Cognitive impairment in Egyptian euthymic patients with bipolar I disorder compared with controls

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Background
The issue of persistent cognitive deficits in euthymia is of profound importance because of its potential as a trait marker for bipolar disorder. The residual neurocognitive dysfunction in euthymic patients with bipolar disorder raises the possibility of primary cognitive changes that are independent of mood state.

Aim
This study aimed to ascertain whether patients with bipolar I disorder show different pattern and deficits in neuropsychological performance compared with well-matched apparently healthy controls.

Patients and methods
Thirty euthymic bipolar I patients (Hamilton depression score <7 and Young mania scale <7) were recruited from the Institute of Psychiatry; they fulfilled the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. criteria for bipolar I disorder. We compared them with 30 healthy controls for neurocognitive functions. We assessed them using the Wechsler Adult Intelligence Scale (WAIS), the Wechsler Memory Scale (WMS), the Continuous Performance Test (CPT), and the Wisconsin Card Sorting Test (WCST).

Results
Patients with bipolar I scored significantly lower in the total and all subscales of both WAIS and WMS, almost in all domains of the tests than did the controls ($P=0.000$). On the CPT, the control group had statistically significant fewer total commissions ($P=0.000$) and fewer total omissions ($P=0.003$) than did bipolar I patients.
The patient group obtained worse scores compared with the controls in almost all the subtests of WCST.

Conclusion
The present study highlighted that cognitive impairment persists in the euthymic phase of bipolar disorder, which may represent a trait variable independent of mood state.

Keywords:
bipolar, cognition, cognitive impairment, euthymic, Wisconsin Card Sorting Test

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Introduction

Comprehension of the extent of cognitive difficulties in patients with bipolar disorder (BD) is currently a hot focus of research. An accumulating body of evidence research has shed light on the cognitive impairments in patients with BD even during euthymic periods [1].

Study of persistent cognitive deficits in euthymic states of bipolar patients is very important because of the possibility of being a trait rather than a state marker for BD [2]. The residual effects in executive functioning in euthymic patients with BD raise the possibility of primary cognitive changes that are independent of mood state [3].

Cognitive impairment is considered the last roadblock to functional remission in patients with BD [4]. Various clinical researches have addressed the social complication of cognitive impairment and poor job performance [3].

Data have shown that patients with BD show impairments in a wide variety of neuropsychological tasks, including attention, memory, and executive functions [5,6]. Some clinical factors contribute toward cognitive deficits in patients with BD such as the number of episodes and duration of illness [7], chronicity, and treatment non compliance [8].

Previous investigators have also documented that neurocognitive deficits during euthymia seem to be negatively related to poor clinical outcome and recovery [9,10] and were strong predictors of poor quality of life [11].

Hypothesis

We hypothesized that euthymic patients with bipolar I disorder would show an impairment in neurocognitive performance compared with controls.

Aim

This study aimed to ascertain whether patients with bipolar I disorder show different pattern and deficits in neuropsychological performance compared with well-matched apparently healthy controls.

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Patients and methods

We carried out a case–control study. The study protocol was approved by the Ethical Committee of the Faculty of Medicine, Ain Shams University. The study was carried out at the outpatient department of the Institute of Psychiatry, Ain Shams University, which is located in eastern Cairo, serving as a catchment area for eastern and greater Cairo. We enrolled 60 patients in this study, divided into two groups: bipolar I patients' group and control group.

Operational definition

Euthymic patients were patients who fulfilled the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV) criteria for BD I or II, reported being euthymic for the last 6 months, and obtained scores of less than 7 on the Hamilton Rating Scale for Depression (HRSD) and less than 7 on the Young Mania Rating Scale (YMRS) [12].

Patient group

A sample of 30 patients in the euthymic phase of bipolar I disorder who attended the outpatient clinic for follow-up and medication was included in this study. The study included equal numbers of Egyptian male and female patients ranging in age from 18 to 50 years who could read and write, and fulfilled the DSM-IV criteria for bipolar I disorder and our operational definition.

In order to control for confounding effects, those who had comorbid Axis I and Axis II conditions, a history of substance misuse, or had received treatment with ECT in the last 6 months, significant uncontrolled medical or neurological diseases, and patients with learning disability were excluded.

All participants were screened to determine eligibility for participation in the study and potential participants were asked to provide informed consent before enrollment. Screening was performed through an interview form, which examined demographic data, and psychiatric and medical history. On the basis of response, individual participants were approved to continue participation in this study. Patients were recruited over a 6-month period by the researchers. All patients were reinterviewed by a senior professor of psychiatry to reconfirm the diagnosis.

Control group

The control group included 30 Egyptian apparently healthy male and female participants. They were matched as far as possible with the case group for age, sex, and other demographic variables. Controls with a current and a past history of psychiatric and medical illness were excluded. They were recruited from among students, employees, and workers of Ain Shams University.

The tools applied in this study were as follows.

Tools

The sample studied was subjected to the following:

(1) Structured Clinical Interview for DSM-IV [13], to provide coverage of psychiatric diagnosis of bipolar II disorder according to DSM-IV. We used the Arabic version [14].
(2) YMRS [15]: this scale is one of the most frequently utilized rating scales to assess manic symptoms and it is administered by clinicians. The average scores on the YMRS were 13 for minimal severity, 20 for mild, 26 for moderate, and 38 for severe. This scale was used in the current research to ensure that the patient was in symptomatic remission and his/her score was less than 6.
(3) HRSD [16]: the HRSD was designed to measure the severity of depressive symptoms in patients with a primary depressive illness. The following norms were used: very severe >23; severe 19–22; moderate 14–18; mild 8–13; and normal <7.
(4) Wechsler Adult Intelligence Scale (WAIS) [17] was used as an individually administered general intelligence test reflected in both verbal and performance abilities and as a broad assessment of cognitive functions. It consists of 11 separate subtests, which are broken into the verbal scale (six subtests) and the performance scale (five subtests). Each patient received a full-scale intelligence quotient (IQ) score, a verbal IQ score, a performance IQ score, as well as scaled scores on each of the subtests. We used the Arabic standardized version [18].
(5) Wechsler Memory Scale (WMS) [19] was used to assess memory functions; it includes information and orientation questions, eight short-term memory tasks, and four delayed recall trials. Summary scores include the following: General Memory, Verbal Memory, Visual Memory, Attention/Concentration, and Delayed Recall. These indexes reflect disturbances in memory function and also show certain disease-associated patterns of memory impairment.
(6) Continuous Performance Test [20] (CPT) is used as a measure of sustained attention deficits. The CPT requires participants to respond to predesignated targets among stimuli that are presented at a rapid fixed rate.
(7) Wisconsin Card Sorting Test (WCST), the computerized version [21], 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 behavior beyond such basic indices.
(8) Fahmy and El-Sherbini's Social Classification Scale: participants were classified into social class 1, 2, 3, and 4 according to an Egyptian classification developed by Fahmy and El-Sherbini [22]. The classification is based on the following parameters: education of the father, education and work of the mother, income, crowding index, and sanitation.
(9) Information sheet: an information sheet was devised to collect patient data on the following parameters: name, sex, age, years of education, occupation, diagnosis, specifier of diagnosis, previous hospitalization, number of episodes, index episode, number depressive episodes, number of manic episodes, number of mixed episodes, history of psychotic

features, average duration of episode (months), average duration of illness (years), family history, medications received, and physical health status.

Data processing and statistical analysis

All data were recorded and entered into a statistical package on a compatible computer and varied. Analysis was carried out using an SPSS, version 17 (SPSS Inc., Chicago, Illinois, USA). The results were tabulated, grouped, and statistically analyzed using the following tests.

Descriptive statistics (for quantitative data), as we used mean ($\overline{X}$) and ± SD, and frequency with percentage (for qualitative data). The Kolmogorov–Smirnov test was used to study normality of data distribution. The Student *t*-test used to test for significance of an independent variable (to compare between two independent means). χ^2 was used to test the significant of the difference between the frequencies of the different observations (i.e. qualitative data). *P* value used to indicate the level of significance was *P* less than 0.05, *P* less than 0.01 for a highly significant difference, and *P* less than 0.001 for a very highly significant difference.

Results

Demographic data

The demographic characteristics of the euthymic bipolar patients and controls, as shown in Table 1, showed that the mean age of the participants in the control group was not statistically significantly different from the mean age of the patients in the bipolar I group ($P = 0.058$).

The mean years of education received were significantly higher in the control group versus the bipolar I patients' group, being 13.93 and 10.97 years, respectively ($P = 0.000$).

There was no statistically significant difference in the social class between the two groups, with the majority of the patients in the bipolar I group in the low social class (43.3%) and the majority of the participants in the control group in the low middle social class (43.3%) ($P = 0.269$).

Even though there was no statistically significant difference in occupation, the majority of bipolar I patients (almost 75%) were either unemployed (26.7%), manual workers (23.3%), or housewives (23.3%), whereas the majority of controls were either unemployed (26.7%), professionals (26.7%), or housewives (23.3%), perhaps reflecting the difference in the years of education.

There was also no statistically significant difference in marital status between the two groups, as the majority of the patients in the bipolar I group (56.7%) and the participants in the control group (60%) were not married ($P = 0.500$).

Clinical characteristics

All patients were euthymic for at least 6 months at the time of testing; most of them reported histories of predominantly manic episodes (mean number 3.27 episode) with a mean duration of episodes of 1.97 months. They developed their illness at 20.83 years of age, with an average duration of illness of 7.83 years (Table 2).

Performance in neurocognitive functions

Bipolar I patients scored significantly lower on all subscales of the WAIS, and also on the verbal, performance, and total scores ($P = 0.000$) (Table 3). On almost all domains of the WMS, the control group obtained a statistically significantly higher mean score than did bipolar I patients ($P = 0.000$) (Table 4).

On the CPT, the control group had statistically very highly significant fewer total commissions ($P = 0.000$) and fewer total omissions ($P = 0.003$) than did bipolar I patients. The control group had statistically significantly longer median delay ($P = 0.039$) and average delay ($P = 0.034$) than patients with bipolar I disorder (Table 5).

On the WCST, the control group had statistically significant lower percentage of errors, higher percentage of conceptual level responses, more categories completed, fewer failures to maintain set, lower learning to learn category and statistically highly significantly lower percentage of perseverative responses ($P = 0.001$), percentage of perseverative errors ($P = 0.002$), and percentage of non-perseverative errors ($P = 0.006$) (Table 6).

Discussion

BD is a relatively common disabling illness characterized by recurrent episodes of mania and depression. These pathological mood states have a clear impact on cognitive functions [23].

These cognitive impairment can be transient (state related), occurring during the symptomatic phase of the illness, or may be enduring (trait or scar related), which persists in the euthymic periods and is associated with psychosocial difficulties [24–26] Furthermore, many studies have provided evidence that the cognitive impairment in euthymic bipolar patients is to a large extent comparable with that of symptomatic bipolar patients [27].

Our findings clarified the presence of significant deficits across a range of neurocognitive tests in euthymic patients with bipolar I disorder when compared with a matched healthy controls.

Executive functions

Executive functions encompass a group of higher level cognitive processes including strategic planning, problem solving, working memory, strategy development, ability to shift cognitive strategy, inhibitory control, and cognitive flexibility [21,28].

We assessed the executive function in our study using the CPT and WCST. Data obtained from CPT showed that euthymic patients scored higher in the total errors and perseverative errors, which reflect difficulty in cognitive flexibility, and they also obtained worse scores in the total correct answers than the healthy controls.

Table 1 Demographic characteristics: bipolar I patients vs. controls

	Bipolar I ($n=30$) [N (%)]	Controls ($n=30$) [N (%)]	Test	P value
Age (mean ± SD) (years)	28.67 ± 7.241	25.77 ± 3.875	$t=1.93$	0.058 (NS)
Years of education (mean ± SD)	10.97 ± 2.942	13.93 ± 2.664	$t=-4.09$	0.000 (VHS)
Sex				
Male	15 (50)	15 (50)	$\chi^2=1.000$, $d.f.=1$	0.602 (NS)
Female	15 (50)	15 (50)		
Social class				
Middle	4 (13.3)	7 (23.3)	$\chi^2=3.931$, $d.f.=3$	0.269 (NS)
Low middle	10 (33.3)	13 (43.3)		
Low	13 (43.3)	6 (20.6)		
Very low	3 (10)	4 (13.3)		
Occupation				
Unemployed	8 (26.7)	8 (26.7)	$\chi^2=2.933$, $d.f.=5$	0.710 (NS)
Manual	7 (23.3)	3 (10)		
Skilled	2 (6.7)	2 (6.7)		
Clerical	2 (6.7)	2 (6.7)		
Professional	4 (13.3)	8 (26.7)		
Housewife	7 (23.3)	7 (23.3)		
Marital status				
Not married	17 (56.7)	18 (60)	$\chi^2=0.793$, $d.f.=1$	0.500 (NS)
Married	13 (43.3)	12 (40)		

NS, not significant; VHS, very highly significant.

Table 2 Clinical characteristics: bipolar I

Total number of episodes	Number of depressive episodes	Number of manic episodes	Number of hypomanic episodes
5.73 ± (2.62)	1.6 ± (1.75)	3.27 ± 2.67	0
Number of mixed episodes	Age of onset	Average duration of episode (months)	Average duration of illness (years)
0.87 ± 2.193	20.83 ± 6.828	1.97 ± 1.29	7.83 ± 4.41

Table 3 Wechsler Adult Intelligence Scale: bipolar I patients vs. controls

	Abilities assessed	Bipolar I ($n=30$) (mean ± SD)	Control ($n=30$) (mean ± SD)	Test	P value
Verbal IQ	Global verbal function	93.57 ± 7.436	110.67 ± 11.391	$t=-6.885$	0.000 (VHS)
Performance IQ	Global performance function	94.87 ± 5.794	114.07 ± 13.290	$t=-7.254$	0.000 (VHS)
Total IQ	General intellectual capacity	93.43 ± 6.350	112.53 ± 11.476	$t=-7.976$	0.000 (VHS)
Comprehension	Social common sense Organization of information	11.47 ± 1.961	13.53 ± 1.432	$t=-4.662$	0.000 (VHS)
Digit span	Immediate memory Auditory imagination	6.90 ± 1.605	9.87 ± 2.700	$t=-5.173$	0.000 (VHS)
Arithmetic	Mathematical processes	7.33 ± 2.339	10.93 ± 1.552	$t=-7.024$	0.000 (VHS)
Similarities	Abstract thinking	8.83 ± 2.379	12.40 ± 1.522	$t=-6.916$	0.000 (VHS)
Picture completion	Visual perception Visual imagination	9.70 ± 1.393	11.67 ± 1.729	$t=-4.851$	0.000 (VHS)
Block design	Visual perception Visiomotor abilities	7.37 ± 2.008	9.93 ± 2.273	$t=-4.635$	0.000 (VHS)
Digit symbol	Immediate memory Visiomotor coordination	9.90 ± 2.023	14.20 ± 2.631	$t=-7.096$	0.000 (VHS)

IQ, intelligence quotient; VHS, very highly significant.

Table 4 Wechsler Memory Scale: bipolar I patients vs. controls

	Bipolar I ($n=30$) (mean ± SD)	Control ($n=30$) (mean ± SD)	Test	P value
Information and orientation	12.83 ± 2.408	14.00 ± 0.000	$t=-2.654$	0.013 (significant)
Digit span backwards	4.07 ± 1.552	8.93 ± 1.799	$t=-11.218$	0.000 (VHS)
Digit span forwards	5.67 ± 1.583	9.87 ± 1.279	$t=-11.303$	0.000 (VHS)
Visual memory span backwards	4.23 ± 1.813	7.20 ± 1.495	$t=-6.914$	0.000 (VHS)
Visual memory span forwards	6.40 ± 2.044	8.20 ± 1.243	$t=-4.121$	0.000 (VHS)
Visual paired association I	6.70 ± 3.098	14.13 ± 2.515	$t=-10.203$	0.000 (VHS)
Visual paired association II	3.23 ± 1.073	5.93 ± 0.254	$t=-13.417$	0.000 (VHS)
Verbal paired association I	9.57 ± 4.783	15.07 ± 2.840	$t=-5.416$	0.000 (VHS)
Verbal paired association II	4.33 ± 1.539	7.53 ± 0.629	$t=-10.544$	0.000 (VHS)

The overall subtests measure immediate and delayed components of verbal memory, verbal and figural stimuli, visual memory, immediate recall, episodic memory, and visuospatial constructing ability.
VHS, very highly significant.

Table 5 Continuous Performance Test: bipolar I patients vs. controls

	Bipolar I ($n=30$) (mean ± SD)	Control ($n=30$) (mean ± SD)	Test	*P* value
Total commissions	11.27 ± 8.996	4.20 ± 0.997	$t=4.279$	0.000 (VHS)
Total omissions	10.63 ± 10.594	4.20 ± 1.627	$t=3.287$	0.003 (HS)
Median delay	517.490 ± 77.445	570.234 ± 111.845	$t=-2.124$	0.039 (significant)
Average delay	513.943 ± 70.519	561.08 ± 95.730	$t=-2.172$	0.034 (significant)

CPT assesses sustained attention, concentration, reaction time, impulsivity, and working memory.
CPT, Continuous Performance Test; HS, highly significant; VHS, very highly significant.

Table 6 Wisconsin Card Sorting Test: bipolar I patients vs. controls

	Bipolar I ($n=30$) (mean ± SD)	Control ($n=30$) (mean ± SD)	Test	*P* value
%Error	35.47 ± 15.870	19.27 ± 5.369	$t=5.296$	0.000 (VHS)
%Perseverative response	24.63 ± 18.582	12.93 ± 5.477	$t=3.308$	0.002 (HS)
%Perseverative error	20.67 ± 14.177	10.87 ± 3.213	$t=3.693$	0.001 (HS)
%Nonperseverative error	14.87 ± 8.966	9.67 ± 4.130	$t=2.885$	0.006(HS)
%Conceptual level response	55.43 ± 19.838	75.27 ± 6.097	$t=-5.234$	0.000 (VHS)
Categories completed	4.40 ± 1.793	6.00 ± 0.000	$t=-4.888$	0.000 (VHS)
Number of trials to complete one category	14.87 ± 5.746	14.47 ± 5.800	$t=0.268$	0.789 (NS)
Failure to maintain set	1.47 ± 1.224	0.20 ± 0.551	$t=5.168$	0.000 (VHS)
Learning to Learn	−9.1777 ± 13.03349	0.7753	$t=-4.155$	0.000 (VHS)

WCST assesses prefrontal lobe, executive functions, problem solving, strategies across changing stimuli, strategic planning, ability to shift cognitive sets, abstract and concept formation, and working memory.
HS, highly significant; VHS, very highly significant; WCST, Wisconsin Card Sorting Test.

Our study showed that there was a statistically significant difference in performance in WCST between bipolar I patients and controls in almost all domains (except on number of trials to complete one category) (%error, %perseverative response, %perseverative error, %conceptual level response).

Differences between bipolar I patients and control participants were supported by some findings from the literature, whereas others did not.

The extent to which executive dysfunction recovers during remission remains controversial. A number of studies, including our research, have suggested that executive function impairment remains during the euthymic phase and may represent an intrinsic factor to BD [29,30].

In a recent investigation, Torralva *et al.* [31] found a significant difference in the executive function performance between bipolar patients and control using two experimental tasks (the Multiple Errands Test-Hospital Version and the Hotel Task). Other investigators used different assessment tools and showed a trend toward a higher number of WCST perseverative errors compared with healthy controls [32]. Similarly, Hsiao *et al.* [33] found that the bipolar I group performed poorly compared with the control group on measures of executive function using the Trail Making Test part B indicating difficulties with set shifting. Also, Dittmann *et al.* [34] found that bipolar patients showed significantly lower scores in tests of executive functions than healthy controls. In their study, they used the Semantic Fluency subtest of the Repeatable Battery for the Assessment of Neuropsychological Status to measure executive functioning.

Similarly, Kolur *et al.* [35], using the WCST for cognitive flexibility, working memory, problem-solving, and set-shifting abilities; the Stroop Color Word Association Test (SCWT) for selective attention and executive function; and the Tower of London test for forward planning and working memory, concluded that euthymic bipolar I patients showed impairment on tasks of executive functioning and concluded that they are possibly trait abnormalities.

In contrast to the above findings, Van Gorp *et al.* [36] assessed executive function using the Controlled Oral Word Association Test (CWAT) and the WCST in a group of euthymic bipolar I patients with alcohol abuse comorbidity. Half of the patients had a history of alcohol abuse. They found that all patients performed similar to the controls on the CWAT. However, those with a history of alcohol abuse showed impairment in the WCST, particularly in the number of categories achieved, whereas those without such a history performed as well as controls. Also, Rubinsztein *et al.* [37] used the CANTAB battery to compare euthymic bipolar I patients with controls. No deficit was observed in the patients' ability to solve problems correctly but they took much longer than controls to make their decisions.

The contradiction in these results could be attributed to the use of different assessment tools and perhaps different inclusion criteria.

Memory

Memory deficits have been suggested to be a core cognitive deficit associated with acute mania [3]. However, evidence indicates that functional recovery of all memory symptoms is not completed [38] and persists during the asymptomatic phase of the disease.

Visual memory

Our study indicates that visual memory as examined by the visual memory subscale of WMS was significantly impaired in the group of bipolar patients compared with healthy controls. Our results are in agreement with a previous investigation that consistently found, using

a variety of measures, that explicit visual memory is impaired in euthymic bipolar patients [5,27,39,40].

Verbal memory

Verbal memory function includes measures of immediate, recall, and recognition [19]. Most studies have reported that there are deficits in verbal memory in patients with euthymic BD [8,27,41,42]. Similarly, Simonsen *et al.* [42] found that bipolar I patients had poorer verbal memory and recall using WMS and the California Verbal Learning Task compared with the control group.

Reports on the assessment of verbal memory function in bipolar patients across a range of mood states have clarified that recognition and recall are impaired in the symptomatic phase of the illness; however, impaired recall only persists in the euthymic state [1,32].

Our study confirmed that recall memory (which is a subtype of explicit declarative memory) is significantly impaired in euthymic bipolar I patients; thus, our results are in agreement with those of previous investigators in this field [43,44].

Working memory

Working memory is the ability to temporarily store and simultaneously manipulate information [45]. In our study, we used different parameters to assess working memory such as the CPT, digit span backward, and WCST.

Our euthymic patients made more omission and commission errors in the CPT than did the controls and they also scored lower in digit span backwards, which is a presumably a measure of working memory.

Data obtained in the current study confirmed a previous report by Watson *et al.* [46]. In a similar study, Hsiao *et al.* [33] reported results showing poorer performance by bipolar I patients on working memory compared with the control group.

In contrast to these findings, some reports highlighted that working memory is impaired only in symptomatic patients and not in periods of euthymia [47–49].

The discrepancies in the different reports may be related to the methods of assessment as working memory is a multicomponent system that requires assessment of different tasks.

Attention

Impaired sustained attention may represent a trait marker for BP related to vulnerability to the disorder at a structural and/or a neurochemical level [50]. Our study found a statistically significant difference in performance between all patients and controls on CPT, with patients showing significantly more total omissions and commissions and shorter median and average delays than controls. This suggests that euthymic bipolar I patients show more deficits in sustained attention than controls.

Our findings were also in agreement with the study carried out by Burdick *et al.* [27], who concluded that attention is impaired when assessed by MATRICS in a sample of 80 bipolar patients compared with controls. Moreover, Kolur *et al.* [35] carried out a study on 30 euthymic bipolar I patients and 30 matched healthy controls, who were assessed for sustained attention. The tests used were the CPT, the Trail Making Test part A and part B, and the SCWT; the bipolar group showed impairment on tasks of sustained attention. In conclusion, different investigators have reported that observed impairments in sustained attention during mania or depression did not show complete remission during euthymia [3,51].

Attentional and executive functions are critical to academic and professional success and may reflect the disability associated with illness [23].

General intellectual abilities

Our study found a statistically very highly significant difference in performance on all domains of WAIS between the patient and the control groups, with the patient group showing a poorer performance.

Despite the apparent difference between the groups, it is difficult to state whether this difference is a consequence of BD or not as our sample was cross-sectional. It is possible that this difference predated the onset of the illness and that this is a chance association, or that it might be because of confounding factors (e.g. effect of years of education) or that there is a genuine causal association. A more robust method would be a longitudinal study measuring premorbid IQ, for example, using the National Adult Reading Test (NART) and comparing it with current IQ, which would be more accurate in inferring whether this difference was a consequence of BD or not. Unfortunately, there is no Arabic version of the NART.

Similar studies comparing IQ have shown mixed results, and studies comparing bipolar I and control have also differed in their findings.

Simonsen *et al.* [42] used the NART and WAIS for assessment of the patients and controls enrolled in his study. The study groups did not differ significantly on premorbid IQ estimated by the NART. However, current IQ, assessed using the WAIS, differed significantly between the groups. Bipolar I patients group had lower scores compared to the healthy control group.

In the work of Morice [52], a group of 20 bipolar I patients were examined, most of whom had recovered from a manic episode. Bipolar I patients tended to score lower on almost all the performance IQ subtests, although there were no significant differences between their overall IQ scores and that of the controls.

Coffman *et al.* [53] compared controls with bipolar I patients who were in remission according to the authors' own clinical judgment and had a history of psychosis during episodes. There were no group differences in IQ. Similarly, in the study by Sapin *et al.* [54], no differences were found between bipolar I patients and controls; unfortunately, they used the Altus Brief Intelligence Test (a measure of verbal intelligence) instead of more widely used tests. A number

of studies have used the NART to measure premorbid intelligence in bipolar patients. Ferrier *et al.* [55] and Rubinsztein *et al.* [37] found no differences between euthymic bipolar I patients and controls.

The neurobiological substrates of cognitive dysfunction

Deficits in neuropsychological testing can provide insights into the underlying neurobiological process in BD. The most consistent structural neuroimaging studies showed an abnormal reduction in prefrontal cortical gray matter volume in patients with BD, a finding that is consistent with executive dysfunction [56,57].

Impairments in selective attention and attentional shift were attributed to dysfunction in the dorsolateral prefrontal cortex [56] and anterior cingulated gyrus [58].

Memory dysfunction is suggested to be because of abnormalities in the temporal lobe, amygdala, basal ganglia, and frontostriatal structures [23]. However, the structural brain abnormalities observed in BP and their corresponding functional deficits remain unknown [59].

Conclusion

Our findings support the presence of neurocognitive impairments that persist in the euthymic phase and may represent a trait variable independent of mood state.

The persistence of these deficits necessitates including neurocognitive assessment in routine investigation in all stages of the bipolar illness and should receive specific attention in future research to study its impact on social and occupational functioning.

Limitations

Although our study was one of only a few to compare cognitive functions in euthymic bipolar I and healthy controls, our study was limited by the sample size; thus, caution should be exercised in generalization of the results of this study and more research should be carried out on larger samples to replicate these results.

One of the limitations of this study is the difference in the educational attainment of the case group versus the control group. According to Glahn *et al.* [60], educational attainment should not be used to match patients and comparison participants, as appropriate matching of patients and controls is complex, given that cognitive aptitude and achievement measures may be affected by the disease process.

Another limitation of our study was that it was cross-sectional in nature and although it helped identify associations, it was difficult to infer causality in relationships. A longitudinal study would help answer many questions in this area.

It is worth noting that all our patients were receiving mood stabilizers, antidepressants, or antipsychotics; thus, the effect of medication on cognitive functioning cannot be discounted.

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Conflicts of interest

There are no conflicts of interest.

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