**Biological Psychiatry**

**MS Number: BPS-D-16-01003**

**Title: Diffusion tensor imaging correlates of early markers of depression in youth at high familial risk for bipolar disorder**

Abstract:

Background: mood disorders are familial psychiatric diseases, in which patients show reduced white matter (WM) integrity. We sought to determine whether WM integrity was affected in young offspring at high familial risk of mood disorder before they go on to develop major depressive disorder (MDD).

Methods: the Bipolar Family Study is a prospective longitudinal study examining individuals at familial risk of mood disorder on three occasions two years apart. This study used baseline imaging data, categorizing groups according to clinical outcome at follow-up. Diffusion tensor MRI data were acquired for 61 controls and 106 high-risk individuals, the latter divided into 78 high-risk subjects who remained well throughout the study ("high-risk well"), and 28 individuals who subsequently developed MDD ("high-risk MDD"). Voxel-wise between-group comparison of fractional anisotropy (FA) based on diagnostic status was performed using Tract-based Spatial Statistics (TBSS).

Results: compared to controls, both high-risk groups showed widespread decreases of FA (Pcorr<0.05) at baseline. Although FA in the high-risk MDD group negatively correlated with sub-threshold depressive symptoms at the time of scanning (Pcorr<0.05), there were no statistically significant differences at p-corrected levels between the two high-risk groups.

Conclusions: these results suggest that decreased FA is related to presence of familial risk for mood disorder along with sub-diagnostic symptoms at the time of scanning, rather than predictive of subsequent diagnosis. Due to the difficulties performing such longitudinal prospective studies we note, however, that this latter analysis may be underpowered due to sample size within the high-risk MDD group. Further clinical follow-up may clarify these findings.

Comment: This study extends the authors’ previous work on unaffected relatives of BD which showed that compared to the control group, unaffected relatives had reduced FA in a large white matter cluster. The current findings show a widespread decrease in FA in both high-risk groups (for MDD in this case). The authors suggest that decreased FA is potentially related to familiar risk for mood disorder. Caution is recommended given the small sample size of high risk MDD. The findings have significant clinical relevance. Using a longitudinal design in an at-risk population is novel and an obvious strength compared to other studies. The reduced sample size is unfortunately a reality in research in offspring of populations with mood disorders. Although it’s a follow up study I would highly recommend that the authors consider revising their introduction and conclusions to reiterate the relevance of their study approach/findings, the novelty of their approach (design), and the meaning of changes in FA beyond the concept of “integrity of the white matter”. Although the authors mention the small sample size the reader remains a bit confused as to what an ideal sample size would be, and to what extent inferences can be made. I think that this could be improved by providing additional references to other studies in this research field, highlighting the clinical relevance of the study, and potentially mentioning directions/alternative approaches for future studies.

1. Scans: how did the authors control for potential history/maturation biases over time?
2. Could they mention whether the populations were matched for demographic variables, or whether they controlled for specific confounders?
3. Did they consider including other measures of overall functioning or quality of life? If not included in this manuscript please discuss anyway in the conclusions for instance
4. Why did the authors include FA but not AD, RD or MD in their analyses? Could they discuss why they did not? Could these be helpful?
5. When the authors calculated correlations between FA values and mood symptoms, did they compare the coefficients of correlation across groups? Please address this somewhere in the manuscript.
6. Could the authors mention the advantages of TBSS over other methods such as Tracula or tractography for instance?
7. They mention that the sample size of the high risk MDD is small: could they mention how many people did they hope to have/include in this group?
8. Overall I would restructure, shorten, and revise the discussion to highlight the primary findings of this study and the strength of the proposed study. In particular, I would focus on reorganizing the content to provide a single, stronger, concise, clear “take-home message”, clearly stating strengths and weaknesses and how one could address these, and provide alternative approaches for future studies.