

Clinical Psychopharmacology and Neuroscience – Manuscript Submission

- **Manuscript ID:** CPN-22-969
- **Title:** Striatal Dopamine Transporter Availability is Associated with Sleep Disturbance among Patients with Bipolar I Disorder: A Single-photon Emission Computed Tomography (SPECT) Study using [^{99m}Tc] TRODAT-1
- **Running Title:** Sleep and Dopamine Transporter in Bipolar Disorder
- **Article Type:** Brief reports
- **KeyWords:** bipolar disorder, dopamine, euthymic state, single-photon emission computed tomography, sleep

Abstract

Objective: Bipolar disorder (BD) is characterized by the poor sleep quality. Whether the striatal dopamine transporter (DAT) availability is related to sleep quality among patients with BD is unclear.

Methods: Fifty-three euthymic patients with BD (24 BD-I and 29 BD-II) and sixty-eight healthy controls were enrolled. The Chinese Version of the Pittsburgh Sleep Quality Index (PSQI) was used, and the availability of DAT was assessed by single-photon emission computed tomography (SPECT) using [^{99m}Tc] TRODAT-1.

Results: The sleep disturbance component of the PSQI was significantly associated with the level of DAT availability among patients with BD.

Conclusion: The striatal dopaminergic activity that contributes to resilience to adversity was associated with sleep pattern among patients with BD.

Keywords: bipolar disorder; dopamine; euthymic state; single-photon emission computed tomography; sleep.

INTRODUCTION

Sleep plays a vital role in bipolar disorder (BD) [1,2]. BD patients experiencing a manic episode have a shorter rapid eye movement (REM) latency, an increased REM density, increased REM activity, a shorter sleep duration, and later sleep onset [1]. While there is a remarkable lack of consensus with regard to BD patients within a depressive episode [2]. Meanwhile, a longer sleep latency, shorter sleep duration, longer wake time after sleep onset, poor sleep efficiency, and greater night-to-night variability of sleep pattern were found to be characteristics of a remitted BD sample [3,4].

The dysregulation of dopamine plays an important role in different types and stages of BD [5]. The dopamine transporter (DAT) availability is significantly altered in BD patients [6]. Moreover, a role of the dopaminergic system in modulating the sleep-wake cycle has been confirmed by animal study [7]. In healthy controls (HCs), a decrease in dopamine reuptake due to a lower DAT availability could cause a shorter sleep duration [8]. In addition, sleep disturbance is present in patients with various dopamine-related diseases [9,10].

Regardless this evidence imply that sleep disturbance may be associated with DAT availability among patients with BD, whether there is an association between dopamine function and sleep disturbance among patients with BD is unclear. Here, the primary theoretical-driven aim is to test the relationship between striatal DAT availability and

sleep disturbance in patients with BD in the euthymic state. As little is known on the association between striatal DAT with other domains of sleep quality among BD-I and BD-II, the second aim is to probe these associations.

METHODS

Ethics statement

The Institutional Review Board for the Protection of Human Subjects at National Cheng Kung University Hospital approved the research protocol (B-BR-105-086). Patients were recruited from the Psychiatric Outpatient Department of National Cheng Kung University Hospital, and healthy subjects were recruited via internet and public advertisements. Signed written informed consent forms were obtained from all enrolled subjects after the protocol had been fully explained.

Enrollment and measurements of psychopathology in participants

In this study, we enrolled 53 euthymic patients with BD based on the criteria of the DSM-5 who had been receiving mood stabilizer treatment at the Department of Psychiatry of National Cheng Kung University Hospital. Eligible individuals were those aged between 18-70 years. Patients were receiving mood-stabilizer treatment, including valproic acid (VPA) or lithium (n = 14, (26.4 %)), VPA+antipsychotics (n = 29, (54.7 %)), antipsychotics (n = 8, (15.1 %)), and other treatments (including SSRI or no medication use) (n = 2, (3.8 %)). The Hamilton Depression Rating Scale (HDRS) and the Young Mania Rating Scale (YMRS) were used to evaluate the psychopathology of the patients by psychiatrists. The exclusion criteria included (i) a diagnosis of organic

mood disorder, (ii) mood disorder not otherwise specified, (iii) more than one lifetime course of electroconvulsive therapy (ECT) or ECT within the last 6 months, (iv) cerebrovascular disease, (v) neurodegenerative disorder, and (vi) macrovascular disorder.

Sixty-eight HCs were enrolled as the control group in this study. The exclusion criteria included (i) serious surgical treatment or physical illness, (ii) individuals who were pregnant or breastfeeding, (iii) substance abuse within the past three months identified based on the DSM-V criteria, (iv) previous receipt of any psychotropic agent, and (v) an organic mental disease, mental retardation or dementia.

Chinese version of the Pittsburgh Sleep Quality Index (PSQI)

The PSQI contains 19 self-rated questions yielding seven components [11]. Each component is scored on a scale of 0 to 3, yielding a global PSQI score ranging between 0 and 21, with higher scores indicating a poorer sleep quality. This questionnaire has a diagnostic sensitivity of 90% and a specificity of 87% between good and poor sleepers [11]. The Chinese version of the PSQI has been documented as reliable and valid [12].

[^{99m}Tc] TRODAT-1 SPECT

Each subject was given an intravenous injection of 740 MBq (20 mCi)

[99mTc]TRODAT-1 in a quiet environment about ten minutes after inserting an intravenous line. The SPECT data were obtained with an energy window of 15% centered on 140 keV for [99mTc]. Imaging of [99mTc]TRODAT-1 started about 240 minutes after injection, and SPECT images were acquired over a circular 360 rotation in 120 steps, 50 sec/step, in a 128×128×16 matrix. Butterworth and Ramp filters (cut-off frequency = 0.3 Nyquist; power factor = 7) were then used to rebuild the images using the attenuated approach of Chang's method, and the reconstructed cross-sectional images were re-adjusted to be parallel to the canthomeatal line. Each transverse image had a slice thickness of 2.89 mm. Additionally, all subjects underwent magnetic resonance imaging (MRI) (Signa CV-I, 1.5 Tesla, GE Healthcare, Milwaukee, WI, USA). The SPECT image of each subject was automatically co-registered with the corresponding T2-weighted MRI image using PMOD software (PMOD Technologies, Zurich, Switzerland), and then manually adjusted by an experienced nuclear medicine doctor. The MRI image was used as a reference, so the slice thickness of the co-registered image was the thickness of the T2-weighted MRI image (3.3 mm). For co-registration, the rigid transformation was defined by 6 parameters, the rotation angle and translation distance in the three spatial directions. The interpolation method was the trilinear interpolation approach. On the co-registered images, the two adjacent transverse slices containing the strongest striatal radioactivity were further checked to

determine whether the SPECT and MRI images were accurately co-registered and whether the striatum was best seen on the two slices of the MRI images. If this was not the case, co-registration was further manually adjusted until a satisfactory result was achieved. ROIs were then drawn on the two adjacent MRI cross sections. The difference between the average activity of the striatum (St) and the average activity of the occipital cortex (Oc) was divided by the average activity of the occipital cortex (Oc) to obtain the radioactivity ratio [(St-Oc)/Oc ratio] [13,14].

Statistical analysis

Analysis of covariance (ANOVA) was used to test the group differences. Fisher's least significant difference was tested when performing post-hoc analyses. As age and smoking status may be associated with DAT and sleep quality, a series of partial correlations, controlling the effect of age [15] and smoking status [16], were used to probe the association between sleep quality and DAT availability. A supplemental nonparametric correlation test was conducted to test the robustness of the significant finding. Statistical analyses were conducted using SPSS 22.0. Significance was assumed at $P < 0.05$. For the secondary aims of analysis, we controlled the p-value due to multiple comparison.

RESULTS

The demographic and clinical characteristics of the participants are shown in Table

1. The patients with BD had a higher YMRS score and a poorer PSQI score. For the primary hypothesis, a significant association between sleep disturbance component of the PSQI and striatal DAT availability was found in the patients with BD (partial $r = 0.32$, $p = 0.021$). For the secondary exploratory aim of this study, no significant association was found after controlling for the multiple comparison (Table 2).

DISCUSSION

Our study showed that euthymic BD patients had higher PSQI than healthy controls. This is compatible with other studies showing that residual sleep problems is common in euthymic BD patients [3,4,17].

The sleep disturbance component in PSQI had a positive association with DAT availability in euthymic BD patient in this study. The result is different from a previous study with healthy controls that showed lower DAT linked to decreased sleep duration [8]. Both results together imply a possible role of striatal dopamine homeostasis in sleep regulation. In healthy controls, when the DAT availability is low, dopamine might be accumulated in the synaptic. In BD patients, higher DAT availability might link to (i) increased phasic dopamine release from the presynaptic neuron; or (ii) lower tonic dopamine release with super-sensitivity of postsynaptic dopamine receptors [6].

The PSQI sleep disturbance subscale (C5) is composed of eight items related to symptoms that disturb one's sleep, such as difficult falling asleep, sleep fragmentation, sleep-breathing disorder, sensorial discomfort and nightmare. The scores of this component might indicate a higher REM duration and a long night waking time [18]. With the higher DAT availability in BD, greater dopamine release could inhibit slow wave sleep and enhance REM sleep, resulting in sleep disturbance [19].

The current studies about the DAT availability in BD showed controversial results

[5]. In this study, the DAT availability had no significant difference between healthy controls and medication-treated BD patients. This was different from the results of our previous research that showed the DAT availability was significantly higher in patients with medication-free euthymic bipolar disorder [6]. However, another study observed a downregulation of DAT at the dorsal caudate in unmedicated euthymic BD patients, and there was no difference in the striatum [20]. We speculate that medications used to treat BD could modulate DAT availability [21], including antipsychotics, antidepressants and mood stabilizers which might up-regulate or down-regulate the DAT availability in different type of BD, number of episodes, and duration of illness.

In conclusion, the sleep problem was still persistent and prominent in BD patients even achieving remission. Sleep disturbance in PSQI subscales was positively associated with DAT availability in the remitted BD-I patients. Understanding the relationship between DAT and sleep problems in different stage and type of BD is important.

Limitations

First, the study was cross-sectional, and thus causal relationships cannot be inferred. Second, sleep quality was measured using a subjective questionnaire.

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Author contributions

Po See Chen designed the study and wrote the protocol. Nan Tsing Chiu helped to design the study. Shih-Hsien Lin contributed to the statistical analyses. Tsung-Hua Lu wrote the first draft of the manuscript. Tsung-Hua Lu, Huai-Hsuan Tseng, Yen Kuang Yang, and Po See Chen managed the data collection. All authors interpreted the analysis of the results and helped to revise the manuscript.

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Table 1. Demographic and clinical characteristics of the participants.

	HCs	BD-I	BD-II	Test statistic		
	(N=68)	(N=24)	(N=29)	χ^2/F	p	Post-hoc
	Mean (SD)	Mean (SD)	Mean (SD)			
Sex (M/F)	28/40	10/14	15/14	0.97	0.614	
Smoking (Yes/No)	7/61	3/21	7/22	3.29	0.193	
Age (years)	33.63(11.33)	40.54(14.75)	35.48(12.07)	2.83	0.063	Normal<BD-I
HDRS	1.65(1.55)	1.38(1.56)	2.45(2.34)	2.88	0.060	Normal=BD-I<BD-II
YMRS	0.06(0.49)	0.96(1.65)	0.76(1.21)	9.40	0.000	Normal<BD-I=BD-II
<u>DAT availability</u>	1.39(0.25)	1.39(0.27)	1.41(0.19)	0.05	0.952	
PSQI						
Sleep quality C1	0.94(0.64)	1.25(0.53)	1.48(0.78)	7.31	0.001	Normal<BD-II
Sleep latency C2	0.96(0.87)	1.17(0.96)	1.66(0.90)	6.19	0.003	Normal<BD-II
Sleep duration C3	0.72(0.67)	0.29(0.55)	0.59(0.82)	3.47	0.034	Normal>BD-I
Sleep efficiency C4	0.16(0.48)	0.46(1.02)	0.48(1.06)	2.40	0.095	
Sleep disturbance C5	0.99(0.40)	1.21(0.66)	1.48(0.74)	8.38	0.000	Normal<BD-II
Use of sleeping medication C6	0.04(0.21)	1.88(1.30)	2.10(1.35)	73.37	0.000	Normal<BD-I=BD-II
Daytime dysfunction C7	0.59(0.58)	0.92(0.83)	1.72(0.84)	26.64	0.000	Normal=BD-I<BD-II
Sum	4.40(2.19)	7.17(2.46)	9.52(3.77)	38.64	0.000	Normal<BD-I<BD-II

HCs: healthy controls

BD: bipolar disorder

HDRS: Hamilton Depression Rating Scale

YMRS: Young Mania Rating Scale

DAT: dopamine transporter

PSQI: Pittsburgh Sleep Quality Index

Table 2. Partial correlation, controlling for age and smoking status, between DAT availability and PSQI component scores.

	HCs (N=68)		BD (N=53)		BD-I (n=24)		BD-II (n=29)	
	r	p	r	p	r	p	r	p
Sleep quality C1	0.18	0.150	0.23	0.107	0.03	0.895	0.30	0.133
Sleep latency C2	-0.19	0.120	0.06	0.653	-0.20	0.361	0.35	0.071
Sleep duration C3	0.03	0.807	0.06	0.676	0.22	0.333	0.07	0.731
Sleep efficiency C4	-0.15	0.243	0.16	0.269	0.14	0.548	0.25	0.216
Sleep disturbance C5	0.00	0.976	0.32	0.021	0.40	0.067	0.12	0.568
Use of sleeping medication C6	0.03	0.807	-0.01	0.918	0.01	0.950	0.00	0.983
Daytime dysfunction C7	0.01	0.929	0.08	0.560	0.07	0.742	0.20	0.319
Sum	-0.04	0.743	0.21	0.144	0.15	0.511	0.30	0.134

HCs: healthy controls

DAT: dopamine transporter

PSQI: Pittsburgh Sleep Quality Index