White matter disruption of healthy maltreated adolescents

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Introduction

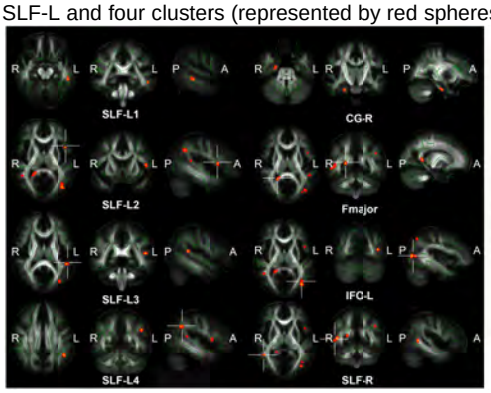
Childhood maltreatment (MALTX), including emotional abuse, physical abuse, sexual abuse and neglect, is widespread in the United States. MALTX has been known to produce long-lasting impairments in behavioral, cognitive and social functioning, but their underlying mechanisms are not well-understood. The developing brain is highly sensitive to the effects of early-life stress and MALTX has been associated with alterations in the size or functional activity of a variety of brain regions, possibly resulting in the above-described impairments. DTI is capable of delineating in-vivo microstructural changes of white matter tracts noninvasively. Recent DTI investigation (1) suggests white matter abnormality of young adults exposed to parental verbal abuse. In this study, 19 MALTX adolescent volunteers and 13 age-matched control volunteers were recruited and underwent DTI scanning. The goal of this study is to find out if white matter disruption precedes the onsets of clinical symptoms and may serve as potential biomarker of pscychiatric disorders such as depression and substance abuse.

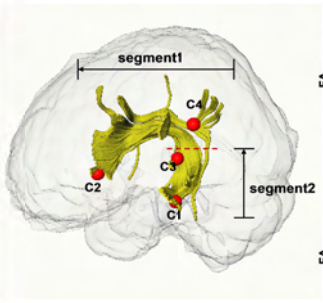
Methods

Participants: 19 adolescent volunteers (age=15.9±2.8) with no personal history of a psychiatric illness, but experienced MALTX prior to age 10 years, and 13 adolescent volunteers (age=16.4±3.9) with no personal or family history of a psychiatric disorder were recruited. All participants were between 12-20 years, and Tanner Stage III, IV or V of pubertal development. Controls were free from any type of psychopathology in their lifetime with no personal or family history of a psychiatric disorder. *DTI acquisition:* 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, repetitions=2. *Voxelwise analysis:* TBSS from FMRIB software library was used for voxel-wise comparison. The single subject template used for nonlinear registration process in TBSS (2) is identical to the template used for establishing JHU ICBM-DTI-81 (3). 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. *Tract-level comparison:* Tract-level analysis was based on the FA values at the skeleton voxels after TBSS registration, projection and skeletonization steps. The entire white matter tract was considered to be possibly disrupted if it contained filtered significant clusters revealed by cluster analyses mentioned above. *Along the tract analysis for left superior longitudinal fasciculus:* The left superior longitudinal fasiculus (SLF-L) was segmented into two parts, the superior and inferior one, by an axial plane at z=90 in MNI coordinate. For the superior and inferior part, the cross-section of a sequential coronal and axial planes and the white matter mask from probabilistic atlas was used as ROI to calculate the mean and standard deviation of FA in the sequential planes, respectively.

Results

Voxel-wise comparison of white matter changes: The maltreated group had significantly lower FA values in several white matter tracts including right cingulum projecting to hippocampus (CGH-R), left and right superior longitudinal fasciculus (SLF-L/R), left inferior fronto-occipital fasciculus (IFO-L), and forceps major of corpus callosum (Fmajor) (see Fig. 1). There are four clusters in SLF-L while single clusters were found for the rest of the white matter tracts listed above. Compared to controls, the maltreated group did not show significantly higher FA values in any white matter tracts Population. *Tract-level comparison of white matter changes*: The maltreated group manifested disruptions of only SLF-L (uncorrected p=0.038) at tract level, suggesting large portion of the skeleton voxels in this tract have decreased FA values. *FA profile along SLF-L in control and maltreated group:* The reconstructed SLF-L and four clusters (represented by red spheres) in this tract are shown on the left panel of Fig. 2. On the right panel of Fig. 2, the FA profiles along superior and inferior segments of SLF-L in control and maltreated group are shown. The FA of maltreated group is generally lower than that of the controls along the two segments of the tract. The differences are dramatic at the clusters identified from TBSS analysis and also pointed by the arrows in the plots of FA profile (right panel of Fig. 2).





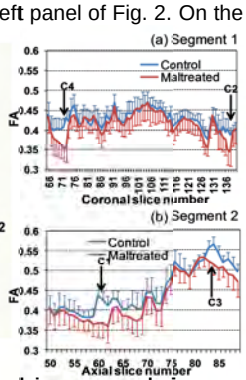


Fig. 1 (left): The significant clusters obtained from voxelwise comparisons between control and maltreated groups. Green color indicates white matter skeletons and red color shows clusters with significant FA reduction in the maltreated group (p <.001). Underlying gray scale images are the averaged FA maps. Left, middle and right graphs of each panel show the images of axial, coronal and sagittal views. White cross hairs indicate the clusters of the specified white matter tracts if multiple clusters are shown in the image. Four clusters of SLF-L are on the left and four clusters of other four tracts are on the right. CGH-R = left cingulum bundle projecting to hippocampus, SLF-L/SLF-R = left or right superior longitudinal fasciculus; Fmajor = forceps major (splenium) of the corpus callosum; IFO-L = left inferior fronto-occipital fasciculus.

Fig. 2 (right): FA profiles of the segment 1 (a) and segment 2 (b) of left superior longitudinal fasciculus. Dramatic FA differences between maltreated and control group in the FA profile coincide with the locations of disrupted clusters (C1, C2, C3 and C4). The three-dimensionally reconstructed fiber bundles of left superior longitudinal fasciculus and four disrupted clusters of this tract are also shown on the left panel.

Conclusion and discussion

White matter disruptions in several white matter tracts including SLF-L/R, CGH-R, Fmajor and IFO-L have been found in the maltreated subjects. It is clear that white matter integrity has changed prior to the clinical symptoms of any psychiatric disorder such as depression. Prefrontal, cingulate cortex and hippocampus are crucial for wide range of emotional and motivational processes, as well as working memory. Fmajor and IFO-L are both white matter tracts connecting to prefrontal cortex and CGH-R connect cingulate gyrus to hippocampus. It is striking to find multiple disruption sites in SLF, a large association fiber bundle connecting cortical regions of frontal, parietal, temporal and occipital lobes. The extensive cortical connections of this tract suggest that SLF-L may be involved in more brain functions besides language. Challenges of traditional role of SLF-L have been found in recent literature (e.g 4). More disrupted locations of SLF-L and general FA decrease along the tract suggest that the SLF-L in maltreated adolescents in our study was more severely affected, compared to structural change of SLF-L in young adults (1). As an on-going study, data from more maltreated adolescents and controls will be acquired.

References: [1] Choi, J et al (2009) Biol Psychiatry 65:227. [2] Smith, SM et al (2006) NeroImage 31:1487. [3] Mori, S et al (2008) NeuroImage 40: 572. [4] Bernal, B and Ardila A (2009) Brain 132: 2309. **Acknowledgement:** NIH EB09545, DA014037, DA015131, DA017804, DA017805, MH062464, MH068391 and RR003032.