Study of memory dysfunction and interleukin-6 in euthymic Egyptian patients with bipolar disorder

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Background
There is evidence supporting a pathophysiological role for inflammatory markers in bipolar disorder (BD). Interleukin-6 (IL-6) was assumed to play a role in pathophysiology as well as in memory deficits in BD during euthymia.

Aim of the study
The aim of this study was to assess the level of serum IL-6 in patients with BD during euthymia and its relation to memory dysfunction.

Patients and methods
Forty patients with BD during euthymia and 40 healthy controls matched in age, sex, and educational level to the patients' group were assessed and compared as regards the level of serum IL-6 and memory functions.

Results
The mean level of serum IL-6 of patients with BD was significantly higher than that of healthy control group. Patients showed poorer performance in verbal memory. There was a statistically significant negative correlation between the level of serum IL-6 and some memory functions such as information, orientation, mental control, figural memory, visual paired association, visual memory span, digit span, and verbal memory. Also, there was a statistically significant positive correlation between the level of serum IL-6 and the age, number of episodes, and duration of illness in the patient's group.

Conclusion
The level of serum IL-6 in patients with BD during euthymia is higher than that of healthy controls and correlated positively with memory dysfunctions, age, number of episodes, and duration of illness in BD during euthymia.

Keywords:
bipolar disorder, euthymia, memory functions, serum interleukin-6

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Introduction

Inflammation has been shown to be involved in the pathophysiology of bipolar disorder (BD) and cognitive impairment [1]. BD is accompanied by moderately increased plasma levels of proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor in the postmortem frontal cortex of bipolar patients [2].

IL-6 is one of the most important cytokines involved in the pathogenesis of immune and inflammatory disorders. Several studies have shown increased levels of IL-6 in manic and depressive episodes and also during euthymia in patients with BD [3]. Also, Remlinger-Molenda *et al.* [4], found that elevated IL-6 has been one of the most consistent findings in BD.

BD has been associated with marked cognitive impairment, including euthymic periods [5]. There is evidence of stable and lasting cognitive impairment in all phases of BD, including the remission phase, particularly in the following domains: sustained attention, memory, and executive functions [6].

Euthymic bipolar patients exhibit cognitive deficits, which are correlated with clinical variables such as the number, type of episodes, and previous hospitalization [7].

The study aimed to compare the level of serum IL-6 and memory dysfunctions in patients with BD with that of healthy controls and to study the relation between serum level of IL-6 and memory dysfunctions in these patients with BD.

Patients and methods

Patients

Patients consisted of two groups: group A (case group) consisted of 40 patients with BD [18 (45%) patients were diagnosed as having bipolar I disorder and 22 (55%) patients diagnosed as having bipolar II disorder] diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (DSM-5) of the American Psychiatric Association [1]. Clinical criteria were established by the same psychiatrist taking care of the patients. Patients were recruited from the Psychiatry

Outpatient Clinic, Fayoum University, Fayoum, Egypt. Patients were recruited in euthymic state if they did not meet the criteria for any mood episodes in the last 2 months and had Hamilton Depression Rating Scale (HAMD-17) and Young Mania Rating Scale (YMRS) scores lower than 7 in the week before the assessment.

Group B (control group) consisted of 40 healthy control patients matched in age, gender, and educational levels to the patients group who were volunteers from the paramedical staff of Fayoum University Hospital and had no past history of psychiatric disorders.

Participants were in the range from 18 to 50 years old and both men and women were included in the study. Although, patients with a history of other psychiatric disorders, drug dependence or abuse, mental retardation, any clinical disorder which affect memory (including epilepsy and seizures, encephalitis, trauma to the skull, or any central nervous system disorders), any autoimmune disorders, or history of ECT administration in the past 6 months before assessment were excluded from the study.

Methods

All patients were diagnosed using the Structured Clinical Interview for DSM-IV Disorders (SCID-I) [8] that had been modified to DSM-5 clinical criteria by the same psychiatrist taking care of the patients. The following instruments were administered: questionnaire for sociodemographic and clinical data, 17-item Hamilton Depression Rating Scale (HAMD-17) to assess severity of depressive symptoms [9], and Young Mania Rating Scale (YMRS) [10] to assess severity of manic symptoms. Patients were classified as euthymic if they did not meet the criteria for any mood episodes in the last 2 months and had HAMD-17 and YMRS scores of lower than 7 in the week before the assessment. Then, both the patient group and the control group were evaluated for memory functions by short forms of the Wechsler Memory Scale [11] and the serum IL-6 level was assessed.

Neuropsychological tests

All participants were referred to the same psychologist who was trained to the Wechsler Memory Scale-Revised (WMS-R) short form [11] in Psychiatry Department, Fayoum University Hospitals for the evaluation of possible memory dysfunctions. The WMS-R comprises a series of brief subtests, each one measures a different facet of memory. The eight subtests measure short-term learning and recall of both verbal and figural material. Verbal stimuli were read to the examinee and figural stimuli were presented visually. The verbal and figural subtests were alternated to provide variety and to maintain the examinee's interest. The eight tests contribute to the assessment of the general memory (five subtests) and attention/concentration/psychomotor speed (three subtests). The general memory group is further subdivided into two subgroups measuring verbal memory (two subtests) and visual memory (three subtests). The test takes around 35 min.

IL-6 assay

Plasma levels of IL-6 were quantified by means of high sensitivity enzyme-linked immunosorbent assay methods (R&D Systems, Minneapolis, Minnesota, USA) with all samples from both groups assayed at the same time, in a single run with a single lot number of reagents and consumables used by a single operator, with intra-assay coefficients of variation for all variables less than 5%.

Ethical consideration

This study reviewed by the Faculty of Medicine Research Ethical Committee. The researcher informed the participants about the objectives of the study, the examination, and investigation that will be done. Also, the confidentiality of their information and their right not to participate in the study were done. A written informed consent was obtained from all patients included in the study.

Statistical analysis

Data were collected and coded to facilitate data manipulation and double entered into Microsoft Access and data analysis was performed using the SPSS software, version 18 in Windows 7. Simple descriptive analysis in the form of numbers and percentages for qualitative data, and arithmetic means as central tendency measurement, SDs as measure of dispersion for quantitative parametric data, and inferential statistic tests:

(1) For quantitative parametric data: Independent Student's *t*-test was used to compare measures of two independent groups of quantitative data.
(2) For quantitative nonparametric data: Mann–Whitney test was used to compare two independent groups.
(3) For qualitative data: χ^2-test was used to compare two or more than two qualitative groups and bivariate Pearson's correlation test was used to test the association between variables.
(4) A P value less than or equal to 0.05 was considered the cutoff value for significance.

Results

The demographic and clinical data of the studied groups is shown in Table 1. It showed that there was no statistically significant difference between the case and control groups as regards age, sex, and education which indicated a proper matching between two groups ($P = 0.9$, 0.5, 0.9, respectively).

Table 1 also shows that 30% had a positive family history of BD versus 70% of patients who had negative family history. Of that, 32.5% had a positive history of hospitalization versus 67.5% for negative history. The mean number of previous episodes was 1.1 ± 1.5 which ranged between one and seven episodes; and the mean for age of disease onset was 24.5 ± 5.5 which ranged between 16 and 38 years; and the mean for duration of illness was 3.8 ± 3.8 years which ranged between 1 and 15 years.

The mean of the serum levels of IL-6 was statistically significant which is higher in the case group than in the control group ($P=0.05$). Also, logical memory and verbal paired association (easy and hard) were highly statistically significantly lower in the case group than in the control group ($P<0.001$). However, there was no statistically significant difference between case and control groups as regards information, mental control figural memory, visual memory, digit span forward and backward, visual paired association and visual reproduction which indicated that BD had no effect on these variables of memory ($P>0.05$) as shown in Table 2.

The mean serum levels of IL-6 was statistically significantly high among cases with a positive history of hospitalization ($P=0.01$); however, there was no statistically significant association between the mean of serum levels of IL-6 and neither of gender nor positive family history among cases which indicated that patients' sex or family history had no effect on serum IL-6 level ($P=0.1$ and 0.2, respectively) as shown in Table 3.

Also, the mean serum levels of IL-6 had a highly statistically significant positive correlation with each of age, number of previous attacks, and duration of illness, which indicated that the higher the age, the number of previous attacks, and disease duration, the higher the

Table 3 Association between IL-6 level and each of sex, family history, and hospitalization among the case group

	IL-6			
Variables	Mean	SD	Test of sig	*P* value
Sex				
Male	28.5	7.3	$U=1.56$	0.1
Female	44.1	41.7		
Family history				
Positive	46.8	45.8	$U=1.27$	0.2
Negative	32.9	23.7		
History of hospitalization				
Positive	55.38	51.6	$U=2.71$	0.01
Negative	28.22	7.4		

IL, interleukin; *U*, Mann–Whitney test.
$P<0.05$ is significant.
$P<0.0001$ is highly significant.

Table 1 Demographic and clinical data in studied groups

	Case group		Control group			
Variables	Mean	SD	Mean	SD	Test of significance	*P* value
Age (years)	28.1	6.8	28.3	6.9	$t=0.13$	0.9
Education period (years)	9.7	3.3	9.6	3.2	$U=0.14$	0.9
Sex [n (%)]						
Male	18 (45)		21 (52.5)		$\chi^2=0.45$	0.50
female	22 (55)		19 (47.5)			
Family history						
Positive	12 (30)		5 (12.5)		$\chi^2=3.66$	0.055
Negative	28 (70)		35 (87.5)			
History of hospitalization in psychiatric hospitals [n (%)]						
Positive	13 (32.5)		––		–	
Negative	27 (67.5)		–		–	
Variables	Range	Mean/median	SD/IQR			
Number of previous episodes	0–7	1.1/1	1.5/1	–		
Age of onset (years)	16–38	24.5/23.5	5.5/7	–––		–
Duration of illness (years)	1–15	3.8/1.5	3.8/6	–––		

IQR, interquartile range; *t*, Students' *t*-test; *U*, Mann–Whitney test; χ^2Chi squared test.
$P<0.05$ is significant.
$P<0.0001$ is highly significant.

Table 2 Comparative data between the case group and the control group as regards mean serum IL-6 levels and mean scores of memory tests ($N=40$)

	Case group		Control group			
Variables	Mean	SD	Mean	SD	Test of significance	*P* value
IL-6	37.1	31.9	26.6	8.9	$U=2.01$	0.05
Information and orientation	9.7	0.45	9.8	0.39	$t=1.06$	0.3
Mental control	4.33	1.1	4.47	1.1	$t=0.57$	0.5
Logical memory	15.5	3	19.7	4	$t=5.31$	<0.001
Visual memory span	6.48	1.4	6.5	1.4	$t=0.06$	0.9
Digit span	6.58	1.2	6.7	1.2	$t=0.45$	0.7
Visual paired association	8.32	2.4	8.4	2.4	$t=0.15$	0.9
Visual reproduction	22.2	7.9	22.4	7.7	$t=0.11$	0.9
Verbal paired association						
Easy	7.68	1.8	9.25	1.7	$t=4.01$	<0.001
Hard	3.48	1.6	5.65	1.8	$U=5.7$	<0.001

t, Students' *t*-test; *U*, Mann–Whitney test; χ^2Chi squared test.
$P<0.05$ is significant.
$P<0.0001$ is highly significant.

Table 4 Correlation between IL-6 with age, educational level, number of previous attacks, age of onset of bipolar disorder, and duration of illness among the case group

	IL-6		
Variables	*r*	*P* value	Significance
Age (years)	0.46	0.003	HS
Educational level (years)	−0.42	0.007	HS
Number of previous attacks	0.82	<0.001	HS
Age of onset of bipolar disorder	0.24	0.1	NS
Duration of illness	0.47	0.002	HS

HS, highly significant; IL, interleukin.
$P<0.05$ is significant.
$P<0.0001$ is highly significant.

Table 5 Correlation of IL-6 levels with mean scores of memory tests among the case group

	IL-6		
Variables	*r*	*P* value	Significance
Information and orientation	−0.52	0.001	HS
Mental control	−0.49	0.001	HS
Logical memory	−0.22	0.2	NS
Figural memory	−0.46	0.003	HS
Visual paired association	−0.32	0.04	S
Visual reproduction	−0.31	0.06	NS
Visual memory span	−0.32	0.04	S
Digit span	−0.49	0.001	HS
Verbal paired association			
Easy	−0.47	0.002	HS
Hard	−0.51	0.001	HS

HS, highly significant; IL, interleukin; S, significant.
$P<0.05$ is significant.
$P<0.0001$ is highly significant.

serum IL-6 level among cases ($P=0.003$, <0.001, 0.002, respectively). Also, the mean serum levels of IL-6 had a statistically significant negative correlation with educational level, which indicated that the lower the education level, the higher the serum IL-6 level among cases ($P=0.007$). However, there was no statistically significant correlation between the mean serum levels of IL-6 and age of disease onset ($P=0.1$) as shown in Table 4.

The mean serum levels of IL-6 had a highly statistically significant negative correlation with some memory functions such as information, orientation level, mental control, figural memory, digit span, and verbal paired association (easy and hard) levels which indicated that a decrease in their levels will be associated with an increase in serum IL-6 level among cases ($P=0.001$). Also, the mean serum levels of IL-6 had a statistically significant negative correlation with visual paired association and visual memory span ($P=0.04$). However, there is no statistically significant correlation between IL-6 level and neither logical memory nor visual reproduction ($P>0.05$) as shown in Table 5.

Discussion

BD has been associated with increased peripheral levels of proinflammatory cytokines, and this mild chronic inflammation tends to exacerbate during mood episodes [12]. BD patients in mania exhibited increased circulating levels of IL-6 and tumor necrosis factor-α (TNF-α) [13]. The immune changes already observed in euthymia are enhanced during mania and depressive state [14]. This altered cytokine levels during symptomatic (i.e. mania and depression) and asymptomatic intervals of the illness corroborate the hypothesis that inflammatory mediators could be related to the cognitive decline in BD [15].

In this study, the mean of serum levels of IL-6 was statistically significantly higher in the case group than the control group ($P=0.05$). This results was in accordance with those obtained by Jacoby *et al.* [16], Hamdania *et al.* [17], and Grande *et al.* [18], who found that IL-6 significantly increased in BD during euthymic state. Also, Brietzke *et al.* [3] observed that several studies showed increased levels of IL-6 in manic and depressive episodes and also during euthymia in patients with BD.

In a prospective 6–12 months follow-up study that investigated state-specific, intraindividual alterations in levels of brain-derived neurotrophic factor, high sensitivity C-reactive protein, IL-1β, IL-6, IL-8, IL-18, and TNF-α in 60 patients with bipolar I disorder with an acute severe manic episode and in subsequent euthymic and depressive or manic states and compared with repeated measurements in healthy controls. The levels of IL-6 and IL-8 were increased by 64 and 24%, respectively, in patients with BD overall compared with healthy controls. Considering only euthymic states, the levels of IL-6 were increased by 57% and IL-8 were increased by 22% compared with healthy controls [16].

However, these findings were not consistent with that of the study conducted by Kunz *et al.* [19], which aimed at characterizing serum levels of IL-6, IL-10, and TNF-α in patients with BD and schizophrenia. They found that there was no statistically significant difference in the mean level of serum IL-6 between patients with BD in euthymic state and healthy controls though it was still relatively higher in the BD group. This discrepancy may be due to the small BD group in the latter study (20 participants) being compared with 80 healthy controls and so perhaps a statistically significant difference may have been found between the patients and control group if a larger BD group was included. Moreover, in the latter study, obese and smoking participants were excluded, which might have acted as a confounding factor due to the effect of obesity and smoking on IL-6 level.

In this study, logical memory and verbal paired association (easy and hard) was highly statistically significantly lower in the case group than in the control group ($P<0.001$). However, there was no statistically significant difference between case and control groups regarding information, mental control figural memory, visual memory, digit span forward and backward, visual paired association, and visual reproduction, which indicated that BD had no effect on that variables of memory ($P>0.05$) shown in Table 2.

These results were consistent with many authors such as Okasha *et al.* [7], who studied cognitive functions in euthymic Egyptian patients with BD and found that

euthymic bipolar patients exhibit cognitive deficits. Also, Klara *et al.* [6], who studied cognitive impairment in BD found that there was evidence of stable and lasting cognitive impairment in all phases of BD, including the remission phase, particularly in the following domains: verbal memory and executive functions. Other studies [20,21] also found that euthymic bipolar patients demonstrate relatively marked impairment in aspects of executive function and verbal memory.

Also, this finding was consistent with that of the comparative study conducted by Zubieta *et al.* [22], who studied cognitive function in euthymic bipolar I disorder in comparison with healthy controls. The latter study showed a statistically significant difference between the BD group and the control group as regards verbal memory, executive functioning, and motor coordination.

However, it is now clear that the 'remitted' euthymic bipolar patients have distinct impairments of executive function, verbal memory, psychomotor speed, and sustained attention. Mood stabilizers and atypical antipsychotics may reduce cognitive deficits in certain domains and may have a positive effect on the quality of life and social functioning [6].

In the present study, the mean levels of IL-6 was statistically significantly high among cases with a positive history of hospitalization ($P=0.01$). However, there was no statistically significant association between the mean of serum levels of IL-6 and neither of gender nor positive family history among cases which indicated that patients' sex or family history had no effect on IL-6 level ($P>0.05$) (Table 3).

This finding was concordant with studies conducted by Kim *et al.* [23] and Grassi-Oliveira *et al.* [24], which showed that there was no correlation between IL-6 and clinical variables such as sex and family history. However, there was a statistically significant relation between IL-6 level and hospitalization history with high mean of IL-6 among patients with a positive history of hospitalization, although hospitalization is usually indicated in severe cases and severe mood symptoms. So, IL-6 increased with severe cases and severe mood symptoms. This finding was consistent with the study conducted by Brietzke *et al.* [25], who revealed that mood symptoms and severity of the disease showed a positive correlation with IL-6.

This study showed that there was statistically significant positive correlation between IL-6 and age with *P* values less than 0.05. This means that increasing age is associated with an increase in IL-6 level. This result was consistent with the findings of the studies conducted by Roubenoff *et al.* [26], who showed that production of IL-6 was increased in the elderly compared with healthy young individuals. Also, it was consistent with the study by Ferrucci *et al.* [27], who found that in both men and women, older age was associated with higher levels of IL-6.

As regards the correlations between the number of previous episodes and disease duration with IL-6, there was a statistically significant positive correlation between IL-6 and each of the number of previous episodes and disease duration ($P<0.05$). These results were in accordance with those obtained by Grande *et al.* [18], who studied the distinction between two clusters of bipolar patients, early and late stage. Early-stage bipolar patients typically have better functioning, fewer episodes, older age of onset of the disorder, and lower levels of IL-6. Conversely, late-stage bipolar patients present a higher number of episodes and clinical correlates of a more severe disorder in terms of their ability to function and in terms of bodily changes such as increased inflammatory states.

In this study, there was a statistically significant negative correlation with *P* values less than 0.05 between IL-6 and duration of education, which indicated that a decreasing in educational duration will be associated with an increase in IL-6 level among cases. This finding was consistent with the study conducted by Hemingway *et al.* [28], in a sample of 283 nonsmokers and found that social position and educational level were inversely associated with IL-6 and C-reactive protein. Also, the study conducted by Marsland *et al.* [29] showed that correlational analyses supported the existing literature and showed that higher levels of the inflammatory mediator IL-6 were associated with fewer years of education (a proxy for lower socioeconomic status).

In contrast, in this study, there was no statistically significant correlation between the level of IL-6 and age of disease onset. These results were concordant with the results of the meta-analysis conducted by Kim *et al.* [23], who found that there were no significant correlations between IL-6 and age of onset.

In the present study, there was a statistically significant negative correlation between IL-6 and each of mental control, information, and orientation which indicated that a decrease in IL-6 levels will be associated with an increase in IL-6 level among cases. This result was consistent with the findings of the studies conducted by Mooijaart *et al.* [30], who found that higher IL-6 concentration was associated with low scores of attention and concentration.

In this study, there was a statistically significant negative correlation between IL-6 and visual memory span level, which indicated that a decrease in its level will be associated with an increase in IL-6 levels. This result was concordant with the findings in the study conducted by Hamdania *et al.* [17], who conducted a study on 42 euthymic BD patients and 36 controls, which showed that there is a negative correlation between IL-6 and visual memory span level.

In the present study, there was statistically significant negative correlation between IL-6 and digit span, which indicated that a decrease in its level will be associated with an increase in the IL-6 level. This was consistent with the findings of the studies conducted by Marsland *et al.* [29] and Frydecka *et al.* [31], who found a statistically significant negative correlation between serum IL-6 and performance on digit span.

As regards figural memory and visual paired association memory, there was a statistically significant negative correlation between IL-6 and each of figural memory and

visual paired association, which indicated that a decrease in their levels will be associated with an increase in IL-6 level. This was consistent with the findings of the studies conducted by Joshua *et al.* [1], who studied inflammation as a neurobiological substrate of cognitive BD. This study showed that each of figural memory and visual paired association had a negative correlation with IL-6.

However, there was no statistically significant correlation between IL-6 level and each of logical memory and visual reproduction. This is consistent with the finding of the study conducted by Mooijaart *et al.* [30], which showed that there was no association between IL-6 and each of logical memory and visual reproduction.

In the present study, the verbal paired association memory showed statistically significant negative correlations with IL-6 level, which was consistent with the finding of the study conducted by Marioni *et al.* [32], and Elderkin-Thompson *et al.* [33]. Also, it was consistent with the finding of the study conducted by Grassi-Oliveira *et al.* [24], who found that low performances in verbal paired association memory was associated with increase in IL-6 levels.

Proinflammatory cytokines would act as major 'toxic players', contributing to psychopathological changes, cognitive impairment, and related comorbidities and could be regarded as potential biomarkers for neuroprogression in BD [34].

The neurobiological processes underlying neuroprogression are still undetermined, but inflammatory mechanisms seem to play a major role. Proinflammatory cytokines are being capable of inducing neuronal cell death through the activation of caspases and apoptotic machinery [35]. TNF-mediated process might contribute to the volumetric reduction, and hypoactivation of frontal lobes in BD [36], which are associated with disinhibition of limbic structures [37].

This corticolimbic dysfunction may underlie the emotional dysregulation and cognitive impairment associated with BD. In line with this, there is a positive correlation between increased proinflammatory cytokine levels and cognitive impairment, particularly involving frontal lobe functions [38].

Conclusion

Patients with BD during euthymia showed a high serum level of IL-6 and some memory deficits especially in the domains of verbal paired association memory and logical memory, reflecting a possible underlying association between inflammatory or immune pathophysiology of the illness and cognitive deficit. The mean serum levels of IL-6 during euthymia had a highly statistically significant positive correlation with age, number of previous attacks, and duration of illness, but a significant negative correlation with some of the memory functions such as information, orientation, mental control, figural memory, digit span, verbal paired association (easy and hard), visual paired association, and visual memory span.

Limitations of the study

The sample size in our study was relatively small and some patients were on mood stabilizers and antipsychotics, which had an effect on their IL-6 level and memory function. Moreover, a lack of premorbid cognitive assessment limits generalization of the findings.

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Conflicts of interest

There are no conflicts of interest.

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