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Research paper

Night sleep influences white matter microstructure in bipolar depression

Francesco Benedetti*, Elisa M.T. Melloni, Sara Dallaspezia, Irene Bollettini, Clara Locatelli, Sara Poletti, Cristina Colombo

Department of Clinical Neurosciences and CERMAC, Scientific Institute Ospedale San Raffaele and Vita-Salute San Raffaele University, Milano, Italy

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ABSTRACT

Background: Alteration of circadian rhythms and sleep disruption are prominent trait-like features of bipolar disorder (BD). Diffusion tensor imaging (DTI) measures suggest a widespread alteration of white matter (WM) microstructure in patients with BD. Sleep promotes myelination and oligodendrocyte precursor cells proliferation. We hypothesized a possible association between DTI measures of WM microstructure and sleep quantity measures in BD.

Methods: We studied 69 inpatients affected by a depressive episode in course of type I BD. We used whole brain tract-based spatial statistics on DTI measures of WM microstructure: axial, radial, and mean diffusivity (AD, RD, MD), and fractional anisotropy (FA). Self-assessed measures of time asleep (TA) and total sleep time (TST) were extracted from the Pittsburgh Sleep Quality Index (PSQI). Actigraphic recordings were performed on a subsample of 23 patients.

Results: We observed a positive correlation of DTI measures of FA with actigraphic measures of TA and TST, and with PSQI measure of TA. DTI measures of RD inversely associated with actigraphic measure of TA, and with PSQI measures of TA and TST. Several WM tracts were involved, including corpus callosum, cyngulate gyrus, uncinate fasciculus, left superior and inferior longitudinal and fronto-occipital fasciculi, thalamic radiation, corona radiata, retrolenticular part of internal capsule and corticospinal tract.

Limitations: The study is correlational in nature, and no conclusion about a causal connection can be drawn.

Conclusions: Reduced FA with increased RD and MD indicate higher water diffusivity associated with less organized myelin and/or axonal structures. Our findings suggest an association between sleep disruption and these measures of brain microstructure in specific tracts contributing to the functional connectivity in BD.

1. Introduction

Consistent observations from preclinical and clinical research linked well-being and mental health to appropriate internal timing and control of the sleep-wake rhythm (Bhattacharjee, 2007; Buysse, 2013). According to the Research Domain Criteria perspective (Insel et al., 2010), the regulation of the sleep-wake rhythm is a core construct, reflecting coordinated changes in the dynamic functional organization of the brain, and optimizing physiology, behavior, and health. This relationship is striking for mood disorders. Systematic review and meta-analyses suggest that sleep disturbances in general, as well as insomnia and nightmares individually, are associated with depression and with increased risk of suicidal behaviors (Gangwisch et al., 2010; Malik et al., 2014; Pigeon et al., 2012). Suicidal ideation, and a perseverative thinking focus on negative aspects of experience, are favoured by shorter sleep duration (Nota and Coles, 2015; Park et al., 2013).

In bipolar disorder (BD), specific interactions between sleep and the disease are suggested by a high dependence of psychopathology on the individual characteristics of sleep, and of the biological clock machinery: extended sleep and darkness have antimanic (Barbini et al., 2005) and mood stabilizing effects (Wehr et al., 1998; Wirz-Justice et al., 1999), mood episodes are predicted by a disruption of sleep integrity (Bauer et al., 2006), sleep loss triggers and worsens mania (Barbini et al., 1996; Wehr, 1989), sleep deprivation or phase advance are effective antidepressants (Benedetti, 2012), and common genetic variants of clock genes are associated with core psychopathological features of the disorder (Benedetti and Terman, 2013). In rodents, sleep disruption and manipulations of clock genes lead to behavioral changes mimicking mania and depression (Benedetti et al., 2008; McClung, 2013). A bidirectional relationship between impaired affect and sleep has been proposed, with bipolar mood episodes disrupting sleep, and sleep disruption contributing to daytime difficulties in the cognitive control of emotions and generation of affective states (Harvey, 2008). Sleep and circadian rhythms disruption worsen together with the

* Correspondence to: Istituto Scientifico Universitario Ospedale San Raffaele, Dipartimento di Neuroscienze Cliniche, San Raffaele Turro, Via Stamira d'Ancona 20, 20127 Milano, Italy.
E-mail address: benedetti.francesco@hsr.it (F. Benedetti).

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Table 1
Clinical and demographic characteristics of the whole sample (N = 69), and of the subsample with complete actigraphic measurements(N = 19). Statistical analyses compare patients with actigraphic measures and the subset of the overall sample that does not include this subgroup. χ^2 test of Independence was used for gender, while T tests for all other variables.

	Whole sample	Patients with ACT	t or χ^2 (df = 68 or 1)	p
Age	47.17 ± 11.08	46.21 ± 9.39	0.44	0.659
Sex (M/F)	24/45	6/13	0.11	0.73
Education (yrs at school)	10.85 ± 4.14	10.21 ± 4.25	0.79	0.43
Age at onset of illness (yrs)	32.03 ± 10.40	27.58 ± 6.43	2.25	0.027*
Number of previous depressive episodes	5.04 ± 3.92	4.21 ± 3.01	1.08	0.279
Number of previous manic episodes	3 ± 2.65	3.05 ± 2.48	−0.10	0.919
Duration of current episode (wks)	22.34 ± 24.78	18.53 ± 14.33	0.79	0.248
Severity of depression (HDRS)	20.16 ± 4.27	20.26 ± 4.13	−0.12	0.902
Medication load	4.10 ± 2.07	3.63 ± 2.38	1.16	0.248
PSQI Time asleep (min)	448 ± 95.01	458.42 ± 88.43	0.24	0.809
PSQI Total sleep time (min)	507.22 ± 79.86	503.42 ± 81.21	−0.55	0.578
ACT Time asleep (min)	–	410.47 ± 58.86	–	–
ACT Total sleep time (min)	–	489.05 ± 80.9	–	–

* $p < 0.05$.

increasing severity of the disease, and have then been proposed as a biobehavioural marker for the staging of disease progression in BD (Kupfer et al., 2015; Wirz-Justice et al., 2013).

BD is associated with marked changes of brain function and structure, including spread signs of white matter (WM) disruption. WM microstructure can be in vivo studied by exploiting the preferential diffusion of water along myelinated axons in the WM skeleton of the brain. Diffusion Tensor Imaging (DTI) studies consistently documented a pattern of increased mean diffusivity of water (MD) in BD, with increased diffusivity perpendicular to the main axis of WM tracts, although coated by myelin sheaths (radial diffusivity, RD), and with decreased or unchanged diffusivity along the main axis of the WM fiber (axial diffusivity), thus resulting in a decrease of the preferential diffusivity along WM tracts (fractional anisotropy, FA) (Benedetti et al., 2011b). These measures reflect the myelination, orientational coherence, and microtubular axonal structure of fibers (Benedetti and Bollettini, 2014; Heng et al., 2010; Marlinge et al., 2014), and their changes have been associated both, with the genetic risk for BD (Chaddock et al., 2009; Whalley et al., 2013), with environmental stressors increasing the risk (Benedetti et al., 2014), and with core clinical features including impulsivity and suicide (Matsuo et al., 2010), cognitive performance (Oertel-Knochel et al., 2014; Poletti et al., 2015), and response to treatment (Bollettini et al., 2015).

Studies in patients affected by multiple sclerosis showed that FA and MD correlate with *post-mortem* histological indices of myelin content and – to a lesser degree – axonal count (Schmierer et al., 2007). Consistent *post-mortem* observations in BD affirm expression of oligodendrocyte and myelin genes, with a loss of oligodendroglial cells (Ongur et al., 1998; Rajkowska, 2002; Savitz et al., 2014; Tkachev et al., 2003; Uranova et al., 2004), which parallel the abnormalities of DTI measures (Bellani et al., 2016).

Sleep promotes myelination and oligodendrocyte precursor cell proliferation (Bellesi et al., 2013), and modulates the neuronal membrane homeostasis (Hinard et al., 2012). It can then be surmised that sleep measures could correlate with DTI measures reflecting axonal and myelin structures. Studies are scarce: one study associated primary insomnia with reduced FA within the right anterior internal capsule (Spiegelhalder et al., 2014), and another detected a circadian rhythmicity of DTI measures in healthy volunteers, with increased FA during daytime and decreased FA after a night of sleep deprivation (Elvsashagen et al., 2015), and no study explored this relationship in BD.

The aim of the present study was to correlate measures of sleep quantity with DTI measures of WM microstructure in a homogeneous sample of patients affected by BD.

2. Methods

2.1. Participants and data collection

We studied 69 (45 females) consecutively admitted inpatients affected by a major depressive episode, without psychotic features, in course of Bipolar Disorder type I (DSM-IV criteria, SCID I interview). To be included in the study the patients had to meet the following criteria: to be willing to participate; absence of other diagnoses on Axis I; absence of primary sleep disorders and of sleep apnea; absence of mental retardation on Axis II; absence of pregnancy, history of epilepsy, major medical and neurological disorders; no treatment with long-acting neuroleptic drugs in the last three months before admission; absence of a history of drug or alcohol dependency or abuse within the last six months. Physical examinations, laboratory tests and electrocardiograms were performed at admission. After complete description of the study to the subjects, a written informed consent was obtained. All the research activities were approved by the local ethical committee, and are in accordance with the Helsinki Declaration of 1975.

Self-scoring of total sleep time (TST; from sleep onset to sleep offset) and of time asleep (TA; total sleep time minus interspersed awakenings) during the night were assessed extracting two subscales of the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), in a modified setting where the time frame of a month was replaced by the one of a single night. Moreover, 23 patients were instructed to wear activity monitors (Mini Motionlogger Actigraphs by Ambulatory Monitoring, Inc., Ardsley, NY) on their non-dominant wrist. They never removed actigraphs during the study period. Data were collected in Zero-Crossing Mode using 1-min epochs. Patients started actimetry soon after hospitalization, before psychiatric treatment of their condition was started. Following usual polysomnographic standards, adaptation was allowed, and the first day and night were not analyzed. Automatic scoring of wrist activity (UCSD Zero-Crossing algorithm) (Jean-Louis et al., 2001) were performed with Action 4 software (v1.7, Ambulatory Monitoring, Inc., Ardsley, NY) for the automated scoring of sleep onset, TST, TA, time awake during the night, sleep ratio (time asleep/time awake), and sleep offset. PSQI and actimetric objective measures of sleep quantity referring to the night before the MRI scan were considered for the analyses.

In our sample 36 patients were on sedative hypnotics, 34 were taking antidepressants medications, 11 were on second-generation antipsychotics and 47 were on mood stabilizers.

2.2. Image acquisition, processing, and analysis

Diffusion tensor imaging was performed on a 3.0 T scanner