Profile of cognitive impairment in euthymic bipolar I patients: relation to clinical characteristics
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Background
Bipolar disorder has been identified as the sixth cause of disability among all medical illnesses, as it had been widely accepted that patients recovered completely and remain free in-between episodes. However, recent studies have shown that euthymic bipolar patients continue to have psychosocial difficulties and have reduced ability to regain premorbid levels of social and vocational functioning even after episodes of remission, suggesting that a gap exists between syndromal recovery and functional recovery, and this gap may be because of cognitive impairments. Cognitive deficits, most notably in attention, verbal learning, and executive function, can be observed across multiple phases of bipolar disorder.

Aim of the study
To show the range of neuropsychological deficits in the various cognitive domains in euthymic bipolar I patients depending on the previous clinical state and to correlate these cognitive deficits with illness characteristics and profile.

Participants and methods
This was a case–control study that included 60 patients divided into two major groups: a stratified random sample of 30 patients in the euthymic phase of bipolar I disorders and a control group. The patient group was diagnosed using Structured Clinical Interview for DSM-IV (SCID-I) and the euthymic state was determined using the Young Mania Rating Scale (YMRS) and the Hamilton Rating Scale for Depression (HRSD); we used Wechsler Adult Intelligence Scale (WAIS) and Wechsler Memory Scale-Revised (WMSR) for cognitive assessment.

Results
Euthymic patients with bipolar I performed poorer than controls on tests of intelligence, attention, memory, and executive functions. Performance on most domains of Wechsler Adult Intelligence Scale (WAIS) was associated with age of onset of illness and the number of depressive episodes. These differences were statistically significant, with residual symptoms not reaching clinical significance.

Conclusion
We conclude that cognitive deficits associated with euthymia in bipolar disorder can be considered both a consequence of the disorder and a determinant of outcome in recovery for bipolar I disorder.

Keywords:
bipolar I, cognitive deficits, euthymia

Introduction
Bipolar disorder has been identified by the WHO as the sixth cause of disability among all medical illnesses [1]. Until recently, it had been widely accepted that in-between episodes of mania and depression, patients with bipolar disorder recovered completely and that euthymia was in essence normality [2]. However, recent studies have cast serious doubt on this assumption and have shown that euthymic bipolar patients continue to have psychosocial difficulties and have reduced ability to regain premorbid levels of social and vocational functioning even after episodes of remission, suggesting that a gap exists between syndromal recovery and functional recovery; this gap might be because of cognitive impairments [3]. Some of the evidence suggests that recurring episodes of bipolar disorder are associated with greater cognitive disturbance. It has been proposed that successive episodes cause subtle damage to brain areas, leading to the neurological and cognitive impairment observed in patients with bipolar disorder. However, the evidence linking cognitive deficits with indicators of severity and progression of illness is not always consistent [4].

Furthermore, cognitive deficits, most notably in attention, verbal learning, and executive function, can be observed across multiple phases of bipolar disorder, with deficits during acute episodes that are comparable in
severity to those reported in schizophrenia [5–7]. More recent research suggests that the presence of cognitive dysfunction in bipolar disorder is a core and enduring deficit of the illness. The deficit is best characterized as impairment in attention and executive control of action, and represents an important marker for future neurobiological and pharmacological research [8]. The episodic nature of bipolar disorder requires that studies account for current mood symptoms, and clinical course factors, including the number of previous episodes, age at onset, and duration of illness, exert a direct effect on cognitive functioning [6]. These cognitive impairments are associated with poorer long-term psychosocial functional outcome. Wingo et al. [9] found that neurocognitive impairment was significantly associated with impaired psychosocial functioning, even after adjusting for residual mood symptoms and relevant demographic and clinical variables; ~55% of patients with bipolar disorder were unemployed [10].

The issue of persistent cognitive deficits in euthymia is very important because of its potential as a trait marker for bipolar disorder. Low-functioning patients are found to have greater cognitive impairment in verbal recall and executive functions and the variable that best predicts psychosocial functioning in euthymic bipolar patients is verbal memory [11]. This indicates that cognitive rehabilitation may be an important factor for restoring quality of life to baseline levels among patients with bipolar disorder [12].

Aim of the study

(1) To search for the difference between bipolar I and control groups in terms of cognitive functions.
(2) To explore the relation between clinical profile and illness characteristics of bipolar I disorder and cognitive decline in euthymic patients.

Participants and methods

Study design
This is a case–control study.

Participants
A total of 60 patients participated in this study; they were divided into two major groups. One group included a stratified random sample of 30 patients in the euthymic phase of bipolar I disorder; their diagnosis was confirmed by the Structured Clinical Interview for DSM-IV (SCID-I) to establish that all patients who previously had a bipolar I disorder episode were in a euthymic state at the time of the study. They attended the outpatient clinic at the Institute of Psychiatry, Ain Shams University, for follow-up. The other group included 30 individuals as controls.

Inclusion criteria
The study included male and female Egyptian patients who fulfilled the following criteria:

(1) Age: 18–50 years.
(2) Those who could at least read and write.
(3) In the euthymic phase of bipolar disorder I.

Exclusion criteria
Age: above 50 years, below 18 years.

(1) Patients in acute exacerbation whether manic, depressive, or mixed episode.
(2) Presence of comorbid psychiatric illness in the last 6 months.
(3) Significant uncontrolled medical or neurological conditions.
(4) Patients with learning disability or those who were illiterate.

Control group
The control group included 30 Egyptian individuals matched for age, sex, and other sociodemographic variables to the first group. Patients with a history of bipolar illness, a history of other psychiatric conditions, or a family history of psychiatric disorders were excluded.

Tools

Structured Clinical Interview for DSM-IV (SCID-I)
The study used the Arabic version of the SCID-I [13] for the diagnosis of bipolar patients.

Young Mania Rating Scale (YMRS) [14]
YMRS was designed to measure the severity of symptoms and the effect of treatment. It can also be used to detect a return of manic symptoms (e.g. relapse or recurrence), and can therefore be used to confirm that the patients were in the euthymic state during the research. The scale has 11 items and is based on the patient's subjective report of his or her clinical condition over the previous 48 h. The average scores were 13 for minimal severity, 20 for mild, 26 for moderate, and 38 for severe.

Hamilton Rating Scale for Depression (HRSD)
HRSD was designed to measure the severity of depressive symptoms in patients with a primary depressive illness to detect a return of symptoms (e.g. relapse or recurrence). The following thresholds were used: very severe >23; severe 19–22; moderate 14–18; mild 8–13; and normal <7 [15,16].

Wechsler Adult Intelligence Scale (WAIS) [17]
WAIS is used for the assessment of general intelligence and for the broad assessment of cognitive functions. It is an individually administered measure of intelligence and is intended to measure human intelligence reflected in both verbal and performance abilities. The study used the Arabic version.
Wechsler Memory Scale-Revised (WMSR) [18]
WMSR was used to assess memory functions in adults as it provides normative information from ages 16 to 74 years. It includes information and orientation questions, short-term memory, and delayed recall; its summary scores are General Memory, Verbal Memory, Visual Memory, Attention/Concentration, and Delayed Recall.

Statistical analysis
Analysis was carried out using an SPSS, 17th version (Chicago, USA). The results were tabulated, grouped, and statistically analyzed using the following tests:

1. Descriptive statistics (for quantitative data)
   a. Mean (\(\bar{X}\)) and \(\pm SD\)
   b. Frequency with percentage (for qualitative data).
2. The Kolmogorov–Smirnov test was used to study normality of data distribution.
3. The Student test was used to test the significance of an independent variable in experiments in which there are only two levels of this variable (to compare between two independent means).
4. \(\chi^2\) was used to test the significance in the difference between the frequencies of the different observations, that is qualitative data.
5. The Spearman correlation test \((r)\) was used when studying the relationship (direction and power) of quantitative variables simultaneously.
6. Logistic regression analysis was used to examine the extent to which a set of variables independently predicts a dependent variable.

\(P\) value was used to indicate the level of significance: insignificant \((P>0.05)\), significant \((P<0.05)\), highly significant \((P<0.01)\), very highly significant \((P<0.001)\).

Results
Sociodemographic data
Comparison of bipolar I patients versus controls in terms of demographic characteristics showed that the mean age of the individuals in the control group was 25.77 versus 28.67 years for the bipolar I group, which was not statistically significantly \((P = 0.058)\). Furthermore, the mean years of education for the bipolar I group was 10.97 versus 13.93 years for the control group, which was very highly significant \((P = 0.000)\). There was no statistically significant difference in sex, social class, marital state, and occupation between the two groups.

Cognitive function
Comparison of bipolar patients with controls in terms of cognitive functions indicated that on all domains of the WAIS, the control group had a statistically very highly significant \((P = 0.000)\) higher mean score than the bipolar I group. In addition, in almost all domains of the WMS, the control group had a significantly higher mean score than the bipolar I group \((P = 0.000)\).

The study showed that there was a significant positive correlation between the age of the patients on the one hand and total, verbal, and performance IQ on the other, that is, the higher the age, the higher the score on IQ. However, this may be a confounder related to the method of calculation of IQ in relation to age rather than having significance in our study. Furthermore, better occupation was significantly associated with better comprehension state \((r = 2.964, P = 0.032)\) (Table 1), and was associated with a better score in Information and orientation \((r = 3.974)\).

<table>
<thead>
<tr>
<th>Test used</th>
<th>(r)</th>
<th>(t)</th>
<th>(F)</th>
<th>(F)</th>
<th>(t)</th>
<th>(t)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal IQ</td>
<td>0.18*</td>
<td>0.486</td>
<td>0.229</td>
<td>0.249</td>
<td>0.422</td>
<td>0.541</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>0.026*</td>
<td>0.903</td>
<td>0.315</td>
<td>0.768</td>
<td>0.500</td>
<td>0.523</td>
</tr>
<tr>
<td>Total IQ</td>
<td>0.031*</td>
<td>0.717</td>
<td>0.236</td>
<td>0.393</td>
<td>0.532</td>
<td>0.938</td>
</tr>
<tr>
<td>Comprehension</td>
<td>0.835</td>
<td>0.281</td>
<td>0.148</td>
<td>0.032*</td>
<td>0.451</td>
<td>0.363</td>
</tr>
<tr>
<td>Digit span</td>
<td>0.231</td>
<td>0.74</td>
<td>0.043*</td>
<td>0.63</td>
<td>0.429</td>
<td>0.023*</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>0.237</td>
<td>1.00</td>
<td>0.322</td>
<td>0.230</td>
<td>0.356</td>
<td>0.472</td>
</tr>
<tr>
<td>Similarities</td>
<td>0.173</td>
<td>0.77</td>
<td>0.638</td>
<td>0.356</td>
<td>0.295</td>
<td>0.094</td>
</tr>
<tr>
<td>Picture completion</td>
<td>0.747</td>
<td>0.898</td>
<td>0.701</td>
<td>0.156</td>
<td>0.791</td>
<td>0.817</td>
</tr>
<tr>
<td>Block design</td>
<td>0.159</td>
<td>0.929</td>
<td>0.511</td>
<td>0.736</td>
<td>0.781</td>
<td>0.229</td>
</tr>
<tr>
<td>Digit symbol</td>
<td>0.824</td>
<td>0.329</td>
<td>0.114</td>
<td>0.906</td>
<td>0.505</td>
<td>0.229</td>
</tr>
</tbody>
</table>

*Significant.
**Highly significant.
and with family history ($r = 0.391$) and lower with older age ($r = -0.469$) (Table 4).

**Discussion**

The aim of our study was to explore the relationship between the effect of previous clinical states of bipolar I patients and performance on tests of cognitive function in a euthymic state.

Thus, we examined cognitive domains that are commonly affected in euthymic bipolar I patients and explored the factors associated with impaired cognitive function [7,10].

In bipolar disorder, functional recovery often lags behind recovery from symptoms. It is estimated that 30–50% of bipolar patients in remission fail to attain premorbid levels of psychosocial functioning and that much of this disability may be linked to cognitive impairment [19].

Some studies such as that of Burdick et al. [20] did not find significant differences between euthymic bipolar disorder patients and symptomatic patients; although symptomatic patients showed significant impairment on
Verbal paired
Visual paired
Visual memory
Verbal paired
Digit span forwards
Visual memory span forwards
Visual paired association I
Visual paired association II
Verbal paired association I
Verbal paired association II

Table 4 Wechsler Memory Scale: correlation of illness characteristics and profile with cognitive functions in bipolar I patients

<table>
<thead>
<tr>
<th></th>
<th>Total Number of episodes</th>
<th>Number of depressive episodes</th>
<th>Number of manic episodes</th>
<th>Number of mixed episodes</th>
<th>Age of onset</th>
<th>Average duration of episode in months</th>
<th>Average duration of illness in years</th>
<th>Psychotic features Specifier</th>
<th>Index episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information and orientation</td>
<td>0.175</td>
<td>0.764</td>
<td>0.051</td>
<td>0.294</td>
<td>0.842</td>
<td>0.000***</td>
<td>0.093</td>
<td>0.237</td>
<td>0.242 0.696</td>
</tr>
<tr>
<td>Digit span backwards</td>
<td>0.314</td>
<td>0.430</td>
<td>0.031*</td>
<td>0.513</td>
<td>0.168</td>
<td>0.724</td>
<td>0.315</td>
<td>0.037*</td>
<td>0.254 0.377</td>
</tr>
<tr>
<td>Digit span forwards</td>
<td>0.093</td>
<td>0.794</td>
<td>0.246</td>
<td>0.422</td>
<td>0.416</td>
<td>0.517</td>
<td>0.120</td>
<td>0.940</td>
<td>0.920 0.656</td>
</tr>
<tr>
<td>Visual memory span backwards</td>
<td>0.419</td>
<td>0.255</td>
<td>0.132</td>
<td>0.925</td>
<td>0.498</td>
<td>0.745</td>
<td>0.720</td>
<td>0.012*</td>
<td>0.965 0.678</td>
</tr>
<tr>
<td>Visual memory span forwards</td>
<td>0.043*</td>
<td>0.992</td>
<td>0.011*</td>
<td>0.582</td>
<td>0.775</td>
<td>0.604</td>
<td>0.274</td>
<td>0.503</td>
<td>0.237 0.836</td>
</tr>
<tr>
<td>Visual paired association I</td>
<td>0.201</td>
<td>0.246</td>
<td>0.012*</td>
<td>0.018*</td>
<td>0.729</td>
<td>0.197</td>
<td>0.921</td>
<td>0.072</td>
<td>0.046 0.009**</td>
</tr>
<tr>
<td>Visual paired association II</td>
<td>0.84</td>
<td>0.758</td>
<td>0.295</td>
<td>0.210</td>
<td>0.222</td>
<td>0.198</td>
<td>0.678</td>
<td>0.306</td>
<td>0.603 0.064</td>
</tr>
<tr>
<td>Verbal paired association I</td>
<td>0.136</td>
<td>0.571</td>
<td>0.745</td>
<td>0.360</td>
<td>0.223</td>
<td>0.826</td>
<td>0.337</td>
<td>0.235</td>
<td>0.907 0.174</td>
</tr>
<tr>
<td>Verbal paired association II</td>
<td>0.128</td>
<td>0.052</td>
<td>0.570</td>
<td>0.694</td>
<td>0.089</td>
<td>0.976</td>
<td>0.132</td>
<td>0.179</td>
<td>0.250 1.00</td>
</tr>
</tbody>
</table>

*Significant.
**Highly significant.
***Very highly significant.

Reasoning and Problem-solving and Social Cognition, euthymic bipolar disorder patients did not significantly differ from the healthy controls in these domains [20]. However, the most consistent finding across studies seems to be that cognitive impairments are fewer and relatively less severe in euthymic patients. Findings of persistent neuropsychological deficits in euthymic patients with long-standing illness and the relationship of this impairment with the length of illness suggest that episodes of depression and mania may cause damage to learning and memory systems [21].

Results vary across studies considerably partly because of the heterogeneity of the studied populations in addition to different medication status and illness characteristics such as mood state at the time of testing, diagnostic category (e.g. bipolar I vs. bipolar II, rapid-cycling with or without psychotic features), severity, chronicity of illness, and age.

The current study found no significant difference between patients and controls in terms of age, sex, marital status, social class, and occupation. However years of education were significantly more in bipolar I group rather than control group. Although there was no statistically significant difference in occupation and social class, the majority of bipolar I patients (almost 75%) were either unemployed (26.7%), manual workers (23.3%), or housewives (23.3%); most bipolar I patients were from a low social class whereas controls were from a low to middle social class. It is possible that these differences may reflect the impact of the disorder on occupational and social outcome. Dickerson et al. [22] found that 51% of their study participants (117 patients with bipolar disorder) had no current employment, 21% worked part-time or as volunteers, and only 27% had full-time competitive employment.

Similar findings were obtained in the study of Rosa et al. [3], which included 71 euthymic bipolar I and bipolar II patients and 61 healthy controls. The Functioning Assessment Short Test (FAST) was used to assess multiple areas of functioning such as autonomy, occupational functioning, cognitive functioning, interpersonal relationships, financial issues, and leisure time. Sixty percent of the patients had overall functional impairment (defined as a FAST total score >11) compared with 13.1% of the control group. Bipolar patients showed worse functioning in all the areas of the FAST, indicating that there is a significant degree of morbidity and dysfunction associated with BD, even during remission periods [3].

Cognitive function

Our study found a very highly significant difference in performance on all domains of WAIS between the group of bipolar I patients and the control group, in addition to a lower total IQ in the bipolar I group. Similar results were obtained by Yates et al. [23] and Elshahawi et al. [4], who found statistically significant differences between patients with bipolar I and the control group on all WAIS subscales. Other studies comparing IQ have shown mixed results, with most of them not showing a difference in the overall IQ as in the study of Lex et al. [25], who found that the patients in remission did not differ significantly from the healthy controls in explicit or in implicit cognition measurements. Similarly, Sapin et al. [24] found no differences 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. The difference between this study and previous studies may be because many of these studies had not controlled for residual affective symptoms, which
would have a major effect on their results [4]. Another cause for the difference was the use of different tools of assessment as in the case of Sapin et al. [24]. Also, Lex et al. [25] used the Emotional Stroop Test (EST), which measures the interference induced by emotional information, and the EMO-AVLT, which was designed by the authors to measure Auditory Verbal Learning but in response to emotional verbal stimuli. Similarly, Ferrier et al. [8] and Rubinstein et al. [26] used the National Adult Reading Test (NART), which measures premorbid intelligence in bipolar patients.

In our study, bipolar I patients had a lower score on almost all domains of WMS than the control group, especially verbal memory, visual memory, attention and concentration, and delayed recall. That was in agreement with the study of Simonsen et al. [27], who found that bipolar I patients performed significantly poorer than the control group on measures of verbal memory and recall using subtests of the WMS and the California Verbal Learning Task (CVLT), and that of Dittmann et al. [28] and Hsiao et al. [29], who found that patients with bipolar I disorder showed significantly lower scores in psycho-motor speed, working memory, verbal learning, and delayed memory than controls. Similar results were obtained by Elshahawi et al. [4], who reported that patients with a single manic episode showed impairment in attention, executive function, and total memory score compared with the controls.

Relation between cognitive function, social, and occupational function in bipolar I patients

As can be seen in Tables 1 and 2, better occupational and marital functions were associated with a higher score on comprehension and digit span tests of WAIS. At the same time, better occupational, social, and marital function was associated with a higher score on all domains of WMS (Table 2). Similarly, Dickerson et al. [22] found that current employment status was significantly associated with cognitive performance, especially immediate verbal memory, total symptom severity, history of psychiatric hospitalization, and maternal education.

Cognitive function and illness characteristics

In our study, better IQ was associated with older age of onset and relatively more depressive episodes rather than manic or mixed episodes, which may affect IQ more, although we did not find statistical significance in this study. In addition, psychotic symptoms in bipolar I patients did not seem to affect Cognitive function as it was associated with better comprehension, and higher scores on Visual memory span backwards and Digit span backwards. However, Yates et al. [23] found that, in the subtests in which the euthymic patients had a lower score than the controls, such as Comprehension, Matrix Reasoning, and Similarities, the predictors were the number of depressive and (hypo) manic episodes, use of mood stabilizers, and score on HARS.

Another issue in this study was the relation between a positive family history and cognitive function, which yielded different results with different tests; thus, cognitive function may not be affected by family history or genetic predisposition, although too early to decide. Similar findings were obtained by Cavanagh et al. [30], who concluded that impaired verbal learning and memory may be a trait variable in bipolar I disorder as it correlated negatively with the number of manic episodes, and by Atre-Vaidya et al. [31], who found that the most significant predictor of memory impairment was the degree of anhedonia reported by the patients whereas a history of psychosis appeared to have very limited impact; this can be explained by the fact that in bipolar disorders, the main disturbance is in the mood rather than thinking as in schizophrenic disorders.

Strengths and limitations

Although our study was one of the fewer studies to compare cognitive functions in euthymic bipolar I and control individuals in Arab countries, it was limited by the sample size, even though it was based on a literature search from previous studies with power calculations; hence, caution should be exercised in generalizing the results of this study and more research should be carried out on larger samples.

Another limitation of our study was that as it was cross-sectional, it did not allow exploration of causality and effect of control of clinical variables on cognitive performance; thus, a longitudinal study would help answer these questions. Another issue was the measurement of premorbid IQ, which was limited by the lack of an Arabic version of the National Adult Reading Test (NART), which measures premorbid IQ and could better compare the impact of the clinical state on IQ. Finally, a known problem with descriptive studies is that of recall bias associated with retrospective data collection.

Conclusion

Euthymic bipolar I patients had cognitive deficits that can be considered a consequence of the disorder and may be a determinant of outcome in recovery.

Euthymic bipolar I patients performed poorer than controls on tests of intelligence, attention, memory, and executive functions, which may help as a trait marker for the disorder.

In addition, a better score on WAIS was associated with older age of onset, less manic, mixed episodes, and less duration of episodes, whereas a better score in WMS was associated with good occupational and marital status.

Recommendations

Future multicenter studies should examine cognitive function in bipolar disorder on a larger group of patients for generalization of the results, and with more tools that help to measure premorbid function and assessment of the course and effect of treatment.

In addition better control of illness variables that associated with more impairment in cognitive function.
as type, duration and number of episodes through drugs targeting manic and mixed episodes and strategies to enhance compliance.

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Conflicts of interest
There are no conflicts of interest.

References
There are no conflicts of interest.

الملخص العربي

نمط الوظائف المعرفية عند مرضى الاضطراب الوجداني ثنائي القطب معتدلي المزاج وعلاقته بالصورة الأكلينية

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حتى وقت قريب كان يعتقد أن مرضى الاضطراب الوجداني ثنائي القطب يتعافون تماماً من الاعراض ما بين نوبات الهوس والاكتئاب ويسترجعون وظائفهم المعرفية. لكن الدراسات مؤخرًا أظهرت أن هناك فجوة تفصل بين التعافي من الاعراض وتعافي الوظيفي. وقد تم تصميم هذا البحث بهدف إظهار مدى العجز المعرفي لدى مرضى الاضطراب الوجداني القطب النوع الأول، أسواء المزاج، وربط العجز المعرفي مع الخصائص الديموغرافية، وخصائص المرض وخصائص الدواء. تم تقييم 60 فرد تم تقسيمهم إلى مجموعتين رئيسيتين، 30 من الذين كانوا يعانون من الاضطراب الثنائي القطب النوع الأول وحاليًا أسواء المزاج، والمجموعة الضابطة (30 فرد). وقد أجريت هذه الدراسة في قسم العيادات الخارجية في مركز الطب النفسي، جامعة عين شمس، الأدوات شملت المقابلة الأكلينية المجزئة لنسخة الرابعة الكتيب التشخيصي والإحصائي، مقياس بونج لتقسيم الهوس الوجداني، مقياس هاميلتون لتقسيم الاكتئاب، مقياس وكسلر للذكاء في البالغين، مقياس وكسلر للذاكرة أظهرت