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Research paper

Functional connectivity differences in the amygdala are related to the antidepressant efficacy of ketamine in patients with anxious depression

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ABSTRACT

Background: The antidepressant effects of ketamine in patients with anxious depression (AD) remain unclear. Functional connectivity (FC) differences in the amygdala have been linked to depression improvement after ketamine treatment in depressed patients, but their role in AD patients is uncertain. We investigated the correlation between depression improvement after ketamine treatment and amygdala FC in AD patients.

Methods: Thirty-one AD patients and 18 non-anxious depression (NAD) patients received six intravenous ketamine infusions (0.5 mg/kg) over two weeks. AD patients were further divided into responders (defined as a ≥50% MADRS total score reduction on day 13) and non-responders. The FC of the amygdala subregions, including the laterobasal amygdala (LBA), centromedial amygdala (CMA), and superficial amygdala, were compared between the groups. Receiver operating characteristic curves were used to predict treatment response after ketamine infusions.

Results: The baseline FC difference in the left LBA and the left precuneus between responders and non-responders among AD patients was found to be associated with depression improvement and was a significant predictor of treatment response to ketamine. A marked reduction in baseline LBA-precuneus FC after ketamine infusion was observed in responders. Unlike in patients with NAD, a lower right CMA-right middle temporal gyrus FC was found in AD patients.

Limitations: The sample size is rather small.

Conclusions: Our findings may suggest that amygdala FC is a significant predictor of treatment response to ketamine infusions in patients with AD. Further studies exploring the potential antidepressant mechanisms of ketamine may aid in the treatment of AD patients.

1. Introduction

Anxious depression (AD), defined as the diagnosis of major depressive disorder (MDD) with a high level of anxiety, is a common subtype of depression. According to a Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, 53 % of 2876 patients with MDD were diagnosed with AD (Fava et al., 2008). A Chinese population study showed that nearly 70 % of 375 patients with MDD had AD (Wu et al., 2013). Patients with AD have more severe depressive symptoms (Fava et al., 2004; Lin et al., 2014) and higher rates of suicidal ideation and suicide attempts (McIntyre et al., 2016; Seo et al., 2011) than patients with non-anxious depression (NAD). Patients with AD have poor depression improvement outcomes when treated with traditional antidepressant drugs than patients with NAD (Fava et al., 2008; Wu et al., 2013).

Ketamine, a glutamatergic non-competitive *N*-methyl-D-aspartate

Abbreviations: AD, anxious depression;; MDD, major depressive disorder; NAD, non-anxious depression; FC, functional connectivity; HAMA, Hamilton Anxiety Scale; LBA, laterobasal amygdala; CMA, centromedial amygdala; SFA, superficial amygdala; rsfMRI, resting-state functional magnetic resonance imaging; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; EPI, echo-planar imaging; MNI, Montreal Neurological Institute; ROC, receiver operating characteristic; MTG, middle temporal gyrus..

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receptor antagonist, has been studied for its antidepressant efficacy in patients with AD (Chen et al., 2021; Ionescu et al., 2014; Liu et al., 2019; Salloum et al., 2019). Patients with AD showed better depression improvement after a single dose of ketamine than patients with NAD (Ionescu et al., 2014), whereas another study pointed out that patients with AD are less likely to respond to ketamine treatment (Chen et al., 2021). Some studies have found no difference in depression improvement between patients with AD and NAD (Liu et al., 2019; Salloum et al., 2019). Given the inconsistency of depression improvement after ketamine treatment in patients with AD, it is necessary to investigate the potential biomarkers predicting the antidepressant efficacy of ketamine in patients with AD.

Functional differences in the amygdala of patients with AD have been reported in various studies. A functional neuroimaging study has revealed that stronger amygdala functional connectivity (FC) is found in patients with MDD with lower Hamilton Anxiety (HAMA) scale scores, while weaker amygdala FC is identified in those with higher HAMA scale scores (He et al., 2019). Analogously, Altinay et al. have shown that lower FC of the amygdala with the cerebral cortex and pons, as well as greater task-induced activity in the left amygdala, is found in patients with AD than in healthy controls (Altinay et al., 2016). However, all of these studies defined the amygdala as a unified whole region, ignoring the distinct function of each amygdala subregion. According to cytoarchitectonic characteristics (Amunts et al., 2005; Kedo et al., 2018), the amygdala is suggested to be functionally segregated into three subregions: the laterobasal amygdala (LBA), centromedial amygdala (CMA), and superficial amygdala (SFA). The LBA receives both cortical and subcortical input signals (Bzdok et al., 2013; LeDoux, 2003). The CMA integrates and outputs information (Kerestes et al., 2017; LeDoux, 2003). The SFA modulates avoidance behavior and reward-related information (Bzdok et al., 2013; Janak and Tye, 2015). A resting-state functional magnetic resonance imaging (rsfMRI) study has indicated that lower FC between the right CMA/LBA and right middle frontal gyrus is observed in patients with AD than in patients with NAD, highlighting the different neuropathological mechanisms of the CMA and LBA in emotion processing (Qiao et al., 2020).

Previous studies have shown similar findings with regard to the role of the amygdala in predicting improvement in depressive symptoms following antidepressant therapy in patients with AD (Ellard et al., 2018; Gorka et al., 2019). A study conducted on adults with depression and/or anxiety revealed that higher baseline amygdala activity during emotion perception predicts greater anxiety and depressive symptom improvement in response to selective serotonin reuptake inhibitors or cognitive-behavioural therapy treatments (Gorka et al., 2019). Stronger baseline FC between the bilateral amygdala and dorsal anterior insula predicts greater emotion regulation improvement and has been demonstrated in bipolar disorder patients with anxiety, regardless of the antidepressant medication they received (Ellard et al., 2018). Moreover, an exploratory rsfMRI study performed in patients with treatment-resistant depression indicated that the difference in baseline FC in the right amygdala and the right subgenual anterior cingulate gyrus between responders and non-responders is an important biomarker for predicting treatment response to ketamine infusions (Nakamura et al., 2021).

In this study, we aimed to explore the association between baseline FC differences in amygdala subregions between patients with AD and NAD and depression improvement following repeated-dose ketamine infusions using a seed-based rsfMRI analysis. Furthermore, among patients with AD, we investigated whether the difference in baseline FC in the amygdala subregion between responders and non-responders is related to depression improvement and is a significant predictor of response to ketamine treatment. In addition, the changes of significant baseline FC difference in the amygdala subregion between responders and non-responders after ketamine treatment were used for post-hoc analyses in responders and non-responders.

2. Materials and methods

This study was part of an open-label clinical trial approved by the ethics committees of the Affiliated Brain Hospital of Guangzhou Medical University and registered in the Chinese Clinical Trials Registry (registration number: ChiCTR-OOC-17012239). The clinical trial was conducted from November 2016 to December 2017 at the Affiliated Brain Hospital of Guangzhou Medical University, China, investigating the antidepressant efficacy of repeated-dose ketamine infusions on patients with MDD (Wang et al., 2022, 2021; Zheng et al., 2018; Zhou et al., 2018a, 2018b). All participants fully understood the study procedure and provided written informed consent before entry into the current clinical trial.

2.1. Participants

A total of 54 patients with MDD who met the following inclusion criteria were enrolled: (1) men or women aged between 18 and 65 years; (2) a DSM-5/SCID diagnosis of MDD without comorbid psychotic symptoms; (3) a total score of ≥17 on the 17-item Hamilton Depression Rating Scale (HAMD-17) (Hamilton, 1960) on the day of the rsfMRI scan; (4) treatment resistance (defined as failure of two or more antidepressant treatments with adequate dosage and duration); (5) completion of the baseline rsfMRI scanning; and (6) completion of the six ketamine infusions. The detailed exclusion criteria have been described in our previously published article (Zhou et al., 2018a). Before the rsfMRI screening, all patients with MDD were required to maintain a stable dosage of their current antidepressant medication regimen for more than four weeks, and they continued receiving the same medication regimen throughout the procedure. And physiotherapies such as electroconvulsive therapy were not allowed during the study. A more complete study design for the current trial can be found in our previously published article (Zhou et al., 2018a).

Using the dimensional definition of AD, we defined it as a diagnosis of MDD plus a HAMD-17 anxiety/somatization factor score ≥7 (Chen et al., 2021; Qiao et al., 2020). The anxiety/somatization factor consists of psychic anxiety (Item 10), somatic anxiety (Item 11), gastrointestinal somatic symptoms (Item 12), general somatic symptoms (Item 13), hypochondriasis (Item 15), and insight (Item 17) and was proven reliable in systematically assessing the anxiety characteristics of patients with MDD (Fava et al., 2008).

We defined response as a ≥50 % Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) total score reduction on day 13 (24 h following the sixth infusion) compared to baseline (Murrough et al., 2013; Shiroma et al., 2014).

2.2. Procedure

All participants received six intravenous ketamine infusions in total (0.5 mg/kg, lasting 40 min) on days 1, 3, 5, 8, 10, and 12. The severity of depressive symptoms was assessed daily from baseline to day 13 (24 h following the sixth infusion) using the MADRS, and the rsfMRI data were obtained at baseline and on day 13. Further details of the procedure can be found in our previously published article (Zheng et al., 2018).

2.3. rsfMRI data acquisition

All rsfMRI data were obtained using a 3.0-Tesla Philips scanner (Achieva X-series, the Netherlands) and were acquired using a gradient echo-planar imaging (EPI) sequence with the following parameters: repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°, 33 slices, interslice gap = 0.6 mm, slice thickness = 4 mm, field of view = 220 mm × 220 mm × 256 mm, acquisition matrix = 64 × 64, voxel size = 3.44 mm × 3.44 mm × 4 mm. All participants were instructed to keep their eyes closed during the scanning procedure.

2.4. fMRI data preprocessing

The DPARSFA (http://rfmri.org) toolkit based on MATLAB R2014a software (Mathworks, Inc., Natick, Massachusetts, USA) was used to preprocess the rsfMRI data. The first ten timepoint volumes were discarded. All images were then subjected to slice timing and head motion correction. The Friston 24-parameter model was applied to regress the effects of the head motion (Friston et al., 1996; Yan et al., 2013). Non-neural noise from the cerebrospinal fluid and white matter was also regressed, while the global signal was not regressed (Fox et al., 2009; Murphy et al., 2009). Data were processed using detrending and band-pass filtering (0.01–0.10 Hz). The images were then resliced to 3 × 3 × 3 mm^3 and were normalized to the Montreal Neurological Institute (MNI) space using EPI templates. Spatial smoothing was performed using a Gaussian kernel (6 mm full-width-half-maximum). Four responders and one non-responder were excluded from further analyses because their images failed to normalize well to the EPI template. In total, 49 patients with MDD were included in the study.

2.5. Regions of interest definition

Regions of interest of the amygdala subregions were extracted using the SPM Anatomy Toolbox (www.fz-juelich.de/inm/inm-1/DE/Forschung/_docs/SPM Anatomy Toolbox/SPM Anatomy Toolbox_node.html) (Eickhoff et al., 2005), which is based on probabilistic maps from the JuBrain Cytoarchitectonic Atlas (Amunts et al., 2020). The amygdala was segmented into three subregions: LBA, CMA, and SFA (Amunts et al., 2005; Kedo et al., 2018). These subregions of the bilateral amygdala were then resliced to 3 × 3 × 3 mm^3.

2.6. Whole brain voxel-wise FC analyses

DPARSFA was used to perform whole-brain voxel-wise FC analyses of each amygdala subregion. Whole-brain FC maps for each amygdala subregion were generated using the correlation coefficient that was computed between the averaged time course of each voxel within the seed and the time course of every other voxel in the other brain areas. Then, Fisher's z-transformation, which converts correlation coefficients to z-values, was used to improve normality.

2.7. Statistical analyses

First, two-sample *t*-tests and Mann–Whitney *U* tests were used to compare the continuous variables, and chi-square tests were performed to compare the categorical variables of the demographic and clinical characteristics between patients with AD and NAD, as well as between responders and non-responders, using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA).

Then, two-sample independent *t*-tests in each amygdala subregion were performed to explore the FC differences between patients with AD and NAD as well as between responders and non-responders using the Statistical Parametric Mapping (SPM 12, https://www.fil.ion.ucl.ac.uk/spm/) toolbox. The significance threshold at the cluster level with family wise error (FWE) correction was set at $p < 0.05$ and that at the voxel level was set at $p < 0.001$. Bivariate correlation analyses were conducted to identify the association between the significant baseline FC difference and the change in MADRS total scores. In addition, receiver operating characteristic (ROC) curves were generated to determine the optimal cut-off value of the significant baseline FC difference between responders and non-responders for predicting the response to ketamine treatment. The optimal cut-off value of the significant baseline FC that had both high sensitivity and specificity was obtained by calculating the Youden index (maximum [sensitivity + specificity − 1)]. Finally, the changes of significant baseline FC difference in the amygdala subregion between responders and non-responders after ketamine treatment were used for post-hoc analyses in responders and non-responders.

3. Results

3.1. Demographic and clinical characteristics

Among the 235 participants, 49 patients with MDD were included in this study (Fig. 1). Thirty-one patients (63.3 %) were classified as having AD, whereas 18 patients (36.7 %) were classified as having NAD (Table 1). Among the 31 patients with AD, 20 (64.5 %) were responders and 11 (35.5 %) were non-responders (Table 2). Higher baseline MADRS total scores and anxiety/somatization factor scores were found in the patients with AD than in those with NAD ($t = 2.226$, two-tailed: $p = 0.030$; $Z = -5.836$, two-tailed: $p < 0.001$), whereas no significant difference was found between responders and non-responders among the patients with AD.

3.2. Difference in amygdala FC between patients with AD and NAD

The patients with AD had a lower baseline FC between the right CMA and the right middle temporal gyrus (MTG) than the patients with NAD (MNI coordinates: x = 60, y = −39, z = 3; voxel = 69; $t = 4.6526$; FWE-corrected $p = 0.031$) (Fig. 2a). No significant differences in FC of the other amygdala subregions were identified between the two groups.

In the patients with AD, the significant difference in baseline FC between the right CMA and right MTG was positively correlated with the MADRS total score reductions on days 5, 7, 8, 9, and 11 compared to baseline (two-tailed: $p = 0.035$, 0.044, 0.046, 0.025, and 0.049, respectively) (Fig. 3).

3.3. Difference in FC between responders and non-responders among patients with AD

A higher FC between the left LBA and left precuneus (MNI coordinates: x = −6, y = −69, z = 51; voxel = 288; $T = 5.7803$; FWE-corrected $p < 0.001$) was found in the responders at baseline than in the non-responders (Fig. 2b). No significant differences in FC of the other amygdala subregions were found between the groups.

Bivariate correlation analysis revealed that the FC between the left LBA and left precuneus was positively correlated with the MADRS total score reduction on day 13 relative to baseline among all responders and non-responders ($r = 0.440$, two-tailed: $p = 0.013$) (Fig. 4a).

ROC analysis indicated that the FC between the left LBA and left precuneus was a significant predictor of response to ketamine infusions on day 13. The significant baseline FC difference showed an effective differential capability with an area under the curve of 0.9727 (95 % CI = 0.925–1.000) for discriminating responders from non-responders (Fig. 4b).

Moreover, the post-hoc analysis conducted on the responders showed that the baseline FC between the left LBA and left precuneus was significantly reduced on day 13 compared to baseline after six ketamine infusions ($t = 1.816$, one-tailed: $p = 0.045$) (Fig. 4c).

4. Discussion

In the current study, we found that the FC difference between the left LBA and the left precuneus in the responders and non-responders among the patients with AD was positively correlated with improvement in depressive symptoms and was also a significant predictor of treatment response to ketamine infusions. Indeed, the post-hoc analysis revealed that the LBA-precuneus FC identified at baseline was significantly reduced following six ketamine infusions in the responders. To the best of our knowledge, this is the first report of FC in amygdala subregions acting as a potential predictor of treatment response to ketamine in patients with AD. Here, we also found that the lower right CMA-right MTG FC observed in patients with AD than in those with NAD was positively associated with depressive symptom improvement after ketamine infusions.

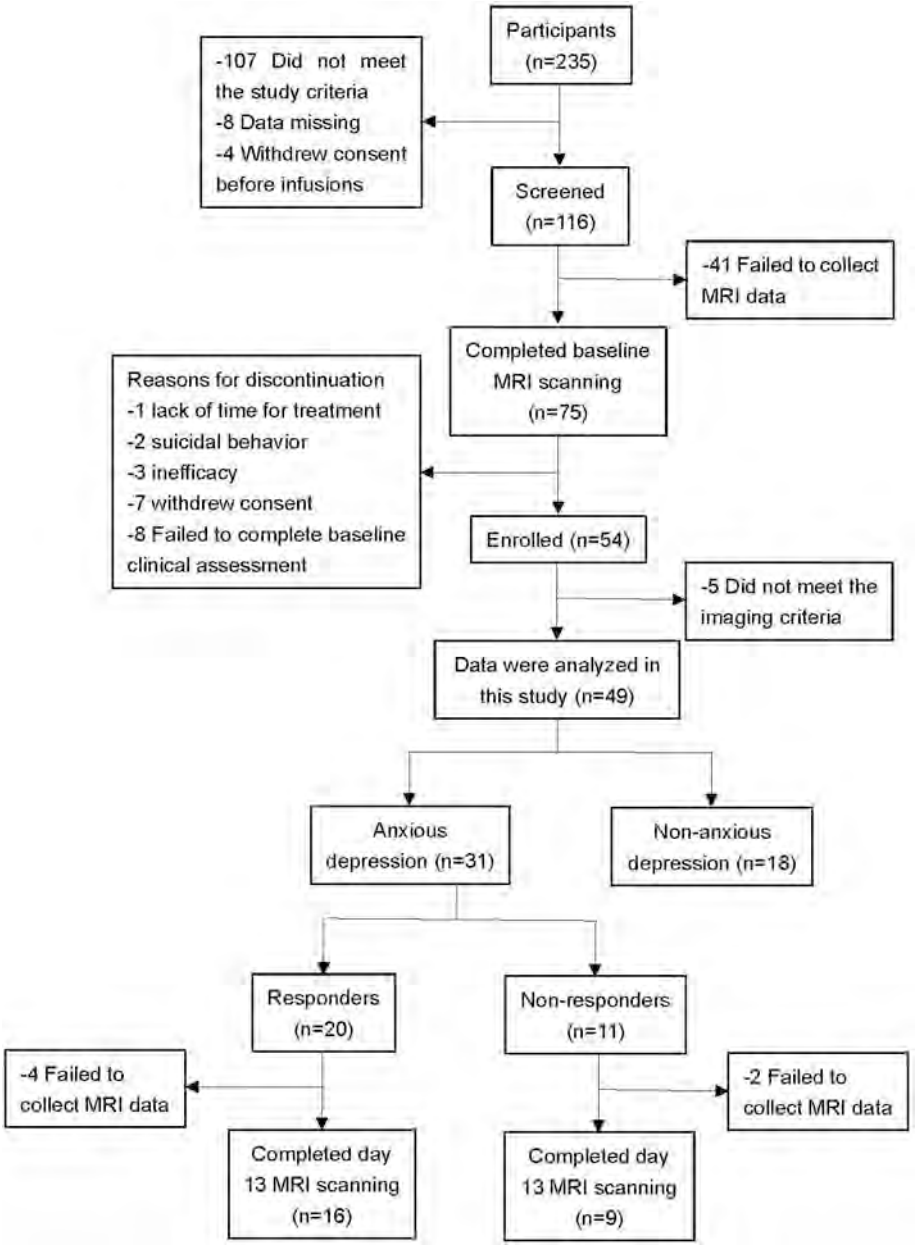

Fig. 1. Flow diagram of the current study.

Consistent with the finding of He et al., a weaker FC between the amygdala and left MTG was found in patients with MDD with higher HAMA scale scores in contrast to those with lower HAMA scale scores (He et al., 2019), a lower FC between the right amygdala and right MTG was identified in patients with AD than in those with NAD in our study. Nevertheless, given the distinct roles in emotion processing of each amygdala subregion (Bzdok et al., 2013; Janak and Tye, 2015; Kerestes et al., 2017; LeDoux, 2003), further research on amygdala subregions is needed in patients with AD. Decreased FC between the right CMA/LBA and right middle frontal gyrus is observed in patients with AD compared with that in patients with NAD (Qiao et al., 2020), suggesting that the decreased top-down inhibition of the middle frontal gyrus to the CMA and LBA may result in hyperactivity of the amygdala, leading to a high degree of anxiety and negative emotion (Luscher et al., 2011). However, decreased FC between the right CMA and right MTG, but not the middle frontal gyrus, was found in patients with AD in the current study. These inconsistent findings may be attributed to the different characteristics of the participants, all of whom were patients with treatment-resistant depression in our study. The MTG is considered to participate in emotional processing and attention selection (Corbetta and Shulman, 2002). A task-state neuroimaging study on MDD patients showed that greater activation in the right MTG during the emotion-generative process is related to a lower negative affect (Davis et al., 2018). Here, a higher baseline FC between the right CMA and right MTG was found in patients with NAD whose MADRS total scores were significantly lower than those of patients with AD.

Although previous studies have revealed baseline differences in amygdala FC between responders and non-responders after ketamine infusion in patients with depression and used the significant baseline FC in the amygdala to predict depressive symptom improvement after ketamine treatment (Nakamura et al., 2021), the amygdala-related FC in responders and non-responders among patients with AD remains unclear. In this study, we found that the responders had greater baseline FC between the left LBA and left precuneus than the non-responders. A rsfMRI study revealed that stronger amygdala-precuneus FC was identified in adolescents with depression than in healthy controls (Cullen

Table 1
Comparison of demographic and clinical characteristics at baseline between patients with AD and NAD.

	Total (n = 49)		AD (n = 31)		NAD (n = 18)		Statistic	
	N	%	N	%	N	%	x^2	P-value
Gender (female)	27	55.1	20	64.5	7	38.9	3.023[c]	0.082
Married	26	53.1	19	61.3	7	38.9	2.294[c]	0.130
History of psychiatric hospitalization	13	26.5	8	25.8	5	27.8	0.000[d]	1.000
Family history of psychiatric disorders	20	40.8	13	41.9	7	38.9	0.044[c]	0.834

	Mean/median	SD/quartiles	Mean/median	SD/quartiles	Mean/median	SD/quartiles	t/Z	P-value
Age (years)	36	(28,46.5)	40	(28,47)	29	(26.5,41.75)	−1.157[a]	0.129
Education (years)	12	(9,15)	12	(8,15)	12	(9.75,15)	−0.399[a]	0.690
BMI (kg/m^2)	23.14	3.21	23.56	2.76	22.42	3.85	1.099[b]	0.281
Duration of Illness (months)	60	(25,144)	60	(26,192)	84	(16.5,144)	−0.572[a]	0.568
Age of first episode depression	22	(18,39.5)	28	(18,41)	20	(17,31)	−1.580[a]	0.114
MADRS Score	31.08	7.51	32.77	8.17	28.17	5.22	2.147[b]	0.037
Anxiety/somatization factor score	7	(5.5,9)	9	(7,10)	5	(4,6)	−5.836[a]	0.000

Abbreviations: SD: standard deviation; AD, anxious depression; NAD, non-anxious depression; BMI, body mass index; MADRS, Montgomery–Åsberg Depression Rating Scale.
[a] Mann–Whitney U test.
[b] Two-sample t-test.
[c] $\chi 2$ test.
[d] Continuity correction $\chi 2$ test.

Table 2
Comparison of demographic and clinical characteristics at baseline between responders and non-responders among patients with AD.

	Total (n = 31)		Response (n = 20)		Non-response (n = 11)		Statistic	
	N	%	N	%	N	%	x^2	P-value
Gender (female)	20	64.5	12	60.0	8	72.7	0.100[c]	0.752
Married	19	61.3	12	60.0	7	63.6	0.000[c]	1.000
History of psychiatric hospitalization	8	25.8	5	25.0	3	27.3	0.000[c]	1.000
Family history of psychiatric disorders	13	41.9	9	45.0	4	36.4	0.007[c]	0.932

	Mean/median	SD/quartiles	Mean/median	SD/quartiles	Mean/median	SD/quartiles	t/Z	P-value
Age (years)	38.29	11.92	40.65	11.14	34.00	12.62	1.518[b]	0.140
Education (years)	12	(8,15)	12	(8,15)	12	(9,15)	−0.271[a]	0.786
BMI (kg/m^2)	23.56	2.76	24.20	2.51	22.38	2.92	1.825[b]	0.078
Duration of illness (months)	60	(26,192)	60	(24.5,216)	60	(26,120)	−0.393[a]	0.694
Age of first episode depression	28	(18,41)	31	(20,42.5)	24	(18,40)	−1.097[a]	0.273
MADRS score	32.77	8.17	31.50	6.57	35.09	10.44	−1.179[b]	0.248
Anxiety/somatization factor score	9	(7,10)	9	(7,9)	8	(8,11)	−0.423[a]	0.672

Abbreviations: SD: standard deviation; AD, anxious depression; BMI, body mass index; MADRS, Montgomery–Åsberg Depression Rating Scale.
[a] Mann–Whitney U test.
[b] Two-sample t-test.
[c] Continuity correction $\chi 2$ tes.

et al., 2014). Greater FC between the amygdala and left precuneus has been reported in participants with grief less than a year after the death of a loved one relative to healthy controls (Chen et al., 2020). These studies indicate the significance of the amygdala-precuneus circuit in emotion processing. Moreover, evidence from a neuroimaging study conducted on adolescents with MDD has shown that decreased amygdala-precuneus FC is related to treatment response to selective serotonin reuptake inhibitors (Cullen et al., 2016). In the current study, the baseline FC between the LBA and precuneus was significantly decreased in responders following six ketamine infusions, indicating that the amygdala–precuneus circuit may be an important target for response of depression. Given the crucial role of the amygdala in negative emotional arousal (Phelps and LeDoux, 2005) and the precuneus in self-referential information processing (Cavanna and Trimble, 2006), the hyper-connectivity of the LBA-precuneus during rest may result in excessive negative emotion generation, and ketamine may partly lead to the amelioration of depressive symptoms by attenuating the connectivity of the amygdala-precuneus.

Nevertheless, there is also a limitation of the study. The sample size of the current study is relatively small, and studies with larger sample sizes are needed to validate the current findings.

In conclusion, the current study suggests a potential predictor of treatment response to ketamine infusions in patients with AD and may point to a potential neural underpinning by which ketamine exerts its antidepressant effect in patients with AD, though further validation is required.

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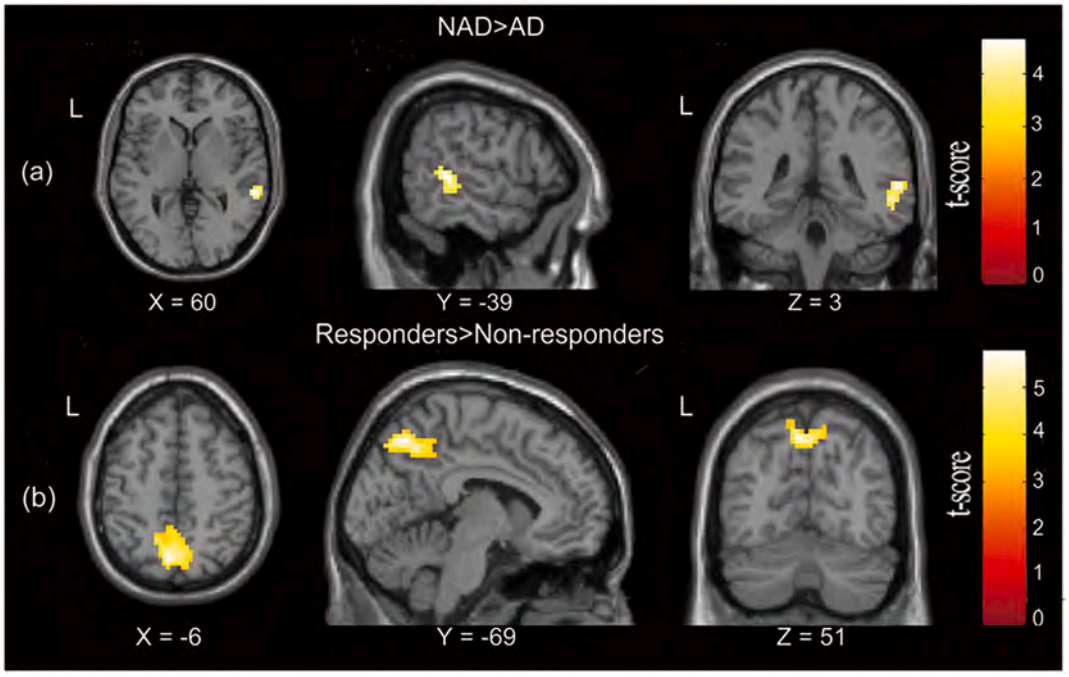

Fig. 2. The difference in FC between groups in amygdala subregions. (a) Patients with NAD exhibited increased FC between the right CMA and right MTG compared with that in patients with AD ($p_{FWE} < 0.05$). (b) Responders showed increased FC between the left LBA and left precuneus compared with that in non-responders ($p_{FWE} < 0.05$). Abbreviations: FC, functional connectivity; NAD, non-anxious depression; AD, anxious depression; CMA, centromedial amygdala; MTG, middle temporal gyrus; LBA, laterobasal amygdala.

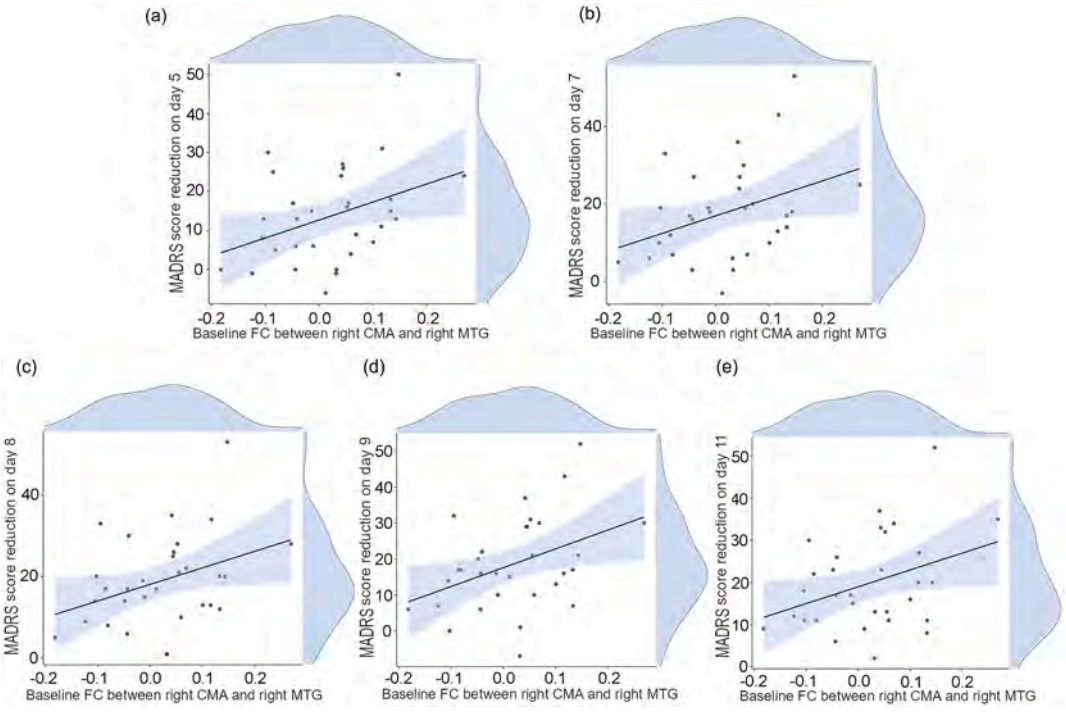

Fig. 3. The relationship between baseline amygdala subregion FC and depressive symptom improvement in patients with AD. (a–e) Correlations between baseline CMA-MTG FC and MADRS score reduction respectively on day 5 (a), day 7 (b), day 8 (c), day 9 (d), and day 11 (e) compared to baseline. Abbreviations: FC, functional connectivity; AD, anxious depression; MADRS, Montgomery–Åsberg Depression Rating Scale; CMA, centromedial amygdala; MTG, middle temporal gyrus.

CRediT authorship contribution statement

Bin Zhang and Yuping Ning conceived of and designed the study. Yanling Zhou participated in the participants recruitment and data collection. Data analysis and results interpretation were performed by Yuan, Luo, Chen, Wang, and Hu. Shiqi Yuan drafted the manuscript, and all authors revised and approved the final manuscript.

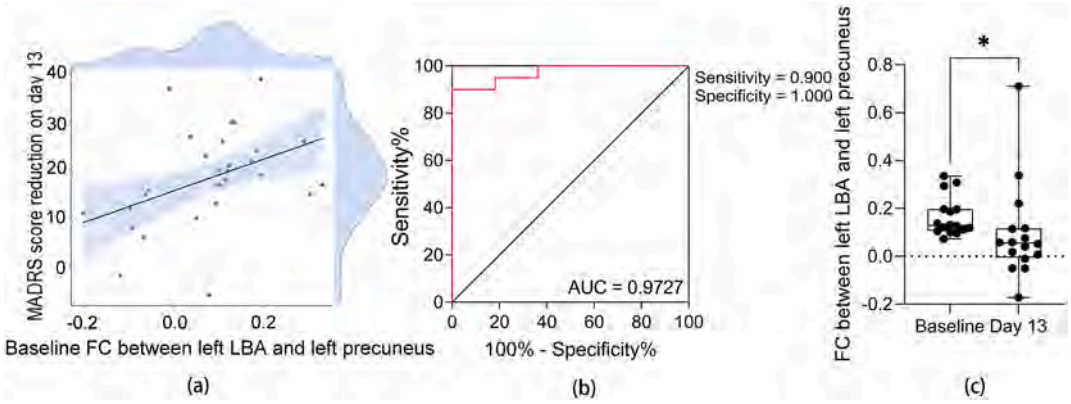

Fig. 4. The relationship between baseline FC difference in amygdala subregions and response to ketamine in responders and non-responders. (a) Correlations between baseline LBA-precuneus FC and MADRS score reduction on day 13 compared to baseline. (b) Receiver operating characteristic curve analysis predicting treatment response to ketamine on day 13. (c) The FC between the left LBA and left precuneus at baseline and on day 13 in responders. Abbreviations: FC, functional connectivity; AD, anxious depression; LBA, laterobasal amygdala; MADRS, Montgomery–Åsberg Depression Rating Scale.

Declaration of competing interest

None.

Acknowledgments

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