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Effects of Serial Ketamine Infusions on Corticolimbic Functional Connectivity in Major Depression

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ABSTRACT

BACKGROUND: Ketamine is a highly effective antidepressant for patients with treatment-resistant major depressive disorder (MDD). Resting-state functional magnetic resonance imaging studies show disruptions of functional connectivity (FC) between limbic regions and resting-state networks (RSNs) in MDD, including the default mode network, central executive network (CEN), and salience network (SN). Here, we investigated whether serial ketamine treatments change FC between limbic structures and RSNs.

METHODS: Patients with MDD (n = 44) were scanned at baseline (time 1 [T1]) and 24 hours after the first (T2) and fourth (T3) infusions of ketamine. Healthy control subjects (n = 50) were scanned at baseline, with a subgroup (n = 17) being rescanned at 2 weeks. Limbic regions included the amygdala and hippocampus, and RSNs included the default mode network, CEN, and SN.

RESULTS: Ketamine increased right amygdala FC to the right CEN (p = .05), decreased amygdala FC to the left CEN (p = .005) at T2 versus T1 (p = .015), which then increased at T3 versus T2 (p = .002), and decreased left amygdala FC to the SN (p = .016). Decreased left amygdala to SN FC at T2 predicted improvements in anxiety at T3 (p = .006). Ketamine increased right hippocampus FC to the left CEN (p = .001), and this change at T2 predicted decreased anhedonia at T3 (p = .005).

CONCLUSIONS: Ketamine modulates FC between limbic regions and RSNs implicated in MDD. Increases in FC between limbic regions and the CEN suggest that ketamine may be involved in restoring top-down control of emotion processing. FC decreases between the left amygdala and SN suggest that ketamine may ameliorate MDD-related dysconnectivity in these circuits. Early FC changes between limbic regions and RSNs may be predictive of clinical improvements.

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Numerous effective pharmacotherapies are available to treat major depressive disorder (MDD); however, less than half of patients remit within the first 3 months of treatment (1), and ~30% remain unresponsive to ≥2 pharmacotherapies (2,3). This may be explained by large heterogeneity of MDD (4). Ketamine, an NMDA receptor antagonist, is shown to induce fast-acting and robust antidepressant effects in 60% to 70% of patients with treatment-resistant depression (TRD) (5). Growing evidence also suggests that multiple ketamine treatments may lead to a more durable response (6–8). Depressive symptoms improve within hours to days post-infusion, suggesting that ketamine perturbs neural pathways mediating the regulation and expression of mood and emotion, thereby playing a downstream role in therapeutic response.

While the cause of MDD remains elusive, a large body of literature points to systems-level disruptions in corticolimbic networks mediating mood, emotion, and cognition. Resting-state functional magnetic resonance imaging (rsfMRI) provides a powerful noninvasive means to examine disruptions in functional connectivity (FC) of these networks in MDD (9–11), implicating several resting-state networks (RSNs) (12–14). The default mode network (DMN), including the anterior cingulate cortex (ACC), posterior cingulate cortex, precuneus, angular gyrus, and medial prefrontal cortex (PFC), is widely implicated in MDD, specifically with features such as rumination, impaired attention, and cognitive control (15–17). The DMN is hyperactive in patients with MDD (18) and has been reported to normalize with standard antidepressant treatments (19,20). The salience network (SN) is also hyperactive in MDD (21) and comprises the insula, dorsal ACC, and frontopolar cortex. The SN is involved in detecting and filtering salient stimuli in order to contribute to functions such as communication, social behavior, and self-awareness through the integration of

SEE COMMENTARY ON PAGE 676

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sensory, emotional, and cognitive information (22,23). The lateral parietal cortices and dorsolateral PFC (DLPFC) comprise the central executive network (CEN), which is involved in goal-directed functions such as attention, decision making, working memory, and executive control (24,25) and has been reported to show decreased connectivity in depression (26,27). Taken together, rsfMRI studies support the theory that MDD is associated with an imbalance between hyperactive ventral and hypoactive dorsal corticolimbic systems (28–30).

Numerous studies have also implicated the amygdala and hippocampus in the pathophysiology of MDD. In addition to its role in episodic memory, the hippocampus is involved in the regulation of motivation and emotion, responses to emotion, and regulation/susceptibility of stress, and the amygdala is involved in the autonomic responses to emotion, emotional memory, and emotion regulation (31–34). Several neuroimaging studies have reported dysfunction and treatment modulation of the hippocampus in MDD (35–38). Specifically, smaller hippocampal volume is reported in individuals with MDD compared with nondepressed individuals (39,40), and lower nodal centralities of the left hippocampus are related to longer duration of disease (37). MRI investigations have also implicated the amygdala in MDD, including disrupted connectivity with the dorsal cingulate (11) and insula (41,42), increased amygdala activation to faces task that resolves after antidepressant treatment (43), and lower white matter integrity between the amygdala and regions of the CEN, SN, and DMN correlated to symptom severity (44). Notably, both the amygdala and hippocampus are thought to be nodes of the SN (amygdala) and DMN (amygdala and hippocampus); therefore, targeting connectivity between these limbic regions and cortex-dominant RSNs may help to illuminate the mechanisms of antidepressant response to interventions such as ketamine.

The current neuroimaging literature investigating effects of ketamine in MDD is small; however, a few studies have suggested effects of a single infusion of ketamine on the subgenual ACC, posterior parietal cortex, hippocampus, PFC, and DMN (18,45,46). In a task-based fMRI study, ketamine treatment was associated with a significant increase in activity within the right caudate (47). It is important to note that the studies so far are limited in finding neural correlates of clinical change with ketamine and mostly have not addressed the more durable effects of multiple ketamine infusions. However, two recent studies from our group reported changes in cerebral blood flow in precuneus and occipital regions and changes in amygdala activity for emotional face processing after multiple ketamine infusions, although this remains an underrepresented area of research (48,49).

To address how single and serial ketamine treatment perturbs FC and clinical correlates of ketamine-related clinical response, using rsfMRI we investigated whether intravenous ketamine leads to similar or distinct changes in connectivity between limbic regions (amygdala and hippocampus) and the cortical networks that might be involved in regulating the activity of those structures (CEN, DMN, and SN). We hypothesized that FC between the amygdala and/or hippocampus and cortical RSNs might be deficient in depression and could be restored following a single infusion and serial infusions of ketamine in patients with TRD. If a significant change in FC with treatment was observed, post hoc analyses investigated cross-sectional differences between patients and control subjects and clinical correlations with longitudinal change in FC to further understand the acute antidepressant effects of ketamine. Previous randomized placebo-controlled trials have clearly established the superiority of ketamine over placebo in improving depression (5,7,50); therefore, we chose an open-label design to minimize patient burden and to address our goal of understanding the effects of ketamine on corticolimbic networks.

METHODS AND MATERIALS

Participants

Participants included 44 patients with MDD and 50 nondepressed healthy control subjects (HCs). Handedness was not considered because 94% of participants were right-handed. Patients with MDD received a clinical evaluation battery at baseline (time 1 [T1]), 24 hours after a single subanesthetic dose of 0.5 mg/kg of intravenous ketamine (T2), and 24 to 72 hours after a fourth infusion of ketamine (T3) (Figure 1). The study lasted 2 to 2.5 weeks, depending on the day the first infusion started. Data were not collected on weekends. These intervals were predetermined based on scheduling availabilities. Five patients with MDD did not complete T3 owing to scheduling conflicts. In total, 33 HCs were scanned once only and an additional 17 HCs were scanned twice 2 weeks apart. HCs did not receive ketamine. Patients were recruited from the Southern California region and were consented for participation as approved by the University of California, Los Angeles, Institutional Review Board (Table 1). Eligibility criteria for all patients included a diagnosis of MDD by clinical consultation using DSM-5 criteria (Structured Clinical Interview for DSM-5) (51), unsuccessful response to ≥2 prior antidepressant trials, 20 to 65 years of age, pretreatment 17-item Hamilton Depression Rating Scale (HDRS) (52) of >16 (exhibiting

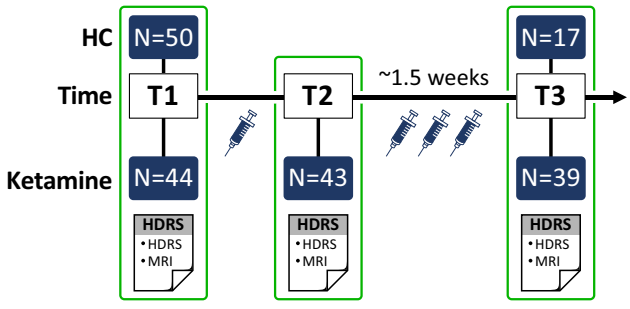

Figure 1. Study design. The ketamine group was administered clinical scales and received a magnetic resonance imaging (MRI) scan at three time (T) points (T1: pretreatment/baseline; T2: 24 hours after first infusion of ketamine; T3: 24–72 hours after fourth infusion of ketamine). The study length varied from 2 to 2.5 weeks, depending on which day the first infusion started. A total of 50 nondepressed healthy control subjects (HC) received an MRI scan at baseline (T1), and a subgroup of the 50 HC (n = 17) received a repeat assessment 2 weeks after T1. HDRS, 17-item Hamilton Depression Rating Scale.

Table 1. Demographics and Clinical Characteristics

	Ketamine (n = 44)	HCs (n = 50)	HCs With Repeat (n = 17)[a]
Gender, Female/Male, n	18/26	27/23	9/8
Age, Years, Mean ± SD	38.2 ± 10.9	32.3 ± 11.9	28.2 ± 6.9
Education, Years, Mean ± SD	10.1 ± 2.4	10.8 ± 1.9	11.5 ± 1.5
Lifetime Illness, Years, Mean ± SD	20.2 ± 12.1	–	–
Current Episode, Years, Mean ± SD	5.3 ± 6.6	–	–
Response[b], n (%)	23/39 (59%)	–	–

[a]Healthy control subjects (HCs) with repeat (n = 17) are a subgroup of the total cohort of HCs (n = 50).
[b]Response was defined as 50% improvement in 17-item Hamilton Depression Rating Scale 24 to 72 hours after the fourth ketamine infusion (Time 3).

moderate to severe depressive symptoms), and a referral letter from their treating physician. Exclusion criteria included neurological/physical/developmental disorders; substance abuse/dependence history within the preceding 3 months; current or past history of psychosis, schizoaffective disorder, or schizophrenia; first episode or late onset of depression (>50 years); depression related to a medical condition; ketamine, electroconvulsive therapy, or other neuromodulation therapy within the previous 6 months; or suicide attempt 1 month prior to study start.

Ketamine

Patients were permitted to remain on stable antidepressant medications (unchanged for at least 6 weeks prior to treatment). Benzodiazepines that influence cortical excitability and other medications considered as contraindications to ketamine were discontinued 72 hours prior to the first infusion and throughout the treatment trial. Treatment included 40-minute intravenous infusions of a subanesthetic dose (0.5 mg/kg) of ketamine diluted in 60 mL of saline with continuous clinical and hemodynamic monitoring (5). Psychotomimetic effects, blood pressure, blood oxygen saturation, heart rate, and respiratory rate were monitored during the infusion by a psychiatrist, followed by additional monitoring for 3 hours by a trained nurse.

Clinical Outcome Measures

The HDRS was used to track overall response with ketamine after the fourth infusion (T3). Patients were identified as responders if HDRS scores decreased by ≥50% at T3 from baseline (53). The Snaith-Hamilton Pleasure Scale (SHAPS) (54), Depression Anxiety Stress Scale (DASS) (55,56), behavioral inhibition system (BIS) scale (57), and a combined rumination scale (58,59) were administered at all 3 time points to evaluate the effect of ketamine on specific symptoms of MDD. These scales were chosen based on wide use in depression literature.

Imaging Protocol and Processing

All imaging of participants was performed on a Siemens 3T Prisma MRI system at the Brain Mapping Center at the University of California, Los Angeles, using a 32-channel head coil. Image acquisition sequences from the Human Connectome Project Lifespan studies were used in this study. For resting-state scans, two runs of a multiband echo-planar images sequence with inverse phase encoding were acquired: repetition time = 800 ms, echo time = 37 ms, flip angle = 52°, 72 axial slices, 2 × 2 × 2 mm^3 spatial resolution, multiband factor = 8, phase encoding direction = anteroposterior to posteroanterior, acquisition time = 6:41 minutes per run. The structural scans consisted of one T1-weighted acquisition (voxel size = 0.8 mm isotropic, repetition time = 2500 ms, echo time = 1.81:3.6:5.39:7.18 ms, inversion time = 1000 ms, flip angle = 8.0°, acquisition time = 8:22 minutes) and one T2-weighted acquisition (voxel size = 0.8 mm isotropic, repetition time = 3200 ms, echo time = 564 ms, acquisition time = 6:35 minutes). All data were preprocessed using the Human Connectome Project minimal preprocessing pipeline (60). Independent components representing artifacts were identified using independent component analysis for each run and removed from voxel time courses using FSL regfilt. To identify RSNs, group independent component analysis was run using FSL Melodic (50 components) on all MDD and HC volunteers, and dual regression extracted time courses for each independent component for each volunteer. Three RSNs associated with MDD (DMN, CEN, and SN) were chosen to investigate changes in FC with anatomical regions of interest selected a priori, including the hippocampus (right and left) and amygdala (right and left) (13). Group independent component analysis identified 4 independent components that encompassed the 3 RSNs of interest: 1 DMN, 2 CENs (left and right), and 1 SN. Time courses for the amygdala (right and left) and hippocampus (right and left) were extracted using region of interest masks derived from the Harvard–Oxford subcortical structural atlases (61). Correlations were calculated between time courses of the networks and seeds (Fisher's z scores).

Statistical Analyses

Baseline demographic and clinical measures were evaluated using χ^2 tests for categorical variables and independent two-sample t tests for continuous variables. Main effects of ketamine treatment on FC were investigated using linear mixed models (compound symmetry covariance) on Fisher's z scores with time, run, and hemisphere as repeated factors in patients with MDD. These omnibus analyses were Bonferroni corrected for the two main hypotheses tested (α = .05/2 = .025), namely that 1) FC of the amygdala to RSNs and 2) FC of the hippocampus to RSNs change with ketamine treatment in patients with MDD.

A number of follow-up analyses were considered. If a time-by-hemisphere effect was present ($p_{corr} < .05$), follow-up analyses investigated the main effect of treatment (time) separately for each hemisphere with time and run as repeated

measures. If an effect of time was present, cross-sectional post hoc analyses (independent-samples *t* test) were performed to study differences between HCs and patients with MDD at baseline. In addition, to study clinical correlations, 1) change in FC after a single infusion of ketamine and percentage change in clinical scores (BIS scale, SHAPS, rumination scale, and DASS) after full treatment and 2) change in FC after serial infusions of ketamine and percentage change in clinical scores (BIS scale, SHAPS, rumination scale, and DASS) after full treatment were investigated. These clinical correlations were investigated only if an effect of time was present in patients with MDD. These analyses were Bonferroni corrected for 8 tests ($\alpha = .05/8 = .006$; 2 hemispheres and 4 clinical scales) within each metric (limbic structure to 3 RSNs). The approach for post hoc cross-sectional and clinical correlation investigation was chosen to facilitate interpretation of the significant effects of ketamine and to reduce multiple comparisons. To further investigate significant treatment effects, paired *t* tests were performed to examine effects of time in HCs ($n = 17$).

RESULTS

Subject Characteristics

The MDD and HC groups did not differ significantly in gender ($\chi^2 = 1.60$, $p = .205$) or education ($t_{1,91} = 1.58$, $p = .12$). A significant difference in age ($t_{1,92} = -2.52$, $p = .013$) was observed; therefore, cross-sectional analysis included age as a covariate (Table 1). Overall, there was a 54.9% decrease in HDRS scores for all patients at T3. A significant decrease during treatment was observed for the SHAPS, DASS, and rumination scale, while the BIS scale did not significantly change (Table 2).

Effects of Ketamine on Amygdala-to-RSN Connectivity

The omnibus mixed model used to investigate effects of time showed significant effects for FC between the amygdala and 2 RSNs of interest. Amygdala FC to the left CEN showed a significant effect of time ($F_{2,461.1} = 5.33$, $p = .005$), which was consistent across hemispheres (i.e., no significant time-by-hemisphere interaction) (Figure 2). Pairwise comparisons showed a drop in FC after a single infusion (T1 vs. T2, $p = .015$) and a subsequent increase after serial infusion (T2 vs. T3, $p = .002$). In HCs, FC between the amygdala and left CEN did not differ from patients at baseline or change over time ($p > .05$ for both).

FC between the amygdala and both right CEN and SN showed time-by-hemisphere effects ($F_{2,455.6} = 3.98$, $p = .019$ and $F_{2,456.0} = 4.24$, $p = .015$, respectively); therefore, follow-up analysis were completed for the left and right amygdala separately. FC between the right amygdala and right CEN showed significant changes with ketamine treatment ($F_{2,207.2} = 2.99$, $p = .05$). Specifically, FC increased after serial ketamine infusion (T1 vs. T3, $p = .016$). Cross-sectional analysis showed that HCs had greater connectivity between the right amygdala and right CEN than patients with MDD at baseline ($F_1 = 9.90$, $p = .002$); therefore, serial ketamine could be considered to have a normalizing effect toward HCs. No effect of time was observed between the right amygdala and right CEN for HCs ($p > .05$). FC between the left amygdala and right CEN showed a decreasing trend but did not reach significance ($F_{2,206.2} = 2.61$, $p = .076$).

FC between the left amygdala and SN showed significant decreases with ketamine treatment ($F_{2,206.8} = 4.25$, $p = .016$) (Figure 2). After a single infusion, a trend toward lower FC was apparent (T1 vs. T2, $p = .065$). After serial infusions, FC decreased significantly (T1 vs. T3, $p = .005$). In HCs, FC between the left amygdala and SN did not differ from that in patients with MDD at baseline or change over time ($p > .05$ for both). FC between the right amygdala and SN did not change significantly with ketamine treatment ($F_{2,206.7} = 2.07$, $p = .13$) (Figure 2).

Effects of Ketamine on Hippocampus-to-RSN Connectivity

The omnibus mixed model used to investigate effects of time showed significant effects for the hippocampus FC to 1 RSN of interest. Hippocampal FC to the left CEN showed a time-by-hemisphere effect ($F_{2,455.9} = 3.90$, $p = .022$); therefore, follow-up analysis were completed for the left and right hippocampus separately. FC of the right hippocampus to the left CEN went from no connectivity to negative connectivity (i.e., anticorrelated) after ketamine treatment ($F_{2,206.6} = 7.75$, $p = .001$) (Figure 3). Pairwise comparisons for the left CEN showed increased negative connectivity after both a single ketamine infusion (T1 vs. T2, $p = .001$) and serial ketamine infusions (T1 vs. T3, $p = .001$). In HCs, FC between the right hippocampus and left CEN did not differ from that in patients with MDD or change over time ($p > .05$ for both). FC between the left

Table 2. Clinical Measures for Patients at Baseline (T1), 24 Hours After First Infusion of Ketamine (T2), and 24 to 72 Hours After Fourth Infusion of Ketamine (T3)

				Analysis of Variance	
	T1	T2	T3	*F*	*p*
HDRS	19.3 (5.2)	13.0 (4.6)	8.3 (4.2)	57.8	<.0001
Rumination Scale	13.0 (3.1)	11.7 (3.2)	10.3 (2.2)	9.4	<.0001
BIS Scale	23.8 (3.2)	23.0 (4.0)	22.5 (3.4)	1.3	.27
SHAPS	7.7 (4.0)	6.4 (4.4)	3.2 (3.7)	13.4	<.0001
DASS	5.1 (4.7)	3.7 (3.7)	1.6 (2.0)	9.2	<.0001

Values are mean (SD).

BIS, behavioral inhibition system; DASS, Depression Anxiety Stress Scale; HDRS, 17-item Hamilton Depression Rating Scale; SHAPS, Snaith-Hamilton Pleasure Scale; T, time.

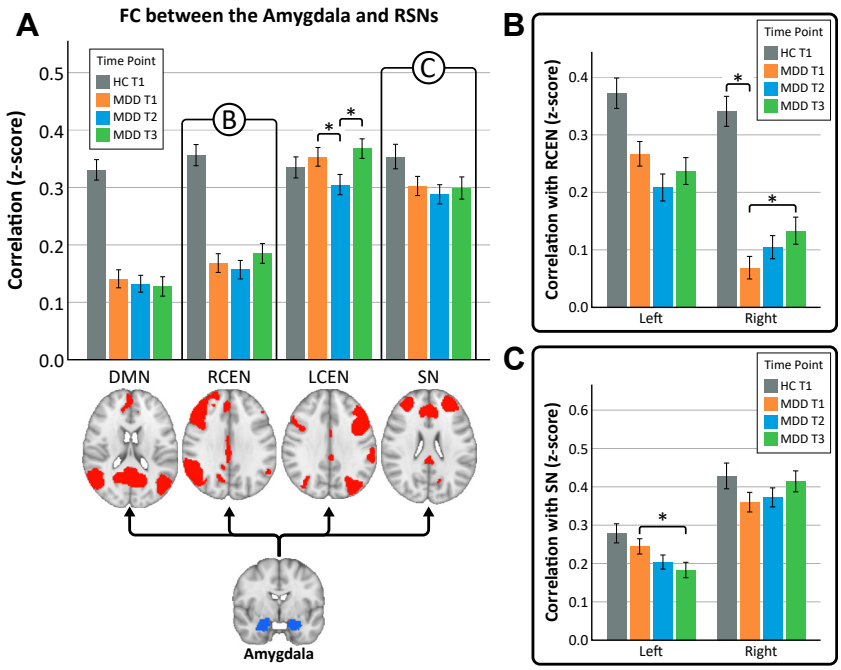

Figure 2. Amygdala connectivity to resting-state networks (RSNs). **(A)** Functional connectivity (FC) between the bilateral amygdala and RSNs (default mode network [DMN], right central executive network [RCEN], left central executive network [LCEN], and salience network [SN]). Connectivity between the amygdala and RCEN and SN showed a time-by-hemisphere effect; therefore, the right and left amygdala were looked at separately in **(B)** and **(C)**. **(B)** FC between the left and right amygdala and RCEN. **(C)** FC between the left and right amygdala and SN. *$p < .05$. HC, healthy control subjects; MDD, patients with major depressive disorder; T, time.

hippocampus and left CEN showed no significant change with ketamine treatment ($F_{2,206.6} = 0.77$, $p = .46$) (Figure 3).

Clinical Correlations

Amygdala. Acute change in FC between the left amygdala and SN after a single infusion of ketamine was correlated with posttreatment improvement in the BIS scale after all infusions (Pearson's $r = .44$, $p = .006$) (Figure 4A). BIS scale improvement was also correlated with change in FC between the left amygdala and SN at the end of treatment (Pearson's $r = .46$, $p = .004$) (Figure 4B). No other correlations were significant for amygdala FC.

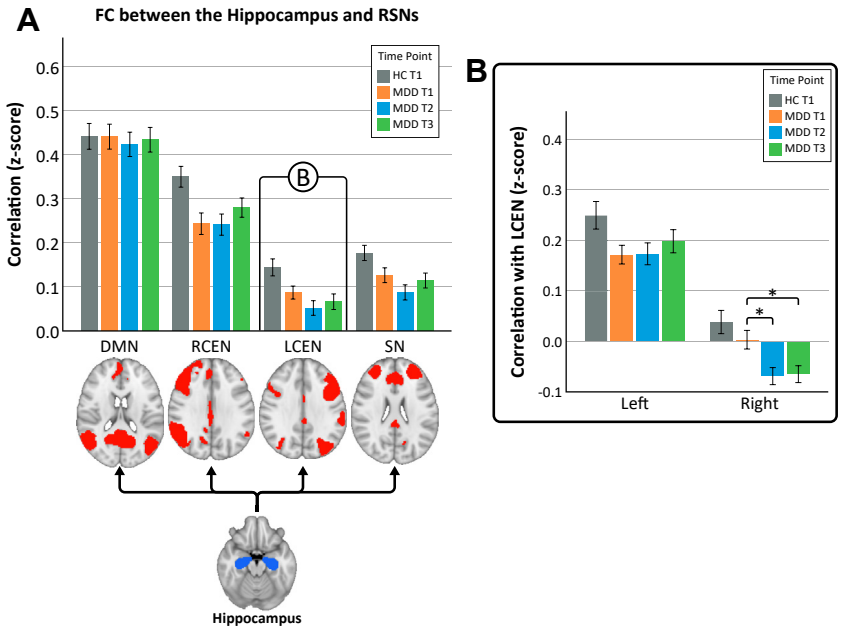

Figure 3. Hippocampal connectivity to resting-state networks (RSNs). **(A)** Functional connectivity (FC) between the bilateral hippocampus and RSNs (default mode network [DMN], right central executive network [RCEN], left central executive network [LCEN], and salience network [SN]). Connectivity between the hippocampus and the LCEN showed a time-by-hemisphere effect; therefore, the right and left hippocampus were looked at separately in **(B)**. **(B)** FC between the left and right hippocampus and LCEN. *$p < .05$. HC, healthy control subjects; MDD, patients with major depressive disorder; T, time.

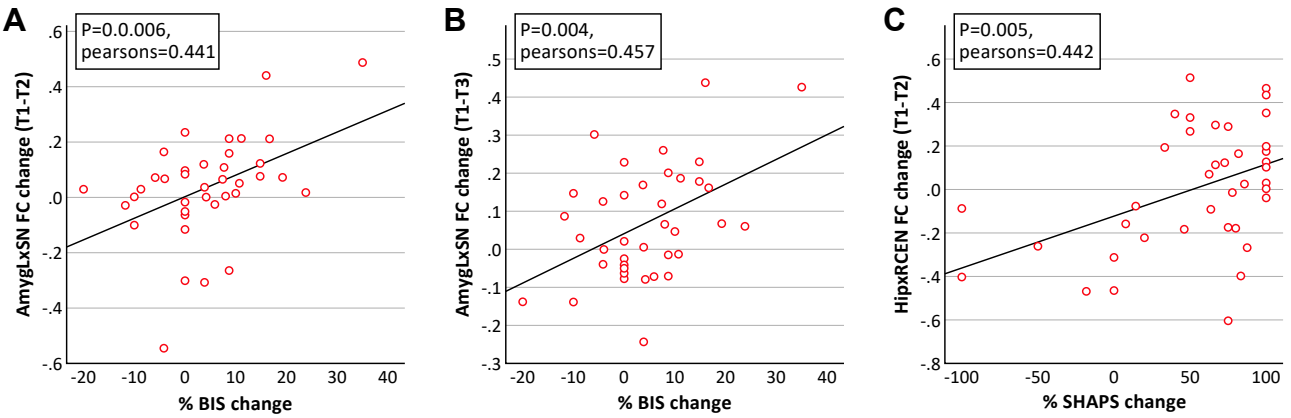

Figure 4. Correlations between measures of clinical improvement and reductions in FC between limbic regions and resting-state networks. **(A)** Change in FC between the left amygdala (AmygL) and salience network (SN) after a single infusion of ketamine correlated with change in BIS at the end of treatment. **(B)** Change in FC between the AmygL and SN at the end of treatment correlated with change in BIS at the end of treatment. **(C)** Change in FC between the hippocampus (Hip) and right central executive network (RCEN) after a single infusion of ketamine correlated with change in SHAPS at the end of treatment. BIS, behavioral inhibition system; SHAPS, Snaith-Hamilton Pleasure Scale; T, time.

Hippocampus. Acute change in FC between the hippocampus and right CEN after a single infusion of ketamine was correlated with the SHAPS (Pearson's r = .45, p = .004) (Figure 4C). No other correlations with hippocampal FC reached our criterion for significance.

DISCUSSION

Experimental models informed by current evidence suggest that MDD is a brain–network disorder affecting several regions and networks within the brain (13) that can be mediated with antidepressant treatments (14,62). Here, we studied the acute effects of single and serial ketamine infusions in patients with TRD on the modulation of FC between 2 limbic regions (amygdala and hippocampus) and 3 target RSNs (SN, CEN, and DMN). The regions and RSNs were selected a priori based on their implications in MDD (12–14,37,49). Investigations included longitudinal analysis, cross-sectional analysis, and clinical correlations of longitudinal changes in FC. Our results showed that connectivity of the amygdala and hippocampus to RSNs changed with treatment and that these changes were related to improvements in features of depression such as anxiety and anhedonia. FC also did not change over time in HCs, providing further evidence that these effects in MDD are related to ketamine and not due to poor test–retest reliability.

Longitudinal Changes With Ketamine Treatment

Effects of Treatment on FC Between Amygdala and RSNs. FC of the amygdala to the left CEN showed a significant decrease after a single infusion of ketamine that then stabilized after serial ketamine infusions, increasing toward FC observed in HCs. While this change in FC between the amygdala and left CEN was higher at T3 than at T1, it did not reach significance. Similarly, amygdala connectivity to the right CEN increased with treatment in the direction of HCs, implying normalization, although this effect did not reach significance for the left amygdala. This is in line with previous literature implicating CEN and PFC hypoconnectivity in MDD (26,63). An exploratory investigation reported decreased amygdala connectivity with regions involved in cognition and executive control such as the DLPFC and inferior frontal gyrus (both regions are parts of the CEN) in women with MDD (64). Cognitive behavioral therapy has also shown increases in CEN connectivity (65) and increases in FC between the amygdala and cognitive control network (66). Jenkins *et al.* also reported recently that FC between the amygdala and CEN is important in the cognitive control of emotion, which may improve performance during emotional face recognition tasks (67). Therefore, ketamine may be involved in increasing connectivity between the amygdala and CEN, leading to increased top-down control of emotion processing frequently observed as disturbed in patients with MDD (10,27,68,69).

FC of the left amygdala to the SN was decreased in MDD at baseline and was further decreased with ketamine treatment in the MDD group. This is consistent with a previous study reporting that a single infusion of ketamine reduced FC between the insula (part of the SN) and DMN, which was also decreased in patients with MDD compared with HCs (45). However, prior findings have also reported increased SN FC in patients with MDD compared with HCs. An analysis of causal connectivity showed significantly higher effective connectivity of the amygdala to the anterior insula (a node of the SN) in MDD (41), an rsfMRI analysis demonstrated increased insula FC with the amygdala (42), and another study showed increased SN connectivity in MDD (21). With the role of the amygdala and SN in emotion processing and perception, disruptions in this network may be the cause of decreased ability to process emotions (70). Our results show that ketamine may resolve disrupted connectivity and lead to more normalized FC potentially underlying emotion regulation.

Effects of Treatment on FC Between Hippocampus and RSNs. The right hippocampus showed greater negative FC (anticorrelation) to the left CEN with treatment. Our results

showing an anticorrelation effect after a single infusion and then sustained anticorrelation after serial infusion show that ketamine may be restoring negative connectivity. Negative FC between the hippocampus and regions of the CEN, including the bilateral PFC and bilateral parietal lobe, have been reported in HCs (71). These results are consistent with the corticolimbic dysregulation model of MDD as proposed by Mayberg (27,69,72). The cortical compartment, including the inferior parietal cortex and DLPFC, is associated with depressive symptoms, including apathy, anhedonia, and cognitive performance, while the limbic compartment, including the hippocampus, mediates vegetative and somatic aspects of MDD. Depressive symptoms can be linked to decreases in activity in cortical regions and increases in limbic areas (27,33,69,72,73), implicating different and interacting roles of cortical and limbic areas in regulation of emotion and cognition as well as in the pathology of MDD. Therefore, we propose that an absence of negative FC in MDD before ketamine treatment in our study may reflect weak functional segregation between cortical and limbic compartments, perhaps leading to cognitive and emotional symptoms in MDD. Notably, our findings show that ketamine restored the functional segregation between the right hippocampus and left CEN, which is compatible with the idea that ketamine restores top-down regulation of ventral limbic structures and may be related to symptom remission. This interpretation is consistent with previous neuroimaging studies indicating that a single infusion of ketamine can induce treatment effects in similar regions such as the subgenual ACC, posterior parietal cortex, hippocampus, PFC, caudate, and DMN (18,45–47). Our results provide further evidence of single ketamine infusion–induced blood oxygen level–dependent changes and provide the first evidence of changes due to serial ketamine treatment.

Neural Correlates of Clinical Change

Previous investigations have reported relationships between changes in global depression score and changes in fMRI after a single infusion of ketamine. For example, a recent study demonstrated increased global connectivity in the PFC, insula, and caudate in responders to a single ketamine infusion, suggesting that baseline prefrontal and striatal circuitry may be relevant to successful clinical outcomes (46). Another recent study reported that FC increases between the lateral PFC and subgenual ACC were associated with symptom reduction and that lower baseline FC predicted response (74). A pilot study also showed differences in diffusion metrics in frontolimbic pathways between responders and nonresponders after a single infusion of ketamine (75). As a follow-up analysis to further understand the changes in FC observed, we targeted several different symptom dimensions (inhibition/avoidance, anxiety, rumination, and anhedonia). We investigated potential associations of these clinical scales with FC changes after a single ketamine infusion and multiple ketamine infusions.

The BIS scale, a measure of inhibition and avoidance that is typically elevated in depression (76,77), did not change after ketamine treatment on average. However, posttreatment decreases (improvements) in the BIS scale were significantly correlated with acute and posttreatment decreases in FC between the left amygdala and SN. Critically, this initial decrease in FC may show plasticity of this network that relates to improvements in anxiety symptoms elevated in MDD (78). We also report that improvement in the SHAPS, a measure of anhedonia that is increased in depression (79), was correlated with acute decreases in FC between the hippocampus and right CEN. Taken together, these results indicate that acute FC change after a single infusion of ketamine predicts improved anxious avoidance and anhedonia after serial ketamine infusions.

Limitations

Several limitations with this investigation need to be considered. First, the results of this study should be validated in a larger sample, particularly with respect to less powered cross-sectional effects. Second, we designed this mechanistic trial as open label both because the primary goal targeted longitudinal effects of ketamine on brain connectivity (i.e., not efficacy of ketamine to treat depression) and because of the ethical implications of including a placebo group in volunteers with TRD. We felt that it would be unnecessarily burdensome for patients to receive a placebo treatment in this multivisit study. Given that previous randomized placebo-controlled trials have clearly established the superiority of ketamine to improve the symptoms of depression compared with placebo, it is very unlikely that the changes in connectivity we report here can be explained by the placebo effect. Nevertheless, the neurobiological basis of the placebo effect in depression in an underrepresented area of research and could be addressed by larger multisite mechanistic studies. Our participants with MDD had a limited range of symptoms with a mean of 19.3 on the HDRS. This may affect their baseline FC; however, we show no correlation between baseline FC and HDRS scores, and ketamine is also most likely to be used in a population exhibiting moderate to severe depressive symptoms (5,50,80).

Conclusions

This is the first study to investigate imaging effects of serial ketamine infusions on resting-state FC. Findings from the current analysis support previous findings and demonstrate that ketamine therapy leads to neuroplasticity between limbic regions (amygdala and hippocampus) and RSNs that are essential for emotion regulation, executive function, goal-oriented behavior, self-awareness, and social behavior. A restoration of FC is observed between the amygdala and SN, between the amygdala and right CEN, and between the hippocampus and left CEN with ketamine treatment. Neuroplasticity of these networks also was related to clinical improvements in anxiety and anhedonia. Furthermore, results suggest that early neuroplasticity may serve as a biomarker for clinical outcomes. Although ketamine did not appear to influence DMN FC in our study, future studies targeting other aspects of DMN connectivity beyond the amygdala and hippocampus may be more informative given the importance of the DMN to the neurobiology of depression. Overall, the current findings support that repeated ketamine therapy leads to regulation of limbic regions by large-scale RSNs, and this

reestablished regulation may be a neural correlate of symptom reduction.

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