Default Mode Connectivity in Major Depressive Disorder Measured Up to 10 Days After Ketamine Administration

Supplemental Information

Supplemental Methods

Imaging Parameters

First, a high resolution anatomical scan was acquired (3D fast spoiled gradient recalled echo (FSPGR), repetition time (TR): 8.8 s, echo time (TE): 3.4 ms, inversion recovery time (IR): 450 ms, flip angle (FA): 13 degrees, 1mm isotropic resolution). A whole brain, eight-minute gradient recalled echo planar image (EPI) resting state scan with the subject's eyes closed was then performed (fMRI parameters: 192 time points, TR:2.5 s, TE: 25 ms, FA: 90 degrees, resolution: 3.75x3.75x3.5 mm, matrix 64x64, 45 sagittal slices, phase encode direction: anterior-posterior, interleaved acquisition).

Data Preprocessing

Preprocessing was performed using the afni_proc.py script and included: despiking, slice timing correction, physiological noise correction (slice based, generated with McRetroTS), and motion correction (12-parameter affine, registered to the third volume), blurring to 6 mm full-width-at-half-maximum (FHWM), motion censoring, bandpass filtering between 0.01 and 0.1 Hz, and alignment to Montreal Neurological Institute (MNI) 152 standard space. For the alignment procedure, the anatomical image was first aligned to the EPI image using an affine transform with the LPC cost-function (align_epi_anat.py) using a weight mask created from the square root of

fALFF (1) (3dRSFC, truncated at a maximum value of 60 for intensity normalization purposes) calculated from the resting state time series. This was done to improve alignment of the low contrast EPI to the internal brain structures of the anatomical image. The anatomical image was then non-linearly warped to the MNI 152 standard template. The EPI was transformed to standard space using the concatenated transformation matrices generated from the anatomical alignment steps. Motion (de-meaned and derivative) regressors were also removed from the original time series simultaneously with bandpassing.

Data points were censored if there was more than an estimated 0.2 mm of motion (Euclidean norm) per TR. The dataset was excluded from further analysis if there were more than 15 censored time points.

Supplemental Tables

Supplemental Table S1. Demographics for MDD and HC groups

	MDD (n = 33)		HC (n = 25)	
Age (mean, std. dev)	36	10	33	10
Sex (n F, %)	20	61	15	60
BMI (mean, std. dev)	27	5	27	4
Age of Onset (years, std. dev)	15	6		
Length of Current Illness (months, std. dev)*	43	69		
Length of Illness (years, std. dev)	20	11		
Number of failed antidepressant trials (mean, std. dev.)	6	3		

* Two subjects did not report the length of their current illness. MDD: major depressive disorder; HC: healthy control; BMI: body mass index.

Supplemental Table S2. Number of scans conducted in the MDD and HC groups*.

		baseline (*b*)	ketamine Day 2 (*k2*)	ketamine Day 10 (*k10*)	placebo Day 2 (*p2*)	placebo Day 10 (*p10*)
MDD	total scans	30	29	27	26	27
	analysis	24	26	24	25	26
HC	total scans	24	22	17	20	14
	analysis	21	19	12	19	10

*The table lists the total number of scans completed as well as the number of scans used in the analysis that had complete physiological data and motion within the limit. MDD: major depressive disorder; HC: healthy control.

Supplemental Table S3. Centers of mass of significant regions for the group difference maps for each scan day

Scan	Volume	Center of Mass				Mean (Z)	SEM
		location	RL	AP	IS		
Baseline *(b)*	309	Left Precentral Gyrus	50.2	7.9	13.9	1.75	0.02
	270	Right Inferior Frontal Gyrus	-48.4	-9.4	24.5	1.83	0.02
Ketamine, Day 2 (*k2*)	532	Left Cingulate Gyrus	4.9	-6.4	43	1.94	0.02
	425	Left Inferior Parietal Lobule	49.6	37.8	22.3	1.93	0.02
	395	Right Inferior Parietal Lobule	-51.7	34	34.2	1.96	0.02
	223	Right Middle Frontal Gyrus	-42.2	-12.3	32.6	1.82	0.02
	7	Right Inferior Frontal Gyrus	-46.9	-10.8	21.1	2.60	0.02
Ketamine, Day 10 *(k10)*	668	Right Inferior Parietal Lobule	-41.5	45.2	44.3	2.63	0.02
	622	Right Cingulate Gyrus	-0.9	-7.7	45.9	2.38	0.02
	595	Left Inferior Frontal Gyrus	44.6	-8.1	23.8	2.42	0.02
	537	Left Inferior Parietal Lobule	40.2	44.3	44	2.39	0.02
	307	Right Supramarginal Gyrus	-40.4	53	24.6	-2.28	0.05
	254	Left Middle Frontal Gyrus	43.3	-40.7	16.1	2.83	0.04
Placebo, Day 2 *(p2)*	770	Right Precentral Gyrus	-53.3	6.5	21.2	2.02	0.01
	297	Left Inferior Parietal Lobule	56.1	24.9	29.8	2.02	0.02
	288	Left Superior Frontal Gyrus	6.5	-6.1	56.3	2.01	0.02
	193	Left Insula	46.3	-2.9	10.6	1.82	0.02
Placebo, Day 10 *(p10)*	880	Right Precentral Gyrus	-45.3	22.9	36.2	2.23	0.02
	686	Left Cingulate Gyrus	23.3	10.9	40.3	2.02	0.01
	325	Right Posterior Cingulate	-5.3	70.1	10.6	1.93	0.02

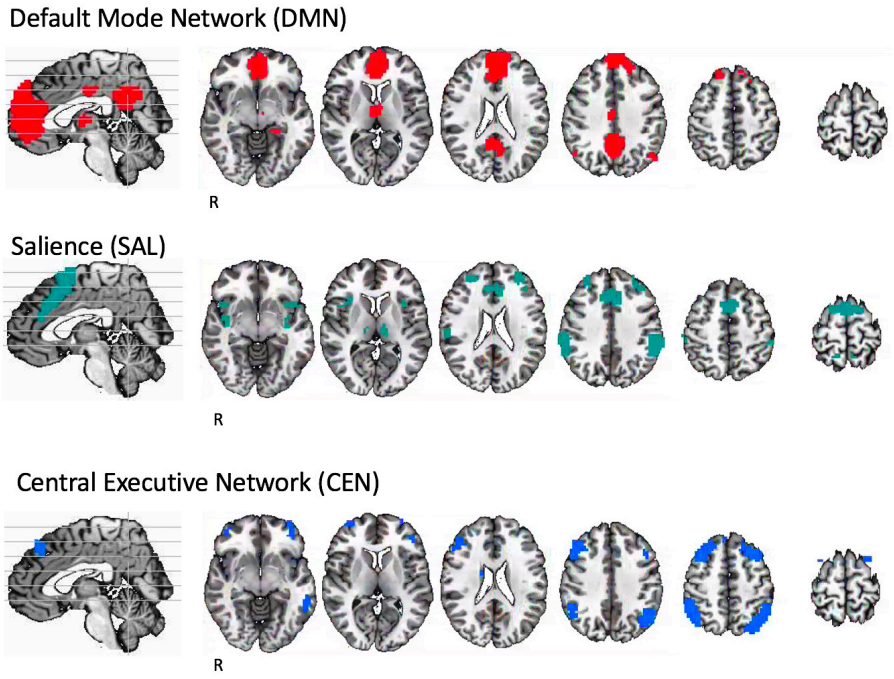
Cluster centers of mass are indicated in Montreal Neurological Institute (MNI) coordinates where RL: right/left; AP: anterior/posterior; IS: inferior/superior. SEM: standard error of the mean.

Supplemental Table S4. Centers of mass of the significant clusters for the group maps for the *ketamine-placebo* contrast at Day 2 and Day 10 in both MDD and HC subjects.

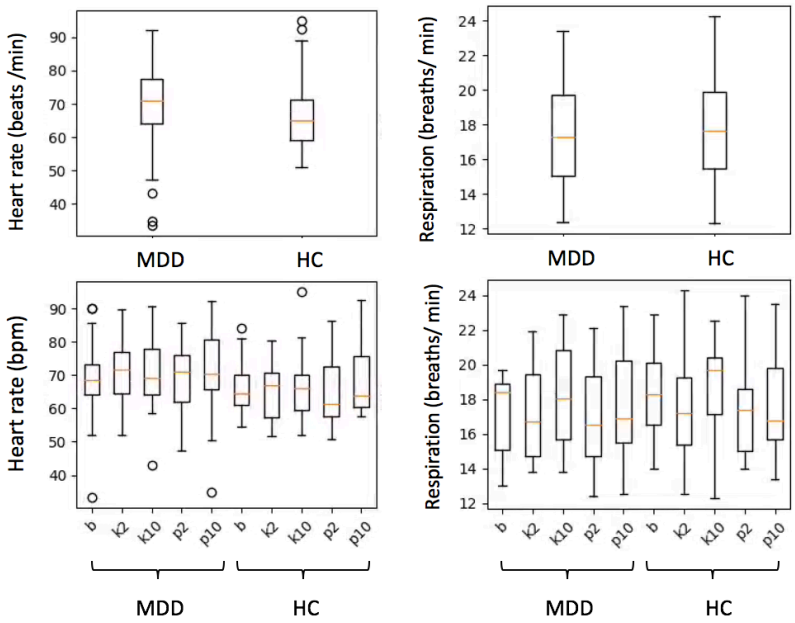
Group	Scan	Volume	Center of Mass				Mean (Z)	SEM
			location	RL	AP	IS		
MDD	Day 2	2231	Right Paracentral Lobule	-10.5	22.4	47	1.38	0.01
		730	Right Middle Occipital Gyrus	-26.7	72	1.1	1.43	0.01
		701	Left Lingual Gyrus	22.1	65.9	-6	1.35	0.01
		387	Left Postcentral Gyrus	55.6	13	24.5	1.38	0.01
	Day 10	1804	Right Cuneus	-0.9	67.1	4.7	-1.40	0.01
		569	Right Medial Frontal Gyrus	-20.1	-10.5	48.9	1.47	0.01
		490	Left Medial Frontal Gyrus	3.8	-52.9	18.8	-1.63	0.02
		293	Left Middle Frontal Gyrus	42.5	-28.6	18.1	1.47	0.01
		204	Right Inferior Parietal Lobule	-47	49.3	46.5	1.69	0.02
HC	Day 2	523	Right Middle Frontal Gyrus	-25.4	-5.3	41.5	1.64	0.02
		403	Left Insula	27.2	32.6	17	1.46	0.01
		293	Left Cuneus	1.2	72	9.8	1.71	0.02
	Day 10	399	Left Middle Frontal Gyrus	40.9	-26.6	29.9	-2.34	0.02
		266	Right Precentral Gyrus	-31.7	6	29.4	1.84	0.02
		218	Left Precentral Gyrus	31.4	9.9	31	1.68	0.02
		196	Right Supramarginal Gyrus	-49.3	51.3	24.1	2.24	0.03

Cluster centers of mass are indicated in MNI coordinates. RL: right/left; AP: anterior/posterior; IS: inferior/superior. MDD: major depressive disorder; HC: healthy control; SEM: standard error of the mean.

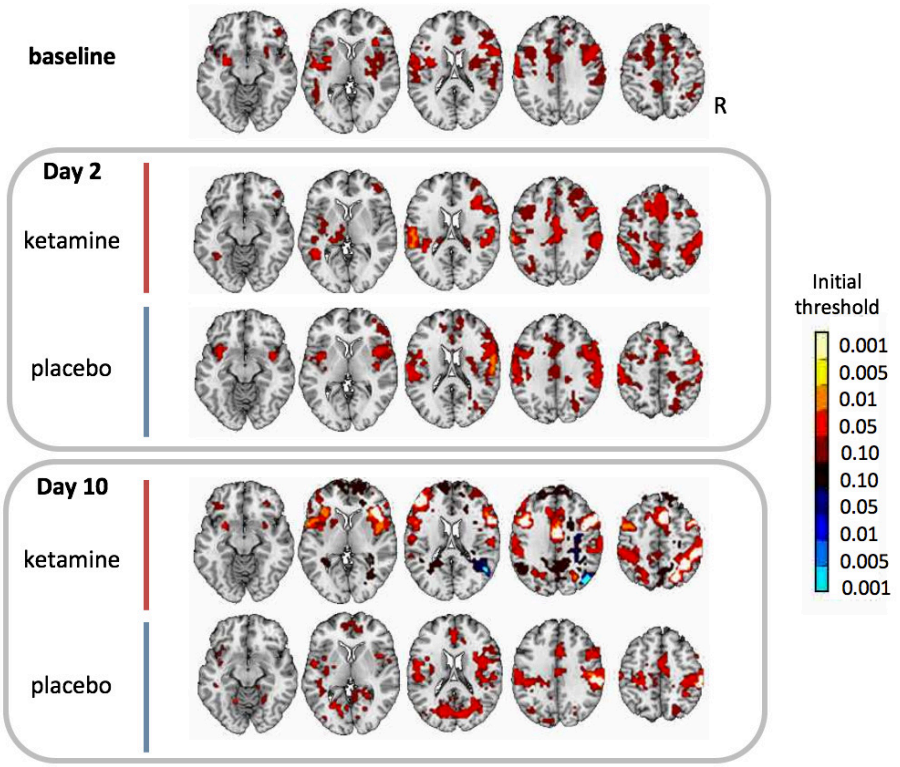
Supplemental Figures



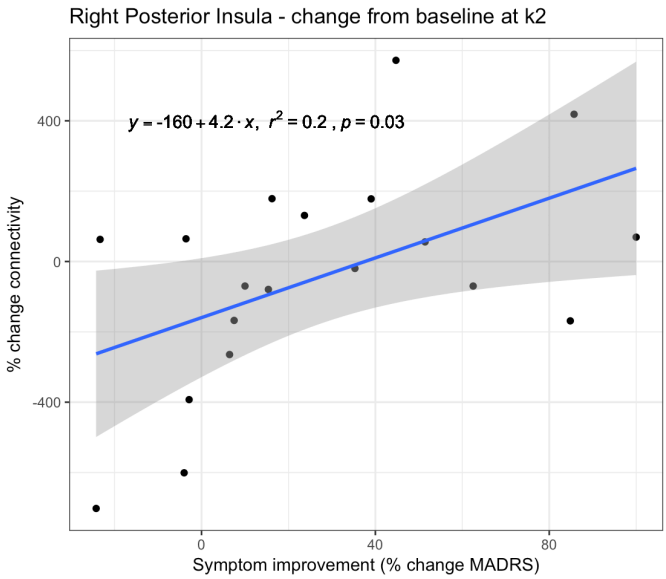
Supplemental Figure S1. Graphical region of interest (ROI) definitions for the default mode network (DMN), salience network (SAL), and central executive network (CEN). Further details and ROI files for download can be found at https://findlab.stanford.edu/functional_ROIs.html.



Supplemental Figure S2. Box-and-whisker plots of the heart (left column) and respiratory rate (right column) across groups (major depressive disorder (MDD), healthy control (HC)) in the first row and scans (*b,k2,p2,k10,p10*) in the second. The box outlines the first quartile, the median is indicated by the peach line within the box, whiskers show 1.5 of the inter-quartile range with outlier points shown as circles. Heart rate (beats/minute) is shown in the left column of plots, and respiration rate (breaths/minute) is shown on the right. The first row of plots shows a trend for higher heart rates in MDD (median=70 bpm) than HC (median=63 bpm) subjects, but no significant difference in respiration rate. The second row shows no significant different in heart rate or respiration between any scans.



Supplemental Figure S3. Group difference maps for healthy controls (HCs) and major depressive disorder (MDD) subjects shown at familywise error (FWE) corrected $p<0.05$. The overlay color indicates the lowest initial threshold the cluster survived. The maps were created by first choosing an initial threshold, calculating the FWE cluster size, and cluster correcting to $p<0.05$. The map from each initial threshold was overlaid and assigned a color.



Supplemental Figure S4. Correlation between symptom improvement and change in connectivity between the right posterior insula and the DMN posterior cingulate cortex (PCC) between baseline and Day 2 post-ketamine administration scans. Symptom improvement is percent change in MADRS *b-k2* (such that a positive change is reflected by a decrease in depressive symptoms), and percent change in connectivity is *k2-b*. The black dots are individual subject data, the blue line is the line of best fit, and the gray area is the confidence region of the fit. The equation of the line of best fit is shown on the graph along with the r^2 and *p*-values.

Supplemental Reference

1. Zou Q-H, Zhu C-Z, Yang Y, Zuo X-N, Long X-Y, Cao Q-J, *et al.* (2008): An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. *J Neurosci Methods*. 172: 137–41.