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Accelerated decline in white matter integrity in clinically normal individuals at risk for Alzheimer's disease

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ABSTRACT

Prior studies have identified white matter abnormalities in Alzheimer's disease (AD). Yet, cross-sectional studies in normal older individuals show little evidence for an association between markers of AD risk (APOE4 genotype and amyloid deposition), and white matter integrity. Here, 108 normal older adults (age, 66–87) with assessments of apolipoprotein e4 (APOE4) genotype and assessment of amyloid burden by positron emission tomography underwent diffusion tensor imaging scans for measuring white matter integrity at 2 time points, on average 2.6 years apart. Linear mixed-effects models showed that amyloid burden at baseline was associated with steeper decline in fractional anisotropy in the parahippocampal cingulum ($p < 0.05$). This association was not significant between baseline measures suggesting that longitudinal analyses can provide novel insights that are not detectable in cross-sectional designs. Amyloid-related changes in hippocampus volume did not explain the association between amyloid burden and change in fractional anisotropy. The results suggest that accumulation of cortical amyloid and white matter changes in parahippocampal cingulum are not independent processes in individuals at increased risk for AD.

1. Introduction

Damage to white matter, including demyelination and axonal loss, is a frequent observation in postmortem examinations of patients with Alzheimer's disease (AD), and histopathological studies have shown that microstructural white matter damage in AD can occur independent of gray matter neurodegeneration (e.g., Bartzokis et al., 2004; Brun and Englund, 1986; Englund et al., 1988; Han et al., 2002).

Reduced integrity of white matter in AD has also been found with human in vivo magnetic resonance imaging (MRI) studies. These studies suggest a predominance of AD-related changes in the parietal and temporal white matter (e.g., Bozzali et al., 2002; Brickman et al., 2012; Head et al., 2004; Medina et al., 2006). Consistent with AD pathology and the notion of AD as a "disconnection" disorder (Hyman et al., 1984), analyses of specific fiber tracts using diffusion tensor imaging (DTI) have refined these results to identify a pronounced reduction of fractional anisotropy (FA) and increases in diffusivity in the parahippocampal cingulum, a collection of fibers which connect the hippocampal formation and the posterior cingulate cortex. Several studies have reported reduced parahippocampal white matter integrity already in mild cognitive impairment and normal individuals with cognitive complaints, and suggested this fiber bundle may play an important role in declining memory functions in the path to AD (Ito et al., 2015; Wang et al., 2012; Zhang et al., 2007). Further reductions in FA and increases in diffusivity in AD have been noted in nearby white matter pathways including the main cingulum bundle, the corpus callosum and the superior longitudinal fasciculi (e.g., Rose et al., 2000; Salat et al., 2010).

Elevated amyloid burden measured with positron emission tomography (PET) imaging of 11C-Pittsburgh Compound B (PIB) is a

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biomarker of amyloid plaques, a neuropathological hallmark of AD, and is detectable in a subset of clinically normal older adults (Klunk, 2011; Rabinovici and Jagust, 2009; Sojkova and Resnick, 2011). Despite reliable associations between AD diagnosis and reduced white matter integrity, in the subset of clinically normal older adults with amyloid burden, evidence for white matter damage is inconsistent. Heightened amyloid deposition in older adults without AD diagnosis has been associated with subtle decreases (Chao et al., 2013), but also with paradoxical increases in FA, and no changes in diffusivity, in the medial temporal lobe, cingulum and corpus callosum (Racine et al., 2014), as well as no differences in FA, unless accompanied by gray matter neurodegeneration (Kantarci et al., 2014). Similarly, large white matter lesions observed as white matter hyperintensities (WMH) on T2-weighted MRI that are elevated in AD (Brickman, 2013, for review; Scheltens et al., 1995) show no association with amyloid burden in clinically normal individuals (e.g., Hedden et al., 2012; Marchant et al., 2012; Rutten-Jacobs et al., 2011; Vemuri et al., 2015). There is also little evidence that the presence of the apolipoprotein e4 (APOE4) allele is reliably associated with reduced FA in large samples of clinically normal older adults (Nyberg and Salami, 2014; Westlye et al., 2012), although it is a major risk factor for amyloid accumulation (Ossenkoppele et al., 2015) and AD (Corder et al., 1993). Notably, widespread increases in diffusivity for e4 carriers were noted in some studies, suggesting that diffusivity measures may be more sensitive to subtle white matter changes in healthy individuals at increased risk for AD (Heise et al., 2011; Westlye et al., 2012; but see; Nyberg and Salami, 2014).

Collectively, the previously mentioned observations provide mixed evidence for an association between markers of AD risk and imaging-based measures of white matter integrity in clinically normal older adults. It is possible that white matter tract disruption may emerge relatively late in the cascade of detectable biomarkers and may only become apparent when following individuals over time.

A major advantage of longitudinal studies is that within-person change can be directly examined instead of relying on the inference of age-related change through between-person comparisons. Longitudinal DTI studies have demonstrated that DTI measures are reliable within older individuals (Jovicich et al., 2014) and that white matter integrity shows significant decline in clinically normal older adults at a rate of approximately 0.5–1.0% per year for FA (Barrick et al., 2010; Charlton et al., 2010; Sexton et al., 2014; Teipel et al., 2010). The estimates of longitudinal change in FA have been shown to exceed those from cross-sectional designs, which could point to a positive selection bias for very old adults in cross-sectional studies (Charlton et al., 2010; Lövdén et al., 2014). One recent DTI study found markedly different associations between age-related declines in FA and a third variable (here, change in cognition) depending on whether age associations with FA were estimated longitudinally or cross-sectionally (Lövdén et al., 2014), and another study reported little convergence between cross-sectional and longitudinal age associations in a sample of adults between 19 and 78 years (Bender and Raz, 2015).

The present study revisits the question of when changes in white matter microstructure occur in individuals at increased risk for developing AD by examining longitudinally measured DTI metrics in clinically normal individuals with elevated amyloid burden. We predict that, even though associations between amyloid burden and white matter tract disruption are not always detectable cross-sectionally, they emerge when following individuals at increased risk for AD over time. The analyses are based on linear mixed-effects models with APOE4 status and amyloid burden as estimated by PET at baseline as predictors of longitudinal change in regional FA and diffusivity over an average duration of 2.6 years. In the analyses, we control for possible confounding effects such as age, sex, and head motion during MR imaging and investigate the influence of WMH on the association between markers of AD risk and longitudinal decline in DTI measures of white matter integrity. Informed by a significant finding in the parahippocampal cingulum, we also perform an additional analysis in which we investigate the relation between amyloid and hippocampal atrophy and whether an association between amyloid burden and FA in the parahippocampal cingulum is independent of this cascade.

2. Materials and methods

2.1. Sample

Participants were recruited as part of the Harvard Aging Brain Study, an ongoing longitudinal study. A total of 254 clinically normal older participants (Clinical Dementia Rating [CDR] = 0, mini mental-state examination score [MMSE] $\geq$ 26) with complete DTI data, structural MRI data, a ^{11}C-PiB PET scan, and APOE genotyping at baseline entered the study. Of these, 117 participants completed a second MRI exam 2.6 years later (range = 2.3–3.3). After exclusion of DTI data due to excessive head motion during a DTI scan (average motion exceeded 2.0 mm), 247 participants were included at baseline of which 108 had longitudinal DTI and structural MRI data. Where appropriate, we occasionally refer to the entire baseline sample for comparisons (Supplement 1 and 2). The main analyses and results are focused on longitudinal data from the 108 participants (61 women; mean age at baseline = 73.7, range = 66–87 years; mean education = 16.5 years, range = 8–20; mean MMSE at baseline = 29.1, range = 26–30; mean MMSE at follow-up = 29.3, range = 27–30). Subjects with a history of neurological or psychiatric disease or who were found ineligible for MRI were not allowed into the study. Based on self-report, 65 individuals had received a diagnosis and treatment of hypertension by their physician. In addition, a radiologist reviewed MRI images to rule out cortical infarcts, tumor, or other brain abnormalities. At follow-up, 12 individuals had changed from 0 to 0.5 on the CDR.

Allelic variation in the APOE gene was assessed by genotyping, and participants were grouped by the presence of at least one APOE e4 allele (N = 247: 25.5% e4+; N = 108: 28.7% e4+). None of the e4 carriers carried an APOE e2 allele. All participants gave written informed consent.

2.2. Amyloid imaging

PET images were acquired with an HR+ (CTI, Knoxville, TN, USA) PET camera at Massachusetts General Hospital (3D mode, 63 adjacent slices of 2.4 mm interval, 15.2-cm axial field of view, 5.6-mm transaxial resolution). Approximately 15-mCi 11C-PiB were intravenously administered as a bolus over 20–30 seconds. Dynamic images were acquired in 39 frames of increasing duration for a total of 60 minutes (8 $\times$ 5 seconds, 4 $\times$ 1 minute, 27 $\times$ 2 minutes). PET data were reconstructed using a filtered back-projection algorithm. Before the emission scans, a transmission scan of 10 minutes was performed, and photon attenuation measurements were used to correct the emission data. The participant's head was stabilized using a beaded cushion and velcro straps, and correction for residual head motion was performed on the dynamic data by registration to a common reference frame.

Dynamic data from the first 8 minutes were averaged to create an initial uptake image. The initial uptake image was used for normalization of native PET space to a standard PET template in Montreal Neurological Institute (MNI) space. Then, emission data were coregistered to standard space using the normalization