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Effectiveness of regional DTI measures in distinguishing Alzheimer's disease, MCI, and normal aging

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ABSTRACT

The Alzheimer's Disease Neuroimaging Initiative (ADNI) recently added diffusion tensor imaging (DTI), among several other new imaging modalities, in an effort to identify sensitive biomarkers of Alzheimer's disease (AD). While anatomical MRI is the main structural neuroimaging method used in most AD studies and clinical trials, DTI is sensitive to microscopic white matter (WM) changes not detectable with standard MRI, offering additional markers of neurodegeneration. Prior DTI studies of AD report lower fractional anisotropy (FA), and increased mean, axial, and radial diffusivity (MD, AxD, RD) throughout WM. Here we assessed which DTI measures may best identify differences among AD, mild cognitive impairment (MCI), and cognitively healthy elderly control (NC) groups, in region of interest (ROI) and voxel-based analyses of 155 ADNI participants (mean age: 73.5 ± 7.4; 90 M/65 F; 44 NC, 88 MCI, 23 AD). Both VBA and ROI analyses revealed widespread group differences in FA and all diffusivity measures. DTI maps were strongly correlated with widely-used clinical ratings (MMSE, CDR-sob, and ADAS-cog). When effect sizes were ranked, FA analyses were least sensitive for picking up group differences. Diffusivity measures could detect more subtle MCI differences, where FA could not. ROIs showing strongest group differentiation (lowest *p*-values) included tracts that pass through the temporal lobe, and posterior brain regions. The left hippocampal component of the cingulum showed consistently high effect sizes for distinguishing groups, across all diffusivity and anisotropy measures, and in correlations with cognitive scores.

1. Introduction

Alzheimer's disease (AD) is the most common type of dementia, affecting 1 in 8 people over age 65 in the U.S. alone (Alzheimer's Disease Association, 2012). Its prevalence is predicted to more than double in the next 40 years (Hebert et al., 2003). It is important to identify individuals most likely to develop AD, so that those at greater risk can be treated earlier. One high-risk group consists of people with mild cognitive impairment (MCI) — a transitional stage between normal aging and AD. People with MCI convert to AD at a rate of about 10–15% per year (Petersen et al., 2001; Bruscoli and Lovestone, 2004). In addition to the more widely-accepted measures from anatomical MRI, PET, and CSF measures of pathology, one major neuroimaging study of AD – the Alzheimer's Disease Neuroimaging Initiative (ADNI) – recently incorporated additional neuroimaging techniques including diffusion tensor imaging (DTI) (Jack et al., 2010; Jahanshad et al., 2010a; Zhan et al., in press). DTI is a variant of MRI that measures the diffusion of water molecules in brain tissue. Here we set out to assess which standard DTI measures may best identify neuroanatomical differences between AD, MCI, and normal aging. In the end, DTI offers a range of measures that might be sensitive to pathology, including measures of brain connectivity (Daianu et al., 2012, 2013a,b; Nir et al., 2012; Prasad et al., 2013; Toga and Thompson, 2013). For these initial analyses, however, we aimed to analyze more traditional measures and maps that are perhaps most likely to be used in standardized multi-site DTI analyses, at least in the near future (Jahanshad et al., 2013).

Abbreviations: NC, normal control; RD, radial diffusivity; AxD, axial diffusivity; ADNI, Alzheimer's Disease Neuroimaging Initiative.

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[1] Many investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data, but most of them did not participate in the analysis or writing of this report. A complete list of ADNI investigators may be found at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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MRI-based image analysis methods have long been used to track structural atrophy of the aging brain. MRI studies of AD reveal widespread neuronal loss and atrophy in the brain's gray matter, especially in medial temporal and hippocampal regions (Atiya et al., 2003; Chetelat and Baron, 2003; Thompson et al., 2003; Anderson et al., 2005; Apostolova and Thompson, 2008; Bakkour et al., 2009; Risacher et al., 2009; Apostolova et al., 2010; Desikan et al., 2010a; Desikan et al., 2010b; Chiang et al., 2011; Weiner et al., 2012; Leung et al., 2013). Beta-amyloid and tau proteins accumulate in the brain, leading to inflammation, neuronal atrophy and cell death (Braak and Braak, 1991; Braak and Braak, 1995). As neurons are lost, white matter volume is also reduced, due to both myelin degeneration and axon loss in neural fiber tracts (Braak and Braak, 1996; Bartzokis, 2011; Braskie et al., 2011; Hua et al., 2013). Standard anatomical MRI is still the imaging technique most often used in AD studies and clinical trials, but DTI is sensitive to microscopic changes in white matter (WM) integrity not always detectable with standard anatomical MRI (Xie et al., 2006; Canu et al., 2010). Although this is debatable until more evidence is collected, some DTI changes may even precede and predict volume loss (Hugenschmidt et al., 2008; Nir et al., 2012), making it a potentially beneficial tool for capturing additional or complementary markers of early neurodegeneration. Carriers of some AD risk genes show differences on DTI as young adults, decades before the typical age of onset of AD (Braskie et al., 2011).

Fractional anisotropy (FA) is perhaps the most widely accepted DTI measure and reflects how directionally constrained the diffusion of water is along axons. While higher FA values may imply more coherent or intact axons, or a higher degree of myelination, lower FA may reflect loss of WM integrity and injury. These physiological correlates of the DTI signal are widely accepted, but the differences may have other interpretations, especially where fibers cross (Leow et al., 2009; Zhan et al., 2009). Mean diffusivity (MD) captures the average rate of diffusion in all directions, and generally increases with WM injury, especially if normal barriers to diffusion are damaged (such as myelin sheaths on axons). Axial diffusivity (AxD) captures diffusion parallel to axonal fibers, while radial diffusivity (RD) reflects perpendicular diffusion. These measures are linked to axonal injury and demyelination, respectively (Song et al., 2003; Song et al., 2005). To date, numerous DTI studies of AD and MCI find that greater cognitive impairment, or poorer diagnosis, is associated with lower FA in the corpus callosum, fornix, cingulum, superior longitudinal fasciculus, and inferior longitudinal fasciculus (Ukmar et al., 2008; Stricker et al., 2009; Mielke et al., 2009; Liu et al., 2011) and DTI measures correlate with widely used clinical or cognitive ratings including the mini-mental state exam (MMSE) (Bozzali et al., 2002).

Despite growing diffusion imaging evidence of AD-related WM changes, it is not clear which regions and DTI measures are the most sensitive for detecting diagnostic differences. In order to evaluate the power of drug trial treatment to counteract degeneration, optimizing statistical power for discerning differences and changes is crucial. We focused this current paper on cross-sectional differences in patients and controls, as there are a number of DTI measures, regions, and approaches that need to be compared and ranked in terms of their effect sizes for picking up group differences. We set out to rank the effect sizes for different DTI-based scalar measures in detecting differences in both white matter voxel-based analyses (VBA) and within regions of interest (ROIs). We first examined differences in DTI anisotropy and diffusivity measures between groups of cognitively healthy normal elderly controls (NC), MCI, and AD patients in both voxel-based and ROI analyses. We also examined the association of anisotropy and diffusivity maps with widely used clinical or cognitive ratings including the MMSE (Folstein et al., 1975), the "sum-of-boxes" clinical dementia rating (CDR-sob) (Berg, 1988), and the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-cog) (Rosen et al., 1984). Finally, in a supplementary test, we compared our ROI results to ROIs extracted along the skeleton from the widely used tract-based spatial statistics (TBSS) method (Smith et al., 2006). Despite the popularity of FA, we hypothesized that we would find the highest effect size and discriminative power for MD measures, as recently suggested in a review of DTI studies of AD by Clerx et al. (Clerx et al., 2012). We also hypothesized that we would find the greatest differences in temporal lobe WM and the corpus callosum (CC), as the temporal lobe is usually the earliest region to be affected by amyloid and tau pathology in AD, and DTI studies are often better powered to find group differences in regions such as the CC where fiber coherence is highest.

2. Materials and methods

2.1. Clinical sample and demographics

Baseline MRI, DTI, clinical, and neuropsychological data were downloaded from the ADNI database (http://adni.loni.ucla.edu). When the analysis was performed (September 2012), data collection for the ADNI2 project was still in progress. Here we performed an initial analysis of 155 participants from 14 data acquisition sites, of whom 44 were normal controls (NC), 88 amnestic MCI subjects, and 23 AD patients (see Inline Supplementary Table S1 for distribution of subjects across sites). Unlike ADNI1, ADNI2 MCI participants include the enrollment of a new early MCI cohort (e-MCI; $n = 62$), with milder episodic memory impairment than the MCI group of ADNI1. The MCI group of ADNI1 is now referred to as late MCI (l-MCI; $n = 26$) in ADNI2. Levels of MCI (early or late) were determined using the Wechsler Memory Scale — Logical Memory II (Wechsler, 1987). We evaluated the l-MCI and e-MCI groups both separately and as one large MCI group. Detailed inclusion and exclusion criteria are found in the ADNI2 protocol (http://adni-info.org/Scientists/Pdfs/ADNI2_Protocol_FINAL_20100917.pdf).

Inline Supplementary Table S1 can be found online at http://dx.doi.org/10.1016/j.nicl.2013.07.006.

Each subject underwent cognitive evaluations. The Mini-Mental State Examination (MMSE) was used to provide a global measure of cognitive status, based on evaluating cognitive domains including orientation to place, orientation to time, registration, attention and concentration, recall, language, and visual construction (Folstein et al., 1975). The total score ranges from 1 to 30, with lower scores indicating impairment. The Clinical Dementia Rating (CDR) was also used as a global measure of dementia severity (Berg, 1988). The "sum-of-boxes" CDR (CDR-sob) score is the sum of 6 measures each assessing the degree of impairment in memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The CDR-sob score ranges from 0 to 18 (no dementia to severe dementia, respectively). Finally, the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-cog), a global measure encompassing memory, reasoning, language, orientation, ideational, praxis and constructional praxis (Rosen et al., 1984), was collected where scores range from 0 to 70 (no dementia to severe dementia respectively). In *post-hoc* analyses, we further homed in on specific cognitive domains using the available ADNI composite scores for executive function (ADNI-EF) (Gibbons et al., 2012) and memory (ADNI-MEM) (Crane et al., 2012) derived using data from the ADNI neuropsychological battery. Detailed psychometric calculation protocols are available for download at https://ida.loni.ucla.edu/. ADNI-EF was calculated using a combination of WAIS-R Digit Symbol Substitution, Digit Span Backwards, Trails A and B, Category Fluency, and Clock Drawing scores (Gibbons et al., 2012), and ADNI-MEM was calculated as a composite of the Rey Auditory Verbal Learning Test (RAVLT), ADAS-Cog, and Logical Memory data (Crane et al., 2012).

Demographics and diagnostic information for the participants are shown in Table 1. Diagnostic groups did not differ in age, however, education, an AD risk factor (Sattler et al., 2012), was marginally significant between controls and AD. As would be expected, clinical measures that index cognitive decline (MMSE, ADAS-cog, CDR-sob, ADNI-MEM, ADNI-EF) did show significant graded differences between groups.

We further assessed whether these measures revealed more fine-grained differences between the l-MCI and e-MCI subgroups. We found