Cognitive functions in euthymic adolescents with juvenile bipolar disorder

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Introduction
Bipolar disorder in adolescents is often referred to as juvenile bipolar disorder. A peak in the prevalence of bipolar disorder has been documented between the ages of 15 and 19 years. Wide-ranging neuropsychological deficits have been found in many studies of juvenile bipolar disorder. Persistent neuropsychological deficits present in the euthymic state suggest that such deficits could be vulnerability trait markers of the illness.

Aim
To identify and assess cognitive functioning in euthymic adolescents diagnosed with bipolar disorder.

Participants and methods
A case–control cross sectional study, in which 30 euthymic bipolar adolescents were recruited from the psychiatric adolescent clinic of Kasr al Ainy and compared with 30 healthy controls.

Psychometric procedure
The Hamilton Rating Scale of Depression, the Young Mania Rating Scale, the letter cancellation test, the digit span and digit symbol/coding tests, the Bender gestalt test and the Wisconsin card sorting test were used.

Results
Cases had significantly higher mean scores than controls in the letter cancellation test and its omission errors as well as in the perseverative errors of the Wisconsin card sorting test, and lower mean scores in the digit span, digit symbol coding and the Bender gestalt tests. There was a significant positive correlation between the number of omission errors on the letter cancellation test and both of the number of manic episodes and the age of onset of the illness.

Conclusion
There are neuropsychological deficits in the areas of sustained attention, set shifting, processing speed and visual and auditory short-term memory in euthymic bipolar adolescent patients, type I. There is a significant correlation between the number of manic episodes as well as age of illness onset and sustained attention.

Keywords:
euthymia, juvenile bipolar disorder, neuropsychological deficits

Introduction

Bipolar disorder in adolescents is often referred to as juvenile bipolar disorder (Cahill *et al.*, 2009). It is a disabling condition characterized by extreme affective and behavioural dysregulation, aggression, severe irritability and a chronic course (Biederman, 2003). In clinical trials, euthymia in bipolar disorder is conventionally defined as scores below a certain threshold, but not zero, on the Young Mania Rating Scale and the Hamilton Rating Scale for Depression (HRSD) (Pizzagalli *et al.*, 2008). During euthymia, bipolar patients exhibit minimal symptoms by definition, although a persistent vulnerability for mood dysregulation is always present. This persistent vulnerability has been hypothesized to result from over-reactive emotional (i.e. anterior limbic) brain networks (Phillips *et al.*, 2003). If correct, this hypothesis suggests that, even during euthymia, dysfunction within the anterior limbic network persists, leaving patients at risk for mood and cognitive disturbances (Strakowski *et al.*, 2004). Wide-ranging deficits have been found in many studies of juvenile bipolar disorder (Olvera *et al.*, 2005; Bearden *et al.*, 2007). Persistent neuropsychological deficits present in the euthymic state of bipolar affective disorder, particularly impairment in sustained attention, suggest that such deficits could be vulnerability trait markers of the illness (Thompson *et al.*, 2005).

Aim

The aim of this work is to identify and assess the cognitive impairment of euthymic adolescents diagnosed with bipolar disorder on neuropsychological measures of

sustained attention, short-term memory, processing speed and set shifting after exclusion of other comorbid psychiatric disorders.

Participants and methods

A total of 30 adolescents diagnosed with bipolar disorder type I participated in this research. All the patients were selected from the Kasr Al Aini adolescent outpatient psychiatric clinic. Both male and female patients were included. They were between the ages of 13 and 19 years, met the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for bipolar disorder type I and were euthymic during application of the psychometric tools, which was defined in our study as scores of 7 or below on both the 17-item HRSD and the Young Mania Rating Scale. All patients with comorbid psychiatric disorder, a history of attention deficit hyperactivity disorder before the onset of the disorder, intelligence quotient less than 90, any neurological deficit or chronic illness, a history of significant head trauma, electroconvulsive therapy in the past 6 months or those who were illiterate were excluded. The control group was selected to match the patients' group for age, sex and educational level. All control participants had no past history of psychiatric or neurological disorders or family history of psychiatric disorders. The diagnosis of bipolar disorder type I as well as the exclusion of psychiatric co morbidities and history of attention deficit hyperactivity disorder starting before the onset of the bipolar disorder was established by interviewing the patients and at least one of their parents using the Kiddie Schedule for Affective Disorders and Schizophrenia in school-aged children (K-SADS-PL) (Kaufman *et al.*, 1997). A written informed consent was obtained from parents for their minor adolescents and from the participants themselves if they were aged 18 years or older.

Tools

Semistructural interview
A specially designed semistructural interview derived from the Kasr Al Aini psychiatric sheet was used to cover demographic data, personal data, past history and family history.

The Kiddie Schedule for Affective Disorders and Schizophrenia in school-aged children (Kaufman et al., 1997)
The K-SADS-PL is a semistructured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents according to DSM-III-R and DSM-IV criteria. Probes and objective criteria are provided to rate individual symptoms. The K-SADS-PL is administered by interviewing the parent(s), the child and finally achieving summary ratings that include all sources of information (parent, child, school). When administering the instrument to preadolescents, the parent interview should be conducted first. In working with adolescents, the interview should be conducted first with them, followed by the parent, which was followed in our research. The majority of the items in K-SADS-PL are scored using a 0–3-point rating scale. Score of 0 indicate that no information is available; a score of 1 suggests that

the symptom is not present; a score of 2 indicates subthreshold levels of symptomatology; and a score of 3 represents threshold criterion. The remaining items are rated on a 0–2-point rating scale, in which 0 implies no information; 1 implies that the symptom is not present; and 2 implies that the symptom is present.

Hamilton Rating Scale for Depression (Hamilton, 1960)
The HRSD is the most widely used clinician-administered depression assessment scale. We have used the 17-item version, where a score of 0–7 is accepted to be within the normal range or in clinical remission. It has been used to ensure the euthymic state of cases after interviewing them using the K-SADS-PL.

Young Mania Rating Scale (Young et al., 1978)
It is a clinician-rated scale used to rate the severity of manic symptoms. The items rated are elevated mood, increased motor activity, sexual interest, sleep, irritability, speech and language, content of thought, disruptive or aggressive behaviour, appearance and insight. Scoring of each item is between 0 and 4 points. The cases had to score 7 or less to be considered euthymic and thus to be included in the study.

Letter cancellation test (Diller et al., 1974)
It is a measure of sustained attention (Ronald *et al.*, 2000). It has been applied in its Arabic version, where participants were asked to cancel two fixed Arabic letters whenever they found them amidst 19 rows of Arabic letters, as fast as they could. The time in seconds taken by each participant to complete this task was calculated. Whenever any of the letters to be cancelled was missed, this was considered an omission error. We used the Arabic version by El Kholi (1985).

Digit span (Meleka and Ismail, 1996, 1999)
It is one of the subtests of both the adult and the child Wechsler Intelligence Scale used to measure auditory short-term memory. The candidate was asked to repeat a dictated series of digits forward and another backward, with two trials each time. The final score was calculated by adding the score of the forward series to that of the backward series.

Digit symbol coding (Meleka and Ismail, 1996, 1999)
It is one of the subtests of the Wechsler Intelligence Scale used to measure processing speed (Doyle *et al.*, 2005). In the Arabic version of the Wechsler Intelligence Scale for children that was applied with participants below 16 years, the participants had to transcribe a digit symbol code as quickly as possible for a duration of 2 min, whereas in the adult version, used when participants were 16 years or above, participants had to transcribe the digit symbol code as quickly as possible for a duration of 90 s. The number of correct transcriptions completed by the participant in the given time was counted to yield the final score.

Bender gestalt test (Bender, 1938)
It is a measure of visual short-term memory and visual motor maturity (McCarthy *et al.*, 2002). It was formulated

by Lauretta Bender, a child neuropsychiatrist. The version used in our study comprises six figures on six separate cards. The cards were shown one after the other to each participant, who was instructed to draw each figure carefully, bearing in mind that he would be asked to recall the six figures after about 2 min. Scoring was carried out according to a standardized scoring system, where each recalled figure would receive a score between 0 and 5 points according to the accuracy of the details recalled.

Wisconsin card sorting test

The purpose of this test is to assess the ability to form abstract concepts, to shift and maintain set and to utilize feedback. The test is considered a measure of executive function (Heaton et al., 1993) in that it requires strategic planning, organized searching, the ability to use environmental feedback to shift cognitive set, goal-oriented behaviour and the ability to modulate impulsive responding. The test can be used with individuals aged 5 to 89 years. The time required is about 15–30 min (Strauss et al., 2006).

The statistical methods

Statistical analysis was performed using the Statistical Package of Social Science, version 16 (SPSS-V16, IBM, Chicago, IL, USA). Descriptive analysis was performed using frequency tests, pie and bar charts. The student's unpaired t-test was used to compare quantitative data between two groups and the analysis of variance and the post-hoc tests were used to compare quantitative data between more than two groups. The correlation between different quantitative data was assessed using the Pearson correlation test. Finally, the χ^2-test with Yates correction was used for the analysis of categorical data. The level of significance was set at P less than 0.05.

Results

53.3% of the cases were women and 46.7% were men. The mean age of the cases was 18.03. The case and control groups were matched in terms of age, sex and educational level ($P = 1, 1, 0.6$, respectively) (Tables 1–4).

There were no statistically significant differences between cases with positive and negative intake of any of the classes of psychotropic drugs used by the cases at the time of assessment as regards the mean scores of the neuropsychological tests.

Table 1 Clinical data of cases

Clinical data	Mean	SD	N
HRSD	0.4000	1.19193	30
YMRS	1.3667	1.67091	30
Age of onset	14.9667	1.06620	30
Manic episodes	1.6667	0.88409	30
Depressive episodes	0.7333	0.86834	30
Hospitalization	0.2667	0.44978	30
Duration of illness	3.0667	1.14269	30

HRSD, Hamilton Rating Scale for Depression; YMRS, Young Mania Rating Scale.

Table 2 Pattern of intake of psychotropic medication

Type of medication	% of negative intake	% of positive intake
Typical antipsychotic	23.3	76.7
Atypical antipsychotic	56.7	43.3
Antiepileptic drug	10.0	90.0
Lithium	93.3	6.7
SSRIs intake (fluoxetine)	93.3	6.7
Anticholinergic drug	43.3	56.7

Table 3 Neuropsychological test scores in both groups

Neuropsychological tests		Mean	SD	P
Letter cancellation				
Controls	30	75.5667	10.45741	0.000
Cases	30	116.07	25.44220	
Omission errors in letter cancellation				
Controls	30	0.0000	0.00000	0.000
Cases	30	2.4667	3.54024	
Digit span				
Controls	30	10.0000	1.64002	0.000
Cases	30	8.3667	1.44993	
Digit symbol coding				
Controls	30	51.1667	5.63293	0.000
Cases	30	29.6333	9.33840	
Bender gestalt				
Controls	30	19.9333	2.66437	0.000
Cases	30	15.2667	3.05053	
Perseverative errors in WCST				
Controls	30	3.5667	2.45909	0.000
Cases	30	39.5333	13.23979	

WCST, Wisconsin card sorting test.

Discussion

Our study aimed at assessing the performance of euthymic adolescent patients with bipolar disorder on neuropsychological measures of sustained attention, short-term memory, processing speed and set shifting. The comparison between the neuropsychological test scores of our cases and controls revealed that the euthymic patients showed poorer performance than controls in the letter cancellation test, which is a measure of sustained attention, with a highly significant statistical difference between the mean scores of both groups on this test. This is consistent with findings in the study conducted by Kolur et al. (2006) and where euthymic bipolar patients showed poorer performance than healthy controls on tests of sustained attention. However, this finding is not concordant with the study by DelBello et al. (2004), where no statistically significant difference was found between the performance of euthymic bipolar patients and healthy controls in tests of sustained attention, but this may be due to the small sample size in their study (10 cases and a matched control group).

The euthymic patients in our study also showed poorer performance than controls on the digit span test, which is a measure of auditory short-term memory, with a highly significant difference between the mean scores of both groups in this test. This finding is consistent with the findings by Gruber et al. (2007), where euthymic bipolar patients showed an impaired auditory short-term memory in comparison with healthy controls. However, this finding was in contrast to a recent study by Langenecker et al. (2010), where euthymic patients showed no impairment

Table 4 Correlation between clinical data and neuropsychological test scores

	Letter cancellation	Omission errors	Digit span	Digit symbol	BG	Perseverative errors
Age of onset						
Pearson's correlation	− 0.086	0.443*	0.075	0.078	− 0.061	− 0.304
P-value	0.650	0.014	0.693	0.681	0.750	0.102
Manic episodes						
Pearson's correlation	− 0.207	0.602**	0.152	0.043	− 0.196	− 0.011
P-value	0.271	0.000	0.421	0.821	0.299	0.955
Depressive episodes						
Pearson's correlation	− 0.254	0.199	− 0.194	− 0.289	− 0.076	0.289
P-value	0.176	0.292	0.305	0.122	0.688	0.122
Hospitalization						
Pearson's correlation	0.258	− 0.146	− 0.049	0.008	− 0.305	− 0.146
P-value	0.169	0.442	0.796	0.968	0.101	0.440
Duration ff illness						
Pearson's correlation	− 0.027	0.077	0.089	− 0.253	0.084	0.098
P-value	0.886	0.685	0.641	0.178	0.660	0.607

BG, bender gestalt test.
*Statistically significant.
**High statistical significance.

in auditory memory ability, although the sample size in the latter was larger.

Moreover, the patients in our study showed poorer performance than controls in the Bender gestalt test, which is a measure of visual short-term memory, also with a statistically significant difference between both groups. This is concordant with the study by Langenecker *et al.* (2010) but is inconsistent with the study by Pavuluri *et al.* (2006), where there was no difference between euthymic patients and controls as regards visual short-term memory.

In addition, the cases and controls in our study showed a statistically significant difference between their mean scores on the digit symbol coding test, where cases showed a poorer performance, revealing impairment in mental processing speed. This finding is consistent with the findings obtained in a study conducted by Langenecker *et al.* (2010).

Regarding the performance on the Wisconsin card sorting test, the patients in our study committed more perseverative errors than controls, with a statistically significant difference, which revealed a deficit in set shifting ability in cases. This finding is in agreement with the findings in the study by Trivedi *et al.* (2007), where euthymic patients committed more perseverative errors than healthy controls on the Wisconsin card sorting test, also with a statistically significant difference between both groups.

As for the correlation between the clinical variables and the mean neuropsychological scores of the patients in our study, the number of manic episodes was positively correlated to the mean number of omission errors in the letter cancellation test, which is statistically significant (i.e. the number of manic episodes was negatively correlated to the sustained attention function of the euthymic patients in our study).This is consistent with the findings in the study by Clark *et al.* (2002), where sustained attention performance suffered with increasing burden of manic episodes.

In our study, the age of illness onset, like the number of manic episodes, was positively correlated to the mean

number of omission errors on the letter cancellation test, which is consistent with the finding obtained by Martinez Aran *et al.* (2004b), where the age of onset of illness was also positively correlated to a score on a measure of sustained attention (i.e. those with a later onset of illness performed more poorly on measures of sustained attention).

In our study, no statistically significant correlation was found between the duration of illness and any of the neuropsychological test scores, which was concordant with a study assessing the same neuropsychological functions in euthymic bipolar patients (Kolur *et al.*, 2006).

As regards the number of depressive episodes, no significant correlation was found between the number of depressive episodes and any of the neuropsychological scores in our study, which is in agreement with the findings obtained in the study conducted by Martinez Aran *et al.* (2004b), where no significant correlation was found between the number of depressive episodes and scores on measures of verbal memory and sustained attention.

Moreover, no significant correlation was found between the number of hospitalizations and any of the neuropsychological scores in our study, which is similar to the findings obtained by Cavanagh *et al.* (2002), where no significant relationship was found between the total number of hospitalizations and executive function, psychomotor speed and visual recognition. It is also concordant with the finding obtained by Clark *et al.* (2002), where no significant relationship was found between the total number of hospital admissions and measures of sustained attention, set shifting, verbal memory and speed of information processing. Moreover, this similarity was present despite the fact that these two studies included patients of an older age group than those in our study, with more number of hospitalizations.

As for the intake of psychotropic medication, no statistically significant difference was found between cases with positive and negative intake of typical antipsychotics, atypical antipsychotics, antiepileptics, anticholinergic drugs and antidepressants as regards neuropsychological

test scores, which are consistent with the finding in the study by Kolur *et al.* (2006). Moreover, there was no statistically significant difference between cases with positive and negative intake of lithium as regards neuropsychological test scores, which is similar to the finding in the study conducted by Martinez Aran *et al.* (2004a) and also by Kolur *et al.* (2006).

Limitations

Our study was cross sectional, whereas longitudinal studies can track the decline in neuropsychological function with illness progression better and can also track the impact of medication on cognition more accurately.

Our study was not drug free; although no significant relationship was found between psychotropic drug intake and neuropsychological test scores in our study and similar others, yet, the effect of psychotropic drugs on cognition cannot be excluded. However, for euthymia to be established, being drug free is quite a remote possibility; moreover, it gives rise to ethical issues.

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