

Anxiety Symptoms in Amnestic Mild Cognitive Impairment Are Associated with Medial Temporal Atrophy and Predict Conversion to Alzheimer Disease

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Objective: To test the hypothesis that anxiety in amnestic mild cognitive impairment (aMCI) increases rates of conversion to Alzheimer disease (AD) and to identify potential neural mechanisms underlying such an association. **Methods:** Participants ($N = 376$) with aMCI from the Alzheimer's Disease Neuroimaging Initiative (ADNI) were studied over a median period of 36 months. A Cox proportional-hazards model was used to assess the association between anxiety severity ratings on the Neuropsychiatric Inventory Questionnaire and AD risk. Other variables were depression, memory loss, and MRI-derived AD-related regions of interest (ROIs), including hippocampal, amygdalar, entorhinal cortical (EC) volumes, and EC thickness. In addition, a linear regression model was used to determine the effect of anxiety in aMCI on rates of atrophy within ROIs. **Results:** Anxiety severity increased rate of aMCI conversion to AD, after controlling for depression and cognitive decline. The association between anxiety and AD remained significant even with inclusion of ROI baseline values or atrophy rates as explanatory variables. Further, anxiety status predicted greater rates of decrease in EC volume. An association between anxiety and EC thickness missed significance. **Conclusion:** Anxiety symptoms in aMCI predict conversion to AD, over and beyond the effects of depression, memory loss, or atrophy within AD neuroimaging biomarkers. These findings, together with the greater EC atrophy rate predicted by anxiety, are compatible with the hypothesis that anxiety is not a prodromal noncognitive feature of AD but may accelerate decline toward AD through direct or indirect effects on EC. (Am J Geriatr Psychiatry 2015; 23:466–476)

Key Words: Alzheimer disease, anxiety, depression, mild cognitive impairment, neuropsychiatric symptoms, amygdala, entorhinal cortex, MRI biomarker

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INTRODUCTION

Amnesic mild cognitive impairment (aMCI) is characterized by memory impairment with preservation of functional independence and is considered a transitional stage between normal aging and Alzheimer disease (AD).^{1–3} However, rates of conversion to AD are highly variable. Although 10%–15% of people with aMCI convert to AD within a year, others remain stable or improve in memory performance.^{3,4} Most models incorporating cerebrospinal fluid, neuroimaging, and neuropsychological biomarkers have inadequate predictive value in identifying aMCI patients at high risk for disease progression.^{5–8} These findings suggest that other variables contribute to AD risk.

Neuropsychiatric symptoms, such as depression and anxiety, are frequent in aMCI.^{9–13} Much research has focused on the link between depression and AD, with converging evidence of a one and a half to two times increased risk of conversion in individuals with aMCI and concurrent depression.¹⁴ Whether anxiety is a risk factor for AD is unclear. Past or current anxiety in aMCI may augment the risk of AD conversion by as much as 2.5-fold.^{15–18} Conversely, anxiety may be protective against AD^{19–21} or have no impact.^{22–25} Although methodologic differences such as shorter follow-up^{22–25} and clinical versus community samples^{19–21} may account for the discrepant findings, an important consideration is the potential impact of concurrent depression, given the well-established comorbidity between anxiety and depression in the general population.^{26,27} Notably, studies that included depression as a covariate reported an inverse or no association between anxiety and AD.^{19–21,25} One of the first studies to demonstrate a nearly twofold increased AD risk in individuals with aMCI and anxiety reported that anxiety at baseline remained a significant predictor when depression was included as a covariate, although the results were not presented.¹⁷ Other studies that demonstrated an association between aMCI with anxiety and conversion excluded depression as a covariate in longitudinal models of AD risk.^{15,16,18} Thus, although evidence from large observational studies supports an association between anxiety in aMCI and AD risk, the degree to which depression contributes toward or confounds the association is unclear.

An association between anxiety and AD risk is suggested by studies that have demonstrated links between anxiety or stress and AD-related pathology. Anxiety in individuals with aMCI was associated with abnormal concentrations of A β 42 and t-tau in cerebrospinal fluid, whereas conversely depression and apathy were not.²⁸ In animal models of AD, stress-level glucocorticosteroid administration resulted in increases in amyloid formation and tau accumulation.²⁹ The well-established relationships among stress, cortisol, and hippocampal atrophy in humans^{30–32} suggest that anxiety may increase AD risk indirectly through cortisol-mediated hippocampal neurotoxicity. Elevated cortisol levels have been found in older adults with clinically significant anxiety.³³ Chronic stress may also contribute to AD risk through other pathways related to increased allostatic load, such as effects on the cardiovascular system and plasticity changes to brain structures.³⁴

The purpose of the current study was to test the hypothesis that anxiety symptoms in individuals with aMCI increase the risk of AD, independent of depressive symptoms. We also sought to identify potential neural mechanisms underlying such an association by determining the relationships among anxiety symptoms in aMCI, AD-related brain regions, and conversion to AD. Medial temporal lobe structures, which together play an integral role in memory formation and are robust predictors of progression to AD,⁸ were selected as regions of interest (ROIs). These structures are hippocampal (HC-vol), amygdala (AMYG-vol), and entorhinal cortex volumes (EC-vol) and cortical thickness measures (EC-thickness). We additionally included EC surface area measures (EC-surface) based on neuropathologic studies of early AD.³⁵ We hypothesized that anxiety symptoms in aMCI (aMCI anxiety+) would be associated with greater rates of atrophy within ROIs relative to nonanxious aMCI (aMCI anxiety–).

METHODS

Subjects

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database.³⁶ ADNI was launched in 2003 by the National Institute of Aging,

National Institute of Biomedical Imaging and Bioengineering, the U.S. Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations as a \$60M, 5-year public–private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography, other biologic markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

The principal investigator of this initiative is Michael W. Weiner, M.D., VA Medical Center, UCSF. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations. Subjects have been recruited from over 50 sites across the United States and Canada. The initial goal of ADNI was to recruit 800 subjects. ADNI has been followed by ADNI-GO and ADNI-2. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2.⁸ For up-to-date information, go to www.adni-info.org.

Diagnoses were established by site investigators at screening and baseline visits using quantitative and qualitative global measures. General inclusion criteria were as follows: age 55–91 years for MCI and AD and 60–90 years for normal controls (NC), availability of family member/caregiver to provide collateral information, modified Hachinski ischemia score of no more than 4, stability of permitted medications, no significant neurological conditions, and good general health. Individuals with active mood disorders such as major depressive or bipolar disorder or those with Geriatric Depression Scale score less than 5³⁷ were excluded. Criteria for single- or multiple-domain aMCI¹ included memory complaint by subject or family member/caregiver, objective memory loss (performance 1.5 standard deviations below education-adjusted cutoff scores on Wechsler Memory Scale-Revised Logical Memory-IIa), no significant impairment in other cognitive domains, Mini-Mental Status Exam score of at least 24,³⁸ Global Clinical Dementia Rating score of 0.5,³⁹ Global Clinical Dementia Rating memory score of at least 0.5, preserved activities of daily living, and absence of dementia. Detailed inclusion and exclusion criteria are available in the ADNI protocol.³⁶

Clinical, neuropsychological, and neuroimaging assessments were collected at baseline and at 6-month intervals for 2 years and then annually

thereafter. Data were downloaded from the ADNI public database on or before February 9, 2014 and reflect the status of the database at that point. The ADNI study was approved by the local institutional review board of each participating site. Before performance of any study procedures, informed consent was obtained from all subjects and study partners. The current study included 376 aMCI participants from ADNI-1 and was approved by Baycrest's Research Ethics Board (REB).

Assessment of Exposure of Interest

Anxiety in ADNI-1 was assessed using the Neuropsychiatric Inventory (NPI-Q),⁴⁰ a caregiver-based report of neuropsychiatric symptoms associated with dementia that have occurred over the last month. The NPI-Q uses a two-part screening question for anxiety, probing whether the patient becomes upset when separated from caregiver *or* whether the patient has physiologic symptoms of anxiety (e.g., shortness of breath, feeling tense). Endorsement of either is recorded as a positive response for anxiety. Severity of anxiety is then rated (1 = mild, 2 = moderate, 3 = severe). NPI-Q responses were available for baseline and follow-up visits (every 6 months until 24 months, then annually). As a summary measure of exposure to anxiety during the observation period, we used the highest reported anxiety severity rating (NPI-Anxiety_{max}) recorded during the period of risk, defined as baseline through to the study visit immediately before AD diagnosis, or to the second-to-last study visit in stable aMCI participants. Negative responses on NPI-Q anxiety were coded as 0 for severity.

Other Potential Predictors of AD Risk

Baseline age, sex, education, Hachinski ischemia score,⁴¹ and the following depression, cognitive, and AD neuroimaging biomarkers were included as explanatory variables of AD risk.

Depression. Assessments included the Geriatric Depression Scale (GDS), administered at baseline and then yearly, and the NPI-Q. We used the highest GDS score (GDS_{max}) and NPI-Q depression severity rating (NPI-Dep_{max}) recorded during the period of risk as measures of exposure to depression.

Cognition. Baseline MMSE³⁸ and neuropsychological measures of memory and executive function

TABLE 1. Demographic, Clinical, and Neuroimaging Characteristics of aMCI Participants

| Variable | Total MCI Sample (N = 376) | MCI Without Anxiety (N = 220) | MCI with Anxiety (N = 156) | d ^a |
|----------------------------------------------------------------------------------------------|----------------------------|-------------------------------|----------------------------|-----------------|
| Age at baseline, year | 75.0 (7.26) | 75.2 (7.55) | 74.7 (6.84) | 0.07 |
| Male, % | 64 | 70 | 56 | 0.30 |
| Education, year | 15.6 (3.03) | 15.6 (3.08) | 15.6 (2.98) | <0.01 |
| Modified Hachinski ischemia score | 0.63 (0.71) | 0.64 (0.69) | 0.63 (0.76) | 0.01 |
| Duration of follow-up/period of observation, year | 31.0 (11.4) | 31.2 (11.7) | 30.6 (11.0) | 0.06 |
| Percent followed for minimum of 24 months | 80.3 | 80 | 80.7 | |
| Number converted to AD | 165 | 87 | 78 | |
| Cognition | | | | |
| MMSE at study entry | 27.0 (1.77) | 27.0 (1.73) | 26.9 (1.84) | 0.06 |
| Memory composite score (ADNI-MEM) at baseline | -0.0997 (0.57) | -0.0766 (0.57) | -0.1322 (0.58) | 0.10 |
| Executive function composite score (ADNI-EF) at baseline | -0.0581 (0.76) | -0.0578 (0.80) | -0.0584 (0.70) | <0.01 |
| Anxiety | | | | |
| Baseline NPI-Q anxiety response (yes/no), % yes | 18 | 0 | 44 | |
| % Mild/moderate/severe | | | 68/29/3 | |
| Depression | | | | |
| Baseline GDS score, possible range 0–15 | 1.53 (1.36) | 1.38 (1.29) | 1.74 (1.42) | 0.27 |
| Highest GDS score during period of observation, mean (SD) | 2.59 (2.25) | 2.24 (1.95) | 3.08 (2.54) | 0.38 |
| Highest GDS score during period of observation, % participants | 7.9 | 6.8 | 9.6 | |
| Baseline NPI-Q depression response (yes/no), % yes | 19 | 14 | 26 | 0.31 |
| Any positive NPI-Q depression response during period of observation, % yes | 45 | 33 | 62 | 0.61 |
| Highest NPI-Q depression severity score during period of observation, % mild/moderate/severe | 65/32/3 | 78/22/0 | 55/40/5 | |
| Baseline values for AD neuroimaging biomarkers | | | | |
| Number | | 192 | 140 | |
| ICV, ×10 ³ mL | | 1 586 (174) | 1 556 (158) | 0.18 |
| AMYG-vol, mL | | 1 027 (202) | 950 (202) | 0.38 |
| HC-vol, mL | | 2 967 (518) | 2 827 (459) | 0.28 |
| EC-vol, mL | | 1 735 (409) | 1 612 (358) | 0.32 |
| EC surface area, mm ² | | 359 (78) | 370 (78) | 0.14 |
| EC thickness, mm | | 3.14 (0.521) | 3.11 (0.520) | 0.06 |

Note: Summary statistics are means (SD) for continuous measures and % for categorical measures.

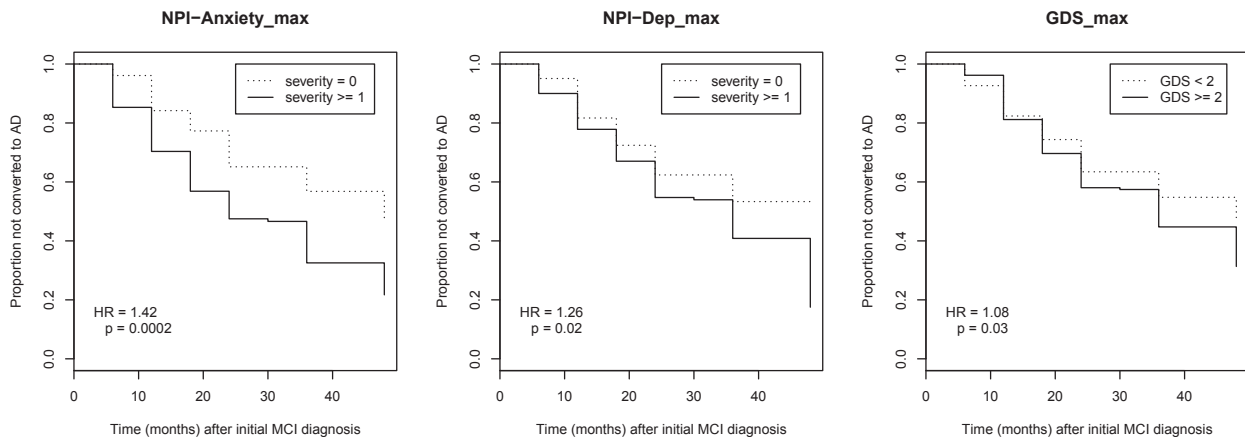
^aCohen's d statistic to quantify difference between aMCI anxiety+ and noaMCI anxiety-: small (d = 0.20), medium (d = 0.50), large (d = 0.80).

were included. ADNI memory (ADNI-MEM) and executive function (ADNI-EF) are composite scores created to address site-to-site variability in neuropsychological test versions administered.⁴² ADNI-MEM is based on the Rey Auditory Verbal Learning Test,⁴³ AD Assessment Scale-Cognitive subscale,⁴⁴ MMSE three-item recall, and Wechsler Memory Scale-Revised Logical Memory-I.⁴⁵ ADNI-EF is based on Category Fluency (animals, vegetables), Trails B, Digit Span backward, Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol Substitution, and five Clock Drawing items. Each metric was constructed with a mean of 0 and standard deviation of 1 based on the pool of 800 participants who completed baseline neuropsychological assessment in ADNI-1. ADNI-MEM and ADNI-EF have been validated as predictors of AD risk and were associated with AD structural

neuroimaging biomarkers.^{42,46} ADNI-EF and ADNI-MEM scores at baseline and ADNI-MEM scores at each follow-up during the period of risk were incorporated into analyses.

Structural Neuroimaging ROIs. MRI-derived measures of total intracranial volume (ICV), HC-vol, AMYG-vol, EC-vol, EC-thickness, and EC-surface at baseline and at each study visit (every 6 months until 24 months, then annually) were extracted from the dataset UCSF-Longitudinal FreeSurfer (FreeSurfer Version 4.4; <http://freesurfer.net/>). The dataset includes MRI measures of cortical volume and thickness, standard deviation of cortical thickness, and surface area for 34 ROIs. Participants were scanned on 1.5-T scanners at 56 different sites using a standardized ADNI protocol for high-resolution magnetization-prepared rapid gradient-echo (MPRAGE) structural

FIGURE 1. Kaplan-Meier survival curves of progression from aMCI to AD dementia as predicted by NPI-Q anxiety severity (left), NPI-Q depression severity (middle), and GDS (right). Survival indicates absence of progression from aMCI to AD dementia.



MRI. Images were preprocessed using gradient warping, scaling, B1 correction, and N3 inhomogeneity correction. Original scans and preprocessed images are available at <http://www.loni.ucla.edu/ADNI/Data/>.³⁶ Cortical reconstruction and volumetric segmentation of scans was performed using FreeSurfer (<http://surfer.nmr.mgh.harvard.edu/>). Because MRI scans were acquired at multiple time points, scans were run through FreeSurfer using longitudinal processing, which involves creating a within-subject template space and average image unbiased toward the chronologic scan order using robust, inverse consistent registration.⁴⁷ Several processing steps, including skull stripping, Talairach transforms, atlas registration, and spherical surface maps and parcellations, were then initialized with common information from the within-subject template to optimize statistical power and reliability.⁴⁸ Further details on longitudinal processing are available elsewhere.⁴⁸

Statistical Analyses

A Cox proportional-hazards regression model was used to evaluate the effects of anxiety and other factors on time to conversion to AD. Factors were NPI-Anxiety_{max}, GDS_{max}, NPI-Dep_{max}, sex, education, baseline age, Hachinski ischemia score, ADNI-MEM, ADNI-EF, and ROIs. This model yields a hazard ratio (HR) that gives the ratio of the probability of converting to AD at a given time per 1 unit of the predictor (anxiety

severity rating), relative to the probability of converting to AD for aMCI with no anxiety. For multivariable regression models, we report the HR for the predictor conditional on other variables in the model (HR_p). To account for variability in anxiety and depression severity across the observation period, NPI-Anxiety_{max}, NPI-Dep_{max}, and GDS_{max} were entered as time-dependent variables.⁴⁹

To appreciate the unconditional contribution of individual factors on AD risk, we fit bivariate Cox models with each factor as the independent variable. We then fit a multivariable Cox model using NPI-Anxiety_{max} and all demographic and clinical factors to determine the association between anxiety and AD, conditional on other predictors of AD risk. We used backward elimination to sequentially remove variables with $p > 0.10$. This final model was confirmed by reintroducing each eliminated variable into the model to ensure $p > 0.10$ and to determine whether the regression coefficient estimate for anxiety was substantively altered ($\geq 20\%$) by inclusion of the variable.

To evaluate the extent to which anxiety was predictive of AD over and beyond extent of memory decline, we challenged the final model by including a measure of change in memory (Δ ADNI-MEM) and determined its impact on the size of the regression coefficient estimate for anxiety. Δ ADNI-MEM was calculated as the difference between ADNI-MEM at baseline and at each follow-up visit during the period of risk and then entered into the model as a time-dependent variable.

TABLE 2. Multivariable Cox Proportional-Hazards Regression Models of AD Risk (165 Events) in aMCI (N = 376)

| Predictor Variable | Model Without NPI-Q Depression | | | | Model Adjusted for NPI-Q Depression | | | |
|-----------------------------|--------------------------------|-----------------|--------------|---------|-------------------------------------|-----------------|--------------|---------|
| | Regression Coefficient | HR _p | Wald z Value | p | Regression Coefficient | HR _p | Wald z Value | p |
| Anxiety | 0.299 | 1.35 | +3.04 | 0.002 | 0.287 | 1.33 | +2.56 | 0.01 |
| Baseline memory | -1.258 | 0.28 | -7.19 | <0.0001 | -1.26 | 0.28 | -7.17 | <0.0001 |
| Baseline executive function | -0.477 | 0.62 | -3.92 | <0.0001 | -0.478 | 0.62 | -3.92 | <0.0001 |
| Sex | 0.532 | 1.70 | +3.23 | 0.001 | 0.529 | 1.70 | +3.21 | 0.001 |
| Education | 0.044 | 1.04 | +1.67 | 0.09 | 0.044 | 1.04 | +1.65 | 0.10 |

TABLE 3. Effect of Individual Baseline Structural Neuroimaging Measures on Hazard for AD and on Hazard Ratio (HR_p) for Anxiety

| ROI | HR _p for ROI | Wald z Value | p | HR _p for Anxiety with Inclusion of ROI in the Model ^a |
|----------------------------------|-------------------------|--------------|--------|-----------------------------------------------------------------------------|
| ICV, ^b mL | 1.00 | +0.71 | 0.48 | 1.25 |
| HC volume, mL | 0.52 | -2.88 | 0.004 | 1.20 |
| Amygdala volume, mL | 0.18 | -3.12 | 0.002 | 1.18 |
| EC volume, mL | 0.42 | -3.35 | 0.0008 | 1.16 |
| EC thickness, mm | 0.64 | -2.55 | 0.01 | 1.21 |
| EC surface area, cm ² | 0.94 | -0.54 | 0.59 | 1.24 |

^aCox proportional-hazards models (130 events, N = 332) additionally included sex, education, baseline memory, and baseline executive function (see text).
^bIncluded in all models.

TABLE 4. Effect of Change in ROI (ΔROI)^a at Each Visit from Baseline on Hazard of AD and on Hazard Ratio (HR_p) for Anxiety

| ROI | HR _p | Wald z Value | p | HR _p for Anxiety with Inclusion of ΔROI in the Model ^b |
|-------------------------------------|-----------------|--------------|-------|------------------------------------------------------------------------------|
| ΔICV, ^c mL | 1.01 | +1.57 | 0.12 | 1.27 |
| ΔHC, mL | 0.33 | -1.09 | 0.28 | 1.27 |
| ΔAmygdala, mL | 0.27 | -0.98 | 0.33 | 1.28 |
| ΔEC volume, mL | 0.08 | -2.23 | 0.03 | 1.29 |
| ΔEC thickness (mm) | 0.12 | -3.28 | 0.001 | 1.29 |
| ΔEC surface area (cm ²) | 0.74 | -0.78 | 0.43 | 1.27 |

^aSee text for calculation of ΔROI.
^bCox proportional-hazards models (130 events, N = 332) additionally included sex, education, baseline memory, and baseline executive function (see text).
^cIncluded in all models.

Structural Neuroimaging Predictors of AD Risk

MRI data were available for a subset of the sample (N = 332). To determine whether anxiety was predictive of AD conversion over and beyond the contribution of structural neuroimaging biomarkers of AD, we refit the Cox regression model to the

subsample using the previously described procedure. Baseline ICV was added to the model to account for variability in total brain volume across participants, and then baseline values for each ROI were entered individually into the model to determine their impact on the regression coefficient estimate for anxiety.

The same procedure was followed to evaluate the impact of change in each ROI (ΔROI) over time in the model. ΔROI was calculated as the difference from baseline to each scan obtained during the period or risk. ΔICV was included in these models.

Anxiety as a Predictor of Rate of Atrophy Within ROIs

To explore potential neural mechanisms underlying an association between anxiety and AD, we evaluated whether aMCI anxiety+ versus aMCI anxiety- status was predictive of the rate of atrophy (R_{atrophy}) within ROIs over the entire observation period using a linear regression model. A least-squares slope estimate of R_{atrophy} for each ROI from all available scans (for participants with at least four scans) was expressed as an annual rate of change. Conversion status was included in the model to ensure our estimation of the anxiety effect was not attributable to greater R_{atrophy} due to AD.

RESULTS

Sample characteristics and conversion status at study end are summarized in Table 1. Although all aMCI participants entered ADNI-1 with GDS scores of no more than 5 as per eligibility criteria, 8% of the sample reported GDS scores greater than 5 on at least one study visit during the period of risk. The numbers of aMCI participants with any positive response for NPI-Q depression or anxiety during the

TABLE 5. Rate of Change (R_{atrophy}) in AD Structural Neuroimaging Biomarkers by Anxiety Status in aMCI

| R_{atrophy} Within ROI | MCI Anxiety- (N = 132) | MCI Anxiety+ (N = 104) | t Statistic ^a |
|---------------------------------|------------------------|------------------------|--------------------------|
| ICV | +1.78 (SD = 7.43) | +2.34 (SD = 6.69) | +0.55 (p = 0.58) |
| HC volume | -0.072 (SD = 0.054) | -0.086 (SD = 0.053) | -1.36 (p = 0.18) |
| Amygdala volume | -0.023 (SD = 0.035) | -0.022 (SD = 0.035) | +0.35 (p = 0.73) |
| EC volume | -0.020 (SD = 0.047) | -0.070 (SD = 0.049) | -2.55 (p = 0.01) |
| EC thickness | -0.078 (SD = 0.080) | -0.106 (SD = 0.084) | -1.93 (p = 0.0546) |
| EC surface area | -0.035 (SD = 0.097) | -0.047 (SD = 0.104) | -0.68 (p = 0.50) |

^aConversion status included as a covariate, df = 233.

period of risk were comparable (45% versus 41%). Similarly, NPI-Anxiety_{max} and NPI-Dep_{max} distributions were comparable.

In bivariate models, NPI-Anxiety_{max}, NPI-Dep_{max}, and GDS_{max} were significantly associated with rates of conversion to AD (Kaplan-Meier survival curves and HRs in Fig. 1), as were all cognitive variables (MMSE: HR = 0.82, Wald z = -4.50, p < 0.0001; ADNI-MEM: HR = 0.23, Wald z = -8.73, p < 0.0001; ADNI-EF: HR = 0.52, Wald z = -6.42, p < 0.0001). The initial multivariable Cox proportional-hazards model included NPI-Anxiety_{max}, NPI-Dep_{max}, GDS_{max}, MMSE, ADNI-MEM, ADNI-EF, age, sex, education, and Hachinski score. The final model after backward elimination included NPI-Anxiety_{max}, ADNI-MEM, ADNI-EF, sex, and education and was confirmed with reintroduction of excluded variables. The HR_p for anxiety (HR_p-anxiety) in this model was 1.35 (summarized in Table 2). Neither NPI-Dep_{max} nor GDS_{max} met criteria for inclusion into the model, but we report a second model with NPI-Dep_{max} added to interpret the effects of anxiety on AD independent of depression (Table 2). Inclusion of NPI-Dep_{max} resulted in reduction of the regression coefficient estimate for anxiety by 17%, and HR_p-anxiety was minimally reduced. GDS_{max} reduced the regression coefficient estimate for anxiety by less than 5%. When either model was challenged by adding Δ ADNI-MEM, the effect of anxiety on AD conversion remained significant and not substantively altered (HR_p-anxiety remained at 1.30 and 1.27 [Wald z = 2.07, p = 0.04] for final or depression-adjusted model, respectively).

Neuroimaging Predictors of AD Risk

Baseline volumes of HC, AMYG, and EC were smaller in aMCI anxiety+ participants (Table 1). The

multivariable Cox proportional-hazards model based on the subsample of 332 aMCI participants with MRI data was identical to the model indicated by the larger sample: retained predictors were NPI-Anxiety_{max}, ADNI-MEM, ADNI-EF, sex, and education. Estimated HR_p from this subsample was similar to the estimate from the full data set for each predictor. Estimated HR_p-anxiety in this subsample was 1.25.

Effect of Baseline ROIs. Table 3 summarizes the models with ICV and each baseline ROI added individually to the model. Baseline HC-vol, EC-vol, AMYG-vol, EC-vol, and EC-thickness, but not EC-surface, were strongly associated with AD risk. Although these neuroimaging associations reduced the magnitude of the effect of anxiety on AD conversion, anxiety remained a significant predictor of AD.

Effect of Change in ROIs Over Time. Table 4 summarizes the models with Δ ICV and each Δ ROI added individually. Only Δ EC-vol and Δ EC-thickness were associated with AD. The regression coefficient estimate for anxiety was nominally increased with inclusion of Δ ROIs in the model.

Anxiety as a Predictor of Rate of Atrophy Within ROIs

R_{atrophy} for each ROI in aMCI anxiety+ and aMCI anxiety- are summarized in Table 5. Anxiety status predicted R_{atrophy} of EC-vol. The association between anxiety and EC-thickness R_{atrophy} missed significance.

DISCUSSION

Anxiety severity in aMCI increased rates of conversion to AD, independent of depression or extent of memory decline. The HR_p for anxiety was 1.33, indicating AD risk increased by 33%, 78%, and 135%

for mild, moderate, and severe anxiety, respectively. The association between anxiety and AD remained significant even with inclusion of baseline HC, AMYG, EC, or their extent of atrophy over time in the model. Further, anxiety status predicted greater annual rates of decrease in EC-vol.

Previous studies reported conflicting results on the contribution of depression to the association between anxiety and AD^{19–21,25} or did not document results.^{15–17} Further, the impact of depression developing after baseline on conversion has not been reported.^{15,16} Although depression is an exclusion criterion for enrollment into ADNI, 8% of aMCI participants developed clinically significant depression symptoms during follow-up, an incidence rate similar to the general population.⁵⁰ Depression and anxiety-severity score distributions were comparable in the sample. Thus, it is noteworthy that the HR_p for anxiety remained significant and was minimally altered with depression severity included in the model (HR_p of 1.35 decreased to 1.33). Earlier studies reported similar HRs for baseline NPI-anxiety severity in MCI despite failing to adjust for depression.^{15,18} A recent retrospective study in primary care demonstrated that anxiety attenuated the association between depression and dementia and that AD risk was similar for anxiety comorbid with depression or anxiety alone.⁵¹ Collectively, these findings suggest that anxiety in aMCI increases risk of AD independently of depression.

If anxiety in aMCI accelerates progression toward AD, is it possible that anxiety is simply a prodromal symptom of AD—because of the presence of AD pathology in limbic brain regions⁵²—or is anxiety a subjective reaction to worsening memory? Against these possibilities are the significant associations between anxiety and AD, over and beyond extent of memory decline, baseline ROI volumes, or ROI atrophy rate. We also observed no differences in frequency of endorsing the GDS question, “Do you feel you have more problems with memory than most?”, between aMCI anxiety+ and aMCI anxiety–, implying anxiety was not simply related to concerns regarding memory.

Instead, we found that anxiety was associated with increased rate of atrophy within EC-vol (an association with EC-thickness, specifically, missed significance), suggesting anxiety may accelerate decline toward AD through effects on EC. Decreased EC-vol

and EC-thickness were in turn associated with more rapid progression toward AD. The EC, along with perirhinal, parahippocampal cortices and HC, form the medial temporal lobe, which plays an integral role in memory formation.⁵³ A link between anxiety and EC was previously demonstrated in a study of AD patients where NPI anxiety scores were inversely correlated with metabolism in EC and anterior parahippocampal gyrus, after controlling for MMSE and NPI depression.⁵⁴

Contrary to hypotheses, anxiety was not associated with greater HC or AMYG atrophy rates. However, decreases in HC-vol or AMYG-vol was also not predictive of conversion to AD. This pattern of results is consistent with pathologic staging of AD, where neurofibrillary tangles appear initially in EC, followed by HC and then AMYG in preclinical AD.⁵² Further, in healthy older adults, AD pathology as measured by amyloid- β deposition was associated with abnormal neural activity during recall within EC but not HC, suggesting that amyloid deposition is associated specifically with EC neuronal dysfunction.⁵⁵

One limitation to the current study is the use of NPI-Q in assessment of anxiety. Caregiver ratings may not accurately reflect the extent of anxiety experienced by individuals with aMCI. The NPI-Q also assesses a narrow range of anxiety symptoms and does not characterize onset or chronicity. In a study focused on anxiety profiles in MCI, chronic severe anxiety, as opposed to recent onset, was associated with aMCI and correlated with memory impairment.⁵⁶ Thus, it is possible that anxiety symptoms were underreported in the current study, resulting in a lower HR_p estimate for anxiety and AD risk. Broader anxiety measures that are self- and clinician-rated are ideal but are challenging to implement in a large-scale, long-term observational study for which participant retention is critical. A second limitation relates to exclusion of comorbid depression on study entry in ADNI, a criterion implemented in other longitudinal AD studies because depression itself is associated with cognitive impairment.⁵⁷ Thus, whether an association between anxiety and AD would be detected in aMCI with high levels of depression remains to be determined.

In summary, we demonstrated an association between anxiety symptoms in aMCI and rate of conversion to AD independent of depression, extent of

memory loss, or atrophy of AD neuroimaging biomarkers. Further, anxiety in aMCI predicted greater EC atrophy rate, which itself was associated with AD risk. These findings are compatible with the hypothesis that anxiety is not a prodromal noncognitive feature of AD but may accelerate decline toward AD through direct or indirect effects on EC. Anxiety in aMCI has been understudied relative to other neuropsychiatric symptoms such as depression and apathy, despite well-established associations between stress, cortisol, and hippocampal integrity.^{30–32} This may, in part, be attributable to the tendency to subsume anxiety symptoms within the rubric of depression.⁵⁸ Future research should clarify the clinical profile of anxiety and its association with AD in community samples of aMCI, and evaluate whether progression to AD can be delayed through routine monitoring and timely management of anxiety symptoms in aMCI, for example, using cognitive-behavioral interventions developed for anxiety in dementia.⁵⁹

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