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White matter signal abnormality quality differentiates mild cognitive impairment that converts to Alzheimer's disease from nonconverters

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ABSTRACT

The objective of this study was to assess how longitudinal change in the quantity and quality of white matter signal abnormalities (WMSAs) contributes to the progression from mild cognitive impairment (MCI) to Alzheimer's disease (AD). The Mahalanobis distance of WMSA from normal-appearing white matter using T1-, T2-, and proton density–weighted MRI was defined as a quality measure for WMSA. Cross-sectional analysis of WMSA volume in 104 cognitively healthy older adults, 116 individuals with MCI who converted to AD within 3 years (mild cognitive impairment converter [MCI-C]), 115 individuals with MCI that did not convert in that time (mild cognitive impairment nonconverter [MCI-NC]), and 124 individuals with AD from the Alzheimer's Disease Neuroimaging Initiative revealed that WMSA volume was substantially greater in AD relative to the other groups but did not differ between MCI-NC and MCI-C. Longitudinally, MCI-C exhibited faster WMSA quality progression but not volume compared with matched MCI-NC beginning 18 months before MCI-C conversion to AD. The strongest difference in rate of change was seen in the time period starting 6 months before MCI-C conversion to AD and ending 6 months after conversion ($p < 0.001$). The relatively strong effect in this time period relative to AD conversion in the MCI-C was similar to the relative rate of change in hippocampal volume, a traditional imaging marker of AD pathology. These data demonstrate changes in white matter tissue properties that occur within WMSA in individuals with MCI that will subsequently obtain a clinical diagnosis of AD within 18 months. Individuals with AD have substantially greater WMSA volume than all MCI suggesting that there is a progressive accumulation of WMSA with progressive disease severity, and that quality change predates changes in this total volume. Given the timing of the changes in WMSA tissue quality relative to the clinical diagnosis of AD, these findings suggest that WMSAs are a critical component for this conversion and are a critical component of this clinical syndrome.

1. Introduction

White matter (WM) damage is a common occurrence in older adults and is often incidentally detected through magnetic resonance imaging (MRI). These patches of tissue damage are increasingly recognized as a substantial correlate of age-associated cognitive decline (de Leeuw et al., 2001; Frisoni et al., 2007; Grueter and Schulz, 2012). Although most often recognized as a hyperintense signal on T2 and fluid-attenuated inversion recovery MRI, this damage can also appear as hypointense on T1-weighted images and therefore, are

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[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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more generically referred to as white matter signal abnormalities (WMSAs). Vascular dysfunction is a primary mechanism of WM damage in older adults, and this damage is likely to contribute to the development of cognitive impairment and dementia (Barker et al., 2014; Bocti et al., 2005; Brickman et al., 2009a, 2009b; Debette and Markus, 2010; DeCarli et al., 2005; Delano-Wood et al., 2009; Frisoni et al., 2007; Gurol et al., 2006; Iadecola, 2013; Levy-Cooperman et al., 2008; Tullberg et al., 2004; Yoshita et al., 2006). Little is known, however, about the development and time course of WM tissue damage in patients transitioning from normal cognition to dementia. Additionally, little is known regarding the degree to which WMSAs contribute to different states of cognitive decline—for example, whether WMSAs are associated with conversion from a cognitively healthy status to mild cognitive impairment (MCI), or from MCI to dementia such as Alzheimer's disease (AD) (DeCarli et al., 1996; Medina et al., 2006; Smith et al., 2008; Wolf et al., 2000).

There is currently a strong interest in predicting individuals that will eventually develop AD as it is now assumed that trials for novel therapeutics will require intervention before substantial neurodegeneration (Jack et al., 2013). Studies using structural imaging have demonstrated a greater total WM damage burden in individuals with AD compared with those with MCI (Huang et al., 2012; Pievani et al., 2010; Prins et al., 2004). Several groups have highlighted promising evidence of WMSAs potentially being a structural predictor of AD development (Carmichael et al., 2010); some suggesting that this measure is on par with hippocampal volume (a traditional imaging marker of AD) (Brickman et al., 2012; Canu et al., 2012).

Neuropathology studies demonstrate histopathologic and imaging heterogeneity within and across WM lesions (Gouw et al., 2011; Iadecola, 2013; Maillard et al., 2014; Pettersen et al., 2008; Viswanathan, 2014; Wardlaw et al., 2013; Young et al., 2008), suggesting that quantifying WMSA on MRI by measuring total volume, as is usually done, may not accurately reflect the total severity of the damage. For example, on a T2-weighted scan some damaged tissue may evince signal intensities as bright as fluid, while other locations exhibit just a slight brightening relative to normal-appearing white matter (NAWM) intensities. These irregular signal properties contribute to poorly-defined boundaries and create difficulties in automatically segmenting damaged tissue from healthy tissue. Previous attempts at automatic segmentation have obtained increased sensitivity and specificity using a combination of T1-weighted, T2-weighted, proton density (PD), and fluid-attenuated inversion recovery imaging, demonstrating advantages of a multispectral approach (Maillard et al., 2008; Schwarz et al., 2009). Additionally, the current "gold standard" for WMSA quantification and validation is the manual delineation of WMSA labels. This is labor intensive and suffers from poor levels of both inter-rater and intrarater reliability (Grimaud et al., 1996; Zijdenbos et al., 1994). Thus, improvements in the automated segmentation and quantification of WMSAs would contribute to increased reliability, and potentially enhance the clinical utility of this marker of tissue damage (García-Lorenzo et al., 2013; Mortazavi et al., 2012).

In the present study, we examine how the quality of WMSAs change over time with respect to NAWM via a novel image quantification technique that implements the Mahalanobis distance (MD) of WMSA to NAWM. The implementation of WM lesion quality to study cognitive decline is relatively novel but is well-supported by studies describing heterogeneity in healthy WM as well as within lesions in the context of vascular integrity, normal aging (Chen et al., 2013; Spilt et al., 2006), and cognitive impairment (Delano-Wood et al., 2009; Viswanathan, 2014). We demonstrate here for the first time that WM damage and within-lesion quality in individuals with MCI changes in a manner that is closely timed to their conversion to a clinical diagnosis of AD. Furthermore, associations between WMSA quality and MCI conversion are similar to those exhibited by hippocampal volume, a known structural imaging indicator of AD (Convit et al., 1997; Gosche et al., 2002; Jack et al., 1999). These novel findings provide critical information for understanding the pathophysiology of the clinically manifested AD dementia syndrome, as WM damage is not considered in traditional models (e.g., Jack et al., 2013) of AD pathology and may provide an important and tenable mechanism for therapeutic targeting.

2. Materials and methods

2.1. Data

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.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, positron emission tomography, 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, as well as lessen the time and cost of clinical trials.

The principal investigator of the ADNI initiative is Michael W. Weiner, MD, VA 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 over 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 Grand Opportunity (ADNI-GO) and ADNI-2. To date, these 3 protocols have recruited >1500 adults, ages 55–90 years, 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.

All data in the present study are taken from ADNI-1. A cross-sectional analysis was conducted using images across 4 diagnostic groups, and a longitudinal analysis was then conducted on 2 of these groups. The first set of images comprised a single scanning time point for 459 individuals. These data encompass individuals who fall into 1 cognitive status categories: (1) older controls without clinical diagnosis during the study (other controls [OC], n = 104), (2) MCI without conversion to AD during the course of the study (mild cognitive impairment nonconverters [MCI-NC], n = 116), (3) MCI with conversion to AD during the study (mild cognitive impairment converters [MCI-C], n = 115), and (4) those diagnosed with AD throughout the study (AD, n = 124) as described by ADNI (www.adni-info.org). Briefly, all MCI participants have reported a subjective memory concern either autonomously or via an informant or clinician but do not have significant levels of impairment in other cognitive domains and have essentially preserved activities of daily living with no signs of dementia (i.e., all MCI individuals are amnestic MCI only). AD participants were evaluated and met the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD. Through this evaluation process, ADNI aims to reduce the risk of including subjects with vascular and other types of dementia.