Altered White Matter Microstructure in Elderly Major Depressive Disorder Patients: A DTI Study

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Purpose: Major depressive disorder, characterized by an all-encompassing low mood, low self-esteem, and general loss of interest in normally enjoyable activities, is one of the leading causes of disability worldwide [1]. Though MDD has traditionally been viewed as an affective disorder, research has demonstrated that MDD is also associated with significant disturbances to cognitive functioning, and can be correlated with brain region abnormalities corresponding to executive function, attention, memory, and psychomotor speed. Of interest are the abnormalities in the white matter (WM) of the brain. The neural tracts in WM normally exhibit a high degree of spatial organization, which largely restricts the diffusion of water to along the axes of internal fibrous structures. Diffusion tensor imaging (DTI) allows the in vivo measurement of the directionality of water diffusion, and changes to the microstructure can thus be characterized as altered diffusivity in terms of fractional anisotropy (FA), which is the measure of the degree of anisotropy, and mean diffusivity (MD), which is the measure of total diffusion. Findings from previous DTI studies, of which the majority examined changes to WM integrity using a region-of-interest (ROI) method, have found the loss of integrity of WM fiber tracts in the frontal, temporal, and cingulate cortex of MDD subjects. However, ROI-based methods seldom examine changes in WM integrity in areas of the brain outside the etiology of MDD, and thus little is known about whole-brain differences in white matter integrity. Using tract-based-spatial-statistics (TBSS), a robust method for comparing diffusivity maps across the entire brain, we examined the FA and MD values between normal control (NC) subjects and MDD patients.

Methods: A total of 58 subjects were scanned with a Siemens 3T MRI scanner. The diffusion tensor images were acquired with a spin-echo single-shot EPI sequence with 64 encoding directions. The demographic characteristics were matched between the two groups. The NC subjects (n=30; 17 male, 13 female) had a mean age ± stdev of 72.1±7.5, and the MDD subjects (n=28; 13 male, 15 female) had a mean age ± stdev of 70.43±7.0. All preprocessing and statistical analysis were performed with the FSL software package from Oxford's Analysis Group [2]. The FA maps from 58 brains were analyzed with TBSS, with registration of individual FA maps to the most representative FA map within the cohort. MD maps were processed using the same nonlinear registration and projection vectors as the FA maps. Once the skeletonized maps were obtained, the FA and MD values were compared in a voxel-wise fashion between the NC and MDD group using a permutation test with threshold-free cluster enhancement. All tests were taken to be significant at $p<0.05$.

Results: Group-wise voxel-based comparisons between the NC and MDD revealed significantly decreased FA values in MDD subjects corresponding to the neural tracts of the corpus callosum and the forceps minor of the cingulate gyrus. Significant decreases in FA were also found in the inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and uncinate fasciculus of the sagittal stratum and anterior corona radiata (Figure 1). No significant differences were noted for comparison of MD maps.

Discussion: The comparison of FA and MD maps between the NC and MDD groups revealed significant differences in FA maps corresponding to white matter tracts associated with the limbic, parietal, frontal, and temporal lobes. The inferior fronto-occipital fasciculus, which integrates auditory and visual association cortices with the prefrontal cortex, the inferior longitudinal fasciculus, which is involved in the integration of auditory and speech nuclei, and the uncinate fasciculus, which plays a role in memory integration, are all associated with cognitive emotional function. Decreased FA values in these tracts indicate a possible change in axonal integrity or fiber degeneration relative to NC subjects, while no significant changes in MD values suggest conservation of cell-matrix integrity between the two groups. These findings are in agreement with the increasing body of evidence from literature, which hypothesizes that MDD may be associated with acute microstructural WM changes.

[1] The World Health Organization. The global burden of disease: 2004 update, Table A2: Burden of disease in DALYs by cause, sex and income group in WHO regions, estimates for 2004. Geneva, Switzerland: WHO, 2008.

[2] S.M. Smith, et al. NeuroImage, 23(S1):208-219, 2004.

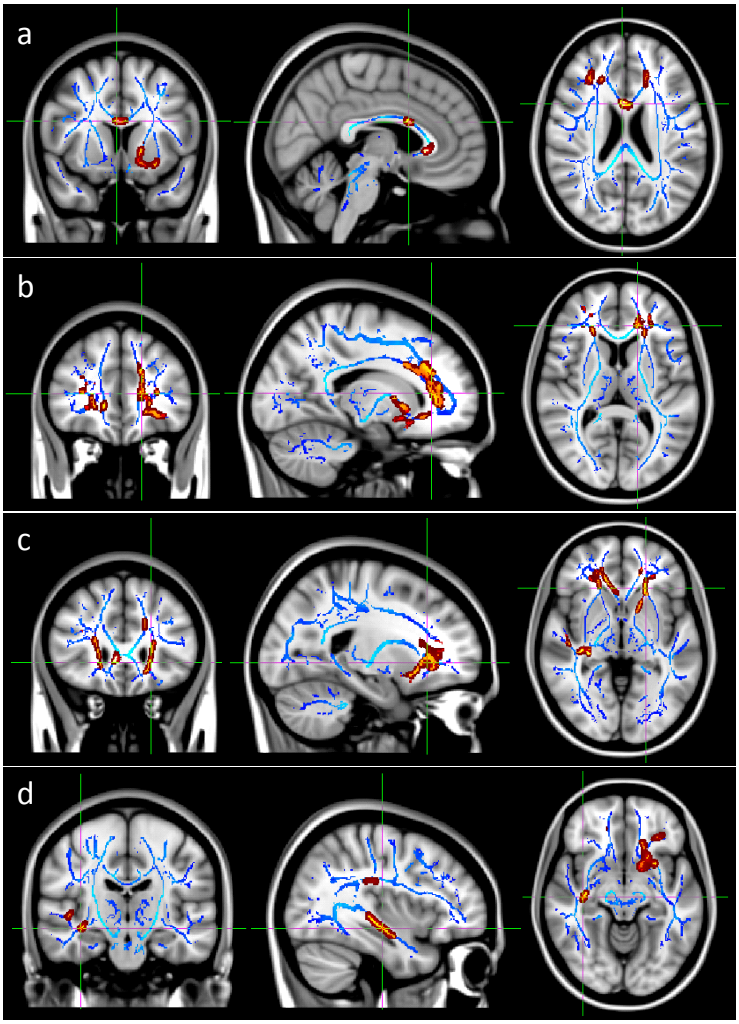

Figure 1. White matter tracts where FA values of MDD subjects are lower than those of NC subjects. The respective coronal, sagittal, and axial views, represented on an averaged T1-weighted brain from 152 subjects provided by the Montreal Neurological Institute, are depicted here. The significant areas projected onto the group mean FA skeleton correspond to the (a) corpus callosum *p<0.05*, (b) forceps minor *p<0.05*, (c) uncinate fasciculus *p<0.05,* and (d) inferior fronto-occipital fasciculus *p<0.05.*