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Research report

Cognitive performance is impaired in euthymic Chinese patients with Bipolar 1 Disorder

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ABSTRACT

Background: Data from euthymic patients with Bipolar Disorder (BD) has shown cognitive impairment and the notion that sufferers of BD achieve full recovery between illness episodes is questionable. These findings have not been replicated in a Chinese population. The present study examined the cognitive profile of euthymic Chinese patients with Bipolar 1 Disorder (BD-1) and matched healthy control participants.
Methods: Euthymic patients with BD-1 and matched controls ($n=104$ in total) completed serial measures to assess mood and also completed an IQ test and the Central Nervous System Vital Signs (CNSVS) computerized battery assessing memory (verbal and visual), executive functions, attention, psychomotor and processing speed.
Results: Patients with BD-1 performed worse than controls on all cognitive domains. When using 2 or more scores below the 5th percentile as a cutoff for neurocognitive impairment, 46.2% of the patients with BD-1 and none of the control sample scored in this range ($p<.001$). Correlational analysis among the illness variables in BD-1 revealed that cognitive performance was inversely correlated with the number of manic episodes and duration of illness.
Limitations: It was not possible to determine the causal relationship between associated illness and performance. The effect of medication on cognitive performance requires further study.
Conclusions: Euthymic Chinese patients with BD-1 demonstrate marked cognitive impairments and these correlated with illness parameters. Cognitive impairment in BD may be independent of language and culture.

1. Introduction

Bipolar Disorder (BD) is associated with cognitive impairment during the acute phases (Martinez-Aran et al., 2004a) and this impairment persists even in the euthymic phase. A majority of BD patients demonstrate high rates of functional and cognitive impairment even during periods of sustained remission of mood symptoms (Wingo et al., 2009).

Marked impairments are reported in executive functioning and verbal memory performance in euthymic BD patients (Robinson et al., 2006). Deficits of similar magnitude have been reported in measures of executive function, verbal learning, immediate and delayed verbal memory, abstraction, sustained attention and psychomotor speed in BD euthymic patients (Arts et al., 2008). In general, greater neurocognitive impairment was associated with worse illness course (number of mood episodes, hospitalizations and length of illness) (Robinson and Ferrier, 2006). Previous studies have been predominantly in European and North American patient groups. This study extends the previous work on euthymic BD, to a group of Chinese BD-1 patients, seeks to establish if these impairments are also present in this group and how the illness courses are associated with these impairments.

2. Methods

This study was conducted in the Tuen Mun Mental Health Centre (TMMHC), a regional psychiatric outpatient clinic in Hong Kong. This study was approved by the Ethnic Committee of the New Territories West Cluster.

2.1. Participants

A list of all active outpatients with an *ICD-10* diagnosis of BD was generated from the local centralized computer register.

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Participants included had to be outpatients with present or prior history of a (mood disorder component) diagnosis of BD-1 Disorder based on the SCID. All participants were ethnic Chinese, aged 18–64 years, euthymic, with Cantonese as their first language. Participants were excluded if they were mentally incompetent to provide consent, mentally retarded, had a change in psychotropic medication during the past 4 weeks, current case or history of Diagnostic and Statistical Manual of Mental Disorder 4th Version (DSM-IV) alcohol or substance abuse (within the last 12 months), previous head injury with loss of consciousness, neurological disorder, any history of psychiatric illness (other than BD-1 disorder) or a significant physical health problem which might interfere with cognitive functioning.

Healthy control participants, matched for age, gender and race, were recruited within the nursing, occupational therapists and allied health staff (security guard, health care assistant, cleaner and clerk). They were confirmed as healthy by medical examination and the SCID to be free of neurological or psychiatric disorder. No control participants gave a history of having a first-degree relative with psychiatric disorder. Controls were excluded if they had a neurological or medical condition, recent history of substance or alcohol misuse. Written informed consent was obtained from all participants.

3. Measures

3.1. Central Nervous System Vital Signs (CNSVS)

The CNSVS is a computerized cognitive assessment battery for use in clinical research in psychiatric settings. Previous studies have administered the CNSVS to patients with BD. See Iverson et al. (2009) for detailed description of the CNSVS and the analyses. CNSVS is administered via a computer and takes approximately 30–40 min to complete.

3.2. Cognitive measures

CNSVS comprises of 7 common neuropsychological measures, including Verbal and Visual Memory Test, Finger Tapping Test (FTT), Symbol Digit Coding (SDC) Test, the Stroop Test (ST), a Shifting Attention Test (SAT) and a Continuous Performance Test (CPT). The battery generates 15 primary scores, which are used to calculate 7 domain scores (Memory, Psychomotor speed, Processing speed, Reaction time, Cognitive flexibility, Complex attention and Executive function) and a summary score (Neurocognition Index) (Iverson et al., 2009). Table 1 summaries how the domain scores were derived from the 7 neuropsychological measures.

The process of translation from English to Traditional Chinese was completed in 2005. The forward translation (English to Chinese) followed by a backward translation was performed by a different translation vendor. A comparison was performed to look for a discrepancy. A snapshot of results from several cultures and countries was analyzed in 2005 to verify the tests behaved cross-culturally. The conclusion is that they behave reliably across different cultures.

3.3. SCID – Chinese-bilingual version of Structured Clinical Interview for DSM-IV Axis I Disorders – Patient version (SCID-I/P)

The diagnosis of BD was based on the SCID (First et al., 2002). The Chinese-bilingual SCID-I/P has an inter-rater reliability of .91 for mood disorders and rater-clinician reliability of .84 for BD's and .76 for depression (So et al., 2003).

Table 1
Summary of the domain score and the test employed.

Neurocognitive Index	Test employed
Composite Memory	Correct responses of Verbal and Visual Memory Test
Verbal Memory	Correct responses of Verbal Memory Test
Visual Memory	Correct responses of Visual Memory Test
Psychomotor Speed	Finger Tapping Test and total correct responses of SDC
Reaction Time	Average 2 complex reaction time scores of ST
Complex Attention	Number of errors in CPT, SAT, ST (the lower the better)
Cognitive Flexibility	Correct responses of SAT minus the number of errors of SAT and ST
Processing Speed	Number of correct responses minus errors of SDC
Executive Function	Number of correct responses minus errors of SAT

3.4. Young Mania Rating Scale (YMRS)

YMRS was used to measure the severity of manic symptoms (Young et al., 1978). There are 11 items: elevated mood, increased motor activity energy, sexual interest, sleep, irritability, speech (rate and amount), language – thought disorder, content, disruptive–aggressive behaviour, appearance and insight.

3.5. Hamilton Rating Scale for Depression (HAM-D)

The HAM-D was used to measure the severity of depressive symptoms among persons diagnosed with depressive illness (Hamilton, 1960). The reliability of the HAM-D varies with conditions but is generally acceptable. Internal consistency as measured by Cronbach's alpha is from .48 to .92.

3.6. Beck Depression Inventory (BDI-II)

The BDI-II (Beck et al., 1996) is a widely used self-administered scale measuring symptoms of depression. BDI-II is positively correlated with the Hamilton Depression Rating Scale with a Pearson r of .71, showing good agreement. The test has also been shown to have a high 1-week test–retest reliability (Pearson $r=.93$).

3.7. Altman Mania Rating Scale (AMRS)

The AMRS is a 5-item self-rating scale, which was used to assess the presence and severity of manic symptoms. It is compatible with DSM-IV criteria, and it correlates significantly with Young Mania Rating Scale. It has a good specificity of 85.5% and good sensitivity of 87.3% for a cutoff score of 6 or higher indicating manic or hypomanic condition (Altman et al., 1997).

3.8. Wechsler Adult Intelligence Scale (WAIS) – 3-subtest short form

IQ of the participants was estimated using a 3-subtest short form (Similarities, Digit Span and Arithmetic) of the Chinese version of WAIS-R (Gong, 1992). This has been adapted cross-culturally and widely used in recent local studies (Lui et al., 2011a, 2011b).

3.9. Procedure

All participants completed 2 visits. Each visit took around one to one-and-a-half hours to complete.

3.9.1. 1st visit

All participants were rated prospectively over 4 weeks and defined as in remission if they satisfied the criteria of Newcastle Euthymia Protocol (Thompson et al., 2005). These criteria consisted of a SCID diagnosis of Bipolar Disorder, with a 21-item HAMD score of <7 and a YMRS score <7 both at baseline and when repeated 4 weeks later. Participants also completed BDI-II (Beck et al., 1996) and the AMRS (Altman et al., 1997) each week during the euthymia verification month.

Demographic information such as age and education, occupation, medication history, illness characteristics (age at onset, duration of illness, number of hospitalizations, number of depressive and manic episodes, number of psychotic episodes, duration of illness and euthymia) were recorded and IQ was assessed. Participants were given a copy of the AMRS and BDI-II to be completed every 7th day after the first visit during the euthymia verification month.

3.9.2. 2nd visit

The second visit was scheduled 4 weeks after the first visit. For female participants, the visits were scheduled between day 3 and 10 (start from the first day of menstruation) of their menstrual cycle, to minimize variation created by the luteal phase (Symonds et al., 2004). Participants completed the CNSVS. The HAMD and YMRS were administered to assess mood.

3.10. Statistical analysis

All data were analyzed by the Statistical Package for the Social Sciences Windows version 16.0 (SPSS, Chicago [IL], USA). Descriptive statistics was used for the sociodemographic and clinical characteristics.

The sociodemographic data, IQ score and cognitive performance of the 2 groups were analyzed using *t*-tests. A mixed model multivariate analyses of variance (MANOVA) was carried out with group as the independent factor and the different cognitive domains as the dependent factors. Significant findings and interactions were followed by ANOVA. Correlation analysis was used to examine the associations between chronicity of illness and cognitive performance.

4. Results

4.1. Demographic characteristics

There was no drop-out, refusal or relapse of any of the 104 participants (52 in each group) during the study period. There were 33 females (63.5%) in each group. The mean age of patients suffering from BD-1 was 38.57 with a standard deviation (SD) of 10.70 years, while that of healthy comparison participants was 37.76 with a SD of 10.27 years. Their average self-reported years of education were 12.0 (SD=2.94) and 14.04 (SD=3.11) for BD-1 and healthy participants respectively. There was a statistically significant difference in years of education between the 2 groups ($t=3.439$, $p=.001$).

Regarding the occupation status in BD-1 patients, 30.8% were professional/technical employees, 9.6% were laborers, 17.3% were in managerial/office positions, 42.3% were retired/not working. In the health control samples, 73.1% were professional/technical employees, 9.6% were students, 9.6% were in labor positions and 7.7% were in managerial/office positions. None of the control sample was identified as disabled.

4.2. Clinical characteristics

4.2.1. Chronicity of the illness

Among the patients with BD-1, the mean age of onset was 24.63 years (SD=7.6). The mean duration of illness was 13.3 years (SD=8.3). The mean number of hospitalizations was 4.23 (SD=4.9). The mean number of depressive episodes was 5.1 (SD=5.2). The mean number of manic episodes was 5.2 (SD=5.0). The mean number of psychotic episodes was 2.0 (SD=3.0). The mean duration of euthymia was 4.1 years (SD=3.9)

4.2.2. Mood state

All patients were euthymic. The mean YMRS scores were .46 and .15 with SD of .85 and .5 for their 1st and 2nd assessment respectively. The mean HAMD scores were .84 and .21 with SD of 1.18 and .66 for their 1st and 2nd assessment respectively.

4.2.3. WAIS-R 3-subtest short form estimated IQ

The mean estimated IQ of patients with BD-1 was 106.3 with a SD of 13.96, whereas that of healthy control participants was 113.8 with a SD of 11.66. There was statistically significant difference in the estimated IQ between the 2 groups ($t=2.958$. $p=.004$).

The significant difference between the 2 groups on IQ and years of education was controlled for in subsequent analyses.

4.2.4. Medication status

Regarding the psychiatric medication in BD-1, 2 patients (3.8%) were not on any medication. Twenty-five patients (48.1%) were on monotherapy (either Epilim, Lithium, First or Second Generation Antipsychotic, Tegretol or Lamotrigine). Twenty-five patients (48.1%) were taking combination medications. Eight patients (15.3%) were taking anticholinergic drugs (Benzhexol) with a daily dosage ranging from 2 mg to 6 mg. Two patients received short-acting low-dose benzodiazepine (Lorazepam .5 mg) 12 h before the assessment. No healthy control participants were taking psychiatric medications.

4.2.5. Comparison of cognitive performance

The 2 groups were compared on the 8 index scores using MANOVA followed by univariate ANOVAs. The multivariate effect was significant (Pillai's Trace=.409; $F=8.049$; $p<.001$; partial eta squared=.409), indicating a significant main effect of the group i.e. there was significant difference between the healthy control and the patient group on the cognitive performance. Although there was a significant difference on years of education between BD and healthy control, it did not have a significant multivariate effect on cognitive performance.

In view of significant differences in IQ, a series of univariate analyses of covariance (ANCOVA) were performed to assess the group difference in the 8 index scores with IQ as covariate. After controlling for IQ, the standard cognitive domains revealed significantly worse neuropsychological performance in the BD-1 on all 8 index scores. See Table 2 for group differences in cognitive performance in BD-1 and matched control after controlling for IQ.

4.3. Verbal Memory

The mean score of Verbal Memory Test of patients with BD-1 was 49.29 (SD=6.77), whereas that of healthy participants was 53.38 (SD=4.38). The mean Verbal Memory Test score of patients with BD-1 was significantly lower than that of healthy control participants ($F=13.423$, $p\leq.001$).

When using 2 or more scores below the 5th percentile as a cutoff for neurocognitive impairment (i.e. Verbal Memory Standard score

Table 2
Group difference in cognitive performance in BD-1 and matched control after controlling for IQ.

ANCOVA	BD-I (SD)	Healthy control (SD)	*F* test (*p*-value)	Cohen's effect size (*d*)
Neurocognition (NCI)	73.71 (24.1)	102.7(6.8)	57.359 (< .001)	1.88
Composite Memory Standard	88.1 (20.1)	100.2 (18.7)	5.997 (.016)	.62
Psychomotor Speed Standard	86.1 (23.9)	111.6 (12.4)	34.699 (< .001)	1.41
Reaction Time Standard	67.9 (29.7)	96.6 (21.2)	22.711 (< .001)	1.13
Complex Attention Standard	64.2 (38.4)	101.2 (9.3)	33.736 (< .001)	1.55
Cognitive Flexibility Standard	62.9 (31.2)	103.6 (11.2)	66.063 (< .001)	1.92
Processing Speed Standard	87.5 (19.3)	111.3 (13.1)	41.817 (< .001)	1.41
Executive Function Standard	63.8 (30.8)	104.1 (11.1)	65.976 (< .001)	1.92

The domain scores initially established through a factor analysis of the raw data, were derived by summing multiple primary raw scores. Domain scores are presented as index scores with a mean of 100 and standard deviation of 15.

of < 76), 28.8% of the patients with BD-1 and 5.8% of the control sample scored in this range.

4.4. Visual Memory

The mean score of Visual Memory Test of patients with BD-1 was 43.21 (SD=5.23), whereas that of healthy participants was 46.40 (SD=4.53). The mean Visual Memory score of patients with BD-1 was significantly lower than that of healthy control participants (F=11.07, p=.001).

When using 2 or more scores below the 5th percentile as a cutoff for neurocognitive impairment (i.e. Visual Memory Standard score of < 76), 11.5% of the patients with BD-1 and 3.8% of the control sample scored in this range.

4.5. Composite Memory

The mean score of Composite Memory of patients with BD-1 was 92.50 (SD=10.56), whereas that of healthy participants was 99.79 (SD=7.52). The mean Composite Memory score of patients with BD-1 was significantly lower than that of healthy control participants (F=16.45, p < .001).

When using 2 or more scores below the 5th percentile as a cutoff for neurocognitive impairment (i.e. Composite Memory Standard score of < 76), 30.8% of the patients with BD-1 and 5.8% of the control sample scored in this range.

4.6. Psychomotor Speed

The mean score of Psychomotor Speed of patients with BD-1 was 157.85 (SD=37.62), whereas that of healthy participants was 193.40 (SD=22.34). The mean Psychomotor Speed score of patients with BD-1 was significantly lower than that of healthy control participants (F=34.34, p < .001).

When using 2 or more scores below the 5th percentile as a cutoff for neurocognitive impairment (i.e. Psychomotor Speed Standard score of < 76), 30.8% of the patients with BD-1 and 1.9% of the control sample scored in this range.

4.7. Reaction Time

The mean score of Reaction Time of patients with BD-1 was 805.50 (SD=209.01), whereas that of healthy participants was 657.19 (SD=101.82). The mean Reaction Time score of patients with BD-1 was significantly higher (the lower the better) than that of healthy control participants (F=21.16, p < .001).

When using 2 or more scores below the 5th percentile as a cutoff for neurocognitive impairment (i.e. Reaction Time Standard score of < 76), 44.2% of the patients with BD-1 and 13.5% of the control sample scored in this range.

4.8. Complex Attention

The mean score of Complex Attention of patients with BD-1 was 17.58 (SD=11.70) whereas that of healthy participants was 5.96 (SD=3.04). The mean Complex Attention score of patients with BD-1 was significantly higher (the lower the better) than that of healthy control participants (F=47.98, p < .001).

When using 2 or more scores below the 5th percentile as a cutoff for neurocognitive impairment (i.e. Complex Attention Standard score of < 76), 51.9 % of the patients with BD-1 and 1.9% of the control sample scored in this range.

4.9. Cognitive Flexibility

The mean score of Cognitive Flexibility of patients with BD-1 was 20.17 (SD=23.07), whereas that of healthy participants was 49.52 (SD=9.82). The mean Cognitive Flexibility score of patients with BD-1 was significantly lower than that of healthy control participants (F=73.4, p < .001).

When using 2 or more scores below the 5th percentile as a cutoff for neurocognitive impairment (i.e. Cognitive Flexibility Standard score of < 76), 57.7 % of the patients with BD-1 and none of the control sample scored in this range.

4.10. Processing Speed

The mean score of Processing Speed of patients with BD-1 was 49.58 (SD=15.64), whereas that of healthy participants was 66.81 (SD=12.64). The mean Processing Speed score of patients with BD-1 was significantly lower than that of healthy control participants (F=38.20, p < .001).

When using 2 or more scores below the 5th percentile as a cutoff for neurocognitive impairment (i.e. Processing Speed Standard score of < 76), 26.9% of the patients with BD-1 and none of the control sample scored in this range.

4.11. Executive Function

The mean score of Executive Function of patients with BD-1 was 21.69 (SD=22.64), whereas that of healthy participants was 50.58 (SD=8.66). The mean Executive Function score of patients with BD-1 was significantly lower than that of healthy control participants (F=73.82, p < .001).

When using 2 or more scores below the 5th percentile as a cutoff for neurocognitive impairment (i.e. Executive Function Standard score of < 76), 53.8% of the patients with BD-1 and none of the control sample scored in this range.

4.12. Neurocognition Index (NCI)

The mean score of NCI of patients with BD-1 was 73.71 (SD=24.1), whereas that of healthy participants was 102.7 (SD=6.8). The mean score of NCI of patients with BD-1 was significantly worse than that of healthy control participants ($F=57.359$, $p<.001$).

Of the patients with Bipolar 1 Disorder, 61.5% obtained 2 or more index scores below 1 SD, compared to 1.9% of the control group. When using 2 or more scores below the 5th percentile as a cutoff for neurocognitive impairment (i.e. NCI Standard score of <76), 46.2% of the patients with BD-1 and none of the control sample scored in this range. When using 2 or more scores below 2 SDs as cutoff, 40.4% of the bipolar sample and none of the control sample scored in this range.

4.13. Cognitive performance and associated illness variables

Correlational analyses revealed that the Neurocognition Index (NCI) of BD-1 patients was associated with the number of manic episodes ($r=-.454$, $p=.001$), duration of illness ($r=-.416$, $p=.002$) and number of hospitalizations ($r=-.337$, $p=.014$), whereas the number of depressive episode ($r=-.221$, $p=.115$), the number of psychotic episodes ($r=-.237$, $p=.090$), duration of euthymia ($r=-.141$, $p=.318$) and age of onset ($r=-.114$, $p=.423$) were not associated with the cognitive performance.

When looking at the individual domains, the cognitive performance of euthymic Bipolar 1 patients were inversely correlated with the number of manic episodes and duration of illness i.e. the greater the number of manic episode, the worse the cognitive performance; the longer the duration of illness, the worse the cognitive performance.

When looking at the associated illness variables, the number of manic episodes was also positively associated with the duration of illness ($r=.591$, $p\leq.001$) i.e. the greater the number of manic episodes, the longer the duration of illness and vice versa, see Table 3 for correlations between cognitive performance and illness variables in the BD-1 group.

4.14. Manic episodes

In view of significant correlations between the number of manic episodes and cognitive performance, and its clinical importance and implications in BD-1 patients, further subgroup analyses were performed. The BD-1 patients were divided into 3 groups according to their number of manic episodes (i.e. 1, 2–5 or >5). The numbers of patients were 10, 26 and 16. Results revealed that the greater the number of manic episodes, the worse the cognitive performance. There were significant differences among the 3 groups in NCI Standard ($F=4.374$, $p=.018$) and Reaction Time Standard ($F=3.862$, $p=.028$). There was a trend for differences among the 3 groups in Verbal Memory Standard ($F=2.862$, $p=.067$), Complex Attention Standard ($F=3.007$, $p=.059$) and Cognitive Flexibility Standard ($F=3.004$, $p=.059$), which were marginally not statistically significant.

Table 3
Correlations between cognitive performance and illness variables in BD-1

Bipolar 1 Disorder	No of manic episodes	Number of Depressive episodes	Number of psychotic episodes	Duration of illness	Duration of euthymia	Age of onset	Number of hospitalization
NCI Standard							
Pearson Correlation	−.454**	−.221	−.237	−.416**	−.141	−.114	−.337*
Sig. (2-tailed)	.001	.115	.090	.002	.318	.423	.014
Verbal Memory Standard							
Pearson Correlation	−.331*	−.147	−.278*	−.410**	−.77	−.098	−.324*
Sig. (2-tailed)	.016	.298	.046	.003	.585	.490	.019
Visual Memory Standard							
Pearson Correlation	−.137	−.090	−.119	−.370**	−.161	−.064	−.210
Sig. (2-tailed)	.334	.524	.400	.007	.255	.650	.135
Composite Memory Standard							
Pearson Correlation	−.284*	−.137	−.245	−.453**	−.143	−.103	−.317*
Sig. (2-tailed)	.041	.333	.080	.001	.312	.468	.022
Psychomotor Speed Standard							
Pearson Correlation	−.339*	−.180	−.143	−.538**	−.276	−.331***	−.296*
Sig. (2-tailed)	.014	.203	.312	.000	.048	.017	.033
Reaction Time Standard							
Pearson Correlation	−.430**	−.166	−.293*	−.259	−.065	−.070	−.326*
Sig. (2-tailed)	.001	.238	.035	.064	.647	.621	.018
Complex Attention Standard							
Pearson Correlation	−.420**	−.252	−.190	−.280*	−.122	.015	−.259
Sig. (2-tailed)	.002	.072	.178	.045	.391	.913	.064
Cognitive Flexibility Standard							
Pearson Correlation	−.383**	−.160	−.138	−.299**	−.136	−.065	−.239
Sig. (2-tailed)	.005	.257	.331	.031	.338	.649	.088
Processing Speed Standard							
Pearson Correlation	−.358**	−.151	−.206	−.391**	−.108	−.178	−.273
Sig. (2-tailed)	.009	.286	.142	.004	.445	.207	.050
Executive Function Standard							
Pearson Correlation	−.367**	−.140	−.134	−.303*	−.171	−.067	−.240
Sig. (2-tailed)	.008	.322	.344	.029	.227	.636	.087

* Correlation is significant at the .05 level (2-tailed).
** Correlation is significant at the .01 level (2-tailed).

Of the patients with BD-1, when using 2 or more scores below the 5th percentile as a cutoff for neurocognitive impairment (i.e. NCI Standard score of <76), 30% of the patient group with history of 1 manic episode, 42.3% of the patient group with history of 2–5 manic episodes and 62.5% of the patient group with more than 5 manic episodes scored in this range.

5. Discussion

This study found that the cognitive performance of Chinese subjects in remission from Bipolar 1 Disorder (BD-1) differed from that of the matched controls. This is one of the very few neurocognitive studies that have estimated how many percentages of patients with BD-1 versus the healthy control have clinically significant cognitive impairment (see Table 4). When comparing with the first neurocognitive study using CNSVS in Bipolar Disorder in Canada (Iverson et al., 2009), this study used a gold standard diagnostic criteria with stringent inclusion, exclusion criteria and prospectively well-defined euthymic state. The sample consisted of a homogenous group of patients with euthymic BD-1, without other comorbidities such as substance misuse, alcohol and other significant medical problems. Furthermore, after controlling for IQ, BD-1 patients performed significantly worse than matched controls on all cognitive measures, and that difference was associated with both the number of manic episodes and duration of illness.

Characterization of the neuropsychological profile in BD-1 has proved challenging for a number of reasons. Firstly, several domains of cognitive function are disrupted including attention, executive function, emotional processing and memory (Clark and Goodwin, 2008). Secondly, a wide range of clinical factors, including medication (Clark and Goodwin, 2008), chronicity of the illness itself (Robinson and Ferrier, 2006), mood state (Martinez-Aran et al., 2004b) and the presence of comorbid conditions such as alcohol and substance misuse might impact on cognitive function in BD. However, the present study controlled for the potentially confounding effects of both mood state and presence of substance misuse.

The results of this study are consistent with many of the empirical neurocognitive studies included in 3 meta-analytic reviews in euthymic Bipolar Disorder (Robinson et al., 2006; Arts et al., 2008; Torres et al., 2007). The effect sizes of the cognitive measures in this study were either similar (e.g. Verbal Memory, Visual Memory, Processing Speed and Psychomotor Speed; Cohen's $d=.62$–1.41) or even greater (e.g. Complex Attention, Cognitive Flexibility and Executive Function; Cohen's $d=1.55$–1.92) than the effects sizes in the euthymic BD patients reported on the traditional neuropsychological test measuring similar abilities (Cohen's $d=.5$–1.2). One possible explanation may be related to the fact that the current study focused mainly on the most disabled Bipolar subgroup i.e. BD-1, whereas the previous studies did not all differentiate between the bipolar subtypes. Other possible explanation may be related to variation in the assessment tools, the difference of IQ and years of education between the BD-I patients and the healthy control group. Nevertheless in our study population, Executive Dysfunction (Executive Function, Cognitive Flexibility) remained the most severely impaired in BD-1 patients, followed by deficits in complex attention, processing speed, psychomotor speed, verbal memory and visual memory, which were very consistent with many of the empirical studies mentioned.

It is important to reiterate that memory is hierarchically subserved by multiple cognitive processes that occur earlier in processing, including attention and information processing speed. Hence, memory may not be reliably assessable in patients with attentional problems (Elgamal et al., 2008). Attention is a complex neurocognitive domain with several subcomponents and represents an important area of focus, because intact attentional capacity is essential to all higher cognitive skills. Attention is often disturbed in BD-1 patients. It is quite conceivable that many of the learning and memory problems experienced by patients with Bipolar Disorder may be secondary to these underlying deficits in attention (Elgamal et al., 2008). Moreover, it remains to be established whether much of the memory impairment observed was accounted for by concurrent medication use.

There is some evidence that verbal memory deficits are present in euthymic state in BD-1. It was found that twins of BD-1 patients were also impaired in verbal learning and memory after controlling for other confounding factors, which suggested that deficits in verbal memory may be related to predisposing genetic factors of BPI (Kieseppa et al., 2005). A recent study revealed that among 4 single-nucleotide polymorphisms (SNP) of the Catechol-O-Methyltransferase (COMT) gene tested for association with BD and cognition, a significant association was found between a SNP in the COMT gene and BD-1. There was also a relationship found between COMT rs165599 genotype and a measure of verbal memory, with regard to the prefrontal cortex-based encoding strategy (Burdick et al., 2007).

This study showed that cognitive deficits were significantly associated with the number of manic episodes and duration of illness in all cognitive measures. However, the correlation between the number of hospitalization and individual cognitive domains was equivocal.

A history of recurrence of manic episodes appears to be correlated with the presence of cognitive deficits (Goldberg and Burdick, 2008; Lopez-Jaramillo et al, 2010). The findings of the current study were consistent with the results of a systematic review (Robinson and Ferrier, 2006) i.e. a greater number of manic episodes was associated with greater deficits in cognitions; age at onset was not associated with cognition. However in this review, the impact of duration of illness was inconsistent with 5 studies reporting significant association with neuropsychological function whilst 6 found no significant association, which was different from the findings of the present study. Interestingly, the review showed that a greater number of depressive episodes were associated with poorer performance in executive function, which was not found in this study. One possible explanation that may account for the difference is that the review did not differentiate between the bipolar subtypes, i.e. patients with Bipolar II Disorder (BD-1I) were also included. Though it resembles a milder form of the BD-1 with regard to the cross-sectional symptom intensity of hypomania, patients with BD-1I often experience a higher episode frequency, especially of depressive episodes (Vieta et al., 1997). The heterogeneity of Bipolar Disorder itself, with the presence of both BD-1 and BD-1I, makes it difficult to make a definitive conclusion (i.e. the greater number of depressive episodes in BD-1I might have

Table 4
Comparison of the percentage of clinically significant neurocognitive impairment from patients with BD-I and healthy controls.

Two or more scores below 5th percentile	BD-I (%)	Healthy control (%)
Neurocognition (NCI)	46.2	0
Verbal Memory Standard	28.8	5.8
Visual Memory Standard	11.5	3.8
Composite Memory Standard	30.8	5.8
Psychomotor Speed standard	30.8	1.9
Reaction Time Standard	44.2	13.5
Complex Attention Standard	51.9	1.9
Processing Speed Standard	26.9	0
Executive Function Standard	53.8	0

significant correlations with the cognitive deficits in the empirical studies in the review).

6. Limitations

There are some limitations of the present study. The causal relationship between the cognitive performance and its associated illness variables could not be definitively concluded due to the cross-sectional design. The effects of hypomanic episodes or mixed state were not included due to its absence in BD-1 patients.

The study included a high functioning control group which is a limitation to the study. Future studies should include a control group that is matched on IQ and years of education.

The WAIS Manual states that the average time required to carry out a full-scale assessment is 60–90 min. Patients with BD may take even longer to complete the tests. This long assessment time may lead to fatigue and decreased motivation for patient, therefore abbreviated versions of IQ tests using a 3-subtest short form (Similarities, Digit Span and Arithmetic) of the Chinese version of WAIS-R (Gong, 1992) were used. Though this is an IQ estimate widely used in local Chinese studies (Lui et al., 2011a, 2011b) due to its convenience, a full-scale IQ assessment was not done due to resource limitation.

The effect of psychotropic medication on cognitive performance will require further investigation. The use and reporting of medications varied between patients and it was very difficult to control for the potentially negative effect of medication on neurocognitive function. Around half of the BD patients were on combination therapy and the remaining sample was too small for a detailed analysis of the cognitive effects of the medication.

The cognitive effects of the medication used in BD may potentially go in either direction, even with the same drug. For example, lithium and divalproex at higher doses can interfere with some cognitive functions, while their neuroprotective effects against mood episodes might well be expected to translate into some positive cognitive effects over time. It is still unknown as how to reconcile the adverse cognitive effects of agents such as mood stabilizers with their neuroprotective effects. Variations in dosage and polypharmacy regimens pose further challenges. Future studies should aim at differentiating medication from illness-induced cognitive dysfunction, which will require comprehensive assessment with an appreciation for the cognitive domains mostly affected by specific medication. In our study, a convenience sampling method may have restricted the representativeness of the sample. A multi-centre approach together with a randomization involving all BD outpatients would have increased the representativeness of the study.

6.1. Clinical implications

The patients in this study obtained significantly lower domain scores across the entire battery compared to healthy adults. As seen in clinical practice and recent meta-analytic reviews, BD-1 patients have frank cognitive impairment. The present study confirmed that Chinese remitted BD-1 patients demonstrate significant cognitive deficits in memory, executive function, attention, processing speed and psychomotor speed, which may be independent of language and culture. These measured cognitive deficits reflect underlying brain impairment. Despite the possibility that variables such as medication status may have some impact on cognitive function, the demonstrated cognitive deficits in this study were consistent with many of the empirical bipolar studies in 3 recent meta-analyses (Robinson et al., 2006; Arts et al., 2008; Torres et al., 2007). Medication effects alone are not likely to fully account for the deficits described in these patients.

Understanding the psychosocial, functional, adaptive and real-life implications of these cognitive impairments have lagged empirical findings for several reasons. Firstly, these neuropsychological tests have been validated primarily to identify brain dysfunction rather than to predict the "real world" functioning. Secondly, there are many potential aspects of functioning that constitute psychosocial and functional outcome. Thirdly, an understanding of associations between cognitive deficits and functional outcome requires measurement at both levels, which makes research in this area more difficult as most studies looked exclusively at cognitive deficits associated with the disorder.

Results from this study may thus be particularly useful to help anticipate or predict functional limitations in newly diagnosed Chinese patients with BD-1. The time of initial illness onset typically occurs during a period in life when patients are heavily engaged in academic, early occupational, interpersonal and social roles that have the potential to be diminished by cognitive impairment (Torres et al., 2008). Detection of the neuropsychological profile at this important life stage can facilitate the identification and isolation of specific cognitive targets for treatment via medical, psychological, or rehabilitative and compensational treatments. Neuropsychological assessment at this time may also provide useful baseline cognitive data that can serve as a basis to compare future changes in cognitive status that may result from intervening treatments, illness progression and comorbidity variables.

Recovered BD-1 patients have persistent deficits in cognitive function, which might result in failure to reach optimal levels of psychosocial functioning, medication adherence and the ability to benefit from psychoeducation effectively. One example is executive function, which is a prerequisite for the capacity to understand and consent to treatment, whether routine or experimental. Poor adherence to treatment, which characterizes more than half of all bipolar patients and is probably the largest single factor contributing to poor response, in some cases derives from cognitive dysfunction, that is poor insight into the illness and failure to remember or appreciate the consequence of not treating it (Torres et al., 2008). These problems also point to other factors that are likely to mediate functional recovery, including the ability to plan and think clearly, exercise reasonable judgment, solve problems with novelty and creativity, remember important information, recognize alternative points of view, and appreciate the ramification of decisions made in everyday life.

Finally, each manic episode is likely not biologically benign. Thus early diagnosis and treatment of BD-1 is important to reduce possible cognitive problems and associated co-morbidities of these patients.

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Conflict of interest
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