Ref: PSYN\_2017\_31

Title: A distinctive abnormality of diffusion tensor imaging parameters in the fornix of patients with bipolar II disorder

Journal: Psychiatry Research: Neuroimaging

Corresponding Author: Corresponding Author: Akeo Kurumaji

Co-authors: Co-authors: Michio Itasaka, Akihito Uezato, kazuo takiguchi, Daisuke Jitoku, Mizue Hobo

Abstract:

Diffusion tensor imaging (DTI) studies have revealed a changed integrity in the white matter of bipolar disorders. However, only a few investigations have examined the bipolar II disorder (BP-II) in spite of the distinctive clinical characteristics from the bipolar I disorder. A cross-sectional study was conducted to compare thirty-eight patients with BP-II under naturalistic treatment with thirty-eight age- and gender-matched healthy controls. A whole brain voxelwise analysis of the fractional anisotropy (FA) using Tract Based Spatial Statistics (TBSS) was carried out, then a complementary atlas-based region-of-interest (ROI) analysis was done to confirm the results of the TBSS. The ROI method also analyzed the axial diffusivity (AD) and radial diffusivity (RD) to obtain further information about the white matter. The patients with BP-II showed a significant decrease in FA in the corpus callosum (commissure fibers), fornix (association fibers) and right anterior corona radiata (projection fibers) compared to the controls. Moreover, a significant increase in the RD was observed in all of the fibers of the BP-II patients, while the AD significantly increased only in the fornix of the patients. Thus, the present study suggested that the altered DTI measures of the fornix may underlie a different neuropathology from the other tracts.

Feedback: Relevant topic as, despite the increasing number of DTI studies in BD populations and advancement in DTI analyses/approaches, a general consensus on which tracts show alterations in BD and whether these alterations appear prior to or following the onset of the disease, is still lacking. Another strength of this paper is undoubtedly the population (BD II). These strengths make this paper a valuable contribution to the literature. However, I would recommend that the author tighten up their introduction and focus on highlighting the gaps in the literature, explicitly describing the novelty of their approach. I would also encourage the authors to broaden their statistical analyses to investigate a few more issues (e.g. medication load, mood), and consider discussing in their discussion additional topics of interest such as cognitive functioning, global functioning and limitations of current DTI measures etc.

1. Abstract should contain the N of participants in each group (along with mean age and gender ratio), mention of statistical approach used, and covariates used. Since the corpus callosum has been linked to BD in previous papers please try to highlight the additional contribution to current knowledge of this paper and potential future directions.
2. In the introduction I would summarize basic such as meaning of FA, RD etc. and rather focus on how variability in imaging parameters and analyses could affect results. For instance what is the difference between voxel based DTI, ROI based, tractography, and Tracula. Also some mention of potential sources of error that should be taken into account (e.g. CSF contamination) or importance to use quantitative tractography based on DTI technology would show to what extent we can rely on DTI data and what current findings really mean.
3. Could you please clarify if you performed the following analyses and, if not not, why you did not and whether you would consider performing them: 1.didd you test for or treat each hemisphere as separate, 2. Did you covary for age, sex,medication status or load, and severity of mood symptoms; 3. did you adjust your spss analyses for multiple comparisons 4. What was your statistical threshold; 5. and did you check correlations between FA, RD, AD, age at onset, number of mood episodes. Could you please provide this correlation matrix?
4. A way to strengthen the credibility of these findings would be to use a discriminatory analysis to see if relevant FA values can separate BD from HC.
5. Conclusions: please comment on the lack of correlations between clinical evaluations and DTI measures in any white matter tract. Also please talk about the effect of medication on white matter integrity, and illness duration.
6. How should we interpret the effect sizes of your results? Please comment on this in your conclusions.
7. A depiction of white matter tracts (for instance output on fslview) could be helpful. E.g. FA skeleton.
8. Please provide captions for your tables and figures. As a rule of thumb captions for figures should convey as much as information as possible so that the reader does not need to re-read the manuscript. it should include summary statistics plotted, explanatory information to interpret the results shown etc.
9. Please provide comorbidities, IQ estimate, current mood, GAF for your participants
10. Minor comment: I would reformulate the following sentence on page 13 “between the brain cells of the cerebral cortex and the brain cells in the brain stem”. You could drop “brain cells” and talk of “carry information from brain cortex to the brain stem” or be more precise and indicate where exactly in the brain cortex.