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Longitudinal measures of cholinergic forebrain atrophy in the transition from healthy aging to Alzheimer's disease

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ABSTRACT

Recent evidence from cross-sectional in vivo imaging studies suggests that atrophy of the cholinergic basal forebrain (BF) in Alzheimer's disease (AD) can be distinguished from normal age-related degeneration even at predementia stages of the disease. Longitudinal study designs are needed to specify the dynamics of BF degeneration in the transition from normal aging to AD. We applied recently developed techniques for in vivo volumetry of the BF to serial magnetic resonance imaging scans of 82 initially healthy elderly individuals (60–93 years) and 50 patients with very mild AD (Clinical Dementia Rating score = 0.5) that were clinically followed over an average of 3 ± 1.5 years. BF atrophy rates were found to be significantly higher than rates of global brain shrinkage even in cognitively stable healthy elderly individuals. Compared with healthy control subjects, very mild AD patients showed reduced BF volumes at baseline and increased volume loss over time. Atrophy of the BF was more pronounced in progressive patients compared with those that remained stable. The cholinergic BF undergoes disproportionate degeneration in the aging process, which is further increased by the presence of AD.

1. Introduction

Degeneration of basal forebrain (BF) cholinergic cells and loss of cortical cholinergic innervation is a well established characteristic of Alzheimer's disease (AD). A range of postmortem studies on AD found severe neurofibrillary degeneration and cell loss in the cholinergic BF, most pronounced in the nucleus basalis of Meynert (NBM), and a depletion of cortical choline-acetyl transferase activity (Lehericy et al., 1993; McGeer et al., 1984; Perry, 1980; Whitehouse et al., 1981). The extent of cholinergic loss was also found to correlate with dementia severity and several lines of evidence suggest that the cholinergic lesion in AD is, at least partly, responsible for specific cognitive impairments in the domains of memory and higher attentional functions (Bartus, 2000; Muir, 1997). Number and size of BF cholinergic neurons and activity of cortical cholinergic markers were also found to decrease along the human lifespan, suggesting that the cholinergic degeneration in AD occurs against a background of considerable age-related atrophy (Lowes-Hummel et al., 1989; Mann et al., 1984; McGeer et al., 1984; Perry, 1980).

The onset and temporal dynamics of augmented cholinergic degeneration in AD compared with normal age-related degeneration are not well understood (Mesulam, 2004). Mild cognitive impairment (MCI) is regarded a transitional state between normal aging and AD, and research has focused on this patient group to study early pathologic alterations in the course of AD progression (Gauthier et al., 2006). Postmortem studies on MCI found no cholinergic cell loss or reduced cortical cholinergic markers when compared with cognitively healthy control subjects of the same age (DeKosky et al., 2002; Gilmor et al., 1999). However, cholinergic cells of the BF showed significantly increased neurofibrillary burden (Mesulam et al., 2004; Sassin et al., 2000), axonal abnormalities (Geula et al., 2008), and reduced trophic support (Mufson et al., 2007) in MCI and early stages of AD, indicating an accelerated and qualitatively different neurodegenerative process compared with normal aging.

Complementary to postmortem studies that are usually limited to small sample sizes and do not allow for longitudinal observations, in vivo imaging approaches help to study the course of BF atrophy in normal and pathologic aging. Previous studies have developed a structural magnetic resonance imaging (MRI) marker of BF

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integrity, based on cytoarchitectonic maps of BF cholinergic nuclei and deformation-based morphometry, enabling the in vivo study of volumetric changes of the cholinergic BF in aging and AD (Grothe et al., 2010, 2012; Teipel et al., 2005, 2011; Zaborszky et al., 2008). In a recent study (Grothe et al., 2012) we applied this technique to a relatively large, publicly available dataset of cross-sectional MRI scans covering the whole adult age range and early stages of AD (Marcus et al., 2007; Open Access Series of Imaging Studies [OASIS], www.oasis-brains.org). We found a decline of BF volume with advanced age that was further pronounced in early stages of AD, allowing for the use of BF atrophy as a diagnostic marker of AD.

In addition to cross-sectional analysis, in vivo imaging allows for longitudinal observations of the same subjects, to assess subject-specific atrophy rates and the association between imaging measures at baseline and the clinical outcome at follow-up. Here we applied our previously established method for in vivo assessment of BF volume to the recently released longitudinal dataset of the OASIS database (Marcus et al., 2010), including serial MRI scans of healthy elderly subjects and clinically stable and clinically declining patients with very mild AD (vmAD; Clinical Dementia Rating [CDR] score = 0.5). The dataset also includes subjects that were cognitively normal at baseline and declined to a diagnosis of vmAD over follow-up, thus providing the possibility to study atrophic brain changes in subjects with presumptive AD pathology before the onset of cognitive symptoms. In vivo measures of BF volume at baseline and rates of BF volume loss over time were compared between diagnostic groups. To the best of our knowledge, this is the first study examining longitudinal changes in BF volume in healthy elderly subjects and subjects in early stages of AD. For comparison, we also investigated cross-sectional and longitudinal measures of hippocampus atrophy and whole-brain patterns of atrophic changes within and across diagnostic groups, using automated hippocampus segmentation and voxel-based analysis, respectively.

2. Methods

2.1. Subjects

MRI scans were retrieved from the longitudinal collection of the OASIS database (Marcus et al., 2010; http://www.oasis-brains.org). Detailed inclusion and diagnostic criteria of the OASIS database are described in the OASIS documentation (Marcus et al., 2007, 2010). Briefly, all subjects of the OASIS cohort participated in accordance with guidelines of the Washington University Human Studies Committee. Approval for public sharing of the data was also specifically obtained. Participants were clinically screened and exclusion criteria included use of psychoactive drugs, serious head injury, history of clinically meaningful stroke, active neurological or psychiatric illness, and primary causes of dementia other than AD. Subjects underwent full clinical assessment at each visit and MRI acquisitions were typically obtained within 1 year before or after a subject's clinical assessment (mean = 111 days; range, 0–352 days). Twelve subjects with AD were scanned after a somewhat longer duration (mean = 653 days; range, 374–924 days) but were included because each subject had several previous clinical assessments with CDR scores greater than 0. Two subjects without dementia were scanned somewhat more than 1 year before a clinical assessment (392 and 431 days) but were included because their subsequent clinical assessments yielded a CDR score of 0. Each subject was scanned on 2 or more separate occasions, with an average delay of 719 days (range, 183–1707 days) between visits.

Dementia status was established and staged using clinical interviews and the CDR scale (McKhann et al., 1984; Morris, 1993). After the staging of AD based on CDR scores, a global CDR of 0 indicates no dementia, and CDRs of 0.5, 1, 2, and 3 represent very mild, mild, moderate, and severe dementia, respectively (Berg et al., 1982, 1998). Based on a CDR score of 0.5 (questionable dementia), subjects with very mild AD present with mild consistent memory problems but show preserved function or only doubtful impairment in the other domains of the CDR interview, including orientation, judgment and problem solving, function in community affairs, home and hobbies, and personal care (Berg et al., 1982; Morris et al., 1991). Although this classification differs slightly from the Petersen criteria for the diagnosis of MCI (Gauthier et al., 2006), autopsy studies suggest that the diagnoses of very mild AD and MCI represent similar levels of early AD pathology (Morris and Price, 2001; Morris et al., 2001; Storandt et al., 2006).

The present study included the baseline scan and the last follow-up scan of 82 healthy elderly subjects (HE; age at baseline: 75.7 ± 8.2 years) and 50 subjects with vmAD (CDR = 0.5, Mini Mental State Examination [MMSE] = 26.1 ± 2.5; age at baseline: 75.2 ± 6.0 years). A total of 79.5% of the subjects, equally distributed across the diagnostic groups, overlapped with the cross-sectional OASIS sample we used in our previous study on BF degeneration in aging and AD (Grothe et al., 2012). Of the 82 healthy elderly subjects, 69 remained cognitively normal (s-HE) and 13 declined cognitively to a diagnosis of vmAD over follow-up (p-HE). In the vmAD group, 37 patients remained cognitively stable (s-vmAD) and 13 progressed to a diagnosis of clinically manifest AD (p-vmAD) over follow-up. Demographic characteristics and global neuropsychological profiles of the studied samples are summarized in Table 1. MMSE scores at baseline differed significantly between the vmAD groups and the s-HE sample (both $p < 0.001$) and between s-vmAD and p-vmAD ($p = 0.05$) but not between s-HE and p-HE ($p = 0.38$). Diagnostic groups did not differ significantly in age, with the exception of the p-vmAD group, being significantly younger than the s-vmAD group ($p < 0.02$) and showing a trend for younger age compared with the s-HE group ($p = 0.06$). Mean follow-up time in years differed significantly between s-HE (3.3 ± 1.4) and both vmAD groups (s-vmAD: 2.5 ± 1.4; $p = 0.004$; p-vmAD: 2.0 ± 0.9, $p < 0.001$) and there were trends for longer follow-up times in p-HE (4.0 ± 1.5) compared with s-HE ($p = 0.06$) and in s-vmAD (2.5 ± 1.4) compared with p-vmAD (2.0 ± 0.9; $p = 0.06$). There were significantly more women than men in the s-HE group (21% male; $\chi^2 = 12.2$, $p < 0.001$). The sex distribution of the stable control group differed significantly from the s-vmAD group (Fisher's exact test, $p = 0.003$) but not from the p-HE ($p = 1$) or the p-vmAD group ($p = 0.1$). Also, sex distribution did not differ significantly between the s-vmAD and p-vmAD groups ($p = 0.7$).

2.2. MRI acquisition

All images of the OASIS database were acquired on a 1.5-T Vision scanner (Siemens, Erlangen, Germany) using a sagittally oriented T1-weighted magnetization prepared rapid gradient-echo sequence with a resolution of 1.25 mm × 1 mm × 1 mm and empirically

Table 1
Subject demographic characteristics

	s-HE	p-HE	s-vmAD	p-vmAD
Number of subjects	69	13	37	13
Age-BL, y (SD)	75.3 (8.4)	78.0 (7.1)	76.1 (4.6)	72.7 (6.8)
Sex (F/M)	49/20	9/4	15/22	6/7
Follow-up, y (SD)	3.3 (1.4)	4.0 (1.5)	2.5 (1.4)	2.0 (0.9)
MMSE-BL (SD)	29.2 (0.9)	29.3 (0.9)	26.6 (3.4)	24.8 (2.8)
MMSE-FU (SD)	29.2 (0.9)	27.9 (SD1.9)	25.9 (5.0)	22.3 (3.5)

Key: AD, Alzheimer's disease; BL, baseline; F, female; FU, follow-up; M, male; MMSE, Mini Mental State Examination; p-HE, healthy elderly subjects who declined cognitively to a diagnosis of vmAD over follow-up; p-vmAD, vmAD patients who progressed to a diagnosis of clinically manifest AD; s-HE, stable cognitively normal elderly healthy control subjects; s-vmAD, vmAD patients who remained cognitively stable; vmAD, very mild AD.