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

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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 tensor imaging (DTI) and 14-day actigraphy recordings were obtained in 51 BD I patients and 55 age-and-gender-matched 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

mood disorder; actigraphy; DTI; TBSS

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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.

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. Water diffuses more easily along white matter tracts than perpendicular to them. This directional dependence is usually quantified with fractional anisotropy (FA), a scalar variable which ranges from 0 to 1, in which higher values indicate a higher directional dependence of diffusion. More organized and myelinated axon will cause water molecules to diffuse in a particular direction rather than randomly in all directions. Therefore, FA is thought to reflect integrity of white matter with lower FA values pointing to sparse, poorly myelinated, or divergent fibers (Beaulieu, 2002). 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 as core symptoms of bipolar mood episodes (American Psychiatric Association, 2013). 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; Winkelmann 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). Mechanisms of the link between sleep and integrity of white matter remain largely unknown. Animal studies have shown that oligodendrocyte proliferation and myelin-related gene expression strongly increase during sleep and reduce during wake time and experimental sleep deprivation (Bellei et al., 2013). Conversely, chronic sleep loss has been associated with down-regulation of the expression of two myelin-related genes coding for plasmalogen and a membrane protein expressed in the mature myelin sheath (Cirelli et al., 2006). Human studies using DTI measures found that

variability in sleep duration during weekdays was associated with reduced FA in the parietocortical, frontocortical and frontostriatal tracts (Telzer et al., 2015). Furthermore, a sleep deprivation study in adult males found widespread changes in DTI measures after just one day of sleep deprivation (Elvsåshagen et al., 2015). These findings suggest that effective sleep relates to white matter microstructure and that sleep disruptions could lead to changes in oligodendrocytes, myelination, and axonal integrity and organisation.

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). Physical activity, defined as bodily movements produced by skeletal muscles (Caspersen et al., 1985), 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-sectionally, longitudinally, and after a physical exercise intervention (Bherer et al., 2013; Erickson et al., 2014). Indeed, a meta-analysis of 29 studies on the association between white matter and physical activity in healthy older adults tentatively concluded that physical exercise leads to both global and local improvements in white matter (micro)structure (Sexton et al., 2015). Possible underlying mechanisms involve the increased expression and release of brain-derived neurotrophic factor and oxygen supply as a result of increased physical activity (Burzynska et al., 2014). 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. The current study investigates the link between white matter microstructure and objectively measured physical activity and sleep patterns of bipolar patients and controls. Both physical activity and sleep are measured using actigraphy. We hypothesize that both sleep and physical activity are positively related to increased integrity of white matter, and we further explore whether these associations are similar for patients and controls.

2. Methods

2.1 Sample

Participants were recruited from 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. After completion of the DBC protocol, we invited subjects by telephone and mail who had indicated that they were available for future research and invited them to participate in two cross-sectional actigraphy and MRI measurements. The medical ethical committee of the UMCU approved the DBC study and the actigraphy and MRI protocols. Written informed consent was obtained from all participants prior to participation. The majority of participants underwent MRI scanning prior to the two-week actigraphy protocol, with the exception of 6 participants who started

with actigraphy measurements. The mean time difference between MRI and actigraphy measurements was 1.4 years.

All participants had a minimum age of 18 years old. The inclusion criterion for patients was a diagnosis of bipolar disorder type I, in order to create a clinically homogeneous sample. Controls 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. Any other type of psychiatric disorder was not an exclusion criterion in order to avoid the recruitment of a 'super-normal control sample', that is not representative of the general population. Exclusion criteria for all participants were sleep apnoea, pregnancy, head trauma and neurological disorders. An independent radiologist blindly evaluated all MRI scans. Participants with any clinical findings were excluded from further analyses. Patient diagnoses were verified using the Structured Clinical Interview for DSM-IV (SCID) and controls subjects were assessed using the Mini-International Neuropsychiatric Interview (M.I.N.I) (First et al., 1997; Sheehan et al., 1998).

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). Mean activity level was calculated over 24 hours, followed by mean activity levels in four 6-hr periods corresponding to morning, afternoon, evening, night time: midnight to 6 AM (24-6 hr), 6 AM to noon (6 – 12 hr), noon to 6 PM (12 – 18 hr), and 6 PM to midnight (18 – 24 hr). To measure the degree of day-to-day stability of the 24-h activity rhythm, we calculated interdaily stability (IS), which is the ratio between the variance of the average 24-h pattern around the mean and the overall variance (Van Someren et al., 1996). IS ranges from 0–1, with higher values indicating more stable activity rhythms.

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, $0.75 \times 0.75 \times 0.80$ mm³ 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). Compared to the other DTI metrics (i.e. axial diffusivity, radial diffusivity and mean diffusivity), FA is the most elaborate studied diffusion parameter and correlates well with microscopic changes in white matter such as myelination, axonal diameter, density and organization (Beaulieu, 2009). 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

Whole-brain voxelwise analyses were carried out using 'randomise' in FSL v5.0, a tool for permutation-based non-parametric testing using the general linear model (Nichols and Holmes, 2002; <https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/GLM>). All statistical tests were performed with 5000 permutations. Our statistical threshold was a threshold-free cluster enhancement (TFCE) and family-wise error corrected P-value of 0.05. (Smith and Nichols, 2009). First, we investigated the difference in FA between patients and controls for each voxel. The MNI coordinates of the centre of gravity of significant clusters were calculated and the anatomical regions of these clusters were identified using the 'JHU ICBM-DTI-81 White-Matter Labels' atlas, similar to Liu et al. (2016). Next, we analysed the association between actigraphy measures and FA for each voxel, in the overall sample of patients and healthy controls. Furthermore, we investigated whether actigraphy measures were differently associated with DTI measures in patients and controls. For this, we analysed the association

between an interaction term for Group*actigraphy measures with FA, again using the general linear model as implemented in FSL. In case of significant voxels in the overall sample, we created scatterplots to visualize the association between average FA of the significant clusters and actigraphy measures in IBM SPSS Statistics 21.0. For variables with significant interaction effects, we created stratified scatterplots to determine the direction of association between actigraphy measures and the average FA of significant clusters. We analysed the confounding effect of illness-specific variables (number of episodes, history of psychotic symptoms, illness duration and use of psychotropic medication) by testing the correlation with average FA of the significant cluster and the actigraphy measures in SPSS Statistics 21.0. In case these variables showed significant associations with both FA and actigraphy measures, they were considered as potential confounders and separately entered as covariates in the stratified patient regression analyses, using the Enter method, with all variables entered in one block.

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 or handedness. Patients worked on average fewer days during the actigraphy measurement period and had higher BMI levels as compared with controls. Although none of the patients reported being in a mood episode, patients reported significantly more current depressive symptoms.

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.

Patients showed widespread reductions in FA compared to controls (Figure 1 and Table 2). These differences were located in the corpus callosum, cerebral peduncle, internal capsule, corona radiata, thalamic radiation, external capsule and the posterior limb of internal capsule.

Mean scores and standard deviations of the 7 sleep measures and 5 activity measures are shown in table 3. 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 Bonferroni-corrected significance level of 0.004.

3.2 Activity measures

Voxelwise correlations in the overall sample (corrected for age and gender, and patient/control group) revealed positive associations between FA and mean activity throughout the day, activity between noon and 6 PM, and between 6 PM and midnight (Figure 1). Also, a

more stable 24-h activity rhythm was associated with increased FA (Supplementary figure 1 and supplementary table 3). 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 (Table 2). 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 FA. 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 callosum and the bilateral corona radiata (Table 2). 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, while mean FA was negatively associated with sleep duration in patients (Figure 3A). Similar contrasting relations were found for sleep onset and sleep inertia, with positive associations in patients and negative associations in controls (Figure 3B and 3C). We analyzed the possibility of a U-shaped relation between sleep duration and FA and found that squaring, or centering plus squaring the sleep duration variable yielded similar results (Supplementary table 1C). We also tested whether there is a difference in association between the 22 patients that could be classified as long sleepers (> 8 hours) vs. 25 patients classified as normal sleepers (6–8 hours). We found that the association between sleep duration and FA in ‘normal sleepers’ ($\beta = -0.27$, $p = 0.10$, $R^2 = 0.53$) was lower compared to long sleepers ($\beta = -0.43$, $p = 0.06$, $R^2 = 0.21$), but still in the same direction, indicating that the relation between sleep duration and FA is linear.

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. First, we analyzed the association between the sleep parameters with average FA of the significant clusters resulting from the TBSS analysis (Supplementary table 1A). Next, we analyzed the association of the possible confounders with both sleep parameter and white matter integrity outcomes (Supplementary table 2). Sleep onset and average FA were significantly associated with the number of episodes. History of psychotic symptoms was also significantly associated with sleep onset and average FA. However, adding number of episodes and history of psychotic symptoms as covariate to the association between sleep onset and average FA did not alter the results (Supplementary table 1B). Antipsychotic drug use was associated with sleep duration and average FA (Supplementary table 2). Subsequent addition of antipsychotic drug use as covariate to the model rendered the previous association between sleep duration and average FA in patients non-significant (Supplementary 1B). When the TBSS analysis for sleep duration was restricted to patients not using antipsychotic

medication (N=25 patients and 55 controls), the interaction effect between sleep duration and group was no longer significant providing further support for a confounding effect of medication. 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 2 and supplementary table 3).

4. Discussion

The current study investigated the association between sleep and physical activity patterns and integrity of white matter microstructure in bipolar disorder. Bipolar patients were characterized by widespread reductions in fractional anisotropy (FA) in several major white matter tracts, including the corpus collosum, cerebral peduncle, corona radiata, internal and external capsule, thalamic radiation and superior longitudinal fasciculus. Furthermore, we found that daytime and evening physical activity correlated with higher 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 in line with previous studies reporting on the effects of sleep on cell proliferation, synaptic plasticity and neurogenesis (Bellei, 2013; Kopp, 2006; Kreutzmann, 2015; Mirescu, 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, 2015; Voelcker-Rehage and Niemann, 2013). This may be partly explained by an up-regulation of the expression of brain-derived neurotrophic factor (BDNF) by physical activity. This neurotrophin has consistently been related to increases in gray matter volume and evidence also points to a relation with myelinogenesis and white matter microstructure (Du et al., 2003; Tost et al., 2013). Alternatively, higher levels of cardiorespiratory fitness lead to improvements in the cerebral blood flow, resulting in increased brain volume and white matter integrity (Chen et al., 2013; Zhu et al., 2015). Here, we extend these findings, and show that physical activity and white matter integrity are similarly related 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, 2015).

A longer sleep duration, earlier onset of sleep and shorter sleep inertia are all indicative of a more healthy sleep pattern (Merikanto et al., 2012), 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, 2010; Diekelmann, 2010; Joo, 2011, 2010, 2009; Kang, 2009; Ooms, 2014; Tononi, 2006; Wang, 2011; Winkelmann, 2013; Xie, 2013). Our study is one of the first to expand these findings to

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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

Figure 1.

TBSS was used to assess the difference in FA between patients and controls. Significant correlations are shown in yellow to red, depending on the significance level. 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) and corresponding Montreal Neurological Institute (MNI) coordinates are displayed below. P-values are TFCE and FWE corrected for multiple comparisons across space, and corrected for age and gender.

Figure 2. Daytime activity is positively associated with integrity of white matter microstructure TBSS was used to assess the association of activity counts (per minute) 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**). Significant correlations are shown in yellow to red, depending on the significance level. 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) and corresponding Montreal Neurological Institute (MNI) coordinates are displayed below. P-values are TFCE and FWE corrected for multiple comparisons across space and corrected for age, gender and (patient/control) group.

Figure 3. 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 sleep onset*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 correlations are shown in yellow to red, depending on the significance level. 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) and corresponding Montreal Neurological Institute (MNI) coordinates are displayed below. P-values are TFCE and FWE corrected for multiple comparisons across space, and corrected for age and gender.

Figure 4. Sleep measures are associated with integrity of white matter microstructure within the patient group as well as within the control group

Scatterplots showing the association of sleep measures with average FA of the voxels with a significant interaction effect. Sleep duration (measured in minutes) is negatively associated with FA in patients and positively associated with FA in controls (**A**). Sleep onset (minutes prior or post midnight) is positively associated with FA in patients and negatively associated with FA in controls (**B**). Similarly, sleep inertia (measured in minutes) is positively associated with FA in patients and negatively associated with FA in controls (**C**).

Table 1

Sample characteristics

	Patients	Controls	F/ χ^2	p-value
	N=51	N=55		
Age M (sd)	49.5 (11.4)	45.5 (15.8)	2.18	0.14
Gender M/F (% male)	28/23 (54.9%)	25/30 (45.5%)	0.44	0.22
Handedness R/L/B (% right)	42/6/3 (82.4%)	44/11/0 (80.0%)	4.37	0.11
IQ M (sd)	99.6 (15.7)	105.7 (14.4)	4.18	0.04 *
Level of education n (%)			1.28	0.53
1. Low education	13 (25.5%)	9 (16.7%)		
2. Intermediate education	16 (31.4%)	20 (37.0%)		
3. Higher education	22 (43.1%)	25 (46.3%)		
Inventory of Depressive Symptoms M (sd)	14.3 (10.1)	5.2 (3.9)	35.60	<0.001 *
Altman Self-Rating Mania Scale M (sd)	1.9 (1.8)	1.7 (2.3)	0.41	0.53
Body Mass Index M (sd)	27.4 (4.3)	25.2 (3.3)	8.45	0.01 *
Nr of workdays M (sd)	4.2 (3.5)	5.7 (3.7)	4.11	0.05 *
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 $p < 0.05$

Table 2

Cluster size (number of voxels), p-value, t-value, MNI coordinates of center of gravity and anatomical location of significant differences in FA between patients and controls

Analysis	Cluster size	Corrected p-value	T-value	MNI coordinates (x; y; z)	Anatomical region
<i>Significant group difference in FA between patients and controls</i>					
	44232	<0.001	3.08	2.37; -21.4; 16.8	Genu of corpus callosum
					Body of corpus callosum
					Splenium of corpus callosum
					R cerebral peduncle
					L cerebral peduncle
					R posterior limb of internal capsule
					L posterior limb of internal capsule
					L retrolenticular part of internal capsule
					R anterior corona radiata
					L anterior corona radiata
					R superior corona radiata
					L superior corona radiata
					Right posterior corona radiata
					L posterior corona radiata
					R posterior thalamic radiation (include optic radiation)
					L posterior thalamic radiation (include optic radiation)
					R external capsule
					L external capsule
					L cingulum (cingulate gyrus)
					R superior longitudinal fasciculus
					L superior longitudinal fasciculus

Table 3

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 inertia 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. Sleep duration, sleep onset latency, sleep inertia and WASO are measured in minutes. Sleep onset and sleep offset describe minutes prior or past midnight. Sleep efficiency is a percentage ranging from 1–100. All activity variables are activity counts averaged per minute.

Table 4

Cluster size (number of voxels), p-value, t-value, MNI coordinates of center of gravity and anatomical location of significant associations between sleep and activity parameters with FA

Analysis	Cluster size	Corrected p-value	T-value	MNI coordinates		Anatomical region
				(x; y; z)		
Significant Group*Sleep duration interaction with FA Significant Group*Sleep onset interaction with FA	651	0.04	3.74	10.2; 20.5; 19.5		Genu of corpus callosum
	16	0.05	2.34	-6.25; 12.7; 22		Body of corpus callosum
	292	0.039	4.36	37.6; -11.9; 29.4		R superior longitudinal fasciculus
	266	0.038	4.85	-37; -15.6; 27.2		L superior longitudinal fasciculus
	134	0.047	3.39	2.29; 24.9; 13.2		Genu of corpus callosum
	75	0.046	3.78	18.1; -51.6; 30.4		Splenium of corpus callosum
						R posterior corona radiata
	45	0.047	3.63	12.2; 37.9; 21		Splenium of corpus callosum
	33	0.047	4.96	38; -40.5; 24.8		R superior longitudinal fasciculus
	21826	0.006	3.46	12.2; -13.3; 17.2		Genu of corpus callosum
Significant Group*Sleep inertia interaction with FA						Body of corpus callosum
						Splenium of corpus callosum
						Cerebral peduncle
	227	0.047	3.10	-11.6; 8.42; -7.77		Posterior limb of left internal capsule
						R corticospinal tract
						Pontine crossing tract
	202	0.049	2.19	8.01; -26; -28.8		R cerebral peduncle
						L corticospinal tract
						Pontine crossing tract
	162	0.046	3.96	-7.18; -28.3; -30.7		L cerebral peduncle
Significant Group*Sleep inertia interaction with FA						Retrolenticular part of left internal capsule
	104	0.049	2.63	-29.4; -23.4; -1.7		Sagittal stratum
						Fornix (cres) / Stria terminalis
	78	0.049	2.58	-37.9; -47.6; 1.23		Posterior thalamic radiation
						Sagittal stratum
	38	0.05	3.57	-35.1; -58.4; -5.16		Posterior thalamic radiation
						Sagittal stratum

Analysis	Cluster size	Corrected p-value	T-value	MINI coordinates		Anatomical region
				(x; y; z)		
Significant correlation of mean activity with FA	15	0.05	1.93	-40.6; -25.7; -4.6		Sagittal stratum
	13	0.05	2.39	-32; -203; 0.769		L external capsule
						Genu of corpus callosum
	3153	0.019	2.84	9.01; 19.2; 18.7		Body of corpus callosum
Significant correlation of activity from 12h to 18h with FA						R anterior corona radiata
						Genu of corpus callosum
	2466	0.028	3.24	7.37; 17; 19.7		Body of corpus callosum
						R anterior corona radiata
Significant correlation of activity from 18h to 24h with FA						Genu of corpus callosum
	333	0.044	3.46	3.64; 25.7; 10.9		Body of corpus callosum