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Are Apathy and Depression Independently Associated with Longitudinal Trajectories of Cortical Atrophy in Mild Cognitive Impairment?

Laura B. Zahodne, Ph.D.[1], **Assawin Gongvatana, Ph.D.**[2,3], **Ronald Cohen, Ph.D.**[2,3], **Brian R. Ott, M.D.**[4,5], and **Geoffrey Tremont, Ph.D.**[2,6] **for the Alzheimer's Disease Neuroimaging Initiative***

[1]Cognitive Neuroscience Division, Department of Neurology and Taub Institute for Research on Alzheimer's Disease and The Aging Brain, Columbia University College of Physicians and Surgeons

[2]Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University

[3]Centers for Behavioral and Preventive Medicine, The Miriam Hospital

[4]Department of Neurology, Rhode Island Hospital

[5]Department of Neurology, Alpert Medical School of Brown University

[6]Department of Psychiatry, Rhode Island Hospital

Abstract

Objective—We sought to examine whether depression and apathy are independently associated with longitudinal trajectories of cortical atrophy in entorhinal cortex compared to frontal subregions previously implicated in late-life mood disturbance.

Design—Data from 334 participants classified as having Mild Cognitive Impairment (MCI) in the Alzheimer's Disease Neuroimaging Initiative (ADNI) were analyzed using multilevel models for change adjusted for age, global cognitive status, and total intracranial volume at enrollment.

Setting—Participants in ADNI were recruited from over 50 clinical research sites in the United States and Canada.

Measurements—Depression and apathy were identified by informants with the Neuropsychiatric Inventory Questionnaire. Serial MRI was carried out on 1.5T scanners according to standardized ADNI-1 protocol on an average of 5 occasions over an average of 2.5 years. Regional cortical thickness values were derived from longitudinal data processing in Freesurfer version 4.4.

Corresponding author: Geoffrey Tremont, Neuropsychology Program, Rhode Island Hospital, 593 Eddy St, POB 430, Providence, RI 02903, Tel: (401) 444-4500, Fax: (401) 444-6643, gtremont@lifespan.org.

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Results—Depression was associated with reduced cortical thickness in the entorhinal cortex at baseline and accelerated atrophy in anterior cingulate cortex. Similarly-sized relationships between depression and orbitofrontal cortex and between apathy and anterior cingulate cortex were not significant.

Conclusions—In MCI, depression signs are a better marker of longitudinal cortical atrophy than apathy. Results are consistent with hypotheses that depression is an early sign of a more aggressive neurodegenerative process or that depression lowers brain reserve capacity, allowing for more rapid progression of AD neuropathology.

Keywords

MRI; Alzheimer's disease; mild cognitive impairment; apathy; depression

Objective

As the population ages and the prevalence of Alzheimer's disease (AD) increases, identifying risk factors for rapid neurodegeneration is increasingly important. Apathy and depression are strongly associated with both brain structural abnormalities (1-2) and dementia conversion (3-4) among individuals with Mild Cognitive Impairment (MCI), a transition state between normal aging and dementia. However, few studies have directly compared the relative prognostic values of apathy and depression in this population. While they can manifest independently, apathy and depression share many of the same features and are often co-morbid (5). Studies attempting to differentiate apathy and depression show unique neuroanatomical correlates (6) among older adults and suggest that apathy, not depression, is a clinical predictor of conversion in MCI (7-8). However, no study has yet examined the unique associations of apathy and depression with longitudinal trajectories of brain atrophy in MCI.

Recently, Alzheimer's Disease Neuroimaging Initiative (ADNI) researchers demonstrated a relationship between depression and longitudinal white matter atrophy in frontal, parietal, and temporal lobes in MCI (9). These authors further showed that individuals with persistent depressive symptoms experienced greater cognitive and functional decline, compared to individuals with no neuropsychiatric symptoms over the two-year study period. However, this study did not examine relationships between apathy and these variables. In addition, the analysis was limited to total lobar changes rather than specific brain regions.

The present study sought to examine associations between apathy and depression and longitudinal trajectories of regional cortical atrophy in a sample of 334 older adults with MCI who participated in ADNI. This study attempted to expand on several aspects of previous work. First, multilevel models for change were employed to measure associations between neuropsychiatric symptoms and both baseline brain structure as well as longitudinal changes in brain structure over four years. Second, both apathy and depression were included in all models in order to examine their unique contributions to structural abnormalities in MCI. Third, rather than total lobar volumes, we examined cortical thickness within specific regions of interest: entorhinal cortex, middle frontal gyrus (MFG), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC). Entorhinal cortex was examined based on evidence that this region exhibits the largest difference between groups of healthy elderly and MCI, and it is a primary focus of atrophy in early AD (10-11). Frontal subregions of MFG, OFC, and ACC were examined based on evidence that these regions are associated with late-life depression or apathy. Depression has been associated with atrophy within both MFG and OFC, whereas apathy has been associated with atrophy within ACC (6,12-13). In addition, atrophy within these frontal subregions has been shown to occur in MCI (11,14-15). We hypothesized that apathy and depression would be differentially

associated with changes in the four regions. Based on the above findings, we predicted that apathy would be related to greater longitudinal atrophy in ACC, while depression would be related to greater longitudinal atrophy in MFG and OFC.

Methods

Alzheimer's Disease Neuroimaging Initiative

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI; http://www.adni.loni.ucla.edu/). The ADNI was initiated in 2003 as a 5-year public-private partnership (see Acknowledgments). The ADNI is a multisite initiative with the overall goal of identifying clinical and biomarker measures across the AD spectrum (16-17). The ADNI recruited healthy older adults, as well as older adults with amnestic MCI or AD, from over 50 sites in the United States and Canada. All participants were followed up at approximately 6-month intervals in an unstructured multicohort longitudinal design. Only data from ADNI-1 were included in the present study. More information can be obtained through www.adni-info.org.

Participants

Data were downloaded from the ADNI website on May 1, 2012. Inclusion criteria for all participants in ADNI-1 were: (1) Hachinski score ≤4; (2) age between 55 and 90; (3) stability of permitted medications for 4 weeks; (4) Geriatric Depression Scale score <6; (5) study partner with 10+ hr/wk contact; (6) adequate visual and auditory acuity; (7) good general health; (8) inability to become pregnant; (9) 6th grade education or work history; (10) fluent in English or Spanish; (11) agreement to study procedures (e.g., neuroimaging, DNA, blood, and urine); and (12) non-enrollment in other trials or studies.

Only participants classified as having MCI at baseline assessment were included in the present study. Diagnosis of amnestic MCI was made based on Petersen/Mayo criteria (18). Inclusion criteria for the MCI group were: (1) memory complaints; (2) abnormal memory function based on education-specific cut scores on Logical Memory II from the Wechsler Memory Scale – Revised; (3) normal activities of daily living; (4) global Clinical Dementia Rating (CDR) and Memory box scores of 0.5; (5) Mini-Mental State Examination (MMSE) scores ≥24.

The present study included 122 females and 212 males with amnestic MCI who ranged in age from 55 to 90 years at study entry (mean=74.9 years; SD=7.3). Participants reported attaining 6 to 20 years of education (mean=15.7 years; SD=3.0). Dichotomous variables representing participant's self-reported smoking status, cardiovascular disease, and endocrine/metabolic disorders were available for a subset (N=147) of the sample. These variables, body mass index, and education were not related to depression or apathy status, as defined below.

All 334 participants underwent MRI on at least 3 separate occasions. 298 underwent MRI on 4 occasions, 239 underwent MRI on 5 occasions, 129 underwent MRI on 6 occasions, and 28 underwent MRI on 7 occasions. The average participant was assessed on 5 occasions (SD=1.1; range: 3 to 7) over 30.5 months (SD=10.3; range: 11.9 to 53.3). The mean length of time between assessments was 7.5 months (SD=2.8; range: 2.2 to 25.4).

Neuropsychiatric assessment

Apathy and depression were measured with the Neuropsychiatric Inventory Questionnaire (NPIQ; 19). The NPIQ is a brief version of the semi-structured Neuropsychiatric Inventory that is completed by an informant. The NPIQ measures 12 behavioral and psychological

domains. Each domain is assessed with a screening question containing core symptom manifestations. Informants are instructed to respond “yes” or “no” to each screening question. In the case of “yes” responses, informants additionally rate the severity of the symptom on a 3-point scale as well as the informant’s subjective distress related to the symptom on a 5-point scale. In the present study, apathy was indexed with item 7 (Does the patient seem less interested in his/her usual activities or in the activities and plans of others?), and depression was indexed with item 4 (Does the patient seem sad or say that s/he is depressed?). Both variables were coded as 0 (not present) or 1 (present) based on informants’ responses to screening questions.

MRI procedures

All participants received high-resolution structural brain MRI scans on 1.5T scanners from General Electric or Siemens according to standardized ADNI protocol (17). While images were acquired on MRI scanners at 56 different sites, ADNI has implemented multiple procedures to minimize cross-site variation, including standardized MRI protocols and acquisition parameters, system-specific post-acquisition corrections for gradient nonlinearity and intensity nonuniformity due to multiple causes, and systematic phantom-based monitoring of instruments (17). Raw 3D T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) images were pre-processed (gradient warping, scaling, B1 correction and N3 in homogeneity correction) by Mayo Clinic and downloaded from the ADNI site by researchers at the University of California, San Francisco (UCSF).

Longitudinal image processing was performed using FreeSurfer version 4.4 by researchers at UCSF (20). Scans from each time point were averaged together to create an unbiased, within-subject template space and “base image” using robust, inverse consistent registration (21-22). This base image was used in place of the FreeSurfer atlas, providing information about structural changes over time and reducing the confound of intra-individual morphological variability. The FreeSurfer image analysis suite is documented and freely available online (http://surfer.nmr.mgh.harvard.edu/) (23). Images that did not pass quality control inspection were excluded from analysis. Variables of interest included cortical thickness of entorhinal cortex, MFG (sum of rostral and caudal MFG), OFC (sum of medial and lateral OFC), and ACC (sum of rostral and caudal ACC). Total intracranial volume (ICV) was included in all models as a covariate.

Statistical Analysis

Data were analyzed in SPSS version 20. The multilevel model (MLM) for change (i.e., growth curve modeling) is a powerful, flexible method for examining longitudinal data over multiple occasions. Models were run using Maximum Likelihood estimation, assuming homoscedasticity and independence of errors (scaled identity with variance components). Outcome variables used in each model were thickness in mm for the cortical regions, averaged between left and right hemispheres. Specifically, cortical thickness values for left and right hemispheres downloaded from the ADNI website were averaged for each region of interest, and these averaged values were used as dependent variables in each multilevel model. Left and right hemispheres were averaged based on inconsistent reports of hemispheric-specific relationships between brain structure and behavioral dysfunction in MCI. Averaging also served to reduce the total number of models run.

For each cortical region, model-building included four stages. *Unconditional means models* have an intercept but no slope, as they assume no change over time for all individuals. In *unconditional growth models*, a continuous time variable reflecting months since study entry was entered as a within-person predictor of the dependent variable. For each region of interest, an unconditional growth model was first tested with linear time only. Then, the

potential for quadratic effects of time was explored. Confirming that there is variance left to explain in both unconditional means and unconditional growth models is a precondition for further analysis in MLM. *Conditional intercept models* were the first theoretical models in which all of the predictors were added to the best fitting unconditional growth model. They estimated the effects of predictor variables (i.e., apathy and depression) and covariates (i.e., age, MMSE, ICV) on intercepts only. All predictor variables and covariates were measured at baseline (i.e., time-invariant). Covariates were chosen based on 1) previous reports of their associations with cortical thickness; and 2) significant univariate relationships with dependent variables in this study. To facilitate interpretation of parameter estimates, covariates were centered at the group means. Specifically, values of zero correspond to a total ICV of 1,574,329mm^2, age of 75, and MMSE of 26. In addition to estimating the effects of predictor variables on intercepts, *conditional growth models* estimate interactions between predictor variables and time. Thus, whether predictor variables moderate trajectories of change can be evaluated. In conditional models, intercepts reflect average cortical thickness when all predictor variables and covariates are equal to zero. All fixed effects were estimated. Random effects were estimated one at a time. If the model could not converge due to an inability to estimate the very small random effect of the added parameter, that parameter was removed from the model.

Results

Of the entire sample, 62 participants (19%) were rated by their informants as exhibiting depression, and 43 (13%) were rated as exhibiting apathy. There was significant overlap in apathy and depression, as 16 participants were rated as exhibiting both apathy and depression ($\chi^2(1)=11.35$; $p=.001$).

Unconditional means models

For all regions of interest, estimated within-person variances were significant in the unconditional means models, indicating sufficient variability in cortical thickness within each region for model building to proceed. Estimated between-person variances also differed significantly from zero for all regions of interest, indicating it may be useful to add predictors to the models. The relative magnitudes of the within-persons and between-persons variance components can be estimated with computation of the intraclass correlation coefficient (ICC), which measure the proportion of total variation in the dependent variable that is among persons (24). A significant ICC indicates that multilevel modeling improves the estimating of fixed effects over traditional methods. In the present models, the ICC's for entorhinal cortex, MFG, OFC, and ACC were .94, .86, .90, and .92, respectively. These values indicate that between 86 and 94% of the total variation in cortical thickness was due to differences between patients. This value also represents the estimated average stability of regional cortical thicknesses over time.

Unconditional growth models

For each region of interest, fixed and random effects of linear time were significant in all models. Models including both linear and quadratic parameterizations of time were unable to estimate the very small random effects of quadratic time. Therefore, only the fixed effects of quadratic time were estimated in subsequent models. The fixed effect of quadratic time was significant only in the entorhinal cortex model ($t(1282.743)=2.998$; $p=.003$). Adding the fixed effect of quadratic time to the entorhinal cortex model significantly improved fit over the model that included only linear time ($\Delta\chi^2(1)=-11.384$; $p>.001$). Thus, subsequent models of entorhinal cortex thickness included both linear and quadratic time. Subsequent models of other cortical regions included only linear time. Significant negative effects of linear time across models correspond to decreasing cortical thickness over the course of the study. This

cortical thinning was greatest in the entorhinal cortex, where cortical thickness was estimated to decline 0.007mm per month. Cortical thickness values in the three frontal subregions decreased by approximately 0.005mm per month. A positive effect of quadratic time in the entorhinal cortex model indicates that cortical thinning was greatest at the beginning of the study and began to level off over the course of the study. Because both within-person and between-person variances were significantly different from zero for all regions of interest, model building proceeded.

Conditional intercept models

Age, MMSE, ICV, apathy, and depression were added to the unconditional growth models. Lower MMSE scores were independently associated with smaller cortical thickness values in each region of interest at baseline. Specifically, each MMSE point below 26 was associated with smaller cortical thickness values by 0.049mm in entorhinal cortex, 0,024mm in MFG, 0.029 in OFC, and 0.043 in ACC. Each year of age above 75 was associated with smaller cortical thickness values by 0.018mm in entorhinal cortex, 0.017mm in MFG, and 0.017mm in OFC at baseline. Age was not independently associated with ACC thickness. The presence of depression was associated with 0.178mm thinner entorhinal cortex at baseline (Cohen's d = .28), but not with cortical thickness of any other regions of interest. Apathy was not associated with baseline cortical thickness of any region of interest.

Conditional growth models

Interactions between time and the predictors (i.e., age, MMSE, ICV, apathy, depression) were estimated. As shown in Table 1, the group's average rates of thinning in entorhinal cortex and MFG were independently moderated by age such that younger individuals exhibited steeper trajectories of atrophy in these regions. The group's average rates of thinning in entorhinal cortex and ACC were moderated by MMSE such that individuals who scored lower at baseline exhibited accelerated atrophy in these regions. Finally, depression significantly moderated the trajectory of ACC atrophy such that individuals with baseline depression exhibited accelerated cortical thinning in this region. Similar associations between baseline depression and accelerated OFC atrophy and between baseline apathy and accelerated ACC atrophy were of similar magnitudes but did not reach significance.

In order to determine whether this lack of significance was related to the inclusion of both apathy and depression in the models, we re-ran OFC and ACC models, excluding apathy or depression. In these models, the relationship between apathy and longitudinal ACC atrophy was significant ($t(265.914)=-2.257$; $p=.025$), but the relationship between depression and longitudinal OFC atrophy was not $t(215.006)=-1.690$; $p=.093$).

In order to examine the influence of averaging left and right hemispheres on the results, we re-ran all models separately within each hemisphere. Greater baseline depression was significantly associated with baseline atrophy within right entorhinal cortex ($t(321.056)=-2.704$; $p=.007$), and this association was at trend in the left hemisphere ($t(316.598)=-1.884$; $p=.06$). Greater baseline depression was significantly associated with accelerated ACC atrophy within the left hemisphere only ($t(230.912)=-2.355$; $p=.019$). No other associations between the regions of interest and depression or apathy were significant.

The random effects of the predictors and covariates were all non-significant or too small to be estimated, suggesting no individual differences in the relationships between the variables and regional cortical thickness. Modeling the predictors, covariates, and their interactions with time reduced between-individual variance in cortical thinning trajectories for all models. However, significant residual within and between-individual variances remained in

all models, suggesting that additional variables may be associated with cortical thickness in all regions.

Discussion

Results of this study suggest that in MCI, baseline entorhinal cortex thickness is associated with depression but not apathy. Contrary to hypotheses regarding frontal subregions, depression was associated with longitudinal anterior cingulate cortex (ACC) atrophy, and apathy was not associated with atrophy in any of the frontal subregions. Finally, results showed that younger age and lower global cognitive status at baseline are associated with both baseline cortical thickness and longitudinal atrophy in entorhinal cortex and certain frontal subregions. These relationships involving age and cognitive status are in line with previous work (25).

With regard to depression, our finding that it was associated with accelerated ACC atrophy is consistent with the non-mutually exclusive hypotheses that depression may be an early manifestation of a more aggressive neurodegenerative process (i.e., early symptom hypothesis) or that depression independently lowers brain reserve capacity, allowing for more rapid progression of AD neuropathology (i.e., risk factor hypothesis) (26).

In the early symptom hypothesis, both depression and aggressive AD share the same underlying pathology (e.g., vascular damage). In the case of AD, such vascular damage may be related to vascular amyloid deposition. While vascular risks have been associated with both late-life depression and MCI (27), epidemiologic data has not supported the idea that vascular pathology underlies the association between depression and MCI (26). In the risk factor hypothesis, depression causes neuronal injury, perhaps via glucocorticoid toxicity (28). Indeed, glucocorticoid receptors are highly expressed in prefrontal cortex, and hypothalamic-pituitary-adrenal (HPA) axis dysregulation has been linked to reduced ACC volumes and subjective memory complaints in older adults (29-30). Therefore, it is possible that depression contributed to ACC thinning in this sample. In the present study, depression was negatively associated with baseline entorhinal cortex thickness, but not with longitudinal atrophy in this region. This pattern of findings does not suggest that baseline depression accelerates atrophy within the entorhinal cortex. Indeed, a recent study involving over 600 older adults found that the negative association between depression and entorhinal cortex volume was *not* explained by HPA activity (31).

In the present study, depression (but not apathy) was associated with accelerated cortical atrophy. This finding suggests that the previously-described link between apathy (but not depression) and dementia conversion may not be attributable to more rapid neurodegeneration (7-8). Given that dementia conversion is defined by decreased functional abilities, it is possible that patients with apathy complete daily activities less successfully due to reduced effort and motivation rather than greater brain pathology. There are several differences between this and previous studies demonstrating a relationship between apathy and reduced anterior cingulate cortex integrity. These studies were not conducted in MCI populations, included participants with a wider range of depression severity than ADNI, did not include a continuous measure of depression severity as a covariate, and did not examine longitudinal change in atrophy (6,32-33). Our findings do not conflict with these studies, as we also identified a relationship between apathy and accelerated ACC atrophy when depression was not included as a covariate. Thus, apathy may indicate future brain atrophy when considered alone, but it does not add predictive value above and beyond that of depression at the group level. Depression, on the other hand, did add predictive value above and beyond apathy in this study.

Several weaknesses of this study should be acknowledged. First, the sample did not include participants with more than minimal depression, as having a score greater than 6 on the self-report Geriatric Depression Scale (GDS) was an exclusion criterion in ADNI. Despite this, prevalence rates of depression (19%) and apathy (13%) defined by the NPIQ in this study are highly consistent with prevalence estimates in a previous population-based study (34). Further, it is possible that the NPIQ captured depressive symptoms that were not identified with the self-report GDS in the present MCI sample, as more than 50% of individuals with MCI exhibit reduced awareness (35). Also, the NPIQ may not have captured the full spectrum of apathy symptoms, as the screening question for apathy asks only about level of interest. Apathy can manifest not only in the cognitive domain (e.g., lack of interest), but also behavioral (e.g., reduced productivity) and emotional (e.g., affective flattening) domains (36). Future studies should employ a more comprehensive measure of apathy to more fully explore the potential for unique relationships with longitudinal cortical changes, particularly given that many previous reports of associations between apathy and brain structure included only behavioral (37) or emotional (38) apathy. Finally, participants in ADNI were predominantly educated, Caucasian males. Future studies examining the prognostic value of neuropsychiatric symptoms in more diverse MCI populations are critical, particularly given the increased incidence of AD among African Americans and Hispanics (39).

Important strengths of this study include its longitudinal design and use of multilevel modeling to maximize the accuracy of measurement of change in cortical thickness over time. Another key strength of this study compared to previous work is its inclusion of both apathy and depression in models of cortical atrophy. This study extends previous work by examining specific cortical regions of interest rather than total lobar volumes over a longer study period.

This study underscores the importance of recognizing subclinical depression in MCI, as it appears to be an independent marker of entorhinal cortex integrity as well as a predictor of future ACC atrophy. This latter point is particularly important given recent evidence from ADNI that ACC atrophy rate correlates with cognitive decline (40). Thus, depressive symptoms are an important prognostic indicator in MCI, even among individuals without self-reported clinical depression.

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Table 1

Fixed effects from conditional growth models

	Entorhinal	MFG	OFC	ACC
Initial status				
Intercept	3.091 (0.036) **	4.304 (0.025) **	4.691 (0.025) **	5.418 (0.032) **
Age	-0.019 (0.004) **	-0.018 (0.003) **	-0.017 (0.003) **	-0.005 (0.003)
MMSE	0.044 (0.015) *	0.021 (0.011) *	0.027 (0.011) *	0.037 (0.014) *
ICV	0.000 (0.000)	0.000 (0.000)	-1.0e-6 (0.000) **	-1.0e-6 (0.000) **
Apathy	0.136 (0.087)	0.040 (0.059)	-0.011 (0.062)	0.038 (0.014)
Depression	-0.181 (0.080) *	-0.075 (0.049)	-0.066 (0.055)	0.018 (0.064)
Rate of change				
Time (linear)	-0.009 (0.001) **	-0.005 (0.001) **	-0.005 (0.001) **	-0.005 (0.001) **
X Age	1.2e-4 (5.0e-5) *	1.5e-4 (5.5e-5) *	-9.0e-6 (5.3e-5)	9.1e-5(5.4e-5) +
X MMSE	0.001 (2.0e-4) **	2.9e-4 (2.3e-4)	3.1e-4 (2.2e-4)	0.001 (2.1e-4) **
X ICV	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
X Apathy	0.001 (0.001)	-6.0e-4 (0.001)	4.5e-4 (0.001)	-0.002 (0.001) +
X Depression	0.001 (0.001)	-0.001 (0.001)	-0.002 (0.001) +	-0.002 (0.001) *
Time (quadratic)	4.1e-5 (1.5e-5) *	-	-	-

** $p < .001$

* $p <. 05$

+ $p < .1$

Note. Fixed effects reflect unstandardized parameter estimates from the four multilevel models. Significance of these effects is determined with a t-statistic. Degrees of freedom ranged from 241 to 385.

MFG: Middle Frontal Gyrus; OFC: Orbitofrontal Cortex; ACC: Anterior Cingulate Cortex