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Stress and inflammation reduce BDNF expression in first-episode psychosis: a pathway to smaller hippocampal volume

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Abstract

Background—Reduced brain-derived neurotrophic factor (BDNF) levels have been reported in the serum and plasma of patients with psychosis. The aim of this study was to investigate potential *causes* and *consequences* of reduced BDNF expression in these patients, by examining the association between BDNF levels and measures of stress, inflammation and hippocampal volume in first-episode psychosis.

Methods—BDNF, interleukin (IL)-6, and tumour-necrosis-factor (TNF) alpha mRNA levels were measured in leukocytes of 49 first-episode psychosis patients (DSM-IV criteria) and 30 healthy controls, recruited between January 2006 and December 2008. In the same subjects, we measured salivary cortisol levels, and collected information about psychosocial stressors (number of childhood trauma, number of recent stressors, and perceived stress). Finally, hippocampal volume was measured, using brain MRI, in a subsample of 19 patients.

Results—Patients had reduced BDNF (effect size d=1.3, p<0.001) and increased IL-6 (effect size d=1.1, p<0.001) and TNF-alpha (effect size d=1.7, p<0.001) gene expression levels, when compared with controls, as well as higher levels of psychosocial stressors. A linear regression analysis in patients showed that a history of childhood trauma and high levels of recent stressors

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predicted lower BDNF expression through an inflammation-mediated pathway (adjusted R square=0.23, p=0.009). In turn, lower BDNF expression, increased IL-6 expression, and increased cortisol levels, all significantly and independently predicted a smaller left hippocampal volume (adjusted R square=0.71, p<0.001).

Conclusions—Biological changes activated by stress represent a significant factor influencing brain structure and function in first-episode psychosis, through an effect on BDNF.

Introduction

Several studies have reported reduced brain-derived neurotrophic factor (BDNF) levels in the brain [1] and in the serum and plasma of patients with schizophrenia [2-7]. BDNF is widely expressed in the adult mammalian brain and is known to play a crucial role promoting proliferation, regeneration and survival of neurons [8]. This is particularly important in this context, since a number of studies has shown brain volume changes at the onset of psychosis, or during the transition to psychosis, suggesting a critical role for neuroplasticity, especially in the hippocampus, in the development of psychosis [9-11]. Moreover, BDNF has also been involved in more complex processes in adulthood, such as regulation of cognitive function [12] that is known to be impaired in patients with psychosis [13;14]. However, the clinical and biological mechanisms behind the lower BDNF levels and the progressive brain volume changes in psychosis are still unknown.

Stress and the biological systems involved in the stress response have been suggested to play a role in BDNF changes. Indeed, animal models have shown that chronic stress down-regulates hippocampal BDNF mRNA expression and impairs processes of neuronal branching and neurogenesis [15]. High levels of both glucocorticoid hormones and pro-inflammatory cytokines, two key players in the response to stress, have been associated with decreased BDNF levels [16;17] and with changes in hippocampal neuronal function such as dendrite atrophy, neuronal death and reduced neurogenesis [18-21]. Interestingly, we and others have shown both abnormal glucocorticoid function and increased inflammatory markers in patients with first-episode psychosis [22;23]. Furthermore, we have recently shown a negative correlation between cortisol levels and left hippocampal volume in first-episode psychosis [24]. Previous studies have also shown that childhood trauma, a powerful psychosocial stressor, is associated with smaller left hippocampal volume in patients with other psychiatric disorders such as depression and post-traumatic stress disorder [25;26]. However, the potential pathways linking stressful events to BDNF and to hippocampal volume have never been studied in psychosis.

In the present study, we aim to investigate the pathways leading from psychosocial stress to reduced BDNF levels in patients with first-episode psychosis, and to evaluate the putative consequence of these reduced BDNF levels on hippocampal volumes. Of relevance, BDNF in the blood seems to reflect the BDNF content in the brain: this notion is substantiated by animal experiments, showing that BDNF serum levels are correlated with BDNF expression in cortical and hippocampal brain regions [27-29], and further supported by a positive correlation between plasma and cerebrospinal fluid (CSF) BDNF levels recently reported in drug naïve first-episode psychosis patients [30]. We have specifically measured BDNF

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expression in leukocytes, as leukocyte gene expression profile shows similarities to those observed in the brain, especially for genes linked to neurotransmitters, cytokines, hormones, and growth factors [29;31]. BDNF mRNA expression has been recently found to be decreased in leukocytes of depressed patients [32]: however, this has never been studied in psychosis. Moreover, we have measured 1) psychosocial stress (childhood trauma, recent stressful events and perceived stress); 2) inflammatory markers (leukocyte mRNA levels of interleukin (IL-6) and tumour-necrosis factor (TNF)-alpha); 3) diurnal salivary cortisol levels; and 4) hippocampal volume (via Magnetic Resonance Imaging, MRI). Some of the subjects described in this paper belongs to a group of patients and controls previously described [22;24]. This paper is now advancing this work, presenting for the first time the data on BDNF gene expression and on inflammatory markers in these patients, and the association between these variables and the stress and imaging measures.

Methods

Subjects

First-episode psychosis patients were recruited in London (UK) from inpatient and outpatient units, part of the South London and Maudsley (SLAM) NHS Foundation Trust in South-East London (UK), from January 2006 to December 2008. The recruitment strategy was based on contacting inpatients and outpatients services interviewing staff and reviewing clinical notes, and approaching all subjects aged 18-65 who presented for the first time to these services for a functional psychotic illness (ICD10 F10-19, excluding coding F1x.0 for Acute intoxication; F20-29 and F30-39, psychotic codings) [33]. Patients with organic psychosis, learning disabilities or not fluent in English were excluded from the study. Controls were recruited from the same catchment area as the patients through advertisement in local newspapers, hospitals and job centers, as well as from existing volunteer databases. Controls were screened using the Psychosis Screening Questionnaire (PSQ) [34], and excluded if they met criteria for a present or past psychotic disorder. The study was approved by the local Research Ethics Committee, in accordance with the code of ethics of the World Medical Association, and written informed consent was obtained from all participants.

We recruited and assessed 49 patients with first-episode psychosis and 30 healthy controls. All subjects had an assessment of BDNF, IL-6 and TNF-alpha expression; only 19 of these patients accepted to undergo an MRI scan. Twenty-seven patients received a DSM-IV diagnosis of schizophrenia/schizophreniform disorder, 15 schizoaffective or affective psychosis, and 7 psychotic disorder not otherwise specified. Ten patients were drug naïve, 36 were on an atypical antipsychotic (mostly olanzapine, n-19), and 3 on a typical antipsychotic. The mean duration of antipsychotic treatment was 33.4±5.8 days (range from 0 to 170 days).

Questionnaires and Clinical Assessment

Validation of clinical diagnosis was obtained using the Operational Criteria (OPCRIT) [35], reviewing the case notes in the first month following first contact with services. We collected information about stressful life events occurred in the previous six months using the Brief Life Events questionnaire [36], and measured perceived stress in the previous month

using the Perceived Stress Scale [37]. Information about childhood trauma were also collected, using a modified version of the Childhood Experience of Care and Abuse (CECA) Questionnaire [38]. Please see supplemental material for details on childhood trauma assessment.

Gene expression analyses

Blood samples for gene expression of BDNF, IL-6 and TNF-alpha were collected using PaxGene Tubes. The time of blood collection varied for each subject, and subjects did not fast before collection. After blood samples were withdrawn, PaxGene Tubes were kept for two hours at room temperature and then stored at −80°C until they were processed. RNA isolation was performed using the PAXGene Blood RNA Kit (Qiagen S.p.A., Milan, MI, Italy) according to manufacturer's protocols. Please see supplemental material for details on gene expression analyses.

Salivary cortisol assessment

Saliva samples were collected to measure salivary cortisol using Salivettes (Sarstedt, Leicester, UK). Methods of sample collection and analyses have been described in detail before [22]. Subjects were instructed to collect saliva samples immediately after awakening and again at 12 pm and at 8pm. Cortisol levels during the day were measured as Area Under the Curve (AUC) of cortisol levels at the three time points, following the calculation of the AUC derived from the trapezoid formula [39].

Hippocampal volume

Magnetic resonance imaging scans were acquired on 19 of the recruited patients with a GE Signa 1.5-T system (GE Medical Systems, Milwaukee), at the Maudsley Hospital, London. Please see supplemental material for details on MRI scans acquisition. Hippocampal volume was measured blind to group status or BDNF, cytokine and cortisol levels, by one single rater using the software program MEASURE (version 0.8, Johns Hopkins University, Baltimore, MD). This image analysis program uses stereologically unbiased estimation of volume. The program and the measurement procedure have been described in detail elsewhere [40].

Data Analyses

Data were analyzed using the Statistical Package for Social Sciences, Version 15.0 (SPSS Inc.). Continuous variables are presented as mean ± standard error mean. Chi-square test was used to compare categorical variables between patients and controls. Independent T-test was applied to test differences in BDNF expression and other continuous variables between patients and controls. Parametric and non-parametric correlation analyses were used, as appropriate, to test the association between BDNF expression and psychosocial stress, inflammatory markers and cortisol levels, separately in patients and controls. A linear regression model was then used to test for predictors of BDNF expression and of hippocampal volume in patients.

Results

Socio-demographic variables, psychosocial stress measures and biological variables, in first-episode psychosis patients and healthy controls, are shown in Table 1. Patients with first-episode psychosis showed reduced BDNF gene expression (effect size d=1.3) and increased IL-6 (d=1.1) and TNF-alpha (d=1.7) gene expression, compared with controls. Consistent with the data previously described in a sample comprising some of the same subjects [22], measures of psychosocial stress were significantly higher in patients than in controls (Table 1), and cortisol levels were similar in patients and controls (Table 1).

Correlation analyses with BDNF gene expression

We ran exploratory correlation analyses between BDNF gene expression levels and both the immune markers and the psychosocial stress measures, in both patients and controls. In patients, childhood trauma and number of recent stressful life events were negatively correlated with BDNF mRNA levels (respectively Spearman's rho=-0.42, p=0.006, and Spearman's rho=-0.32, p=0.03). IL-6 gene expression was also significantly negatively correlated with BDNF gene expression (Pearson's r=-0.33, p=0.02). Because of the presence of one outlier for IL-6 mRNA levels, we also re-run the analysis without this subject and the correlation remained significant (r=-0.29, p=0.05). There was no significant correlation between BDNF mRNA levels and duration of antipsychotic treatment (see Supplemental Material, Table S1).

In the control group, there was a trend for a negative correlation between number of recent stressful events and BDNF gene expression (Spearman's rho=-0.35, p=0.06). None of the other variables was correlated with BDNF gene expression in the control group (see Supplemental Material, Table S1).

Multiple Linear Regression Analyses for BDNF gene expression in first-episode psychosis

In order to establish possible predictors of BDNF gene expression in patients with first-episode psychosis, we ran a linear regression analysis including all the variables identified statistically to be correlated with BDNF mRNA levels. The first model included only the psychosocial stress variables (the number of childhood trauma and the number of recent stressful events) and accounted for 21% of the variance in BDNF gene expression (adjusted R square, p=0.006). Adding IL-6 gene expression to the model did not increase the variance explained, suggesting that the effects of psychosocial stressors on BDNF may be mediated by the increased IL-6; in fact, a second model including number of childhood trauma, number of recent stressful events and IL-6 gene expression accounted for 23% of the variance in BDNF gene expression (adjusted R square, p=0.009). See Table 2.

Correlation analyses with left hippocampal volume in first-episode psychosis

In our previous paper [24] we have found that only the left hippocampal volume is correlated with cortisol levels during the day. This is consistent with studies showing that the left hippocampal volume is exquisitely sensitive to depression and psychosocial stressors [25;26] and that mainly the left-side hippocampal volume is smaller in first episode psychosis [41;42]. Therefore, for this paper we ran exploratory correlation analyses between left hippocampal

volume and both the immune markers and the psychosocial stress measures. BDNF and IL-6 mRNA levels, and diurnal cortisol levels, all correlated with the left hippocampal volume (respectively r=0.53, p=0.01, r=-0.45, p=0.04, and r=-0.68. p=0.001; see Figure 1 panel A, B and C). None of the other variables was correlated with left hippocampal volume (See Supplemental Material, Table S2).

Multiple Linear Regression Analyses for left hippocampal volume in first-episode psychosis

In order to establish possible predictors of (left) hippocampal volume in patients with first-episode psychosis, we ran a linear regression analysis including all the variables identified statistically to be correlated with this measure. We found that lower BDNF gene expression, higher IL-6 gene expression and higher cortisol levels were *independently* associated with a smaller left hippocampal volume, and that including one, two or three variables in the models progressively increased the variance explained. The first model of the linear regression included only BDNF gene expression; this accounted for 36% of the variance in left hippocampal volume (adjusted R square, p=0.004, see Figure 1). The second model included BDNF and IL-6 gene expression; this accounted for 47% of the variance in left hippocampal volume (adjusted R square, p=0.002). The third model included BDNF, IL-6 gene expression and diurnal cortisol levels; this accounted for 71% of the variance in left hippocampal volume (adjusted R square, p<0.001). See Table 3.

Discussion

Our findings suggest that psychosocial stressors, both during childhood and closer to psychosis onset, play a role in reducing BDNF mRNA levels in leukocytes of first-episode psychosis, possibly through a stress-induced increase in IL-6 expression. In turn, the reduced BDNF expression, together with the increased inflammation and the increased cortisol levels, seem to contribute to the smaller left hippocampal volume in these patients.

Studies in animals have reported that early adverse experiences and chronic stress in adults lead to a persistent reduction of BDNF levels in various areas of the brain [43-45]. In contrast, an enriched early social environment has been shown to increase BDNF levels, especially in the hippocampus [46]. Interestingly, the very few data available in clinical populations seem to support the notion that psychosocial stress has a negative effect on BDNF levels. Indeed, three studies have found that the number of stressful events, and the severity of childhood neglect, are negatively correlated with peripheral BDNF levels in patients with affective disorders [47-49]. Our study is the first to report a negative effect of stressful events, both in childhood and closer to psychosis onset, on BDNF expression in patients with first-episode psychosis. Of note, these effects of psychosocial stressors on BDNF mRNA levels appear stronger in the patients rather than in controls. Although, findings in animal studies show that stress in itself is enough to affect BDNF levels [43-45], the three aforementioned clinical studies examining the effects of psychosocial stressors on BDNF are in samples of patients with depression or bipolar disorder [47-49]. Therefore it is possible that psychosis (or, indeed, an affective disorder) creates a greater biological vulnerability of relevant pathways molecular (including BDNF) to stressful experiences. However, patients in our sample also

show higher rates of psychosocial stressors. Therefore, the larger number of events is another potential, not mutually exclusive, explanation for the stronger associations between stress and BDNF in patients than in controls.

Interestingly, this is also the first clinical study suggesting that the effects of psychosocial stressors on BDNF expression are mediated by increased levels of inflammation, as shown by the fact that independent effect of IL-6 on BDNF levels disappears once the effects of psychosocial stressors are taken into account. Previous preclinical studies have proposed a number of mechanisms underlying the stress-related down-regulation of BDNF expression, including increased release of pro-inflammatory cytokines [50]. Indeed, administration of IL-1 beta has been shown to down-regulate BDNF expression in the rat hippocampus [51;52]. The mechanisms through which cytokines might influence BDNF expression are still unclear. Preclinical studies have suggested that pro-inflammatory cytokines could directly reduce BDNF gene transcription via pathways such as cyclic AMP-response element-binding protein phosphorylation or of nuclear factor-κB activation (NF-kB) [53-55].

We also find a correlation between lower BDNF expression and smaller left hippocampal volume in first-episode psychosis. Our findings are consistent with previous studies investigating the effect of BDNF val66met polymorphism on hippocampal volume [56;57]. Specifically, these studies found a smaller hippocampal volume in healthy subjects and patients with first-episode schizophrenia carrying the met BDNF allele, which has also been associated with lower depolarization-induced production of BDNF [56;57]. However, our data indicate that lower BDNF levels only account for 36% of the variance of hippocampal volume. Adding IL-6 to the model increases the accounted variance to 47%, while the best model predicting hippocampal volume in our patients includes BDNF, IL-6 and cortisol levels, accounting for more than 70% of the variance. This suggests that these three biological pathways *independently* contribute to the regulation of hippocampal volume. Interestingly BDNF and pro-inflammatory cytokines can act on common intracellular pathways relevant to neuroplasticity, like the mitogen-activated protein (MAP) kinase cascade and the phosphotidylinositol-3 kinase/Akt signalling, and downstream regulators of apoptosis such as Bad (a major pro-apoptotic protein) and bcl-2 (a major anti-apoptotic protein) [58]. BDNF and pro-inflammatory cytokines are also well known to exert opposite effect on the regulation of the nuclear translocation of NF-kB, an important transcription factor decreasing cell survival [59;60]. Glucocorticoids influence neuroplasticity through their interaction with excitatory amino acid neurotransmitters and NMDA receptors [61]. Therefore, our findings suggest a synergic effect of BDNF, IL-6 and cortisol in determining smaller hippocampal volume, possibly through the activation of common molecular pathways.

From a clinical point of view, our findings further support the role of stress in the onset and outcome of psychosis, as already suggested by previous studies. Garner et al., [62] reported a larger pituitary volume in people at high risk of developing psychosis who then went on to develop psychosis within 1 year, suggesting that HPA axis hyperactivity is present already before the onset of psychosis and predicts those who made the transition to psychotic episode. Moreover, a more recent study in drug naïve first-episode psychosis patients found that a larger pituitary volume at onset is associated with less improvement in psychotic symptoms after 12 weeks of antipsychotic treatment, further supporting the role of HPA axis

hyperactivity in clinical outcome of these patients [63]. Furthermore, studies using glucocorticoid antagonist mifepristone, to target HPA axis activity, have reported clinical improvement in patients with major psychotic depression[64-66]. More recently, drugs targeting immune system, such as COX-2 inhibitor (celecoxib) or COX-1/COX-2 inhibitor (aspirin), have also been reported to significantly improve psychotic symptoms in patients with schizophrenia spectrum disorders, when used as adjunct therapy to antipsychotics [67-70]. Future pharmacological studies should also take into account the relevance of reduced BDNF in psychosis as possible future target for drugs development.

A few limitations need to be acknowledged. First and foremost, our correlation analyses cannot unequivocally imply causation. Therefore, the observed association between high levels of stress and reduced BDNF expression could also have alternative interpretations. For example, through reversed causality, reduced BDNF expression could lead to the increased number of stressors, through an effect on cognitive performance and personality traits in these patients [12;71;72]. Similarly, the smaller hippocampal volume may determine the higher cortisol and cytokines levels by reducing negative feedback of the HPA axis and inducing glucocorticoid resistance, a condition associated with inflammation [73]. Moreover, our correlation analyses were exploratory and were not corrected for multiple comparisons. Indeed, the large variance of hippocampal volume explained by the three combined stress biomarkers in the linear regression model is surprising, and these findings would need to be confirmed by future studies. A second limitation of this study is represented by our proposition that MRI volumes may represent a measure of neuroplasticity and neuronal function. Indeed, differences in MRI brain volumes might reflect alterations not only in neuronal cells, but also in non-neuronal tissue compartments (e.g., changes in tissue perfusion, fat, and water content) [74]. Finally, only a subsample of patients (and none of the controls) accepted to undergo the brain MRI scan.

In conclusion, our findings suggest that the down-regulation of BDNF expression in first-episode psychosis is partly induced by childhood trauma and adulthood stressful events through a biological pathway that may involve increased inflammation. In turn, stress-related biological pathways, together with decreased BDNF expression, may account for the smaller left hippocampal volume. We believe that these biological pathways should be considered for the development of future therapeutic strategies in this condition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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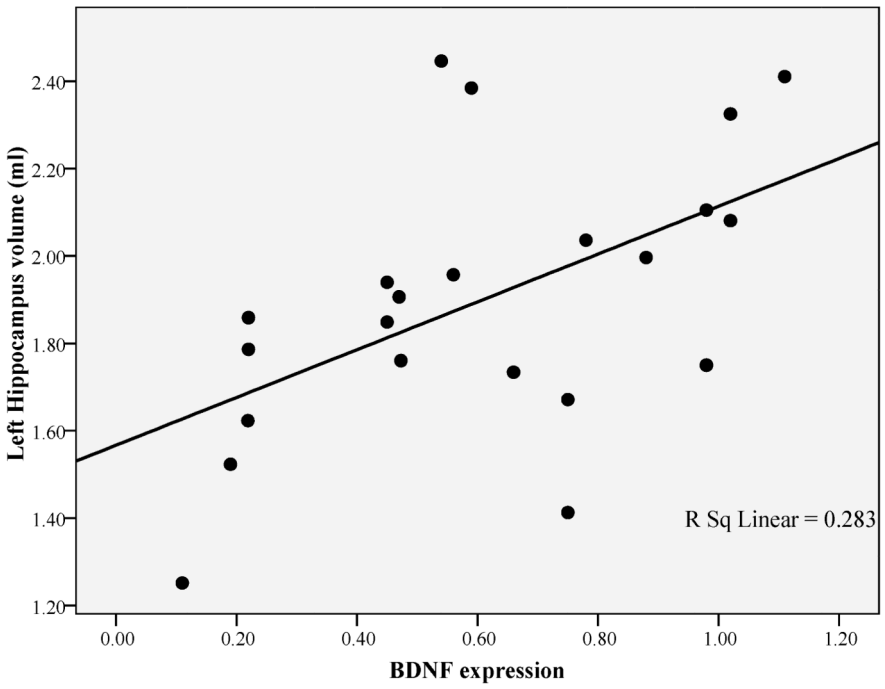
Panel A:



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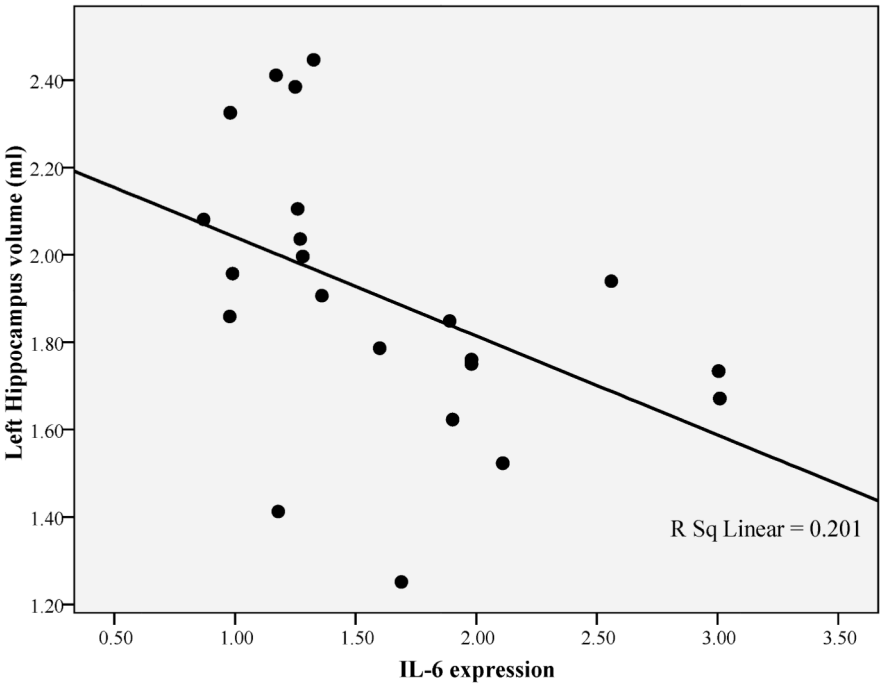

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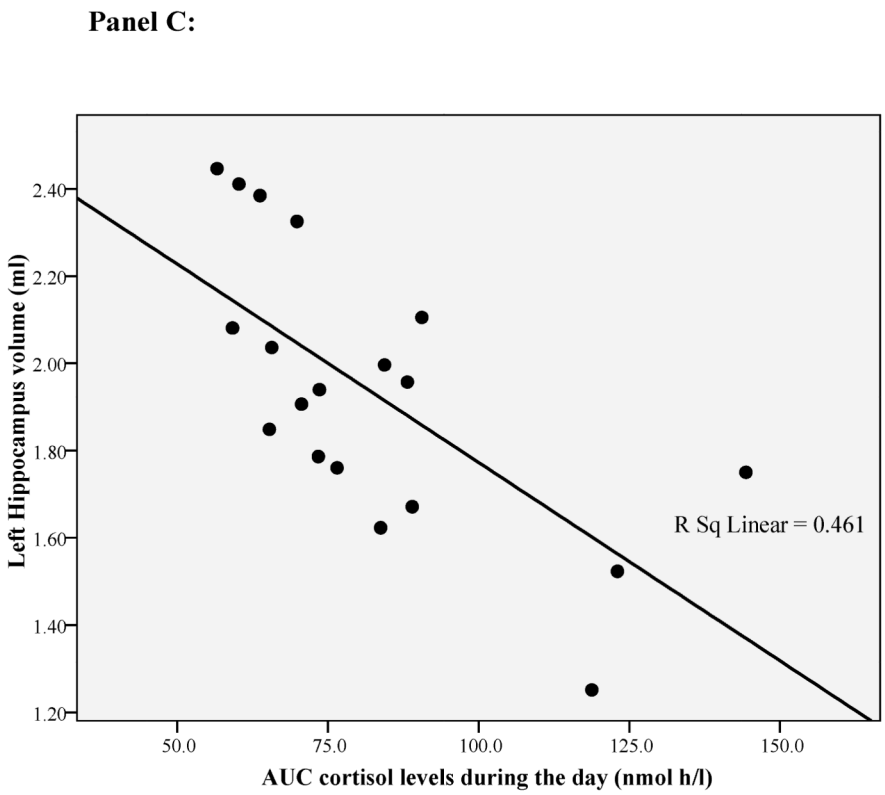

Figure 1.

Correlation of left hippocampal volume with diurnal cortisol levels, IL-6 gene expression and BDNF gene expression in first-episode psychosis patients. **Panel A**: Correlation between left hippocampal volume and BDNF gene expression. **Panel B**: Correlation between left hippocampal volume and IL-6 gene expression. **Panel C**: Correlation between left hippocampal volume and diurnal cortisol levels.

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Table 1

Socio-demographic characteristics, stress variables, IL-6, TNF-alpha and BDNF gene expression of first-episode psychosis patients and healthy controls.

	Patients n=49	**Controls n=30**	**Test and significance**
Age (years)	28.2±0.9	27.0±0.8	t=−1.0, df=1, 77, p=0.3
Gender (M/F)	(33/16)	(19/11)	χ^2=0.1, p=0.8
% of males	67.3%	63.3%	
Body Mass Index (kg/m^2)	24.8±0.8	23.5±0.8	t=−1.2, df=1, 60, p=0.3
Ethnicity (White/Others)	(11/38)	(9/21)	χ2=0.6, p=0.6
% of white British	22.4%	30%	
N. of recent stressors	2.3±0.2	1.3±0.2	t=−3.0, df=1, 71, **p=0.004**
Perceived Stress Scale	21.4±1.1	12.0±1.2	t=−5.6, df=1, 71, **p<0.001**
Childhood trauma (no/yes)	(9/32)	(17/11)	χ^2=10.7, **p=0.002**
% with at least 1 trauma	78%	39.3%	
Day cortisol (nmol hour/l)	79.2±4.6	77.6±7.7	t=−0.2, df=1, 43, p=0.9
IL-6 expression	1.67±0.10	1.04±0.09	t=−4.6, df=1, 73, **p<0.001**
TNF-alpha expression	1.66±0.06	1.04±0.05	t=−7.7, df=1, 75, **p<0.001**
BDNF expression	0.54±0.05	1.17±0.10	t=5.5, df=1, 77, **p<0.001**

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Table 2

Multiple Linear Regression for BDNF expression in first-episode psychosis patients.

		R	Adjusted R square	Significance
1st model	Childhood Trauma + Recent stressful events	0.51	0.21	**p=0.006**
2nd model	Childhood Trauma + Recent stressful events + IL-6 expression	0.54	0.23	**p=0.009**

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Table 3

Multiple Linear Regression for left hippocampal volume in first-episode psychosis patients.

		R	Adjusted R square	Significance
1st model	BDNF expression	0.63	0.36	**p=0.004**
2nd model	BDNF expression + IL-6 expression	0.73	0.47	**p=0.002**
3rd model	BDNF expression + IL-6 expression + Diurnal cortisol levels	0.87	0.71	**p<0.001**