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.

Keywords: bipolar disorder, actigraphy, DTI, sleep disturbances, physical activity

Highlights:

- Physical activity was related to increased fractional anisotropy (FA)
- Controls showed positive associations between higher FA and effective sleep
- In patients sleep was inversely related to FA
- The relation between sleep and FA in patients was confounded by antipsychotics

1. Background

Bipolar disorder is a severe and recurrent psychiatric disorder, characterized by alternating depressive and manic mood episodes (Belmaker, 2004). Although the aetiology of bipolar disorder remains poorly understood, there is an extensive body of evidence suggesting that brain abnormalities are a core feature of the disorder. Previously, structural imaging studies found marked anatomical differences in grey matter volume between patients and healthy controls (Hallahan et al., 2011; Hibar et al., 2016). Moreover, volumes of several areas (i.e. amygdala, globus pallidus) were associated with polygenic risk scores for bipolar disorder and are affected in first-degree relatives (Caseras et al., 2015; Sandoval et al., 2014). In addition to volumetric measures, diffusion tensor imaging (DTI) studies have shown that bipolar disorder is also characterized by changes in white matter microstructure (Mahon et al., 2010). DTI quantifies the integrity and coherence of white matter tracts by measuring the diffusion of water parallel and perpendicular along white matter fibre tracts. The normalized standard deviation of the diffusivities is referred to as fractional anisotropy (FA) and ranges from 0 to 1, in which higher values indicate faster diffusivity (Assaf and Pasternak, 2008). A voxel-based meta-analysis of 18 DTI studies found that bipolar patients have lower FA in the genu of the corpus callosum and left cingulum white matter, suggesting poor integrity of white matter (Wise et al., 2016). This finding has also been established in antipsychotic and mood-stabilizer naïve patients (Yip et al., 2013).

In addition to these brain changes, disturbances in sleep patterns are considered a core symptoms of bipolar mood episodes (First et al., 1997). The majority of patients experience a reduced need for sleep during manic phases of the disorder, and hypersomnia or insomnia during depressive episodes (Harvey, 2008). Sleep has several properties which are crucial for normal brain functioning and integrity (Diekelmann and Born, 2010; Kang et al., 2009; Ooms et al., 2014; Tononi and Cirelli, 2006; Wang et al., 2011; Xie et al., 2013). In clinical studies of sleep disorders several neurophysiological alterations have been observed. For example, insomnia has been linked to reductions in orbitofrontal and parietal grey

matter and larger rostral anterior cingulate cortex volumes (Altena et al., 2010; Winkelman et al., 2013), and narcolepsy and obstructive sleep apnoea are associated with widespread reductions in grey matter volume and thickness (Joo et al., 2011, 2010, 2009). Furthermore, animal studies have demonstrated that sleep deprivation interferes with long term synaptic potentiation and neurogenesis (Kopp et al., 2006; Kreutzmann et al., 2015; Mirescu et al., 2006). Mechanism of the link between sleep and integrity of white matter remain largely unknown. It was found that oligodendrocyte proliferation and myelin-related gene expression strongly increases during sleep and reduces during wake time and experimental sleep deprivation (Bellesi et al., 2013). These findings suggest that sleep quality relates to white matter microstructure and that sleep disruptions could lead to reduced integrity of white matter.

Not only sleep, but also altered levels of physical activity are a hallmark of bipolar mood episodes: while depression is characterized by a marked reduction in overall physical activity, manic episodes stand out for their increased goal-directed behaviour and psychomotor agitation (American Psychiatric Association, 2013). In the general population, physical activity is thought to positively affect brain characteristics; higher levels of physical activity and physical fitness have been associated with increased grey matter volumes, both cross-sectionnally, longitudinally, and after a physical exercise intervention (Bherer et al., 2013; Erickson et al., 2014). Furthermore, a meta-analysis of 29 studies tentatively concluded that physical exercise leads to both global and local improvements in white matter (micro)structure (Sexton et al., 2015). Results from an exercise intervention study in schizophrenia patients indicated that after six months of training, the connectivity in white matter fibre tracts associated with motor functioning improved equally in the schizophrenia patients and a control group (Svatkova et al., 2015). Until now, similar studies in bipolar patients are absent.

Since sleep and physical activity are core features of bipolar disorder and both are associated with white matter changes, the current study investigates the link between white matter microstructure and physical activity and sleep patterns in patients with bipolar disorder.

2. Methods

2.1 Sample

This study is a follow up of the Dutch Bipolar Cohort (DBC) study, which is a collaboration between the University Medical Center Utrecht (UMCU), various health care institutes in the Netherlands and the University of California Los Angeles (UCLA). The objective of the DBC study is to collect a deep phenotype characterization of bipolar I patients, their first-degree relatives and controls. The medical ethical committee of the UMCU approved the DBC study and the current study. Written informed consent was obtained from all participants prior to participation. After completion of the DBC protocol, a subgroup of patients, siblings and controls were re-approached to participate in the actigraphy and MRI protocol. The mean time difference between both protocols was 1.4 years.

All participants had a minimum age of 18, at least three grandparents of Dutch descent and none were pregnant during the actigraphy or DTI measurements. Participants diagnosed with a major somatic illness (e.g. sleep apnoea) were excluded. Additionally, control subjects with a bipolar or psychotic diagnosis were excluded, as were control subjects who had a first or second degree relative with a bipolar or psychotic diagnosis. Participants were assessed using the Mini-International Neuropsychiatric Interview (M.I.N.I) (Sheehan et al., 1998). Participants who had previously experienced head trauma or were diagnosed with a neurological disorder were excluded. An independent radiologist evaluated all MRI scans. Participants with any clinical findings were excluded from further analyses.

2.2 Actigraphy recordings and analyses

Circadian rhythmicity and sleep-wake measurements were recorded with an Actiwatch (the Actiwatch 2; Philips Respironics Inc, Murrysville, PA, USA). The Actiwatch has a solid-state piezo-electric accelerometer and a lithium rechargeable battery. It records wrist movements and the sum of wrist movements is scored in epochs of 1 minute. All participants were instructed to wear the Actiwatch for a

period of 14 consecutive days on their non-dominant wrist and only to remove it when exposed to water for long periods of time (e.g. swimming). During the 14-day recording period, participants kept a sleep diary in which bed times, nap times and off-wrist periods were noted.

To calculate the sleep and activity patterns, a series of algorithms in R statistical package (R Development Core Team, 2014) were used according to the procedure developed by Pagani et al. (2015). These algorithms resulted in 7 sleep measures: sleep duration, timing of sleep onset (i.e. minutes prior or after midnight), timing of sleep offset (i.e. minutes after midnight), sleep onset latency, sleep efficiency (i.e. minutes asleep divided by minutes in bed), wake after sleep onset (WASO) and sleep inertia (i.e. wake interval between sleep offset and time out of bed). The mean of overall activity levels were calculated for the 24-hr period, followed by the mean of activity in four 6-hr periods: midnight to 6 AM, 6 AM to noon, noon to 6 PM, and 6 PM to midnight.

2.3 MRI acquisition

Structural Magnetic Resonance Images were acquired on a 3 Tesla Philips Achieva scanner (Philips Healthcare, Best, the Netherlands), equipped with an 8-channel SENSE-headcoil. Fast field echo scans with 200 contiguous sagittal slices (TE=4.6 ms, TR=10 ms, flip angle=8˚, FOV=240 mm, 0.75 x 0.75 x 0.80 mm^3 voxels) were obtained. Processing was done on the neuroimaging computer network of the University Medical Center Utrecht - Brain Center Rudolf Magnus, Utrecht, the Netherlands. All MRI analyses were conducted using the FMRIB Software Library (FSL v5.0) (Jenkinson et al., 2012). Diffusion weighted images were pre-processed using FMRIB's Diffusion Toolbox (FDT). First, *topup* was used to correct for susceptibility induced distortions (distortions caused by the magnetic susceptibility inhomogeneities in the subject's head), using two non-diffusion weighted (b-value=0) images with opposite phase-encoding directions (anterior to posterior and opposite), which thus have distortions

going in opposite directions. The susceptibility-induced off-resonance field (distortions caused by inhomogeneities to magnetic susceptibility of the subject's head) was estimated using a method similar to that described in Andersson et al. (Andersson et al., 2003) and the two images were combined into a single corrected one. Next, *eddy* was used to correct for eddy-current distortion and head movements, and *bet* (brain-extraction tool) was used to exclude any non-brain tissue (Smith, 2002). Finally, *dtifit* was used to fit a diffusion tensor model at each voxel.

2.4 TBSS analysis

Tract-based spatial statistics (TBSS) was used for voxelwise comparison of fractional anisotropy (FA), between subjects (Smith et al., 2007, 2006). First, the FA maps of all subjects were non-linearly aligned to a standard FA template (FMRIB55_FA; the average of 55 good quality healthy subjects) after which the average was computed. The resulting average FA map was thinned to create a white matter 'skeleton', representing the centre of white matter tracts common to all subjects. This white matter skeleton was thresholded at FA>0.2 to exclude non-white matter and voxels in extremities where there is too much cross-subject variability in alignment, resulting in a white matter skeleton of 141,230 voxels. Next, each subject's FA data was projected onto the white matter skeleton; for each subject the highest FA value perpendicular to each voxel of the skeleton (i.e. the individual's local white matter tract centre) was projected onto the white matter skeleton.

2.5 Statistical analyses

Voxelwise statistics were carried out using the 'randomise' procedure, a tool for permutation-based non-parametric testing using the general linear model (Nichols and Holmes, 2002). All statistical tests were performed with 5000 permutations, threshold free cluster enhancement (TFCE) (Smith and Nichols, 2009) and fully corrected for multiple comparisons across space using family-wise error (FWE)

correction. First, we investigated the correlation between actighraphy measures and FA for each voxel, in the overall sample of patients and healthy controls. In case of significant voxels, we determined the association between average FA of the significant clusters and actigraphy measures using regression analysis. Next, we investigated whether actigraphy measures were differently associated with DTI measures in patients and controls, using an interaction term for Group*Sleep/Activity variable. For variables with significant interaction effects, we performed stratified linear regression analyses to determine the association between actigraphy measures and the average FA of significant clusters. All analyses were corrected for age, gender (and patient/control group in the overall sample). Illness-specific variables (number of episodes, history of psychotic symptoms, illness duration and use of psychotropic medication) were tested for their association with FA and the actigraphy measures. In case these variables showed significant associations with both FA and actigraphy measures, they were considered as potential confounders and entered as covariates in the stratified patient analyses.

3. Results

3.1 Participants

A total of 106 participants were included (51 patients, 55 controls). See table 1 for sample characteristics. No differences between patients and controls were found for age, gender and handedness. Patients worked on average fewer days during the actigraphy measurement period as compared with controls ($F[1,104]=4.1$, $p=0.045$).

Table 1 – Sample characteristics

	Patients	**Controls**
Age M (sd)	49.5 (11.4)	45.5 (15.8)
Gender M/F (% male)	28/23 (54.9%)	25/30 (45.5%)
Handedness R/L/B (% right)	42/6/3 (82.4%)	44/11/0 (80.0%)
Nr of workdays M (sd)*	4.2 (3.5)	5.7 (3.7)
Illness duration/ years M (sd)	16.5 (14.2)	-
Number of episodes M (sd)	10.0 (10.8)	-
Age at onset M (sd)	31.7 (12.2)	-
History of psychotic symptoms N (%)	35 (70.0%)	-

* Significant group difference at $p<0.05$

With the exception of 1, all patients used between 1-4 types of psychotropic medication during the actigraphy measurements; 24 patients used lithium and 17 patients used other mood stabilizing agents. Furthermore, 15 patients received antipsychotic medication, 9 patients used antidepressants and 19 patients used benzodiazepines. Of the control subjects, 1 person received an antidepressant and 1 a benzodiazepine.

Table 2 – Difference between sleep and activity measures for patients and controls

	Patients	**Controls**	p-value
Sleep duration M (sd)	475.2 (86.3)	447.2 (40.4)	0.01
Sleep onset M (sd)	-0.50 (75.3)	17.6 (73.0)	0.22
Sleep onset latency M (sd)	5.0 (5.7)	4.9 (5.2)	0.89
Sleep offset M (sd)	474.7 (88.5)	464.8 (74.8)	0.33
Sleep intertia M (sd)	6.8 (7.2)	5.4 (6.3)	0.37
Wake after sleep onset M (sd)	59.6 (27.0)	48.5 (19.5)	0.03
Sleep efficiency M (sd)	84.8 (8.1)	87.3 (4.9)	0.12
Mean Activity M (sd)	204.7 (89.3)	234.4 (54.5)	0.08
Activity 0 to 6 h M (sd)	42.1 (36.6)	45.0 (41.5)	0.82
Activity 6 to 12 h M (sd)	227.3 (127.8)	260.8 (91.6)	0.12
Activity 12 to 18 h M (sd)	333.4 (143.1)	361.8 (93.9)	0.34
Activity 18 to 24 h M (sd)	215.6 (109.6)	270.4 (84.9)	0.02

Means (M) and standard deviations (sd) on sleep and activity measures. Models are corrected for age and gender.

Mean scores and standard deviations on the 7 sleep measures and 5 activity measures are shown in table 2. Patients had on average a longer sleep duration ($F[1,102]=6.6$, p=0.01, a longer wake time after sleep onset ($F[1,102]=5.1$, p=0.03) and lower activity counts between 6 PM and midnight ($F[1,102]=6.1$, p=0.02). However, after corrections for multiple testing, none of the group difference remained significant at a bonferonni-corrected significance level of 0.004.

3.2 Activity measures

In the overall sample, average FA of the significant voxels was positively associated with mean activity throughout the day (β=0.33, R^2=0.32, p<0.001), activity between noon and 6 PM (β=0.37, R^2=0.31, p<0.001) and between 6 PM and midnight (β=0.41, R^2=0.33, p<0.001) (**Figure 1**). These correlations were found in largely overlapping regions of the brain, most of all in the genu and body of the corpus callosum and the right anterior corona radiata. There were no significant interactions between group and activity measures with any of the DTI measures, suggesting that the association between activity measures and DTI measures was not significantly different for patients and controls.

3.3. Sleep measures

Voxelwise correlations in the overall sample (corrected for age, gender, and patient/control group) revealed no significant correlations between sleep measures and DTI measures. Analyses of the interaction between group and sleep on FA revealed that the association of three sleep measures (i.e. sleep duration, sleep onset, and sleep inertia) with FA differed between patients and healthy controls in several regions of the brain (**Figure 2**). These interaction effects of sleep duration and sleep inertia with FA were primarily localized in the genu, body and splenium of the corpus collosum and the bilateral corona radiata. The interaction effect of sleep onset with group on FA was localized in a small cluster in the left superior longitudinal fasciculus. After stratifying for patients and controls, we found that mean FA of the voxels with a significant interaction effect was positively correlated with sleep duration in controls (β=0.32, R^2=0.35, p=0.01), while mean FA was negatively associated with sleep duration in patients (β=-0.39, R^2=0.32, p=0.004). (**Figure 3A**). Similar contrasting relations were found for sleep onset (patients: β=0.49, R^2=0.37, p<0.001; controls: β=-0.57, R^2=0.48, p<0.001) and sleep inertia (patients: β=0.34, R^2=0.33, p=0.008; controls β=-0.50, R^2=0.51, p<0.001), with positive associations in

patients and negative associations in controls (**Figure 3B and 3C**). A longer sleep duration, earlier onset of sleep and shorter sleep inertia are regarded as indicators of a more healthy sleep pattern.

3.4 Confounder analyses

Stratified analyses of the sleep parameters in patients only allowed us to examine the possible confounding effects of medication and illness characteristics by analyzing the association with both sleep parameter and white matter integrity outcomes. Sleep onset and average FA were significantly associated with the number of episodes (r =-0.26, p=0.05 & r = -0.39, p=0.006). History of psychotic symptoms was also significantly associated with sleep onset (r = 0.27, p=0.03) and average FA (r = -0.35, p=0.005). However, adding number of episodes and history of psychotic symptoms as covariate to the model did not alter the significant association between sleep onset and average FA (**Supplementary table 1**). Antipsychotic drug use was associated with sleep duration (r = 0.47, p<0.05) and average FA (r = -0.31, p<0.05). Subsequent addition of antipsychotic drug use as covariate to the model rendered the previous contrasting association between sleep duration and average FA in patients non-significant (β = -0.26, t=-1.64, p=0.11). When the TBSS analysis for sleep duration was restricted to patients not using antipsychotic medication (N=25), the interaction effect between sleep duration and group was no longer significant providing further support for a confounding effect of mediation. The interaction effect between sleep duration and group remained significant when the TBSS analysis was performed in patients using antipsychotic medication, albeit in a smaller area (**Supplementary figure 1**).

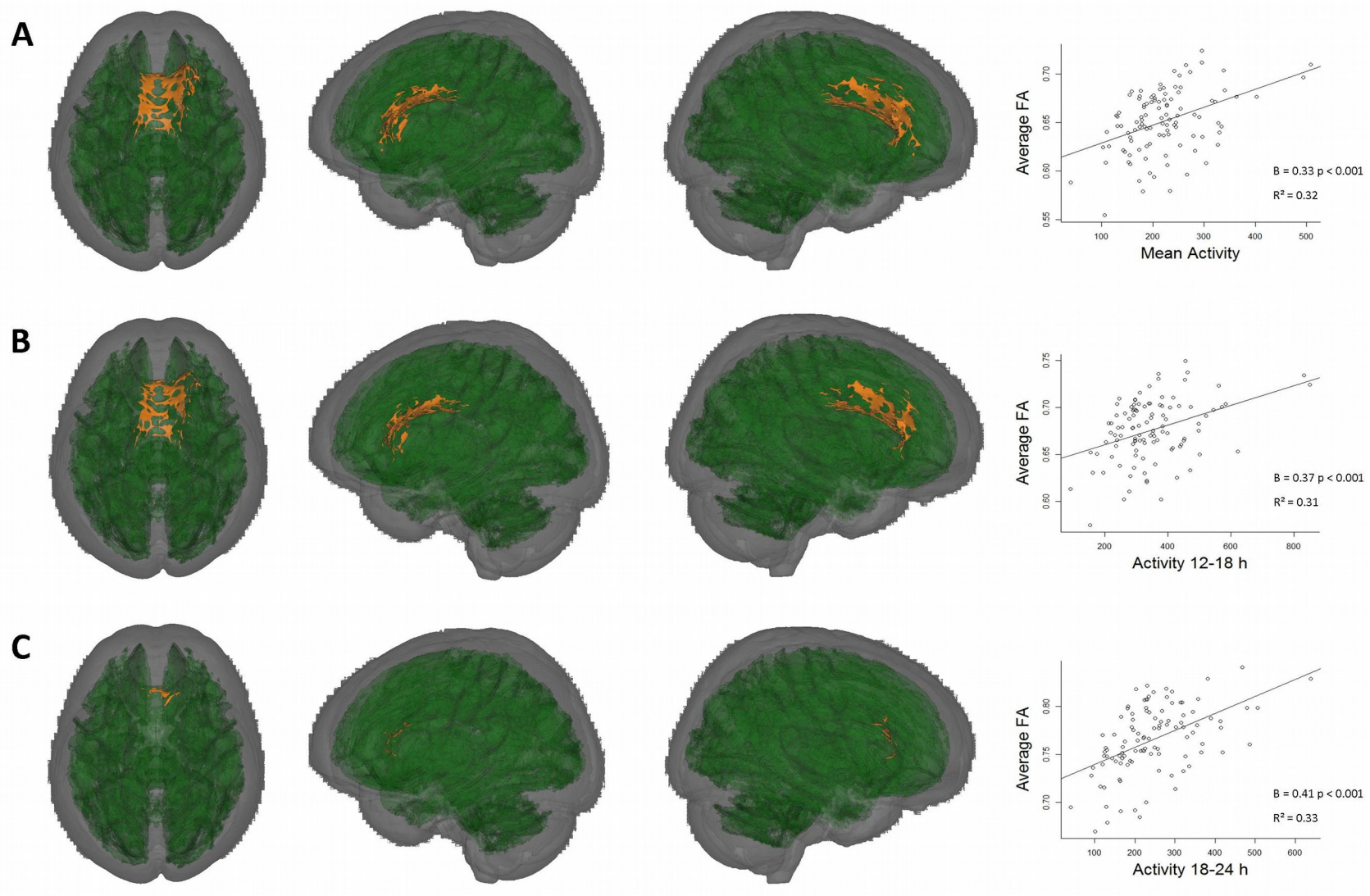

Figure 1: Daytime activity is positively associated with integrity of white matter microstructure. TBSS was used to assess the association of activity with integrity of white matter microstructure. In the combined sample (patients and healthy controls) we found significant positive correlations of mean activity of the whole day (**A**), activity between noon and 6PM (**B**) and activity between 6PM and midnight (**C**). Significantly correlations are shown in orange in a 3D rendering of the results. The white matter skeleton is shown in green and overlaid on the MNI152 template brain. Images are shown in radiological convention (the left is displayed on the right). P-values are TFCE and FWE corrected for multiple comparisons across space and corrected for age, gender and (patient/control) group. Linear regression analyses (corrected for age and gender) were used to assess the association of activity measures with average FA of the significant voxels.

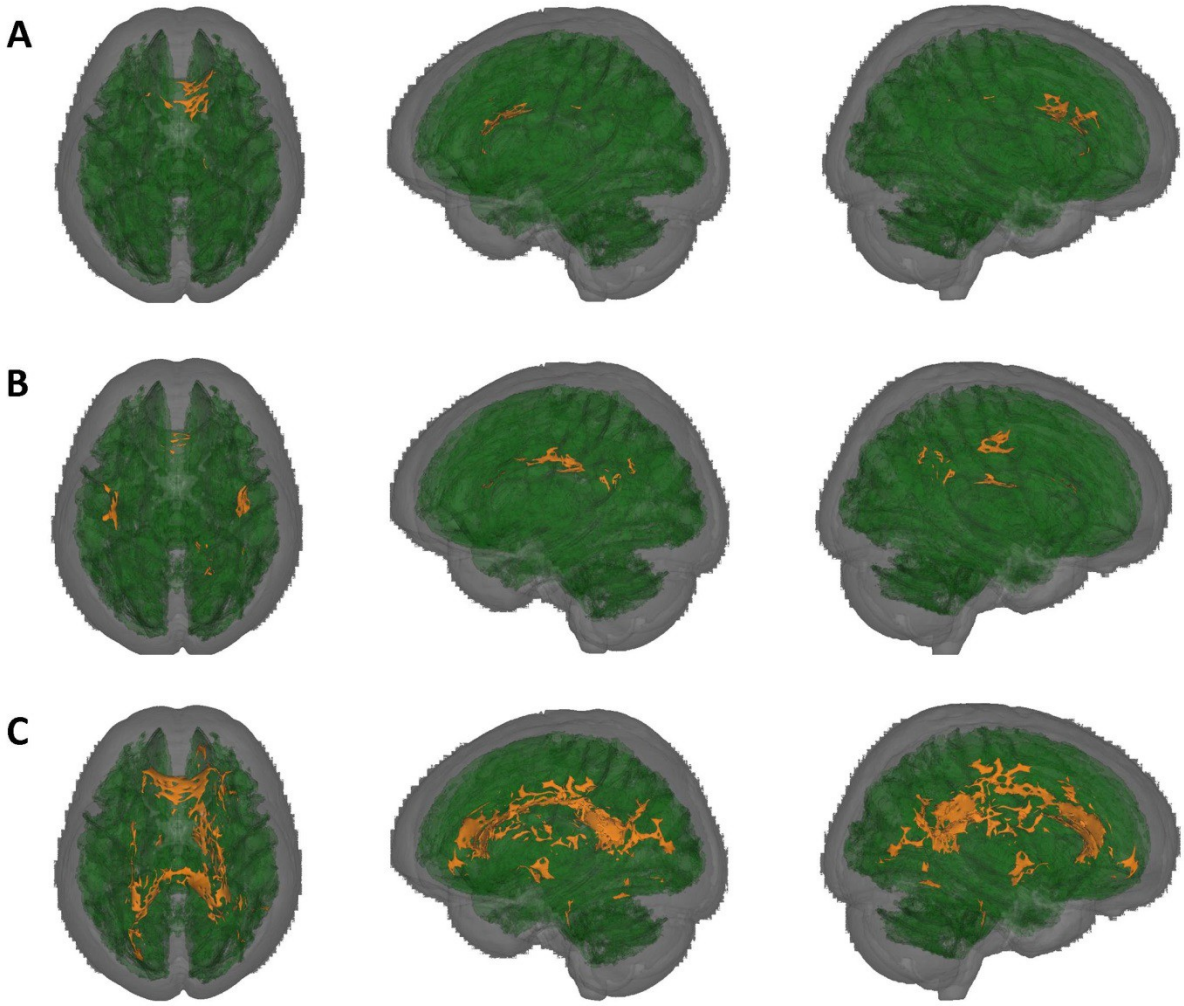

Figure 2: The association of sleep measures with integrity of white matter microstructure differs between patients and controls. TBSS was used to assess the interaction effects of sleep variables and group (Group * Sleep) with integrity of white matter microstructure. There is a significant negative interaction between sleep duration*group and FA (**A**), a positive interaction between sleeponset*group and FA (**B**), a positive interaction between sleep inertia and FA (**C**). Positive interaction effects are defined as interactions where the slope between sleep variables and DTI measures is higher for patients than for controls. Significant interaction effects are shown in orange in a 3D rendering. The white matter skeleton is shown in green and overlaid on the MNI152 template brain. Images are shown in radiological convention (the left is displayed on the right). P-values are TFCE and FWE corrected for multiple comparisons across space, and corrected for age and gender.

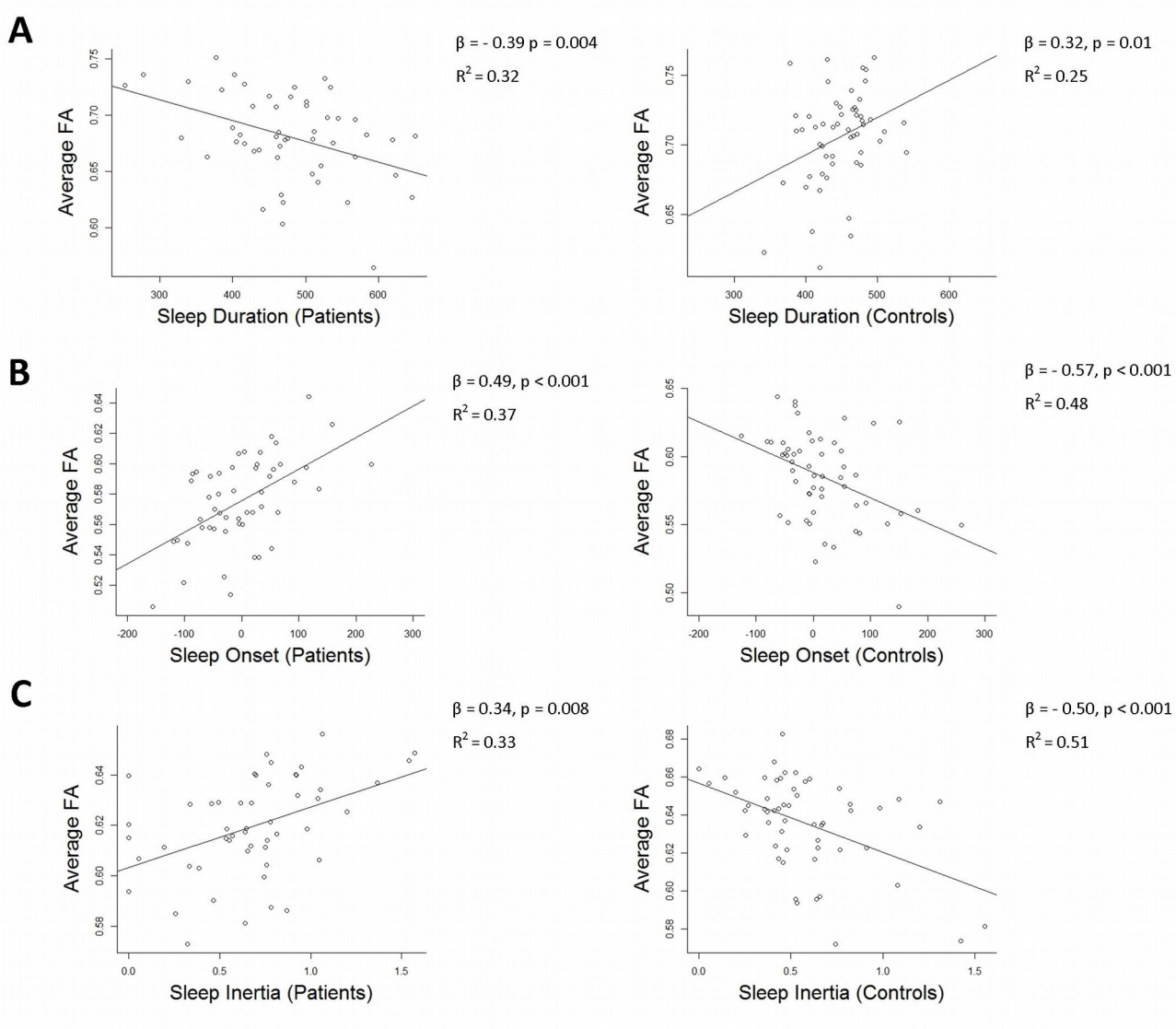
A
Average FA
Sleep Duration (Patients)
β = - 0.39 p = 0.004
R^2 = 0.32
Sleep Duration (Controls)
β = 0.32, p = 0.01
R^2 = 0.25
B
Sleep Onset (Patients)
β = 0.49, p < 0.001
R^2 = 0.37
Sleep Onset (Controls)
β = - 0.57, p < 0.001
R^2 = 0.48
C
Sleep Inertia (Patients)
β = 0.34, p = 0.008
R^2 = 0.33
Sleep Inertia (Controls)
β = - 0.50, p < 0.001
R^2 = 0.51

Figure 3: Sleep measures are associated with integrity of white matter microstructure within the patient group as well as within the control group. Linear regression analyses (corrected for age and gender) were used to assess the association of sleep measures with average FA of the significant voxels. Sleep duration is negatively correlated with FA in patients and positively correlated with FA in controls (**A**). Sleep onset is positively correlated with FA in patients and negatively correlated with FA in controls (**B**). Similarly, sleep inertia is positively correlated with FA in patients and negatively correlated with FA in controls (**C**).

4. Discussion

The current study investigated the association between sleep and physical activity patterns and integrity of white matter microstructure in bipolar disorder. We found that daytime and evening physical activity correlated with higher fractional anisotropy (FA) in bipolar patients and controls. In controls, a longer sleep duration, earlier sleep onset and shorter sleep inertia were related to higher FA, which is consistent with previous reports (Bellesi et al., 2013; Kopp et al., 2006; Kreutzmann et al., 2015; Mirescu et al., 2006). However, several measures of sleep showed opposing associations with integrity of white matter in patients. These differences between patients and controls are most likely the result of confounding factors, such as use of antipsychotic drugs in the patient group.

Our results are in keeping with evidence suggesting that physical activity is positively related to measures of white matter integrity in healthy subjects (Sexton et al., 2015; Voelcker-Rehage and Niemann, 2013). Here, we extent these findings, and show that this is also the case in bipolar disorder patients. This is relevant as integrity of white matter is hypothesized to be a factor in the etiology of bipolar disorder (Heng et al., 2010; Nortje et al., 2013). It raises the question whether symptoms and disease progression of bipolar disorder can be ameliorated by improving integrity of white matter through physical fitness therapy or behavioral activation. Although the effect of such therapies has not yet been studied in a bipolar sample, a first study in schizophrenia patients found that an exercise intervention increased the level of white matter integrity (Svatkova et al., 2015).

A longer sleep duration, earlier onset of sleep and shorter sleep inertia are all indicative of a more healthy sleep pattern, so the finding that this relates to better integrity of white matter in controls confirms the hypothesis that sleep and white matter integrity are positively associated. Previous studies that measured the link between sleep and human brain function concluded that sleep is associated with synaptic homeostasis, clearance of amyloid beta, gray matter volume and cortical thickness (Altena et al., 2010; Diekelmann and Born, 2010; Joo et al., 2011, 2010, 2009; Kang et al., 2009; Ooms et al., 2014;

Tononi and Cirelli, 2006; Wang et al., 2011; Winkelman et al., 2013; Xie et al., 2013). Our study is the first to expand these findings to better integrity of white matter microstructure. In our data bipolar patients show a reversed association between sleep and integrity of white matter. We show that a likely explanation for this counterintuitive association is the use of psychotropic medication. We found that in bipolar patients who received antipsychotic medication longer sleep duration was associated with lower FA. A previous study already reported that chronic use of antipsychotic medication without mood stabilizing effect decreases myelin/oligodendrocyte related gene expression in white matter (Narayan et al., 2007). Moreover, a recent study suggests that sleep may be influenced by antipsychotics via mTORC1- proteins synthesis that in turn is involved in neuronal function, but further studies are required (Bowling et al., 2014). Our findings do warrant further study of the effect per medication type on sleep and white matter microstructure. Randomized clinical trials studying the effect of medication on white matter microstructure could address this by incorporating sleep measures. We found no relationship with other types of medication, but given that the majority of our bipolar sample used more than one type of medication, we cannot reliably distinguish between the effects of medication types (Brambilla et al., 2009). Also, confounding by indication may be at play here, whereby more severely affected patients may receive particular types of medication.

A further limitation of the current study is the average time difference between the MRI acquisition and actigraphy measurement of 1.4 years. Changes in exercise behavior and sleep patterns, might have resulted in variation in white matter microstructure that were now left undetected. However, the time between MRI and actigraphy measurements was similar for patients and controls, and there is no reason to assume that such variation was systematic and has biased the results.

In conclusion, the current study found that higher levels of physical activity were related to better integrity of white matter, regardless of bipolar diagnosis. In controls, less disturbed sleep was associated

with better integrity of white matter, but opposing associations were found in bipolar patients, most likely due to extraneous variables such as use of antipsychotic medication.

Conflict of interest

Dr. van Haren reports personal fees for educational activities from Eli Lilly and Janssen. All other authors declare that they have no competing interests.

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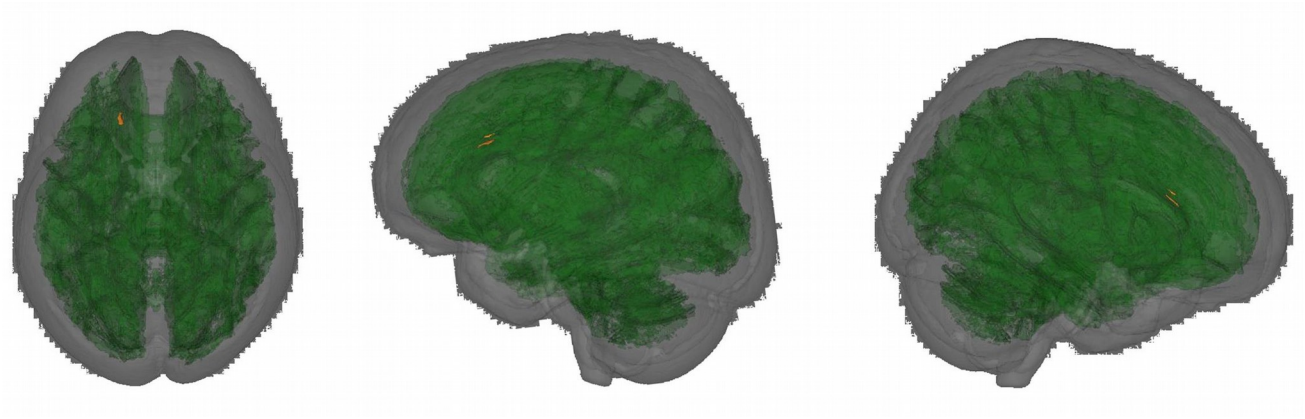
Supplementary material

Suppl. Table 1 Association between sleep onset and average FA while controlling for history of psychotic symptoms or number of episodes

	Beta	**P-value**	**R^2**
History of psychotic symptoms	0.41	0.002	0.35
Number of episodes	0.35	0.02	0.40



Suppl. Figure 1: The association of sleep duration with integrity of white matter microstructure differs between patients using antipsychotics and controls. TBSS was used to assess the interaction effects of sleep duaration and group (Group * Sleep) with integrity of white matter microstructure. There is a significant negative interaction between sleep duration*group and FA. A negative interaction is defined as interactions where the slope between sleep variables and DTI measures is lower for patients than for controls. Significant interaction effects are shown in orange in a 3D rendering. The white matter skeleton is shown in green and overlaid on the MNI152 template brain. Images are shown in radiological convention (the left is displayed on the right). P-values are TFCE and FWE corrected for multiple comparisons across space, and corrected for age and gender.

References

Altena, E., Vrenken, H., Van Der Werf, Y.D., van den Heuvel, O.A., Van Someren, E.J.W., 2010. Reduced Orbitofrontal and Parietal Gray Matter in Chronic Insomnia: A Voxel-Based Morphometric Study. Biol. Psychiatry 67, 182–185. doi:10.1016/j.biopsych.2009.08.003

American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders: DSM-5, Washington DC: American Psychiatric Association. doi:10.1176/appi.books.9780890425596.744053

Andersson, J.L.R., Skare, S., Ashburner, J., 2003. How to correct susceptibility distortions in spin-echo echo-planar images: Application to diffusion tensor imaging. Neuroimage 20, 870–888. doi:10.1016/S1053-8119(03)00336-7

Assaf, Y., Pasternak, O., 2008. Diffusion tensor imaging (DTI)-based white matter mapping in brain research: A review. J. Mol. Neurosci. 34, 51–61. doi:10.1007/s12031-007-0029-0

Bellesi, M., Pfister-Genskow, M., Maret, S., Keles, S., Tononi, G., Cirelli, C., 2013. Effects of sleep and wake on oligodendrocytes and their precursors. J. Neurosci. 33, 14288–300. doi:10.1523/JNEUROSCI.5102-12.2013

Belmaker, R.H., 2004. Bipolar disorder. N. Engl. J. Med. 351, 476 – 486. doi:10.1056/NEJMra035354

Bherer, L., Erickson, K.I., Liu-Ambrose, T., 2013. A review of the effects of physical activity and exercise on cognitive and brain functions in older adults. J Aging Res 2013, 657508. doi:10.1155/2013/657508

Bowling, H., Zhang, G., Bhattacharya, A., Pérez-Cuesta, L.M., Deinhardt, K., Hoeffer, C. a, Neubert, T. a, Gan, W., Klann, E., Chao, M. V, 2014. Antipsychotics activate mTORC1-dependent translation to enhance neuronal morphological complexity. Sci. Signal. 7, ra4. doi:10.1126/scisignal.2004331

Brambilla, P., Bellani, M., Yeh, P.H., Soares, J.C., 2009. Myelination in bipolar patients and the effects of mood stabilizers on brain anatomy. Curr.Pharm.Des 15, 2632–2636.

Caseras, X., Tansey, K.E., Foley, S., Linden, D., 2015. Association between genetic risk scoring for schizophrenia and bipolar disorder with regional subcortical volumes. Transl. Psychiatry 5, e692. doi:10.1038/tp.2015.195

Diekelmann, S., Born, J., 2010. The memory function of sleep. Nat.Rev.Neurosci. 11, 114–126. doi:10.1038/nrn2762

Erickson, K.I., Leckie, R.L., Weinstein, A.M., 2014. Physical activity, fitness, and gray matter volume. Neurobiol. Aging 35, S20–S28. doi:10.1016/j.neurobiolaging.2014.03.034

First, M.B. et, Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1997. Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV), for DSMIV.

Hallahan, B., Newell, J., Soares, J.C., Brambilla, P., Strakowski, S.M., Fleck, D.E., Kiesepp, T., Altshuler, L.L., Fornito, A., Malhi, G.S., McIntosh, A.M., Yurgelun-Todd, D.A., Labar, K.S., Sharma, V., MacQueen,

G.M., Murray, R.M., McDonald, C., 2011. Structural magnetic resonance imaging in bipolar disorder: An international collaborative mega-analysis of individual adult patient data. Biol. Psychiatry 69, 326–335. doi:10.1016/j.biopsych.2010.08.029

Harvey, A.G., 2008. Sleep and circadian rhythms in bipolar disorder: Seeking synchrony, harmony, and regulation. Am. J. Psychiatry 165, 820–829. doi:10.1176/appi.ajp.2008.08010098

Heng, S., Song, A.W., Sim, K., 2010. White matter abnormalities in bipolar disorder: insights from diffusion tensor imaging studies. J Neural Transm 117, 639–654. doi:10.1007/s00702-010-0368-9

Hibar, D.P., Westlye, L.T., van Erp, T.G.M., Rasmussen, J., Leonardo, C.D., Faskowitz, J., Haukvik, U.K., Hartberg, C.B., Doan, N.T., Agartz, I., Dale, A.M., Gruber, O., Krämer, B., Trost, S., Liberg, B., Abé, C., Ekman, C.J., Ingvar, M., Landén, M., Fears, S.C., Freimer, N.B., Bearden, C.E., Sprooten, E., Glahn, D.C., Pearlson, G.D., Emsell, L., Kenney, J., Scanlon, C., McDonald, C., Cannon, D.M., Almeida, J., Versace, A., Caseras, X., Lawrence, N.S., Phillips, M.L., Dima, D., Delvecchio, G., Frangou, S., Satterthwaite, T.D., Wolf, D., Houenou, J., Henry, C., Malt, U.F., Bøen, E., Elvsåshagen, T., Young, A.H., Lloyd, A.J., Goodwin, G.M., Mackay, C.E., Bourne, C., Bilderbeck, A., Abramovic, L., Boks, M.P., van Haren, N.E.M., Ophoff, R.A., Kahn, R.S., Bauer, M., Pfennig, A., Alda, M., Hajek, T., Mwangi, B., Soares, J.C., Nickson, T., Dimitrova, R., Sussmann, J.E., Hagenaars, S., Whalley, H.C., McIntosh, A.M., Thompson, P.M., Andreassen, O.A., 2016. Subcortical volumetric abnormalities in bipolar disorder. Mol. Psychiatry 1–7. doi:10.1038/mp.2015.227

Jenkinson, M., Beckmann, C.F., Behrens, T.E.J., Woolrich, M.W., Smith, S.M., 2012. FSL. Neuroimage. doi:10.1016/j.neuroimage.2011.09.015

Joo, E.Y., Jeon, S., Lee, M., Kim, S.T., Yoon, U., Koo, D.L., Lee, J.-M., Hong, S.B., 2011. Analysis of Cortical Thickness in Narcolepsy Patients with Cataplexy. Sleep 34, 1357–64. doi:10.5665/SLEEP.1278

Joo, E.Y., Tae, W.S., Kim, S.T., Hong, S.B., 2009. Gray matter concentration abnormality in brains of narcolepsy patients. Korean J. Radiol. 10, 552–558. doi:10.3348/kjr.2009.10.6.552

Joo, E.Y., Tae, W.S., Lee, M.J., Kang, J.W., Park, H.S., Lee, J.Y., Suh, M., Hong, S.B., 2010. Reduced brain gray matter concentration in patients with obstructive sleep apnea syndrome. Sleep 33, 235–241.

Kang, J.-E., Lim, M.M., Bateman, R.J., Lee, J.J., Smyth, L.P., Cirrito, J.R., Fujiki, N., Nishino, S., Holtzman, D.M., 2009. Amyloid-b Dynamics Are Regulated by Orexin and the Sleep-Wake Cycle 326, 1005–1007. doi:10.1126/science.1180962

Kopp, C., Longordo, F., Nicholson, J.R., Lüthi, A., 2006. Insufficient sleep reversibly alters bidirectional synaptic plasticity and NMDA receptor function. J. Neurosci. 26, 12456–65. doi:10.1523/JNEUROSCI.2702-06.2006

Kreutzmann, J.C., Havekes, R., Abel, T., Meerlo, P., 2015. Sleep deprivation and hippocampal vulnerability: Changes in neuronal plasticity, neurogenesis and cognitive function. Neuroscience 309, 173–190. doi:10.1016/j.neuroscience.2015.04.053

Mahon, K., Burdick, K.E., Szeszko, P.R., 2010. A role for white matter abnormalities in the pathophysiology of bipolar disorder. Neurosci. Biobehav. Rev. 34, 533–554. doi:10.1016/j.neubiorev.2009.10.012

Mirescu, C., Peters, J.D., Noiman, L., Gould, E., 2006. Sleep deprivation inhibits adult neurogenesis in the hippocampus by elevating glucocorticoids. Proc. Natl. Acad. Sci. U. S. A. 103, 19170–19175. doi:10.1073/pnas.0608644103

Narayan, S., Kass, K.E., Thomas, E.A., 2007. Chronic haloperidol treatment results in a decrease in the expression of myelin/oligodendrocyte-related genes in the mouse brain. J. Neurosci. Res. 85, 757–765. doi:10.1002/jnr.21161

Nichols, T.E., Holmes, A.P., 2002. Nonparametric permutation tests for functional neuroimaging: A primer with examples. Hum. Brain Mapp. 15, 1–25. doi:10.1002/hbm.1058

Nortje, G., Stein, D.J., Radua, J., Mataix-Cols, D., Horn, N., 2013. Systematic review and voxel-based meta-analysis of diffusion tensor imaging studies in bipolar disorder. J. Affect. Disord. 150, 192–200. doi:10.1016/j.jad.2013.05.034

Ooms, S., Overeem, S., Besse, K., Rikkert, M.O., Verbeek, M., Claassen, J. a H.R., 2014. Effect of 1 Night of Total Sleep Deprivation on Cerebrospinal Fluid β-Amyloid 42 in Healthy Middle-Aged Men: A Randomized Clinical Trial. JAMA Neurol. 71, 971–977. doi:10.1001/jamaneurol.2014.1173

Pagani, L., St. Clair, P. a., Teshiba, T.M., Service, S.K., Fears, S.C., Araya, C., Araya, X., Bejarano, J., Ramirez, M., Castrillón, G., Gomez-Makhinson, J., Lopez, M.C., Montoya, G., Montoya, C.P., Aldana, I., Navarro, L., Freimer, D.G., Safaie, B., Keung, L.-W., Greenspan, K., Chou, K., Escobar, J.I., Ospina-Duque, J., Kremeyer, B., Ruiz-Linares, A., Cantor, R.M., Lopez-Jaramillo, C., Macaya, G., Molina, J., Reus, V.I., Sabatti, C., Bearden, C.E., Takahashi, J.S., Freimer, N.B., 2015. Genetic contributions to circadian activity rhythm and sleep pattern phenotypes in pedigrees segregating for severe bipolar disorder. Proc. Natl. Acad. Sci. 10.1073/pnas.1513525113. doi:10.1073/pnas.1513525113

R Development Core Team, R., 2014. R: A Language and Environment for Statistical Computing. doi:10.1007/978-3-540-74686-7

Sandoval, H., Soares, J.C., Mwangi, B., Asonye, S., Alvarado, L.A., Zavala, J., Ramirez, M.E., Sanches, M., Enge, L.R., Escamilla, M.A., 2014. Confirmation of MRI anatomical measurements as endophenotypic markers for bipolar disorder in a new sample from the NIMH Genetics of Bipolar disorder in Latino Populations study. Psychiatry Res. - Neuroimaging 247, 34–41. doi:10.1016/j.pscychresns.2015.11.004

Sexton, C.E., Betts, J.F., Demnitz, N., Dawes, H., Ebmeier, K.P., Johansen-Berg, H., 2015. A systematic review of MRI studies examining the relationship between physical fitness and activity and the white matter of the ageing brain. Neuroimage. doi:10.1016/j.neuroimage.2015.09.071

Sheehan, D. V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development

and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59, 22–33. doi:10.1016/S0924-9338(99)80239-9

Smith, S.M., 2002. Fast robust automated brain extraction. Hum. Brain Mapp. 17, 143–155. doi:10.1002/hbm.10062

Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Cader, M.Z., Matthews, P.M., Behrens, T.E.J., 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 31, 1487–505. doi:10.1016/j.neuroimage.2006.02.024

Smith, S.M., Nichols, T.E., 2009. Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 44, 83–98. doi:10.1016/j.neuroimage.2008.03.061

Smith, S.M., Smith, S.M., Johansen-berg, H., Johansen-berg, H., Jenkinson, M., Jenkinson, M., Rueckert, D., Rueckert, D., Nichols, T.E., Nichols, T.E., Miller, K.L., Miller, K.L., Robson, M.D., Robson, M.D., Jones, D.K., Jones, D.K., Klein, J.C., Klein, J.C., Bartsch, A.J., Bartsch, A.J., Behrens, T.E.J., Behrens, T.E.J., 2007. Acquisition and voxelwise analysis of multi-subject diffusion data with tract-based spatial statistics. Nat. Protoc. 2, 499–503. doi:10.1038/nprot.2007.45

Svatkova, A., Mandl, R.C.W., Scheewe, T.W., Cahn, W., Kahn, R.S., Hulshoff Pol, H.E., 2015. Physical Exercise Keeps the Brain Connected: Biking Increases White Matter Integrity in Patients with Schizophrenia and Healthy Controls. Schizophr. Bull. 41, 869–878. doi:10.1093/schbul/sbv033

Tononi, G., Cirelli, C., 2006. Sleep function and synaptic homeostasis. Sleep Med. Rev. 10, 49–62. doi:10.1016/j.smrv.2005.05.002

Voelcker-Rehage, C., Niemann, C., 2013. Structural and functional brain changes related to different types of physical activity across the life span. Neurosci. Biobehav. Rev. 37, 2268–2295. doi:10.1016/j.neubiorev.2013.01.028

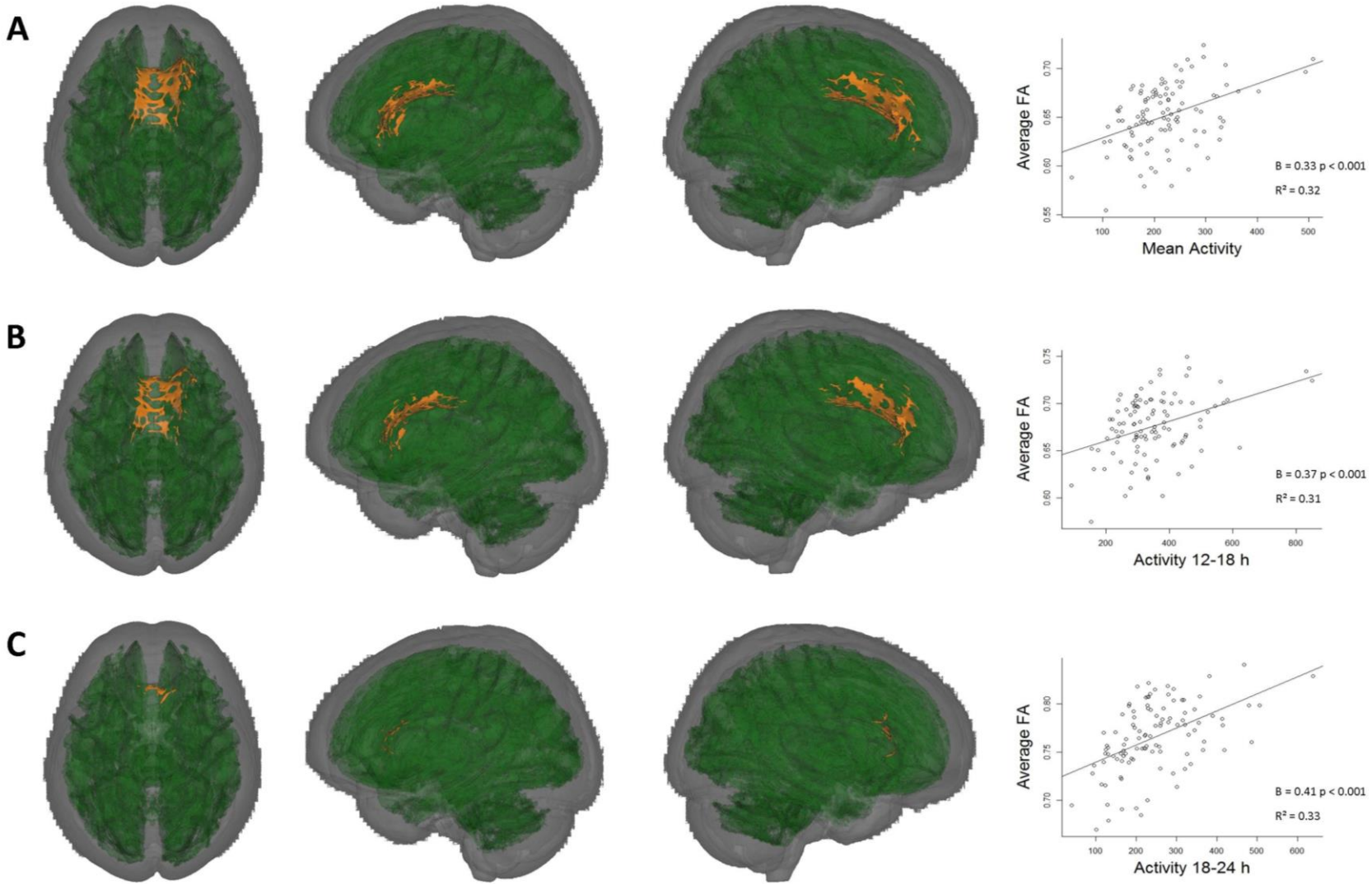
Wang, G., Grone, B., Colas, D., Appelbaum, L., Mourrain, P., 2011. Synaptic plasticity in sleep: Learning, homeostasis and disease. Trends Neurosci. 34, 452–463. doi:10.1016/j.tins.2011.07.005

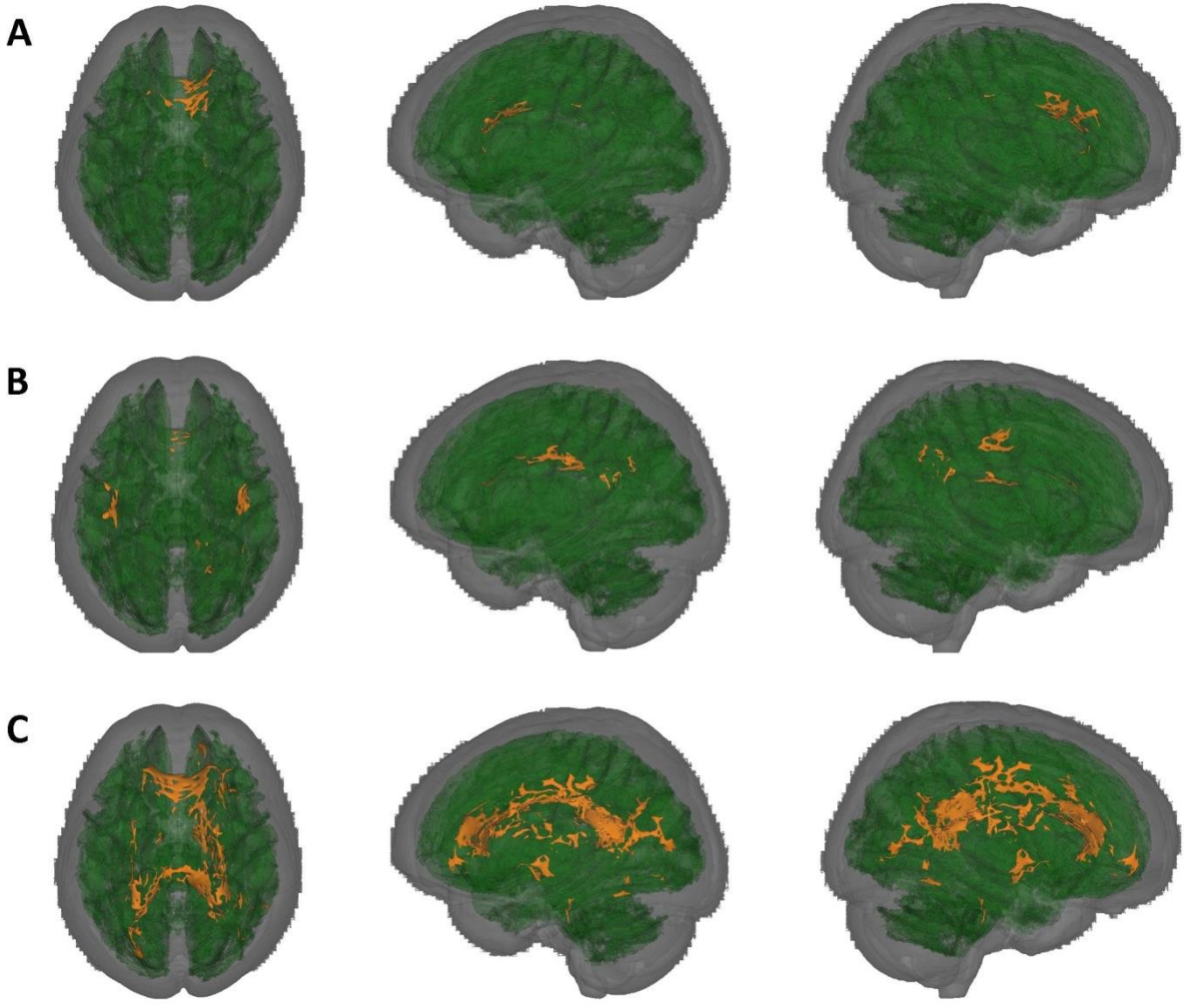
Winkelman, J.W., Plante, D.T., Schoerning, L., Benson, K., Buxton, O.M., O'Connor, S.P., Jensen, J.E., Renshaw, P.F., Gonenc, A., 2013. Increased Rostral Anterior Cingulate Cortex Volume in Chronic Primary Insomnia. Sleep 36, 991–998. doi:10.5665/sleep.2794

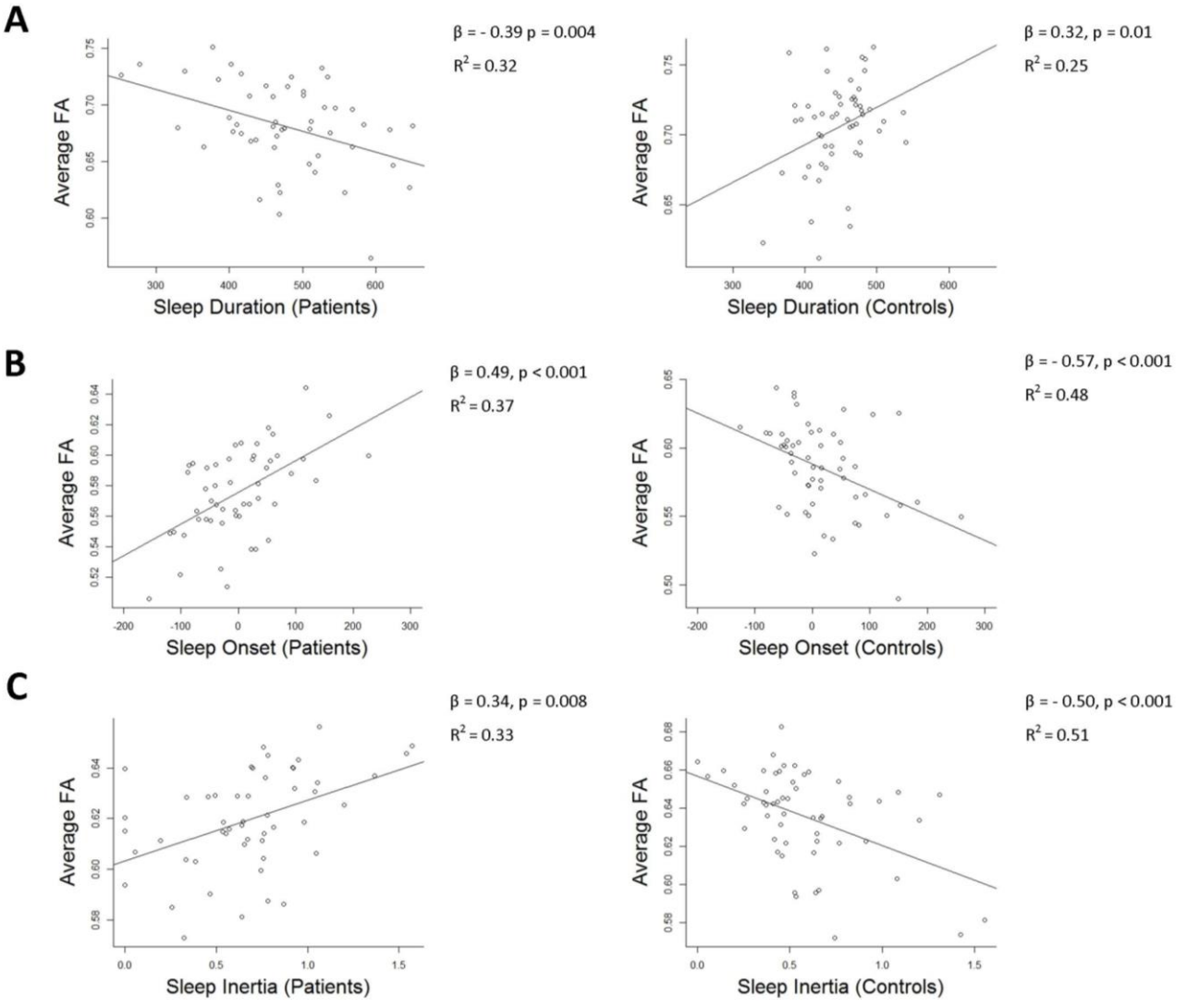
Wise, T., Radua, J., Nortje, G., Cleare, A.J., Young, A.H., Arnone, D., 2016. Voxel-based meta-Analytical evidence of structural disconnectivity in major depression and bipolar disorder. Biol. Psychiatry 79, 293–302. doi:10.1016/j.biopsych.2015.03.004

Xie, L., Kang, H., Xu, Q., Chen, M.J., Liao, Y., Thiyagarajan, M., O'Donnell, J., Christensen, D.J., Nicholson, C., Iliff, J.J., Takano, T., Deane, R., Nedergaard, M., 2013. Sleep drives metabolite clearance from the adult brain. Science 342, 373–7. doi:10.1126/science.1241224

Yip, S.W., Chandler, R. a, Rogers, R.D., Mackay, C.E., Goodwin, G.M., 2013. White matter alterations in antipsychotic- and mood stabilizer-naïve individuals with bipolar II/NOS disorder. NeuroImage. Clin. 3, 271–8. doi:10.1016/j.nicl.2013.08.005


A
B
C
Average FA
Mean Activity
B = 0.33 p < 0.001
R² = 0.32
Activity 12-18 h
B = 0.37 p < 0.001
R² = 0.31
Activity 18-24 h
B = 0.41 p < 0.001
R² = 0.33


A
B
C


A
Average FA
Sleep Duration (Patients)
β = - 0.39 p = 0.004
R2 = 0.32
Average FA
Sleep Duration (Controls)
β = 0.32, p = 0.01
R2 = 0.25
B
Average FA
Sleep Onset (Patients)
β = 0.49, p < 0.001
R2 = 0.37
Average FA
Sleep Onset (Controls)
β = - 0.57, p < 0.001
R2 = 0.48
C
Average FA
Sleep Inertia (Patients)
β = 0.34, p = 0.008
R2 = 0.33
Average FA
Sleep Inertia (Controls)
β = - 0.50, p < 0.001
R2 = 0.51