Are there differences in pattern and magnitude of cognitive deficits between euthymic patients with bipolar I and bipolar II disorder?

Tarek Okasha[a], Marwa Elmissiry[a], Walaa Sabry[a], Reem Elghamry[a], Ahmed Elmissiry[a], Karim Ghazi[b] and Mostafa Kamel[a]

[a]Institute of Psychiatry, Faculty of Medicine, Ain Shams University, Cairo, Egypt and [b]Department of Psychiatry, College of Medicine and Health Science, United Arab of Emirates

Correspondence to Walaa Sabry, MD, Department of Psychiatry, Ain Shams University Hospitals, Dair Al-Malak, 11657 Cairo, Egypt
Tel: +20 121 236 6116/+20 127 847 7746; fax: +02 022 683 6379/+02 022 267 8032; e-mail: sabrywalaa@yahoo.com

Received 22 September 2015
Accepted 9 November 2015

Middle East Current Psychiatry
2016, 23:10–19

Background
Recent preliminarily evidence suggests that types and severity of cognitive dysfunctions may differ between bipolar disorder I and II (BD-I and BD-II). However, available data are scarce and inconsistent.

Aim
We aimed to investigate the differences in cognitive deficits between BD-I and BD-II patients.

Patients and methods
The study included 60 euthymic patients with BD (30 BD-I and 30 BD-II) from a large ongoing project on Egyptian patients with BD; they were compared on the basis of their neuropsychological variables (e.g. executive function, attention, verbal, and visual memory) and compared with 30 healthy controls on cognitive performance. They were subjected to full neuropsychological battery.

Results
Compared with the healthy controls, patients with BD-I and BD-II showed significant impairment in the majority of cognitive tasks including working memory (digit span backwards, $P=0.000$), verbal memory (verbal paired association I and II, $P=0.000$), sustained attention (total errors of omission, $P=0.028$), and overall executive functions (categories completed, $P=0.000$). Post-hoc analysis showed the patients with BD-II having an intermediate level of performance in cognitive functions, between patients with type I disorder and healthy participants, and almost preserved executive functions compared with BD-I patients.

Conclusion
This study showed differences in severity and pattern of cognitive deficits between BD subtypes, and so the difference is not merely quantitative as confirmed by most of the previous studies. However, there were also qualitative differences in the pattern of executive function deficits, being more extensive in BD-I, which may indicate different biological or genetic etiology between the two BD subgroups. Future researches are needed to support this hypothesis.

Keywords:
bipolar I disorder, bipolar II disorder, cognitive functions, executive functions, memory

Middle East Curr Psychiatry 23:10–19

2090-5408

Introduction

There is growing body of research evidence that several cognitive domains are impaired during the acute phases of bipolar disorder (BD) illness [1–3]. These cognitive impairments persist even during the euthymic periods [4–6] and they are highly observed in attention, verbal learning, working memory, and executive function [7,8]. It was suggested that these cognitive impairments are one of the main reasons for the lag between syndromal recovery and functional recovery of BD patients, which may lead to the loss of productivity, greater healthcare costs, and an increased economic burden of the illness [9,10].

Profile of cognitive impairment in BD patients has a significant therapeutic implication, and could act as a nucleus for the future of treatment researches. It might aid in the development of new pharmacological agents with neuroprotective effects, which would improve cognition in BD [11]. Moreover, it could help to modify the psychotherapy strategies to be more effective for those patients, by recognition of neurocognitive deficits and fostering compensatory strategies [12–14].

Cognitive dysfunctions in BD-I have been widely investigated in a large number of studies [15–18]. In contrast, similar studies in BD-II are scarce and have revealed inconsistent results [19,20]. Investigations on cognitive functions to differentiate between BD subtypes yielded conflicting results. Some studies revealed no difference between these subtypes in terms of severity

and type of cognitive impairments [21,22]. Other results showed patients with BD-II outperforming those with BD-I in different domains of cognitive functions, but their cognitive performance was still lower than that of healthy controls [23–25]. These results left mental health professionals with a great challenge of whether cognitive dysfunction is a general trait across BD subtypes or differs between type I and II.

The difference between BD subtypes in cognitive functions is becoming a major area of interest for mental health professionals, not only for its therapeutic implications but also for its clinical and etiological implications. This will support further understanding of different pathophysiological aspects of BD [22] and whether the two BD subtypes could be viewed as qualitatively different entities with different underlying pathophysiology and outcome [26] or whether they represent varying degrees of disease severity on a same continuum [25].

Taking into consideration the paucity and inconsistency of available data regarding the differences in cognitive functions between BD subtypes, and on the basis of the previous findings that BD-II could not only be conceptualized as a milder form of BD-I [23], we aimed to investigate whether patients with BD-I and BD-II were having different cognitive profiles in terms of pattern and severity of impairments. We studied these questions in a sample of euthymic BD patients and matched healthy controls.

Patients and methods

Site of the study

This was a cross-sectional, case–control study; the patients were recruited from the Outpatient Clinics of the Institute of Psychiatry, Ain Shams University, Egypt. It is located in eastern Cairo, serving a catchment area of eastern greater Cairo together with the nearby provinces.

The study was conducted in compliance with the Helsinki Declaration for Medical Research of 1975 and in accordance with the guidelines of the Research and Ethics Committee of Ain Shams University. It was stated that the participation in the study is voluntary and does not imply a direct benefit to the patients and have no impact on the drug regimen. Participants had the freedom to withdraw at any time without justification. A printed consent was signed by each participant. The research protocol was approved by the Research and Ethics Committee of Ain Shams University.

Participants in the study

Patients group

A total of 60 euthymic BD patients (30 patients were diagnosed with BD-I and the remaining 30 patients were diagnosed with BD-II) were included in the study. All participants were part of a larger research project on Egyptian BD patients. The methodology has previously been outlined in detail [2,6,20,27]. They were recruited over a 2-year period, their age range was between 18 and 45 years, and both sexes were included. They had to fulfill the inclusion criteria of being literate and in the euthymic phase of BD-I or BD-II. Exclusion criteria were as follows: extreme age ranges, illiteracy, active BD symptoms, comorbid medical and psychiatric disorders, antecedent or current history of substance abuse, head trauma with lost consciousness, recent treatment with electroconvulsive therapy within the past 6 months, and uncontrolled medical or neurological conditions that could affect the cognitive performance.

For diagnosis of the euthymic state of BD, we used an operational definition, which required that the patient should fulfill the *Diagnostic and statistical manual of mental disorders*, 4th ed., text revision, criteria for BD-I or BD-II, and report being in remission/baseline mood in the past 6 months, with a score of less than 7 on the Hamilton Rating Scale for Depression and less than 7 on the Young Mania Rating Scale [28]. All patients were receiving psychotropic medication; we did not study the impact of drugs on cognitive functions depending on the earlier studies that suggested that pharmacological treatment did not exhibit any significant association with neurocognitive impairment [29,30].

Control group

For the purpose of comparison, we recruited 30 Egyptian male and female healthy individuals. They were recruited among volunteer students, employees, and the workers of Ain Shams University. Exclusion criteria for the control group included: (i) any current or past history of psychiatric illness as confirmed by the General Health Questionnaire [31]; (ii) any current or past medical or neurological disorder; (iii) family history of psychiatric illness in their first-degree relatives; and (iv) current treatment with any psychotropic medications. They were matched with the case group for age, sex, educational level, and other demographic variables as much as possible.

Clinical assessment for the patient group

We used the following tools for clinical evaluation:

The Structured Clinical Interview for DSM-IV-TR Axis I disorder, clinician version [32]

A semistructured diagnostic interview was conducted on the basis of an efficient and thorough clinical evaluation. It was used to confirm the diagnosis of BD, to determine its type, and exclude other Axis I comorbid psychiatric conditions. We used the clinical version for relatively easier administration in clinical setting.

Hamilton Rating Scale for Depression [33]

This is a 21-item rating scale for assessing the severity of depressive symptoms. It is the most commonly used observer-rated depressive symptom rating scale. In this study, it was used to validate the euthymic state (score < 7) of the patient group.

Young Mania Rating Scale [34]

We used the clinician-rated questionnaire that assesses the severity of manic symptoms. It was used in this study

to validate that the patients were in the euthymic phase of BD (score < 7).

A designed questionnaire was used to gather data about the patients' sex, age, years of education, occupation, diagnosis, previous hospitalization, number of episodes, duration of illness (in years), and family history.

Clinical assessment for the control group

The General Health Questionnaire [31]

We used it for the control group as a screening instrument for psychiatric illness to confirm the absence of past or current psychiatric history. The version used in this study was the Arabic version of a short 28-items scale with the sample scorer method, which is 0–0–1–1. The cut-off point of General Health Questionnaire was 7 according to similar previous national studies to minimize the associated fallacies with the original low threshold score [35].

Neurocognitive assessment

Patients and healthy controls underwent a neurocognitive battery.

Intelligence and general intellectual function were assessed by using Wechsler Adult Intelligence Scale (WAIS) [36], which consists of 11 separate subtests broken into the verbal scale (six subtests) and the performance scale (five subtests). A person taking the test receives a full-scale IQ score, a verbal IQ score, a performance IQ score, as well as scaled scores on each of the subtests. We used the Arabic translated and validated form with Egyptian norms as a reference [37].

Memory functions were assessed by using Wechsler Memory Scale-Revised (WMS-R) [38], which is most widely used instruments to assess memory functions in adults; the scores reflect general, verbal, and visual memory, attention/concentration, and delayed recall.

Sustained attention was assessed by using Continuous Performance Test (CPT) [39]; it was used to assess lapses in attention or vigilance and impulsivity. The scores reflect the total number of stimuli, the number of correct targets, omission errors (the number of targets the person did not respond to), commission errors (the number of times the person responded to a nontarget), and various reaction times.

Executive functions by using Wisconsin Card Sorting Test (the computerized version) (WCST) [40], which is used to assess abstraction ability and the ability to shift cognitive strategies in response to changing environmental contingencies and as a measure of frontal lobe executive function; it also provides information on several aspects of problem-solving ability and strategic planning. All neuropsychological tests were conducted by experienced senior clinical psychologists with proper working experience in the use of those tools.

Statistical analysis

Data were recorded and analyzed using the statistical package of the social sciences (SPSS, 17th version, 2009; SPSS Inc., Chicago, Illinois, USA). The results were tabulated, grouped, and statistically analyzed using the following tests: mean (X), SD for quantitative data, and frequency with percentage for qualitative data. The Kolmogorov–Smirnov test was used to study the normality of data distribution. The independent-samples t-test was used for comparison of continuous variables. Group differences between the BD-I, BD-II, and control samples were tested using one-way analysis of variance (ANOVA), followed by Tukey's post-hoc comparison procedure when significant main effects were present. A statistical level of significance was set at 0.05.

Results

The clinical features of patients with both types BD are shown in Table 1; data indicate that there was no statistical significant difference between BD-I and BD-I patients with regard the age of onset of BD illness, being in the early 20s ($P = 0.462$). BD-I patients had significantly longer duration of illness than did BD-II patients (7.83 ± 4.41 vs. 2.52 ± 1.92; $P = 0.000$); they also suffered from higher number of episodes (5.73 ± 2.62 in BD-I vs. 2.5 ± 0.5 in BD-II; $P = 0.000$).

It was noticed that both groups experienced almost similar mean number of depressive episodes and almost similar average duration of episodes. However, BD-I patients had experienced more frequent psychotic symptoms in the last episode (13 vs. 4%) and had been more frequently hospitalized than were their BD-II counterparts (9 vs. 2.5%). BD-I patients had higher rates of family history of psychiatric disorders (33.3%) when compared with BD-II patients (16.7%). Table 2 revealed that the mean age of the participants in the control group was not statistically significantly different from the mean age of the patients in either the BD-I group ($P = 0.058$) or the BD-II group ($P = 0.65$).

Meanwhile, BD-I patients were found to be significantly older (28.67 ± 7.24) ($P = 0.026$) than BD-II patients (25.37 ± 2.83).

The number of years of education was comparable across groups, as shown in Table 2. Data of post-hoc analysis revealed that BD-II patients had significantly received more years of education than had their BD-I counterparts (14.67 ± 2.24 vs. 10.97 ± 2.94 years; $P = 0.000$); however, there was no significant difference when BD-II patients were compared with healthy controls ($P = 0.254$). The mean years of education received were significantly higher in the control group versus the BD-I group (13.93 and 10.97 years, respectively; $P = 0.000$).

Assessment of neurocognitive function is detailed under the following headings:

Assessment of general intellectual abilities

Overall, on ANOVA test, BD patients performed significantly worse than did controls on all domains of the WAIS, where the control group had a statistically higher

Table 1 Clinical characteristics: bipolar I versus bipolar II patients

	Bipolar I ($n=30$) (mean±SD)	Bipolar II ($n=30$) (mean±SD)	Test (t)	P value
Age of onset	20.83±6.83	21.82±2.44	−0.74	0.462
Average duration of illness in years	7.83±4.41	3.52±1.92	4.91	0.000**
Total number of episodes	5.73±2.62	2.5±0.5	6.69	0.000**
Number of depressive episodes	1.6±1.75	1.5±0.51	0.3	0.766
Average duration of episode in months	1.97±1.29	1.93±0.93	0.14	0.887

**Very high statistical significance.

Table 2 General intellectual abilities among the studied groups

	Mean±SD					Post-hoc test		
	Bipolar I ($n=30$)	Bipolar II ($n=30$)	Healthy controls ($n=30$)	ANOVA test (f)	P value	BD-I vs. BD-II	BD-I vs. control	BD-II vs. control
Age (years)	28.67±7.24	25.37±2.83	25.77±3.87	3.87	0.025*	0.026*	0.058	0.650
Years of education	10.97±2.94	14.67±2.24	13.93±2.66	16.60	0.000**	0.000**	0.000**	0.254
Wechsler Adult Intelligence Scale								
Verbal IQ	93.57±7.44	103.00±7.31	110.67±11.39	27.69	0.000**	0.000	0.000**	0.003**
Performance IQ	94.87±5.79	99.60±8.25	114.07±13.29	32.36	0.000**	0.013	0.000**	0.000**
Total IQ	93.43±6.35	101.20±5.40	112.53±11.47	41.28	0.000**	0.000	0.000**	0.000**
Comprehension	11.47±1.96	12.40±1.52	13.53±1.43	11.74	0.000**	0.044	0.000**	0.004**
Digit span	6.90±1.61	9.20±1.50	9.87±2.70	18.02	0.000**	0.000	0.000**	0.243
Arithmetic	7.33±2.34	10.00±2.49	10.93±1.55	22.29	0.000**	0.000	0.000**	0.088
Similarities	8.83±2.38	10.40±1.77	12.40±1.52	25.86	0.000**	0.005	0.000**	0.000**
Picture completion	9.70±1.39	9.43±1.50	11.67±1.73	18.64	0.000**	0.479	0.000**	0.000**
Block design	7.37±2.01	7.80±1.19	9.93±2.27	16.02	0.000**	0.313	0.000**	0.000**
Digit symbol	9.90±2.02	13.00±1.93	14.20±2.63	30.06	0.000**	0.000	0.000**	0.049*

*High statistical significance.
**Very high statistical significance.

mean scores than had both BD-I and BD-II patients as shown in Table 2.

Post-hoc analysis revealed significant poor performance of BD-I patients than that of healthy controls on all the subscales of WAIS. Similarly, BD-II patients showed poorer performance in all items of WAIS compared with the control group, except for the scores on arithmetic ($P=0.088$) and digit span subscales ($P=0.243$) (which measure the auditory attention and short-term retention capacity), indicating that those functions are spared in BD-II patients. In contrast, BD-I patients scored significantly worse than did BD-II patients for those items ($P=0.000$ on both subtests).

Comparing BD-I and BD-II patients revealed a better significant performance on comprehension subtest in patients with BD-II ($P=0.044$) compared with BD-I patients; however, their scores were still inferior to that of the controls ($P=0.004$). This subtest was used to detect the ability of using abstract concepts, social common sense, and organization of information.

Similarly, on digit symbol subtest, which measures immediate memory and visuomotor coordination, and on similarities subtest, which measures abstract thinking, our results found that BD-II patients scored significantly better than did BD-I patients ($P=0.000$ and 0.005, respectively).

Both patient groups had similar worse performance on block design and picture completion subscales, denoting that they had similar impairment in visuomotor ability and visual perception ($P=0.131$ and 0.497, respectively), whereas their scores on both subtests were significantly lower than that of the control group ($P=0.000$). All data are illustrated in Table 2.

In general, BD-II patients had more or less a similar pattern of impairment as that of BD-I, but BD-II patients' scores in most of the general intellectual functions were found to be intermediate between those of healthy controls and BD-I patients.

Assessment of memory functions

Verbal and visual memory functions were measured by the WMS-R. Results are shown in Table 3, and revealed significant higher scores obtained by those in the control group than by BD-I and BD-II patients in most of WMS-R subtests by using ANOVA; however, they were indistinguishable from BD-II patients in items of information orientation and verbal paired association.

Comparing BD-I and BD-II patients by using post-hoc analysis revealed that BD-I patients did show an overall tendency toward more impairment in items of digit span backward (which is a measure of working memory), digit span forward, visual memory span backward, and verbal paired association I and II (which are measures of verbal memory). In contrast, BD-II patients performed as poorer as did BD-I patients in the measures of visual memory span ($P=0.07$) and visual paired association I and II ($P=0.265$ and 0.423).

It is evident from Table 3 that almost the same pattern of memory impairments were detected in both BD-I and BD-II patients on all WMS-R test items, but were less pervasive in the latter group.

Table 3 Memory functions among the studied groups using Wechsler Memory Scale-Revised

	Mean ± SD					Post-hoc test		
Wechsler memory scale	Bipolar I ($n=30$)	Bipolar II ($n=30$)	Healthy controls ($n=30$)	Test (f)	P value	BD-I vs. BD-II	BD-I vs. control	BD-II vs. control
Information and orientation	12.83 ± 2.41	14.00 ± 0.00	14.00 ± 0.00	7.04	0.001**	0.013	0.013	–
Digit span backwards	4.07 ± 1.55	5.80 ± 0.41	8.93 ± 1.79	94.23	0.000**	0.000**	0.000**	0.000**
Digit span forwards	5.67 ± 1.58	8.00 ± 1.29	9.87 ± 1.28	86.74	0.000**	0.000**	0.000**	0.000**
Visual memory span backwards	4.23 ± 1.81	5.60 ± 0.81	7.20 ± 1.49	32.08	0.000**	0.001**	0.000**	0.000**
Visual memory span forwards	6.40 ± 2.04	7.20 ± 1.19	8.20 ± 1.24	10.26	0.000**	0.071	0.000**	0.002**
Visual paired association I	6.70 ± 3.10	8.00 ± 5.50	14.13 ± 2.51	30.75	0.000**	0.265	0.000**	0.000**
Visual paired association II	3.23 ± 1.07	3.50 ± 1.46	5.93 ± 0.25	59.73	0.000**	0.423	0.000**	0.000**
Verbal paired association I	9.57 ± 4.78	15.60 ± 4.75	15.07 ± 2.84	18.76	0.000**	0.000**	0.000**	0.600
Verbal paired association II	4.33 ± 1.54	6.27 ± 1.68	7.53 ± 0.63	41.84	0.000**	0.000**	0.000**	0.000**

*High statistical significance.
**Very high statistical significance.

Assessment of sustained attention

Data shown in Table 4 clarify that the healthy control group had statistically significantly fewer total commission and total omissions errors than had both groups of BD patients. Scores of BD-II patients in median and average delay were not statistically different from those of the control group ($P = 0.23$ and 0.516, respectively); however, they were dissimilar from the scores obtained by BD-I patients, denoting that those function were impaired only in BD-I patients ($P = 0.001$ and 0.004, respectively). Data showed that BD-I patients had more deficits in sustained attention than had BD-II patients as evidenced by more total commission ($P = 0.03$), reflecting that BD-II patients performed better in tests measuring sustained attention than did their BD-I counterparts.

Executive functions

Executive functions were measured using the WCST. As illustrated in Table 5, healthy participants obtained significant better scores on almost all items of tests measuring executive functions.

In comparison with the healthy control group, patients with BD-II displayed a significantly lower number of completed categories ($P = 0.012$), which reflects having lower overall executive performance than that of the healthy control group; they also scored significantly higher in failures to maintain set item ($P = 0.008$), denoting inability to continue using successful strategies.

However, they showed no significant differences compared with the healthy control group on other items of WCST (percentage of errors, percentage of preservative errors, percentage of conceptual level response), which mean that the initial concept formation, concentration ability, cognitive flexibility, abstraction, and problem-solving were almost preserved in patients with BD-II and that the cognitive errors start to become more evident with sustained mental activities, affecting the overall cognitive performance reflected in the significantly lower number of completed categories.

Patients with BD-I displayed a highly significantly impaired executive functions than did healthy controls, as is shown in their scores in most of the WCST subtests. On comparing the scores of patients with BD-II and patients with BD-I using post-hoc analysis, we found that BD-I patients got significant higher percentage of errors ($P = 0.026$), significant higher percentage of preservative errors ($P = 0.018$), and significantly lower percentage of conceptual level responses ($P = 0.016$), which denote that BD-I patients showed more impairment in concentration abilities, abstraction, problem-solving abilities, and cognitive flexibility than did BD-II patients.

In summary, compared with the control group, patients with BD-II scored significantly worse in most of the neurocognitive tasks; however, they could not be distinguished from controls in auditory attention, short-term retention capacity (WAIS), information, orientation, verbal paired association (WMS-R1), median and average delay (CPT), and most of the executive functions, whereas BD-I patients were more severely impaired as they scored significantly worse on the majority of the neurocognitive battery.

Comparison between neurocognitive performance in patients with both BD subtypes revealed that BD-II patients were significantly better in all measures; however, they scored as worse as did BD-I patients in visuomotor ability, visual perception (WAIS), visual memory functions (WMS-R), total omission (CPT), and nonpreservative errors, categories completed, failure to maintain set, and learning to learn.

Discussion

Several studies have illustrated that cognitive deficits in the asymptomatic phase of the illness may contribute to persistent psychosocial difficulties and may prevent patients from attaining optimal adaptation in their lives [41]; cognitive deficits are one of the main reasons behind poor outcome [42]. A plethora of studies have primarily focused only on BD-I [43,44] and not BD-II, because BD-II is often underdiagnosed or misdiagnosed [45]. In addition, boundaries for clinical distinction between BD-II and BD-I are not so clear-cut [46].

It is still largely not understood whether or not BD-I patients perform differently from BD-II patients on

Table 4 Sustained attention among studied groups using Continuous Performance Test

	Mean ± SD					Post-hoc test		
Continuous Performance Test	Bipolar I (*n*=30)	Bipolar II (*n*=30)	Healthy controls (*n*=30)	Test (*f*)	*P* value	BD-I vs. BD-II	BD-I vs. control	BD-II vs. control
Total commissions	11.27±8.99	6.80±6.32	4.20±0.99	9.45	0.000**	0.030*	0.000**	0.033*
Total omissions	1 0.63±10.59	9.80±13.45	4.20±1.63	3.72	0.028*	0.791	0.003**	0.031*
Median delay	517.49±77.45	606.78±122.62	570.23±111.85	5.41	0.006**	0.001**	0.039*	0.233
Average delay	513.94±70.52	576.80±90.51	561.83±95.73	4.31	0.016*	0.004**	0.034*	0.516

*High statistical significance.
**Very high statistical significance.

Table 5 Executive functions among the studied group using Wisconsin Card Sorting Test

	Mean ± SD					Post-hoc test		
Wisconsin Card Sorting Test	Bipolar I (*n*=30)	Bipolar II (*n*=30)	Healthy controls (*n*=30)	Test (*f*)	*P* value	BD-I vs. BD-II	BD-I vs. control	BD-II vs. control
% Error	35.47±15.87	25.60±17.48	19.27±5.37	10.24	0.000	0.026**	0.000**	0.066
% Perseverative response	24.63±18.58	13.90±11.39	12.93±15.48	7.52	0.001	0.010**	0.002**	0.677
% Perseverative error	20.67±14.18	13.00±9.79	10.87±3.21	7.78	0.001	0.018**	0.001**	0.264
% Nonperseverative error	14.87±8.97	12.70±7.85	9.67±4.13	3.86	0.025	0.324	0.006**	0.068
% Conceptual level response	55.43±19.84	68.90±22.32	75.27±6.09	9.93	0.000**	0.016*	0.000**	0.141
Categories completed	4.40±1.79	5.20±1.63	6.00±0.00	9.83	0.000**	0.076	0.000**	0.012*
Number of trials to complete 1 category	14.87±5.74	12.90±2.20	14.74±5.80	1.36	0.262	0.088	0.789	0.172
Failure to maintain set	1.47±1.22	1.50±2.46	0.20±1.71	6.29	0.003**	0.947	0.000**	0.008**
Learning to learn	−9.18±13.03	−4.87±10.67	0.77±1.51	7.84	0.001**	0.167	0.000**	0.007**

*High statistical significance.
**Very high statistical significance.

measures assessing neurocognitive functions [19,21]. Studies in this field may offer the potential to explore objective markers to help delineating boundaries across the two types of BD.

The current study aimed at investigating whether the cognitive profile in BD-II patients is different in terms of pattern and severity from that of BD-I patients in comparison with healthy controls.

In agreement with previous studies, we reported that BD-II patients had significantly shorter illness duration and experience fewer number of episodes [46,47]. Several studies, including our research, have reported that BD-I patients had worse clinical course, more often experienced multiple episodes, and had a history of more frequent previous hospitalization and psychotic symptoms, which reflect that BD-I is more severe than BD-II [23,26,30,48].

In contrast to the previous literature [49–51], which showed that BD-II patients experienced significantly more depressive episodes than did BD-I patients, our results revealed that BD-II patients had similar mean number of depressive episodes as did BD-I patients. The difference in results could be attributed to the fact that in the Egyptian culture, people tend to mask their depressive symptoms with somatic complaints. This may be because of a greater social acceptance of physical complaints than of psychological complaints, which are either not taken seriously or are believed to be cured by rest or praying [52]. This fact resulted in underdiagnosis or misdiagnosis of these depressive episodes.

The current study revealed that BD-I patients were significantly older than the patients with BD-II and healthy controls; our findings were not in agreement with those of a study by Dittmann *et al.* [21], who found that BD-II patients were older than both BD-I patients and healthy controls. However, differences could be attributed to different sampling processes.

Three main issues were evident from the current study. First, the study confirmed previous findings that euthymic BD patients showed impairment in memory functions, sustained attention, and executive functions compared with healthy controls [5,7,8]. Second, nearly similar pattern of cognitive impairments existed for both BD-I and BD-II patients except for measures of executive functions, where BD-I patients showed more widespread impaired executive functions domains than did BD-II patients when both were compared with the control group. Third, there were significant differences between BD-I and BD-II patients in terms of degree and severity of cognitive impairments.

An assessment of general intellectual abilities using WAIS showed that euthymic BD-II patients were less intellectually impaired than were BD-I patients, whereas patients in both groups showed a lower IQ than did controls. Similarly, Simonsen *et al.* [23] found that BD-I patients had significantly lower IQ than that of both BD-II patients and healthy controls. In contrast, Summers *et al.* [53] found that BD-II patients had a significant decline in the IQ than did BD-I patients.

Estimation of intellectual abilities in BD patients persists as a matter of debate. In a systemic review of a number of

studies, it was concluded that there is no detected significant differences in the IQ of BD-I compared with BD-II patients and healthy controls owing to the differences in the tools used for assessment [19].

The interpretation of our results could be related to the differences in the years of education being longer in both BD-II patients and healthy controls or it could be attributed to a longer duration of illness in BD-I patients, or that there is a genuine causal association of a more severe pathology. In a study by Bora *et al.* [5], it was concluded that IQ deficits in BD patients were likely to reflect a decline in functioning due to the onset of the disease.

Unfortunately, in our study, we could not assess the premorbid IQ because of the unavailability of the Arabic-translated National Adult Reading Test, which would be more accurate in inferring whether this difference was a consequence of BD-I or not [54,55].

In our study, patients with BD exhibited deficits across a range of memory tasks assessed by the WMS-R and digit span subtests of WAIS. Data obtained revealed pronounced deficits in BD-I patients compared with BD-II patients.

Verbal memory assessment includes tasks for both immediate recall and recognition as detected by verbal paired association I and II subtests of WMS-R. Our data revealed impairment in those functions in both euthymic BD-I and BD-II patients; similar findings were reported by Martínez-Arán *et al.* [7] and Depp *et al.* [56]. Our results incorporate the finding from an earlier study by Torrent *et al.* [25], who found a defect in learning and verbal memory in euthymic BD-II patients compared with controls and that BD-I patients showed quantitatively more dysfunctions in verbal memory measures than did BD-II patients.

It is worth mentioning that verbal memory may have a great impact on occupational, social function, and quality of life, and has a negative impact on functional outcome [57].

Data concerning visual memory impairment in euthymic patients with BD are inconsistent. While it was reported that euthymic patients had a lower proportion of correct responses than did healthy controls in measures assessing spatial recognition [58]. In contrast to this finding, Altshuler *et al.* [15] found that visual memory was not impaired in euthymic BD patient.

Our study proved that BD-I patients obtained worse scores in measures of visual memory span backward than did patients with BD-II.

Both BD patient groups were similar in other measures related to visual memory. This is in agreement with the results of a previous study that found that the control group performed significantly better than did both BD groups on measures of visual memory [44].

We assessed working memory by Wechsler digit backward subtest; their number of correctly responded sequences in backward order was used to test the ability to manipulate the information in the verbal working memory. We also utilized WCST in detecting deficits in the working memory. Data obtained from our study reflect that the working memory capacity was impaired in patients with BD and was more pronounced in BD-I patients. Deficits in working memory have been found consistently in euthymic BD patients compared with controls [8], while other investigators reported negative results [59].

The underlying deficit of working memory impairment in patients with BD is unknown [60,61]. This conflicting finding may reflect the different tools of assessment or variable task examined.

Sustained attention: it is a complex neurocognitive domain, which includes arousal, vigilance, orienting, and attentional shifting [62].

The persistent impairment of sustained attention in euthymic patients with BD may represent a possible candidate intermediary phenotype [43] and may represent a trait marker for BD related to vulnerability to the disorder at a structural or/and neurochemical level [63].

In our study, we assessed sustained attention and vigilance by CPT and digit span forward of WAIS, which is used as a measure of focused attention [23].

Both groups of euthymic patients with BD performed worse than did healthy controls; moreover, the group of BD-I patients had significantly worse scores than did BD-II patients, which indicates that BD-I patients exhibit greater deficit in focusing attention and attentional shifting.

Our results are in agreement with those of other investigators who reported that BD-I patients had more impulsive response and fewer targets than did controls [64,65].

Executive function is a broad term that refers to a multiple range of higher level cognitive processes that contribute to strategy development, shift of attention focus, cognitive flexibility, planning, problem solving, decision-making, inhibitory control, and working memory [66].

Executive function is considered to be intrinsically related to integrity of dorsal prefrontal cortex and anterior cingulated gyrus. WCST is thought to assess prefrontal cortex executive functions. Thus, it can provide insight into the underlying neuropathological process [40].

In the current study, executive functions were measured using the WCST. Results showed that BD-II patients performed significantly poorer than did controls only on few domains (categories completed, failure to maintain set, and learning to learn) in comparison with BD-I patients who performed worse than did controls on almost all domains of WCST. This finding denotes that initial executive functions were almost preserved in patients with BD-II and that the cognitive errors start

to become more evident with sustained mental activities that would impair the overall cognitive performance.

In accordance with other studies [8,15,67], our study revealed that patients in the BD-I group were showing a trend toward a higher percentage of errors, perseverative and nonperseverative errors, and conceptual level response than were those in the BD-II patient group. This denotes that BD-I patients have worse planning ability, set shifting cognitive control, impaired strategic thinking, and ability of fixation on a dominant reward response. Our results are supported by those of other studies showing that the BD-I group had significantly reduced performance on most measures of attention and executive functioning, whereas the BD-II group only had a significantly reduced performance on a subset of these measures, and they suggested that there might be a neurobiological difference or different genetic vulnerability between the two BD subgroups [23].

Moreover, Hsiao *et al*. [44] revealed higher degree of impairment in executive functions domains in BD-I patients compared with BD-II patients and controls by using the Trail Making Test part B, which indicates difficulties with set-shifting, but found no significant difference between BD-II patients and controls.

In contrast to our results, Dittmann *et al.* [21] found similar pattern of deficits in executive dysfunction in both subtypes of BD, but the two patient groups did not differ significantly from each other on any domain tested. The possible explanation for this difference in results is that, in their study, they used a different test (semantic fluency subtest of the Repeatable Battery for the Assessment of Neuropsychological status) as a means for measuring executive functioning [21].

In general, the quantitative difference in cognitive functions between BD-I and BD-II could be explained by the fact that BD-II is often conceptualized as a 'milder' form of BD-I. However, the fact that the two groups differ in cognitive pattern, with executive deficits only being prominent in BD-I patients, may reflect underlying neurobiological differences between the two BD groups. Recently, MRI structural scans (under publishing process) from 885 BD-I patients, 329 BD-II patients, and 2613 controls [68] found volume reductions in amygdala, hippocampus, thalamus, and ventricular enlargement in BD-I patients compared with controls. However, BD-II patients showed amygdala, hippocampal, and ventricular volumes in between those of controls and BD-II patients, although not significantly different from the either group. It is this intermediate performance of BD-II patients relative to BD-I patients and controls that we have identified in the attention and memory tasks.

Conclusion

Both types of BDs (I and II) have shown a similar qualitative pattern of cognitive dysfunction including deficits in attention and verbal memory with a slight difference in the pattern of the executive dysfunction. Whereas there was a pronounced magnitude of severity in cognitive dysfunction in BD-I patients compared with their BD-II counterparts, suggesting that BD-I and BD-II are varying degrees of severity of a disease continuum.

Cognitive dysfunctions have been associated with poor functional, psychosocial outcome, and quality of life in BD. Therefore, our data clarify the severe nature and malignant course of BD-II.

Underdiagnosis and misdiagnosis is more of a rule than an exception in BD-II; hence comes the importance of routine cognitive functioning examination equally in patients with either subtype.

The difference in the pattern of executive functions deficits, being more extensive in BD-I, may reflect different biological or genetic etiology between the two BD subgroups. Further studies are needed to support this suggestion.

Strength and limitations

It is one of the few studies that investigated the pattern and severity of cognitive dysfunctions in both subtypes of BD, whereas most of the other studies have either focused exclusively on BD-I or have analyzed mixed patient groups. A particular strength of the present study is the use of meticulous and extensive test battery providing a broad neurocognitive profiling.

However, our study was limited by its cross-sectional design; a longitudinal follow-up might provide more information about the progression of cognitive deficits. It remains unclear whether cognitive dysfunction is a premorbid issue or actually progressive in the course of the illness. A larger sample size would have allowed more analyses and might have shown clearer differences between the groups – for instance, with respect to the executive functions. Other limitation for this study is the difference in the educational attainment of the case group versus the control group. Our study is also limited by the lack of evaluation of the premorbid intellectual abilities because of the unavailability of the proper test in Arabic.

Acknowledgements

This study was made possible by the generous support and valuable contribution of Professor Afaf Hamed Khalil, and Professor Aida Seif Eldawla throughout the work. Also, the researchers are deeply grateful to Dr Suzan El-Kholy, Consultant Neuropsychology, for her support in the interpretation of the results; Abdel Gawad Khalifa, Senior Psychologist, for the performance of the neurocognitive battery; and Dr Mohamed Taha for the statistical analysis. They are also thankful to the research team at the Institute of Psychiatry, Ain Shams University Hospitals, and lastly to all participants who agreed to be enrolled in this research.

Conflicts of interest

There are no conflicts of interest.

References

1 Kurtz MM, Gerraty RT. A meta-analytic investigation of neurocognitive deficits in bipolar illness: profile and effects of clinical state. Neuropsychology 2009; 23:551–562.

2 Okasha TA, El Sheikh MM, El Missiry AA, El Missiry MA, El Serafi D, El Kholy S, Abdel Aziz K. Cognitive functions in euthymic Egyptian patients with bipolar disorder: are they different from healthy controls? J Affect Disord 2014; 166:14–21.

3 Stefanopoulou E, Manoharan A, Landau S, Geddes JR, Goodwin G, Frangou S. Cognitive functioning in patients with affective disorders and schizophrenia: a meta-analysis. Int Rev Psychiatry 2009; 21:336–356.

4 Arts B, Jabben N, Krabbendam L, van Os J. Metaanalyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. Psychol Med 2008; 38:771–785.

5 Bora E, Yucel M, Pantelis C. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. J Affect Disord 2009; 113:1–20.

6 Khalil AH, Eissa AM, Hassan GAM, Abdel Aziz K, Kassem T. Profile of cognitive impairment in euthymic bipolar I patients: relation to clinical characteristics. Middle East Curr Psychiatry 2013; 20:22–29.

7 Martínez-Arán A, Vieta E, Colom F, Torrent C, Sánchez-Moreno J, Reinares M, *et al*. Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. Bipolar Disord 2004; 6:224–232.

8 Thompson JM, Gallagher P, Hughes JH, Watson S, Gray JM, Ferrier IN, Young AH. Neurocognitive impairment in euthymic patients with bipolar affective disorder. Br J Psychiatry 2005; 186:32–40.

9 Martínez-Arán A, Penadés R, Vieta E, Colom F, Reinares M, Benabarre A, *et al*. Executive function in patients with remitted bipolar disorder and schizophrenia and its relationship with functional outcome. Psychother Psychosom 2002; 71:39–46.

10 Zarate CA Jr, Tohen M, Land M, Cavanagh S. Functional impairment and cognition in bipolar disorder. Psychiatr Q 2000; 71:309–329.

11 Kumar C, Frangou S. Clinical implications of cognitive functions in bipolar. Ther Adv Chronic Dis 2010; 1:85–93.

12 Goldberg JF, Burdick KE. *Cognitive dysfunction in bipolar disorder: a guide for clinicians*. Washington, DC: American Psychiatric Press Inc.; 2008.

13 Post RM, Leverich GS. The role of psychosocial stress in the onset and progression of bipolar disorder and its comorbidities: the need for earlier and alternative modes of therapeutic intervention. Dev Psychopathol 2006; 18:1181–1211.

14 Scott J, Paykel E, Morriss R, Bentall R, Kinderman P, Johnson T, *et al*. Cognitive-behavioural therapy for severe and recurrent bipolar disorders: randomised controlled trial. Br J Psychiatry 2006; 188:313–320.

15 Altshuler LL, Ventura J, van Gorp WG, Green MF, Theberge DC, Mintz J. Neurocognitive function in clinically stable men with bipolar I disorder or schizophrenia and normal control subjects. Biol Psychiatry 2004; 56:560–569.

16 Balanzá-Martínez V, Tabarés-Seisdedos R, Selva-Vera G, Martínez-Arán A, Torrent C, Salazar-Fraile J, *et al*. Persistent cognitive dysfunctions in bipolar I disorder and schizophrenic patients: a 3-year follow-up study. Psychother Psychosom 2005; 74:113–119.

17 Donaldson S, Goldstein LH, Landau S, Raymont V, Frangou S. The Maudsley Bipolar Disorder Project: the effect of medication, family history, and duration of illness on IQ and memory in bipolar I disorder. J Clin Psychiatry 2003; 64:86–93.

18 Kravariti E, Dixon T, Frith C, Murray R, McGuire P. Association of symptoms and executive function in schizophrenia and bipolar disorder. Schizophr Res 2005; 74:221–231.

19 Solé B, Martínez-Arán A, Torrent C, Bonnin CM, Reinares M, Popovic D, *et al*. Are bipolar II patients cognitively impaired? A systematic review. Psychol Med 2011; 41:1791–1803.

20 Zaki N, El-Batrawy A, El-Missiry A, Ibrahim D, Abdel-Aziz K. Cognitive functions in euthymic patients with bipolar II disorder and their correlation with the clinical profile. Middle East Curr Psychiatr 2014; 21:139–147.

21 Dittmann S, Hennig-Fast K, Gerber S, Seemüller F, Riedel M, Emanuel Severus W, *et al*. Cognitive functioning in euthymic bipolar I and bipolar II patients. Bipolar Disord 2008; 10:877–887.

22 Pålsson E, Figueras C, Johansson AG, Ekman CJ, Hultman B, Östlind J, Landén M. Neurocognitive function in bipolar disorder: a comparison between bipolar I and II disorder and matched controls. BMC Psychiatry 2013; 13:165.

23 Simonsen C, Sundet K, Vaskinn A, Birkenaes AB, Engh JA, Hansen CF, *et al*. Neurocognitive profiles in bipolar I and bipolar II disorder: differences in pattern and magnitude of dysfunction. Bipolar Disord 2008; 10: 245–255.

24 Sole B, Bonnin CM, Torrent C, Martinez-Aran A, Popovic D, Tabarés-Seisdedos R, Vieta E. Neurocognitive impairment across the bipolar spectrum. CNS Neurosci Ther 2012; 18:194–200.

25 Torrent C, Martínez-Arán A, Daban C, Sánchez-Moreno J, Comes M, Goikolea JM, *et al*. Cognitive impairment in bipolar II disorder. Br J Psychiatry 2006; 189:254–259.

26 Vieta E, Gastó C, Otero A, Nieto E, Vallejo J. Differential features between bipolar I and bipolar II disorder. Compr Psychiatry 1997; 38:98–101.

27 Radwan DN, Okasha T, Elmissiry M, Sadek H, Khalifa A, Abdelaziz K. Cognitive impairment in Egyptian euthymic patients with bipolar I disorder compared with controls. Middle East Curr Psychiatr 2013; 20:197–204.

28 Dias VV, Brissos S, Frey BN, Andreazza AC, Cardoso C, Kapczinski F. Cognitive function and serum levels of brain-derived neurotrophic factor in patients with bipolar disorder. Bipolar Disord 2009; 11:663–671.

29 Bourne C, Aydemir Ö, Balanzá-Martínez V, Bora E, Brissos S, Cavanagh JT, *et al*. Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. Acta Psychiatr Scand 2013; 128:149–162.

30 Sparding T, Silander K, Pålsson E, Östlind J, Sellgren C, Ekman CJ, *et al*. Cognitive functioning in clinically stable patients with bipolar disorder I and II. PLoS One 2015; 10:e0115562.

31 Goldberg W. User's Guide to the General Health Questionnaire. In: John A, Harold A, Michael B, Deborah B, editors. *Handbook of psychiatric measures*. Washington, DC: American Psychiatric Press; 1991. pp. 75–79.

32 First MB, Spitzer RL, Williams W, Gibbon M. *Structured Clinical Interview for DSM-IV-Clinician Version (SCID-CV) (users guide and interview)*. Washington, DC: American Psychiatric Press; 1997.

33 Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56.

34 Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978; 133:429–435.

35 Okasha A, Khalil A, El Fiky MR, Ghanem M, Abdel Hakeem R. Prevalence of depressive disorders in a sample of rural and urban Egyptian communities. Egypt J Psychiatry 1988; 11:167–181.

36 Wechsler D. *Wechsler Adult Intelligence Scale-revised (WAIS-R) Manual*. New York: Psychological Corporation; 1981.

37 Melika LK. *Wechsler Adult Intelligence Scale – Arabic Version*. Cairo: El-Nahda Arabic Library; 1996.

38 Wechsler D. *Wechsler Memory Scale-Revised*. New York: Psychological Corporation; 1987.

39 Conners CK. *Conners' continuous performance test II: computer program for windows technical guide and software manual*. North Tonawanda, New York: Mutli-Health Systems; 2000.

40 Heaton RK, Chelune GJ, Talley JL, Kay GG, Curtiss G. *Computerized Wisconsin Card Sort Task Version 4 (WCST)*. USA: Psychological Assessment Resources Inc.; 2003.

41 Ozdel O, Karadag F, Atesci FC, Oguzhanoglu NK, Cabuk T. Cognitive functions in euthymic patients with bipolar disorder. Ann Saudi Med 2007; 27:273–278.

42 Merikangas KR, Lamers F. The 'true' prevalence of bipolar II disorder. Curr Opin Psychiatry 2012; 25:19–23.

43 Arts B, Jabben N, Krabbendam L, van Os J. A 2-year naturalistic study on cognitive functioning in bipolar disorder. Acta Psychiatr Scand 2011; 123:190–205.

44 Hsiao YL, Wu YS, Wu JYW, Hsu MH, Chen HC, Lee SY, *et al*. Neuropsychological functions in patients with bipolar I and bipolar II disorder. Bipolar Disord 2009; 11:547–554.

45 Paris J. Problems in the boundaries of bipolar disorders. Curr Psychiatry Rep 2014; 16:461.

46 Osher Y, Dobron A, Belmaker RH, Bersudsky Y, Dwolatzky T. Computerized testing of neurocognitive function in euthymic bipolar patients compared to those with mild cognitive impairment and cognitively healthy controls. Psychother Psychosom 2011; 80:298–303.

47 Vieta E, Martines-Arán A. Cognitive functioning in bipolar disorder. Actas Esp Psiquiatr 2008; 36 (Suppl 1):58–60.

48 Yates DB, Dittmann S, Kapczinski F, Trentini CM. Cognitive abilities and clinical variables in bipolar I depressed and euthymic patients and controls. J Psychiatr Res 2011; 45:495–504.

49 Ayuso-Gutiérrez JL, Ramos-Brieva JA. The course of manic-depressive illness. A comparative study of bipolar I and bipolar II patients. J Affect Disord 1982; 4:9–14.

50 Judd LL, Schettler PJ, Akiskal HS, Maser J, Coryell W, Solomon D, *et al*. Long-term symptomatic status of bipolar I vs. bipolar II disorders. Int J Neuropsychopharmacol 2003; 6:127–137.

51 Kupka RW, Altshuler LL, Nolen WA, Suppes T, Luckenbaugh DA, Leverich GS, *et al*. Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder 1. Bipolar Disord 2007; 9:531–535.

52 Okasha A. Focus on psychiatry in Egypt. Br J Psychiatry 2004; 185:266–272.

53 Summers M, Papadopoulou K, Bruno S, Cipolotti L, Ron MA. Bipolar I and bipolar II disorder: cognition and emotion processing. Psychol Med 2006; 36:1799–1809.

54 Andersson S, Barder HE, Hellvin T, Løvdahl H, Malt UF. Neuropsychological and electrophysiological indices of neurocognitive dysfunction in bipolar II disorder. Bipolar Disord 2008; 10:888–899.

55 Savitz JB, van der Merwe L, Stein DJ, Solms M, Ramesar RS. Neuropsychological task performance in bipolar spectrum illness: genetics, alcohol abuse, medication and childhood trauma. Bipolar Disord 2008; 10:479–494.

56 Depp CA, Moore DJ, Sitzer D, Palmer BW, Eyler LT, Roesch S, *et al*. Neurocognitive impairment in middle-aged and older adults with bipolar disorder: comparison to schizophrenia and normal comparison subjects. J Affect Disord 2007; 101:201–209.

57 Carla T, Martínez-Arán A, Daban C, Sánchez-Moreno J, Comes M, Goikolea JM, *et al.* Differences between bipolar I and II patients regarding neurocognitive performance. Ann Gen Psychiatry 2006; 5 (Suppl 1):S232.

58 Rubinsztein JS, Michael A, Paykel ES, Sahakian BJ. Cognitive impairment in remission in bipolar affective disorder. Psychol Med 2000; 30:1025–1036.

59 Harmer CJ, Clark L, Grayson L, Goodwin GM. Sustained attention deficit in bipolar disorder is not a working memory impairment in disguise. Neuropsychologia 2002; 40:1586–1590.

60 Alloy LB, Abramson LY, Walshaw PD, Keyser J, Gerstein RK. A cognitive vulnerability–stress perspective on bipolar spectrum disorders in a normative adolescent brain, cognitive, and emotional development context. Dev Psychopathol 2006; 18:1055–1103.

61 Elgamal S, Sokolowska M, MacQueen G. Memory deficits associated with bipolar disorder. In: Goldberg JF, Burdick KE, editors. *Cognitive dysfunction in bipolar disorder: a guide for clinicians*. Washington, DC: American Psychiatric Publishing, Inc.; 2008. pp. 49–67.

62 Petersen SE, Posner MI. The attention system of the human brain: 20 years after. Annu Rev Neurosci 2012; 35:73–89.

63 Clark L, Iversen SD, Goodwin GM. Sustained attention deficit in bipolar disorder. Br J Psychiatry 2002; 180:313–319.

64 Clark L, Iversen SD, Goodwin GM. A neuropsychological investigation of prefrontal cortex involvement in acute mania. Am J Psychiatry 2001; 158:1605–1611.

65 DelBello MP, Adler CM, Amicone J, Mills NP, Shear PK, Warner J, Strakowski SM. Parametric neurocognitive task design: a pilot study of sustained attention in adolescents with bipolar disorder. J Affect Disord 2004; 82:S79–S88.

66 Stuss DT, Levine B. Adult clinical neuropsychology: lessons from studies of the frontal lobes. Annu Rev Psychol 2002; 53:401–433.

67 Trivedi JK, Dhyani M, Sharma S, Sinha PK, Singh AP, Tandon R. Cognitive functions in euthymic state of bipolar disorder: an Indian study. Cogn Neuropsychiatry 2008; 13:135–147.

68 Hibar DP, Westlye LT, van Erp TGM, Rasmussen J, Leonardo CD, Haukvik UK, *et al.* Robust subcortical volumetric reductions in bipolar disorder: findings from the ENIGMA bipolar disorder working group. Proc Natl Acad Sci USA; 2015 Submitted for publication.