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Basal forebrain atrophy and cortical amyloid deposition in nondemented elderly subjects

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Abstract

Background: Both neurodegeneration of the cholinergic basal forebrain (BF) and deposition of β-amyloid are early events in the course of Alzheimer's disease (AD). Associations between increased amyloid pathology and cholinergic atrophy have been described in autopsy studies.
Methods: We used structural MRI and AV45-PET amyloid imaging data of 225 cognitively normal or mildly impaired elderly subjects from the Alzheimer's Disease Neuroimaging Initiative to assess in vivo associations between BF atrophy and cortical amyloid deposition. Associations were examined using region-of-interest (ROI) and voxel-based approaches with reference to cytoarchitectonic mappings of the cholinergic BF nuclei.
Results: ROI- and voxel-based approaches yielded complementary evidence for an association between BF volume and cortical amyloid deposition in presymptomatic and predementia stages of AD, irrespective of age, gender, and *APOE* genotype.
Conclusions: The observed correlations between BF atrophy and cortical amyloid load likely reflect associations between cholinergic degeneration and amyloid pathology as reported in neuropathologic examination studies.

Keywords: Alzheimer's disease; Mild cognitive impairment; Preclinical; Predementia; AV45-PET; Amyloid; MRI; Voxel-based; Cytoarchitectonic; Cholinergic basal forebrain; Substantia innominata; Nucleus basalis Meynert

1. Introduction

Cholinergic neurons of the basal forebrain (BF) provide the cholinergic innervation of the entire cortical mantle [1]. In normal aging these neurons are known to undergo moderate neurodegenerative changes, whereas Alzheimer's disease (AD) is characterized by severe cholinergic neuron loss and cortical cholinergic denervation [2–5].

The cholinergic deficit in AD does not arise in isolation. Cerebral amyloid deposition, as caused by altered processing of the membrane-bound amyloid precursor protein (APP), is widely considered to be a primary etiologic factor in AD. Thus, the amyloid cascade model proposes a sequence of pathologic events in AD that begins with cerebral amyloid deposition several years to decades before the first symptoms appear. Over the years, the primary amyloid-related molecular pathology initiates downstream pathologic events, such as the formation of intracellular

[1]Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu/). As such, the investigators within the ADNI contributed to the design and implementation 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/about/centers-cores/study-sites/.

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neurofibrillary tangles, which ultimately lead to neuronal dysfunction, atrophy, and cognitive decline [6].

An increasing body of evidence suggests that amyloid accumulation and cholinergic dysfunction are tightly interrelated and may mutually influence each other [7]. Transgenic animal models of amyloid pathology develop alterations of the cholinergic system [8] and cortical cholinergic denervation leads to increased amyloid deposition in wild-type animals [9]. Histopathologic studies on the relationship between amyloid deposition and cholinergic decline in AD brain specimens showed that increased cortical amyloid load was associated with degeneration of cholinergic BF neurons [10,11] and reduced cortical choline acetyltransferase (ChAT) activity [4,12]. Similar findings were observed in autopsies from nondemented elderly subjects showing evidence of AD pathology [13,14], but so far there is no in vivo evidence for a relationship between cholinergic degeneration and increased amyloid deposition in humans.

In the present study, we combined novel amyloid-sensitive positron emission tomography (AV45-PET) [15] with morphometric analysis of structural magnetic resonance imaging (MRI) scans guided by cytoarchitectonic maps of the BF cholinergic nuclei [16–19] to assess the relationship between cortical amyloid deposition and BF atrophy in a large sample of nondemented subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI).

2. Methods

Data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu/). The ADNI was launched in 2003 with the primary goal of testing whether neuroimaging, neuropsychologic, and other biologic measurements can be used as reliable in vivo markers of AD pathogenesis. A fuller description of ADNI and up-to-date information is available at www.adni-info.org.

2.1. Subjects

AV45-PET and structural MRI scans were retrieved from the ADNI-GO/-2 extensions of the ADNI project and included imaging data of 57 cognitively normal (CN) elderly subjects, 156 subjects with early-stage mild cognitive impairment (EMCI), and 32 subjects in a more advanced stage of MCI (LMCI). Detailed inclusion criteria for the diagnostic categories can be found at the ADNI website (http://adni.loni.usc.edu/methods/). Briefly, CN subjects are those with: MMSE scores of between 24 and 30 (inclusive); a CDR of 0; no depression; no MCI; and no dementia. EMCI subjects are those with: MMSE scores between 24 and 30 (inclusive); a subjective memory concern reported by subject, informant, or clinician; objective memory loss as measured by education-adjusted scores on delayed recall (Wechsler Memory Scale Logical Memory II); a CDR of 0.5; absence of significant levels of impairment in other cognitive domains; essentially preserved activities of daily living; and an absence of dementia. Diagnosis of LMCI differs from that of EMCI only with regard to a higher degree of impairment according to the logical memory test.

2.2. Imaging data acquisition

ADNI-GO/-2 MRI data were acquired on multiple 3-T MRI scanners using scanner-specific T1-weighted sagittal 3D MPRAGE sequences. To increase signal uniformity across the multicenter scanner platforms, original MPRAGE acquisitions in ADNI undergo standardized image preprocessing correction steps.

AV45-PET data were acquired on multiple instruments of varying resolution and following different platform-specific acquisition protocols. Similar to the MRI data, PET data in ADNI undergo standardized image preprocessing correction steps aimed at increasing data uniformity across the multicenter acquisitions.

More detailed information on the different imaging protocols employed across ADNI sites and standardized image preprocessing steps for MRI and PET acquisitions can be found on the ADNI website (http://adni.loni.usc.edu/methods/).

2.3. MRI processing

Imaging data were processed using SPM8 (Wellcome Trust Center for Neuroimaging) implemented in MATLAB R2007a (The MathWorks, Natick, MA). MRI scans were automatically segmented into gray-matter (GM), white-matter (WM), and cerebrospinal fluid (CSF) partitions using the segmentation routine of the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/). The GM partitions were then high-dimensionally warped [20] to an aging/AD-specific reference template, based on a previous study [18]. Voxel values were modulated for volumetric changes, and for voxel-based analyses modulated warped GM segments were smoothed with a Gaussian smoothing kernel of 8-mm full-width at half-maximum (FWHM). All preprocessed GM maps passed a visual inspection for overall segmentation and registration accuracy.

Individual GM volumes of regions-of-interest (ROIs) were extracted automatically from the warped GM segments by summing up the modulated GM voxel values within the respective ROI masks in the reference space (see later). For further analyses, extracted regional GM volumes were divided by the total intracranial volume (TIV), calculated as the sum of total volumes of the GM, WM, and CSF partitions.

2.4. Definition of BF and hippocampus ROIs

According to Mesulam's nomenclature [1], the cholinergic BF is composed of four groups of cholinergic cells, which correspond to the medial septum (Ch1), the vertical and horizontal limb of the diagonal band of Broca (Ch2 and Ch3), and the nucleus basalis Meynert (NBM, Ch4).