**Ref: PSY\_2016\_933**

**Title: The association of sleep and physical activity with integrity of white matter microstructure in bipolar disorder patients and healthy controls**

**Journal: Psychiatry Research**

Abstract:

We investigate how the sleep disruptions and irregular physical activity levels that are prominent features of bipolar disorder (BD) relate to white matter microstructure in patients and controls. Diffusion tension imaging (DTI) and 14-day actigraphy recordings were obtained in 51 BD I patients and 55 healthy controls. Tract-based spatial statistics (TBSS) was used for voxelwise analysis of the association between fractional anisotropy (FA) and sleep and activity characteristics in the overall sample. Next, we investigated whether the relation between sleep and activity and DTI measures differed for patients and controls. Physical activity was related to increased integrity of white matter microstructure regardless of bipolar diagnosis. The relationship between sleep and white matter microstructure was more equivocal; we found an expected association between higher FA and effective sleep in controls but opposite patterns in bipolar patients. Confounding factors such as antipsychotic medication use are a likely explanation for these contrasting findings and highlight the need for further study of medication-related effects on white matter integrity.

Comment

This study investigated the association between white matter structure and sleep in patients with BDI and healthy controls. The authors collected DTI, physical activity, and sleep measures, and used regression analyses to evaluate associations between these measures. Confounding factors included medication and illness-specific variables. The author reported a positive relationship between physical activity and white matter. The relationship between sleep and DTI was more equivocal and differed between BD and HC.

General: the manuscript is fairly well-written and the topic is of relevance for the field of brain stimulation and quality of life in bipolar disorder. The strength of the findings is, however, questionable. To start with the DTI component of this study is lacking. Using FA without mentioning RD, AD (and to a certain extent MD) is restrictive as these parameters may provide information on myelination and other white matter alterations. The authors do not mention ROIs or white matter tracks where differences in FA between BD and HC were observed. No FA skeleton map is provided and they use an average FA value of the brain without explaining the rationale for this approach. Little is said about previous work and data correlating sleep/physical activity and DTI. Further, the authors should have addressed the potential biological correlates between the proposed variables. The term “physical activity” appears in the title and in the manuscript but is not well defined. The authors obviously do not mean “physical exercise”, are they talking about movements while individuals sleep? Although promising the current findings are too general, hard to interpret and do not advance knowledge in this field.

Major comments:

Introduction: 1.provide additional information on biological mechanisms that may link DTI changes and sleep or physical activity (oxygen-related, cardiovascular health etc.).

2.Provide additional information on previous studies on DTI and sleep/physical activity and explain why DTI is an ideal technique to study associations between these variables.

3.Please explain, even if briefly, what FA changes mean in biological and functional connectivity terms.

Methods 4. when reading the methods it was unclear to me if this was a cross-sectional or longitudinal study, and whether BD or siblings and BD were included. Please make it clear (for instance by adding “we used a subsample of participants recruited as part of the DBC study..”, “Participants included HC and BDs..”.

5. explain why a.only BD I, b.why 3 Dutch grandparents are needed, c.what are your inclusion/exclusion criteria for neurological, cardiovascular, substance use disorders

6.was the data used in this manuscript collected in this manuscript data from the subgroup tested after 1.4 years?

7. physical activity: please define what you measured exactly. Did you collect information on lifestyle and dietary habits too?

8. how did the authors correct for a potential “Hawthorne bias”? did they record information on usual sleep activity etc.?

9.Statistical analyses: was the TBSS pipeline performed on entire FA dataset or did the authors perform analyses in specific ROIs?

10.Please provide maps showing FA differences between BD and HC or at the very least mention which tracts could be of interest. 10b. have the authors considered entering the avarge FAs of significant tracts when conducting their regression analyses?

11. did the authors analyse RD, AD and MD too? if not please discuss or mention in the manuscript why you did not.

12. as part of your regression analyses please define method of entry of relevant variables e.g. stepwise, enter? And did you enter variables in blocks? If so please explain which variables were included in each block. Could you please clarify if you conducted an ordinal regression including a dummy variable for BD/HC?

13. what was your statistical p-threshold?

14. the number of confounding variables is elevated. Did you enter confounding variables all at the same time? Did you consider the negative impact of confounding variables on the statistical power of this study? please discuss in the conclusions e.g. limitations.

15. which software did you use for statistical analyses?

16. Table 1. Please provide measures of IQ, education, and current mood (HAMD, YMRS etc. ) and please specific if BDs were euthymic or remitted etc. Please provide F and p-values too.

17. Table 2. What does “mean activity 0 to 24h” refer to?

18. please provide a table with FA statistical maps showing differences between BD and HC. this table should include size of ROI, name of tract (cite name of atlas too), MNI coordinates of ROI, F and p values

19. please provide a summary table of the results of your regressions including B, b value, p, R2 and also N after including confounding variables. I was a bit confused by the N cited on page 10.

20. Discussion: the authors do not mention any region in particular where differences were found between BD and HC and it’s therefore hard to understand what the current findings mean. Also it’s hard to know why the authors used a whole-brain FA value? This is way too general and doesn’t inform the reader on potential mechanistic or connectivity alterations in the brain. Please discuss or mention this in your introduction.

21.Include a paragraph discussing biological changes (e.g.VO2 max and FA, blood flow increase-activity and FA, BDNF, reduced volume loss

22.Figures: please improve your captions to include reference to L-R coordinates, name of tracts highlighted in the picture

Minor comments

Title: consider removing or rewording physical activity

Abstract: please provide essential demographic information such as age, gender and N. Please provide basic information on statistical analyses. Names of regions or tracts where significant FA differences were found should be mentioned.