

White Matter Structural Changes in High-risk Major Depressive Disorder Youths Detected by Diffusion Tensor Images

H. Huang^{1,2}, X. Fan¹, A. Bidesi³, and U. Rao³

¹Advanced Imaging Research Center, UT Southwestern Medical Center, Dallas, TX, United States, ²Department of Radiology, UT Southwestern Medical Center, Dallas, TX, United States, ³Psychiatry, UT Southwestern Medical Center, Dallas, TX, United States

Introduction

More evidence suggests that depression, as a psychiatric disorder, can result in structural changes of human brain [e.g. 1-5]. DTI-derived parameter, fractional anisotropy (FA), is sensitive to the white matter structural changes caused by abnormalities. White matter disruption has been found in late-life depression [1-3]. Recently it has been revealed that there is white matter tract abnormality in young adults exposed to parental verbal abuse [6]. It suggests that white matter structures in youths are vulnerable to psychiatric and emotional effects. In this ongoing longitudinal study, we hypothesized that the structural abnormalities can be detected in youths at high-risk for major depressive disorder (MDD). Data were acquired in normal control and high-risk MDD youths. The ages of the volunteers are from 13 to 18. Voxel-based morphometry (VBM) approach, specifically tract-based spatial statistics (TBSS), was used to detect the locations with statistically low FA values in the high-risk MDD group. We further normalized the count of statistically significantly low FA voxels with the voxel count of the total tract to characterize the severity of tract "abnormalities". A digital white matter atlas in the same template space [7] was used to label the voxels in the 3D template image with the anatomical information of the white matter tracts and obtain voxel count of the total tract. Superior longitudinal fasciculus (SLF) on both sides of the brain, left uncinate fasciculus (UNC), right hippocampal part of cingulum (CGH) are among the tracts which are most affected in terms of FA decreases.

Methods

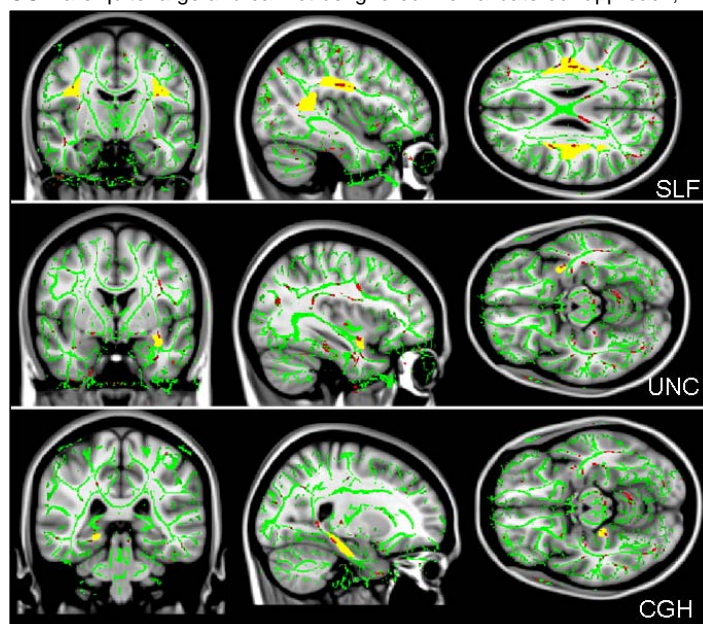
Participants and data acquisition: DTI data were acquired in 8 patients (age: 15.7 ± 1.80) at high-risk for MDD and 6 control subjects (age: 16.6 ± 1.14) with no personal or family history of psychiatric illness using a 3.0 T Philips Achieva MR system. The high-risk MDD subjects had no psychiatric disorder in their lifetime based on structured diagnostic assessment. However, either one or both parents had a history of MDD that required treatment. Both groups were medically healthy based on history, physical examination and laboratory investigations. DTI parameters were: single-shot echo-planar imaging (EPI) sequence with SENSE parallel imaging scheme (SENSEitivity Encoding, reduction factor =2.3); imaging matrix=112x112; FOV (field of view)=224x224mm (nominal resolution of 2mm, zero filled to 256x256); 2.2mm axial slice thickness, parallel to the anterior-posterior commissure line (AC-PC); total slice number=60 to 65 to cover the entire hemisphere and brainstem without gap, TE=97ms; TR=11.88s without cardiac gating; 30 independent diffusion weighting orientations; DWI b value=1000s/mm². **TBSS analysis:** Tract-based spatial statistics (TBSS) was used to locate the voxels with statistically significantly lower FA in the template space. In the same template space, a white matter digital atlas was used to obtain the voxel count of a specific white matter tract and label the voxels with statistically significantly lower FA from TBSS analysis. The count of voxels with statistically significantly lower FA was then normalized with the count of total core voxels of each tract.

Results

From Fig. 1, the red voxels which have significantly low FA values are scattered in 3D image. It shows lower FA can be detected in multiple tracts. The tract size which is the number of core white matter voxels was used to normalize the count of the red voxel in each tract. All the major tracts were surveyed and we found SLF on both sides, left UNC and right CGH have most extensive lower FA values in the tracts. In Fig. 1, the clustered red voxels of each of three tracts are shown in coronal, sagittal and axial slices from left to right. For quantification purpose, the count of red voxels and total core white matter voxels within these three tracts are listed in Table 1. The ratios of the red voxel count for these tracts range from 16% to 27%.

Discussion

White matter abnormalities have been reported in late-life depression studies [1-3]. Studies in depressed youths are limited. To the best of our knowledge, this is the first study to report findings in at-risk youth who had no evidence of depressive or any other psychiatric disorder at the time of recruitment. From Table 1, it can be noted that the normalized ratios of all three most affected tracts are low (less than 30%), suggesting that the white matter disruption is not severe. However, for samples that have no evidence of psychopathology, the ratios of the abnormal voxels in SLF, UNC and CGH are quite large and cannot be ignored. To validate our approach, we applied TBSS to test if there are voxels with statistically significant higher FA values in the skeleton and it turned out we could not find any. As low FA values are usually associated with disruption of the white matter tracts, our results indicate that even prior to the onset of the disorder, there are already some changes in the structural integrity of the white matter in youth at high-risk for depression. Longitudinal follow-up will reveal whether the observed white matter tract changes in the high-risk group are associated with increased risk for developing depression. As VBM approach is intrinsically affected by noise, registration error or partial volume effects, further analysis is needed to validate our results.



Tract Name	Count of total tract voxels (A)	Count of abnormal tract voxels (B)	Ratio (B/A)
UNC-L	37	10	0.2703
CGH-R	46	12	0.2609
SLF-L	1715	360	0.2099
SLF-R	1123	190	0.1692

Figure 1 (left): Upper, middle and lower rows show the coronal, sagittal and axial slices of SLF at both sides, left UNC and right CG-Hipp. The red voxels are the ones where the FA values of high risk MDD group is significantly lower than those of control youth group ($P < 0.05$). The yellow mask denotes the anatomical location of the tract from a digital white matter atlas of the same template.

Table 1 (upper right): List of three tracts with largest portion of disrupted voxels.

References: [1] MacFall, J.R. et al (2001) Biol. Psychiatry 49, 803. [2] Kumar, A. et al. (2000) Am. J. Psychiatry 159, 630. [3] Taylor, W.D. et al. (2004) Am. J. Psychiatry 161, 179. [4] Bae, J.N. et al (2006) Biol. Psychiatry 60, 1356. [5] Taylor, W.D. et al (2008) PLoS One 3, e3267. [6] Choi, J. et al. (2008) Biol. Psychiatry (in press). [7] Mori, S. et al (2008) NeuroImage 40, 572.

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