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The effects of white matter hyperintensities and amyloid deposition on Alzheimer dementia

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ABSTRACT

Background and purpose: Elevated levels of amyloid deposition as well as white matter damage are thought to be risk factors for Alzheimer Disease (AD). Here we examined whether qualitative ratings of white matter damage predicted cognitive impairment beyond measures of amyloid.
Materials and methods: The study examined 397 cognitively normal, 51 very mildly demented, and 11 mildly demented individuals aged 42–90 (mean 68.5). Participants obtained a T_2-weighted scan as well as a positron emission tomography scan using ^{11}[C] Pittsburgh Compound B. Periventricular white matter hyperintensities (PVWMHs) and deep white matter hyperintensities (DWMHs) were measured on each T_2 scan using the Fazekas rating scale. The effects of amyloid deposition and white matter damage were assessed using logistic regressions.
Results: Levels of amyloid deposition ($ps < 0.01$), as well as ratings of PVWMH ($p < 0.01$) and DWMH ($p < 0.05$) discriminated between cognitively normal and demented individuals.
Conclusions: The amount of amyloid deposition and white matter damage independently predicts cognitive impairment. This suggests a diagnostic utility of qualitative white matter scales in addition to measuring amyloid levels.

1. Introduction

Alzheimer disease (AD) is a rapidly expanding health crisis affecting over 26 million people, with the prevalence expected to rise dramatically (Brookmeyer et al., 2007). Research examining AD biomarkers suggests a rise in underlying pathology a decade or more before the onset of dementia, and continuing throughout the early stages of the disease (Bateman et al., 2012; Benzinger et al., 2013; Jack et al., 2010). There is need to translate such biomarkers from a laboratory setting into a clinical environment to assist with disease diagnosis and prognosis.

The hallmarks of AD pathology are the formation of amyloid beta (Aβ) plaques and the aggregation of tau into neurofibrillary tangles (NFTs) (Braak and Braak, 1995; Hardy and Higgins, 1992). Early elevations in such pathology are subsequently followed by hypometabolism, structural atrophy, and cognitive impairment (Bateman et al., 2012; Benzinger et al., 2013; Jack et al., 2010). Atrophy of cortical and subcortical gray matter has long been noted in AD (e.g. Fox et al., 1996; Gordon et al., 2013; Scheltens et al., 1992). Less attention has been paid to white matter damage and declines tied to AD disease progression.

Early work with computed tomography (CT) images noted increased incidence of white matter leukoaraiosis in individuals with AD (Blennow et al., 1991; Rezek et al., 1987). Similar results were found with the introduction of magnetic resonance imaging (MRI) (Barber et al., 1999; Fazekas et al., 1987). In this initial work the most common way to characterize white matter damage was to use semi-quantitative scales (Fazekas et al., 1987; Kapeller et al., 2003; Scheltens et al., 1995) to grade the severity of white matter hyperintensities (WMHs) on T_2-weighted or fluid-attenuated inversion recovery (FLAIR) scans. At a pathological level, the tissue suffering from WMHs demonstrates the loss of myelin and gliosis. Higher ratings on these scales are associated with both cognitive decline (Debette et al., 2007; Schmidt et al., 2005; van Straaten et al., 2008) and cortical atrophy (Capizzano, 2004; Schmidt et al., 2005). In general there is a rising interest on the clinical importance of WMH across diseases (Debette and Markus, 2010).

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The relationship between WMH and amyloid is complex and has not been fully evaluated, although there are suggestions that both contribute to cognitive impairment (Provenzano et al., 2013). White matter damage may be both a downstream result of elevated Aβ levels, as well as a marker of comorbid pathology (e.g. cardiovascular disease). Aβ leads to oxidative damage and the formation of free radicals (Hensley et al., 1994; Park et al., 2004; Thomas et al., 1996), and the administration of Aβ damages oligodendrocytes in vitro (Roth et al., 2005) and in vivo (Jantaratnotai et al., 2003). Conversely damage to myelin releases iron molecules that promote Aβ oligomerization (Bartzokis et al., 2007; Bartzokis, 2011). An initial rise in Aβ would damage white matter, which in turn would elevate Aβ levels, subsequently leading to more white matter damage in a continuing cyclical process. Alternatively, white matter lesions from a secondary process (e.g. head injury) may release iron, and initiate or accelerate the pathological influences of Aβ on white matter. Such results can been seen in the literature as circulating levels of Aβ are associated with WMH (Gurol et al., 2006), and baseline levels of white matter lesions predict an accelerated accumulation of amyloid over time (Grimmer et al., 2012).

Using semi-quantitative scales, white matter lesions have often been seen in individuals with compromised cardiovascular systems (Breteler et al., 1994; Longstreth et al., 1996). Consistent with these results, there has been a suggestion that AD may have a larger vascular component than often recognized (Bartzokis, 2011; de la Torre, 2010; Launer, 2002). Indeed, in epidemiological studies, cardiovascular risk factors such as diabetes or stroke lead to increased risk of AD (Luchsinger et al., 2001). Damage to the cardiovascular system, such as a thickening and sclerosis of arteries, may lead to an impaired drainage of molecules such as Aβ (Huang et al., 2010). Due to their potentially related nature, it is of interest to know whether the incidence of WMHs provides any diagnostic value above and beyond levels of Aβ pathology in the brain.

White matter damage in the brain can be assessed using visual ratings of WMH, quantification of WMH volumes, and using diffusion tensor imaging (DTI). While there is a clear utility to quantifying damage using DTI and WMH volumetric measurement, visual rating scales are an easily obtained radiological measure available across both research and clinical settings. Here we examine the relationships between Aβ deposition, white matter damage, and dementia in a population of cognitively normal, very mildly demented, and mildly demented individuals. Based upon prior work in the literature, we hypothesize that more severe semi-quantitative ratings of white matter damage will be related to an impaired cognitive status.

2. Materials and methods

2.1. Study population

Middle aged and older adults were drawn from studies on aging and dementia conducted through the Knight Alzheimer's Disease Research Center (ADRC) at Washington University in St. Louis. Based upon the Clinical Dementia Rating (CDR) Scale (Morris, 1993) participants were classified as cognitively normal (CDR = 0, n = 397, female = 256), very mildly demented (CDR = 0.5, n = 51, female = 20), or mildly demented (CDR = 1, n = 11, female = 1). Individuals with dementia are also given a primary diagnosis by the examining neurologist. Using these diagnoses individuals whose dementia was thought to be from a non-Alzheimer cause (e.g. Lewy bodies, vascular dementia, depression) were excluded from all analyses. The population ranged in age from 42 to 90, with a mean age of 68.5 years (Table 1). All participants underwent a structural imaging session as well as positron emission tomography (PET) to estimate amyloid deposition using ^{11}[C] Pittsburgh Compound B (PiB) (Klunk et al., 2004). All procedures where approved by Washington University's institutional review board and were conducted in accordance with the Declaration of Helsinki.

Table 1
Population demographics. Values represent the mean, standard deviation, and then range of the values.

	CDR = 0	CDR = 0.5	CDR = 1
Number	397	51	11
Gender	36% male*+	61% male	91% male
Age	67.1 (9.5)*+	76.8 (7.1)	78.1 (5.5)
	42–89	60–90	67–90
MMSE	29.2 (1.1)*+	26.7 (2.5)x	22.3 (3.8)
	25–30	20–30	16–30
MCBP_raw	.14 (.23)*+	.44 (.35)	.65 (.36)
	−.26–1.47	−.04–1.22	−.01–1.06
MCBP	.32 (.43)*+	.91 (.69)	1.32 (.66)
	−.21–2.41	.01–2.57	.12–1.92
PiB+_raw	21%*+	65%	82%
PiB+	21%*+	71%	82%

MCBP_raw = mean cortical binding potential. MCBP = partial-volume adjusted mean cortical binding potential. PiB+_raw = percentage PiB+ using unadjusted MCBP cutoff of .18. PiB = percentage PiB+ using partial-volume corrected MCBP cutoff of .23.
* $p < .05$ between CDR 0 and CDR 0.5.
+ $p < .05$ between CDR 0 and CDR 1.
x $p < .05$ between CDR .5 and 1.

2.2. T_2 protocol

High-resolution T_2-weighted images were acquired on a Siemens Trio 3 T scanner (Siemens Medical Systems, Iselin, NJ). Scan parameters were: repetition time (TR) of 3200 ms, echo time (TE) of 455, flip angle (FA) = 120°, with a 256 × 256 field of view, and a 1 mm isotropic resolution.

2.3. Clinical ratings

A trained neurologist (S.N.), blind to clinical diagnosis, examined the T_2-weighted images. The presence and severities of WMH were rated using criteria outlined by Fazekas et al. (1987). Briefly, periventricular hyperintensities (PVWMHs) were rated as follows: 0 absence of WMH; 1 "caps" or pencil-thin linings; 2 "halos"; and 3 irregular PVH extending into deep white matter. Ratings of WMH in the deep white matter (DWMH) were rated as follows: 0 absence of WMH, 1 solitary foci; 2 the beginning aggregation of foci; and 3 large confluent areas of WMH. Examples are given in Fig. 1 and distributions of scores across the three clinical groups are presented in Fig. 2. A subset of 29 individuals was rated two times to establish reliability. The intraclass correlation was .91 for periventricular ratings and .98 for deep white matter ratings.

2.4. PiB imaging

Participants underwent a 60-minute dynamic scan with PiB. Binding potentials were calculated for multiple regions of interest (ROIs) derived from Freesurfer using a cerebellar reference for regions-of-interest. The raw time–activity curve for each region was adjusted by a CSF dilution factor in a given voxel to yield partial volume corrected data. An average across both left and right lateral orbitofrontal, interior parietal, precuneus, rostral middle frontal, superior frontal, superior temporal, and middle temporal ROIs yielded the mean cortical binding potential (MCBP). All analyses used MCBP as a continuous variable.

As supplementary analyses, individuals were also codified as PiB positive or negative using a previously published value from our center of unadjusted MCBP of 0.18 (Vlassenko et al., 2011). A second supplementary analysis defined the cutoff on partial-volume corrected MCBP data derived from a ROC analysis comparing 212 cognitively normal individuals to 59 CDR = 0.5 with an AD diagnosis. Using this approach the partial-volume adjusted MCBP cutoff was determined to be .23, which was the point that maximized the Youden Index (sensitivity + specificity − 1). Distributions of partial-volume adjusted MCBP scores are presented in