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White matter hyperintensities and amyloid are independently associated with entorhinal cortex volume among individuals with mild cognitive impairment

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Abstract

Background: Current hypothetical models of Alzheimer's disease (AD) pathogenesis emphasize the role of β-amyloid (Aβ), tau deposition, and neurodegenerative changes in the mesial temporal lobe, particularly the entorhinal cortex and hippocampus. However, many individuals with clinical AD who come to autopsy also exhibit cerebrovascular disease. The relationship between AD and vascular pathology is unclear, especially whether they represent additive and independent effects on neuronal injury. We used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to (1) confirm whether entorhinal cortex and hippocampal volume are associated with memory among individuals with amnestic mild cognitive impairment (MCI) who are at risk for AD; and (2) determine whether regional white matter hyperintensity (WMH) volume, a radiological marker of small-vessel cerebrovascular disease, is associated with entorhinal cortex and hippocampal volume independent of putative AD biomarkers in this group.
Methods: Cognitive test scores, entorhinal cortex volume, hippocampus volume, intracranial volume, and cerebrospinal fluid-derived phosphorylated tau and Aβ1-42 protein levels were measured in 199 subjects with amnestic MCI (mean age = 74.89 ± 7.47). Lobar WMH volumes were derived from T1-, proton-density-, and T2-weighted magnetic resonance imaging scans. We examined the association between entorhinal cortex volume and cognition. Next, we examined the association of tau and Aβ1-42 with entorhinal cortex volume and between lobar WMH and entorhinal cortex volume. Finally, tau, Aβ1-42, and regional WMH volumes were entered simultaneously to predict entorhinal cortex volume. We repeated the analyses with hippocampal volume instead of entorhinal cortex volume. The analyses were also repeated with the sample restricted to those MCI patients who transitioned to AD on subsequent ADNI follow-up visits (n = 86).
Results: Larger entorhinal cortex volume was associated with better memory but not with performance on a task of executive functioning. Lower levels of Aβ1-42 and higher temporal WMH volumes were associated with smaller entorhinal cortex volume. When entered simultaneously, temporal lobe WMH volume was more reliably associated with entorhinal cortex volume than was Aβ1-42. The findings were similar for hippocampus volume and when the sample was restricted to MCI patients who subsequently transitioned to AD.

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[†]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.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.ucla.edu/wp- content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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Conclusions: The findings confirm the role of entorhinal cortex and hippocampus volume in influencing memory decline in amnestic MCI, and emphasize that even in this nominally AD prodromal condition, WMH may be influencing regional neurodegeneration.

Keywords: Mild cognitive impairment; Alzheimer's disease; White matter hyperintensities; β-amyloid; Tau

1. Introduction

The prevailing hypothesis of Alzheimer's disease (AD) pathogenesis suggests a temporal ordering of biomarker abnormalities that is biphasic [1]. According to the model, β-amyloid (Aβ) plaque formation precipitates a neurodegenerative cascade hallmarked by the formation of neurofibrillary tangles, which leads to neuronal injury, dysfunction, and degeneration. Among the most significant advances in AD research during the past several years has been the ability to operationally define these putative biological markers through neuroimaging and neurochemical analysis. For example, Aβ can be measured in vivo in the cerebrospinal fluid (CSF) or with amyloid positron emissions tomography (PET) techniques [2–4]. Likewise, the severity of neurofibrillary tangle formation can be inferred by measuring the amount of total or phosphorylated tau (p-tau) protein in the CSF [2,3]. Early signs of neurodegeneration can be appreciated through analysis of metabolic changes on PET [5], and frank neurodegenerative changes manifest as local atrophy in the mesial temporal lobe [1]. Temporal lobe atrophy, particularly in the entorhinal cortex (EC) and hippocampal formation, is thought to be the biological change most proximal to the onset of cognitive symptoms [1].

Hippocampal and EC atrophy have been recorded in patients diagnosed with AD and those with mild cognitive impairment (MCI), although EC is believed to be the more sensitive biomarker [6,7]. Pathological staging of AD [8] suggests that the EC is damaged before the hippocampus by neurofibrillary tangles and thus should be a more sensitive marker of earlier change, which is supported by in vivo studies [7].

In addition to the roles of Aβ, tau, and regional atrophy in AD, there is an emerging literature linking small-vessel cerebrovascular disease to the clinical presentation and course of AD [9,10], and many individuals with AD who come to autopsy evidence significant amounts of cerebrovascular disease [11]. Visualized as white matter hyperintensities (WMH) on T2-weighted magnetic resonance imaging (MRI), increased small-vessel cerebrovascular disease, particularly when distributed in posterior regions, has been linked to increased future risk for AD [12,13] and to course of disease progression [14]. However, it is unclear whether WMH should be incorporated as an additional biological marker for AD risk. One way of addressing this question is to determine whether WMH burden is associated with neurodegenerative markers of AD pathology, such as medial temporal lobe atrophy.

Here, we examined whether Aβ1-42, tau, and regional WMH are associated with EC and hippocampus atrophy [15] among individuals with amnestic MCI in the Alzheimer's Disease Neuroimaging Initiative (ADNI). MCI is considered an intermediate stage between normal cognitive aging and AD-related dementia [16,17], and in the ADNI cohort there was an effort to target individuals with the amnestic form of MCI thought to be at greatest risk for AD. Thus, an MCI cohort is enriched with individuals in the mildest stages of AD. The study of individuals with MCI affords the opportunities to examine some of the earliest changes associated with AD. Given the current hypothetical model of AD pathogenesis [1], we hypothesized that Aβ1-42 and tau would predict medial temporal lobe atrophy. Additionally, given the link of regional WMH to AD [13], we predicted that WMH severity would be independently associated with medial temporal lobe atrophy, suggesting a role of small-vessel cerebrovascular disease.

2. Methods

2.1. Subjects

Data from ADNI were downloaded (www.loni.ucla.edu/ADNI), including demographic, biomarker, neuropsychological, and structural MRI data. The ADNI study was designed to mirror a clinical trial and thus only included participants who were in good health. It is important to note that only individuals without significant vascular risk factors, operationally defined as a modified Hachinski score [18] of less than or equal to 4, and good general health were included in the study. For the current analyses, we limited the sample to those meeting criteria for MCI and with available measures of CSF-derived biological markers. Diagnostic criteria for MCI included age between 55 and 90, a memory complaint (study subject or informant), objective evidence of abnormal memory, Clinical Dementia Rating (CDR) score of 0.5, a Memory Box score of at least 0.5, Mini-Mental State Examination score between 24 and 30 (inclusive), general cognition preserved such that a diagnosis of AD could not be made, stable medication, and not depressed (Geriatric Depression Scale [19] score of less than 6). Recruitment and diagnostic procedures for ADNI have been reported previously [17] (www.loni.ucla.edu/ADNI).

The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the U.S. Food and Drug Administration (FDA), private pharmaceutical companies,