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Functional Dysconnectivity of Frontal Cortex to Striatum Predicts Ketamine Infusion Response in Treatment-Resistant Depression

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Abstract

Background: Frontostriatal disconnectivity plays a crucial role in the pathophysiology of major depressive disorder. However, whether the baseline functional connectivity of the frontostriatal network could predict the treatment outcome of low-dose ketamine infusion remains unknown.

Methods: In total, 48 patients with treatment-resistant depression were randomly divided into 3 treatment groups (a single-dose 40-minute i.v. infusion) as follows: 0.5 mg/kg ketamine, 0.2 mg/kg ketamine, and saline placebo infusion. Patients were subsequently followed-up for 2 weeks. Resting-state functional magnetic resonance imaging was performed for each patient before infusion administration. In addition, the baseline frontostriatal functional connectivity of patients with treatment-resistant depression was also compared with that of healthy controls.

Results: Compared with the healthy controls, patients with treatment-resistant depression had a decreased functional connectivity in the frontostriatal circuits, especially between the right superior frontal cortex and executive region of the striatum and between the right paracingulate cortex and rostral-motor region of the striatum. The baseline hypoconnectivity of the bilateral superior frontal cortex to the executive region of the striatum was associated with a greater reduction of depression symptoms after a single 0.2-mg/kg ketamine infusion.

Conclusion: Reduced connectivity of the superior frontal cortex to the striatum predicted the response to ketamine infusion among patients with treatment-resistant depression.

Key Words: frontostriatal network, treatment-resistant depression, low-dose ketamine infusion, treatment response

Significance Statement

A single low-dose ketamine infusion was effective for treatment-resistant depression (TRD). In the current study, approximately one-half (46.9%) of patients with TRD reached a ≥50% reduction in depressive symptoms at postinfusion. However, the brain biomarker to predict the treatment response to low-dose ketamine remains unknown. In our study, we compared the baseline frontostriatal functional connectivity (FC) between patients with TRD and healthy controls and further investigated whether frontostriatal FC may predict the treatment response to ketamine infusion. We found that patients with TRD had a decreased FC in the frontostriatal circuits compared with the controls and also that reduced connectivity of the superior frontal cortex to the striatum predicted the response to ketamine infusion among patients with TRD.

Introduction

Major depressive disorder, which has an estimated lifetime prevalence of 10%–25% among women and 5%–12% among men, is a chronic debilitating mental disorder (Malhi and Mann 2018). It has been the leading contributor to disease burden worldwide since 2015 (Kupfer et al., 2012; Otte et al., 2016). The sequenced treatment alternatives to relieve depression (STAR*D) study revealed that up to 40% of patients with major depressive disorder did not experience symptomatic remission despite at least 2 trials of conventional antidepressants, which was classified as treatment-resistant depression (TRD) (Sinyor et al., 2010; McIntyre et al., 2014; Johnston et al., 2019). TRD led to worse clinical outcomes, such as high relapse rates, suicidal thoughts, and diminished quality of life and psychosocial functioning (Sinyor et al., 2010; McIntyre et al., 2014; Johnston et al., 2019).

In this decade, growing evidence has supported the rapid antidepressant effect of low-dose ketamine infusion on TRD (McGirr et al., 2015; Su et al., 2017). Unfortunately, approximately 30%–40% of Caucasian patients and at least one-half of Taiwanese patients with TRD poorly responded to a single low dose of ketamine infusion (McGirr et al., 2015; Su et al., 2017). Clinical studies have suggested that a higher body mass index, no prior history of suicide attempt, slower cognitive processing speed, and Val allele of BDNF rs6265 polymorphism were associated with a better treatment response to ketamine infusion (Niciu et al., 2014; Rong et al., 2018). However, few studies have investigated the association between pretreatment neurofunctioning and the rapid antidepressant effect of ketamine infusion (Niciu et al., 2014; Rong et al., 2018). A magnetoencephalographic study with a small sample size of 11 patients with TRD who received a single dose of ketamine infusion revealed that the rostral anterior cingulate cortex (ACC) activation at baseline was a biomarker identifying a subgroup of patients who responded favorably to ketamine's antidepressant effects (Salvadore et al., 2009). Our previous positron emission tomography study indicated that the increased activity of the prefrontal cortex after ketamine infusion predicted the responses of antidepressants to ketamine infusion at 240 minutes after treatment (Li et al., 2016).

Furthermore, a recent study of 10 patients with TRD who were i.v. administered a single ketamine dose of 0.5 mg/kg and underwent a game-like reward task during functional magnetic resonance imaging (fMRI) demonstrated that the improvement of depression scores and the enhanced sensitivity for rewarded items were accompanied by an increased activity of the reward-related regions in the brain, such as the orbitofrontal cortex and ventral striatum (Sterpenich et al., 2019). Murrough et al. included 20 patients with TRD who underwent fMRI at baseline and after 24 hours following a single i.v. dose of ketamine and revealed that a greater connectivity of the right caudate during positive emotion perception was related to depression reduction following ketamine infusion (Murrough et al., 2015). Ye et al. (Ye et al., 2018) further reported that the differential restructuring of the corticostriatal and limbic circuits, including the delta high-frequency oscillations cross-frequency coupling in the dorsal striatum, may contribute to ketamine's antidepressant benefits.

Previous studies have demonstrated that the integrity of frontostriatal connectivity played a major role in the pathophysiology of major depression and TRD (Furman et al., 2011; Segarra et al., 2016; Avissar et al., 2017; Walsh et al., 2017). Investigating the brain responses to unexpected rewards in 24 patients with depression and 21 controls using fMRI, Segarra et al. (Segarra et al., 2016) discovered that the hypofunction in the ventral striatal and orbitofrontal regions was related to depression psychopathology. Furman et al. (Furman et al., 2011) demonstrated that patients with major depression exhibited attenuated functional connectivity (FC) between the ventral striatum and both the ventromedial prefrontal cortex and subgenual ACC compared with the controls. A meta-analysis of the neural biomarkers of clinical response to antidepressant drugs in depression indicated that the increased activation in the amygdala, striatum, and insula enhanced the likelihood of poor response to the drugs and suggested that the dysfunction of the frontostriatal–limbic network may predict the response to pharmacological treatment in depression (Fu et al., 2013). Conflicting evidence indicated that a greater attenuation of the connectivity between the putamen and orbitofrontal cortex was related to the treatment response to psychotherapy, but a higher FC between the dorsolateral prefrontal cortex and striatum predicted a better treatment response to repetitive transcranial magnetic stimulation (Avissar et al., 2017; Walsh et al., 2017). However, the role of FC in the frontostriatal network in the treatment response to low-dose ketamine infusion for TRD remains unknown.

In the present study, 48 patients with TRD were randomly administered a single dose of ketamine (0.5 or 0.2 mg/kg) or a normal saline placebo infusion and were subsequently followed-up for 2 weeks. The baseline resting-state functional connectivity-MRI of frontostriatal connectivity was analyzed for the treatment response to ketamine infusion. We attempted to investigate whether disconnectivity of the frontostriatal network may predict the treatment response to low-dose ketamine infusion.

Methods

Inclusion Criteria of Patients and the Study Procedure

Details of the clinical trial protocol of an adjunctive ketamine study of Taiwanese patients with treatment-resistant depression was comprehensively reported in our previous studies (Li et al., 2016; Su et al., 2017). TRD was defined as the failure of

treatment response for at least 2 different antidepressants with adequate dosage and treatment duration (Su et al., 2017). The exclusion criteria included any major medical or neurological illness (i.e., stroke or seizure) or a history of alcohol or substance abuse. Following at least 2 weeks of concomitant stable antidepressant treatment, 48 patients with TRD received an add-on i.v. R,S-ketamine infusion using a randomized, double-blind, placebo-controlled design. Each patient received a single dose of ketamine infusion with 0.5 or 0.2 mg/kg, or normal saline (placebo), which was i.v. administered over 40 minutes. Baseline resting-state functional MRI was performed before a single dose of ketamine or placebo infusion. Patients were assessed using the 17-item Hamilton Depression Rating Scale (HAMD) prior to initiation of test infusions and at 40, 80, 120, and 240 minutes postinfusion. Telephone or face-to-face ratings were subsequently conducted on days 2, 3, 4, 5, 6, 7, and 14 after ketamine infusion. All clinical assessments were performed by the first author, Dr Mu-Hong Chen. Responder status was identified by response (≥50% reduction of mood ratings) at any 2 daily HAMD measures during the period of 24 to 96 hours (days 2–5) after infusion (Su et al., 2017). In addition, 48 age-/sex-matched healthy controls were included for the baseline FC analysis. This study was performed in accordance with the Declaration of Helsinki and was approved by the Taipei Veterans General Hospital Institutional Review Board. Written informed consent was provided by all of the participants (clinical trials registration: UMIN Clinical Trials Registry: registration no.: UMIN000016985 (https://www.umin.ac.jp/ctr/).

MRI Acquisition and Preprocessing

Image Acquisition—MRI images were acquired using a 3.0T Discovery MR750 (GE Healthcare) MRI scanner with an 8-channel head coil at the Department of Radiology, Taipei Veterans General Hospital. Head stabilization was achieved using cushioning, and all participants wore earplugs (29 dB rating) to attenuate noise. During the functional scans, participants were instructed to remain awake with their eyes open and look at a fixation cross. The resting-state functional images were obtained using a gradient echo T2*-weighted sequence (repetition time/repetition time/Flip = 2500 ms/30 ms /90°). Forty-three contiguous horizontal slices parallel to the intercommissural plane (voxel size: 3.5 mm × 3.5 mm × 3.5 mm) were acquired interleaved. These slices covered the cerebellum of each participant. During the functional scans, the participants were instructed to remain awake with their eyes open (each scan lasted 8 minutes and 24 seconds across 200 time points). In addition, a high-resolution structural image was acquired in the axial plane using FSPGR sequence (BRAVO) on GE equipment with parameters (repetition time = 12.23 ms, echo time = 5.18 ms, inversion time [TI] = 450 ms, and flip angle = 12°) and an isotropic 1-mm voxel (field-of-view 256 × 256).

Analysis of Functional Connectivity in the Resting State

Functional Connectivity Preprocessing—Resting-state fMRI data preprocessing was performed using the Data Processing & Analysis for (Resting-State) Brain Imaging, Data Processing & Analysis for (Resting-State) Brain Imaging (DPABI) (http://rfmri.org/dpabi), which is based on the statistical parametric mapping software package (SPM 12) toolbox on the platform of Matlab R2016b. Preprocessing of functional scans included slice-timing correction and motion correction, and the scans were registered to the Montreal Neurological Institute (MNI152) atlas. Additional preprocessing steps were used to prepare the data for FC analysis. These were as follows: spatial smoothing using a Gaussian kernel (6-mm full width at half-maximum), linear detrending, nuisance covariate regression (removal of spurious or nonspecific sources of variance by regression of the following variables: Friston 24 head motion parameters model, the mean whole-brain signal, and the mean signal within a deep white matter (WM) region and cerebrospinal fluid (CSF) signal, and temporal filtering (0.009 Hz < f < 0.08 Hz). The first temporal derivatives of these regressors were included in the linear model to account for the time-shifted versions of spurious variance. The regression of each of these signals was computed simultaneously, and the residual time course was retained for the correlation analysis.

Functional Connectivity Analysis—The regions of interest (ROIs) were adopted from previous studies describing frontostriatal connectivity regions that were based on the structural connectivity between functionally distinct frontal cortical regions and striatum (supplementary Table 1) (Alexander et al., 1986; Tziortzi et al., 2013). The striatal ROIs are publicly available as part of the Oxford-GSK-Imanova Striatal Connectivity Atlas (Tziortzi et al., 2013) (supplementary Table 1). To avoid the artifacts produced by movement or preprocessing, the adequate procedures based on previous studies (Fox et al., 2009; Satterthwaite et al., 2013; Power et al., 2017; Makowski et al., 2019) were adopted, which effectively removed noise related with motion or physiological signals to minimize the influence of nuisance variable as much as possible and also increase the spatial specificity in seed-based functional connectivity analysis. The FC maps of the striatum for each participant were identified based on correlations of low-frequency fMRI fluctuations with the ROIs, and Fisher's r-to-z transformation was used to convert the correlation maps into z maps. The z-transformed maps were compared by ANCOVA with age, sex, and education as the covariates of no interest. We used an uncorrected threshold of $P < .001$ for the initial voxel-wise comparisons. To correct for multiple comparisons, a Monte Carlo simulation with 10 000 times was performed by 3dclustsim function of AFNI (http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html) to determine statistical thresholds for voxel cluster size (Cox, 1996). Only the clusters with a significance threshold of $P < .05$ at the cluster level (a minimum cluster size of 36 in this study) were reported. WM and CSF masks were generated in 2 ways: (1) setting a probability threshold (i.e., 0.99) on one's own tissue segmentation maps based on his/her structural image; or (2) using SPM's a priori tissue probability maps (empirical thresholds: 90% for WM mask and 70% for CSF mask) (Yan et al., 2016). The signals from WM and CSF were regressed out to reduce respiratory and cardiac effects (Yan et al., 2016). Furthermore, we limited our analysis to the frontal and basal ganglia ROIs for regression analysis because of their greater relevance in the pathophysiology of depression (Li et al., 2016; Gärtner et al., 2019). The spatial mean connectivity values (Z) of each cluster were then extracted for each participant to perform a logistic regression on ketamine response and baseline FC at each frontal cluster selected previously. Furthermore, we use general linear model to access the effect of ketamine dose, response to ketamine, and their interaction as well as strength of functional connectivity on average percentage of HAMD score reduction between day 2 and day 5. The data that support the findings of this study are available on request from the corresponding

author. The data are not publicly available due to privacy or ethical restrictions.

Results

In total, 15 (46.9%) of the 32 patients with TRD who were administered a single ketamine dose of 0.5 or 0.2 mg/kg achieved the treatment response in contrast to 3 (18.8%) among the 16 patients who received the placebo (Table 1). Age at onset ($P = .538$), duration of illness ($P = .853$), baseline medications (antidepressants: $P = 1.000$; mood stabilizers: $P = .067$; atypical antipsychotics: $P = .543$), and psychiatric comorbidities (panic disorder: $P = .226$; generalized anxiety disorder: $P > .999$) did not differ between the responders and nonresponders (Table 1). Responders had lower HADM scores from day 2 postinfusion to day 5 postinfusion (all $P < .001$) than nonresponders (Table 1).

Patients with TRD exhibited frontostriatal hypoconnectivity mainly in the executive (i.e., bilateral superior frontal cortex) and rostral-motor (i.e., paracingulate cortex and precentral cortex) divisions compared with the healthy controls (Table 2; Figure 1). However, FC between the right frontal pole and corresponding executive and rostral-motor regions of the striatum was increased in patients with TRD compared with the controls (Table 2; Figure 1).

General linear model analyses reported that FC of the right superior frontal cortex to the striatum was independently associated with the reduction of depression symptoms ($P = .019$) (Table 3). Furthermore, the interactions between the FCs of the bilateral superior frontal cortex (right: $P = .007$; left: $P = .044$) to the corresponding striatum regions and ketamine infusion groups were related to the average percentage of HAMD score reduction between day 2 and day 5 (Table 3). Among patients with TRD who received ketamine infusion, the baseline functional hypoconnectivity of the bilateral superior frontal cortex to the striatum predicted the treatment response, especially among patients who received a 0.2-mg/kg dose of ketamine infusion (Figure 2).

Discussion

Our study findings supported the study hypothesis that patients with TRD exhibit a decreased FC in the frontostriatal circuits, especially between the right superior frontal cortex and executive region of the striatum and between the right paracingulate cortex and rostral-motor region of the striatum compared with the healthy controls. Furthermore, the baseline hypoconnectivity of the bilateral superior frontal cortex to the striatum was associated with a greater reduction of depression symptoms after a single low-dose ketamine infusion.

The frontostriatal circuits played crucial roles in the executive and psychomotor functions, reward processing, and pathophysiology of major depression (Porter et al., 2007; Eshel and Roiser, 2010, Furman et al., 2011; Segarra et al., 2016). As aforementioned, Segarra et al. (Segarra et al., 2016) studied the brain responses to unexpected rewards between patients with depression and healthy controls and observed hypofunction in the ventral striatal and orbitofrontal regions in patients with depression during unexpected reward receipt. Furman et al. (Furman et al., 2011) demonstrated that patients with depression exhibited hypoconnectivity between the ventral striatum and ventromedial prefrontal and subgenual ACCs but presented a stronger connectivity between the dorsal caudate and dorsal prefrontal cortex compared with controls. Resting-state fMRI studies have indicated pervasive deficits in dorsolateral, ACC, medial frontal, and basal ganglion structures in depression (Rogers et al., 1998). Naismith et al. (Naismith et al., 2006) further

Table 1. Demographic Data of Patients With TRD and Controls

	Patients with TRD (n = 48)			
	Responders (n = 18)	Nonresponders (n = 30)	Healthy controls (n = 48)	P
Age (years, SD)	43.00 ± 10.26	48.03 ± 10.68	42.44 ± 7.38	.116
Sex (n, M/F)	4/14	9/21	26/22	.557
Education level (years, SD)	13.89 ± 3.12	11.57 ± 3.27	14.71 ± 1.73	.019
Age at onset (years, SD)	34.83 ± 13.98	37.27 ± 12.65		.538
Duration of illness (years, SD)	10.67 ± 8.46	11.13 ± 8.37		.853
Psychiatric comorbidities (n, %)				
Panic disorder	5 (27.8)	15 (50.0)		.226
Generalized anxiety disorder	11 (61.1)	19 (63.3)		>.999
History of attempted suicide (n, %)	9 (50.0)	12 (40.0)		.558
Baseline medications (n, %)				
Antidepressants	18 (100.0)	30 (100.0)		1.000
Mood stabilizers	1 (5.6)	9 (30.0)		.067
Atypical antipsychotic	10 (55.6)	20 (66.7)		.543
Treatment group (n, %)				.155
0.5 mg/kg ketamine	7 (39.9)	9 (30.0)		
0.2 mg/kg ketamine	8 (44.4)	8 (26.7)		
Placebo	3 (16.7)	13 (43.3)		
HAMD-17 Total score (SD)				
Baseline	21.06 ± 5.35	22.43 ± 4.21		.327
Day 2	7.50 ± 3.11	17.83 ± 5.94		.000
Day 3	8.06 ± 3.70	17.45 ± 6.20		.000
Day 4	7.11 ± 2.87	18.24 ± 6.07		.000
Day 5	7.44 ± 3.22	19.07 ± 5.73		.000
Average from D2 to D5	7.53 ± 2.65	18.15 ± 5.65		.000

Abbreviations: HAMD-17, Hamilton Depression 17 items Scale; TRD, treatment-resistant depression.

Table 2. Difference of Functional Connectivity of Frontostriatal Circuits at Baseline Between Patients With TRD and Controls

	p(FWE-corr)	qFDRcorr	kE	x	y	z	Harvard-Oxford Cortical Structural Atlas
Executive							
TRD > HC	0.787	0.765	49	24	68	2	R. Frontal pole
HC > TRD	0.215	0.156	130	28	2	8	R. Putamen
	0.042	0.276	84	−26	−2	6	L. Putamen
	0.476	0.054	227	24	22	32	R. Superior frontal cortex
	0.888	0.701	37	−22	28	34	L. Superior frontal cortex
Rostral-motor							
TRD > HC	0.915	0.578	33	24	70	4	R. Frontal pole
	0.377	0.333	97	2	44	−24	R. Frontal medial cortex
	0.909	0.578	34	32	58	−10	R. Frontal pole
HC > TRD	0.029	0.038	246	−22	8	4	L. Putamen
	0.005	0.010	358	24	18	2	R. Putamen
	0.049	0.047	215	34	−2	−26	R. Amygdala
	0.334	0.230	104	−20	26	32	L. Superior frontal cortex
	0.002	0.008	430	12	34	38	R. Paracingulate cortex
	0.922	0.688	32	−58	12	34	L. Precentral cortex

Abbreviations: HC, healthy control; L, left; R, right; TRD, treatment-resistant depression.
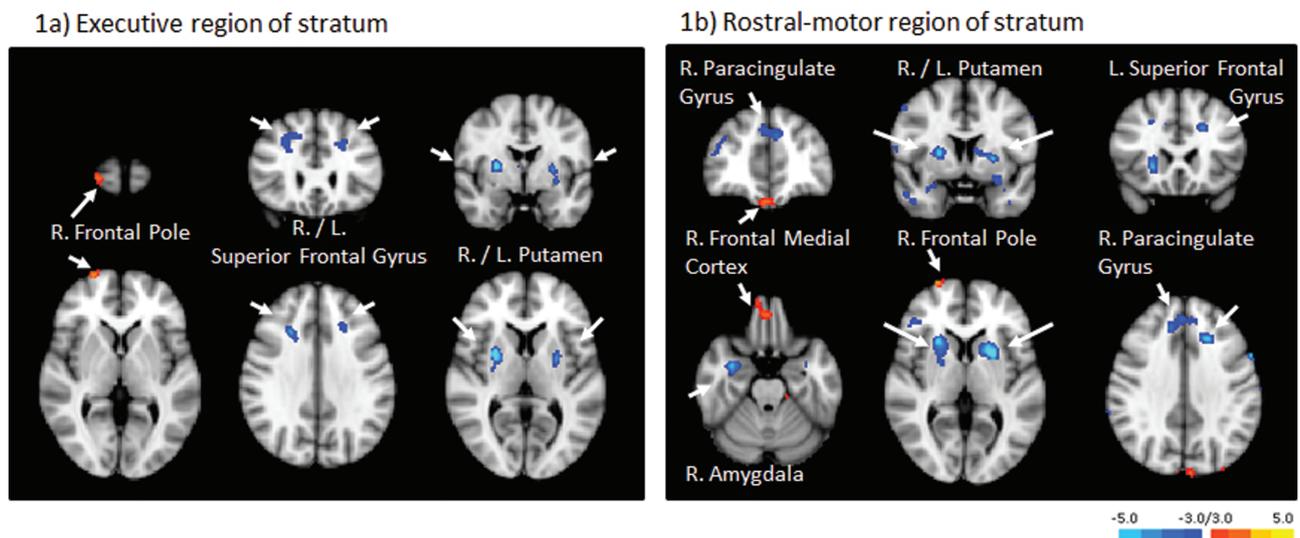
Figure 1. Functional connectivity of the executive (1a) and rostro-motor (1b) frontostriatal projections in patients with TRD vs healthy controls. Abbreviations: L, left; R, right.

revealed that frontostriatal dysconnectivity may be related to impaired executive functions (i.e., visual motor speed and mental flexibility), longer duration of depressive episodes, severity of acute stress, and past suicide attempts. In our study, the majority of hypoconnectivity was noted in the frontostriatal networks, including bilateral superior frontal cortex, paracingulate cortex, putamen, and amygdala, in patients with TRD compared with healthy controls.

Previous studies have assessed the predictive role of the frontostriatal structure and connectivity in the therapeutic response to depression treatments, including antidepressant medications, psychotherapy, and repetitive transcranial magnetic stimulation (Fu et al., 2013; Avissar et al., 2017; Drysdale et al., 2017; Walsh et al., 2017). A meta-analysis revealed that the area in the right putamen extending into the caudate nucleus presented an increased activation significantly associated with the reduced likelihood of the treatment response to

antidepressant drugs (Fu et al., 2013). Fu et al. (Fu et al., 2013) demonstrated that reduced baseline activation in the right striatum was predictive of a better clinical response to medication treatment. Walsh et al. (Walsh et al., 2017) revealed that a greater attenuation of the connectivity between several frontostriatal seeds (i.e., striatum, dorsal ACC, and medial prefrontal cortex) and the paracingulate gyrus was associated with an improved response to behavioral activation treatment for depression. In our study, we discovered that the hypoconnectivity between the superior frontal cortex and executive region of the striatum may predict depression reduction after the administration of a low-dose (especially 0.2 mg/kg) ketamine infusion. This evidence suggests that an attenuated baseline activation in the brain regions including frontostriatal networks was a common predictor of the response to various depression treatments, such as conventional antidepressants, psychotherapy, and low-dose ketamine infusion.

Table 3. Relationship Between Groups, Dose of Ketamine, and Strength of Functional Connectivity Among Patients Receiving Low-Dose Ketamine Infusion

FC of frontostriatal circuits at baseline	Main effect of ROIs FC		Main effect of ketamine dose		Interaction: FC× ketamine dose		Corrected model
	B	Sig.	B	Sig.	B	Sig.	Sig.
R. Putamen	−0.51	0.838	−0.12	0.889	0.34	0.826	0.983
L. Putamen	0.35	0.857	0.17	0.814	−0.21	0.886	0.985
R. Superior frontal cortex	5.40	0.019	0.06	0.705	−3.75	0.007	0.033
L. Superior frontal cortex	2.77	0.122	0.04	0.821	−2.13	0.044	0.096
L. Putamen	−0.73	0.701	−0.16	0.808	0.41	0.729	0.966
R. Putamen	0.18	0.939	0.12	0.893	−0.10	0.949	0.990
R. Amygdala	−3.20	0.247	0.03	0.872	1.60	0.322	0.638
L. Superior frontal cortex	1.76	0.416	−0.04	0.825	−1.53	0.275	0.608
R. Paracingulate cortex	3.09	0.127	0.01	0.936	−2.41	0.070	0.273
L. Precentral cortex	1.49	0.397	0.10	0.604	−0.53	0.632	0.584

Abbreviations: FC, functional connectivity; HAMD, Hamilton Depression 17 items Scale; L, left; R, right; ROI, region of interest.
General linear model in groups of HAMD scores (responder/nonresponder) and ketamine infusion dose.
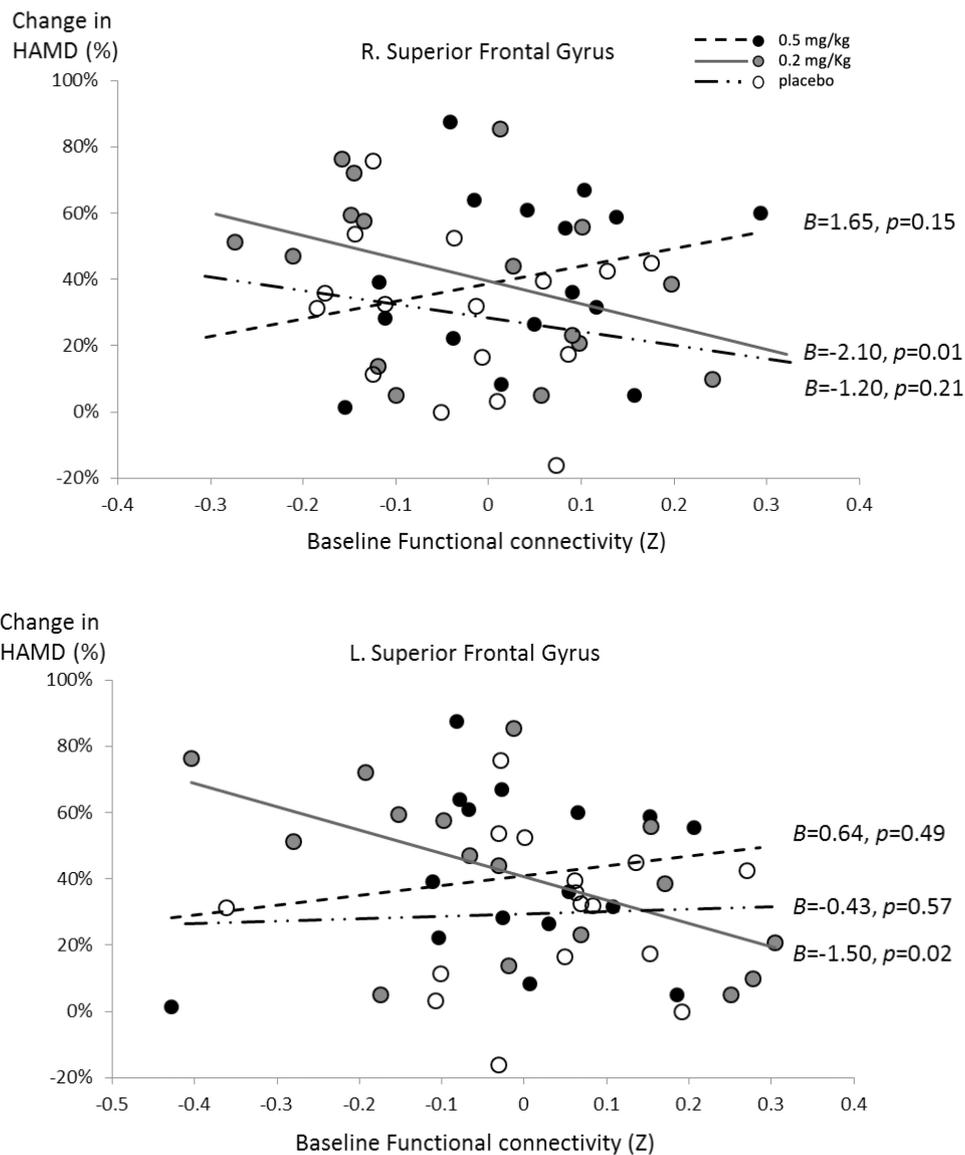
Figure 2. Baseline functional connectivity of left superior frontal cortex and right superior frontal cortex to the executive region of the striatum predicts the depression reduction after low-dose ketamine infusion. Abbreviations: HAMD: Hamilton Depression 17 items Scale; L: left; R: right.

However, in the current study, we observed that the reduced FC between the superior frontal cortex and striatum predicted the treatment response only to 0.2 mg/kg but not to 0.5 mg/kg of ketamine infusion in Taiwanese patients with TRD. The results may be indirectly consistent with our previous positron emission tomography study according to which a 0.2-mg/kg ketamine infusion more pervasively increased activation in the prefrontal cortex compared with a 0.5-mg/kg ketamine infusion (Li et al., 2016). Combining our current and previous findings, we suggest that a lower baseline connectivity of frontostriatal networks predicted the treatment response to ketamine, and hyperactivation of the prefrontal cortex at the postinfusion stage was related to the rapid antidepressant efficacy of low-dose ketamine infusion. However, whether there were different associations between baseline FC and treatment responses to 0.5-mg/kg and 0.2-mg/kg ketamine infusion and whether 0.5-mg/kg and 0.2-mg/kg ketamine infusion may differently modulate brain functioning would need further investigation.

Limitation

Several limitations of this study need to be addressed here. First, only 3 patients with TRD responded to the placebo infusion in our study, which may be owing to the reason that great treatment refractoriness may reduce the placebo response (Rutherford and Roose, 2013). We could not assess the role of frontostriatal connectivity in the placebo response because the sample size was small. Second, our clinical trial was an add-on ketamine study because the medications used by the patients with TRD were not discontinued during ketamine infusion treatment. Therefore, the observed responses to ketamine could have resulted from a combinative or a regulatory effect of ketamine and other medications already being used by the patients. Specifically, the baseline frontostriatal hypoconnectivity predicted the therapeutic response to a combination therapy of ketamine and antidepressant drugs. However, the add-on study design was ethically more appropriate in such patients with severe depression, and it could provide more naturalistic data. Third, we performed the procedure of global signal regression for image pre-processing because previous studies suggested that the procedure effectively removed noise related to motion or physiological signals (Power et al., 2017) and also increased the spatial specificity in seed-based functional connectivity analysis (Fox et al., 2009). However, the procedure may induce artificial anti-correlation between different brain regions (Murphy et al., 2009). In our previous study (Tu et al., 2019), we performed an analysis without the global signal regression method and indicated the absence of prefrontal cortex-related findings. The result was consistent with a recent analysis suggesting that some case-control difference emerged only after global signal regression were adopted (Parkes et al., 2018). Therefore, we should be more cautious in interpreting our results with global signal regression method. Fourth, despite that the total sample size of TRD patients was relatively large (n = 48) in current study, the sample size became quite small for a functional connectivity MRI study when dividing them into 3 equal groups. Further clinical functional connectivity MRI studies with a large sample size would be necessary to validate our results. Fifth, in our study, telephone or face-to-face ratings were subsequently conducted on days 2 through 7 and day 14 after infusion. The inconsistency regarding the interviewing modalities (either via telephone or in person) may skew the rating scores. Sixth, various information, such as smoking status, was not collected in our clinical trial. Without that information, we could not investigate the effects of these parameters.

In conclusion, patients with TRD exhibited frontostriatal hypoconnectivity, especially between the right superior frontal cortex and executive region of the striatum and between the right paracingulate cortex and rostral-motor region of the striatum, compared with the healthy controls. Furthermore, a reduced baseline FC between the bilateral superior frontal cortex and executive region of the striatum was associated with the better treatment response to add-on low-dose (0.2 mg/kg) ketamine infusion. Further studies may be required to elucidate the role of the frontostriatal network in ketamine infusion monotherapy.

Supplementary Materials

Acknowledgments

Statement of Interest

None of the authors in this study had any conflict of interest to declare.

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