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Adjunct ketamine treatment effects on treatment-resistant depressive symptoms in chronic treatment-resistant schizophrenia patients are short-term and disassociated from regional homogeneity changes in key brain regions – a pilot study

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ABSTRACT

BACKGROUND: To investigate the effects of adjunct ketamine treatment on depressive symptoms and brain activity in chronic treatment-resistant schizophrenia (CTRS) patients with treatment-resistant depressive (TRD) symptoms.

METHODS: Calgary Depression Scale for Schizophrenia (CDSS), positive and negative syndrome scale (PANSS), and regional homogeneity (ReHo) results were compared before versus after ketamine treatment in 12 CTRS patients with TRD symptoms.

RESULTS: From 7 days to 14 days after the first ketamine administration, CDSS and PANSS total scores were reduced by 63.8% and 12.9%, respectively. By day 21, ReHo values had increased in the main components of the default mode network (DMN) and bilateral orbitofrontal cortex (OFC) after family-wise error correction. ReHo alterations did not correlate with TRD symptom changes. TRD symptoms relapsed by the 21-day time point, while increased ReHo was sustained. No adverse secondary effects (ASEs) necessitating medical intervention occurred.

CONCLUSIONS: Adjunct ketamine alleviation of TRD symptoms lasted only a week, whereas increased ReHo in DMN regions and the OFC in CTRS patients was maintained beyond 2 weeks, indicating that adjunct ketamine is not well-suited for CTRS patients with TRD symptoms and that effects on functional activity dissociate from effects on TRD symptoms. This small-sample pilot study provides clues for further research into therapy for TRD symptoms in CTRS patients.

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Introduction

Some 20% of chronic schizophrenia patients experience moderate to severe depressive symptoms [1,2]. Contrary to prior models suggesting a dichotomy between schizophrenia and depression [3], recent evidence has suggested that depressive systems may predict poorer outcomes in schizophrenia [2,4]. Moreover, depressive symptoms have been linked to suicidality [5], poor functional recovery, and poor quality of life in patients with schizophrenia [1,5]. The addition of antidepressant drugs to treat depressive symptoms in patients with schizophrenia taking antipsychotics has been reported to have poor efficacy [6–8]. Researchers have undertaken the development of animal models to

explore depression treatment possibilities for patients with schizophrenia [9].

Ketamine is an effective antidepressant agent, especially in patients with treatment-resistant depressive (TRD) symptoms [10–13]. A single administration of ketamine (0.5 mg/kg) can induce immediate psychotomimetic symptoms that recede within 2 h in healthy adults [14]. It is unclear whether single or repeated sub-anesthetic-dose ketamine administration has any severe or long-term side effects [15–21]. Antidepressant effects of ketamine have been associated with brain functional activity alterations, mainly in the medial prefrontal cortex (mPFC), anterior cingulate cortex, posterior cingulate cortex, precuneus, angular

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gyrus, orbitofrontal cortex, subgenual anterior cingulate cortex, superior temporal gyrus, middle temporal gyrus, and hippocampus [22–27].

Atypical brain activity findings have been reported for both schizophrenia [28–30] and major depressive disorder [31–33]. Interestingly, some similarities have been identified between schizophrenia- and major depressive disorder-related brain alteration patterns, particularly in regional homogeneity (ReHo) data, which represent local temporal homogeneity of regional blood oxygen level-dependent signals and can be used to assess resting-state neural activity [34–39]. Similar antidepressant and antipsychotic brain activity normalization effects have been reported for these two patient populations, most notably in the default mode network (DMN), temporal lobes, and frontal lobes [32,40–42].

Inspired by the aforementioned findings, we investigated the effects of combining ketamine with therapeutic agents on TRD symptoms and brain ReHo in chronic treatment-resistant schizophrenia (CTRS) patients. We hypothesized that the addition of ketamine to therapeutic treatment regimens would improve TRD symptoms in CTRS patients and that such effects would be accompanied by alterations in pivotal brain regions.

Methods

Patients

This study was approved by the Ethics Committee of Tianjin Mental Health Center. The IRB number is TJ2015KR052. All the informed consents were noticed and obtained from the recruited patients. The inclusion criteria were: (1) a diagnosis of CTRS, as described by Howes [43]; (2) comorbid TRD symptoms, according to Nierenberg's criteria [44,45]; (3) active disorder presentation; (4) an intelligence quotient > 80; and (5) willingness of the patient (and guardian when appropriate) to volunteer to participate in the study. The exclusion criteria were: (1) moderate to severe physical disease (e.g. respiratory, cardiovascular, endocrine, neurological, liver, or kidney disease) comorbidity; (2) personal or family history of substance abuse; (3) current nicotine addiction; (3) currently receiving electroconvulsive therapy; (4) a history of loss of consciousness for more than 5 min by any cause; (5) left-handedness, as determined with the Annett Hand Preference Questionnaire; and (6) any magnetic resonance imaging (MRI) contraindication, including claustrophobia. With these strict enrolment criteria, we were able to enrol only 15 patient participants.

Adjunct ketamine administration

Following baseline assessment of depressive and psychotic symptoms, medication dosages were

standardized during a 4-week adjunct ketamine treatment period. Intravenous ketamine (0.5 mg/kg body weight, H35020148, Fujian Gutian Pharmaceutical Co., Ltd), and 25 of the study starting at 6 pm. Heart rhythm, blood pressure, and blood oxygen were monitored during and for the 2 h after ketamine infusion. Liver and renal function were tested twice a week. Heart rhythm, blood pressure, and blood oxygen were monitored from 9 am to 10 am during the period of ketamine administration. Physical signs and patient-reported symptoms were also noted during this monitoring period. Adjunct ketamine treatment was ceased immediately if a patient exhibited any adverse secondary effects (ASEs) that were considered high risk by the patient's neurologist or cardiologist.

Main and secondary effect assessment

The Calgary Depression Scale for Schizophrenia (CDSS) and Positive and Negative Syndrome Scale (PANSS) were used to assess depressive and psychotic symptoms one time per week, respectively. Monitoring indices, consults with neurologists and cardiologists, and the Treatment Emergent Symptom Scale [46] were used to detect ASE emergence.

Brain MRI data acquisition

We acquired functional MRI (fMRI) data at five time points relative to the initiation of adjunct ketamine treatment: at baseline (pretreatment) and day 7, day 14, day 21, and day 28 after treatment initiation. The fMRI examinations were performed with a 3.0-T Discovery MR750 system (GE, Milwaukee, WI). Each participant was instructed to lie still while staying awake with a relaxed mind during scanning; and they were fitted with foam padding and ear plugs to limit head motion and the effects of external noises. A single-shot echo-planar sequence for resting-state fMRI was applied as follows: repetition/echo times = 2000/45 ms, field of view = 220 mm², matrix = 64 × 64, flip angle = 90°, slice thickness = 4 mm, and gap = 0.5 mm. Each functional run consisted of 180 image volumes over a 32-axial-slice brain volume in each patient. T1-weighted three-dimensional images (188 slices) were obtained with a brain volume sequence constituted by the following parameters: repetition/echo/inversion times = 8.17/3.18/450 ms, field of view = 256 mm², matrix = 256 × 256, and slice thickness = 1 mm.

The fMRI data were preprocessed in SPM8 and DPARSF V2.3 programs. The first 10 images were excluded from each patient's scan dataset to allow signal equilibration, and slice timing was performed to correct for inter-slice temporal differences. Head motion was screened and corrected for by the rigid body realignment method.

Statistical analysis

Before versus after treatment differences in ReHo were subjected to family-wise error correction. A paired *t*-test was used to compare the CDSS and PANSS scores to ketamine treatment-induced ReHo changes. *P* values < 0.05 were considered statistically significant.

Image data preprocessing

Pre- and post-treatment fMRI datasets were preprocessed separately in three programs: FMRIB Software Library, version 5 (fmrib.ox.ac.uk/fsl), Analysis of Functional NeuroImages (afni.nimh.nih.gov/afni/), and FreeSurfer, version 5.3 (surfer.nmr.mgh.harvard.edu/). High-resolution T1 images aligned to the cortical surface of each patient were reconstructed in accordance with the FreeSurfer pipeline. Briefly, after registering the images to the Talairach atlas and bias-field correction, we conducted skull stripping, intensity normalization, surface modelling, and spherical mapping. Subsequently, we applied slice timing correction, deobliquing, and motion correction processes to the data. Whole images were normalized according to their mean intensity values and then scaled 10,000 times. We removed linear and quadratic trends from the signals. We applied a transformation matrix generated by boundary-based registration to co-register each image with the T1 images, and then employed principal component analysis of the time course to regress out five major components of white matter and cerebrospinal fluid, thereby reducing physiological (and other) noise.

Reho estimation and analysis

We used ReHo analysis to investigate spontaneous neuronal activity and short-range connectivity, without the need for an *a priori* hypothesis [39]. Briefly, regional similarity across the time series was determined by calculating Kendall's coefficient of concordance of target-region surrounding voxels ($n = 26$) for each target voxel. Preprocessed fMRI data were subjected to low-band pass filtering (0.009–0.1 Hz) and then re-sampled as 3-mm isotropic voxels without spatial smoothing. Voxel ranks were computed at each repetition time. ReHo values were calculated along the middle of the gray matter-white matter boundary and projected to surface vertices. Surface alignment of functional signals can reduce inter-individual variability related to cortical folding and limit activation spread over distant regions in spatial smoothing processes. Surface fMRI data obtained before and after ketamine treatment were subjected to pair-wise registration. Surface data were moved to a common spherical surface (the fsaverage) and then smoothed spatially with a 5-mm full-width at half-maximum Gaussian kernel. The ReHo values obtained were transformed into *Z*

scores in the surface model, which were used in our group-level statistical analysis.

To assess drug treatment effects, we applied general linear modelling (participant age and intelligence quotient were controlled for). The criteria for identifying significant clusters were as follows: cluster $p < 0.0001$; cluster size > 10 voxels after 10,000 Monte-Carlo *z* statistic simulations; and cluster $p < 0.05$ after two-tailed test and correction for hemispheric tests.

To identify potential cluster-wise ReHo change relationships with changes in symptoms (which varied across participants initially), we performed a correlation analysis between percent changes in the ReHo and symptom presentation measures. Spearman's rank-order method was used for correlation analysis ($N = 12$ participants), which was conducted using in-house code written in MATLAB software (MathWorks, Inc., Natick, MA). ReHo change values were subjected to family-wise error correction.

Results

Demographic and clinical characteristics of the analyzed cohort

All 15 enrolled participants completed adjunct ketamine treatment (0% drop-out). However, complete fMRI data could not be obtained from 3 participants who were thus not included in the final analysis. CDSS and PANSS changes before versus after ketamine administration were similar regardless of whether these 3 patients were included or excluded. Demographic and clinical summaries of the final cohort of 12 participants are provided in Table 1. None of the participants complained of ketamine-induced AEs, though 1 patient reported that he experienced visual hallucinations, wherein he hallucinated objects (e.g. an apple, an eggplant) seven times (longest duration, 2 min). The hallucinations occurred only within the first half hour after the first ketamine infusion.

Ketamine treatment effects

Adjunct ketamine (0.5 mg/kg, intravenous over 1 h) reduced both CDSS (depressive symptoms) scores (63.7% decrease) and PANSS general psychopathological symptom scores (30.04% decrease) significantly from the 7th day after the first ketamine treatment to the 14th day (Table 1). Subsequently, the mean CDSS score for the cohort increased from day 14 to day 21. By day 28, the mean CDSS score had increased to a level that was statistically similar to the mean CDSS score at baseline, despite maintenance of the fixed ketamine treatment strategy. The CDSS score trajectory change can be seen in Figure 1. However, PANSS negative (0.23% decrease) and positive (0.06% decrease) scores did not change significantly from pre- to post-ketamine adjunct treatment

Table 1. Mean demographic and clinical characteristics of analyzed participants ($N = 12$).

Variable	Before treatment	After 2 weeks of treatment	After 4 weeks of treatment	<i>F</i>	<i>P</i>
Age, years	35.16 ± 7.63	–	–	–	–
Education, years	16.62 ± 3.96	–	–	–	–
Illness duration, years	5.38 ± 1.42	–	–	–	–
Gender, males/females	7/5	–	–	–	–
Chlorpromazine equivalent dose	1250.70 ± 200.80	–	–	–	–
CDSS score	16.50 ± 3.94	5.98 ± 1.94	14.28 ± 2.30	14.298	<.001
PANSS scores					
Total	83.90 ± 9.23	73.04 ± 10.10	80.23 ± 8.51	3.051	.016
Positive	25.60 ± 3.75	25.44 ± 4.05	26.11 ± 5.14	0.198	.921
Negative	27.71 ± 5.19	27.31 ± 4.93	26.00 ± 5.36	0.194	.848
General psychopathological symptoms	29.90 ± 5.41	20.81 ± 4.97	26.00 ± 3.85	4.286	<.001
Treatment Emergent Symptom Scale score	22.57 ± 6.55	21.54 ± 5.33	20.99 ± 4.70	0.688	.433

Note: Mean values are reported with standard deviations.

time points (Table 1). Furthermore, the non-effect on PANSS positive scores indicates that the adjunct ketamine treatment did not induce psychotic symptom activation. None of the patients exhibited or reported ASEs requiring medical intervention.

ReHo alterations

Compared to pretreatment observations, we observed increased ReHo mainly in the medial prefrontal cortex (mPFC), ACC, posterior cingulate cortex, precuneus, angular gyrus, and bilateral OFC, beginning from the 7th day after commencement of ketamine administration (Figure 2A). ReHo values peaked on day 14 (Figure 2B), remained high on day 21 (Figure 2C), and then were notably decreased on day 28 at which time they did not differ significantly from baseline levels (unable to withstand family-wise error correction) (Figure 2D). CDSS and PANSS alterations from day 7 to day 14 did not correlate with any regional ReHo changes.

Discussion

To the best of our knowledge, this pilot study is the first study to examine adjunct ketamine effects on

psychiatric symptoms in CTRS patients with TRD symptoms. Importantly, the present data demonstrate a dissociation between ketamine effects on TRD symptoms and ketamine effects on functional brain activity over time. That is, we found that adjunct ketamine alleviated TRD symptoms without activating psychotic symptoms for only 1 week, but increased ReHo in the mPFC, anterior cingulate cortex, posterior cingulate cortex, precuneus, angular gyrus, and OFC for 2 weeks, albeit with a gradually decreasing trend.

The mPFC, anterior cingulate, posterior cingulate, precuneus, and angular gyrus, which have been identified as components of the DMN, and the OFC, which is part of the affective network, are key regions related to mood processing [47–50]. Notably, neural activities in the DMN and OFC have been reported to be markedly decreased in depressive patients [51–56]. Furthermore, structural and functional deficits in the DMN and OFC have been related to affective and memory processing disturbances in patients with schizophrenia [57–64].

ReHo, which focuses on similarities over time, can be used to assess functional brain alterations [34,65]. The present ReHo results indicating that ketamine can enhance activity in the DMN and OFC while reducing depressive symptom severity are consistent with Reed and colleagues' prior work demonstrating that ketamine can normalize brain activity during emotionally valenced attentional processing in depressive subjects [24]. Previous studies reporting that a single ketamine treatment may alleviate treatment resistant depression by normalizing aberrant activity in DMN components and the frontal cortex [66–68]. Although it is well established that ketamine can decrease functional activity in the DMN and other brain regions [47–60], we found increased ReHo in the DMN in CTRS patients with TRD symptoms in this pilot study. We postulated that this seemingly contradictory finding may be related to neuropathological features of depressive symptoms in patients diagnosed with schizophrenia. Indeed the neuropathological features of depressive symptoms in patients with major depressive disorder have been reported to differ from those of depressive symptoms in patients with schizophrenia [69–71]. Hence, we posit that

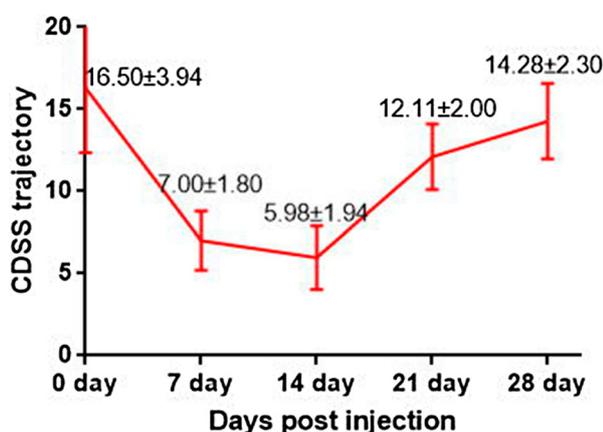


Figure 1. Trajectory of CDSS scores among patients with chronic, treatment-resistant schizophrenia and treatment-resistant depression receiving ketamine injections.

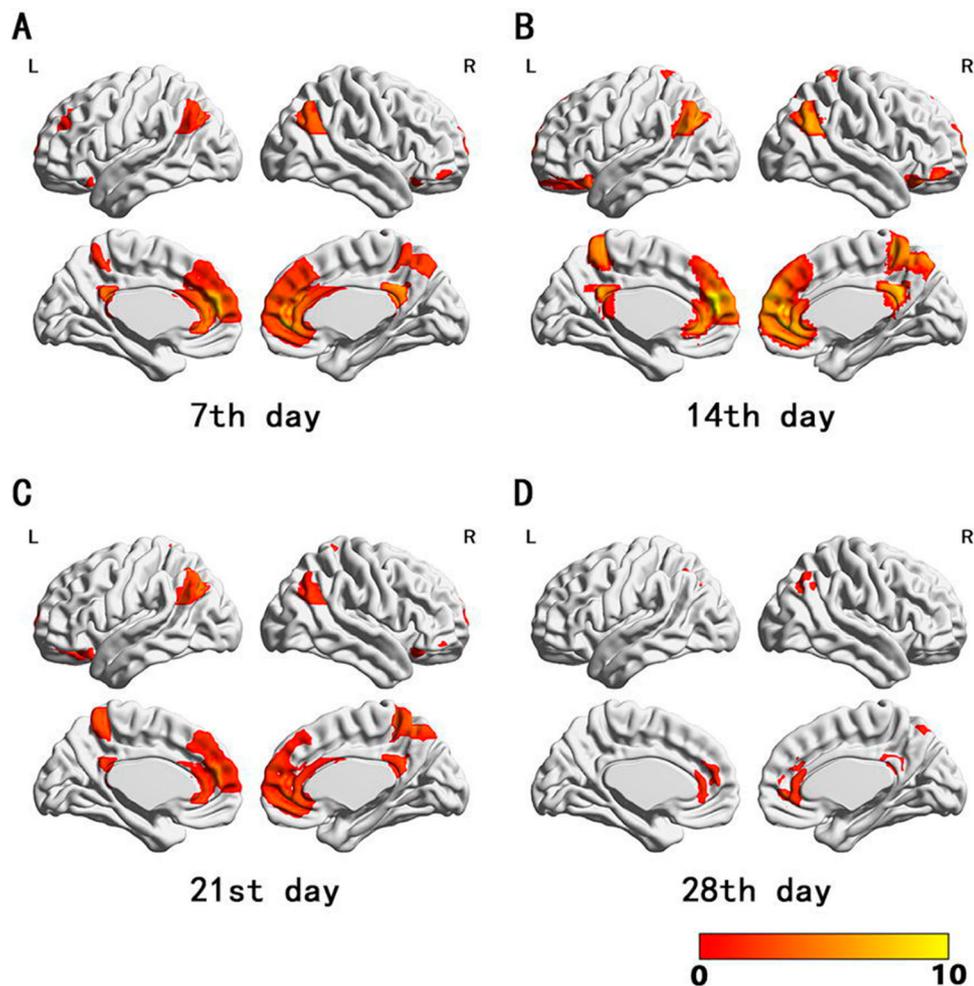


Figure 2. The ReHo in medial prefrontal cortex, ACC, posterior cingulate cortex, precuneus, angular gyrus, and bilateral OFC after the administration of ketamine. (A) 7 days, (B) 14 days, (C) 21 days, and (D) 28 days.

ketamine-induced ReHo alterations in schizophrenics may also be different from those in patients with major depressive disorder. Further research is needed to explain these findings.

The antidepressant effect of ketamine has been related to ketamine-induced increases in glutamate release [72]. However, ketamine has been used to make a schizophrenia animal model, which would suggest that ketamine might activate psychotic symptoms. In our study, we did not find evidence of any ketamine-induced psychotic symptoms. It may be that such effects require a higher dose of ketamine given that mid-range doses are used for both animal model induction and psychedelic use, and high doses are used for anesthesia. Meanwhile, we posit that low-dose ketamine might be antidepressant. Indeed, low-dose ketamine has been reported to lead to the repair of disrupted dendrites in the frontal lobes [73]. Hence, we postulate that low-dose ketamine appears to not trigger negative effects in patients with schizophrenia, and might even have positive effects. In the context, it is interesting to note that the glutamatergic system has been reported to affect the efficacy of antipsychotic medications [74]. It has been suggested that

pharmacological modulation of NMDA receptor function might reverse the hypothesized abnormal glutamatergic transmission in schizophrenia [75].

The present demonstration of a dissociation between clinical and functional brain changes following adjunct ketamine administration raises issues to be addressed in future research. We postulate three possible reasons that may explain, perhaps in part, this dissociation phenomenon. First, neuronal interactions depend on action potentials and synaptic transmission. It may be that fMRI-detected blood oxygenation level-dependent signals (which are delayed relative to real time neuronal activity) remain after they are no longer reflective of current neural electric activity, or that the changes they reflect are no longer sufficient to affect ongoing neural network activity. This possibility is challenged by the fact that a week far exceeds the delay from electric activity to blood oxygenation level-dependent signals. Second, the characteristics of our study cohort, CTRS patients with TRD symptoms, may include particularly rapid neurotransmitter desensitization, thereby weakening a synergistic ketamine effect. However, one week would be a short time period for such desensitization

regardless. If these patients have rapid desensitization characteristics, it would be expected to affect their addiction tendency. Third, we postulate that DMN ReHo values may not be suitable indices of clinical effects given that ReHo data are derived from calculations rather than being derived directly from micro-imaging. Thus, ReHo does not provide direct evidence for neural structural alterations or discharge activities.

Limitations

This pilot study had several limitations. First, this line of research is in an exploratory stage with little information in the literature regarding the effects of low-dose ketamine on TRD symptoms in treatment-resistant schizophrenia. The present evidence is based on a small sample in which only patients with treatment-resistant depression and treatment-resistant schizophrenia were included. Although this emergent evidence is not strong enough to influence clinical practice at this stage, it provides important clues for further study. Large-cohort studies are needed to delineate and explain ketamine effects on depressive symptoms in schizophrenia. Secondly, the patients in our sample were taking a variety of antidepressants, with most taking drugs from two different chemical constitution categories at the same time. Because we did not transfer antidepressant dosages to a uniform dosage, we cannot regress out the possible influence of antidepressants on our ReHo data. However, during the study, we did fix the dosage of all therapeutic agents to reduce dynamic antidepressant influences on ReHo. Third, although ketamine has been reported previously to normalize aberrant functional connectivity [26,76], we found that functional connectivity alterations do not withstand family-wise error correction, possibly due to our small sample size providing insufficient power. Fourth, we also calculated amplitudes of low-frequency fluctuation before and after ketamine treatment (data not shown due to space limitations), and found that brain regions with increased fluctuation amplitudes following ketamine administration overlapped to a large extent with brain regions exhibiting increased ReHo and that those increases also did not correlate with symptom changes. Fifth, to better monitor ASEs, we included only patients with full insight, which excludes most schizophrenics and thus may limit the generalizability of the current findings. Sixth, we compared only symptoms and ReHo changes before versus after ketamine treatment in a single group sample. Thus, although the strength of this study is not comparable to that of a randomized controlled trial, our findings provide important clues for future trials. Seventh, although most studies examining potential adverse effects of ketamine interaction with antidepressants have not found any [72], such effects were suggested in a recent study

[72]. Our patients' liver and renal function test results were in normal range. Because ketamine is metabolized by 3A4 and 2B6 enzymes, which are expressed primarily in the liver, we must be highly cautious about potential metabolic ASEs. Eighth, although ketamine alone has been reported to alleviate TRD symptoms [77], we did not ask our patients to stop taking their prescribed antidepressants because of the potential that doing so might lead to a worsening of psychotic symptoms.

Conclusion

To the best of our knowledge, this pilot study is the first study to investigate adjunct ketamine treatment effects on treatment-resistant depressive symptoms and concomitant functional brain alterations in patients with treatment-resistant schizophrenia. Importantly, we found that a low dosage regimen of adjunct ketamine can alleviate depressive symptoms and increase functional activity in the DMN and OFC of this patient population. Although our findings should be interpreted with appropriate caution given the limitations of our study, they provide important clues for further research exploring treatment strategies for this patient population.

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All authors made substantial, direct, and intellectual contributions to the work, and approved it for publication.

Disclosure statement

No potential conflict of interest was reported by the authors.

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