Quantification of Fronto-Occipital and Thalamo-Frontal Connectivity in Alzheimer's Disease by DTI-Tractography

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Introduction

Quantitative electroencephalography (EEG) shows a prominent loss of coherence between the frontal and occipital electrodes in Alzheimer's Disease (AD) [1], consistent with a disruption in the fronto-occipital tracts. Dementia is also likely to disrupt fronto-subcortical loops including the thalamo-frontal tracts. The objective of this paper was to quantify the fronto-occipital and thalamo-frontal connectivities by DTI-tractography in AD patients and compare to age-matched normal control (NC) subjects.

Method

A FLAIR diffusion weighted imaging (DWI) sequence was used to acquire 128x128, field-of-view 30cmx30cm, multi-slice (5 mm thick, no gap) spin-echo EPI data on a 1.5 T Siemens scanner using six encoding gradient directions at b-values of 0, 160, 360, 640, and 1000 sec/mm^2 from a cohort of NC (n=4) and probable AD patients (n=4). Two sets of data, where the gradient polarity was reversed in the second set, were averaged to reduce eddy current and field inhomogeneity effects. The DWIs were co-registered to higher resolution (1mmx1mm in-plane resolution) T1 weighted images using SPM99 and fractional anisotropy (FA) maps were reconstructed from the diffusion tensor. Signal-to-noise-ratio weighted multivariant least-square fitting [2] was used to reduce noise in the diffusion tensor elements at each voxel. An example of FA maps is presented in **Fig.1**. A 4th-order Runge-Kutta method with an integration step of 0.23mm, i.e., ten linear samples along the voxel's x-y directions, FA threshold at 0.2, and change-in-angle threshold at 45 degrees was used for tracking. Tracking was initiated from all voxels, and global tracking results were stored in a database. Thalamo-frontal and fronto-occipital tracts were selected from the data base by defining corresponding regions in the underlying anatomical images [3]. An example of fronto-occipital and thalamo-frontal tracts is presented in **Fig. 2**. Compared to NC, the reduction in the number of tracts for the probable AD subjects are obvious in Fig. 2. Two metrics were evaluated to quantify tract-based connectivity. The first metric was a normalized tract-count where all tracts crossing specified boundaries were counted and normalized by the subject's intra-cranial volume (ICV). The ICV has been used previously in many studies to correct for premorbid brain size variations in AD under the assumption that it is unaffected by cerebral atrophy [4]. The total ICV was estimated by using SPM to segment the total gray matter, white matter and CSF in the T1 weighted images. The second metric was the average FA over the entire extent of the selected tracts. The FA was also averaged separately over three segments (the beginning, middle and end) of each tract but no significant differences were detected among these three sub-averages. An alternative approach of warping images to SPM normalized space and using the volume-scaling factor of voxels containing tracts to normalize the tract-count was found to be unreliable because it minimized the volume loss due to atrophy, and thus reduced the atrophy related effects we were seeking.

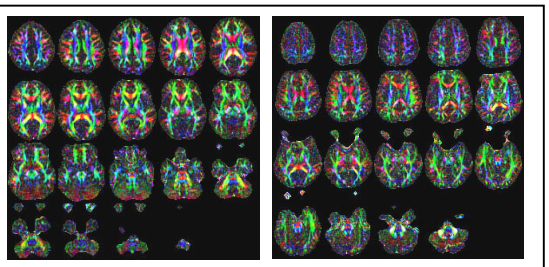
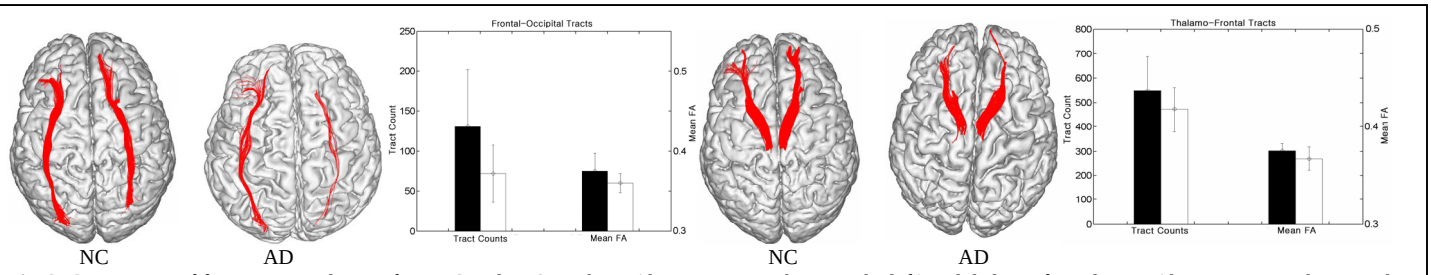


Fig. 1: FA images for a NC (left) and an AD (right).



NC AD NC AD

Fig. 2: Comparison of fronto-occipital tracts for a NC and an AD subject (the two images shown at the left) and thalamo-frontal tracts (the two images shown at the right), superposed on the individual's 3D rendered brain. The normalized tract-count and average FA plots for 4 NC (black bars) and 4 AD patients (white bars) are displayed to the right of corresponding images.

Results

The results of the tract-count and FA metrics for the 4 NC and 4 probable AD subjects are also presented in **Fig. 2** on the right of the images**.** The corresponding effect sizes (Fronto-occipital tract-count: 1.05, average FA: 0.65; Thalamo-frontal tract-count: 0.66, average FA: 0.78) suggest that the tract-count of the fronto-occipital tracts would be a sensitive measure to separate AD from NC.

References [1]: Leuchter A. et al., *Brain* Vol 115(5): 1543-1561, 1992. [2]: Basser PJ. et al., *Biophys J*, Vol 66, 259-257, 1994.
[3]: Mori S. et al., *Magn Reson Med* 47:215-223, 2002 [4]: Jack CR Jr. et al., *Neurology* 52:1397-1403, 1999.