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Cholinergic basal forebrain atrophy predicts amyloid burden in Alzheimer's disease

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ABSTRACT

We compared accuracy of hippocampus and basal forebrain cholinergic system (BFCS) atrophy to predict cortical amyloid burden in 179 cognitively normal subjects (CN), 269 subjects with early stages of mild cognitive impairment (MCI), 136 subjects with late stages of MCI, and 86 subjects with Alzheimer's disease (AD) dementia retrieved from the Alzheimer's Disease Neuroimaging Initiative database. Hippocampus and BFCS volumes were determined from structural magnetic resonance imaging scans at 3 Tesla, and cortical amyloid load from AV45 (florbetapir) positron emission tomography scans. In receiver operating characteristics analyses, BFCS volume provided significantly more accurate classification into amyloid-negative and -positive categories than hippocampus volume. In contrast, hippocampus volume more accurately identified the diagnostic categories of AD, late and early MCI, and CN compared with whole and anterior BFCS volume, whereas posterior BFCS and hippocampus volumes yielded similar diagnostic accuracy. In logistic regression analysis, hippocampus and posterior BFCS volumes contributed significantly to discriminate MCI and AD from CN, but only BFCS volume predicted amyloid status. Our findings suggest that BFCS atrophy is more closely associated with cortical amyloid burden than hippocampus atrophy in predementia AD.

1. Introduction

According to the amyloid cascade hypothesis, cortical amyloid accumulation is the first event in the pathogenesis of Alzheimer's disease (AD) instigating further pathological events, including the formation of neurofibrillary tangles and disruption of synaptic connections, which then lead to a reduction in neurotransmitter levels, death of tangle-bearing neurons, and dementia (Selkoe, 2000). Therefore, detection of cortical amyloid accumulation using positron emission tomography (PET) with amyloid binding compounds has become a disease defining marker of AD (Barthel et al., 2011; Klunk et al., 2004).

The interaction between PET markers of cortical amyloid accumulation and structural imaging markers of atrophy in AD has found increasing attention. Hippocampus volume, the best established structural imaging marker of AD (Dubois et al., 2007; Wahlund et al., 2005), was not different or even larger in amyloid-positive (+) compared with amyloid-negative (−) healthy subjects (Becker et al., 2011; Bourgeat et al., 2010), but yet inversely correlated with amyloid load in amyloid+ healthy subjects in some, but not all studies (Apostolova et al., 2010; Bourgeat et al., 2010; Chetelat et al., 2010a, 2010b). In mild cognitive impairment (MCI) stages of AD, hippocampus atrophy has not been associated with global or regional amyloid accumulation in most studies (Apostolova et al., 2010; Chetelat et al., 2010b). Thus, associations between cortical amyloid deposition and hippocampus atrophy were relatively weak, consistent with postmortem evidence that amyloid pathology occurs in the hippocampus only secondary to neurofibrillary pathology (Braak and Braak, 1997; Royall et al., 2012).

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Besides amyloid accumulation, cholinergic degeneration is regarded as a key event in AD pathogenesis (Mesulam, 2004). Degeneration of basal forebrain cholinergic nuclei occurs in early and predementia stages of AD (Mann et al., 1984; Perry et al., 1978; Sassin et al., 2000; Whitehouse et al., 1981). Animal models and postmortem brain studies provide evidence for a 2-way interaction between cholinergic transmission and amyloid accumulation (Schliebs and Arendt, 2006), with a specific vulnerability of cholinergic basal forebrain neurons to amyloid toxicity (Boncristiano et al., 2002) and increased amyloid formation with decline of cholinergic transmission (Beach, 2008). Volumetric measurement of cholinergic nuclei in the basal forebrain has become available (Grothe et al., 2010, 2012; Teipel et al., 2005) using in vivo structural magnetic resonance imaging (MRI) and masks of the basal forebrain cholinergic nuclei derived from postmortem MRI and histology (Heinsen et al., 2006).

Other than amyloid end points, changes in hippocampus volume were consistently found to be associated with episodic memory impairment (Grothe, et al., 2010; Mortimer et al., 2004; Reitz et al., 2009; Teipel et al., 2010), the defining clinical criterion for MCI. Accordingly, hippocampus volume was superior to cortical amyloid load in discriminating amnestic MCI subjects from healthy control subjects in a previous study (Jack et al., 2008). So far, BFCS volume has been little studied for diagnosis of MCI, reaching an accuracy below that of hippocampus volume in one previous study (Grothe et al., 2012).

Based on these findings, our primary hypothesis was that BFCS volume would be more sensitive to cortical amyloid accumulation than hippocampus volume in cognitively healthy elderly and MCI subjects. Our secondary hypothesis was that hippocampus volume would be more sensitive than BFCS volume to predict a diagnosis of MCI. We used data from 670 subjects retrieved from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu) comprised of subjects with AD dementia, early and late stages of MCI, and cognitively healthy elderly subjects. Based on this sample, we determined the accuracy of BFCS and hippocampus volumes to predict PET-based classification into amyloid+ or amyloid− subgroups and to differentiate MCI subjects from cognitively healthy control subjects irrespective of amyloid status.

2. Methods

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.ucla.edu). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, and lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, Veterans Affairs Medical Center and University of California, San Francisco. ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and subjects have been recruited from more than 50 sites across the United States and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date, these 3 protocols have recruited more than 1500 adults, ages 55–90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow-up duration of each group is specified in the protocols for ADNI-1, ADNI-2, and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org.

2.1. Subjects

(AV45)-amyloid-PET and structural MRI scans were retrieved from the ADNI-GO and ADNI-2 extensions of the ADNI project and included imaging data of 179 cognitively normal elderly subjects (CN), 269 subjects with early stage MCI (EMCI), 136 subjects in a more advanced stage of MCI (LMCI), and 86 subjects in dementia stages of AD. A subset of this sample, 57 CN, 155 EMCI, and 31 LMCI subjects, had been included in a previous study (Grothe et al., in press).

Detailed inclusion criteria for the diagnostic categories can be found at the ADNI Web site (http://adni.loni.usc.edu/methods/documents/). Briefly, CN subjects have Mini Mental State Examination (MMSE) scores between 24 and 30 (inclusive), a Clinical Dementia Rating (CDR) score = 0, are nondepressed, non-MCI, and nondemented. EMCI subjects have MMSE scores between 24 and 30 (inclusive), a subjective memory concern reported by the subject, informant, or clinician, objective memory loss measured using education-adjusted scores on delayed recall (1 paragraph from Wechsler Memory Scale Logical Memory II; education-adjusted scores: ≥16 years: 9–11; 8–15 years: 5–9; 0–7 years: 3–6), a CDR = 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 in a higher degree of objective memory impairment (education-adjusted scores: ≥16 years: ≤8; 8–15 years: ≤4; 0–7 years: ≤2). Subjects with AD dementia have initial MMSE scores between 20 and 26 (inclusive), a CDR = 0.5 or 1.0 and fulfill National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria for clinically probable AD (McKhann et al., 1984).

2.2. Imaging data acquisition

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

(AV45)-amyloid-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 used across ADNI sites and standardized image preprocessing steps for MRI and PET acquisitions can be found on the ADNI Web site (http://adni.loni.usc.edu/data-samples/).

The average acquisition delay between AV45 scans and corresponding MRI scans used in this study was 33.8 ± 30.5 days.

2.3. Imaging data processing

Imaging data were processed using statistical parametric mapping (SPM8, Wellcome Trust Center for Neuroimaging) and the