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Regional staging of white matter signal abnormalities in aging and Alzheimer's disease

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ABSTRACT

White matter lesions, quantified as 'white matter signal abnormalities' (WMSA) on neuroimaging, are common incidental findings on brain images of older adults. This tissue damage is linked to cerebrovascular dysfunction and is associated with cognitive decline. The regional distribution of WMSA throughout the cerebral white matter has been described at a gross scale; however, to date no prior study has described regional patterns relative to cortical gyral landmarks which may be important for understanding functional impact. Additionally, no prior study has described how regional WMSA volume scales with total global WMSA. Such information could be used in the creation of a pathologic 'staging' of WMSA through a detailed regional characterization at the individual level. Magnetic resonance imaging data from 97 cognitively-healthy older individuals (OC) aged 52–90 from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study were processed using a novel WMSA labeling procedure described in our prior work. WMSA were quantified regionally using a procedure that segments the cerebral white matter into 35 bilateral units based on proximity to landmarks in the cerebral cortex. An initial staging was performed by quantifying the regional WMSA volume in four groups based on quartiles of total WMSA volume (quartiles I–IV). A consistent spatial pattern of WMSA accumulation was observed with increasing quartile. A clustering procedure was then used to distinguish regions based on patterns of scaling of regional WMSA to global WMSA. Three patterns were extracted that showed high, medium, and non-scaling with global WMSA. Regions in the high-scaling cluster included periventricular, caudal and rostral middle frontal, inferior and superior parietal, supramarginal, and precuneus white matter. A data-driven staging procedure was then created based on patterns of WMSA scaling and specific regional cut-off values from the quartile analyses. Individuals with Alzheimer's disease (AD) and mild cognitive impairment (MCI) were then additionally staged, and significant differences in the percent of each diagnostic group in Stages I and IV were observed, with more AD individuals residing in Stage IV and more OC and MCI individuals residing in Stage I. These data demonstrate a consistent regional scaling relationship between global and regional WMSA that can be used to classify individuals into one of four stages of white matter disease. White matter staging could play an important role in a better understanding and the treatment of cerebrovascular contributions to brain aging and dementia.

1. Introduction

White matter signal abnormalities (WMSA; also commonly referred to as 'white matter hyperintensities of presumed vascular origin') (Wardlaw et al., 2013a; Benedictus et al., 2014; Wardlaw et al., 2013b) as detected on magnetic resonance imaging (MRI) (Lindemer et al., 2015; Fazekas et al., 1988; Wei et al., 2002) are a common pathology found in the aging brain. To date, the integration of WMSA into an understanding of both normal and diseased brain aging has been challenging. Prior studies have demonstrated that WMSA are associated with a range of altered neurological and psychological profiles and contribute to the profile of dementia in individuals with compounded neurological disease (de Leeuw et al., 2001; Frisoni et al., 2007; Grueter and Schulz, 2012; Brickman et al., 2009a; Brickman et al., 2009b; DeCarli et al., 2005; Iadecola, 2013; Yoshita et al., 2006; de Groot et al., 2002; de Groot et al., 2001), yet they are often treated as a benign comorbidity of aging due to their high prevalence of 80–95% in older adults (de Leeuw et al., 2001; Dufouil et al., 2001; Longstreth,

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1998). In order to better understand the development of WMSA without the complications of concurrent cognitive impairments, the aim of the current study is to outline a staging procedure for WMSA in cognitively healthy older adults that can be applied to disease populations such as Alzheimer's disease (AD) and mild cognitive impairment (MCI) to determine how WMSA involvement relates to disease state.

Visual rating scales exist for describing the degree of WMSA within an individual (Fazekas and Chawluk, 1987; Scheltens et al., 1993). These scales have been useful in ranking individuals based primarily on the degree of periventricular compared to deep WMSA. While individual variation exists, imaging studies have demonstrated that WMSA generally first appear and are most prominent in periventricular areas when total lesion burden is low, but they progressively expand to include white matter distal to the ventricles and proximal to the cortex with greater disease burden (Zimmerman et al., 1986; Spilt et al., 2006). It is still unclear, however, whether or not aging individuals show a stereotypical pattern of WMSA development. This study investigates whether there exists a consistent relationship between global and regional WMSA burden and uses this information in the quantitative staging of white matter disease based on vulnerable brain regions.

Here we used an approach to perform an individual staging of WMSA that is inspired from prior neuropathological studies that quantify the degree of regional pathology in conditions such as Alzheimer's disease by sorting individuals based on the severity of the given pathology and determining if a spatial pattern emerges (Braak and Braak, 1991; Augustinack et al., 2012). This creation of a WMSA staging procedure is limited to cognitively healthy older adults enrolled in the Alzheimer's Disease Neuroimaging Initiative to avoid complications of comorbid neurodegenerative processes. In addition to this staging procedure, we devise a method to study the relationship between regional and global WMSA burden in order to understand how the WMSA burden in different regions of the WM scales with total WMSA, demonstrating specific regional vulnerabilities to WMSA. To provide an example of this method's utility, the final staging procedure is then applied to individuals with AD and MCI to determine the relationship between disease prevalence and WMSA stage.

2. 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 present study used data from the ADNI-1 database. Ninety-seven individuals were selected who had no present or history of cognitive impairment and no history of stroke. Data were selected based on the availability of images that had been already locally processed with FreeSurfer and limited to datasets with available T1-weighted, T2-weighted, and proton density (PD)-weighted images for WMSA processing. Demographic data such as age, sex, years of education, history of hypertension, history of endocrine-metabolic disorder, and Mini Mental State Examination (MMSE) scores were additionally acquired from the ADNI database.

Three diagnostic groups were used in this study: older controls (OC, n = 97), mild cognitive impairment (MCI n = 121), and Alzheimer's disease (AD n = 127). 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. All individuals in the MCI group were within three years of converting to AD as determined by longitudinal ADNI follow-up data. Creation of the staging methods was performed solely with OC data, and the MCI and AD groups were only used in the final analyses after secondary staging cut-off values were chosen.

2.2. MRI acquisition

All data were acquired on a 1.5-T scanner at rigorously validated sites, which all followed a previously described standardized protocol (Jack et al., 2008). The protocol included a high-resolution, T1- weighted sagittal volumetric magnetization prepared rapid gradient echo sequence and axial PD and/or T2-weighted fast spin echo sequence. The ADNI MRI core optimized the acquisition parameters of these sequences for each make and model of scanner included in the study. All scanner sites were required to pass a strict scanner validation test before being allowed to scan ADNI participants. Additionally, each scan of ADNI participants included a scan of the phantom, which was required to pass additional strict validation tests.

2.3. MRI preprocessing

Each individual's T1-weighted MRI was processed using FreeSurfer's main recon-all processing stream with a recently described extension for the segmentation of WMSAs (Lindemer et al., 2015). Cortical reconstruction and volumetric segmentation was performed using FreeSurfer (surfer.nmr.mgh.harvard.edu/, version 5.1). The technical details of these procedures are described in prior publications (Dale and Sereno, 1993; Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 1999; Fischl et al., 2001; Fischl et al., 2002; Fischl et al., 2004a; Fischl et al., 2004b; Han et al., 2006; Jovicich et al., 2006).

2.4. WMSA segmentation

Images were processed with an automatic WMSA segmentation stream that has been previously described (Lindemer et al., 2015). Briefly, this procedure performs intensity normalization of an individual's T1-, T2- and PD-weighted images using a multimodal atlas, and segments WMSA from normal-appearing white matter (NAWM) using a multimodal Gaussian classifier as well as individual-based heuristics.

The WM was divided into 70 regions of interest (ROIs) that encompassed the entire subcortical WM as well as the periventricular WM as described previously (Salat et al., 2009). These ROIs were automatically created during FreeSurfer's recon-all processing stream, and correspond to the WM areas below the surface of the anatomically-defined cortical gray matter areas. ROIs were then combined across hemispheres for a total of 35 final ROIs, as WMSA have been shown to be a generally symmetrical pathology (Wardlaw et al., 2013a). For each ROI, the WMSA burden was calculated in three different ways. First, the raw volume of WMSA in each ROI was calculated. Second, due to the known decrease in WM volume with increasing age (Salat et al., 2009), the WMSA volume as a percent of the individual's native space total WM volume (NAWM + WMSA) was also calculated. Finally, WMSA volume as a percent of a standard atlas ROI's total WM was calculated to account for the possibility that atrophy of WMSA and NAWM regions occurred at differing rates. All three methods generated nearly identical staging results, and therefore the only metric that is fully presented here is WMSA as a percent of the individual's total native space WM volume.

2.5. Quartile-based staging

After WMSA segmentation, the 97 OC individuals were sequentially ordered based on total global WMSA volume (rank ordered from lowest to highest WMSA volume) for an initial/preliminary staging. Four stages were defined by dividing individuals into simple quartiles corresponding to those with the lowest total WMSA (Quartile I, n = 25), mid-low