# The Relationship of Interleukin-18 and Interleukin-6 Levels with Cognitive Functions in Bipolar Disorder

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**SUMMARY**

**Objective:** Immune function impairment has been proposed to play a key role in the cognitive decline of those with bipolar disorder (BD); however, there is little research regarding the impact of inflammation on cognitive function. This study aimed to compare levels of IL-18 and IL-6 in BD patients vs controls and to determine the relationship between these levels and cognitive impairment.

**Method:** Thirty-six euthymic BD-I patients and 38 age, sex, and educational level matched healthy controls were enrolled in this study. All participants were evaluated with neurocognitive tests. The plasma IL-6 and IL-18 levels of both groups were measured by ELISA.

**Results:** The levels of IL-6 and IL-18 in the patients and healthy controls were not significantly different. In the patients, IL-18 had a positive correlation with the completed categories score and a negative correlation with perseverative response and perseverative errors. Further in the patients, IL-18 was positively correlated with immediate recall, delayed recall, and learning scores, and negatively correlated with Stroop interference scores. There were no correlations between IL-6 levels and neuropsychological test scores in the patient group.

**Conclusion:** This is the first study to investigate the relationship between IL-18 and cognitive function. While the possible detrimental or protective effects of IL-18 in BD are not yet clear, the positive association between IL-18 and neuropsychological test scores might indicate a neuroprotective role of IL-18 in the euthymic period of BD, which is the state that is closest to physiological conditions.

**Keywords:** Bipolar disorder; Cognitive functions; Interleukin 18; Interleukin 6

## INTRODUCTION

Bipolar disorder (BD) is a common psychiatric disease resulting in significant mortality and morbidity. Over the past 20 years, the core feature of BD has been identified as cognitive impairment, which is an important determinant of personal, social, and workplace losses (Rosenblat et al. 2015). It has been shown that cognitive function impairment occurs not only during mood episodes, but also in the euthymic period (Bora et al. 2008, Demirel et al. 2012, Bourne et al. 2013, Civil Arslan et al. 2014). Although several studies have shown that patients with BD experience deterioration in cognitive functions, including verbal recall, attention and executive functions, there are not yet any neurological substrates to account for this deterioration (Rosenblat et al. 2015).

It has been suggested that immune system dysfunction plays a key role in cognitive deterioration in BD (Barbosa et al. 2014a, Bauer et al. 2014). Recently, several studies have shown that inflammation is a significant factor in the pathophysiology of BD (McNamara and Lotrich 2012, Rosenblat et al. 2014).

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In an attempt to clarify the interaction between mood symptoms in BD and inflammation, various pathophysiological mechanisms have been investigated (Guloksuz et al. 2010, Barbosa et al. 2014b). However, few studies have determined the effect of inflammation on cognitive function in BD (Bauer et al. 2014). With the exception of one study (Barbosa et al. 2012), several studies have shown a correlation between elevated proinflammatory cytokine levels in patients with BD and cognitive functions such as recall, executive functions, attention, language, and visual memory (Lotrich et al. 2014, Rolstad et al. 2015, Hoseth et al. 2016).

Experimental and clinical studies have shown that interleukin-18 (IL-18) is a key cytokine of the central nervous system. By binding to its receptor, IL-18 causes a Th1 and Th2 cell response that triggers natural killer cell cytotoxic activity and contributes to the continuation of the apoptotic process (Nakanishi et al. 2001, Dinarello and Fantuzzi 2003, Chandrasekar et al. 2004). IL-18 stimulates signal transduction by acting on the IL-18 receptor; this receptor is present in various regions of the brain, including the hypothalamus, hippocampus, and cerebral cortex. IL-18 and its specific receptor play an important role in the modulation of immune response in the central nervous system by participating in the neuroinflammatory and neurodegenerative processes (Zhang et al. 2013). Very few studies have investigated the role of IL-18 levels in psychiatric diseases. However, higher IL-18 levels have been reported in patients with schizophrenia, major depression, and BD in the manic/hypomanic period compared to healthy controls (Munkholm et al. 2015). The relationship between IL-18 levels and cognitive function has been investigated in patients with schizophrenia and Alzheimer's disease, but to our knowledge, the association between IL-18 and cognitive function in BD has not been investigated.

During inflammation, T cells, macrophages, and microglial cells release interleukin-6 (IL-6), a cytokine that helps to develop an immune response against antigens and to resolve the inflammatory state (Hamdani et al. 2015). IL-6 can cause cognitive impairment, as it stimulates the production of reactive oxygen species in the brain. It has been reported that plasma IL-6 levels are negatively correlated with semantic reasoning, attention, working memory, and executive functions in healthy adults (Gimeno et al. 2008, Marsland et al. 2006). Further, a positive correlation has been shown between IL-6 levels and impairment in working memory, executive functions, attention, immediate verbal recall, long-term memory, and psychomotor speed (Jordanova et al. 2007, Simpson et al. 2013, Mooijaart et al. 2013, Heringa et al. 2014). Serum IL-6 levels have been shown to increase in BD patients, particularly in the manic period (Munkholm et al. 2013).

This study aimed to determine whether IL-18 and Il-6 levels differ between patients with euthymic BD and healthy controls and to investigate the association between IL-18 and IL-6 and cognitive impairment in BD.

## METHODS

### Sampling

This study included 36 euthymic patients between the ages of 18 and 60 years who were referred to the outpatient clinic of Karadeniz Technical University School of Medicine and diagnosed with BD I according to the DSM-IV via structured clinical interview (SCID-I) ( First et al. 1995, Corapcıoglu et al.1999) for DSM-IV axis I disorders. BD patients were included only if they had been in the euthymic period for at least 6 months. The euthymia criteria were defined as a Hamilton Depression Scale (HAM-D) score <7 and a Young Mania Scale score <5 (HAM-D:Hamilton 1967, Akdemir et al. 2001, YMD:Young et al. 1978, Karadag et al. 2002). Patients were excluded from the study if they had any of the following:neurological or psychiatric comorbid disease, physical illness (autoimmune or infectious disease, chronic heart disease, chronic lung disease, neurodegenerative disorders, etc.), use of antiinflammatory drugs or antibiotics, pregnancy, an education level insufficient for understanding the tests, refusal to participate, history of alcohol or substance abuse in the previous 6 months, and head trauma causing loss of consciousness. The control group consisted of 38 healthy volunteers from the hospital staff who were age, sex, and education matched with the patient group. The first degree relatives of those in the control group were also evaluated for any psychiatric disease as exclusion criteria. Written informed consent was obtained from all participants. The study was initiated after ethical approval (no:2014/127) from the Karadeniz Technical University Clinical Research Ethical Committee.

### Neuropsychological Evaluation

**The Wisconsin Card Sorting Test (WCST)**:developed by Berg in 1948, the test handbook was prepared with modifications by Heaton in 1981 and 1993 (Heaton et al. 1993). The WCST measures cognitive processes such as conceptualization, attention, perseveration, working memory, executive functions, abstract thinking, and processing, and is largely concerned with the frontal lobe (dorsolateral prefrontal cortex). Turkish-language validation was established in 1996 (Karakaş et al. 1996). The computer form of the test was used in this study. The current study took into consideration the number of categories completed, the perseverative reaction number, and the perseverative error number.

**Stroop Test BSRG:** The Stroop BSRG (Basic Sciences Research Group) is a combination of the original Stroop test (Stroop 1935) and the Victoria Form (Spreen and Strauss 1998). It essentially evaluates the ability to focus and to sustain attention

in association with time and a given task, the ability to resist confounding stimuli, and the ability to halt and suppress inappropriate stimuli and inappropriate response tendencies. The Stroop test was standardized for Turkish society (Karakaş 2004), and the interference score was used in this study.

**The Rey Auditory Verbal Learning Test (RAVLT):** The original form of the RAVLT was developed by Rey in 1964. This test evaluates verbal recall and learning. The Turkish-language standardization was established in 1995 (Açıkgöz 1995). This study evaluated learning (RAVLT 1-5), recognition, instant recall (RAVLT 1), and delayed recall (RAVLT-7).

## Biochemical Analysis

Fasting serum specimens were taken between 8:00 a.m. and 10:00 a.m. on the day of the neuropsychological tests. The serum samples were centrifuged for 10 min at 3000 rpm; then, the serum was aliquoted into Eppendorf tubes and stored in a freezer at -80 degrees until further analysis. IL-6 and IL-18 levels were measured using commercial ELISA kits (DIA Source IL-6-EASIA-CE KAP1261; SunRed Human IL-18 ELISA Kit).

## Statistical Analysis

Categorical variables were expressed as numbers and percentages and numeric variables were expressed as means and standard deviations. Differences between the rates of categorical variables in independent groups were determined via chi square analysis. Comparisons of normally distributed numeric variables between two independent groups were performed using Student's t test and non-normally distributed variables were evaluated with the Mann-Whitney U test. Correlation analyses for normally distributed variables were performed with the Pearson test and those categories with at least one non-normally distributed variable were evaluated with the Spearman test. A Kolmogorov-Smirnov test was used to determine the compatibility of the variables with a normal distribution. Values of p less than 0.05 were considered significant.

# RESULTS

## Sociodemographic and Clinical Data

There were no differences between the BD patients and the healthy control group in terms of age, sex, education, or smoking status (Table 1). The patient group had a significantly higher body mass index (BMI) than the healthy controls. Although the mean HAM-D and YMRS values were below the standard cutoff score in both groups, the mania and depression scores of the BD patients were significantly higher than those of the controls. Of the BD patients, 75% received lithium, 47.2% valproic acid, and 86.1% antipsychotic medication.

**Table 1**. Sociodemographic and clinical features of patients and controls

| | | Patients | Controls | P |
|---|---|---|---|---|
| Age | | 38± 11.80 | 37.94± 12.01 | 0.984 |
| Gender | Female (%) | 22 (61.1) | 20 (52.6) | 0.616 |
| | Male (%) | 14 (38.9) | 18 (47.4) | |
| Education (years total) | | 10.88 ± 3.63 | 10.26 ± 4.25 | 0.500 |
| Smokers (%) | | 12 (33.3) | 10 (26.3) | 0.685 |
| Body mass index | | 27.75± 6.84 | 24.60±3.41 | 0.014 |
| Age of disease onset | | 25.30±8.04 | | |
| Total remission period (months) | | 27.88±20.42 | | |
| Number of manic episodes | | 2.83±2.03 | | |
| Number of depressive episodes | | 2.77±1.94 | | |
| Lithium treatment (%) | | 27 (75) | | |
| Anticonvulsant treatment (%) | | 17 (47.2) | | |
| Antipsychotic treatment (%) | | 31 (86.1) | | |
| HAM-D | | 2.36±2.05 | 0.21±0.81 | 0.000 |
| YMRS | | 0.33±0.89 | 0.00±0.00 | 0.018 |

HAM-D: Hamilton Depression Rating Scale, YMRS: Young Mani Rating Scale, p<0.05
Data are expressed as mean ±Standard deviation or n (%)

**Table 2**. Comparison of serum levels of IL-6, IL-18, and neurocognitive test scores in bipolar disorder and control groups

| | Patients (Mean± SD) | Controls (Mean±SD) | P |
|---|---|---|---|
| IL-6 (pg/ml) | 22.19±11.68 | 18.17±8.19 | 0.089 |
| IL-18 (ng/ml) | 46.43±34.91 | 56.33±45.25 | 0.863 |
| WCST | | | |
| Number of category achieved | 2.16±1.55 | 2.47±1.62 | 0.410 |
| Number of perseverative responses | 16.05±14.22 | 14.92±11.42 | 0.706 |
| Number of perseverative errors | 13.69±10.83 | 12.71±8.57 | 0.665 |
| RAVLT | | | |
| RAVLT 1 (illeriake necayy) | 5.58±1.84 | 6.39±1.99 | 0.074 |
| RAVLT7 (delayed recall) | 8.38±3.07 | 9.68±2.69 | 0.057 |
| RAVLT 1-5 (learning) | 16.30±4.39 | 19±3.78 | 0.006 |
| RAVLT (recognition) | 11.8±3.15 | 13.39±2.37 | 0.007 |
| Stroop | | | |
| Stroop interference | 21.30±11.03 | 15.05±10.24 | 0.014 |

WCST: Wisconsin Card Sorting Test; RAVLT: Rey Auditory Verbal Learning Test, SD:Standard deviation, p<0.05

## Biochemical Data

There were no significant differences between the IL-6 and IL-18 serum levels of the BD patient and control groups (Table 2). This lack of significant difference remained even after the BMI and HAM-D scores were taken as covariants (Table 3). There were no significant correlations in the IL-6 and IL-18 levels of patients with BD and age at onset of disease, duration of disease, number of mood episodes, HAM-D, YMRS or BMI (Table 4).

**Tablo 3**. The results of adjusted and unadjusted analysis of IL-6 and IL-18 levels of patient and control groups according to BMI and HAM-D scores

| | IL-6 | | | IL-18 | | |
|---|---|---|---|---|---|---|
| | Patients Mean±S.E | Controls Mean±S.E | p | Patients Mean±S.E | Controls Mean±S.E | p |
| BMI | 21.8±1.7 | 18.6±1.7 | 0.191 | 46.6±6.9 | 48.6±6.9 | 0.522 |
| HAM-D | 21.3±1.8 | 18.9±1.8 | 0.416 | 52.1±7.4 | 51.0±7.2 | 0.926 |

HAM-D: Hamilton Depression Rating Scale; BMI: Body Mass Index; Mean±SE: Mean±Standard Error, p<0.05

**Table 4**. The relationship of serum levels of IL-6 and IL-18 with clinical features and neurocognitive test scores in patient and control groups

| | IL-6 | | IL-18 | |
|---|---|---|---|---|
| | Patients | Controls | Patients | Controls |
| Age of disease onset | -0.004 | | -0.256 | |
| Duration of illness (years) | -0.098 | | -0.296 | |
| Total number of episodes | -0.200 | | -0.123 | |
| YMRS | -0.034 | | 0.200 | |
| HAM-D | 0.160 | 0.023 | -0.061 | -0.216 |
| Body Mass Index | 0.112 | 0.213 | 0.162 | 0.232 |
| **WCST** | | | | |
| Number of category achieved | 0.036 | 0.110 | 0.288* | 0.201 |
| Number of perseverative responses | 0.015 | - 0.075 | -0.264* | -0.336* |
| Number of perseverative errors | 0.016 | - 0.084 | -0.279** | -0.309 |
| **RAVLT** | | | | |
| RAVLT 1 (immediate recall) | 0.144 | 0.039 | 0.307** | 0.140 |
| RAVLT 7 (delayed recall) | 0.076 | -0.112 | 0.321** | 0.263 |
| RAVLT 1-5 (learning) | 0.079 | -0.002 | 0.297* | 0.252 |
| RAVLT (recognition) | 0.073 | 0.029 | 0.149 | -0.034 |
| **Stroop** | | | | |
| Stroop interference | | 0.218 | -0.235* | -0.208 |

HAM-D: Hamilton Depression Rating Scale, YMRS: Young Mani Rating Scale, WCST: Wisconsin Card Sorting Test; RAVLT: Rey Auditory Verbal Learning Test, *p<0.05, ** p<0.01

## Neuropsychological Test

Neuropsychological data in the BD and healthy control groups are shown in Table 2. In the BD group, IL-18 levels were positively correlated with number of WCST categories achieved, and were negatively correlated with number of perseverative responses and number of perseverative errors (r=0.288, p=0.05; r=-0.264, p=0.05; r= -0.279, p= 0.01). Additionally in the BD group, IL-18 levels were positively correlated with RAVLT instant recall, delayed recall, and learning scores (r=0.307, p=0.01; r=0.321, p=0.01; r=0.297, p=0.05), while they were negatively correlated with the Stroop interference score (r=-0.235). In the control group, there was a negative correlation between IL-18 levels and the number of WCST perseverative responses (r=-0.336, p=0.039) (Table 4).

There were no significant correlations between IL-6 levels and neuropsychological scores in BD patients or healthy controls.

However, there was a positive correlation between IL-6 and R-AVLT instant memory and between IL-18 and the number of WCST categories completed in BD patients with BMI <25 (r=535, p=0.033; r=504, p=0.047) (Table 5).

In BD patients with BMI ≥25, there was no significant relationship between IL-6 or IL-18 and neuropsychological test scores.

However, in BD patients with BMI<25, there was a positive correlation between IL-18 levels and the number of WCST categories completed (r=455, p=0.033) and a negative correlation between IL-18 levels and WCST perseverative response (r=0.538, p=0.010) and errors (r=0.521, p=0.013). There was no significant correlation between IL-6 levels and neuropsychological test scores (Table 5).

In controls with BMI ≥25, there was no significant correlation between IL-6 or IL-18 and neuropsychological test scores. In the BD patient group, there was no significant difference in individuals with BMI ≥25 compared to those with BMI<25 in terms of age, gender, and educational level. When these two subgroups were compared, the number of WCST perseverative response and perseverative errors were significantly higher in patients with BMI ≥25 (p=0.040).

In the control group, there was no significant difference between individuals with BMI ≥25 and those with BMI <25 regarding gender and educational level, but the age of the controls with BMI ≥25 was significantly higher.

While the number of WCST perseverative responses (p=0.021) and perseverative errors (p=0.008) was statistically higher in controls with BMI ≥25 when compared to those with BMI <25, R-AVLT delayed recall (p=0.019) and learning scores (p=0.003) were significantly lower in the control group with BMI ≥25.

**Tablo 5**.The relationship of serum IL-6 and IL-18 levels with neuropsychological test scores according to body mass index

| | IL-6 | | | | IL-6 | | | |
|---|---|---|---|---|---|---|---|---|
| | BMI<25 | | BMI≥25 | | BMI<25 | | BMI≥25 | |
| | P | C | P | C | P | C | P | C |
| **WCST** | | | | | | | | |
| Number of category achieved | 0.053 | 0.236 | 0.074 | 0.118 | 0.504* | 0.455* | -0.141 | -0.120 |
| Number of perseverative responses | 0.047 | -0.227 | 0.040 | -0.214 | -0.294 | -0538** | -0.232 | -0.192 |
| Number of perseverative errors | 0.053 | - 0.224 | 0.065 | -0.232 | -0.330 | -0.521* | -0.240 | |
| **RAVLT** | | | | | | | | |
| RAVLT 1 (immediate recall) | 0.053* | -0.028 | 0.0284 | -0.028 | 0.155 | 0.357 | 0.356 | -0.119 |
| RAVLT 7 (delayed recall) | 0.267 | -0.057 | 0.080 | -0.057 | 0162 | 0.115 | 0.285 | 0.174 |
| RAVLT 1-5 (learning) | 2.290 | 0.274 | 0.206 | -0.071 | 0.317 | 0.332 | 0.345 | 0,178 |
| RAVLT recognition | 0.269 | -0.096 | 0.150 | -0.096 | 0.386 | -0.209 | 0.345 | 0.058 |
| **Stroop** | | | | | | | | |
| Stroop interference | -0.479 | 0.301 | 0.079 | 0.301 | 0.356 | 0.055 | -0.129 | -0.228 |

WCST: Wisconsin Card Sorting Test; RAVLT: Rey Auditory Verbal Learning Test, BMI:Body mass index ,
P: Patient Group, C: Control Group
*p<0.05, **p<0.01

## DISCUSSION

In the current study, there were no significant differences in the IL-18 and IL-6 levels between euthymic bipolar patients and healthy controls. IL-18 levels were positively correlated with the number of categories achieved on the WCST and negatively correlated with the numbers of perseverative responses and perseverative errors. In addition, in the BD group, there was a positive correlation between IL-18 levels and instant recall, delayed recall, and learning scores, while there was a negative correlation between IL-18 levels and the Stroop interference score. There was no correlation in the BD group between IL-6 levels and cognitive functions. There was a negative correlation between WKET perseverative responses and IL-18 levels, but no relationship between IL-6 levels and cognitive functions.

There were no significant differences in the IL-18 levels between the euthymic BD patients and the controls. To our knowledge, only one study in the literature has investigated the relationship between levels of IL-18 and BD (Munkholm et al. 2015). Similar to our own findings, that study reported significantly higher IL-18 and IL-6 levels in the manic/hypomanic period in patients with rapid cycling BD, and no significant difference in the euthymic period (Munkholm et al. 2015).

In our current study, we found no difference in IL-6 levels between euthymic BD patients and healthy controls. A few studies have investigated IL-6 levels in BD. According to two separate meta-analyses by Munkholm et al., no significant difference between IL-6 levels in patients with BD and those in healthy controls has been reported in the literature (Munkholm et al. 2013a, Munkholm et al. 2013b).

To our knowledge, the current study is the first to investigate the relationship between IL-18 levels and cognitive functions in patients with BD. Some studies have reported that increased levels of proinflammatory cytokines are associated with poorer cognitive function (Dickerson et al. 2013, Doganavsargil-Baysal et al. 2013, Lotrich et al. 2014, Hamdani et al. 2015, Hope et al. 2015). It has been reported that serum levels of TNF-α, IL-1, and IL-6 are negatively correlated with cognitive functions in BD patients (Rosenblant et al. 2015). In the present study, we found a correlation between IL-18 and three cognitive areas we investigated. Specifically, we found a positive correlation between IL-18 levels and the number of categories achieved on the WCST, which assesses executive functions, and we found negative correlations between IL-18 levels and perseverative response and perseverative error. There was a positive correlation between IL-18 levels and instant recall, delayed recall, and learning on the RAVLT, which assesses verbal learning and memory. There was a negative correlation between IL-18 and the Stroop interference score (assessing attention). The consistency of the correlations we found between IL-18 levels, the WCST and RAVLT subscores, and the Stroop interference score is significant, in that it indicates a positive correlation between IL-18 levels and the cognitive functions of executive function, attention, verbal learning, and memory in patients with BD. In the control group, there was a negative correlation between the number of WCST perseverative responses and IL-18 levels. This finding is in accordance with the positive correlation between IL-18 levels and cognitive functions. However, these findings conflict with previously published studies that report a negative correlation in BD patients between proinflammatory cytokines (such as TNF-α, IL-1, and IL-6) and cognitive functions (Rosenblant et al. 2015).

To our knowledge, the only study investigating the relationship between IL-18 levels and cognitive functions was recently performed in a group of schizophrenia patients (Zhang et al. 2013). Similar to the findings of the current study, Zhang et al. observed that IL-18 levels were positively correlated with

the visual-spatial/structural cognitive functions; they reported that this finding was associated with a highly protective, rather than toxic, effect of IL-18 in schizophrenia.

IL-18 is known to play an important role in the pathogenesis of ischemic, traumatic, infectious, and autoimmune diseases of the central nervous system (Losy and Niezgoda 2001, Canella 2004). IL-18 plays a role in neuroinflammation in diseases of the central nervous system, and has also been reported to exhibit neuroprotective effects (Zhang et al. 2013). These neuroprotective effects are attributed to role of IL-18 in stimulating the release of IFN-γ in brain parenchyma in models of viral central nervous system infection; the release of IFN- γ has been shown to cause the elimination of viruses from neurons (Mori et al. 2001). While IL-18 impairs neural function by increasing inflammation in cases of brain injury, it may also have a neuroprotective effect, as shown in viral infection models (Felderhoff et al. 2005).

Under physiological conditions, microglia play an important role in neuroplasticity and the regulation of synapses (Gosselin and Rivest 2007). Activated microglia are known to destroy unused synapses and thereby increase the functional connections of pathways in the brain by enhancing the capacity of used synapses and connections (Harry and Kraft 2012). In some disease conditions, microglia may be pathologically over-reactive and cause an increase in oxidative stress, neuroapoptosis, and inappropriate synapse destruction (Stertz et al. 2013), which can result in neural functioning impairment and compromise of affective and behavioral functions (Ekdahl 2012, Harry and Kraft 2012, Frick et al. 2013). While it has been reported in the majority of studies that interleukin levels are significantly higher in the BD manic period compared to healthy controls, no difference has been shown in the euthymic period. In our current study, we saw a positive association between IL-18 levels and neuropsychological test scores; this may be attributed to the neuroprotective effect of IL-18, rather than a neurotoxic effect, in the euthymic period in BD, which is the closest state to physiological conditions.

IL-18 is involved in neuronal signal conduction in the hypothalamus and is known to increase the release of synaptic glutamate in hippocampal neurons as well as increase postsynaptic AMPA receptor expression (Dinarello and Fantuzzi 2003, Prinz and Hanisch 1999, Kanno et al. 2004). Recently, the concept of a 'dual role' of cytokines has emerged as the result of studies showing that inflammatory mediators can exhibit both neurotoxic and neuroprotective effects. These effects are dependent on arrangement patterns and areas of receptor expression in the injured brain. The probable compromising or protective role of IL-18 in BD has not yet been established, although the positive correlation observed between IL-18 levels and neuropsychological test scores in our current study suggests a likely neuroprotective effect.

In our current study, we found no correlation between IL-6 levels and neuropsychological test scores in euthymic BD patients. To our knowledge, no other studies have investigated this association in a euthymic patient group. The majority of studies presenting evidence suggesting that IL-6 affects cognitive functions have been performed in an elderly population. In these studies, positive relationships have been reported between IL-6 levels and cognitive areas, such as working memory (Simpson et al. 2013), executive functions (Mooijaart et al. 2013), attention (Heringa et al. 2014), and psychomotor speed (Jordanova et al. 2007).

Further, it has been reported that obesity has a deteriorating effect on cognitive functions in patients with BD (Yim et al. 2013, Depp et al. 2014). In the present study, the patients and controls were divided into two subgroups (BMI≥25 and BMI<25) to reveal the effects of BMI on cognitive functions. Among the subgroups of patients and controls, the individuals with BMI ≥25 showed significantly impaired executive functions. While patients with BMI<25 had a positive correlation between IL-6 or IL-18 levels with cognitive functions, those patients with BMI>25 did not. These results suggest that the positive correlation of IL-6 and IL-18 levels with cognitive functions in normal-weight individuals is impaired in the overweight and obese population.

One of the limitations of this study is that the patients undergoing neuropsychological tests were receiving drug therapy. In order to eliminate the effects of drugs on cognitive functions and proinflammatory parameters, euthymic patients not using drugs should also be investigated. However, since such patients are very rare, it is difficult to conduct such an investigation. Another limitation is the small size of the sample group. In addition, factors such as lifestyle and genetic characteristics were not controlled in this study. Although BMI was significantly higher in the patient group, there was no correlation between BMI and neuropsychological test scores. On the other hand, the strict inclusion criteria, the use of SCID-I to evaluate the euthymic bipolar patient and healthy control groups, and the careful examination of medical history represent powerful aspects of this research.

Impairment in cognitive functions is observed in the depressive, manic, and euthymic periods in BD. Further, inflammation has been shown to play a significant role in cognitive impairment and in the pathophysiology of BD. The current study investigated relationships between IL-6 and IL-18 and cognitive functions only in the euthymic period in BD. Biochemical studies with larger sample groups may provide more information about the association between IL-6 and IL-18 and cognitive functions in BD. In addition, studies investigating the relationship between interleukins and cognitive functions are also needed in the manic and depression periods, in which inflammation is reported to be more severe, and proinflammatory cytokines to be at higher levels.

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