which was operationalized as random factors in the mixed-effects models, should provide control for strata-wise differences that might otherwise have been explained by underlying group-wise differences within the match variables.

Matching was effective in reducing imbalance between CI participants with and without apathy even on variables which were not explicitly used as match variables (e.g., years of education, the MoCA, and CDR cognitive subscale scores with the exception of the CDR orientation subscale). However, we note that CI participants with apathy had worse functional impairment, as indicated by clinical assessment scores from the FAQ and CDR functional subscales. One could assert that failing to account for these differences may have led to bias in the selection of matched controls or could otherwise explain strata-wise differences in cortical thickness. Consequently, the effects observed might be attributed to differences in functional impairment rather than apathy. However, the deficits in goal-directed behaviours and related phenomena assessed by the NPI apathy questionnaire are similarly examined in the CDR functional subscales and the FAQ. As a result, measures of functional

TABLE 3. Mixed-effects ANOVA for Grey Matter Thicknesses by Cortical Regions of Interest for the Main Analysis

Model	Effect	SS (Effect)	Mean SS (Effect)	Numerator df	Denominator df [a]	F	p	
Omnibus	Apathy	0.52	0.52	1	185.29	0.78	0.3768	
Mixed-effects	**ROIs**	**33.03**	**1.44**	**23**	**4,975.73**	**2.16**	**0.0011**	
ANOVA	Apathy x ROIs	48.32	2.10	23	4,975.73	3.16	<0.0001	
Post-hoc Mixed-effects Univariate ANOVAs	**ROI**	**SS (Apathy)**	**Numerator df**	**Denominator df[a]**	**F**	**p**	**q**	**R^{2b}**
	R Medial Orbitofrontal	**0.3640**	**1**	**176.91**	**11.66**	**0.0008**	**0.0190**	**0.0222**
	L Rostral Anterior Cingulate	**0.3862**	**1**	**181.45**	**7.76**	**0.0059**	**0.0472**	**0.0171**
	L Medial Orbitofrontal	0.1976	1	184.80	6.04	0.0149	0.0717	0.0134
	L Superior Temporal	0.1266	1	181.43	5.07	0.0255	0.0876	0.0097
	L Supramarginal Area	0.0836	1	181.60	5.07	0.0255	0.0876	0.0097
	R Supramarginal Area	0.1159	1	180.24	7.01	0.0088	0.0528	0.0129
	L Middle Temporal	**0.2235**	**1**	**179.98**	**8.31**	**0.0044**	**0.0472**	**0.0159**

Models were fitted with the restricted maximum likelihood criteria, and results from Type III SS tests are reported for fixed-effects only (i.e. the unique variance attributed to a given effect when all other effects and their interactions are considered). CEM match strata were entered as random factors, serving as a pseudovariable for the match variables of age, sex, APOE4 carrier status, MMSE, and MCI or AD diagnosis. Participant IDs were also entered as random factors in the omnibus model to adjust for within-subject variation across ROI thicknesses.

For the omnibus model, rows containing p-values below 0.05 are bolded and are considered significant findings.

For the post-hoc *univariate models, rows are sorted by increasing t-values for differences in Estimated Marginal Means. (See* ***Table 4****) Rows containing FDR-adjusted q-values below 0.05 are bolded and are considered significant findings. Rows containing uncorrected p-values below 0.05 are identified for completeness. See Supplementary Table 3 for the complete list of results for all ROIs tested.*

AD = Alzheimer's disease; ANOVA = analysis of variance; APOE4 = apolipoprotein E, epsilon 4 allele; CEM = coarsened exact matching; df = degrees of freedom; F = F-statistic; MMSE = Mini-Mental State Examination; MCI = mild cognitive impairment; p = p-value; ROIs = regions of interest; R^2 = partial coefficient of determination; SS = sum of squares.

[a] Satterthwaite's method was used to estimate denominator degrees of freedom.

[b] Nakagawa and Schielzeth's approach was used to estimate partial R^2 for the effect of apathy.

impairment would likely exhibit a high degree of collinearity with apathy as measured by NPI, and this collinearity would not necessarily be reducible. Thus, that CI participants with apathy appeared to have worse functional impairment is expected. Previous studies have also identified the association between apathy and functional impairment.[45,46] With respect to the CDR orientation subscale, a previous study also reported an association between apathy and MMSE items related to temporal orientation; the authors suggest that disorientation could manifest due to apathy itself rather than reflect cognitive deficits.[47]

Our study partially corroborates findings from previous structural MRI studies on apathy in patients with AD. While atrophy in medial frontal areas is a common feature amongst studies investigating apathy, the specific regions identified as having an association with apathy often differ. Atrophy in the ACC is frequently reported,[9,11,12,48–50] though findings vary by laterality ([bilateral][9,11,12,49,50]; [left only][48]) and by region ([caudal and rostral][11,49,50]; [caudal only][9,12,48]). Findings in the orbitofrontal cortex are similarly common,[9,11,48,49] again with differences by laterality ([bilateral][9,11,49]; [left only][48]) and by region ([medial and lateral][11]; [medial only][49]; [lateral only][9,48]). Our study confirms that thinning in the right mOFC and left rACC is associated with apathy. Effect size statistics suggest moderate-sized effects, though the magnitudes of the strata-wise mean differences were small−−about one-tenth of a millimeter, or about 2% of the variation in cortical thicknesses. Meanwhile, the direction of mean differences for the left mOFC, right rACC, and bilateral caudal anterior cingulate cortex appear to be consistent with prior studies; however, these ROI-wise differences were not significant, so we can neither confirm nor refute associations with apathy amongst these ROIs. Nevertheless, the lack of statistically significant differences amongst these ROIs in our study does not necessarily imply a broader dearth of clinically and/or scientifically meaningful differences, especially given emerging theories on the neuroanatomical structures that may mediate goal-directed behaviour and apathy. With specific regard to the left mOFC, since measures of effect size do not depend on sample size, and since the effect size statistic for the significant left rACC ($d = -0.3754$) was nearly identical to the non-

TABLE 4. Estimated Marginal Means for Cortical Thicknesses by Regions of Interest

ROI	Estimated Marginal Mean (SE), mm		Mean Difference (SE), mm	df	t	p	d
	Matched CI With Apathy	*Matched CI Without Apathy*					
R Medial Orbitofrontal	**2.26**	**2.35**	**−0.0879**	**176.91**	**−3.4152**	**0.0008**	**−0.4456**
L Rostral Anterior Cingulate	**2.62**	**2.71**	**−0.0905**	**181.45**	**−2.7863**	**0.0059**	***−0.3574***
L Medial Orbitofrontal	2.23	2.29	−0.0647	184.80	−2.4570	0.0149	−0.3570
L Superior Temporal	2.51	2.46	0.0518	181.43	2.2516	0.0255	0.2493
L Supramarginal Area	2.31	2.27	0.0421	181.60	2.2517	0.0255	0.2603
R Supramarginal Area	2.31	2.26	0.0496	180.24	2.6483	0.0088	0.3233
L Middle Temporal	**2.60**	**2.53**	**0.0688**	**179.98**	**2.8826**	**0.0044**	**0.3311**

Rows are sorted by increasing t-values for differences in estimated marginal means. Only ROIs that reported uncorrected p-values below 0.05 in their respective post-hoc *univariate ANOVA are reported. (See* ***Table 3****) Bolded rows reported FDR-adjusted q-values below 0.05 in their respective ANOVA and are considered significant findings. See Supplementary Table 4 for the complete list of results for all ROIs tested.*

ANOVA = analysis of variance; d = standardized mean difference; df = degrees of freedom; FDR = false discovery rate; p = p-value; ROI = region of interest; SE = standard error of the mean; SS = sum of squares; t = t-statistic.

significant left mOFC ($d = -0.3750$), our study may have been underpowered to detect a significant difference in this ROI.

Both the ACC and ventromedial prefrontal cortex have frequently been implicated in the manifestation of apathy in AD in other neuroimaging modalities[2, 6–8, 51] as well as across neurocognitive and neurodegenerative disorders.[6,7] Two recent studies also performed positron emission tomography (PET) imaging of amyloid-β and tau, proteins putatively involved in the neuropathology of AD, amongst AD patients with apathy.[46,52] Regional tau burden in the bilateral orbitofrontal cortex[52] and right ACC[46] was associated with apathy, while regional amyloid-β burden was not associated with apathy.[52] Discrepant findings could be attributed to the use of different covariates or tau radiotracers; nonetheless, our study partially corroborates these PET findings and supports the notion that neuropathological differences may underlie apathy in AD. Separately, it was proposed that deficits within a medial frontostriatal network responsible for goal-directed behaviour may manifest as apathy.[5] Thus, atrophy of the ventromedial prefrontal cortex may be associated with impairments in the ability to assess the subjective value of a given action, while atrophy in the rACC may be associated with impairments in appropriately activating the motor system towards value-directed behaviours.[5]

Our results also suggest that CI participants with apathy have a sparing of atrophy in the left MTC relative to CI participants without apathy. This sparing is similar to an earlier finding of increased regional cerebral blood flow in the left medial superior temporal gyrus and middle medial temporal gyrus in patients with apathy relative to patients without apathy, even when adjusting for differences in MMSE.[53] Moreover, a recent study observed that apathy was associated with hypoperfusion in the left inferior and middle temporal gyri.[54] However, this study did not control for differences in dementia diagnoses or cognitive impairment.[54] Other studies have found apathy to be associated with hypoperfusion of the right temporoparietal[55] and anterior temporal[56] areas.

Additional subanalyses in the Supplemental Digital Content shed further light toward the specific brain regions associated with apathy in cognitively impaired persons. When mixed-effects ANOVAs in the main analysis were recomputed with additional fixed-effects for MCI or AD diagnosis and the apathy

x diagnosis interaction, significant ROI-wise differences identified in the main analysis (right mOFC, left rACC, and left MTC) remained significant across diagnostic groups (see Supplementary Table 6). Standardized mean differences associated with apathy also shared the same sign and were about the same magnitude compared to those reported in the main analysis. Moreover, no significant apathy x diagnosis interaction was detected for these ROIs, indicating that the effect of apathy in MCI participants was not significantly different from the effect of apathy in AD dementia participants. Further subanalyses involving CI participants with apathy matched to CI and CN participants without apathy showed that thinner cortical thicknesses in the right mOFC and left rACC were specific to CI participants with apathy (see Supplementary Table 13). For the left MTC, only CI participants *without* apathy showed thinner cortical thicknesses relative to CN participants (see Supplementary Table 13).

While significant ROI-wise differences in the main analysis were not significant when tested in a subanalysis using the original (nonmatched) data and a fixed-effects analysis of covariance model (see Supplementary Table 7), the sign of mean differences associated with apathy was the same as those reported in the main analysis. Nevertheless, we caution against interpreting the lack of significant results as discrepant with the main analysis, since the assumption of mutual independence of the fixed effects was not met (the match variables exhibit multicollinearity) and the interaction effects between match variables was ignored. These limitations are implicitly addressed *via* our use of matching and random effects in the main analysis. Thus, compared to the main analysis, results from the fixed-effects model in Supplementary Table 7 have limited construct validity and reduced statistical power. Taken together, these findings provide strong, confirmatory evidence of a specific but moderate association that links thinning in right mOFC and left rACC with apathy. They also affirm that apathy is associated with sparing of atrophy in the left MTC.

Apathy has also been associated with thinning of the inferior temporal cortex in two studies,[13, 57] including one that also used data from ADNI.[13] Although we were not able to replicate this association, we note several methodological differences. First, Donovan et al.[13] examined cortical thickness at baseline as related to worsening apathy over time, whereas we examined cortical thickness in a cross-sectional analysis at the time of neuropsychiatric assessment. Second, both studies examined averaged bilateral cortical thicknesses, whereas we examined left and right ROIs independently. Given that our study shows differences between left and right ROIs associated with apathy, the use of averaged measures could have obscured underlying relationships in these earlier studies. Third, both studies used stepwise backward elimination regression models to select covariates from a larger set of candidate variables, while we used a mixed model approach to incorporate match variables that were identified as potential confounders as a random effect through CEM strata. Differences in methods for statistical control could explain the discrepant findings. We note that, despite its convenience and popularity, the use of stepwise regression has long been criticized in statistical literature as an inappropriate statistical procedure.[58]

Another ADNI study found that apathy was associated with GM atrophy in bilateral lateral temporal areas.[14] Although Hu et al. did not report this association after adjusting for MMSE, our finding of cortical thinning in the left STC of both CI participants with apathy and without apathy relative to age-, sex-, and APOE4 carrier status-matched CN controls (see Supplementary Table 13) partially corroborates this finding. Given that both CI groups showed cortical thinning in the left STC, these findings suggest that the sparing of atrophy in the left MTC may not necessarily extend to the left STC.

Nonetheless, several studies have reported negative findings with respect to cortical GM differences in apathy.[59–62] However, the lack of findings could be attributed to several factors, such as examining advanced-stage AD patients, who may exhibit severe GM atrophy;[59] examining patients with prodromal AD, who may not yet have detectable regional GM atrophy;[60,61] or investigating differences by lobe rather than by region or voxel.[62]

There are several limitations associated with our current investigation. First, while the NPI is recognized as a gold-standard assessment for neuropsychiatric symptoms in dementia, it cannot differentiate between subdomains of apathy.[2] Thus, we cannot make direct inferences about how the brain regions we have identified might mediate the subdomains of

apathy. In light of growing research interest in apathy and its dimensions, we recommend that multi-site clinical trials administer more sophisticated measures of apathy to facilitate research in this area, such as the Dimensional Apathy Scale[63] or the Apathy Inventory.[64] Second, although apathy and depression are both associated with an increased risk of dementia, our study only examines effects associated with apathy. Consequently, any associations with apathy identified in this study are not necessarily independent of depression. However, at the time of screening, ADNI2 excluded participants with any history of major depression within the last year, as well as any participants that reported GDS scores equal to or greater than six, which would reduce the magnitude and likelihood of finding effects attributable to depression. Also, previous neuroimaging studies support the notion that apathy and depression may have distinct anatomical and functional correlates in AD.[2]

Finally, our study examined a cross-sectional sample of cognitively impaired participants from ADNI, so it is unclear whether the observed thinning of the right mOFC and left rACC reflects a discrete neurodegenerative process that happens to develop concurrently with AD. Longitudinal studies that control for differences in Braak staging[15] and could clarify whether ROI-wise neurodegeneration associated with apathy progresses independently from typical AD neuropathology. Moreover, recent literature has highlighted that dimensions of apathy may be mediated by distinct brain regions.[2] Future investigations should aim to characterize associations between the cognitive-behavioural, emotional, and social interaction dimensions of apathy,[65] which may help to identify and guide treatment strategies for apathy in future.

CONCLUSIONS

We investigated the structural neurocorrelates associated with apathy in older adults with cognitive impairment. Using a case-control approach, we matched CI participants from ADNI2 with and without apathy on age, sex, APOE4 carrier status, MMSE score, and MCI or AD diagnosis. We found that apathy was uniquely associated with thinner right mOFC and left rACC. Compared to participants without apathy, participants with apathy also had thicker left MTC. However, our supplementary analyses, which matched participants by age, sex, and APOE4 carrier status only, showed that the left MTC was thinner in both groups compared to CN participants. Further research is warranted to investigate the structural neurocorrelates associated with subdomains of apathy.

AUTHORS' CONTRIBUTIONS

N.K.C. and A.G.G. conceived the idea. P.G., M.M.C., D.M.B., F.C., and E.B. contributed to the study concepts. N.K.C., P.G., M.M.C., D.M.B., and A.G.G. planned the study design, developed the research questions, and considered the analytical approaches. N.K.C. and M.M.C. discussed the statistical and computational approaches and verified the methods. N.K.C. retrieved the data, performed the analyses, drafted the manuscript, and designed the figures. F.C. and E.B. reviewed the draft manuscript and made critical early revisions. P.G. and A.G.G. supervised the writing process. All authors contributed to the manuscript, provided feedback for the interpretation of findings, and have approved the final manuscript.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jagp.2020.12.008.

References

1. Assoc As: 2018 Alzheimer's disease facts and figures. Alzheimers. Dement. 2018; 14:367–425
2. Lanctot KL, Aguera-Ortiz L, Brodaty H, et al: Apathy associated with neurocognitive disorders: Recent progress and future directions. Alzheimers. Dement. 2017; 13:84–100
3. van Dalen JW, van Wanrooij LL, van Charante EPM, et al: Association of Apathy With Risk of Incident Dementia A Systematic Review and Meta-analysis. Jama Psychiatry 2018; 75:1012–1021
4. Bock MA, Bahorik A, Brenowitz WD, et al: Apathy and risk of probable incident dementia among community-dwelling older adults. Neurology 2020
5. Le Heron C, Holroyd CB, Salamone J, et al: Brain mechanisms underlying apathy. J Neurol Neurosurg Psychiatry 2019; 90:302–312

6. Le Heron C, Apps MAJ, Husain M: The anatomy of apathy: A neurocognitive framework for amotivated behaviour. Neuropsychologia 2018; 118:54–67
7. Kos C, van Tol M-J, Marsman J-BC, et al: Neural correlates of apathy in patients with neurodegenerative disorders, acquired brain injury, and psychiatric disorders. Neurosci. Biobehav. Rev. 2016; 69:381–401
8. Theleritis C, Politis A, Siarkos K, et al: A review of neuroimaging findings of apathy in Alzheimer's disease. Int. Psychogeriatr. 2014; 26:195–207
9. Bruen PD, McGeown WJ, Shanks MF, et al: Neuroanatomical correlates of neuropsychiatric symptoms in Alzheimers disease. Brain 2008; 131:2455–2463
10. Huey ED, Lee S, Cheran G, et al: Brain regions involved in arousal and reward processing are associated with apathy in Alzheimer's Disease and frontotemporal dementia. J. Alzheimers Dis. 2017; 55:551–558
11. Kumfor F, Zhen A, Hodges JR, et al: Apathy in Alzheimer's disease and frontotemporal dementia: Distinct clinical profiles and neural correlates. Cortex 2018; 103:350–359
12. Apostolova LG, Akopyan GG, Partiali N, et al: Structural correlates of apathy in Alzheimer's disease. Dement. Geriatr. Cogn. Disord. 2007; 24:91–97
13. Donovan NJ, Wadsworth LP, Lorius N, et al: Regional cortical thinning predicts worsening apathy and hallucinations across the Alzheimer Disease Spectrum. Am. J. Geriatr. Psychiatry 2014; 22:1168–1179
14. Hu X, Meiberth D, Newport B, et al: Anatomical correlates of the neuropsychiatric symptoms in Alzheimer's Disease. Current Alzheimer Research 2015; 12:266–277
15. Braak H, Braak E: Neuropathological staging of Alzheimer-related changes. Acta Neuropathol 1991; 82:239–259
16. Mueller SG, Weiner MW, Thal LJ, et al: Ways toward an early diagnosis in Alzheimer's disease: the Alzheimer's Disease Neuroimaging Initiative (ADNI). Alzheimers Dement 2005; 1:55–66
17. Rosen WG, Terry RD, Fuld PA, et al: Pathological verification of ischemic score in differentiation of dementias. Ann Neurol 1980; 7:486–488
18. Sheikh JI, Yesavage JA: Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. Clinical Gerontologist: The Journal of Aging and Mental Health 1986; 5:165–173
19. Folstein MF, Folstein SE, McHugh PR: Mini-Mental State", a practical method for grading cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189–198
20. Nasreddine ZS, Phillips NA, Bedirian V, et al: The montreal cognitive assessment, MoCA: A brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005; 53:695–699
21. Berg L: Clinical Dementia Rating (Cdr). Psychopharmacol Bull 1988; 24:637–639
22. Pfeffer RI, Kurosaki TT, Harrah CH, et al: Measurement of functional activities in older adults in the community. J Gerontol 1982; 37:323–329
23. Cummings JL, Mega M, Gray K, et al: The neuropsychiatric inventory - comprehensive assessment of psychopathology in dementia. Neurology 1994; 44:2308–2314
24. Tractenberg RE, Weiner MF, Cummings JL, et al: Independence of changes in behavior from cognition and function in community-dwelling persons with Alzheimer's disease: a factor analytic approach. J Neuropsychiatry Clin Neurosci 2005; 17:51–60
25. Jack CR, Barnes J, Bernstein MA, et al: Magnetic resonance imaging in Alzheimer's Disease Neuroimaging Initiative 2. Alzheimers. Dement. 2015; 11:740–756
26. Ponce MvZ Ramses, Northrup Scott, Gruner Daniel, et al: Deploying a Top-100 Supercomputer for Large Parallel Workloads: The Niagara Supercomputer. Chicago, IL, USA: ACM, 2019
27. Loken C, Gruner D, Groer L, et al: SciNet: Lessons Learned from Building a Power-efficient Top-20 System and Data Centre. J. Phys. Conf. Ser. 2010; 256:012026
28. Desikan RS, Segonne F, Fischl B, et al: An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 2006; 31:968–980
29. Raamana PR, Theyers A, Selliah T, et al: VisualQC: Assistive tools for easy and rigorous quality control of neuroimaging data. 2018
30. Klapwijk ET, van de Kamp F, van der Meulen M, et al: Qoala-T: A supervised-learning tool for quality control of FreeSurfer segmented MRI data. Neuroimage 2019; 189:116–129
31. Sowell ER, Peterson BS, Kan E, et al: Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. Cereb. Cortex 2007; 17:1550–1560
32. Schwarz CG, Gunter JL, Wiste HJ, et al: A large-scale comparison of cortical thickness and volume methods for measuring Alzheimer's disease severity. Neuroimage Clin 2016; 11:802–812
33. Ad-Dab'bagh Y, Singh V, Robbins S, et al: Native-space cortical thickness measurement and the absence of correlation to cerebral volume, in 11th Annual Organization of Human Brain Mapping Meeting. Ontario, Canada: Toronto, 2005
34. Iacus SM, King G, Porro G: Causal inference without balance checking: coarsened exact matching. Polit Anal 2012; 20:1–24
35. Ho DEI Kosuke, King Gary, Stuart Elizabeth A: MatchIt: nonparametric preprocessing for parametric causal inference. J Stat Software 2011; 42:1–28
36. Bates DM Martin, Bolker Ben, Walker Steve: Fitting linear mixed-effects models using lme4. J Stat Software 2015; 67:1–48
37. Kuznetsova AB PB, Christensen RHB: lmerTest Package: tests in linear mixed effects models. J Stat Software 2017; 82:1–26
38. Friendly M, Meyer D: Discrete data analysis with R : visualization and modeling techniques for categorical and count data. 2016
39. Luke SG: Evaluating significance in linear mixed-effects models in R. Behav Res Methods 2017; 49:1494–1502
40. Nakagawa S, Schielzeth H: A general and simple method for obtaining R2 from generalized linear mixed-effects models. Methods Ecol Evol 2013; 4:133–142
41. Lorah J: Effect size measures for multilevel models:definition, interpretation, and TIMSS example. Large-Scale Assess E 2018; 6:8
42. Fjell AM, Amlien IK, Westlye LT, et al: Mini-mental state examination is sensitive to brain atrophy in Alzheimer's Disease. Dement. Geriatr. Cogn. Disord. 2009; 28:252–258
43. Lavretsky H, Zheng L, Weiner MW, et al: The MRI brain correlates of depressed mood, anhedonia, apathy, and anergia in older adults with and without cognitive impairment or dementia. Int. J. Geriatr. Psychiatry 2008; 23:1040–1050
44. Pink A, Stokin GB, Bartley MM, et al: Neuropsychiatric symptoms, APOE epsilon4, and the risk of incident dementia: a population-based study. Neurology 2015; 84:935–943
45. Boyle PA, Malloy PF, Salloway S, et al: Executive dysfunction and apathy predict functional impairment in Alzheimer disease. Am. J. Geriatr. Psychiatry 2003; 11:214–221
46. Marshall GA, Gatchel JR, Donovan NJ, et al: Regional Tau Correlates of instrumental activities of daily living and apathy in mild cognitive impairment and Alzheimer's Disease Dementia. J. Alzheimers Dis. 2019; 67:757–768
47. Leontjevas R, Fredrix L, Smalbrugge M, et al: Bayesian analyses showed more evidence for apathy than for depression being

associated with cognitive functioning in nursing home residents. J Am Med Dir Assoc 2018; 19:1110–1117
48. Tunnard C, Whitehead D, Hurt C, et al: Apathy and cortical atrophy in Alzheimer's disease. Int. J. Geriatr. Psychiatry 2011; 26:741–748
49. Stanton BR, Leigh PN, Howard RJ, et al: Behavioural and emotional symptoms of apathy are associated with distinct patterns of brain atrophy in neurodegenerative disorders. J Neurol 2013; 260:2481–2490
50. Zahodne LB, Gongvatana A, Cohen RA, et al: Are apathy and depression independently associated with longitudinal trajectories of cortical atrophy in mild cognitive impairment? Am. J. Geriatr. Psychiatry 2013; 21:1098–1106
51. Stella F, Radanovic M, Aprahamian I, et al: Neurobiological correlates of apathy in Alzheimer's Disease and Mild Cognitive Impairment: a critical review. J. Alzheimers Dis. 2014; 39:633–648
52. Kitamura S, Shimada H, Niwa F, et al: Tau-induced focal neurotoxicity and network disruption related to apathy in Alzheimer's disease. J Neurol Neurosurg Psychiat 2018; 89:1208–1214
53. Lanctot KL, Moosa S, Herrmann N, et al: A SPECT study of apathy in Alzheimer's disease. Dement. Geriatr. Cogn. Disord. 2007; 24:65–72
54. Schroeter ML, Vogt B, Frisch S, et al: Dissociating behavioral disorders in early dementia-An FDG-PET study. Psychiat Res-Neuroim 2011; 194:235–244
55. Ott BR, Noto RB, Fogel BS: Apathy and loss of insight in Alzheimer's disease: A SPECT imaging study. J. Neuropsychiatry Clin. Neurosci. 1996; 8:41–46
56. Craig AH, Cummings JL, Fairbanks L, et al: Cerebral blood flow correlates of apathy in Alzheimer disease. Arch Neurol 1996; 53:1116–1120
57. Guercio BJ, Donovan NJ, Ward A, et al: Apathy is associated with lower inferior temporal cortical thickness in mild cognitive impairment and normal elderly individuals. J. Neuropsychiatry Clin. Neurosci. 2015; 27:E22–E27
58. Smith G: Step away from stepwise. J Big Data 2018; 5:32
59. Aguera-Ortiz L, Hernandez-Tamames JA, Martinez-Martin P, et al: Structural correlates of apathy in Alzheimer's disease: a multimodal MRI study. Int. J. Geriatr. Psychiatry 2017; 32:922–930
60. Kim JW, Lee DY, Choo IH, et al: Microstructural alteration of the anterior cingulum is associated with apathy in Alzheimer Disease. Am. J. Geriatr. Psychiatry 2011; 19:644–653
61. Torso M, Serra L, Giulietti G, et al: Strategic lesions in the anterior thalamic radiation and apathy in early Alzheimer's Disease. PLoS One 2015; 10:e0124998
62. Starkstein SE, Mizrahi R, Capizzano AA, et al: Neuroimaging correlates of apathy and depression in Alzheimer's Disease. J. Neuropsychiatry Clin. Neurosci. 2009; 21:259–265
63. Radakovic R, Starr JM, Abrahams S: A novel assessment and profiling of multidimensional apathy in Alzheimer's Disease. J Alzheimers Dis 2017; 60:57–67
64. Robert PH, Clairet S, Benoit M, et al: The apathy inventory: assessment of apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment. Int J Geriatr Psychiatr 2002; 17:1099–1105
65. Robert P, Lanctot KL, Aguera-Ortiz L, et al: Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. Eur Psychiat 2018; 54:71–76