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TRACT-BASED ANALYSIS OF WHITE MATTER DEGENERATION IN ALZHEIMER'S DISEASE

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Abstract—Although much prior work has focused on the known cortical pathology that defines Alzheimer's disease (AD) histologically, recent work has additionally demonstrated substantial damage to the cerebral white matter in this condition. While there is large evidence of diffuse damage to the white matter in AD, it is unclear whether specific white matter tracts exhibit a more accelerated pattern of damage and whether the damage is associated with the classical neurodegenerative changes of AD. In this study, we investigated microstructural differences in the large fascicular bundles of the cerebral white matter of individuals with AD and mild cognitive impairment (MCI), using recently developed automated diffusion tractography procedures in the Alzheimer's disease Neuroimaging Initiative (ADNI) dataset. Eighteen major fiber bundles in a total of 36 individuals with AD, 81 MCI and 60 control participants were examined with the TRActs Constrained by UnderLying Anatomy (TRACULA) procedure available as part of the FreeSurfer image processing software package. For each fiber bundle, the mean fractional anisotropy (FA), and mean, radial and axial diffusivities were calculated. Individuals with AD had increased diffusivities in both left and right cingulum-angular bundles compared to control participants ($p < 0.001$). Individuals with MCI also had increased axial and mean diffusivities and increased FA in both cingulum-angular bundles compared to control participants ($p < 0.05$) and decreased radial diffusivity compared to individuals with AD ($p < 0.05$). We additionally examined how white matter deterioration relates to hippocampal volume, a traditional imaging measure of AD pathology, and found the strongest negative correlations in AD patients between hippocampal volume and the diffusivities of the cingulum-angular and cingulum-cingulate gyrus bundles and of the corticospinal tracts ($p < 0.05$). However, statistically controlling for hippocampal volume did not remove all group differences in white matter measures, suggesting a unique contribution of white matter damage to AD unexplained by this disease biomarker. These results suggest that (1) AD-associated deterioration of white matter fibers is greatest in tracts known to be connected to areas of pathology in AD and (2) lower white matter tract integrity is more diffusely associated with lower hippocampal volume indicating that the pathology in the white matter follows to some degree the neurodegenerative staging and progression of this condition.

Key words: Alzheimer's disease, mild cognitive impairment, white matter, hippocampus, cingulum and angular bundle.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder and the most common form of dementia in older adults (Ferri et al., 2005). This condition contributes to substantial societal and economic burdens (Rice et al., 1993; Langa et al., 2001), and the pathophysiology of AD remains to be fully understood. Although much work is focused on cortical atrophy and on amyloid and neurofibrillary pathology in the cortex and subcortical gray matter (Bouras et al., 1994; Hyman, 1997; Tiraboschi et al., 2004; Jack et al., 2011), it is also clear that there is significant widespread damage to the cerebral white matter (WM) as the disease progresses, both evidenced by an increased amount of WM abnormalities as seen on

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Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's disease Neuroimaging Initiative; CDR, Clinical Dementia Rating; DA, axial diffusivity; DR, radial diffusivity; DTI, diffusion tensor imaging; FA, fractional anisotropy; ICV, intracranial volume; MCI, mild cognitive impairment; MD, mean diffusivity; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; TRACULA, TRActs Constrained by UnderLying Anatomy; WM, white matter; WMSA, white matter signal abnormality.

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magnetic resonance imaging (MRI) (Yoshita et al., 2006), and by studies showing demyelination, microglial activation, loss of oligodendrocytes and reactive astrocytosis in the WM (Brun and Englund, 1986; Sjobeck et al., 2005, 2006; Gouw et al., 2008). This WM damage likely plays an important role in the clinical presentation of individuals with AD, and better understanding of these changes may provide insight into alternative pathologic mechanisms contributing to AD dementia. In particular, it is of interest to understand where the strongest regional WM changes are found and whether they affect particular fiber bundles in the cerebral WM. Furthermore, it is unclear whether this damage tracks with cortical AD pathology such as hippocampal degeneration.

Several studies have used neuroimaging techniques such as volumetric measurements (Salat et al., 1999a,b; Salat et al., 2009) and diffusion tensor imaging (DTI) (Rose et al., 2000; Bozzali et al., 2002; Choi et al., 2005; Bucur et al., 2008; Madden et al., 2009; Salat et al., 2009; Stebbins and Murphy, 2009; Gold et al., 2010; Smith et al., 2010; Pievani et al., 2010; Douaud et al., 2011; Nir et al., 2012, 2013; Rowley et al., 2013; Lim et al., 2014; Sun et al., 2014) to study WM pathology in AD and show both extensive local and diffuse damage. DTI enables the measurement of several microstructural properties of the WM tissue environment. Commonly-described DTI parameters include fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (DA), and radial diffusivity (DR), which have been respectively correlated histologically with degree of myelination (Beaulieu, 2002; Moseley, 2002; Peters, 2002), cell death and edema (Chenevert et al., 2000; Sotak, 2002), axonal injury and demyelination, loss of oligodendrocytes and reactive astrocytosis (Werring et al., 1999; Song et al., 2002, 2003). In addition to markers of tissue integrity, diffusion-weighted imaging is a useful technique to infer local fiber orientation for the computational modeling of the major fiber bundles in the brain, referred to as 'diffusion tractography' (Basser et al., 2000). Previous studies used a combination of DTI and tractography to study pathology in AD (Madden et al., 2009; Pievani et al., 2010; Douaud et al., 2011; Hasan et al., 2012; Nir et al., 2012; Rowley et al., 2013). We here add to this work by applying a recently developed automated probabilistic tractography procedure for whole-brain modeling of the major cerebral WM fiber bundles, TRActs Constrained by UnderLying Anatomy (TRACULA) (Yendiki et al., 2011) and examining which of the major large fascicles of the brain exhibit the greatest WM deterioration as a consequence of mild cognitive impairment (MCI) and AD. We additionally examined the association between tract integrity measured with DTI and a classical imaging marker of AD, hippocampal volume, to determine whether the WM changes are related to neurodegeneration or to a different cause. We demonstrate for the first time in a large dataset relative effects among fiber bundles showing greatest WM deterioration in cingulum-angular bundles for both MCI and AD, while the corticospinal tracts, superior and inferior longitudinal fasciculi, uncinate fasciculi, corpus callosum, and anterior thalamic radiations were relatively spared. Tract integrity was associated with hippocampal volume in individuals with AD as well as the control cohort; however, the relationship in AD was pronounced for tracts closest/with anatomical connectivity to the hippocampus. These data demonstrate that regional WM pathology tracks with hippocampal degeneration in AD. While we expected a selective loss in individuals with MCI and a more generalized effect in AD related to a greater degree of global cortical degeneration, we did not find this. Instead, we found greater diffusivity differences in AD compared to controls in the same WM tracts where effects are seen in MCI.

EXPERIMENTAL PROCEDURES

Participants

Data used in the preparation of this article were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu/). A description of ADNI as described (on the ADNI website) is provided here: The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and non-profit organizations, as a $60 million, 5-year public–private partnership. The primary goal of ADNI has been to test whether serial MRI, PET, 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 this initiative is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55–90, 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.

At the time of analysis, 232 participants were found to have performed both structural and DTI scans from the ADNIGO and ADNI2 databases. In addition to MRI data, clinical profiles including age, sex, education, Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) were obtained for participant characterization. Group designation of Control, MCI, or probable AD was determined by diagnosis as specified by ADNI based on the criteria of the National Institute of Neurological and Communicative Diseases and Stroke — Alzheimer's Disease and Related Disorders Association (McKhann