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Association of subthreshold manic symptoms and cognitive impairments in euthymic patients with bipolar disorder I

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ABSTRACT

Cognitive impairments exist during the euthymic period of bipolar disorder (BD). However, the impact of clinical factors (e.g., subthreshold symptoms and body mass index) on cognitive function in euthymic patients with bipolar disorder I is inconsistent. This cross-sectional study included 83 patients with euthymic BD I and 115 healthy controls. The Repeatable Battery for the Assessment of Neuropsychological Status indices were used to assess cognitive function. We assessed the relationship between cognitive function and clinical impact factors. Performance in language abilities, attention, and immediate memory was worse in euthymic BD I. Spearman's correlation revealed that indices for immediate memory and attention were negatively correlated with subthreshold manic symptoms, and indices for delayed memory were positively correlated with years of education. Linear regressions indicated that subthreshold manic symptoms were the best predictors of immediate memory and attention. Years of education predicted performance in most cognitive domains, except immediate memory. Individuals with euthymic BD I exhibited cognitive deficits in language learning, attention, and immediate memory. Our study highlights the importance of the effect of subthreshold manic symptoms on cognitive function in remitted BD; these symptoms should receive more attention and be targeted in personalized clinical therapeutic interventions.

1. Introduction

Bipolar disorder (BD) is a serious and highly recurrent mental disease associated with episodic mood symptoms that interfere with cognitive function (Kurtz and Gerraty, 2009; Samame et al., 2013). It affects a patient's life and health with high morbidity and disability (Ketter, 2010; Merikangas et al., 2007, 2011). Approximately 50% of patients with bipolar disorder have significant functional impairments in several domains, even during the euthymic period. Cognitive dysfunction is a vital determinant of functional impairment in bipolar disorder (Konstantakopoulos et al., 2016). Published meta-analyses (Andreou and Bozikas, 2013; Bora et al., 2009) indicate that euthymic bipolar patients perform worse than healthy controls on verbal learning and nonverbal memory, visual, attention, and executive function tasks. Verbal learning and memory are the two main impaired functions in the cognitive domains of euthymic BD I patients (Andreou and Bozikas, 2013; Cardenas et al., 2016; Robinson et al., 2006; Torres et al., 2007). Owing to the strong association between weak social functions and cognitive dysfunction in bipolar disorder (Depp et al., 2012), it is crucial to explore the underlying pathological process of cognitive performance in patients with bipolar disorder.

Most previous studies of bipolar patients have shown that clinical factors that affect cognitive function include the number of episodes (Martínez-Arán et al., 2004; Martino et al., 2013), manic type (López-

Abbreviations: ANOVA, analysis of variance; BD, bipolar disorder; BMI, body mass index; BRMS, Bech–Rafaelsen Mania Scale; HAMD, Hamilton Depression; RBANS, repeatable battery for the assessment of neuropsychological status; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorder*, 4th edition

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Jaramillo et al., 2010; Martino et al., 2013; Sanchez-Moreno et al., 2009; van Gorp et al., 1998; Vrabie et al., 2015), the duration of the illness (Clark et al., 2002; Martino et al., 2013; van Gorp et al., 1998), and subclinical symptoms (Bonnin et al., 2012; Martínez-Arán et al., 2000; Martino et al., 2013; Roux et al., 2017). Euthymia is regarded as clinical remission. However, a large body of remitted patients experience subthreshold symptoms during this period (Deckersbach et al., 2010; Martínez-Arán et al., 2000; Samalin et al., 2016). Previous studies have demonstrated that subthreshold symptoms negatively influence certain functional domains in euthymic patients with bipolar disorder (Martino et al., 2013; Samalin et al., 2014, 2016). However, these studies focused more attention on the association between subthreshold symptoms and functional impairment and quality of life. Therefore, it is less clear whether subthreshold symptoms negatively affect cognitive performance in euthymic bipolar disorder.

Findings regarding the relationship between subthreshold symptoms and cognition have been mixed. One study (Bonnin et al., 2012) showed that verbal memory is associated with subthreshold depressive symptoms. Subthreshold manic symptoms have been strongly associated with two impaired functional domains—autonomy and financial issues—during the euthymic episode (Samalin et al., 2016). Another study (Roux et al., 2017) reported no significant relationship between subthreshold depressive symptoms and cognitive component. New evidence indicates that subthreshold manic symptoms may have a predictive value for BD (Papachristou et al., 2017). A few studies (Bonnin et al., 2012; Deckersbach et al., 2010; Martino et al., 2013; Roux et al., 2017) have directly compared the role of subthreshold symptoms on cognitive function in euthymic bipolar disorder, but with inconsistent results. Based on the findings of previous studies (Samalin et al., 2016), the presence of subthreshold manic symptoms seems to affect functioning in patients with bipolar disorder. However, few studies have focused on the effect of subthreshold manic symptoms on cognitive function.

The unique features of subthreshold manic symptoms are difficult to distinguish from the normal state in euthymic patients who experience functional impairment in their daily lives. Furthermore, because of insufficient knowledge of subthreshold symptoms, psychiatrists may neglect to relieve a patient's symptoms completely in clinical treatment. Hence, subthreshold symptoms are a variable that deserves special mention.

Emerging evidence also indicates that obesity is associated with cognitive dysfunction. Body mass index (BMI) is negatively correlated with attention and psychomotor processing speed in patients with euthymic bipolar disorder (Yim et al., 2012). However, few studies exist focusing on the relationship between BMI and cognitive function. Their results have rarely been replicated.

A few studies (Dittmann et al., 2007, 2008; Deckersbach et al., 2010) have used the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) for the cognitive assessment of patients with bipolar disorder. We aimed to investigate cognitive functioning in euthymic patients with bipolar disorder while focusing on the differences in immediate and delayed memory, and in visuospatial abilities, attention, and language learning between these patients and healthy case-controlled individuals. Furthermore, we focused on the association between cognitive function and clinical factors such as subthreshold symptoms and BMI to explore the influential factors of cognitive dysfunction among a sample of patients with euthymic bipolar disorder. We hypothesized that (1) patients with euthymic bipolar disorder would have cognitive impairment and (2) clinical factors such as subthreshold symptoms and BMI would negatively affect cognitive function.

2. Methods

2.1. Study design and participants

The study protocol was approved by the local Ethical Committee of the Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital, Guangzhou, China). The procedures were explained to all participants. All participants provided signed informed consent. Eighty-three euthymic bipolar disorder I patients and 115 healthy controls were enrolled in this study protocol, all of whom were Chinese Han.

The diagnosis of BD was established by a trained psychiatrist, based on a structured clinical interview that used the criteria of the *Diagnostic and Statistical Manual of Mental Disorder, 4th edition* (DSM-IV; American Psychiatric Association, 1994). Euthymic bipolar disorder I patients were defined as individuals who did not meet the diagnostic criteria for a manic or depressive episode at the time of the cognitive evaluation, or individuals who met the symptomatic remission criteria for at least 1 month [i.e., a Hamilton Depression [HAMD] total score <8 on the 17-item Hamilton Depression Rating Scale (Ramos-Brieva and Cordero-Villafafila, 1988; Hamilton, 1960) and a Bech–Rafaelsen Mania Scale (BRMS) total score <6 (Bech et al., 1979)]. The exclusion criteria were a history of organic mental disorder or sensory disorders, unconsciousness, language delay, substance-related disorders, and chronic somatic diseases such as endocrine disease.

Healthy controls were evaluated by qualified psychiatrists and were recorded as having no current or past history and first-degree family history of any psychiatric disorder or mental retardation. All controls were age- and sex-matched with patients. The demographic and clinical characteristics of patients with BD and the healthy controls are summarized in Table 1.

2.2. Materials

2.2.1. Clinical and psychosocial assessments

The evaluation of clinical subthreshold symptoms included the BRMS (Bech et al., 1979) and the 17-item Hamilton Depression (HAMD-17) Rating Scale (Ramos-Brieva and Cordero-Villafafila, 1988; Hamilton, 1960). Both measures are semi-structured, observer-rated rating scales for the clinical evaluation of bipolar mania and depression. The RBANS Form A (Randolph et al., 1998) was used for neuropsychological assessments. The RBANS consists of 12 items that are used to calculate five index scores and a total score. The test indices are Immediate Memory (subtests: List Learning and Story Memory), Visuospatial Abilities (subtests: Finger Copy and Line Orientation), Language Learning (subtests: Picture Naming and Semantic Fluency), Attention (subtests: Digit Span and Coding), and Delayed Memory (subtests: List Recall, List Recognition, Story Recall, and Figure Recall). Each index score is an age-adjusted standard score. The index scores are combined to calculate the total score and represent a measure of overall cognitive functioning.

2.2.2. Statistical analyses

The Statistical Package for Social Sciences 19.0 (SPSS Inc., Chicago, IL, USA) was used to conduct all statistical analyses. The basic demographic and clinical characteristics between the patients and healthy control groups were compared by using the independent sample *t*-test, Mann–Whitney *U* test, covariance analysis and χ^2 test, as appropriate. We used Spearman's correlation to analyze the relationships between cognitive functions and clinical and demographic variables, and we adjusted the p value six times by using Bonferroni correction. We conducted linear regression analyses to test the influence of clinical and demographic variables on cognitive function. Data are presented as the mean ± the standard deviation. Statistical significance was $p < 0.05$.

Table 1
Demographic and clinical characteristics of patients and controls.

Variable	Euthymic bipolar patients (N = 83)	Healthy controls (N = 115)	T/F	p
Sex[a]				
(Male/Female)	33/50	61/54	0.214	0.11
Age (y)	25.1 ± 7.40 (15–44)	25.27 ± 5.10 (19–51)	−0.632	0.527
Years of education	12.74 ± 2.86 (6–19)	14.86 ± 1.97 (9–18)	−7.189	***0.00***
BMI* (N = 57)	22.64 ± 0.32(15.70–33.00)	20.56 ± 0.25(16.20–31.00)	−4.829	***0.00***
Total duration of illness (months) (N = 79)	59.25 ± 58.261 (1–262)	–	–	–
Age of onset	21.26 ± 6.365 (12–37)	–	–	–
Medication status				
Medication, n(%) no. of medications	65 (81%)	–	–	–
Lithium	32 (40%)	–	–	–
Valproate	36 (45%)	–	–	–
Antipsychotics	54 (68%)	–	–	–
Antidepressants	0	–	–	–
Lamotrigine	2 (3%)	–	–	–

The data are presented as the mean ± the standard deviation (range) or as the number (percentage), unless otherwise indicated.
The bold italic font indicates significant p values.
* BMI, body mass index
[a] The χ^2 test was used for the analysis.

3. Results

3.1. Demographic characteristics

Clinical and demographic characteristics data of the euthymic BD I patients and healthy controls are presented in Table 1. Healthy controls (male/female: 61/54) and BD patients (male/female: 33/50) in the stable phase were not significantly different for sex and age (both, $p > 0.05$). However, they differed in BMI and education ($p < 0.05$), which were controlled as covariates, and medication status (Table 1).

3.2. Comparison of cognitive performance

Analysis of variance (ANOVA) was conducted to compare differences between euthymic patients and healthy controls. Body mass index and education were significantly different between the patient and control groups. Therefore, we added BMI and education as covariates to compare the difference in cognitive function between the groups using Analysis of Covariance (ANCOVA). Both groups differed significantly in the composite RBANS indices of Language Learning ($F = 12.804$, $p < 0.001$, effect size = 0.838), Attention ($F = 13.304$, $p < 0.001$, effect size = 1.021) and total score ($F = 9.477$, $p = 0.003$, effect size = 1.038). Immediate Memory showed a statistical trend of decline in the patient group ($F = 3.148$, $p = 0.078$, effect size = 0.755) (Table 2).

3.3. Cognitive performance and the associated clinical characteristic variables

Spearman's correlation results indicated that BRMS scores were negatively correlated with Immediate Memory (Spearman's $rho = -0.367$, $p = 0.004$), Attention (Spearman's $rho = -0.400$, $p = 0.002$), and total score (Spearman's $rho = -0.333$, $p = 0.010$). After adjusting the p value, we found that BRMS scores were negatively correlated with Immediate Memory (Spearman's $rho = -0.367$, $p = 0.024$) and Attention (Spearman's $rho = -0.400$, $p = 0.012$). In addition, the number of hospitalizations was negatively associated with Immediate Memory ($rho = -0.263$, $p = 0.046$) and Delayed Memory ($rho = -0.261$, $p = 0.048$). However, no statistical difference existed between the number of hospitalizations and the cognitive indices when the p value was adjusted. After adjusting the p value, we still found that Delayed Memory and total score indices were positively correlated with years of education ($rho = 0.341$, $p = 0.048$; and $rho = 0.347$, $p = 0.042$, respectively). We did not find an association between the Language Learning Index and the clinical variables ($p > 0.05$) (Table 3). The BMI data of 57 patients were collected. We did not find a significant relationship between cognitive functions and BMI, as well as total number of episodes, age of onset, number of manic episodes, number of depressive episodes, HAMD scores, and duration of illness.

3.4. Predictor of clinical parameters in euthymic individuals with BD

After conducting Spearman's correlation analyses to identify significant relationships between clinical and demographic variables and cognitive function, we used multiple stepwise regression analyses to further explore predictive variables in these relationships. The sample size included in the regression analysis consisted of 57 patients (i.e., outliers and missing data excluded from the analysis) (Table 4). Statistical analyses demonstrated that years of education and BRMS scores were significant predictors of cognitive function in euthymic patients

Table 2
Difference in cognitive functions between euthymic bipolar disorder patients and healthy controls.

RBANS five-index scores	Euthymic bipolar patients (N = 83)	Healthy controls (N = 115)	F-test[a]	p	Effect size
Immediate memory	75.34 ± 19.23	88.40 ± 15.75	3.148	0.078	0.755
Visuospatial abilities	87.75 ± 16.24	96.09 ± 16.72	0.336	0.563	0.505
Language learning	79 ± 20.78	93.13 ± 13.34	12.804	***0.00***	**0.838**
Attention	93.85 ± 16.29	109.54 ± 14.66	13.304	***0.00***	**1.021**
Delayed memory	82.81 ± 17.93	92.61 ± 11.05	1.060	0.305	0.683
Total score	418.59 ± 71.6	479.77 ± 47.68	9.477	***0.003***	**1.038**

BMI, body mass index; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status
The data are presented as the mean ± the standard deviation.
The bold italic font indicates significant p values.
[a] Evaluated using analysis of covariance with years of education and BMI as the covariates.

Table 3
Spearman's correlation of clinical variables with cognitive functions in patients with euthymic bipolar disorder [*rho* (*p*)].

	Years of education	BMI	BRMS	Hospitalizations	Number of manic episodes	Total duration of illness
Immediate memory	0.284 (0.174)*	0.022 (0.866)	***−0.367 (0.024)****	−0.263* (0.276)	−0.025 (0.122)	−0.084 (0.529)
Visuospatial abilities	0.290 (0.156)*	0.057 (0.670)	−0.220 (0.095)	−0.131 (0.327)	−0.100 (0.457)	−0.044 (0.741)
Language learning	0.150 (0.255)	0.179 (0.175)	−0.174 (0.186)	−0.126 (0.347)	−0.153 (0.252)	0.120 (0.371)
attention	0.304 (0.114)*	0.208 (0.114)	***−0.400 (0.012)****	−0.171 (0.200)	0.020 0.883	0.088 (0.512)
Delayed memory	***0.341 (0.048)****	−0.072 (0.587)	−0.188 (0.153)	−0.261 (0.048)	−0.170 (0.203)	−0.030 (0.825)
Total score	***0.347 (0.042)****	0.105 (0.428)	−0.333 (0.060)*	−0.211 (0.111)	−0.140 (0.294)	−0.004 (0.974)

BMI, body mass index; BRMS, Bech-Rafaelsen Mania Scale.
The bold italic font indicates significant *p* values.
* The *p* value was adjusted six times by using Bonferroni correction.

with BD. Immediate Memory and Attention were predicted by the BRMS score ($B = -0.322$, $t = -2.523$, $p = 0.015$; and $B = -0.246$, $t = -2.328$, $p = 0.023$, respectively). Visuospatial Abilities, Delayed Memory, Attention, and total score were predicted by years of education ($B = 0.421$, $t = 5.496$, $p = 0.004$; $B = 0.436$, $t = 3.589$, $p = 0.001$; $B = 0.317$, $t = 3.001$, $p = 0.004$; and $B = 0.468$, $t = 4.652$, $p < 0.001$, respectively). An interesting finding was that attention was predicted by the BRMS score and by years of education. (Table 4).

4. Discussion

In this study, we hypothesized that patients with euthymic bipolar disorder would have cognitive impairment, and that subthreshold symptoms and BMI would negatively affect cognitive function. Based on this assessment, we had two principal findings: (1) euthymic BD patients performed worse than healthy controls on the cognitive domains of Immediate Memory, Language Abilities, Attention, and total score, and (2) subthreshold manic symptoms were strong predictors for Immediate Memory and Attention, and years of education was the best predictor for most cognitive domains, except Immediate Memory. To the best of our knowledge, this study is the first direct exploration of the effect of subthreshold manic symptoms on cognitive function using the RBANS battery in patients with euthymic BD I.

Our findings indicating that remitted patients had a poorer performance than healthy controls in Language, Attention, Immediate Memory, and total score on the RBANS were consistent with those of most previous studies that did and did not use the RBANS (Deckersbach et al., 2010; Dittmann et al., 2007, 2008; Lima et al., 2018; Rubinsztein et al., 2000). The RBANS test is an in-depth examination of verbal learning and memory processes. The latest meta-analyses have indicated that euthymic bipolar patients perform worse than healthy controls on verbal learning and nonverbal memory, visual, attention, and executive function (Andreou and Bozikas, 2013; Bora et al., 2009). Other studies (Cavanagh et al., 2002; Ferrier et al., 1999) have also indicated dysfunctional verbal learning and memory in euthymic bipolar patients, after controlling for subclinical pathology and dysfunction in sustained attention in bipolar I and bipolar II patients (Dittmann et al., 2008). The results of the present test indicated that individuals with euthymia were impaired in information processing such as encoding, consolidation, and retrieval. This finding indicated that the RBANS test is a well-validated neuropsychological measure that reliably reflects cognitive dysfunction in patients with euthymic bipolar disorder. Hence, it would be a good choice for researchers to evaluate uncooperative patients in the acute phase.

Furthermore, we found that poor performance, based on the Immediate Memory and Attention scores, was correlated with subthreshold manic symptoms and that subthreshold manic symptoms in euthymic patients may predict 30 percent and 25 percent, respectively, of the variation in the aforementioned cognitive impairments. This finding indicated that subclinical symptomatology may influence some cognitive domains.

These findings are partly consistent with those of previous studies (López-Jaramillo et al., 2010; Martino et al., 2013; Strakowski et al., 2011). The number of manic episodes is positively correlated with brain imaging findings of brain damage (Strakowski et al., 2011). Furthermore, some investigators have found that an impairment in verbal memory was associated with the number of previous manic episodes (Martínez-Arán et al., 2004; López-Jaramillo et al., 2010; Vrabie et al., 2015). A recent study (Papachristou et al., 2017) showed that childhood subthreshold of manic symptoms may predict adolescent and adult psychiatric outcomes. During the euthymic period, subthreshold manic symptoms have also been strongly associated with two impaired functional domains: autonomy and financial issues (Samalin et al., 2016). One previous study (Martino et al., 2013) reported that subclinical symptoms were related to cognitive impairment. These findings altogether suggest that subclinical mania symptoms may be associated with poor neuropsychological performance, even during euthymia.

Our findings have vital clinical implications. On account of the unique features of subthreshold manic symptoms, it is difficult for patients to be aware of their symptoms and be willing to receive appropriate antimanic treatment. In addition, because of insufficient knowledge of subthreshold manic symptoms, psychiatrists may neglect to relieve these symptoms completely in patients undergoing clinical treatment. Based on our findings, adequate treatment to eliminate subthreshold manic symptoms and treatment that targets memory and attention training methods may clinically alleviate cognitive impairment. Furthermore, it is very important for patients to be well-informed about their disease—in particular, subthreshold manic symptoms. We did not find a relationship between the Language Learning Index and subthreshold manic symptoms.

The analysis of relationships between clinical features and neuropsychological indices indicated that worse performance in the

Table 4
Results of linear regression analysis for predicting performance in the cognitive domains.

	BRMS score					Years of education				
	B	*t*	R^2	95%CI	*p*	*B*	*t*	R^2	95%CI	*p*
Immediate Memory	−0.322	−2.523	0.104	−9.381 to-1.075	***0.015***					
Attention	−0.246	−2.328	0.196	−7.229 to −0.564	***0.023***	0.317	3.001	0.138	0.653;3.229	***0.004***
Total Score						0.468	4.652	0.219	6.624;16.54	***0.000***

BRMS, Bech–Rafaelsen Mania Scale.
The bold italic font indicates significant *p* values.

assessment of Delayed Memory and total score was correlated with fewer years of education. Previous studies (Bora et al., 2007; Martínez-Arán et al., 2004; Okasha et al., 2014) have reported that years of education were correlated with a dysfunction in memory performance in euthymic bipolar patients, corroborating our findings. In our study, patients with a higher level of education showed less impairment in the Delayed Memory and total score indices. On further investigation of the contribution of years of education, we found that approximately 30%–40% of the variation in most cognitive domains, except for Immediate Memory, was predicted by years of education. These findings indicated that individuals with longer years of education may focus more attention on their psychological condition and may be more cooperative with treatment, thereby reducing the negative effects on cognitive function. In addition, receiving more school education may be considered recovery training to some extent. Therefore, it is very important to encourage patients to continue their school education after remission.

We did not find a relationship between BMI and cognitive functions, which was inconsistent with the findings of previous studies (McIntyre et al., 2017; Mora et al., 2017; Yim et al., 2012). However, Yim et al. (2012) reported that BMI was negatively correlated with attention and psychomotor processing speed in patients with euthymic bipolar disorder. The main difference between the findings of our study and the aforementioned study may be that the number of overweight patients in our sample was very small. Therefore, the BMI of most patients was in the normal range.

The main limitations of this study are its cross-sectional design and lack of longitudinal observation. In addition, executive function and social cognition are not included in the RBANS battery. Hence, this report did not evaluate more domains of cognitive functioning such as executive function and social cognition. However, the RBANS is a well-standardized instrument used to evaluate several cognitive domains effectively and reliably and is quite suitable for individuals with short attention spans. Owing to its relatively short administration time and handle ability, it is feasible for researchers to use the RBANS as a tool to screen a large number of patients for research or clinical purposes.

In the current study, we have demonstrated that subthreshold manic symptoms can negatively affect cognitive function in patients with euthymic bipolar disorder. This finding highlights that subthreshold manic symptoms are an important problem in euthymic bipolar disorder and the importance of providing adequate treatment to eliminate subthreshold symptoms. In addition, the RBANS can be used to evaluate cognitive function in patients with bipolar disorder. In future studies, the euthymic period should be defined more clearly, and the negative impact of bipolar disease on cognitive function during the euthymic period should be considered. In particular, the definition should emphasize the importance of differences between self-evaluation, and interview assessments that may improve patients' awareness of their mental state. Improved definition of euthymia in patients with bipolar disease may facilitate effective treatment, and specific training methods targeting memory and attention may receive more support by psychiatrists.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.06.032.

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