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Regional white matter hyperintensities: aging, Alzheimer's disease risk, and cognitive function

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ABSTRACT

White matter hyperintensities (WMH) of presumed vascular origin, as seen on T2-weighted fluid attenuated inversion recovery magnetic resonance imaging, are known to increase with age and are elevated in Alzheimer's disease (AD). The cognitive implications of these common markers are not well understood. Previous research has primarily focused on global measures of WMH burden and broad localizations that contain multiple white matter tracts. The aims of this study were to determine the pattern of WMH accumulation with age, risk for AD, and the relationship with cognitive function utilizing a voxel-wise analysis capable of identifying specific white matter regions. A total of 349 participants underwent T1-weighted and high-resolution T2-weighted fluid attenuated inversion recovery magnetic resonance imaging and neuropsychological testing. Increasing age and lower cognitive speed and flexibility (a component of executive function), were both significantly associated with regional WMH throughout the brain. When age was controlled, lower cognitive speed and flexibility was independently associated with WMH in the superior corona radiata. Apolipoprotein E ε4 and parental family history of AD were not associated with higher burden of WMH. The results contribute to a larger body of literature suggesting that white matter measures are linked with processing speed, and illustrate the utility of voxel-wise analysis in understanding the effect of lesion location on cognitive function.

1. Introduction

White matter hyperintensities (WMH) of presumed vascular origin, as seen on T2-weighted fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI), are common features of the aging brain (de Leeuw et al., 2001). By the fifth decade of life, approximately 50% of people will have some WMH (Wen et al., 2009), whereas in healthy adults in their mid-60s, it is likely that most will have some degree of WMH as found using T2-weighted imaging (Wen and Sachdev, 2004). The underlying cause of these hyperintense regions is thought to be small-vessel disease, and accordingly, hypertension and older age are most consistently associated with an increasing burden of WMH (Basile et al., 2006).

Despite the fact that WMH denotes localized white matter damage, the associated cognitive changes and risk conferred by WMH for pathologic cognitive decline remain incompletely characterized. Several studies suggest a link between WMH and cognitive function even in healthy aging (de Groot et al., 2000; de Leeuw et al., 2001; Frisoni et al., 2007; Gunning-Dixon and Raz, 2003; Smith et al., 2011; Soderlund et al., 2006; Van Petten et al., 2004) but other studies have failed to find a link in healthy older adults (for a review see Ferro and Madureira, 2002). While not considered a defining feature of Alzheimer's disease (AD), WMH are elevated in AD and mild cognitive impairment (MCI) (Cuenco et al., 2008; Yoshita et al., 2006). In patients with AD, higher baseline WMH are associated with a greater increase in amyloid-β deposition, potentially because of small vessel disease and subsequently impaired amyloid-β clearance (Grimmer et al., 2012). WMH also appear to play a role in risk for developing AD; a meta-analysis showed that WMH are a risk factor for AD within population studies (Debette and Markus, 2010) and parietal WMH are associated with the risk of incident AD in older adults

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(Brickman et al., 2012). Whether WMH could be considered as a feature of early stage AD, or a result of AD pathologic processes is still unknown, and the literature linking WMH to AD risk factors is mixed. Some studies have found elevated WMH in Apolipoprotein E ε4 (APOE4) carriers (de Leeuw et al., 2004; Lunetta et al., 2007), although, Biffi et al. (2010) did not find a relationship between APOE4 status and WHM in the Alzheimer's Disease NeuroImaging Initiative cohort. The effect of APOE4 may not be specific to AD, as it is also a risk factor for cerebrovascular disease. Parental family history of AD is another well-known risk factor for AD; however, Debette et al. (2009) did not find an effect of parental family history on lesion burden, despite the fact that this risk factor has been linked with white matter alterations as detected with diffusion tensor imaging (DTI) in another study (Bendlin et al., 2010a, 2010b).

Differences among findings may be caused by differences in the population under study or differences in the way that WMH are indexed. WMH in aging and AD have so far focused mainly on global lesion volume (Aggarwal et al., 2010; Brickman et al., 2011; Carmichael et al., 2012) and broadly defined localization (Guzman et al., 2013). Given that both aging and AD are associated with regional patterns of white matter change as detected using DTI or volumetric analysis (Alves et al., 2012; Good et al., 2001; Li et al., 2008), more research may be needed that considers WMH in specific brain locations.

Voxel-wise analysis in which variables of interest can be used to predict WMH throughout the whole brain across a large number of participants can provide regional information with high spatial resolution. Using automated segmentation might also provide a solution to the variability in WMH rating approaches used across laboratories. Largely because of challenges in automated lesion segmentation, voxel-wise approaches to analyzing WMH are still rare in the literature. Rostrup et al. (2012) found differing spatial distribution of WMH with several risk factors for WMH, but did not investigate associations with cognitive symptoms. An elegant study by Smith et al. (2011) reported a relationship between frontal, posterior, and periventricular white matter lesion burden and executive function. In that same study, frequency of lesions in many of the same posterior and periventricular regions was associated with poorer episodic memory function. All the participants in that study were older than 65 years and were cognitively normal or diagnosed with MCI or mild dementia. Whether voxel-wise localization of WMH with age is associated with cognitive function or AD risk factors in asymptomatic adults is relatively unknown.

Thus, the aims of this study were as follows: (1) to determine the pattern of regional WMH found with increasing age; (2) to determine the extent to which regional WMH are associated with cognitive function; and (3) to assess the impact of parental family history and APOE4 genotype on regional distribution of WMH. In addition to regional analyses, secondary analyses also examined total WMH to compare with existing studies. We hypothesized that older age would be associated with higher regional WMH, especially in frontal brain regions, that regional burden would be linked to cognitive dysfunction, and that AD risk would be associated with higher frequency of WMH, especially in AD specific regions, including parietal and temporal lobes.

2. Methods

2.1. Participants

A total of 359 participants from the Wisconsin Registry for Alzheimer's Prevention (WRAP) underwent brain imaging as part of studies on memory, aging, and risk for AD. WRAP is a longitudinally followed cohort comprising participants who have either a family history of late-onset AD or no family history of AD (Sager et al., 2005). Most of the WRAP participants were adult children of persons with AD who were evaluated at the Memory Assessment Clinic at the University of Wisconsin–Madison or satellite memory assessment clinics affiliated with the Wisconsin Alzheimer's Institute, and other participants who learned about the study from educational presentations, health fairs, newsletters, or word of mouth. A positive family history was defined as having 1 or both parents with autopsy-confirmed or probable AD as defined by National Institute of Neurological and Communicative Disorders, and Stroke–AD and Related Disorders Association (NINCDS-ADRDA) research criteria (McKhann et al., 1984) and reviewed by a multidisciplinary diagnostic consensus panel. Absence of family history of AD required that the father survived to at least age 70 and the mother to age 75 without incurring a formal diagnosis of dementia or exhibiting cognitive deterioration. The inclusion criteria for this imaging study consisted of: normal cognitive function determined by neuropsychological evaluation (Mini Mental State Examination $\geq$25), no contraindications for MRI, and a subsequent normal MRI scan, no current diagnosis of major psychiatric disease, or other major medical conditions (e.g., myocardial infarction, or recent history of cancer), and no history of head trauma, stroke, or transient ischemic attack. All participants underwent MRI and neuropsychological testing. Brain images were reviewed by a neuroradiologist to exclude infarcts and other abnormalities. Ten participants were excluded because of abnormal radiological findings from the reviews made by the radiologist, leaving 349 participants. Demographic information for this sample is presented in Table 1. The University of Wisconsin Institutional Review Board approved all study procedures and each participant provided signed informed consent before participation.

2.2. Cognitive testing

As a part of their participation in WRAP, participants received at least 1 comprehensive neuropsychological assessment (Sager et al., 2005). For participants with multiple assessments, factor scores were used from the testing date in closest proximity to the MRI scan. On average, neuropsychological testing occurred within 9 months of the MRI scan (standard deviation [SD] = 5.3 months). We analyzed 4 cognitive factor scores that were determined from a factor analytic study of the WRAP neuropsychological battery and adapted from the work published in (Dowling et al., 2010). Factor scores represented cognitive domains known to change

Table 1
Demographics characteristics of patients (N = 349)

Characteristic	n (%)
Female	238 (68%)
Parental familial history of AD	260 (74%)
ApoE4 carriers	131 (38%)
Diabetic	7 (2.2%)
Current smoker	17 (5%)
History of hypertension	178 (51%)
	Mean ± SD (range)
Age	59.7 ± 6.4 (42–73)
Education	16.2 ± 2.4 (12–20)
Systolic blood pressure	124 ±16 (85–176)
Diastolic blood pressure	73 ± 9.5 (48–104)
WMH volume (mm^3)	11.7 ± 6.7 (2.3–45.4)
WMHr (% of ICV)	0.85 ± 0.49 (0.2–3.3)

Key: AD, Alzheimer's disease; WMH, white matter hyperintensity; WMHr, white matter hyperintensity ratio.