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CLINICAL TRIAL STUDY

Baseline Plasma BDNF Levelsare Associated with Antianhedonic Effects of Repeated-Dose Intravenous Ketamine in Major Depressive Disorder

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Abstract: ***Objective*:** Evidence has shown that brain-derived neurotrophic factor (BDNF) is associated with anhedonia symptoms in major depressive disorder (MDD) patients, while the rapid antianhedonic effects of ketamine may occur independently of depressive symptoms. To our knowledge, the relationship between plasma BDNF (pBDNF) and the effect of repeated-dose intravenous ketamine on anhedonic symptoms has not been investigated.

***Methods*:** Seventy-five Chinese individuals with MDD received ketamine treatments. Anhedonia and pBDNF concentrations were evaluated with a subscale of the Montgomery-Åsberg Depression Rating Scale (MADRS) and enzyme-linked immunosorbent assay (ELISA) at baseline, day 13 and day 26.

***Results*:** Baseline pBDNF levels were associated with changes in anhedonic symptoms on day 13 (r=0.30, *P*=0.008). Interestingly, pBDNF concentrations were associated with changes in anhedonia symptomson day 26 (r= -0.32, *P*=0.02). Baseline pBDNF levels were higher in antianhedonic responders than in antianhedonic nonresponders (F=4.2, *P*=0.04). Ketaminereduced anhedonia symptoms in antianhedonic responders compared to nonresponders on days 13 and 26 (all *P*s<0.05). The baseline high BDNF group had a lower level of anhedonia than the low BDNF group on days 13 (*P*<0.001) and 26 (*P*=0.01).

***Conclusion*:** Our study suggests that baseline pBDNF concentrations may predict the antianhedonic effect in individuals with MDD treated with repeated doses of ketamine.

***Clinicl Trial Registration Number*:** ChiCTR-OOC-17012239.

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1. INTRODUCTION

Anhedonia, the diminished capacity to experience pleasure, has been described in major mental disorders, especially major depressive disorder (MDD) [1]. Approximately 37% of patients experiencing MDD suffer from clinically significant anhedonia [2]. Anhedonia is also an important predictor of suicidal ideation independent of depression [3] and poor prognosis in MDD [4]. However, it is especially difficult to treat anhedonia pharmacologically and psychosocially [5, 6]. The frequent occurrence of reward-based disturbances in subjects suffering from MDD provides the impetus for developing novel pharmacological avenues [7].

Ketamine, a glutamatergic modulator, has rapid (within hours) and long-lasting antisuicidal and antidepressant effects in individuals experiencing MDD [8-12] or bipolar disorder (BD) [8, 13, 14]. Similarly, esketamine also has rapid-acting and sustained antidepressant and antisuicidal activity in subjects suffering from treatment-refractory depression (TRD) [15]. Several clinical studies have been conducted to examine the antianhedonic effects of ketamine [7, 16-18]. For example, a rapid and robust reduction in anhedonic symptoms was observed after depressed patients received single [17] and multiple ketamine infusions [7]. Importantly, recent findings indicate that the rapid antianhedonic effects of ketamine occur independently of depressive symptoms [16, 18].

Accumulating evidence has found that neuronal concentrations of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), are related to reward-related processes and hedonic impairment [19-21] as well as anhedonic-like behaviours [22]. Compared to MDD patients without anhedonia, MDD patients with anhedonia had a higher ratio of mBDNF (mature BDNF)/proBDNF (precursor BDNF),

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and the ratio of mBDNF/proBDNF was positively associated with anhedonia symptoms in patients with MDD [20]. Another N-methyl-D-aspartate receptor (NMDAR) antagonist, memantine, could reverse anhedonia and increase BDNF concentrations in the prefrontal cortex [23]. The role of BDNF in the antisuicidal and antidepressant effects of ketamine at a subanaesthetic dose has been investigated in depressed individuals [24-27]. For example, Zheng *et al.* found that baseline plasma BDNF (pBDNF) concentrations could predict the final antidepressant response to six ketamine treatments [26]. However, to our knowledge, the relationship between pBDNF concentrations and the effect of repeated-dose intravenous ketamine on anhedonic symptoms in individuals with MDD has not been investigated.

Therefore, this post-hoc analysis study aimed to investigate whether pBDNF concentrations can be considered a sensitive indicator to predict the effect of ketamine on reducing anhedonic symptoms. We aimed to verify whether patients with an antianhedonic response had increased pBDNF concentrations compared with those who did not respond to six ketamine infusions and whether baseline pBDNF concentrations would be associated with changes in anhedonic symptoms following ketamine treatments.

2. MATERIALS AND METHODS

2.1. Participants and Study Design

Each patient involved in this study signed an informed consent form. Institutional review board approval of the Affiliated Brain Hospital of Guangzhou Medical University was obtained for this study (Ethical Application Ref. 2016030).

This is an open-label, real-world study of patients with MDD treated with six ketamine infusions (registration number: ChiCTR-OOC-17012239) from September 2016 to December 2017 who met the inclusion and exclusion criteria detailed earlier [9]. In brief, all consecutively admitted patients were diagnosed with MDD using DSM-5 criteria by two independent psychiatrists. All patients experiencing a major depressive episode (MDE) with HAMD-17 (17-item Hamilton Depression Rating Scale) ≥ 17 [28, 29], who suffered from suicidal ideation or TRD indexed by a score of ≥ 2 on the Beck Scale for Suicide Ideation (SSI)-part I [27, 30] or failed to respond to ≥ 2 adequate treatment trials with antidepressants for the current MED [9]. The exclusion criteria included the presence of any serious or unstable medical conditions or comorbid alcohol or substance abuse or dependence.

2.2. Clinical Interview and Assessments

A self-designed questionnaire was collected through face-to-face interviews, including age, gender, education level, and marital status. The depression symptom was measured using the Montgomery-Åsberg Depression Rating Scale (MADRS) [31]. In line with the methodology of previous studies [18, 32-34], the evaluation of anhedonia symptoms was based on the MADRS anhedonia item, including items 1 (apparent sadness), 2 (reported sadness), 6 (concentration difficulties), 7 (lassitude), and 8 (inability to feel) at baseline, day 1 and week 2 after the last ketamine infusion (days 13 and 26). Patients were determined as antianhedonic responders when the reduction rate of anhedonia symptoms was ≥ 50% on day 13 from baseline, while others were determined as antianhedonic nonresponders [18]. Psychiatrists with clinical experience assessed the MADRS with an inter-class correlation coefficient (ICC) >0.90.

2.3. Clinical Intervention

Ketamine hydrochloride (0.5 mg/kg) was diluted in saline (40 ml) and administered over 40min using a continuous intravenous pump. Following an overnight fast, all subjects received six subanaesthetic doses of ketamine (0.5 mg/kg over 40 min) over 12 days. During the injection, each participant's haemodynamic and clinical status was periodically monitored. More details regarding repeated ketamine infusions were presented in earlier studies [9, 35].

2.4. Measurement of pBDNF Concentrations

The whole blood of seventy-five individuals with MDD was collected at baseline and on days 13 and 26 in this study. Fasting blood samples of each patient were collected between 8:00 and 10:00 AM and then centrifuged (3000 rpm/min, at +4°C) for ten minutes within one hour, which were immediately stored at -80°C. Similar to our previous studies [26, 27], measurement of pBDNF concentrations was conducted using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (EMD Millipore Corporation, MA, USA) following the manufacturer's instructions.

2.5. Statistical Analysis

Data from seventy-five individuals experiencing MDD who provided blood samples at baseline were analysed using SPSS 24.0 statistical software, with a significance level of 0.05 (two-sided). The chi-squared test and/or Fisher's exact test, as well as Student's t-test and/or analysis of variance (ANOVA) the test were performed to compare demographic and clinical data and baseline pBDNF concentrations between groups (individuals with antianhedonic response *versus* those without antianhedonic response), when appropriate. Following the methodology of the previous study [36], median segmentation was performed on BDNF levels, and all patients were divided into a low baseline BDNF subgroup (low-BDNF) (below the 50th percentile) and a high baseline BDNF subgroup (high-BDNF) (above the 50th percentile) for further analyses. The relationship between the antianhedonic response to ketamine and pBDNF concentrations was determined by conducting a Pearson correlation analysis. Then, multiple regression analysis models was performed in this study, with age, sex, body mass index, psychiatric family history, previous hospitalization, and age of onset entered as covariate variables. Changes in the levels of pBDNF concentrations over time and subgroup differences (individuals with antianhedonic response versus without antianhedonic response) were examined by performing a linear mixed model with baseline pBDNF levels as the covariate. Changes in the levels of anhedonia as measured by MADRS over time and subgroup differences (low-BDNF group versus high-BDNF group) were examined by performing a linear mixed model, with baseline anhedonic symptoms as the covariate. Bonferroni correction was used for multiple comparisons.

Table 1. Demographic and clinical characteristics of patients with MDD.

Variables	Total Sample (n=75)		Group 1[a] (n=35)		Group 2[a] (n=40)		Statistics		
	N	%	N	%	N	%	χ^2	df	*P*
Male	31	41.3	19	54.3	12	30.0	4.5	1	**0.03**
Married	41	54.7	21	60.0	20	50.0	0.8	1	0.39
Employed	32	42.7	19	54.3	13	32.5	3.6	1	0.06
No history of psychiatrichospitalization	53	70.7	28	80.0	25	62.5	2.8	1	0.10
Having a family history of psychiatric disorders	24	32.0	7	20.0	17	42.5	4.3	1	**0.04**
Having suicidal ideation*	48	64.0	23	65.7	25	62.5	0.1	1	0.77
Lower BDNF group	49	65.3	19	54.3	30	75.0	3.5	1	0.06
On ADs two or more	10	13.3	4	11.4	6	15.0	---[b]	---[b]	0.46
On APs	45	60.0	21	60.0	24	60.0	---[b]	---[b]	0.59
On mood stabilizers	14	18.7	4	11.4	10	25.0	---[b]	---[b]	0.11
	Mean	SD	Mean	SD	Mean	SD	T/F	df	*P*
Age (years)	34.1	11.4	34.9	10.4	33.3	12.3	0.6	73	0.54
Education (years)	12.4	3.3	12.5	3.1	12.4	3.5	0.2	73	0.83
BMI (kg/m^2)	22.2	3.6	22.4	3.8	22.0	3.5	0.4	73	0.66
Age of onset (years)	27.1	11.8	28.4	11.8	26.0	11.9	0.9	73	0.37
Duration of illness (months)	84.3	78.6	78.2	78.4	89.5	79.3	-0.6	73	0.54
FLUeq (mg/day)	36.4	21.9	39.6	23.0	33.5	20.6	1.2	73	0.23
CPZeq (mg/day)	170.6	118.8	144.9	94.7	193.1	134.4	-1.4	---[c]	0.21
Baseline MADRS total score	32.4	7.2	31.6	6.1	33.2	8.1	1.9	73	0.17[d]
Baseline MADRS anhedonia subscale score	20.2	4.3	19.5	4.3	20.9	4.3	0.9	73	0.35[d]
Baseline pBDNF concentrations (ng/ml)	10.5	6.5	12.1	7.1	9.1	5.6	4.2	73	**0.04**[d]

Note: *Suicidal ideation was defined as a score of ⩾2 on the first five items of the Scale for Suicidal Ideations (SSI-part 1).
[a]Fisher's Exact Test.
[b]Group 1: patients with antianhedonic response; group 2: patients without antianhedonic response.
[c]Mann-Whitney U test.
[d]Data were analyzed after controlling for gender and family history of psychiatric disorders.
Bolded values are *P*<0.05. **Abbreviations**: ADs=antidepressants; APs=antipsychotics; BDNF=brain-derived neurotrophic factor; CPZeq=chlorpromazine equivalent milligrams; FLUeq=fluoxetine equivalents equals; BMI=body mass index; MDD=major depressive disorder; MADRS=Montgomery–Åsberg Depression Rating Scale; pBDNF=plasma brain-derived neurotrophic factor.

3. RESULTS

The flow chart of included patients was shown in Fig. (**1**). A total of seventy-five patients suffering from MDD who provided blood samples at baseline were included (the mean age was 34.1 ± 11.4, 31 male and 44 female patients). The demographic and clinical characteristics of patients with MDD are shown in Table **1**.

3.1. Association Between pBDNF Levels and Anhedonic Symptoms in MDD Patients

Baseline pBDNF concentrations were significantly associated with anhedonia symptoms on days 13 and 26 (all *P*s<0.05; Table **2**), but these significances disappeared when controlling for covariates (all *P*s>0.05). Baseline pBDNF concentrations were significantly associated with changes in anhedonic symptoms at day 13 (*P*<0.05; Table **2**), even after Bonferroni correction and controlling for multiple factors. Changes in pBDNF concentrations on day 26 were significantly associated with anhedonia symptoms at baseline (*P*<0.05; Table **2**), but significance disappeared after Bonferroni correction or controlling for covariates (*P*>0.05). Interestingly, pBDNF concentrations on day 26 were significantly associated with changes in anhedonia symptoms on day 26, even after Bonferroni correction and controlling for multiple factors (all *P*s<0.05; Table **2**).

3.2. pBDNF Levels and Anhedonic Symptoms in MDD Patients Between Antianhedonic Responders and Nonresponders

After 13d ketamine administration, 35 patients were determined as antianhedonic responders, while 40 were determined as antianhedonic nonresponders. The rates of antianhedonic response were 46.7% (95% CI=35.1%-58.2%). The demographic and clinical features between antianhedonic responders and nonresponders are shown in Table **1**. Male patients and patients without a family history of psychiatric disorders were likely to be antianhedonic responders (*P*=0.03, *P*=0.04). There was no significant differencein baseline anhedonia symptoms (19.5±4.3 and 20.9±4.3) between antianhedonic responders and nonresponders. We found that baseline

Table 2. Correlation analysis between pBDNF levels and anhedonic symptoms in patients with MDD following ketamine treatments.

Variables		Anhedonic Symptoms[a]			Change in Anhedonic Symptoms	
		At Baseline	At Day 13	At Day 26	At Day 13	At Day 26
Baseline pBDNF concentrations	*r*	-0.03	-0.29	-0.16	0.30	0.21
	p	0.82	**0.01**	**0.049**[b]	**0.008**	0.07
Change in pBDNF concentrations at day 13	*r*	-0.04	0.11	0.03	-0.14	-0.05
	p	0.75	0.39	0.85	0.29	0.73
Change in pBDNF concentrations at day 26	*r*	-0.28	0.07	0.19	-0.23	-0.32
	p	**0.04**[b]	0.64	0.18	0.10	**0.02**

Note: [a]Anhedonia symptoms were assessed by the MADRS anhedonia item.
[b]The significance did not survive after Bonferroni correction.
Bolded values are $P<0.05$.
Abbreviations: MADRS=Montgomery-Åsberg Depression Rating Scale; MDD=major depressive disorder; pBDNF=plasma brain-derived neurotrophic factor; *r*=Pearson coefficient of correlation.

Table 3. Linear mixed model analysis: Comparison of anhedonic symptoms and pBDNF concentrations between antianhedonic responders and nonresponders in patients with MDD.

Variables	Group-by-time Interaction			Time Main Effect			Group Main Effect		
	F	*df*	*P*	F	df	*P*	F	*df*	*P*
Anhedonic symptoms	42.8	2, 146	**<0.001**	117.3	2, 146	**<0.001**	132.2	1, 72	**<0.001**
pBDNF concentrations (ng/ml)	0.5	2, 135	0.59	2.0	2, 135	0.14	2.0	1, 75	0.12

Note: Bolded values are $P<0.05$.
Abbreviations: pBDNF=plasma brain-derived neurotrophic factor; MDD=major depressive disorder.

pBDNF concentrations were higher in antianhedonic responders than in antianhedonic responders (12.1±7.1 and 9.1±5.6, F=4.2, P=0.04).

On day 26, the rates of antianhedonic response were 40% (95% CI=28.7%-51.4%). As shown in Table **3**, linear mixed models comparing anhedonia symptoms over time between antianhedonic responders and nonresponders found significant group (F=132.2, P<0.001) and time (F=117.3, P<0.001) main effects and a significant interaction (F=42.8, P<0.001). No significant group main effects (F=2.0, P=0.12; Table **3**) and time (F=2.0, P=0.14; Table **3**) main effects were found on pBDNF concentrations. Fig.(**2**) shows the trend of changes in anhedonic symptoms between antianhedonic nonresponders and responders on days 13 and 26. Fig.(**3**) showed that pBDNF concentrations did not differ significantly between the two groups on days 13 (P=0.22) and 26 (P=0.94).

3.3. Change in Anhedonic Symptoms in MDD Patients between Low and High BDNF Group

At baseline, patients were divided into baseline low BDNF group and baseline high BDNF group; 49 patients were identified as baseline low BDNF group, while 26 patients were identified as baseline high BDNF group. Linear mixed models (with baseline anhedonic symptoms as a covariate) comparing anhedonia symptoms over time between low and high BDNF groups found significant time main effects (F=78.4, P<0.001), group main effects (F=7.3, P=0.009) and group-by-time interaction (F=5.4, P=0.006). The baseline high BDNF group had a significantly lower level of anhedonia than the low BDNF group on days 13 (P<0.001) and 26 (P=0.01; Fig.**4**).

4. DISCUSSION

To the best of our knowledge, this is the first report examining the relationship between pBDNF concentrations and the effect of repeated-dose ketamine infusions in reducing anhedonic symptoms in patients suffering from MDD. The main results of this study were as follows: (1) baseline pBDNF levels were associated with changes in anhedonic symptoms at day 13. Interestingly, changes in pBDNF concentrations were associated with changes in anhedonia symptoms on day 26; (2) baseline pBDNF levels were higher in antianhedonic responders than those in antianhedonic nonresponders; (3) baseline high BDNF group had a lower level of anhedonia than low BDNF group at days 13 and 26.

Consistent with previous studies [16, 17], a significant reduction in the levels of anhedonia over time was found in the present study. However, pBDNF concentrations showed no significant changes on days 13 and 26 when compared to baseline, in line with the findings of previous studies [24, 25]. Similarly, an animal trial reported that repeated administration of ketamine reversed anhedonia-like behaviour in stressed rats, and no significant changes in hippocampal BDNF protein concentrations were found after acute and chronic ketamine treatment [37]. Several clinical studies have been published to determine the change in pBDNF concentrations after single and repeated administration of ketamine, but with inconsistent findings [25, 26]. For instance, Medeiros *et al.* reported that a single ketamine infusion does

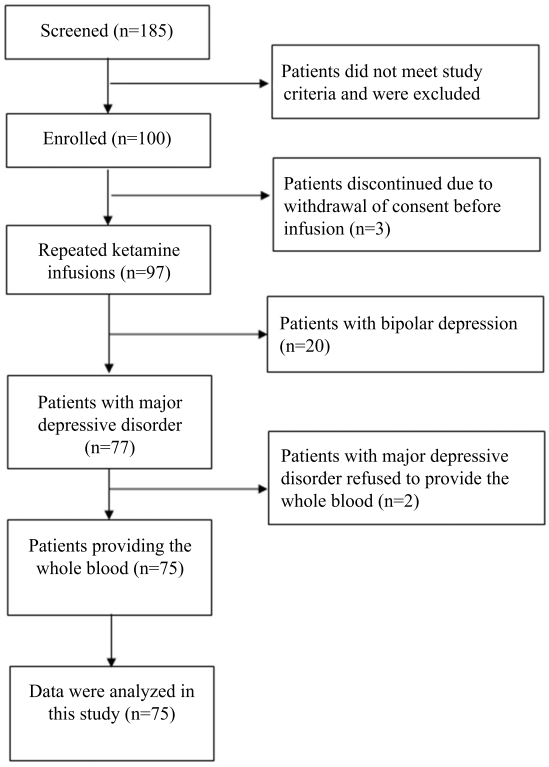

Fig. (1). Flow chart of the patient inclusion process.

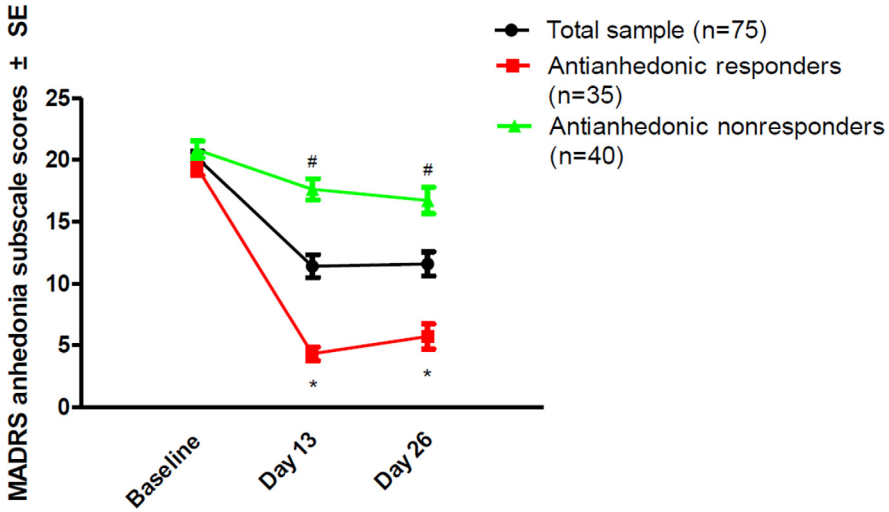

Fig. (2). Change in anhedonic symptoms in patients with MDD between antianhedonic responders and nonresponders. #Significant difference was found when compared to baseline at the indicated times (P<0.05). *Significant difference was found between antianhedonic responders and nonresponders at the indicated times (P<0.05). **Abbreviations**: MADRS=Montgomery–Åsberg Depression Rating Scale; MDD=major depressive disorder;SE=standard error. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

not change pBDNF concentrations [25]. Another study found a significant change in pBDNF concentrations after receiving six intravenous infusions of ketamine compared to baseline [26].

In this study, we are the first to report a significant association between pBDNF concentrations at baseline and the observed antianhedonic effects of ketamine in Chinese individuals suffering from MDD. Early data from ketamine clinical studies were analysed, mainly focusing on the association of peripheral BDNF concentrations and ketamine's antidepressant effects, but with inconsistent findings [24-26, 38-41]. For example, Haile *et al.* reported that pBDNF concentrations significantly increased after ketamine treatment in antidepressant responders compared to nonresponders and that pBDNF concentrations at 240 min after ketamine treatment were significantly higher related to a reduction in depressive symptoms [40]. However, others failed to report a positive finding [24, 38, 41]. After controlling factors that could potentially influence BDNF, the high associations between pBDNF concentrations at baseline and changes in

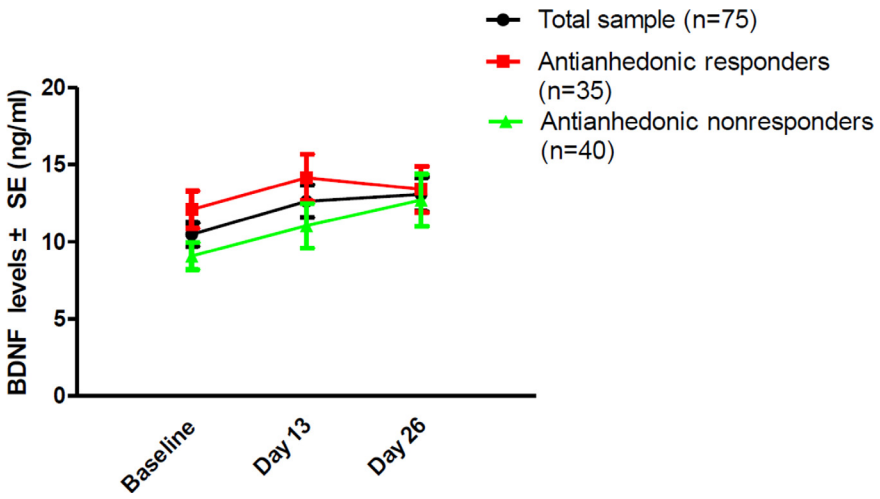

Fig. (3). Change in pBDNF levels in patients with MDD. No significant difference was found when compared to baseline at the indicated times (P>0.05), and no significant difference was found between antianhedonic responders and nonresponders at the indicated times (P>0.05). **Abbreviations**: pBDNF=plasma brain-derived neurotrophic factor; MDD=major depressive disorder. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

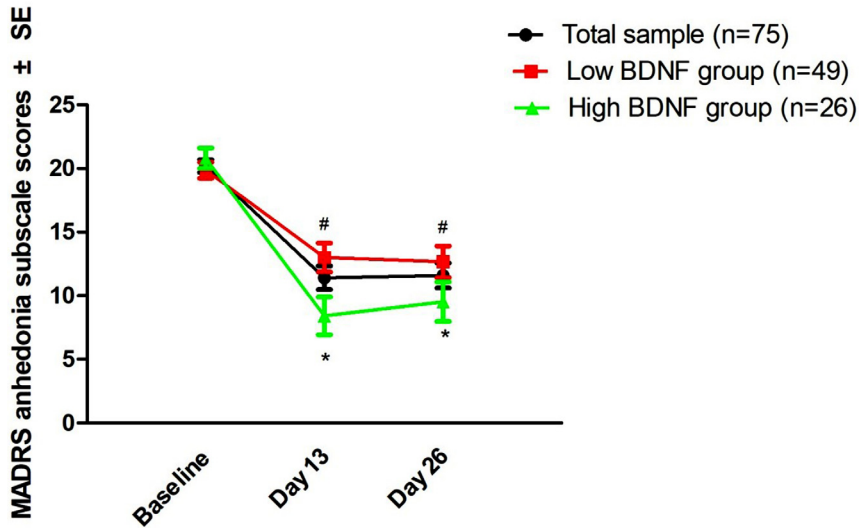

Fig. (4). Change in anhedonic symptoms in patients with MDD between low and high BDNF group. #Significant difference was found when compared to baseline at the indicated times (P<0.05). *Significant difference was found between low and high BDNF group at the indicated times (P<0.05). **Abbreviations**: BDNF=brain-derived neurotrophic factor; MADRS=Montgomery-Åsberg Depression Rating Scale; MDD=major depressive disorder; SE=standard error. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

anhedonic symptoms on day 13 remained significant in this study. Future studies with relatively larger sample sizes are warranted to verify these results.

Interestingly, in this study, patients with high baseline pBDNF levels had an increased capacity for antianhedonic effects of six ketamine infusions compared to patients with low baseline pBDNF levels. Previous studies had examined the association of baseline levels of serum BDNF concentrations and treatment outcomes of antidepressants and electroconvulsive therapy (ECT), but with inconsistent findings [42, 43]. For example, Mikoteit *et al.* found that high serum levels of BDNF at baseline were associated with treatment response in patients with MDD who underwent standardized treatment with duloxetine [43]. However, van Zutphen *et al.* reported thatBDNF concentrations at baseline were relatively lower among respondents with a favourable ECT outcome [42].

Several limitations also bear mentioning despite these interesting findings. First, the primary findings of this preliminary study appear to be statistically robust and should be replicated in a larger patient population. Second, either brain BDNF concentrations or other key neurobiological mediators of the ketamine response, such as the mammalian target of rapamycin (mTOR) [44, 45], were not directly measured. Blood BDNF concentrations appeared to be not associated with cerebrospinal fluid concentrations [46]. Third, although using the MADRS anhedonia item to measure levels of anhedonia has been employed with success in early studies [18,

32, 33], a single application of the MADRS anhedonia subscale may be inadequate. Finally, since this study was conducted based on a single site focusing on Chinese individuals with MDD, the results may not be fully generalizable.

CONCLUSION

In summary, this preliminary study found that baseline pBDNF concentrations may predict the antianhedonic effect in individuals with MDD treated with repeated doses of ketamine.

LIST OF ABBREVIATIONS

BD	=	Bipolar Disorder
BDNF	=	Brain-derived Neurotrophic Factor
ELISA	=	Enzyme-linked Immunosorbent Assay
ICC	=	Interclass Correlation Coefficient
MDD	=	Major Depressive Disorder
TRD	=	Treatment-refractory Depression

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study has been approved by Institutional review board of the Affiliated Brain Hospital of Guangzhou Medical University (Approval no. 2016030).

HUMAN AND ANIMAL RIGHTS

No animal were used in this study, Reported experiments on humans were in accordance with the ethical standards of the committee responsible for human experimentation (institutional national), and with the Helsinki Declaration of 1975, as revised in 2008.

CONSENT FOR PUBLICATION

Each patient involved in this study signed an informed consent form.

STANDARDS OF REPORTING

Consort guidelines and methodology were followed.

AVAILABILITY OF DATA AND MATERIALS

The data supporting this study's findings are available from the corresponding author Yuping Ning upon reasonable request.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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