Interleukin-6 and verbal memory in recurrent major depressive disorder

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Abstract

OBJECTIVE: To evaluate the possible association between peripheral levels of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-alpha) with immediate and delayed verbal recall in a group of recurrent depressed women.
METHODS: Logical Memory Subtests of the Wechsler Memory Scale – Revised was administered to 30 patients with recurrent major depressive disorder with no clinical and psychiatric comorbidities. Blood samples were collected from 8:00 am to 9:00 am, before memory assessments.Plasma was stored and ELISA assay was used to detect IL-6 and TNF-alpha levels.
RESULTS: There was a statistically significant association between IL-6 levels and immediate verbal recall (IVR) (B=–0.787, p=0.000) and delayed verbal recall (DVR) (B=–0.695, p=0.001) even after controlling for age, depression severity and body mass index.
CONCLUSION: The results of this study indicated that low performances in IVR and DVR are associated with IL-6 levels in women with recurrent MDD. The results of this study suggest the existence of an association between inflammatory imbalance and cognitive impairment in MDD.

INTRODUCTION

In the last decade, a body of evidence has consistently demonstrated an association between major depressive disorder (MDD) and cognitive impairment, especially in the domains of attention, working memory, and executive functions (Gotlib & Joormann 2010; Marazziti *et al.* 2010). Moreover, depressed patients show signs of impaired verbal learning, which has been commonly assigned to an inability to transfer information from short-term to long-term storage (Douglas & Porter 2009). However, the degree of progression, chronicity, and reversibility of cognitive impairment in treated or untreated MDD patients remains inadequately understood, and the possible pathophysi-

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ological correlates underlying cognitive impairment have not been determined (Naismith *et al.* 2010).

Major psychiatric disorders, including MDD, have recently been associated with imbalances in inflammation (Grassi-Oliveira *et al.* 2009; Miller *et al.* 2009), which result in increases in peripheral levels of pro-inflammatory mediators, such as the cytokines tumor necrosis factor alpha (TNF-alpha) and interleukin-6 (IL-6)(Miller *et al.* 2009; Pace & Miller 2009). When the release of inflammatory cytokines is excessive or sustained, these mediators have neurotoxic effects on neurons and glial cells (Brietzke & Kapczinski, 2008; Goldstein, Kemp, Soczynska, & McIntyre 2009). In addition, several studies with populations with other conditions (e.g. Alzheimer disease, multiple sclerosis, HIV dementia) described a harmful effect of TNF-alpha and IL-6 on cognition (Guerreiro *et al.* 2007; Medeiros *et al.* 2010; Patanella *et al.* 2010; Rafnsson *et al.* 2007).

The association between MDD and inflammation is well established in the literature (Maes 2008), but its repercussion on the cognition of people with mood disorders has not been fully studied (Gimeno *et al.* 2009; Reichenberg *et al.* 2001). This preliminary study evaluated whether there is an association between cognitive performance in a verbal memory task and the IL-6 and TNF-alpha plasma levels in women with recurrent MDD.

METHODS

Thirty patients (all women, 22 to 55 years) of an outpatient mood disorder unit had their diagnosis of current MDD confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) administered by two trained clinical psychiatrists. All patients were experiencing a depressive episode and were taking antidepressants as monotherapy (serotonin selective reuptake inhibitor or tricyclic). Severity of depressive symptoms was evaluated using the Beck Depression Inventory (BDI). Participants with past or current axis I disorders other than MDD, general medical disorders, psychotic symptoms, or any psychoactive substance use in the last 30 days (except nicotine, caffeine, and antidepressants) were excluded. The Ethics Committee of the institution approved this study where it was conducted, and written informed consent was obtained from all participants.

Memory tests were performed between 8:30 am and 9:30 am, 30 minutes after blood was collected. The Logical Memory (LM) test was administered to all subjects. Logical Memory is a verbal declarative memory subtest of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler 1987); it is a standardized test extensively used in the literature (Elwood 1991; Neuner *et al.* 2007; Savitz *et al.* 2007). The LM was administered and scored by two trained psychologists according to the manual's guidelines. The test generates a score for immediate verbal recall (IVR) and 30-minute delayed verbal recall (DVR).

All participants were instructed not to eat or take medication for at least 8 hours before blood collection. Blood samples were collected from 8:00 am to 9:00 am, before memory assessments. Plasma was separated within 30 minutes, and the supernatant was stored at −80 °C for up to 6 months. For IL-6 and TNF-alpha measurements, a commercially available enzyme-linked immunosorbent assay (ELISA) kit (DuoSet, R&D Systems, Minneapolis, Minn., USA) was used according to the manufacturer's directions. All samples were assayed in duplicates. The detection thresholds for these assays were 25 pg/ml for TNF-alpha and 0.4 pg/ml for IL-6. Interleukin-6 and TNF-alpha levels are reported in pg/ml.

Statistical Analysis

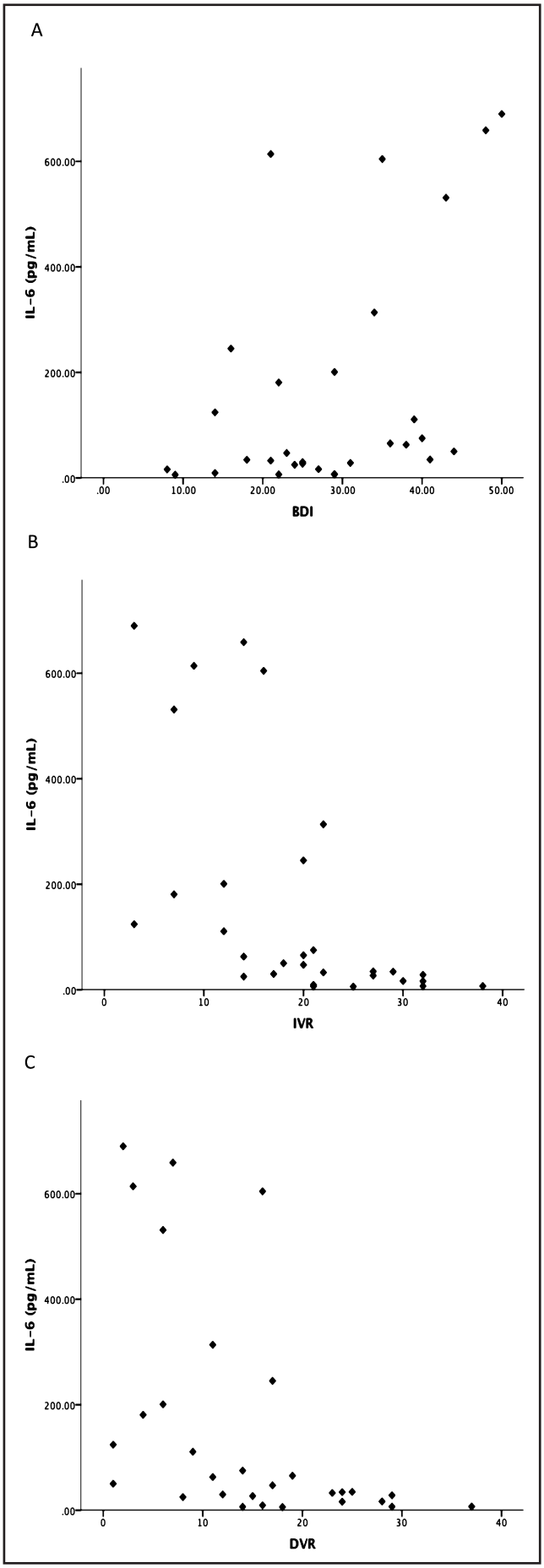
All variables were tested for normality of distribution using the Kolmogorov-Smirnov test. The Pearson's correlation coefficient was used to evaluate the associations of clinical and demographic variables with verbal recall performance. The distribution of IL-6 and TNF-alpha concentrations was not normal, and data were log transformed. The associations of IL-6 and TNF-alfa with clinical variables and verbal recall scores were also determined using Pearson's correlation. For IVR and DVR, linear regression analyses with IL-6 as the independent variable were used; age, BDI scores and years of education were included in the model. The significance level was set at α=0.05 (two-tailed). Statistical analyses were performed using the SPSS 17.0 (SPSS Inc., Chicago, Illinois). Results are reported in the figures and tables as mean and standard deviation or median and interquartile range when appropriated.

RESULTS

The clinical, biological and demographic characteristics of sample are described in Table 1. The performance in both tests of verbal recall (IVR and DVR) was not significantly associated with age, Body Mass Index (BMI), years of education or BDI scores. Graphs of raw data regarding IL-6 levels versus BDI, IVR and DVR are presented in Figure 1.

There were statistically significant correlations between IL-6 level and IVR (r=−0.723, p=0.000) and DVR (r=−0.646, p=0.000). The correlation between IL-6 level and BDI scores was also significant (r=0.486, p=0.007). The other clinical and demographic variables were not correlated with IL-6 levels. There were no significant associations between detected TNF-alpha levels and IVR, DVR or any other variables (n=13).

Regression analysis showed that IVR [R^2=0.53; F(4.25) = 7.17, p=0.001] and DVR [R^2=0.42; F(4.25) = 4.66, p=0.006] were negatively predicted by IL-6 plasma level after controlling for age, years of education and depression severity (IVR-B=−0.78, p<0.001; DVR-B=−0.68, p=0.001). Co-linearity was tested and VIF was <1.5 for all variables.



DISCUSSION

The results of this study indicated that low performances in IVR and DVR are associated with IL-6 levels in women with recurrent MDD. In addition, IL-6 levels were positively correlated with severity of depressive symptoms. Several studies found increased levels of cytokines in mood disorders, with IL-6 and TNF-alpha being the biomarkers most often detected (Brietzke *et al.* 2009; Zeugmann *et al.* 2010) and the only two found to be increased in a recent meta-analysis (Dowlati *et al.* 2010).

There is strong evidence that enhanced neurodegeneration and the defects in neurogenesis in depression are related to inflammatory processes (Maes *et al.* 2009). Reduced hippocampal neurogenesis has been suggested as a final common pathway in major depression and cognitive dysfunction (Duman 2004; Maes *et al.* 2009). However the role of specific cytokines in illness-associated memory disturbances was examined in very few studies, with somewhat inconsistent results (Yirmiya & Goshen 2011).

Although IL-6 and TNF-alpha share some functions in the immune system, they may have a different impact on the brain (Campuzano *et al.* 2009; Phares *et al.* 2006).

Tab. 1. Clinical, biological and demographic characteristics of sample (n=30).

Variable	Mean/ Frequency	SD
Age (years)	39.20	8.67
Education (years)	8.13	3.83
BMI (kg/m^2)	25.76	2.25
Duration of illness (years)	11.5	5.8
BDI	28.5	11.26
Suicide ideation (%)	40	
IVR	19.50	9.03
DVR	14.87	9.44
IL-6 (pg/mL)[a]	161.88	222.41
TNF-alpha[b] (pg/mL)	72.44	54.07

SD- Standard Deviation; BMI - Body Mass Index; BDI - Beck Depression Inventory; IVR - immediate verbal recall; DVR - delayed verbal recall; IL-6 - interleukin-6; TNF-alpha - tumor necrosis factor alpha.
[a] median was 48.73 pg/mL and the interquartile range, 25.87 pg/ml
[b]Plasma TNF-alpha levels mean of 13 participants since 56.7% sample was below the detection threshold, median was 73.85 pg/mL.

Fig. 1. Raw data of IL-6 Plasma levels versus Depression Severity and Verbal Memory Performance.
A) IL-6 plasma levels versus Beck Depression Inventory (BDI) score; **B)** IL-6 plasma levels versus immediate verbal recall (IVR); **C)** IL-6 plasma levels versus delayed verbal recall (DVR).

Increased IL-6 levels have been associated with neural dysfunction and decline in learning and memory (Monje *et al.* 2003). In the brain, IL-6 is synthesized by astrocytes, and to a lesser extent, microglia and neurons. After linking to specific receptors, IL-6 activates signaling pathways, including gene transcription of mediators implicated in the reduction of neurogenesis. Neurogenesis seems to be important in memory consolidation and in some types of hippocampal-dependent learning (McAfoose & Baune 2009). As shown in animal models (Vallieres *et al.* 2002), adult over-expression of IL-6 by astroglia reduced hippocampal neurogenesis in 63%. Such findings demonstrate that the long-term exposure to IL-6, as seen in depression, may interfere with cognitive functioning by impairing adult neurogenesis. Therefore the role of IL-6 in memory depends on the specific condition or context under which it is elevated, as well as on the magnitude and duration of the elevation (Yirmiya & Goshen 2011). This is particularly important because this study included only female participants with recurrent major depression with more than 10 years of illness duration. Depression might induce a sensitization effect with increased inflammatory responses to stressors, particularly in women (Maes *et al.* 2001). Depressive episodes may act as maladaptive responses to stress, thus exerting negative influences on brain structures related to responses to stress, such as the hippocampal and the HPA axis (Maes *et al.* 2009). These influences leave the individual with an increased probability of relapses after each depressive episode and may cause more permanent changes in the stress-system, including memory deficits, predisposing the patient to residual symptomatology and recurrences (Maes *et al.* 2009). Therefore if the immune over-activation is chronic, neurodegenearation may ensue, resulting in reduced neuronal excitability and further impairments in learning, memory and neural plasticity (Yirmiya & Goshen 2011).

The results of the present study must be considered facing some limitations. One of the limitations of this study was the relative small sample size, which prevented the use of more sophisticated analysis to isolate the effect of different confounders of the association between IL-6 and verbal recall performance. In addition, all the patients were experiencing a depressive episode, and the persistence of these findings during euthymia cannot be inferred. Finally, results were also obtained using a cross-sectional design, and inferences about cause and effect cannot be made. On the other hand, the inclusion criteria for this study were rigorous. The inclusion of people without any psychiatric or medical comorbidity ensured that the abnormalities in inflammatory mediators were not due to other conditions. In addition, the selection of people with several depressive episodes prevented the inclusion of other possible diagnosis (e.g. bipolar disorder, schizoaffective disorder) for which depressive episodes may be an early sign. The possible effect of medications was controlled by the inclusion of people without any change in their medication regimen in the last 3 months. In addition, blood samples were collected in a standardized time of the day to rule out possible circadian oscillations in cytokine levels.

Although these findings are preliminary, they are some of the first evidences of an association between inflammatory imbalance and cognitive impairment in MDD. If these results are confirmed in studies with larger samples, the control of imbalances in inflammation may be used in the future as an alternative to limit the damage of recurrent MDD in cognition and its consequential impact on functioning.

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