Regional Cortical Thinning Predicts Worsening Apathy and Hallucinations Across the Alzheimer Disease Spectrum

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Objectives: *To examine regions of cortical thinning and cerebrospinal fluid (CSF) Alzheimer disease (AD) biomarkers associated with apathy and hallucinations in a continuum of individuals including clinically normal elderly, mild cognitive impairment, and mild AD dementia.* **Design:** *Cross-sectional and longitudinal studies.* **Setting:** *Fifty-seven research sites across North America.* **Participants:** *Eight-hundred twelve community-dwelling volunteers; 413 participants in the CSF sub-study.* **Measurements:** *Structural magnetic resonance imaging data and CSF concentrations of amyloid-β 1-42, total tau, and phosphorylated tau derived from the Alzheimer Disease Neuroimaging Initiative database were analyzed. Apathy and hallucinations were measured at baseline and over 3 years using the Neuropsychiatric Inventory-Questionnaire. General linear models and mixed effects models were used to evaluate the relationships among baseline cortical thickness in seven regions, and baseline CSF biomarkers, apathy, and hallucinations at baseline and longitudinally. Covariates included diagnosis, sex, age, apolipoprotein E genotype, premorbid intelligence, memory performance, processing speed, antidepressant use, and AD duration.* **Results:** *Reduced baseline inferior temporal cortical thickness was predictive of increasing apathy over time, and reduced supramarginal cortical thickness was predictive of increasing hallucinations over time. There was no association with cortical thickness at baseline. CSF biomarkers were not related to*

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Data used in the preparation of this article were obtained from the Alzheimer Disease Neuroimaging Initiative (ADNI) database (http://www.loni.ucla.edu/ADNI). The authors are site investigators and research staff for ADNI at Brigham and Women's Hospital and Massachusetts General Hospital. The other site investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of the ADNI investigators is available at http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf. Send correspondence and reprint requests to Nancy J. Donovan, MD, Center for Alzheimer Research and Treatment, Brigham and Women's Hospital, 221 Longwood Avenue, BL-104H, Boston, MA 02115. e-mail: njdonovan@partners.org

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severity of apathy or hallucinations in cross-sectional or longitudinal analyses. **Conclusions:** *These results suggest that greater baseline temporal and parietal atrophy is associated with worsening apathy and hallucinations in a large AD spectrum cohort, while adjusting for multiple disease-related variables. Localized cortical neurodegeneration may contribute to the pathophysiology of apathy and hallucinations and their adverse consequences in AD.* (Am J Geriatr Psychiatry 2013; ■:■−■)

Key Words: Apathy, hallucinations, MRI, cortical thinning, CSF biomarkers, Alzheimer disease

Apathy and hallucinations are neuropsychiatric features of Alzheimer disease (AD) that herald functional and global decline.[1−3] Apathy occurs commonly in early symptomatic stages of AD, persists with disease progression, and is the most prevalent neuropsychiatric symptom in individuals with AD dementia.[4] In contrast, hallucinations typically become evident in later stages of AD and identify a smaller subset of individuals with an accelerated course of illness and early mortality.[3,5,6] Despite the gravity of these neuropsychiatric symptoms in AD, their emergence and expression as part of the AD pathophysiological process are not well understood. In recent longitudinal analyses of the Alzheimer Disease Neuroimaging (ADNI) database, we found that apathy and hallucinations, but not other neuropsychiatric symptoms, were significant predictors of global functional impairment while controlling for numerous confounders in a continuum of older individuals with normal cognition, mild cognitive impairment (MCI), and AD dementia.[1] Building on these findings, this study concerns the relations of these prominent neuropsychiatric symptoms to AD biomarkers in the same ADNI cohort, and examines longitudinal data from individuals potentially in preclinical as well as clinical stages of AD.

A number of studies have defined a characteristic pattern of cortical thinning in AD that includes changes detectable in preclinical, MCI, and dementia stages of AD.[7−9] Moreover, abnormal levels of cerebrospinal fluid (CSF) amyloid-β 1-42 peptide ($A\beta_{1\text{-}42}$), tau phosphorylated at the threonine 181 ($p\text{-}tau_{181p}$), and total tau (t-tau) have been associated with increased atrophy in these AD-related cortical regions in individuals classified as clinically normal and MCI, supporting their utility as markers of early AD pathology.[8,10] The relationship of apathy and hallucinations to neuroimaging and CSF biomarkers of AD has not been investigated longitudinally, across the full spectrum of AD, from preclinical to amnestic MCI and to dementia.

In individuals with AD dementia, apathy has been associated cross-sectionally with reduced perfusion and metabolic activity in bilateral regions of the anterior cingulate cortex on single photon emission computed tomography (SPECT)[11−14] and 18F-fluorodeoxyglocuse positron emission tomography (FDG-PET) imaging,[13] with decreased anterior cingulate cortical volume[15,16] and thickness[17] using structural magnetic resonance imaging (MRI) and with altered microstructural white matter anisotropy in the left anterior cingulate.[18] Reductions in orbitofrontal metabolism and perfusion have also been demonstrated with apathy in multiple studies of AD dementia[11−13,15] with less consistent findings of apathy-associated orbitofrontal cortical tissue loss.[17] No studies have examined the relations of apathy to neuroimaging biomarkers of AD in amnestic MCI or preclinical AD populations despite abundant evidence that apathy often presents in early phases of the AD spectrum.

Prior SPECT studies of comorbid delusions and hallucinations in AD have identified hypoperfusion in diverse regions of the prefrontal, temporal, parietal, and cingulate cortices and, to a lesser extent, the striatum, as cross-sectionally related to the presence of these symptoms in AD dementia.[19−21] In a limited number of neuroimaging studies with more narrowly defined samples, visual hallucinations in AD dementia were cross-sectionally associated with hypoperfusion in the left dorsolateral prefrontal, left