

## Macrostructural and microstructural abnormalities of the neurocircuitry in bipolar disorder: a study of structural MR and diffusion tensor imaging data

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**Introduction** Neuroimaging studies demonstrate increased white matter hyperintensities (WMH) and abnormalities of diffusion measures in deep, periventricular and callosal white matter (WM) in bipolar disorder (BD). Euthymic BD patients exhibit executive impairment, which suggests intra-hemispheric fronto-subcortical circuits are important in the impairment of neuropsychological function in BD. The present study investigated the association between microstructural and macrostructural WM abnormalities and their relationships with the connectivity of WM tracts in BD.

**Methods** Participants included 17 unmedicated BD (M/F=2/15, 31.4±9.2 years) and 18 healthy controls (HC) (M/F=4/14, 30.9±8.6 years). 3T Diffusion-weighted imaging data (Siemens Trio MR scanner, EP2D\_DIFF, TR/TE=8000/88ms, 1.7x1.7x3mm<sup>3</sup>, FOV= 220x220mm<sup>2</sup>, matrix=128x128mm) were acquired by using diffusion sensitizing gradients along 86 non-collinear uniformly distributed directions (b-value=800s/mm<sup>2</sup>), together with additional acquisition of three non-diffusion weighted (b=0). A simple least squares fit of the diffusion tensor model, and fractional anisotropy (FA), mean diffusivity (MD), parallel and radial diffusivity were calculated. MPRAGE (TR/TE/TI=2200/3/766 ms, 0.8x0.8x0.8mm<sup>3</sup>) and FLAIR (TR/TE/TI=5000/353/1800 ms, 0.5x0.5x1mm<sup>3</sup>) MR images were used for WM and WMH segmentation. An automated method for the quantification and localization of WMH were carried out on the FLAIR brain MR images: 1) segmented WM of MPRAGE image using Freesurfer software were transformed to the FLAIR space using linear transformation, 2) identifying WMH seeds based on the intensity histogram (thresholded at mean +3.5\*SDs) of the 8-bit weighted FLAIR WM after considering the partial volume effect, 3) a fuzzy connected algorithm to segment the WMH clusters with iteratively updating, and combining the WMH clusters into the final segmentation. The segmented WMH were transformed to MPRAGE space and labeled using the co-registered white matter atlas (JHU-ICBM-tracts-maxprob-thr0-1mm). The mean connectivity in superior longitudinal fasciculus (*sif*), ventral cingulum at hippocampal area, inferior longitudinal fasciculus (*iff*), inferior fronto-occipital fasciculus (*ifo*), and optic radiation (*or*) were quantitated in left and right hemispheres using probabilistic tractography by defining the starting and ending regions of WM tracts. General linear model analysis evaluated the group difference (HC vs BD) of the normalized WMHs and mean connectivity within the association fiber tracts after correcting the age and gender covariates, as well as total white matter volume covariates for the group comparison of WMHs (no correction for multiple comparisons). A permutation-based non-parametric approach tested voxelwise statistics analysis of the association between diffusion measures and total WMHs and the disease group interaction after regressing out age and gender effects ( $t > 2.3$ , corrected  $P < 0.05$ ).

**Results** BD had larger WMHs than HC in major forceps (occipital radiation of the corpus callosum), right anterior region of corona radiata, left ventral cingulum at hippocampal area, right *sif* at temporal region left *ifo* ( $P < 0.05$ ). BD had larger mean connectivity than HC in right *ifo* and left ventral cingulum. The MD and radial diffusivity in the regions of bilateral superior cerebellar peduncles and left inferior cerebellar peduncle; and the parallel diffusivity in the left cerebral peduncle had significant disease diagnosis interaction with the corrected total WMHs.

**Discussion** The association of microstructural and macrostructural changes is consistent with the effects on the executive processing within each hemisphere, which may underlie the neuropsychological impairment in BD patients.

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