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CLINICAL TRIAL REPORT

Disruptions of p11 (S100A10) and HPA Axis Homeostasis Participate in the Major Depressive Disorder (MDD) Especially in Female Patients

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Objective: Patients suffering from major depressive disorder (MDD) commonly exhibit abnormal p11 (S100A10) and dysregulation of the hypothalamic–pituitary–adrenocortical (HPA) axis. This study was aimed to quantify peripheral p11, cortisol (COR), and adrenocorticotropic hormone (ACTH) levels and further revealed the possible mechanisms of MDD and antidepressant response.

Methods: A total of 60 MDD inpatients and 67 healthy controls (HC) were recruited in this study. Demographic characteristics and neuropsychological assessment including Hamilton rating scale for depression-17 (HAMD-17), Hamilton anxiety rating scale (HAMA), Snaith-Hamilton pleasure scale (SHAPS) and temporal experience of pleasure scale (TEPS) were collected. A main antidepressant was utilized after the patients were enrolled (T0) and at two week follow-up (T2). Peripheral p11 levels including monocyte (MO), natural killer (NK), T-cell, COR, and ACTH were measured by multicolor flow cytometry and enzyme-linked immunosorbent assay at T0 and T2.

Results: CD4+T p11, COR and ACTH were significantly different between the MDD and HC groups at T0 (all $P < 0.05$). Subgroup analysis by gender showed that the MO-C, MO-NC, and NK p11+ cells were higher in female than in male MDD patients (all $P < 0.05$). There was a negative relationship between p11 of MO-NC, CD4+T, CD8+T, and TEPS. However, there was no significant difference between T0 and T2 in MDD patients.

Conclusion: Baseline p11 levels may serve as a peripheral blood biomarker for female depressive patients and further provide more insight into the pathological mechanisms of MDD.

Keywords: major depressive disorder, p11, cortisol, adrenocorticotropic hormone

Introduction

Major depressive disorder (MDD) is characterized by significant and lasting depression, decreased interest and loss of pleasure, and is a common mental disease with a lifelong prevalence of 3.4% in China.[1] MDD accounted for 40.5% of disability-adjusted life years caused by mental and substance use disorder according to the Global Burden of Disease Study 2010.[2] The safety and tolerance of first line antidepressants represented by selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) have been significantly improved, but antidepressant treatment still have the short of slow onset and unsatisfactory efficacy.[3] Previous studies have also identified several novel therapeutic approaches, such as transcranial magnetic stimulation, ketamine, and electroconvulsive therapy, which can be used for treating depression – including even treatment-resistant depression.[4,5] Therefore, it is urgent to understand the mechanism of depression and guide a targeted antidepressant treatment.

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P11 (S100A10), a member of the S100 family of proteins localized in the cytoplasm and/or nucleus of a wide range of cells, has widespread distribution in the brain, adrenal gland, skin and other tissues, where it has a key role in regulation of a number of cellular processes such as membrane trafficking, vesicle secretion, and endocytosis.[6] Previous autopsy from suicide depressed individuals and depressive-like animal model study found the decreased expression of p11 mRNA and protein in frontal cortex, anterior cingulate gyrus, hippocampus and nucleus accumbens.[7,8] Moreover, p11 has been implicated in the actions of antidepressants. P11 constitutive knockout mice results in a depression-like phenotype and blunted behavioral improvements in response to antidepressant regimens.[9,10] Conversely, p11 over-expression and IGF-II-conjugated nanocarrier for brain-targeted delivery of p11 gene mimics the behavioral phenotype presented after antidepressant treatment.[11,12] Several evidence-based approaches have been proposed for the increased p11 expression in the cerebral cortex for treatment MDD using conventional psychotropic medications (such as SSRI), electroconvulsive therapy, and ketamine treatment.[5,13–15]

One of the major characteristics of MDD is hypothalamic–pituitary–adrenal (HPA) axis hyperactivity, presented as high concentrations of corticotropin-releasing hormone and adrenocorticotropic hormone (ACTH). P11 was highly enriched in the paraventricular nucleus and regulates HPA activity. A previous set of experiments provide strong and versatile evidence that p11 knockout mice display HPA axes hyperresponsiveness along with increased stress reactivity, which is partially regulated by p11 deficiency in serotonergic neurons of the raphe nuclei.[16] In addition, the p11 gene is regulated by glucocorticoid receptor by combining with a glucocorticoid receptor element in the p11 promoter region in accordance with the study which demonstrated that a synthetic glucocorticoid-dexamethasone can up-regulate p11.[17–19] The study seeks to explore P11 and HPA function and their association in the MDD population.

For the present study, we investigated whether p11, cortisol (COR) and ACTH changes occur in different subtypes and stages of MDD patients. We carried out baseline and follow-up assessments after a 2-week treatment period. The aims were to explore if: (1) p11, COR, and ACTH in MDD patients are altered; (2) p11, COR, and ACTH change after 2-weeks treatment; and (3) p11, COR, and ACTH correlate with psychopathological assessments, cumulative and different type of antidepressant medication. Combined with the above studies, we hope to provide a new understanding and perspective on the occurrence of depression and antidepressant response.

Materials and Methods

Participants

A total of 60 MDD inpatients and 67 healthy controls (HC) were recruited from the psychosomatics and psychiatry departments of Zhongda Hospital affiliated to Southeast University and community during November 2020 to September 2021. Clinical diagnoses were determined based on the DSM-5 for MDD and conducted independently by two experienced senior psychiatrists. The inclusion criteria were as follows: (1) aged 18–65 years; (2) met the diagnostic criteria of DSM-5 with MDD; (3) total scores on the Hamilton rating scale for depression-17 (HAMD-17) ≥17. All subjects with the following conditions were excluded: (1) comorbidity of other mental disorders (eg, schizophrenia, substance abuse); (2) acute and chronic infections, allergies, or autoimmune diseases; (3) use of antibiotics, corticosteroids, or anti-inflammatory drugs in the previous 4 weeks; (4) severe physical diseases (eg, tumor, liver, or kidney failure). Adult healthy volunteers who met the same exclusion criteria were recruited through advertisements as healthy controls.

This study was approved by the medical ethics committee for clinical research of Zhongda hospital affiliated to Southeast University (approval number: 2020ZDSYLL070-P01) and Chinese Clinical Trail Registry (registration number: ChiCTR2000032037). All participants provided written informed consent after being given a full explanation of the study according to the Declaration of Helsinki.

Antidepressant Treatment

A main antidepressant was utilized according to the clinical features, pharmacological properties, and other additional factors after the patients enrolled. Eighteen patients received SSRIs, 41 received SNRIs, and one received vortioxetine. Doses of antidepressants were adjusted as needed in the process of the study. Low-dose benzodiazepines and antipsychotics were used in some patients to treat serious insomnia and suicidal ideation when necessary.

Clinical Assessments and Outcome Evaluations

The demographic and clinical characteristics of participants were collected including age, sex, body mass index (BMI), education level, marital status, family history of mental disorder, duration, and antidepressants used before admission from all participants.

The severity of depression, anxiety, and anhedonia was evaluated by the HAMD-17, Hamilton anxiety rating scale (HAMA), Snaith-Hamilton pleasure scale (SHAPS), and temporal experience of pleasure scale (TEPS) at baseline (T0) and 2 weeks treatment (T2). During the 2 weeks' follow-up period, 41 patients completed the follow-up study including 14 patients who received SSRIs, 26 who received SNRIs, and one who received vortioxetine.

Sample Collection and Measurement of Peripheral p11 Level, Indexes of HPA Axis

Blood samples (3 mL) were collected in the morning at approximately 6 a.m. from a forearm vein of the fasting participants. We characterized p11 protein levels within monocyte, T-cell subpopulations, and NK cells by multicolor flow cytometry. Fresh whole blood was used with added FcR blocking, cell staining buffer, foxp3 fixed film breaker reagent, multiple antibodies, etc., in sequence according to the manufacturer's instructions. Cells were subsequently washed and incubated in a mixture of antibodies to identify classically activated monocytes ($CD14^{+}CD16^{-}$), non-classically activated monocytes ($CD14^{+}CD16^{+}$) – CD14BV421, BioLegend 325627, CD16PE, milteny 130–100-697, and NK cells ($CD3^{-}CD16^{+}CD56^{+}$) – CD3BV510, BioLegend 300447, CD56APC, milteny 130–100-697, or cytotoxic T cells ($CD8^{+}$) – PE-Vio615, milteny 130–110-823 and helper T cells ($CD4^{+}$) – PE-Vio770, milteny 130–113-789. Cells were fixed and permeabilized for subsequent intracellular p11 staining using a monoclonal mouse anti-human p11 antibody (proteintech 11250-1-AP) or an isotype control mouse IgG monoclonal antibody (BioLegend 400157), and thereafter with an APC-conjugated or PE-conjugated rabbit anti-mouse antibody. To assess p11 protein levels, we respectively used the fluorescence intensity (FI) of the APC- or PE-conjugated secondary antibody targeting the p11 antibody and the percentage (%) of p11+ cells in each cell population. Classically activated monocytes ($CD14^{+}CD16^{-}$) p11 levels were successfully measured in 58 MDD patients and 67 HC subjects; non-classically activated monocytes ($CD14^{+}CD16^{+}$) p11 levels were successfully measured in 57 MDD patients and 65 HC subjects; NK cell ($CD3^{-}CD16^{+}CD56^{+}$) p11 levels were successfully measured in 60 MDD patients and 66 HC subjects; T helper cells ($CD4^{+}$) p11 levels were successfully measured in 58 MDD patients and 64 HC subjects; cytotoxic T cells ($CD8^{+}$) p11 levels were successfully measured in 57 MDD patients and 67 HC subjects.

The levels of cortisol and ACTH were all measured by the hospital clinical laboratory with enzyme-linked immunosorbent assay (ELISA) kits (cortisol and ACTH kits from R&D Systems) according to the manufacturer's instructions. The reference range provided by our clinical laboratory for samples taken at 8:00 a.m. was 7.2–63.3 pg/mL. The value falling outside this reference range was defined as abnormal ACTH. The cortisol was detected at 8 a.m., 4 p.m., and 0 a.m. only for MDD patients to explore the rhythm of cortisol. Cortisol rhythm disturbance was defined as plasma cortisol at 4 p.m. > 50% 8 a.m. or 0 a.m. > 50% 4 p.m. or 0 a.m. > 8 a.m.[20,21]

Data Analysis

All analyses were conducted using SPSS Version 20.0 statistical software (SPSS Inc. Chicago, IL) and Prism 9 software (GraphPad). Data are expressed as the mean ± SD for normal distribution data and median (quartile 1, quartile 3) for non-normal distribution data. Independent sample *t*-test, non-parametric test, and chi-square test was used to evaluate the differences of the continuous variables and categorical variables between two groups at T0 and T2. Paired t-tests or nonparametric tests with two related samples were conducted between T0 and T2 in the MDD group. The correlations between variables were tested by Spearman correlation analysis. Logistic regression analysis was employed to explore the independent influencing factors of MDD patients. All analyses were two-tailed and a P value < 0.05 was considered statistically significant.

Results

Demographic and Neuropsychological Results in T0

A total of 127 subjects including 60 MDD and 67 HC were recruited in this study. There were no significant differences in demography (age, gender, body mass index, education level, and marital status) between two groups (all $P > 0.05$).

The MDD patients have higher frequency of family history of mental disorder than HC group (χ^2= 7.961 P = 0.005). In the MDD group, the duration of illness was 8.35 ± 10.18 months and 42 MDD patients were taking antidepressant drugs before hospitalization. The total scores of HAMD-17, HAMA, and SHAPS were higher than HC group (all P < 0.001, see Table 1). The score of TEPS were lower than in the HC group (P < 0.001, see Table 1). These results showed that MDD patients have more severity of depression, anxiety, and anhedonia.

Comparisons of Peripheral p11 Level and Indexes of HPA Axis between MDD and HC in T0

Comparisons of Peripheral p11 Level, HPA Axis Index between MDD and HC in T0

The p11 of CD4+T were significantly different between MDD and HC group (Z = −2.297, P = 0.022, see Table 2 and Figure 1A). Both COR at 8 a.m. and ACTH were significantly higher in the MDD group than HC group (Z = −4.926, P < 0.001; Z = −4.655, P < 0.001, respectively, see Table 2 and Figure 1B and C).

Comparisons of Peripheral p11 Level, HPA Axis Index in the Subgroup Analysis Stratified by Gender and HPA Function of MDD Patients

Further subgroup analysis of MDD patients by gender revealed the p11 of MO-C, MO-NC, and NK cells in female MDD patients was significantly higher than that in male MDD patients (Z = −2.483, P = 0.013; Z = −2.481, P =

Table 1 The Demographic and Clinical Characteristics of Participants

	MDD (n = 60)	HC (n = 67)	t /χ^2 value	P value
Age (years)	44.07 ± 15.11	42.72 ± 12.86	−0.544	0.588
Gender (male/female)	22/38	18/49	1.409	0.235
BMI	22.65 ± 3.38	23.52 ± 3.03	1.524	0.130
Education level (years)	11.18 ± 3.75	12.79 ± 6.22	1.784	0.077
Marital status (married/single)	46/14	50/17	0.071	0.789
Family history of mental disorder (yes/no)	9/51	1/66	7.961	0.005
Duration (months)	8.35 ± 10.18	–	–	–
Antidepressant (yes/no)	42/18	–	–	–
HAMD-17	22.62 ± 5.75	1.85 ± 1.45	−27.22	<0.001
HAMA	20.77 ± 7.36	1.97 ± 1.59	−19.39	<0.001
SHAPS	7.62 ± 4.70	0.49 ± 0.93	−11.538	<0.001
TEPS	55.18 ± 19.44	80.16 ± 17.07	7.710	<0.001

Abbreviations: MDD, major depressive disorder; HC, healthy controls; BMI, body mass index; HAMD-17, Hamilton rating scale for depression-17; HAMA, Hamilton anxiety rating scale; SHAPS, Snaith-Hamilton pleasure scale; TEPS, temporal experience of pleasure scale.

Table 2 P11 and Peripheral Blood Indexes between MDD and HC Group at T0

	MDD	HC	Z value	P value
MO-C P11	0.858 (0.417–1.848,58)	0.625 (0.276–1.277,67)	−1.906	0.057
MO-NC P11	0.593 (0.282–1.689,57)	0.525 (0.241–1.264,65)	−1.055	0.292
NK cells P11	0.805 (0.166–2.148,60)	0.794 (0.359–1.564,66)	−0.015	0.988
CD4+T cells P11	0.086 (0.034–0.343,58)	0.045 (0.010–0.198,64)	−2.297	0.022
CD8+T cells P11	0.094 (0.031–0.683,57)	0.096 (0.026–0.308,67)	−0.704	0.481
HPA indexes				
COR (8 a.m.)(μg/dL)	17.075 (12.779–22.325,60)	9.938 (7.640–14.500,67)	−4.926	<0.001
ACTH (pg/mL)	26.942 (16.500–41.230,56)	13.738 (9.040–20.079,67)	−4.655	<0.001

Note: Data are presented as median (quartile 1; quartile 3; sample size).
Abbreviations: MDD, major depressive disorder; HC, healthy controls; HPA, hypothalamic–pituitary–adrenal; COR, cortisol; ACTH, adrenocorticotropic hormone.

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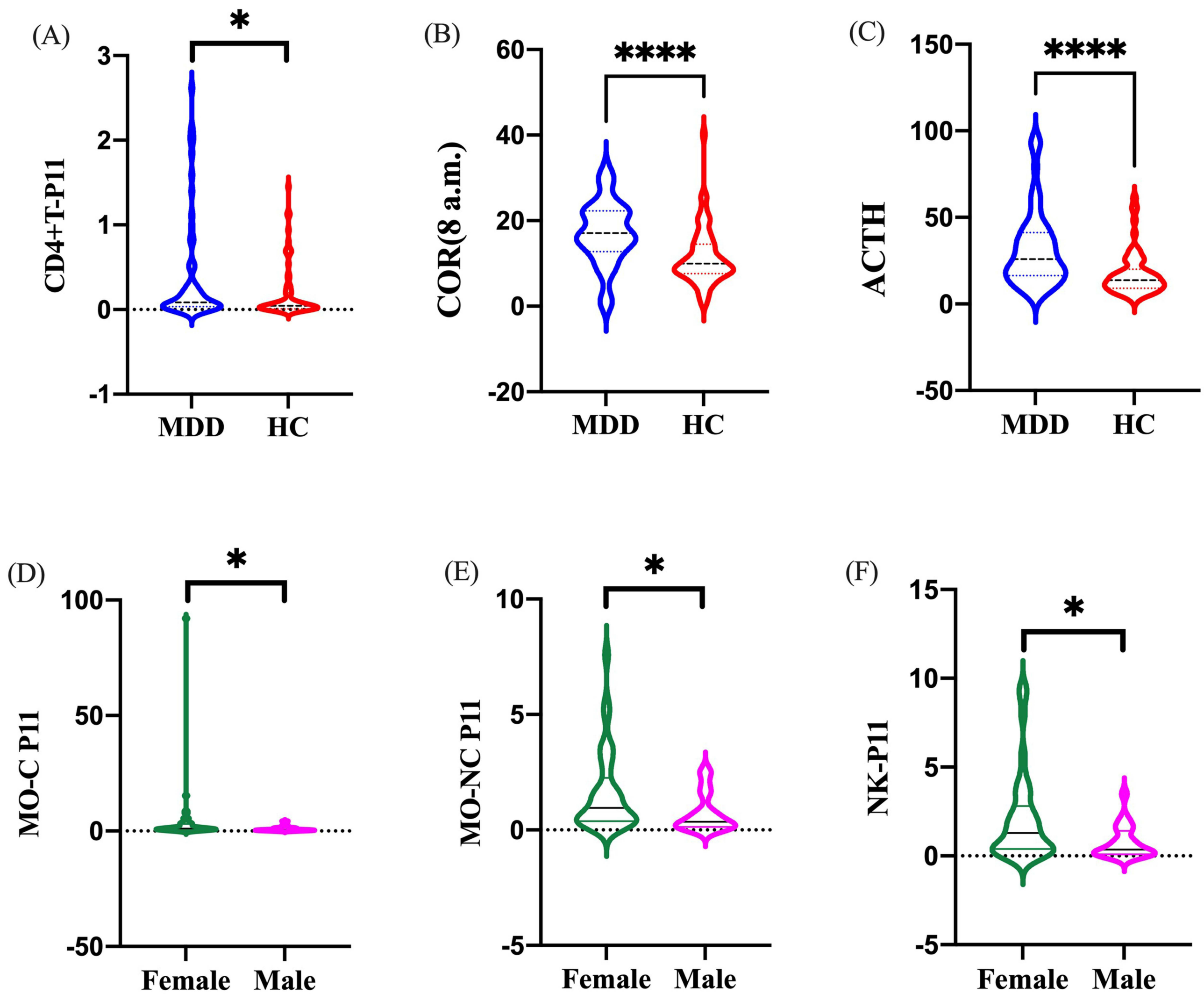

Figure 1 Violin plots showing the differences of peripheral p11 (**A**), COR (**B**), ACTH (**C**) between MDD and HC groups as well as p11 in different peripheral blood cells (**D**–**F**) between female and male MDD patients.

Note: * $P < 0.05$; **** $P < 0.001$.

Abbreviations: MDD, major depressive disorder; HC, healthy controls; COR, cortisol; ACTH, adrenocorticotropic hormone.

0.013; Z = −2.454, P = 0.014, respectively, see Table 3 and Figure 1D–F). However, there was no significant difference of HPA axis index between female and male depressive patients (all $P > 0.05$, see Table 3).

In the subgroup analysis stratified by HPA function (normal/abnormal cortisol rhythm and normal/abnormal ACTH), there is no significant difference between normal and abnormal cortisol rhythm/ACTH (see Table 4).

Relationship between Peripheral p11 Level, Indexes of HPA Axis and Neuropsychological Scale in MDD Patients in T0

Relationship between Peripheral p11 Level and Neuropsychological Scale in MDD Patients

We correlated p11 levels with clinical evaluation in order to further assess the suitability of p11 as a peripheral biomarker. The p11 of MO-NC, CD4+T, and CD8+T were negatively related with TEPS in MDD patients (r = −0.312, P = 0.018; r = −0.301, P = 0.021; r = −0.264, P = 0.048, respectively, see Figure 2A–C). However, no significant correlation was found among p11 of MO-C and NK cells, HPA axis indices, or neuropsychological scales.

Table 3 P11 and Peripheral Blood Indexes between Male and Female in MDD Patients

	Female	Male	*Z* value	*P* value
MO-C P11	1.088 (0.461–3.097,37)	0.453 (0.274–1.257,21)	−2.483	0.013
MO-NC P11	0.955 (0.376–2.258,36)	0.357 (0.133–1.192,21)	−2.481	0.013
NK cells P11	1.294 (0.395–2.808,38)	0.365 (0.087—1.412,22)	−2.454	0.014
CD4+T cells P11	0.124 (0.038–0.675,37)	0.066 (0.028–0.231,21)	−1.044	0.297
CD8+T cells P11	0.163 (0.031–1.010,36)	0.064 (0.023–0.321,21)	−1.307	0.191
HPA indexes				
COR(8 a.m.)	15.757 (10.048–21.900,38)	18.040 (15.559–22.781,22)	−1.580	0.114
COR(4 p.m.)	8.575 (5.447–12.536,38)	10.100 (7.075–13.095,21)	−0.871	0.384
COR(0 a.m.)	1.970 (0.774–4.007,38)	1.910 (1.380–2.610,21)	−0.071	0.943
ACTH	25.297 (12.802–36.411,35)	30.100 (18.800–44.922,21)	−1.185	0.236

Note: Data are presented as median (quartile 1; quartile 3; sample size).
Abbreviations: MDD, major depressive disorder; HPA, hypothalamic-pituitary-adrenal; COR, cortisol; ACTH, adrenocorticotropic hormone.

Relationship between Peripheral p11 Level and Indexes of HPA Axis in MDD Patients

The p11 of CD4+T cells had the positive relationship with ACTH (r = 0.302, *P* = 0.026, see Figure 2D).

Differentiating Values of Peripheral P11 Level and Indexes of HPA Axis for MDD Patients in T0

Given the significant difference of peripheral p11 and indexes of HPA axis levels between MDD and HC group, we assessed the ability of these factors to discriminate between MDD and HC using logistic regression (backward elimination, condition). Two factors including MO-C p11, COR (8 a.m). significantly associated with MDD patients (*P* = 0.021, OR = 1.954, 95% CI = 1.106–3.452; *P* = 0.007, OR = 1.104, 95% CI = 1.027–1.186, see Table 5).

The Clinical Characteristics between T0 and T2 in MDD Patients

After two weeks of antidepressant treatment, the severity of depression (HAMD-17), anxiety (HAMA), and anhedonia (SHAPS and TEPS) in MDD patients were significantly improved (all $P < 0.05$), and the results were the same regardless of the overall sample or SSRI antidepressant treatment groups. There were significant decreased of HAMD-17, HAMA and increased of TEPS in SNRI treatment groups (all $P<0.05$, see Supplementary Table 1).

Comparisons of Peripheral P11 Level, Indexes of HPA Axis between T0 and T2 in MDD Patients

There was no significant difference in the peripheral P11 level, COR (8 a.m). and ACTH between T0 and T2 of MDD patients in whole and SSRI treatment subgroup (all $P > 0.05$, see Supplementary Table 2). However, ACTH was increased on T2 in the SNRI group compared with T0 (Z = −2.191, *P* = 0.028).

Discussion

The present study displayed three important findings. Firstly, increased peripheral p11 of CD4+T, COR (8 a.m). and ACTH were found in the MDD group. Secondly, p11 in MO-C, MO-NC, and NK cells were higher in female than male MDD patients. Thirdly, the correlation analysis displayed that the p11of MO-NC, CD4+T, and CD8+T cells were negatively related with TEPS.

The present study demonstrated higher peripheral p11 of CD4+T cells in MDD patients compared with the HC group. It shows inconsistency in that a decrease in p11 mRNA and protein in the brain at animal studies and postmortem brain tissue from depressed suicide victims.[5,12,22] However elevation of p11 in lateral habenula, a key brain region with hyperactivity in both rodent models of depression and human patients, with depression as a key molecular determinant

Table 4 The Results of Peripheral P11 According HPA Axis in MDD Patients

	Cortisol Rhythm		*P* value (*Z* value)	ACTH		*P* value (*Z* value)
	Normal	Abnormal		Normal	Abnormal	
MO-C P11	0.839 (0.408–2.461,17)	0.890 (0.436–2.206,40)	0.931 (−0.087)	0.820 (0.401–1.528,49)	1.068 (0.439–3.384,5)	0.644 (−0.463)
MO-NC P11	0.605 (0.225–1.863,16)	0.593 (0.321–1.702,40)	0.526 (−0.635)	0.535 (0.280–1.657,48)	1.001 (0.346–3.127,5)	0.626 (−0.487)
NK cells P11	0.800 (0.337–2.743,17)	0.846 (0.161–2.070,42)	0.789 (−0.268)	0.612 (0.145–1.790,49)	1.116 (0.399–3.607,7)	0.193 (−1.301)
CD4+T cells P11	0.164 (0.050–0.907,17)	0.072 (0.034–0.272,40)	0.320 (−0.994)	0.078 (0.034–0.247,47)	0.836 (0.041–2.048,7)	0.052 (−1.944)
CD8+T cells P11	0.419 (0.020–1.039,16)	0.082 (0.031–0.383,40)	0.355 (−0.925)	0.804 (0.022–0.394,47)	1.442 (0.069–2.787,6)	0.056 (−1.909)

Abbreviations: MDD, major depressive disorder; HPA, hypothalamic–pituitary–adrenal; ACTH, adrenocorticotropic hormone.

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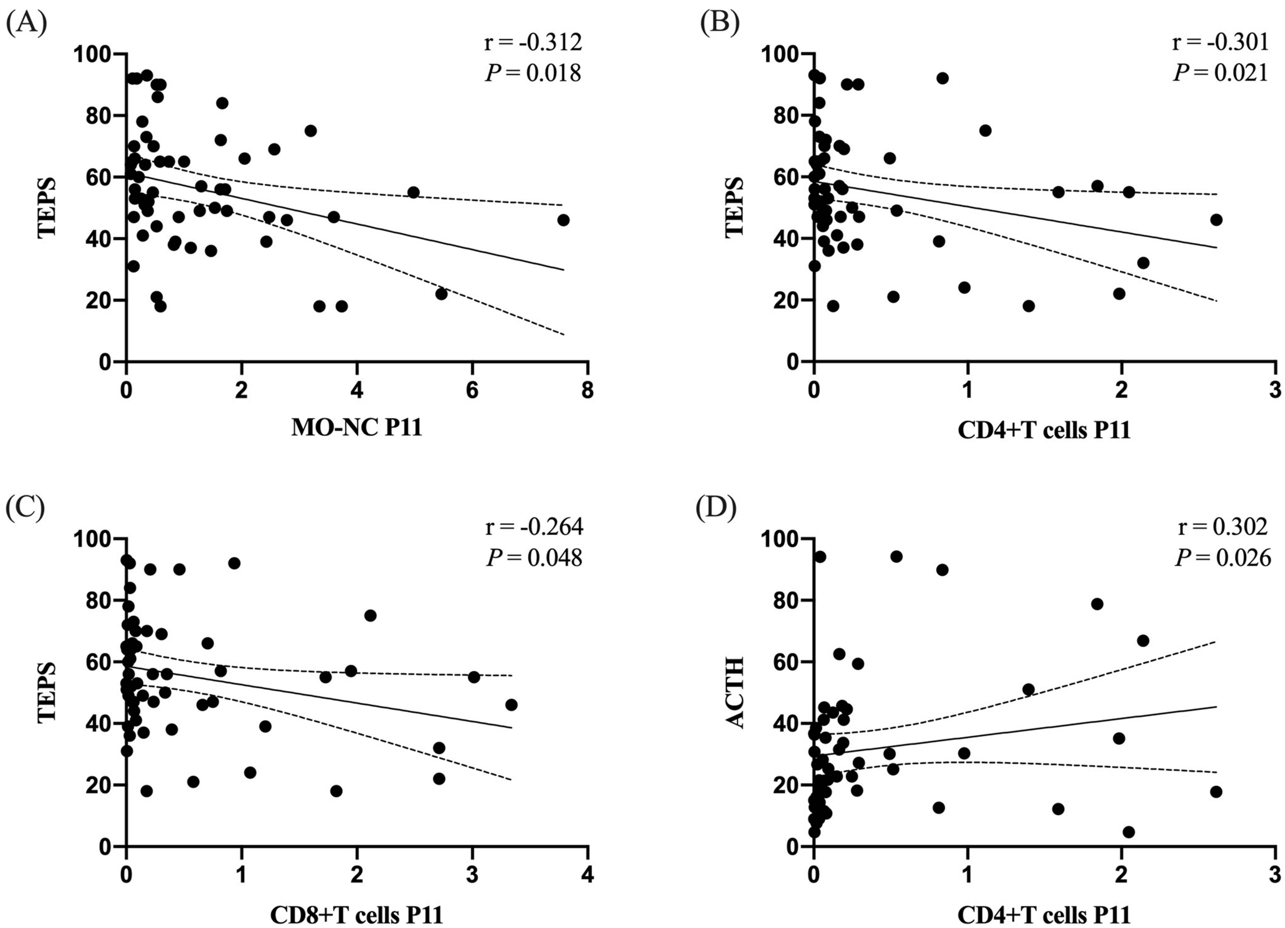

Figure 2 The relationship among peripheral p11 level, indexes of HPA axis and neuropsychological scale in MDD patients. (**A**–**C**) the relationships between P11 and TEPS; (**D**) the relationship between P11 and ACTH.
Abbreviations: TEPS, temporal experience of pleasure scale; ACTH, adrenocorticotropic hormone.

mediating depression-like behavior.[23] Therefore, p11 play a complex role of in depression restricted to distinct brain regions, systems (central/peripheral) and specific cell types (neuronal/astroglia/microglia etc.), which may help to better understanding the molecular and cellular mechanisms of p11 in the pathogenesis of depression.[6] Taking into account that p11 levels are altered in MDD patients in a cell type-specific manner and linked functions of the various cell subtypes, p11 levels in classically/nonclassically activated monocytes and NK cells, T-cell subsets were measured in order to capture any discrete changes in blood p11 levels. Higher p11 in CD4+ T cells was displayed under MDD pathological conditions compared with HC subjects at T0. Interestingly, a previous study showed that T regulatory cells may also participate in depression by dampening chronic inflammatory responses.[24] This study and the past results are in good agreement, with p11 levels increased in classically activated monocytes in MDD or Parkinson's disease patients with depression, suggesting that p11 may play a role in the adaptive and innate immune system.[25] But, unfortunately, we did

Table 5 The Results of Logistic Regression Model in MDD and HC Groups

	βvalue	Standard Error	Warld χ^2	*P* value	OR	95% CI
COR (8 a.m.)	0.099	0.037	7.195	0.007	1.104	1.027–1.186
MO-C p11	0.670	0.290	5.323	0.021	1.954	1.106–3.452

Abbreviations: MDD, major depressive disorder; HC, healthy controls; COR, cortisol; OR, odds ratio; CI, confidence interval.

not find any changes in the expression of p11 in various types of cells after antidepressant treatment although previous evidence showed that early reduction in p11 levels in natural killer cells and monocytes predicts the possibility response to antidepressant.[26] Several factors may explain this discrepancy. First, approximately two-thirds of the patients enrolled in our study were already on antidepressant medication at baseline, which might have influenced baseline p11 expression and obscured treatment-related changes. Second, while previous preclinical studies have suggested that antidepressants may increase serotonin receptor trafficking via upregulation of p11 in the prefrontal cortex, the peripheral p11 levels measured in our study (in immune cells) may not directly reflect central nervous system p11 dynamics or its role in neuronal plasticity.[27,28]

The dysregulation of the HPA axis system has been proposed as a major pathophysiological mechanism in the etiology of MDD. With increased COR (8 a.m), ACTH levels were discovered in MDD patients in our study, which is consistent with our and others previous research, supporting that HPA and inflammatory change were involved in depression.[29,30] It has been found that the psychosocial stress, especially traumatic life events, can cause HPA axis hyperactivity, which not only regulates body peripheral functions such as metabolism, immunity, and gut microbiota, but also has profound effects on the brain, including but not limited to neuronal survival, neurogenesis, and the sizes of complex anatomical structures.[31–33] In general, HPA axis hyperactivity might share the same pathophysiological process in depressed individuals: glucocorticoid resistance, characterised by ineffective action of glucocorticoid hormones on target tissues, was a marker of HPA axis hyperactivity and leads to immune activation. However, this study did not reveal significant differences between patients with normal and abnormal HPA axis function. The underlying reasons for this are likely multifactorial: first, although some indicators (such as the p11 of CD4+/CD8+ T cell) showed a tendency toward elevation in the abnormal ACTH group during subgroup analysis, the differences did not reach statistical significance, likely due to the reduced sample size after stratification. Second, the subgroup analysis categorized patients only into "normal" and "abnormal" groups based on HPA axis function. The "abnormal" group likely encompasses different subtypes of dysregulation (eg, hyperactive vs dysregulated HPA axis), which may exhibit distinct p11 expression patterns. These opposing trends within the abnormal group could have counterbalanced each other, resulting in no overall statistically significant difference between the two broad groups.

It is widely known that the prevalence of MDD is approximately twice as high in women as in men (5.8% vs 3.5%), representing a major health disparity between the genders.[34] Moreover the gender difference peaked in adolescence and remained stable in adulthood.[35] Despite the gender difference in depression being a robust finding in psychopathology research, the biological mechanism behind this is not clearly elucidated. Some scholars proposed ABCs integrating affective, biological, and cognitive models to explain the emergence of the gender difference in depression.[36] In addition, reduction in markers of immune function and microglia, attenuated inflammatory response, and hormonal fluctuations generated a greater probability of MDD in women compared to men.[37–39] We further calculated the subgroup analysis of MDD patients by gender, which revealedthat the p11 of MO-C, MO-NC, and NK cells in female MDD patients was significantly higher than that in male patients, which to a certain extent previously reported data and provides a new possible hypothesis for female patients to be susceptible to depression.

Anhedonia, one of the core symptoms of MDD, was associated with suicide ideation, impaired psychosocial functioning, and poorer disease prognosis.[40,41] The TEPS, including anticipatory and consummatory pleasure, has exhibited satisfactory reliability and is commonly used to measure anhedonia.[42] Cumulative literature implicates that functional changes of HPA and immune system dysfunction may play a role in the pathophysiology of anhedonia.[43,44] Scholars has reviewed p11 levels, especially p11 in the ChAT+ cells or DRD1+ MSN, within the NAc affects hedonic behavior.[45] In the present study, a significant correlation was found between p11 levels and TEPS, reflecting the fact that core depressive symptoms are regulated by p11. From this conceptualization, it is in support of this notion that a dysregulation of p11 in central and peripheral systems could contribute to the pathophysiology of depressive disorders as well as antidepressants.[46] P11 is a promising molecular target and treatments to counter maladaptation of p11 levels may provide novel therapeutic opportunities for MDD.

The diagnosis of MDD is generally based solely on clinical assessment, which often leads to misdiagnosis.[47] Repeatability and robust biomarkers using neuroimaging, neurophysiology, genomics, proteomics, circRNAs, and metabolomics measures to support the diagnosis and track disease prognosis would prompt a scientific breakthrough.[48]

However, MDD is a heterogenous, multifactorial condition, none of their hypotheses fully elucidated all symptoms observed in it. Similarly, an indicator as a peripheral objective biomarker also brings unsatisfactory diagnostic efficiency.[49] While our study identified alterations in p11 levels and HPA axis indexes among MDD patients, these findings are more indicative of associated risk factors rather than serving as validated diagnostic biomarkers. This finding is consistent with previous studies which have established a biomarker panel for diagnosing patients with depression by blood, urine, and tear fluid.[50–52] Further study is needed to find and verify whether peripheral biomarkers of p11 can help clinicians in distinguishing MDD or selecting a particular antidepressant therapy.

The present study has some limitations. Firstly, the sample size was relatively small, and further studies need to be performed in the large samples. Secondly, two-thirds of MDD patients had received antidepressant drug within two weeks before they participate in this study, this may partly explain that no significant difference was found between baseline and following 2 weeks treatment. Thirdly, we measured seven peripheral factors levels, some indicators are not successfully measured in participants. Therefore, in future clinical studies, we should detect these peripheral blood indicators in large drug-naïve and highly homogeneous samples for every sample to increase the possibility of all detections and verify this findings.

Conclusion

In conclusion, this study provides further evidence that p11 levels are altered in depression patients, especially in female MDD patients. We also found abnormal function of the HPA axis in MDD groups. There are complex interactions among p11, COR, ACTH, and clinical symptoms. Early analyses of p11 levels would predict the high-risk female depressive population, guide clinicians in objective diagnosis, and further provide more insight into the pathological mechanisms of MDD.

Abbreviations

MDD, major depressive disorder; HC, healthy controls; HPA, hypothalamic–pituitary–adrenocortical; COR, cortisol; ACTH, adrenocorticotropic hormone; BMI, body mass index; HAMD-17, Hamilton rating scale for depression-17; HAMA, Hamilton anxiety rating scale; SHAPS, Snaith-Hamilton pleasure scale; TEPS, temporal experience of pleasure scale; MO, monocyte; NK, natural killer; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author, Yonggui Yuan, upon reasonable request.

Ethics Statement

This study was approved by the medical ethics committee for clinical research of Zhongda hospital affiliated to southeast university (approval number: 2020ZDSYLL070-P01) and Chinese Clinical Trail Registry (registration number: ChiCTR2000032037, registered on April 18, 2020). All participants provided written informed consent after being given a full explanation of the study according to the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests.

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