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Multivariate network analysis of fiber tract integrity in Alzheimer's disease

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Axonal and dendritic integrity is affected early in Alzheimer's disease (AD). Studies using region of interest or voxel-based analysis of diffusion tensor imaging data found significant decline of fractional anisotropy, a marker of fiber tract integrity, in selected white matter areas. We applied a multivariate network analysis based on principal component analysis to fractional anisotropy maps derived from diffusion-weighted scans from 15 AD patients, and 14 elderly healthy controls. Fractional anisotropy maps were obtained from an EPI diffusion sequence using parallel imaging to reduce distortion artifacts. We used high-dimensional image warping to control for partial volume effects due to white matter atrophy in AD. We found a significant regional pattern of fiber changes ($p < 0.01$) indicating that the integrity of intracortical projecting fiber tracts (including corpus callosum, cingulum and fornix, and frontal, temporal and occipital lobe white matter areas) was reduced, whereas extracortical projecting fiber tracts, including the pyramidal and extrapyramidal systems and somatosensory projections, were relatively preserved in AD. Effects of a univariate analysis were almost entirely contained within the multivariate effect. Our findings illustrate the use of a multivariate approach to fractional anisotropy data that takes advantage of the highly organized structure of anisotropy maps, and is independent of multiple comparison correction and partial volume effects. In agreement with post-mortem evidence, our study demonstrates dissociation between intracortical and extracortical projecting fiber systems in AD in the living human brain.

Keywords: Fiber degeneration; Neuronal loss; PCA; MANCOVA; Magnetic resonance imaging (MRI); Diffusion tensor imaging (DTI); White matter; Grey matter

Introduction

Alzheimer's disease (AD) is characterized by progressive neurodegeneration affecting intracortical projecting neurons (Giannakopoulos et al., 1997; Pearson et al., 1985). Axonal and dendritic integrity is affected early in the disease process (Brun and Englund, 1986; Kowall and Kosik, 1987; Leys et al., 1991; Su et al., 1993).

Diffusion tensor MRI (DTI) is a recent technique to determine the integrity of subcortical fiber tracts in vivo (Mori and Barker, 1999). DTI takes advantage of the inherent properties of the motion of water molecules. In unconstrained media, such as cerebrospinal fluid, diffusion is isotropic. In cerebral white matter, however, the direction of water diffusion is biased in favor of movement parallel to the longitudinal axis of the fibers, resulting in high diffusion anisotropy. Diffusion properties in tissue can be described by a symmetric 3×3 matrix, the diffusion tensor. From the diffusion tensor one can derive the fractional anisotropy (FA), which is one of the most robust measures of anisotropy (Pierpaoli and Basser, 1996). Study of neuronal fiber loss in AD using region of interest (ROI) analysis found FA reductions in posterior corpus callosum, fasciculus longitudinalis superior, temporal lobe and cingulate white matter (Bozzali et al., 2002; Fellgiebel et al., 2005, 2004; Head et al., 2004; Müller et al., 2005; Rose et al., 2000; Stahl et al., 2003; Takahashi et al., 2002; Yoshiura et al., 2002). One study employing voxel-based analysis of low-dimensionally normalized FA maps found significant reductions of FA in posterior white matter areas (Medina et al., 2006). However, low-dimensional normalization as employed in this study determines a limited number of parameters for the transformation of data in standard space and therefore is not able to separate reductions of FA from effects of atrophy. In addition, the single shot echo planar imaging (EPI) acquisitions with long echo times used in most of the previous studies (Bozzali et al., 2002; Fellgiebel et al., 2005, 2004; Head et al., 2004; Müller et al., 2005; Rose et al., 2000; Takahashi et al., 2002; Yoshiura et al., 2002) are prone to susceptibility related distortion, which degrades

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image quality and the accuracy of the following analysis steps, particularly in the region of the skull base (Cusack et al., 2003; Lovblad et al., 1998; Robertson et al., 1999; Schmithorst et al., 2001).

In the current study, we sought to investigate the effects of AD on fiber tract integrity with DTI and a network model using multivariate analysis of covariance (MANCOVA) with canonical variate analysis (CVA). CVA is based on principal component analysis and has previously been applied in functional neuroimaging studies (Friston et al., 1996; Zuendorf et al., 2003). It determines the effect of AD on the covariance profiles of the FA maps. To our knowledge, this is the first application of CVA to DTI data and provides a foundation for applying such multivariate network analysis approaches to characterize the anatomical effects of neurodegenerative disease on a voxel basis throughout the cerebral white matter. For comparison, we determined the effects of diagnosis using univariate analysis. To reduce effects of white matter atrophy, we transformed FA maps in standard space using high-dimensional spatial transformation (Ashburner et al., 1999) applied to the corresponding anatomical MRI scans. The normalization algorithm determines several hundreds of thousand parameters to describe the deformation function and yields an almost complete fit between original and target scans. For data acquisition we used parallel imaging that permits a reduction of the phase-encoding steps leading to shorter echo times without loss of spatial resolution, thereby reducing distortion artifacts (Bammer et al., 2002, 2001; Stahl et al., 2003; Yamada et al., 2003). We hypothesized that AD would be associated with a regionally distributed pattern of reduced integrity of intracortical projecting fiber tracts such as the corpus callosum, fornix, and peduncles of the temporal lobes with sparing of the extracortical projecting somatosensory pathways.

Methods

Subjects

Fifteen patients with AD, and 14 healthy comparison subjects underwent MRI and DTI examinations. The mean ages of the AD and comparison groups were similar: 67.5 years (SD = 10.9), and 66.6 years (SD = 6.2) (two-tailed *t*-test AD vs. control subjects: $t_{27} = 0.27$, $p = 0.79$). The groups showed a similar gender distribution: 6 women and 9 men in the AD group, and 7 women and 7 men in the control group (Pearson chi-square test: $\chi^2 = 0.29$, $df = 1$, $p = 0.59$).

AD patients fulfilled the NINCDS-ADRDA criteria for clinically probable AD (McKhann et al., 1984). Severity of cognitive impairment was assessed with the "Mini Mental State Examination" (MMSE) (Folstein et al., 1975). The MMSE score ranged between 17 and 28 with an average of 20.3 (SD 4.6) for the AD patients, and between 27 and 30 with an average of 28.8 (SD 1.0) for the controls.

Controls did not have cognitive complaints and scored within 1 standard deviation from the age-adjusted mean in all subtests of the CERAD cognitive battery (Morris et al., 1989).

Selection of subjects included a semiquantitative rating of T2-weighted MRI scans (Scheltens et al., 1993). Only subjects were included which had no subcortical white matter hyperintensities exceeding 10 mm in diameter or 3 in number.

All patients and controls were only examined if they gave their written consent. The study was approved by the institutional review board.

MRI acquisition

MRI examinations of the brain were performed on a 1.5-T MRI scanner (Magnetom Sonata Maestro Class, Siemens Medical Solutions, Erlangen, Germany) using an 8-channel phased-array head coil and parallel imaging as previously described (Stahl et al., 2003). We acquired a high resolution T1-weighted magnetization prepared rapidly acquired gradient echo (MPRAGE) 3D-sequence matrix size of 256 × 256, field of view of 270 × 270 mm^2, 160 slices with slice thickness of 1.1 mm (resulting voxel size 1.1 × 1.1 × 1.1 mm^3) and TE/TI/TR of 3.9 ms/800 ms/1570 ms, subsequently named the anatomical scan. Additionally, we obtained a 36 slices T2-weighted axial conventional TSE sequence with matrix size of 208 × 256, field of view of 187 × 230 mm^2, slice thickness of 3.6 mm (resulting voxel size 0.9 × 0.9 × 3.6 mm^3), and TE/TR of 106 ms/7450 ms. The diffusion-weighted data were collected using a spin-echo single-shot EPI sequence (TE/TR 71 ms/6000 ms); diffusion gradients were applied in six different spatial directions as described by (Basser et al., 2000). The *b*-values were 0 and 1000 s/mm^2. The images had a matrix size of 128 × 128 with a FOV of 230 × 230 mm^2 and a slice thickness of 3.6 mm (without gap), the resulting voxel size was 1.8 × 1.8 × 3.6 mm^3. 36 axially oriented slices were acquired. Ten measurements were performed and averaged. During each course, subjects were scanned without changing their position in the scanner. Parallel imaging was performed with a generalized auto-calibrating partially parallel acquisition (GRAPPA, Griswold et al., 2002) reconstruction algorithm and an acceleration factor of 2; information about the coil sensitivity profiles was extracted from 24 reference lines (auto-calibration signals) acquired in the center of k-space.

Data analysis

From the diffusion-weighted sequence, the values for FA in each voxel were calculated with in-house software written in IDL (Interactive Data Language, version 5.4, Research Systems Inc., Colorado, USA). The resulting FA maps, the T2-weighted images (those of the DTI-EPI sequence with a *b*-value of 0) and the MPRAGE images were separately converted into 3D volume data sets using IDL. The analysis method was implemented within Matlab 6.5 (MathWorks, Natwick, Mass.) through Statistical Parametric Mapping (Friston et al., 1995a,b) (SPM 2, Wellcome Department of Imaging Neuroscience, London; available at http://www.fil.ion.ucl.ac.uk/spm). The MRI scans were processed in three subsequent steps.

Fig. 1. Projection of the positive and negative components of the canonical image into voxel space—axial sections. The canonical image in voxel space projected on the rendered axial sections of the T1-weighted template brain. Sections go from dorsal at Talairach–Tournoux coordinate $z = 43$ to ventral $z = -26$, sections are 3 mm apart. Left of image is right of brain (view from inferior). Red to yellow: components of the canonical images that are reduced in AD relative to controls. Blue to green: components of the canonical images that are increased in AD relative to controls.