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Preliminary communication

Cognitive functions in euthymic Egyptian patients with bipolar disorder: Are they different from healthy controls?

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ABSTRACT

Background: There is marked interest to research neurocognitive functions in bipolar disorder during euthymia. Consequently we aimed to study cognitive functions in euthymic bipolar patients and factors affecting them.

Methods: It is a cross sectional case-control study of 60 euthymic bipolar patients and 30 matched healthy controls. They were subjected to: Structured Clinical Interview for DSM-IV disorders, (SCID-I) to ascertain clinical diagnosis, Young Mania Rating Scale (YMRS), Hamilton Rating Scale for Depression (HRSD) to validate euthymia. Wechsler Adult Intelligence Scale (WAIS) for general intellectual abilities, Wechsler Memory Scale-Revised (WMS-R) for memory, Wisconsin Card Sorting Test (WCST) for executive functions, Continuous Performance Test (CPT) for attention and impulsivity, and an information sheet gathering patient data.

Results: Bipolar patients had statistically significant lower mean IQ scores in all WAIS subscales ($p=0.000$), significantly lower memory abilities especially digit span and visual memory, higher impulsivity and inattention ($p=0.000$) but no significant difference in response time by CPT. They displayed significantly lower executive performance on WCST. Patients' years of education correlated positively with IQ. Hospital admission, number, type of episodes and total number of episodes affected memory functions. Hospital admission and number of hypomanic episodes correlated with attention and impulsivity. Previous hospitalization correlated with executive functions.

Conclusions: Euthymic bipolar patients exhibit cognitive deficits, which correlated with clinical variables as number, type of episodes and previous hospitalization, this knowledge could help minimize cognitive impairments for future patients.

Limitations: The small sample size, cross sectional design and lack of premorbid cognitive assessment limit generalization of findings.

1. Introduction

There is growing interest in the research of neuro-cognition as a putative marker for subjects with bipolar disorders (BD) (Martınez et al., 2008), which is a chronic, recurrent affective disorder characterized by cyclic episodes of mania/hypomania and depression, interspersed with periods of euthymia (Torres et al., 2007). The expression of BD includes not only the core abnormality in mood regulation, but also cognitive deficits that are well established in patients during acute manic-depressive states but less established during euthymic states (Clark and Goodwin, 2004; Martínez et al., 2010).

Evidence exists of trait-like deficits in cognitive functions of bipolar patients, and the identification of possible endophenotypes has started (Jamrozinski, 2010). Recent meta-analytic studies of cognitive performance in euthymic patients with bipolar disorder have reported impairments in patients compared to healthy controls in a range of neuropsychological domains such as attention/vigilance, processing speed, response inhibition and set shifting, as well as verbal and visual learning and memory (Bora et al., 2009; Andreoua and Bozikas, 2013).

Neuropsychological testing with standardized assessment procedures provides indirect measures of activity in brain systems. They provide the advantage of being relatively inexpensive and can be readily administered in a clinical or hospital setting (Clark and Sahakian, 2008). Various studies have used different

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neuropsychological tests as Wechsler Adult Intelligence Scale (WAIS) as an indicator of general cognitive abilities (Simonsen et al., 2008); others studied executive functioning and reported a range of discrepant findings from executive deficits (Dixon et al., 2004), the absence of executive impairments (Cavanagh et al., 2002), or marginal impairment in this domain (Torres et al., 2007).

Memory represents another frequently studied cognitive domain, which displays more uniformity in reported deficits as verbal and non-verbal episodic memory deficits relative to healthy controls (Thompson et al., 2005; Torres et al., 2007). When comparing findings of studies measuring attention many researchers report that euthymic patients exhibit deficits in tasks of sustained attention (Clark et al., 2005; Torres et al., 2007).

Due to the limited amount of Egyptian research on cognitive functions in bipolar patients and the scarcity of such research during euthymic states, the authors of this study aimed to describe the neuropsychological functioning in the euthymic phase of bipolar disorder, to evaluate the magnitude of patient-control differences in performance of the cognitive tasks assessing memory, attention, and executive functions, and, finally, to assess the effect of various demographic and clinical factors on cognitive functions in a sample of Egyptian euthymic bipolar patients.

2. Methodology

2.1. Site of the study

This is a cross-sectional, case-control study that was carried out at the outpatient clinics of the Institute of Psychiatry, Ain Shams University [1]. The study was conducted in accordance with the Helsinki Declaration for medical research of 1975 and in compliance with the guidelines of the Research and Ethics committee of the Institute. The research protocol was approved by the Research and Ethics committee of Ain Shams University.

2.2. Participants in the study

2.2.1. Patient group

Sixty euthymic bipolar patients were enrolled in the study. They fulfilled the inclusion criteria of being from 18 to 50 years of age, literate and in the euthymic phase of bipolar, I or bipolar II disorder. To avoid confounding factors extreme age ranges, illiteracy, active bipolar symptoms, comorbid medical and psychiatric disorders, history of substance abuse or recent treatment with electroconvulsive therapy (ECT) within the past six months and uncontrolled medical or neurological conditions were considered as exclusion criteria for participation in the study.

Euthymic state was operationally defined to be achieved in this study when patients fulfilled the DSM-IV criteria for bipolar disorder I or II, reported being in remission/ baseline mood for the past six months, and obtained a score of <7 on the Hamilton Depression Scale (HDRS) and <7 on the Young Mania Rating Scale (YMRS) (Dias et al., 2009).

Control group: consisted of 30 Egyptian male and female subjects matched for age, gender, educational level and other demographic variables as far as possible. Controls who reported current, past or family history of psychiatric disorders were excluded from participation.

[1] The Institute of Psychiatry Ain Shams University is an academic and clinical facility representing the department of Psychiatry in the faculty of medicine of the aforementioned university that is one of the biggest universities in Egypt, located in Cairo and serves a wide catchment area of east and central Cairo.

3. Tools applied in the study

both patients and control subjects were subjected to the following

1. *The Structured Clinical Interview for DSM-IV axis I disorder clinician version* (*SCID I-CV*)(First et al., 1997): to ascertain the diagnosis of bipolar disorder, determine its type and exclude other axis-I comorbid psychiatric conditions, the clinical version was used rather than the research version for its relatively easier administration and coverage of the diagnoses most commonly encountered in clinical settings.
2. *Young Mania Rating Scale* (*YMRS*)(Young et al., 1978): this is an 11-item clinician rated questionnaire that assesses the severity of manic symptoms and detects symptom relapse. It was used in this study to validate patients were in the euthymic phase of bipolar disorder.
3. *Hamilton Rating Scale for Depression* (*HRSD*)(Hamilton, 1960): This is a 21- item rating scale for assessing the severity of depressive symptoms, and monitoring treatment. In this study, it was used to validate the euthymic state of the patient group.
4. *Wechsler Adult Intelligence Scale* (*WAIS*)(Wechsler, 1981): For a broad assessment of general cognitive and intellectual abilities. The study used the Arabic validated version of the WAIS with Egyptian norms as a reference (Melika, 1996).
5. *Wechsler Memory Scale-Revised* (*WMS-R*)(Wechsler, 1987): One of the most widely used tests for evaluating memory functions in adults, the scores reflect general, verbal and visual memory, attention/concentration and delayed recall.
6. *Wisconsin Card Sorting Test*, *the computerized version* (*WCST*) (Heaton et al., 2003): For assessment of cognitive flexibility, executive functions, problem solving, working memory and set-shifting abilities. It is a measure of frontal lobe functions and provides information on problem-solving abilities.
7. *Continuous Performance Test* (*CPT*) (Conners, 2000): For assessment of attention/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 non-target) and various reaction times.
8. *An information sheet* devised to collect patient data, including: gender, age, years of education, occupation, diagnosis, previous hospitalization, number of episodes, index episode, number depressive episodes, number of manic episodes, number of mixed episodes, past history of psychotic features, duration of episode (in months), duration of illness (in years), family history, medications received and physical health status.

3.1. Procedure of the study

A total of 87 patients with bipolar disorder were assessed. 5 were excluded for having had recent ECT, 6 were excluded due to incomplete resolution of symptoms, and 10 were excluded for having comorbid substance misuse and 7 patients were excluded due to having co morbid psychiatric diagnosis as an anxiety disorder or personality disorder. All participants signed an informed consent of the nature of the research, emphasizing the voluntary participation and the right to withdraw at any time without giving reasons, and this will not be followed by withdrawal of any privileges.

The assessment of each subject took 3–4 h. Therefore, was undertaken over a two-session-interview. The first session included the clinical and demographic data collection, administration of SCID-I, HAM-D and YMRS (for the patient group only). The second session was for administration of cognitive tests.

The second session was scheduled on the next day maximally within the same week to avoid changes in the mood status. All neuropsychological tests were administered by experienced senior clinical psychologists with proper working experience in the use of those tools.

3.2. Statistical analysis

Data was recorded and analysed using the statistical package of social sciences SPSS- 17th version (2009). The results were tabulated, grouped and statistically analyzed using the following tests: Mean (X-), standard deviation ($\pm$SD) for quantitative data and frequency with percentage (for qualitative data). Colmogorov–Smirnov test was used to study normality of data distribution. Chi-square test used for the comparison of categorical variables. We Independent-samples *t* test used for comparison of continuous variables. Spearman Correlation Test (*r*) used for studying the relationship (direction and power) of quantitative variables. A statistical level of significance was set at 0.05.

This study is the third in a series of research projects comparing cognitive functions, clinical and demographic characteristics in patients with bipolar I, bipolar II disorder and healthy controls (Khalil et al., 2013; Okasha et al., 2013).

4. Results

90 subjects were enrolled into this study, 60 patients with bipolar disorder and 30 healthy controls. The mean age for the bipolar group was 27.02 $\pm$ 5.7 years compared to 25.77 $\pm$ 3.8 years of the control group ($t=1.08$, $p=0.28$). Similarly, the mean educational years was12.82 $\pm$ 3.1, compared to 13.93 $\pm$ 2.6 ($t=-1.64$, $p=0.10$) in the control group. No statistical difference between patients and controls was found in all demographic variables studied as shown in Table 1. Clinically the mean number of episodes was 4.12 $\pm$ 2.48; the mean number of depressive episodes was 1.55 $\pm$ 1.28; manic episodes was1.63 $\pm$ 2.47; hypomanic episodes was 0.5 $\pm$ 0.504; mixed episodes was 0.43 $\pm$ 1.598. 50% of the patients ($N=30$) had been hospitalized at least once, and 25% ($N=15$) reported positive family history of bipolar disorder.

Table 1
Demographic characteristics of patients and controls.

	Bipolar patients ($n=60$) (Mean $\pm$ SD)		Controls ($n=30$) (Mean $\pm$ SD)		Test	*p* Value
Age in years	27.02 $\pm$ 5.700		25.77 $\pm$ 3.875		1.081	0.283 (NS)
Years of education	12.82 $\pm$ 3.197		13.93 $\pm$ 2.664		−1.647	0.103 (NS)
Gender	№	%	№	%		
Male	30	66.7	15	33.3	$X^2=1.000$	0.588 (NS)
Female	30	66.7	15	33.3	$df=1$	
Social class	№	%	№	%		
Middle	12	20	7	23.3	$X^2=1.368$	0.713 (NS)
Low middle	25	41.7	13	43.3	$df=3$	
Low	18	30	6	20		
Very low	5	8.3	4	13.3		
Occupational status	№	%	№	%	Test	
Unemployed	15	25	8	26.7	$X^2=0.811$	0.976 (NS)
Manual	7	11.7	3	10	$df=5$	
Skilled	6	10	2	6.7		
Clerical	6	10	2	6.7		
Professional	13	21.7	8	26.7		
Housewife	13	21.7	7	23.3		
Marital status	№	%	№	%		
Not married	34	56.6	18	60	$X^2=0.763$	0.472
Married	26	43.3	12	40	$df=1$	

To ascertain the impact of clinical and demographic characteristics of the patients on cognitive functions, we performed a correlation analysis of all performed psychometric tests with the various clinical and demographic variables collected from the patients. In order to restrict the vast range of correlations that could be computed from this data 5 demographic factors were used: age, gender, years of education, occupation and marital status. 7 clinical variables were depicted: total number of episodes, number of depressive episodes, number of manic episodes, number of hypomanic episodes, number of mixed episodes, family history and previous hospital admissions. For simplification, only the variables showing significance with most domains of the applied psychometric tests were displayed in the results and only the variables that displayed statistical significance were formatted in a table.

4.1. Assessment of general intellectual abilities

We used the Wechsler Adult Intelligence scale (WAIS) finding lower mean IQ scores in the patient group compared to the control group with very high statistical significance in the total IQ and in all test subscales as shown in Table 2.

In the correlation analysis, we detected a significant positive correlation between years of education and general intellectual abilities, especially verbal IQ $p=0.000$, $r=0.436$; and at a lower significance with total IQ $p=0.001$, $r=0.379$.

Additionally, the number of hypomanic episodes positively correlated with all the IQ parameters ($p=0.000$, $r=0.545$ for verbal IQ, $p=0.013$, $r=0.320$ for performance IQ, $p=0.000$, $r=0.261$ for total IQ). Likewise, previous hospital admissions displayed positive correlation with IQ levels ($p=0.000$, $t=4.957$ for verbal IQ, $p=0.013$, $t=2.571$ for performance IQ and $p=0.000$, $t=5.104$ for total IQ). Yet it was negatively correlated with the number of mixed episodes ($p=0.050$, $r=-0.255$ for verbal IQ, $p=0.048$, $r=-0.256$ for performance IQ, and $p=0.022$, $r=-0.296$ for total IQ), detailed in Table 6.

4.2. Assessment of memory functions

Exploring memory functions by Wechsler Memory scale (WMS-R) revealed that the control group had better performance on tests of memory functions than patients with bipolar disorder in all assessed subtests. Differential performance was observed in memory subtests as highly significant greater mean scores ($p=0.000$) were evident in the digit span, visual memory span and visual association subtests but were less significant in information and orientation and verbal paired association subtests as shown in Table 3.

Analysis of correlation between patient data and cognitive functions revealed positive correlation between years of education and higher memory functions evident in most domains of the WMS as follows (information and orientation $p=0.050$, $r=0.254$, digit span forwards $p=0.005$, $r=0.355$, verbal paired association, I $p=0.002$, $r=0.397$, visual memory span backwards $p=0.000$; $r=0.437$, verbal paired association II $p=0.001$, $r=0.406$, digit span backwards $p=0.000$, $r=0.500$).

Correlation with clinical variables, however, revealed that memory functions were affected by most of the studied variables, as the number of hypomanic episodes positively correlated with memory abilities (information and orientation $p=0.010$, $r=0.329$, digit span backwards $p=0.000$, $r=0.614$, digit span forwards $p=0.000$, $r=0.635$, visual memory span backwards $p=0.000$, $r=0.443$, verbal paired association, I $p=0.000$, $r=0.541$, and verbal paired association II $p=0.000$, $r=0.521$). Previous hospitalization was also positively correlated with memory functions (digit span backwards $p=0.000$, $t=5.917$, digit span forwards $p=0.000$, $t=6.265$, visual memory span

Table 2
Differences in general intellectual abilities between patients with bipolar disorder and healthy controls.

Wechsler adult intelligence scale (WAIS) subscales	Assessed ability	Bipolar patients ($N=60$, Mean ± SD)	Controls ($N=30$, Mean ± SD)	Test	*p* Value
Verbal IQ	Global verbal function	98.28 ± 8.72	110.67 ± 11.391	$t=-5.720$	0.000*
Performance IQ	Global performance function	97.23 ± 7.461	114.07 ± 13.290	$t=-6.448$	0.000*
Total IQ	General intellectual function	97.32 ± 7.034	112.53 ± 11.476	$t=-6.663$	0.000*
Comprehension	Social common sense/organization of information	11.93 ± 1.803	13.53 ± 1.432	$t=-4.235$	0.000*
Digit span	Immediate memory/auditory imagination	8.05 ± 1.926	9.87 ± 2.70	$t=-3.674$	0.000*
Arithmetic	Mathematical processes	8.67 ± 2.747	10.93 ± 1.552	$t=-4.993$	0.000*
Similarities	Abstract thinking	9.62 ± 2.225	12.40 ± 1.522	$t=-6.159$	0.000*
Picture completion	Visual perception/imagination	9.57 ± 1.442	11.67 ± 1.729	$t=-6.088$	0.000*
Block design	Visual perception/visuomotor ability	7.58 ± 1.65	9.93 ± 2.273	$t=-5.595$	0.000*
Digit symbol	Immediate memory/ visuomotor coordination	11.45 ± 2.507	14.2 ± 2.631	$t=-4.825$	0.000*

* Indicates very high statistical significance.

Table 3
Differences in memory functions between patients with bipolar disorder and healthy controls.

Wechsler memory scale WMS subtests	Bipolar patients ($N=60$, Mean ± SD)	Controls ($N=30$, Mean ± SD)	Test	*p* Value
Information and orientation	13.42 ± 1.788	14.00 ± 0.000	$t=-2.527$	0.014***
Digit span backwards	4.93 ± 1.425	8.93 ± 1.799	$t=-11.482$	0.000*
Digit span forwards	6.83 ± 1.852	9.87 ± 1.279	$t=-9.075$	0.000*
Visual memory span backwards	4.92 ± 1.555	7.20 ± 1.495	$t=-6.652$	0.000*
Visual memory span forwards	6.80 ± 1.705	8.20 ± 1.243	$t=-4.428$	0.000*
Visual paired association I	7.35 ± 4.471	14.13 ± 2.515	$t=-9.196$	0.000*
Visual paired association II	3.37 ± 1.275	5.93 ± 0.254	$t=-15.009$	0.000*
Verbal paired association I	12.58 ± 5.622	15.07 ± 2.840	$t=-2.784$	0.007**
Verbal paired association II	5.30 ± 1.871	7.53 ± 0.629	$t=-8.350$	0.000*

* Indicates very high statistical significance.
** Indicates high statistical significance.
*** Indicates a statistically significance.

backwards $p=0.000$, $t=3.766$, verbal paired association, I $p=0.000$, $t=4.901$, and verbal paired association II $p=0.026$, $r=0.287$).

Total number of episodes correlated negatively with memory (digit span backwards $p=0.000$, $r=-0.525$, digit span forwards $p=0.000$, $r=-0.534$, visual memory span backwards $p=0.001$, $r=-0.410$, visual memory span forwards $p=0.001$, $r=-0.426$, verbal paired association, I $p=0.000$, $r=-0.513$, and verbal paired association II $p=0.000$, $r=-0.518$). Number of manic episodes had a similar negative correlation (digit span backwards $p=0.000$, $r=-0.633$, digit span forwards $p=0.000$, $r=-0.52$, visual memory span backwards $p=0.000$, $r=-0.467$, visual memory span forwards $p=0.000$, $r=-0.444$, verbal paired association, I $p=0.002$, $r=-0.388$, and verbal paired association II $p=0.002$ (*HS*) $r=-0.394$). All correlations are illustrated further in Table 6.

4.3. Assessment of attention and impulsivity

Conversely, when measuring attention and impulsivity by the CPT, patients with bipolar disorder had greater highly significant total errors of commissions denoting impulsivity and total errors of omissions denoting inattention ($p=0.000$) with no significant difference in the delay times as detailed in Table 4.

Correlation analysis revealed that higher impulsivity (assessed by total commission errors) was negatively correlated with the number of hypomanic episodes ($p=0.030$, $r=-0.281$) and previous hospitalization ($p=0.030$, $t=-2.227$). It is worth noting that inattention (assessed by total omission errors) was not significantly correlated to any clinical variable.

Number of hypomanic episodes and previous hospitalization positively correlated with median delay time and average delay time (number of hypomanic episodes-median delay $p=0.001$, $r=0.405$, average delay $p=0.004$, $r=0.367$; previous hospital admission median delay $p=0.001$, $t=3.372$, average delay $p=0.004$, $t=1.896$) as shown in Table 6.

4.4. Assessment of executive functions

On the WCST, patients with bipolar disorder displayed a highly significant greater percentage of errors (denoting lower concentration abilities), lower percentage of conceptual level responses (denoting lower abstraction and problem–solving abilities), lower number of completed categories (denoting lower overall executive performance), higher failures to maintain set (denoting inability to continue using successful strategies) and higher learning to learn scores denoting (lower conceptual efficiency). Nevertheless, the difference in the number of trials to complete the first category was not significant between both groups, which reflected that the initial concept formation before a shift of set is required was not affected in patients with bipolar disorder and that the cognitive errors start to become more evident with sustained mental activities, affecting the overall cognitive performance as shown by the lower mean scores of the total completed categories and percentage of errors, displayed in details in Table 5.

When correlating clinical variables with executive functions, only previous hospital admissions correlated negatively with most domains of executive functions (% of errors $p=0.026$, $t=-2.289$, % of preservative responses $p=0.010$, $t=-2.698$, % of conceptual level responses $p=0.016$, $t=-2.470$, and % of preservative errors $p=0.018$, $t=-2.438$), as further elaborated in Table 6.

Table 4
Differences in attention and impulsivity between patients with bipolar disorder and healthy controls.

Continuous performance test (CPT) subtests	Bipolar patients ($n=60$, Mean ± SD)	Controls ($n=30$, Mean ± SD)	Test	p Value
Total commissions	9.03 ± 8.025	4.20 ± 0.997	$t=4.595$	0.000*
Total omissions	10.22 ± 12.013	4.20 ± 1.627	$t=3.810$	0.000 *
Median delay	562.1342 ± 111.20046	570.2347 ± 111.84569	$t=-0.325$	0.746
Average delay	545.3715 ± 17.282	561.0833 ± 5.369	$t=-0.758$	0.452

* Indicates very high statistical significance.

Table 5
Differences in executive functions and problem solving abilities between patients with bipolar disorder and healthy controls.

Wisconsin card sorting test (WCST) subtests	Bipolar patients ($N=60$, Mean ± SD)	Controls ($N=30$, Mean ± SD)	Test	p Value
Error (%)	30.53 ± 17.282	19.27 ± 5.369	$t=4.623$	0.000*
Perseverative esponse (%)	19.27 ± 16.208	12.93 ± 5.477	$t=2.731$	0.008**
Perseverative error (%)	16.83 ± 12.681	10.87 ± 3.213	$t=3.431$	0.001*
Non perseverative error (%)	13.78 ± 8.427	9.67 ± 4.130	$t=3.110$	0.003**
Conceptual level response (%)	62.17 ± 22.011	75.27 ± 6.097	$t=-4.293$	0.000*
Categories completed (%)	4.80 ± 1.745	6.00 ± 0.000	$t=-5.328$	0.000*
Number of trials to complete 1 category	13.88 ± 4.427	14.47 ± 5.800	$t=-0.530$	0.597
Failure to maintain set	1.48 ± 1.927	0.20 ± 0.551	$t=4.784$	0.000*
Learning to learn	−7.0238 ± 12.00696	0.7753 ± 1.51531	$t=-4.953$	0.000*

* Indicates very high statistical significance.
** Indicates high statistical significance.

Table 6
Correlation of clinical variables with cognitive functions in patients with bipolar disorder.

		Total number of episodes	Number of depressive episodes	Number of manic episode	Number of hypomanic episodes	Number of mixed episodes	Family history	Previous hospital admission	Years of education
		p Value	p Value	p Value	p Value	p Value	p Value	p Value	p Value
WAIS	**Verbal IQ**	0.021***	0.200	0.009**	**0.000** *	**0.050*****	0.029***	**0.000***	**0.000***
	Performance IQ	0.580	0.008**	0.259	**0.013*****	**0.048*****	0.622	**0.013*****	0.165
	Total IQ	0.043***	0.03***	0.010***	**0.000** *	**0.022*****	0.042***	**0.000***	**0.001****
WMS	**Information and Orientation**	0.774	0.768	0.160	**0.010** **	0.494	0.172	**0.013*****	**0.050*****
	Digit span backwards	**0.000***	0.661	**0.000***	**0.000***	0.562	0.144	**0.000***	**0.000***
	Digit span forwards	**0.000***	0.725	**0.000***	**0.000***	0.044***	0.496	**0.000** *	**0.005****
	Visual memory span backwards	**0.001****	0.447	**0.000***	**0.000***	0.303	0.023***	**0.000***	**0.000***
	Visual memory span forwards	**0.001****	0.502	**0.000***	0.69	0.880	0.080	0.070	0.155
	Visual paired association II	0.917	0.435	0.900	0.423	0.215	0.032***	0.423	0.876
	Verbal paired association I	**0.000***	0.249	**0.002****	**0.000** *	0.057	0.000*	**0.000** *	**0.002****
	Verbal paired association II	**0.000** *	0.011**	**0.002****	**0.000***	0.443	0.000*	**0.000***	**0.001****
CPT	**Total commissions**	0.109	0.227	0.116	**0.030*****	0.086	0.071	**0.030*****	0.642
	Median delay	0.019***	0.496	0.011**	**0.001***	0.883	0.098	**0.001****	0.356
	Average delay	0.183	0.881	0.041	**0.004***	0.962	0.007**	**0.004****	0.437
WCST	**% Error**	0.132	0.591	0.400	0.026	0.278	0.122	**0.026*****	0.340
	% Perseverative Response	0.041***	0.155	0.157	0.009	0.616	0.467	**0.010** ***	0.102
	% Perseverative Error	0.057	0.185	0.191	0.018	0.674	0.333	**0.018** ***	0.175
	% Conceptual level response	0.096	0.506	0.297	0.016	0.245	0.093	**0.016** ***	0.292
	Failure to maintain set	0.843	0.753	0.900	0.947	0.437	0.009**	0.947	0.861

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

5. Discussion

The aim of our study was to explore the relationship between the euthymic state of bipolar disorder and performance on tests of cognitive function. We hypothesized that euthymic bipolar patients would perform poorly on tests of IQ, memory, attention and executive function when compared to normal controls; we then explored associated factors that correlated with such performance.

The first significant difference encountered between bipolar patients and controls was the statistically significant lower performance of bipolar patients in tests of general intellectual abilities as the WAIS compared to controls; although their performance remained within the average category of intelligence. Our results concur with previous studies that report significant differences in IQ measures in bipolar probands as compared with healthy controls, however, bipolar patients' performance is still typically noted to be within the normal range according to normative data (McIntosh et al., 2005; Toulopoulou et al., 2006; Frantom et al., 2008). A meta-analytic study reported that scores of general intelligence were lower than those of controls in 2/16 (12.5%) reports, but fell well within the average range in all other studies (Martınez et al., 2008). Although premorbid IQ tests were not completed by bipolar patients to ascertain whether those lower scores were genetically determined or represented a decline due to the onset of the illness, we agree with the explanation provided by Burdick et al. (2009) who reported that when premorbid intellectual capacity has been evaluated, bipolar patients have consistently demonstrated performance comparable to control subjects in many studies (McIntosh et al., 2005; Toulopoulou et al., 2006; Simonsen et al., 2008; Burdick et al., 2009) and with Bora et al. (2009) who reported a meta-analysis, including 1446 euthymic bipolar patients and concluded that premorbid intellectual capacity in bipolar patients did not differ from healthy controls, yet current IQ tended to be lower in the patient sample. Therefore, they concluded that IQ deficits in bipolar patients are likely to reflect a decline in functioning due to the onset of the disease (Bora et al., 2009).

IQ scores correlated positively with the number of hypomanic episodes and previous hospital admissions and negatively correlated with the number of mixed episodes. Detecting the reasons behind this finding is beyond the scope of this research, as many variables are needed before reaching solid reasons; however, one possible explanation could be due to medication effects as most mixed episode patients would be on anti-epileptic mood stabilizers that would add to the cognitive deficits. Another explanation would be from findings of a recent study that full-scale IQ was a significant cognitive predictor of global functioning (Andreoua and Bozikas, 2013). Given that hypomanic episodes are on the milder end of the bipolar spectrum, compared to mixed, manic or depressive episodes, so perhaps better global functioning could be expected. We can also postulate that higher IQ patients would be more able to detect relapses and therefore, can be more frequently admitted for treatment; however, no clear conclusions could be drawn from those incidental correlations.

Euthymic bipolar patients performed more poorly on tests of memory functions than controls in all domains assessed by the WMS denoting impaired memory functions in euthymic bipolar patients compared to controls. Our findings corroborate the findings from earlier studies pointing to memory impairments in euthymic bipolar patients as previous researchers who compared 4 groups: manic or hypomanic bipolar patients, depressed bipolar patients, euthymic bipolar patients, and healthy controls and reported that each of the three bipolar groups showed significant impairments in verbal memory and executive functions in comparison with controls. However, there were no substantial differences among the bipolar groups and concluded that in view of the persistence of cognitive impairment, euthymia cannot be seen as a clinical recovery (Martinez-Aran et al., 2004).

The correlation analysis revealed that better performance on the tests of memory functions were positively correlated with years of education, number of hypomanic episodes, previous hospital admissions and were negatively correlated with the total number of episodes and number of manic episodes. Our results concur with previous studies that reported lower level of education, higher lithium levels, and lower age of onset were correlated with impairment of memory performance in a sample of 63 bipolar patients (Bora et al., 2007).

Additionally corroborating findings by the meta-analysis of Robinson et al. (2006) who concluded that there was greater cognitive dysfunction more closely related to a higher number of episodes than to increased duration of illness and Gorwood et al. (2008) who found correlations of delayed recall deficits with the number of prior episodes of depression in a large sample of 8229 outpatients.

Some explanation may be provided by the findings of an earlier study reporting that within the bipolar group, depressed patients had more memory and motor impairment than euthymic patients, and hypomanic patients had more motor impairments than euthymic ones, and they concluded that each of the mood states is associated with specific cognitive impairments, particularly in the domains of memory and executive function (Malhi et al., 2007). We can only assume that as long as each of the disease states has specific cognitive impairments then the occurrence of one type of those states more than the others might impact the cognitive functions during the euthymic state, although this assumption still needs validation.

An earlier meta analysis found that non-symptomatic bipolar patients performed 0.4–0.9 SD below healthy individuals on measures of attention (Continuous Performance Test; Cohen's $d=0.69$), processing speed (digit symbol substitution; $d=0.66$), working memory (Digit Span Backward; $d=0.65$), declarative memory (Rey or California Verbal Learning Test; $d=0.81$), nonverbal declarative memory (visual reproduction subtest from the Wechsler Memory Scale; $d=0.91$)(Kurtz and Gerraty, 2009). Similar results were later reported in another meta-analysis of 55 articles on cognitive impairments of bipolar II disorder as they reported impaired verbal, visual and working memory in bipolar I, II patients compared to controls in many of the reviewed studies with samples formed of euthymic patients (Sole et al., 2011).

Our results also revealed more deficits in sustained attention (higher errors of omissions), and more impulsivity (higher errors of commissions) in the euthymic bipolar group compared to controls. These findings are in agreement with many previous studies that reported deficits in sustained attention of euthymic bipolar patients (Torrent et al., 2006; Kolur et al., 2006; Kurtz and Gerraty, 2009; Sole et al., 2011). However, other studies did not find such a difference in sustained attention (Simonsen et al., 2008). We agree with the explanation that it could be attributed in part to the attention measures used. Most measures implicate other components such as working memory and psychomotor speed, which may be less sensitive. In this regard, the CPT is a sensitive widespread measure of sustained attention (Sole et al., 2011).

Furthermore impulsive/commission errors negatively correlated with the number of hypomanic episodes and previous hospitalization, and both positively correlated with the delay time which might indicate that impulsivity is higher earlier in the illness and as the number of hypomanic episodes or hospital admission increase, impulsivity reduces and patients take more time to respond. Nevertheless, the confounding effect of medication status for this aspect cannot be overlooked.

When examining executive functions using the WCST, most domains of executive functions were deficient in euthymic patients

compared to controls. Studies comparing bipolar patients and controls using the WCST revealed contradictory results, whereas some researchers did not provide evidence for impairment in executive function performance of bipolar patients (Jamrozinski, 2010), others reported significant differences, especially for perseverative errors in which this score was also positively correlated to the number of hospitalizations (Mur et al., 2008). Two meta-analytic reviews reported that cognitive functions, especially executive functions are most remarkably affected in adult euthymic BD patients, including cognitive flexibility, inhibitory control, working memory and verbal fluency (Torres et al., 2007; Martínez et al., 2010). These cognitive deficits seem to be similarly impaired in BD across the life span in children (Joseph et al., 2008) and geriatric population (Young et al., 2006). Even in unaffected first-degree relatives of BD patients who also manifest similar, though milder, deficits, especially in verbal memory and aspects of executive functions (Bora et al., 2009). In the review by Torres et al. (2007), 39 studies of strictly euthymic patients were reviewed, which evaluated a total of 948 patients and 1128 controls. They reported a moderate to large effect size in executive function deficits and concluded that cognitive deficits for nearly all tasks were homogeneous across studies and that all were euthymic patients, which underscores the likelihood that the observed cognitive deficits reflect a trait feature of the illness (Torres et al., 2007).

We agree with the explanation provided in a recent meta-analysis that cognitive dysfunction in patients with bipolar illness studied in the euthymic state increases as a function of the prior number of episodes and that these deficits, particularly in the domains of attention, memory, and executive functioning existed as a result of the number of prior manic, depressive, or total episodes. The elaboration that the patients in the reviewed studies were in a euthymic so that the results are not confounded by state-related severity of depression or mania gives more solid grounds for our findings (Post et al., 2012).

In conclusion, we report significant cognitive impairments in euthymic bipolar patients in comparison to healthy controls that affect all domains of cognitive functions, including general IQ levels, memory, sustained attention and executive functions. Although all patients were in the euthymic state, some differential cognitive deficits appeared to be related to specific clinical and demographic variables of which the number of previous episodes, the type of the episode and previous hospitalizations were correlated with most cognitive functions assessed. Incorporating those clinical variables into consideration in the treatment plan of future bipolar patients can help minimize their impact on further impairments of cognitive functions during the euthymic states.

5.1. Strengths and limitations

The main strengths of this study are that it is one of very few Egyptian studies addressing the issue of cognitive functions in euthymic bipolar sample, and that it employed the assessment of numerous cognitive functions using specific and validated psychometric tools. Limitations include the relatively small number of the sample studied associated with the plethora of results obtained especially during analysis of the sub-domains of the cognitive tests used, which limited drawing solid conclusions; furthermore, it was a cross-sectional study so caution is still warranted in explaining the findings compared to longitudinal studies that would be more confirmative. Finally cognitive assessment was carried out using tools measuring current cognitive abilities (WAIS) with no measure of premorbid cognitive abilities primarily due to the lack of an Arabic tool to measure that such as the National Adult Reading test (NART); however, it would serve as a pilot research to be followed by more specific research into each cognitive domain separately.

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Conflict of interest

Disclosure of conflict of interest: All authors declare no actual or potential conflict of interest whether financial, personal or otherwise related to this manuscript.

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