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Association between increased serum interleukin-6 levels and sustained attention deficits in patients with major depressive disorder

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Abstract

Background. The pathophysiology of cognitive impairment in patients with the major depressive disorder (MDD) may involve neuroinflammation mediated by cytokines.
Objective. The aim of this study was to examine the serum interleukin-6 (IL-6) levels, sustained attention, and their association in patients with MDD.
Methods. Thirty patients with MDD and 30 healthy controls were enrolled in this case-control study. Sustained attention was measured using the Rapid Visual Information Processing (RVP) task in the Cambridge Neuropsychological Tests Automated Battery. The serum IL-6 levels of all subjects were assessed by sandwich enzyme-linked immunosorbent assays.
Results. There were significant differences in the $\log_{10}$RVP total hits, $\log_{10}$RVP total misses, and $\log_{10}$RVP mean latency between patients with MDD and healthy controls ($F = 6.04$, $p = 0.017$; $F = 19.77$, $p < 0.0001$; $F = 14.42$, $p < 0.0001$, respectively). The serum levels of Log_{10}IL-6 were significantly higher in patients with MDD than in healthy controls ($F = 192.27$, $p < 0.0001$). The $\log_{10}$IL-6 levels were also positively correlated with the $\log_{10}$RVP mean latency in patients with MDD ($r = 0.45$, $p = 0.013$). A further stepwise multivariate regression analysis indicated that the $\log_{10}$IL-6 levels were significantly associated with the $\log_{10}$RVP mean latency in patients with MDD ($\beta = 0.31$, $t = 2.41$, $p = 0.025$).
Conclusions. Our data suggested that increased IL-6 levels were associated with the psychopathology of MDD, and that abnormal IL-6 levels were implicated in the impairment of sustained attention in patients with MDD.

Introduction

Major depressive disorder (MDD) has become a common and severe psychiatric disorder, typically characterized by one or more episodes of depressive mood, markedly diminished interest or pleasure, and even recurrent thoughts of death. The prevalence of MDD is approximately 17% in a Chinese population (Philips *et al.* 2009). Although MDD mainly involves the disturbance of mood, attention impairment has been identified as one of its core features (McDermott & Ebmeier, 2009; Lee *et al.* 2012). The capacity of attention supports the key cognitive processes and reports cognitive problems such as lack of effort, memory deficit, and slowed information processing, which might be secondary to attention impairment (Lezak, 1982; Mesulam, 1985; Williams *et al.* 2000). Previous studies have indicated that the capacity of attention was significantly impaired in patients with MDD (Kemp *et al.* 2009; Cotrena *et al.* 2016). Our recent finding also showed that the score of the attention index in patients with MDD was significantly lower than that in healthy controls (Shao *et al.* 2017). Moreover, the impairment of sustained attention has been regarded as a potential marker of MDD (Rock *et al.* 2014), which has been investigated in different subgroups of MDD. For example, a study showed that sustained attention in adolescents with MDD in the acute episode was impaired compared with healthy controls (Maalouf *et al.* 2011). There was a significant difference in sustained attention between unmediated patients with current MDD and healthy controls (Porter *et al.* 2003; van der Meere *et al.* 2007; Braw *et al.* 2011; Yang *et al.* 2015). Remitted patients with MDD were also found to exhibit a greater impairment of sustained attention than healthy controls (Paradiso *et al.* 1997; Paelecke-Habermann *et al.* 2005; Maalouf *et al.* 2011). Taken together, these studies support the notion that the impairment of

sustained attention in patients with MDD may be considered a potential target for clinical and psychosocial treatments. However, the pathophysiology of sustained attention impairment in patients with MDD remains unclear and requires further investigation.

The pathogenesis of MDD may be involved in the initiation of neuroinflammation, which is associated with several pathophysiological processes, such as activation of the hypothalamic-pituitary-adrenal axis, depletion of tryptophan for serotonin conversion, and decreased neuroplasticity (Danese *et al.* 2008; Miller *et al.* 2009; Felger & Lotrich, 2013). The immune developmental hypothesis for MDD has been supported by several lines of evidence including increased serum levels of inflammatory markers (Liu *et al.* 2012; Howren *et al.* 2009; Dowlati *et al.* 2010), emergence of depressive symptoms following inflammation-based treatments (Capuron *et al.* 2002; Dantzer *et al.* 2008; Raison *et al.* 2013), and the link between inflammatory activation and abnormal functions in the prefrontal cortex of MDD patients (Setiawan *et al.* 2015). Recently, genetic studies have further highlighted the role of the immune system by detecting the susceptible genes and chromosomal regions as the risk loci of MDD (Anders *et al.* 2013; Goodyer, 2015).

Interleukin 6 (IL-6) is a multifunctional cytokine that regulates the growth and differentiation of various cells and plays a critical role in immune response and acute phase reactions (Kopf *et al.* 1994; Kiecolt-Glaser *et al.* 2003). In addition, at the molecular level, the *il-6* gene on human chromosome 7p15 was identified as a risk gene for MDD (Camp *et al.* 2005). The mutations of the *il-6* gene were also involved in susceptibility to MDD (Udina *et al.* 2013; Tartter *et al.* 2015; Zhang *et al.* 2016). Thus, it is possible that the increasing expression of the *il-6* gene was associated with the etiology of MDD (Yi *et al.* 2012; Jansen *et al.* 2016; Zhang *et al.* 2016).

Conversely, at the protein level, serum IL-6 contents were also significantly higher in patients with MDD than in healthy controls (Liu *et al.* 2012; Howren *et al.* 2009; Dowlati *et al.* 2010; Goldsmith *et al.* 2016). Similarly, IL-6 levels were also found to be significantly higher in the CSF of patients with MDD compared with healthy controls (Kern *et al.* 2014). However, after treatment with antidepressants, IL-6 levels were significantly reduced in patients with MDD (Hiles *et al.* 2012; Dahl *et al.* 2014; Yang *et al.* 2015). Collectively, serum IL-6 may be considered a potential biomarker for MDD.

Previous studies have shown that elevated IL-6 levels may influence cognitive functions. For example, there is an inverse relationship between plasma IL-6 levels and cognitive functions in patients with MDD (Marioni *et al.* 2010; Grassi-Oliveira *et al.* 2011; Goldsmith *et al.* 2016). Plasma IL-6 levels were reported to be negatively correlated with semantic fluency, auditory recognition memory, working memory, and executive function in healthy adults (Marsland *et al.* 2006; Wright *et al.* 2006; Gimeno *et al.* 2008). Positive associations between IL-6 levels and cognitive deficits derived from a number of cognitive domains have been reported in older subjects (Jordanova *et al.* 2007; Gimeno *et al.* 2009; van den Kommer *et al.* 2010; Lekander *et al.* 2011; Mooijaart *et al.* 2013; Simpson *et al.* 2013; Heringa *et al.* 2014). Increased IL-6 levels may predict worse cognitive performance in elderly patients with type 2 diabetes (Rafnsson *et al.* 2007). Moreover, several studies have shown that higher IL-6 levels were significantly associated with the impairment of attention function in patients with other psychiatric disorders (Frydecka *et al.* 2015). However, to our best knowledge, no studies have examined serum IL-6 levels in relation to sustained attention in patients with MDD. Therefore, the aim of the present study was to examine whether altered IL-6 levels are associated with the impairment of sustained attention in patients with MDD.

Methods

Ethics statement

This study was conducted between August 2016 and May 2017. Following a complete description of the study protocol and procedures to each individual by a psychiatrist or research coordinator, written informed consent was obtained in accordance with the study protocol that was approved by the Institutional Review Board at the Affiliated Guangji Hospital of Soochow University.

Subjects

Patients with MDD ($n = 30$; male/female = 12/18) were recruited from inpatient unit of the Affiliated Guangji Hospital of Soochow University, a Suzhou City owned psychiatric hospital. The catchment area of this hospital covered a population of approximately 10.6 million individuals. All MDD patients met the following inclusion criteria: (1) aged 18–60 years old, Han Chinese; (2) confirmation of unipolar depression by two psychiatrists using the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV); (3) had a minimum of 6 years of education; (4) had received treatment with oral antidepressants; and (5) had the ability to participate in cognitive assessment. In addition, all patients received a balanced diet during a hospital stay.

For the initial screening, we applied the DSM-IV to define cases of depression. The PHQ-9 evaluates the reliability and validity of Public Health Questionnaires. A recent study (Wang *et al.* 2014) has indicated that the Chinese version of the PHQ-9 is a valid and efficient tool with a sensitivity of 0.86 and a specificity of 0.86 for screening depression. Therefore, we subsequently used the PHQ-9 ($\geqslant 7$) to further confirm the diagnosis.

Healthy controls ($n = 30$; male/female = 13/17) were recruited from the local community in the Gusu District of Suzhou. All enrolled subjects met the following criteria: (1) aged 18–60 years, Han Chinese; (2) received education for at least 6 years; (3) had the ability to participate in cognitive assessment; and (4) had a PHQ-9 total score <7. Current mental status and personal or family history of any mental disorder were assessed using unstructured interviews. None of the healthy controls had MDD. All subjects were in good physical health. Any subjects with schizoaffective disorders, dementia, neurodegenerative and neurological disorders, cardiovascular disease, cerebrovascular disease, infections, cancer, diabetes, hypertension, hyperlipidemia, or pregnant were excluded. Neither patients with MDD nor healthy controls had drug or alcohol abuse/dependence.

Clinical measures

A detailed questionnaire including a complete medical history, physical examination, and medical and psychological conditions was obtained from each subject. Additional information including age, gender, education, smoking, and duration of illness was collected from available medical records.

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The capacity of sustained attention was assessed using the Chinese version of Rapid Visual Information Processing (RVP) task in the Cambridge Neuropsychological Tests Automated Battery (CANTAB). The RVP was useful to evaluate the dysfunctions in the parietal and frontal lobe areas of the brain in patients with MDD and was also a sensitive measure of general focusing performance. Several previous studies have shown that RVP was a valid clinical measure to assess sustained attention in healthy populations and patients with neuropsychiatric disorders (Sahakian & Owen, 1992; Mann, *et al.* 2007). For the RVP task, a white box appeared in the center of the computer screen and inside the box digits (ranging from 2 to 9) appeared in a pseudo-random order at a rate of 100 digits/min. Each subject was required to focus on the screen continuously to detect the target sequences of three digits (2-4-6, 3-5-7, and 4-6-8) and subsequently, to register their responses using a touch pad. A total of three indices of RVP were recorded: (1) total hits (the subject responding correctly to the target sequence; the higher the score, the better); (2) total misses (the subject failed to respond to a target sequence; the lower the score, the better); and (3) mean latency (mean time taken to respond to correct responses in milliseconds).

Moreover, other cognitive functions (online Supplementary Table S1) were assessed using motor screening, delayed matching to sample, big little circle, and intra-extra dimensional in the CANTAB in each subject.

IL-6 measurement

Blood samples without anticoagulants were collected from the MDD patients and healthy controls between 7 and 9 AM following an overnight fasting. The serum was separated, aliquoted, and stored at −80 °C in a refrigerator before laboratory assays. Freedom EVOlyzer (Tecan, Sweden) was used to measure the serum IL-6 levels using a commercially available sandwich enzyme-linked immunosorbent assays kit (Boster, Wuhan, China). A detailed procedure has been published elsewhere (Kouwenhoven, *et al.* 2001; Góra-Gebka, *et al.* 2003). The sensitivity was 0.3 pg/ml, with intra-assay variation coefficients of 5%, and inter-assay variation coefficients of 7%. A standard curve was established in triplicate for each plate. The assays were performed by the same technician who was blind to the sample's ID and clinical information.

Statistical analysis

Demographic and clinical variables were compared between patients with MDD and healthy controls using an analysis of variance (ANOVA) for continuous variables and a c^2 test for categorical variables. The RVP scores and serum IL-6 levels were not normally distributed and were thus log-transformed. We then compared $\log_{10}$ RVP scores and $\log_{10}$IL-6 levels between two groups using an ANOVA. When significance was found in the ANOVA, the potential confounding factors were added as covariates. The relationships between $\log_{10}$IL-6 levels and $\log_{10}$RVP scores in patients with MDD and healthy controls were evaluated with Pearson's product moment correction coefficients. A multivariate regression analysis using the stepwise method was used to identify the potential variables that affected $\log_{10}$RVP scores. SPSS version 17.0 was used to perform all statistical analyses. In addition, correction analysis further investigated the associations between $\log_{10}$IL-6 levels and other cognitive functions in patients with MDD and healthy controls. Continuous data were presented as the mean and standard deviation (mean ± S.D.), and all p values were 2-tailed at a significance level of <0.05.

Results

Demographic and clinical characteristics

There were no significant differences in gender, age, education, smoking, and body mass index (BMI) between patients with MDD and healthy controls (Table 1). The mean and S.D. of heart rate, systolic and diastolic pressures, and illness duration (years) in patients with MDD were 78.87 ± 7.04, 121.70 ± 10.93, 76.97 ± 6.76, and 69.95 ± 85.62, respectively. The types of antidepressants included single selective serotonergic reuptake inhibitor (SSRI, $n = 14$, 46.67%), other single antidepressants ($n = 7$, 23.33%), and combined antidepressants ($n = 9$, 30.00%).

Comparisons of RVP scores and serum IL-6 levels between MDD patients and healthy controls

The mean and S.D. of $\log_{10}$RVP scores in 30 patients with MDD and 30 healthy controls are shown in Table 2. There were significant differences in $\log_{10}$RVP total hits (1.21 ± 0.12 *v.* 1.28 ± 0.12, $F = 6.04$, $p = 0.017$), $\log_{10}$RVP total misses (0.95 ± 0.22 *v.* 0.67 ± 0.26, $F = 19.77$, $p < 0.0001$), and $\log_{10}$RVP mean latency (2.66 ± 0.13 *v.* 2.55 ± 0.10, $F = 14.42$, $p < 0.0001$) between the two groups. Moreover, $\log_{10}$IL-6 levels were significantly higher in patients with MDD than in healthy controls (Fig. 1, 1.05 ± 0.17 *v.* 0.45 ± 0.16, $F = 192.27$, df = 58, $p < 0.0001$).

Associations between RVP scores and serum IL-6 levels

In patients with MDD, the Pearson correlation analysis showed a significantly positive correlation between $\log_{10}$IL-6 levels and $\log_{10}$RVP mean latency in Fig. 2*a* ($r = 0.45$, df = 1, 28, $p = 0.013$). However, such a correlation was not found in healthy controls (Fig. 2*b*, $r = 0.04$, df = 1, 28, $p = 0.82$). A further stepwise multivariate regression analysis showed that $\log_{10}$IL-6 levels were significantly associated with $\log_{10}$RVP mean latency in MDD patients ($\beta = 0.31$, $t = 2.41$, $p = 0.025$). By contrast, $\log_{10}$IL-6 levels were not associated significantly ($p > 0.05$) with other cognitive functions, i.e. $\log_{10}$RVP total hits and $\log_{10}$RVP total miss in MDD patients. There were also no associations between $\log_{10}$IL-6 levels (or $\log_{10}$RVP scores) and antidepressant treatment. The correlation coefficient data between $\log_{10}$IL-6 and other cognitive function measures were detailed in online Supplementary Table S1.

In healthy controls, there were also no correlations between $\log_{10}$IL-6 levels and $\log_{10}$RVP scores. In addition, $\log_{10}$IL-6 levels were not correlated with other cognitive functions.

Discussion

In accordance with our recent data evaluating cognitive functions in MDD patients using the Repeatable Battery for the Assessment of Neuropsychological Status (Shao *et al.* 2017), the present study also demonstrated a higher degree of sustained attention deficits in MDD patients than in healthy controls. Increasing evidence has shown that the deficits of sustained attention appear in different stages of MDD development (Paradiso *et al.* 1997; Porter *et al.* 2003; Paelecke-Habermann *et al.* 2005; van der Meere *et al.* 2007;

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Table 1. Demographic and clinical variables in patients with MDD and healthy controls

Variables	Patients with MDD ($n = 30$)	Healthy controls ($n = 30$)	F or χ^2	p Value
Gender (male/female)	12/18	13/17	0.07	0.79
Age (years)	42.57 ± 11.43	41.60 ± 10.15	0.12	0.73
Education (years)	11.37 ± 3.58	11.97 ± 3.94	0.38	0.54
BMI (kg/m^2)	22.86 ± 2.38	22.74 ± 2.78	0.03	0.86
Smoking (smoker/nonsmoker)	5/25	7/23	0.42	0.52
Duration of illness (months)	69.95 ± 85.62			
Heart rate	78.87 ± 7.04			
Blood pressures				
Systolic pressure	121.70 ± 10.93			
Diastolic pressure	76.97 ± 6.76			
Type of antidepressants				
Single SSRI	14 (46.67%)			
Other single antidepressant	7 (23.33%)			
Combined antidepressants	9 (30.00%)			

Mean ± s.d. (standard deviation); BMI, body mass index; SSRI, selective serotonergic reuptake inhibitor.

Braw *et al.* 2011; Maalouf *et al.* 2011). Collectively, attention deficits may be considered a core feature of MDD (McDermott & Ebmeier, 2009; Lee *et al.* 2012).

Moreover, there was a significant association between attention deficits and brain structural dysfunctions. Specifically, the changes of gray matter volume in the inferior frontal gyrus were significantly correlated with sustained attention in patients with MDD (Yang *et al.* 2015). The abnormal prefrontal cortex was also significantly associated with attention deficits in remitting and non-remitting recurrent depression patients (Li *et al.* 2010). It is possible that brain abnormalities in the lingual gyrus and fronto-parietal network may play a critical role in the regulation of sustained attention (Coull *et al.* 1996; Jung *et al.* 2014). Future investigations in neuroimaging-attention are necessary in a large and independent cohort of MDD patients.

In the brain, IL-6 acts as a neurotrophic factor expressed in both neurons and glia (Loddick *et al.* 1998). Increased levels of IL-6 have been consistently demonstrated in the plasma (Liu *et al.* 2012; Howren *et al.* 2009; Dowlati *et al.* 2010; Goldsmith *et al.* 2016) and CSF (Kern *et al.* 2014) of MDD patients. Moreover, a recent longitudinal cohort study showed that higher IL-6 levels in childhood were significantly associated with subsequent persistent depressive symptoms (Khandaker *et al.* 2017). However, IL-6 levels may be regulated by the presence of antidepressants (Hiles *et al.* 2012; Dahl *et al.* 2014; Yang *et al.* 2015). By contrast, several prospective studies have argued against an altered level of IL-6 in MDD patients (van den Biggelaar *et al.* 2007; Milaneschi *et al.* 2009; Stewart *et al.* 2009; Chocano-Bedoya *et al.* 2014). Such inconsistent findings may be due to several confounding factors including BMI, smoking, antidepressants, sleep, and cognitive dysfunctions (Duivis *et al.* 2011).

It is not clear whether peripheral changes of IL-6 are directly related to the structural and functional changes of the brain. In the present study, serum IL-6 levels were negatively correlated with sustained attention in patients with MDD in a Chinese population. It is surmised that sustained attention may be

Table 2. Comparisons of $\log_{10}$RVP scores between patients with MDD and healthy controls

$\log_{10}$RVP measurement	Patients with MDD ($n = 30$)	Healthy controls ($n = 30$)	F	p Value
$\log_{10}$RVP Total Hits	1.21 ± 0.12	1.28 ± 0.12	6.04	**0.017**
$\log_{10}$RVP Total misses	0.95 ± 0.22	0.67 ± 0.26	19.77	**<0.0001**
$\log_{10}$RVP Mean Latency	2.66 ± 0.13	2.55 ± 0.10	14.42	**<0.0001**

RVP, Rapid Visual Information Processing; MDD, major depressive disorder.
Significant p values (<0.05) are highlighted in boldface.

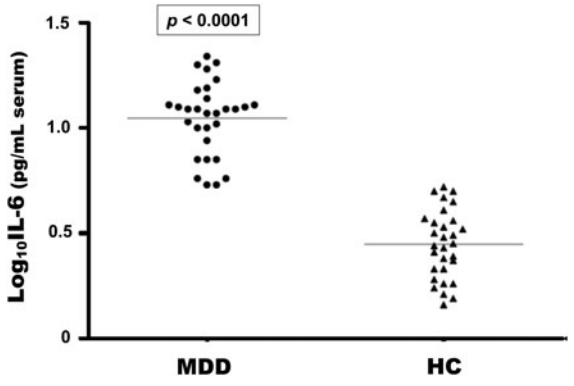

Fig. 1. Comparisons of serum $\log_{10}$IL-6 levels between patients with MDD and healthy controls. Serum $\log_{10}$IL-6 levels were significantly higher in patients with MDD than in healthy controls (1.05 ± 0.17 *v.* 0.45 ± 0.16, $F = 192.27$, df = 58, $p < 0.0001$). MDD, major depressive disorder; HC, healthy controls.

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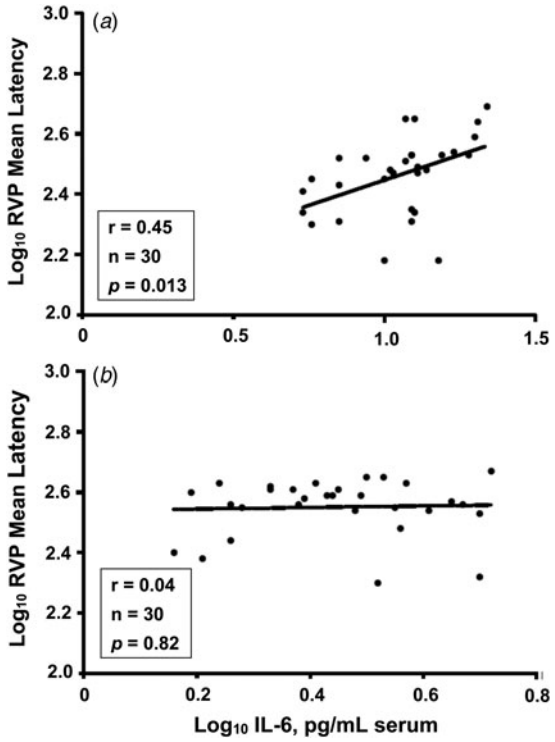

Fig. 2. Correlations between serum $\log_{10}$IL-6 levels and $\log_{10}$RVP mean latency in patients with MDD (*a*) and healthy controls (*b*). A significant correlation was found in MDD patients ($r = 0.45$, $n = 30$, $p = 0.013$), but not in healthy controls ($r = 0.04$, $n = 30$, $p = 0.82$).

mediated through afferent nerves resulting from increased levels of serum IL-6 (Capuron & Miller, 2011). Recent studies have further shown that IL-6 levels are negatively related to cognitive functions in patients with MDD (Marioni *et al.* 2010; Grassi-Oliveira *et al.* 2011; Goldsmith *et al.* 2016). Similarly, elevated IL-6 levels were also involved in attention impairment in patients with other mental disorders (Marsland *et al.* 2006; Frydecka *et al.* 2015) and in cognitive dysfunctions in the elderly with (Rafnsson *et al.* 2007) and without (Gimeno *et al.* 2009; Heringa *et al.* 2014) type 2 diabetes. However, further studies investigating the relationships between other cytokines and sustained attention, and their environmental interactions are warranted in patients with MDD.

There are several limitations in the present study: (1) *A relatively small sample size*. Our findings should be considered a pilot study. (2) *Employing banked samples that were collected from August 2016 to May 2017, and were stored at −80 °C in a refrigerator for differing lengths of time*. Although the storage time may influence the laboratory IL-6 assay, the normal range of serum IL-6 (1.44–5.25 pg/ml) in the present study was very comparable to a previously published range of 1–8.14 pg/ml (Ganguli *et al.* 1994; Akiyama, 1999; Borovcanin *et al.* 2012; Di Nicola *et al.* 2012; Upthegrove *et al.* 2014; Noto *et al.* 2015). (3) *A cross-sectional research design*. Future studies with longitudinal and prospective follow-ups are necessary to clarify the association between serum IL-6 levels and sustained attention in patients with MDD. It is thus not clear whether there is a causative relationship between elevated IL-6 levels and sustained attention deficits in MDD patients. (4) *Limited sample volume*. The present study was only able to focus on serum IL-6 that had direct implications on the pathophysiology of MDD. Thus, future studies shifting the focus from individual cytokines including CRP to networked activation of cytokines are warranted. (5) *Confirmed diagnosis of MDD*. Although the patients were confirmed with a diagnosis for unipolar depression rather than bipolar depression at the entry level of the study, a few unipolar depressive patients may develop to bipolar depressive patients in the follow-ups. (6) *Effect of antidepressants*. As indicated in the Introduction, IL-6 levels were found significantly reduced in patients with MDD after treatment with antidepressants (Hiles *et al.* 2012; Dahl *et al.* 2014; Yang *et al.* 2015). In accordance with previously published data, the present finding also demonstrated significantly higher levels of serum IL-6 in MDD patients than in healthy controls. Thus, our MDD patients may have even higher levels of IL-6 if they were not treated with antidepressants. Finally, (7) the *absence of other clinical assessments* including illness duration, and sleep status. Future studies should be expanded to include those clinical assessments having effects on serum IL-6 levels and sustained attention in MDD patients.

In summary, the serum IL-6 levels were higher and impairment of sustained attention was greater in patients with MDD than in healthy controls. The serum IL-6 levels were positively associated with the RVP mean latency in patients with MDD. Our data further demonstrated that abnormal levels of serum IL-6 may reflect an imbalance between pro- and anti-inflammatory mechanisms underlying the psychopathology of MDD. Furthermore, IL-6 may play a vital role in the impairment of sustained attention in patients with MDD. However, the present findings were only preliminary due to the relatively small sample size and absence of a longitude follow-up. Therefore, future investigations are warranted to confirm the present findings in a large and independent cohort of MDD patients.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291718000090

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Declaration of Interest. The authors declare no conflict of interest.

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