Similar traits of white matter disruption for major depression disorder (MDD) and high risk MDD of adolescents

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Introduction

Unipolar Depression is among the leading causes of disability world-wide [1]. Adolescence is the highest risk period for the development of unipolar depressive disorder, and there is evidence for an increasing secular trend [2,3]. Alterations in white matter integrity of several cortical and sub-cortical circuits have been reported in relation to unipolar major depressive disorder (MDD) [e.g. 4,5]. To test whether these white matter changes precede the onset of illness, 43 adolescents, including control, MDD and high risk MDD, were recruited and underwent diffusion tensor imaging (DTI) studies. An automated tract-based spatial statistics (TBSS) method [6] incorporating JHU digital white matter atlas [7] was used to analyze the scans. Pair-wise comparisons revealed lower FA values for both MDD and high risk MDD at cingulum bundle (CG), splenium of the corpus callosum (SCC), superior longitudinal fasciculus (SLF), uncinate and inferior fronto-occipital fasciculus (UNC-IFO), indicating similar traits of white matter disruption. The altered white matter integrity in healthy adolescents at familial risk for unipolar depression suggests that it might serve as a vulnerability marker for the illness.

Methods

Participants and data acquisition: 12 adolescent controls, 17 youth at high risk for depression and 14 MDD adolescents were recruited. All participants were between 12-20 years (Controls: 17±3.5; high-risk MDD: 16.1±1.8 and MDD=17.2±3.8), and Tanner Stage III, IV or V of pubertal development. Control volunteers have no personal or family history of a psychiatric disorder. High risk volunteers have no personal history of a psychiatric illness including depression, but were at high risk for developing unipolar depression by virtue of parental depression. A 3T Philips Achieva MR system was used for DTI acquisition. DTI data were acquired using a single-shot EPI with SENSE. DWI parameters were: FOV=224/224/143mm, in plane imaging matrix = 112× 112, axial slice thickness = 2.2 mm without gap, slice number=65, 30 independent diffusion-weighted directions with b-value = 1000 sec/mm^2, TE=97ms, TR=7.6s. To increase signal noise ratio (SNR), two repetitions was performed. *Voxelwise analysis:* TBSS from FMRIB software library was used for voxel-wise comparison. This voxel-wise method compared the FA values of each group at core or skeletons of the white matter to effectively alleviate the partial volume effects. Modifications were made to the standard TBSS processing pipeline to better incorporate information of white matter labeling from a JHU digital white matter atlas (JHU ICBM-DTI-81). Specifically, the single subject template used for nonlinear registration process in TBSS is identical to the template used for establishing JHU ICBM-DTI-81. In this way, all the subjects' FA data were transformed into JHU ICBM-DTI-81 space, and the atlas labeling is overlaid to the mean skeleton in the JHU ICBM-DTI-81 space such that each skeleton voxel could be categorized into one of the 50 major tracts. After statistical analysis from TBSS, the significant clusters with $p < .001$ (uncorrected) in the skeleton voxels of white matter were identified. In order to avoid false positive results due to noise, only clusters with continuous voxels larger than 10 and averaged FA values greater than 0.25 were retained. Mean and standard deviation of FA values were calculated at these significant clusters.

Results

Compared to controls, no significantly higher FA values were found in both MDD and high risk MDD groups. The significant clusters with lower FA values were found in almost identical tracts and similar anatomical locations for MDD and high risk MDD groups, as demonstrated in Fig.1. The white matter tracts to which these clusters belong, detailed quantification and statistics of FA measurements at these clusters are listed in Table 1. It is clear from Table 1 that for both MDD and high risk MDD groups integrity changes of white matter occur in SCC, both sides of SLF and both sides of UNC-IFO. Although disruption was found in CG for both groups, it appeared at different hemispheres of the brain (Table 1). This different side of CG is the only difference between MDD and high risk MDD group, as shown in Table 1.

Conclusion and Discussion

Similar traits of white matter disruption for MDD adolescent patients and high risk MDD volunteers were revealed from our study. It suggests white matter tract changes occur before the manifestation of clinical symptoms of depression in at-risk adolescents. Longitudinal studies with larger samples will determine whether the observed microstructural white matter changes in the high-risk youth are associated with increased vulnerability for developing depressive disorder, which could have potential implications for identifying youngsters at highest risk for the disorder.

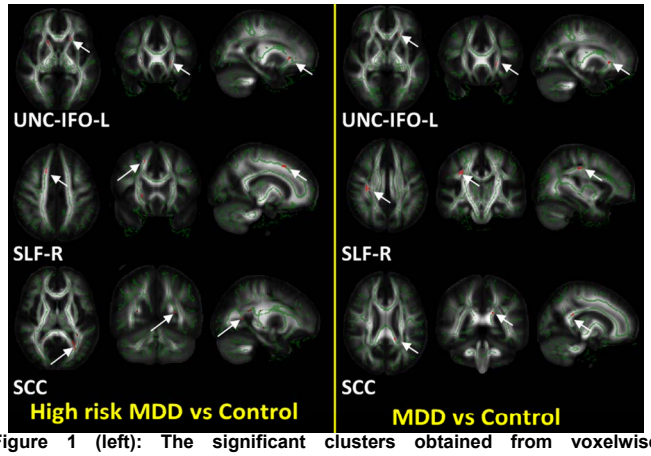

Figure 1 (left): The significant clusters obtained from voxelwise comparisons between control and high risk MDD group (left panel) and between control and MDD group (right panel). Green indicates white matter skeletons and red shows clusters with significant FA reduction in either MDD or high risk MDD group (p<.001, uncorrected). Underlying gray scale images are the averaged FA maps. Top, middle and bottom rows show significant clusters of left UNC-IFO, right SLF and SCC, respectively. Left, middle and right columns of each panel show the images of axial, coronal and sagittal views. White arrows indicate the clusters within the same tracts at similar anatomical locations. Abbreviations: CGC: cingulum bundle at cingulate cortex; SCC: splenium of corpus callosum; SLF: Superior longitudinal fasciculus; UNC-IFO: Uncinate and inferior fronto-occipital fasciculus.

Tract	Compared two groups	Group	Averaged FA	Standard deviation	p
SCC	MDD vs Control	Control	0.736	0.033	0.00012
		MDD	0.684	0.026	
	High risk MDD vs Control	Control	0.800	0.040	0.000002
		High risk MDD	0.662	0.064	
SLF-L	MDD vs Control	Control	0.427	0.069	0.00035
		MDD	0.315	0.069	
	High risk MDD vs Control	Control	0.555	0.048	0.00028
		High risk MDD	0.472	0.052	
SLF-R	MDD vs Control	Control	0.504	0.066	0.00032
		MDD	0.414	0.044	
	High risk MDD vs Control	Control	0.602	0.070	0.0011
		High risk MDD	0.493	0.082	
UNC-IFO-L	MDD vs Control	Control	0.623	0.037	0.0004
		MDD	0.559	0.043	
	High risk MDD vs Control	Control	0.605	0.053	0.00016
		High risk MDD	0.523	0.041	
UNC-IFO-R	MDD vs Control	Control	0.494	0.075	0.0020
		MDD	0.409	0.053	
	High risk MDD vs Control	Control	0.372	0.041	0.00032
		High risk MDD	0.314	0.029	
CGC-R	MDD vs Control	Control	0.550	0.073	0.00062
		MDD	0.455	0.052	
CGC-L	High risk MDD vs Control	Control	0.410	0.057	0.00059
		High risk MDD	0.343	0.028	

Table 1 (right): Average, standard deviation of FA values and p values at clusters where significant difference was found for control versus MDD group and control versus high risk MDD group.

References: [1] Word Bank 2006. [2] Hankin, BL et al (1998) J Abnrom Psychol 107: 128. [3] Kessler, RC et al (2005) Arch Gen Psychiatry 62: 593. [4] Mayberg, HS et al (2003) Br Med Bull 65: 193. [5] Price and Drevets (2010) NPP 35: 192. [6] Smith, SM et al (2006) NeroImage 31:1487. [7] Mori, S et al (2008) NeuroImage 40: 572.

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