Supplemental Information

Dynamic Resting-State Functional Connectivity in Major Depression

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Table S1. Demographic and Clinical Characteristics

Demographic Characteristics

	McLean Hospital				Harvard University				Duke/UNC			
	MDD		HC		MDD		HC		MDD		HC	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
Age[s]	25.57	5.41	25.84	7.38	33.95	11.31	34.89	13.95	33.59	6.89	31.10	8.82
	N	%	N	%	N	%	N	%	N	%	N	%
Female[s]	24/30	80.00	22/32	68.80	18/40	45.00	32/57	56.10	20/29	68.97	14/20	70.00
White	19/29	65.50	22/31	71.00	26/39	66.70	49/57	86.00	20/28	71.43	12/19	63.16
Meds	0/30	0	0/32	0	0/40	0	0/57	0	0/30	0	0/20	0

Depressive Symptoms and Rumination

	McLean Hospital				Harvard University				Duke/UNC			
	MDD		HC		MDD		HC		MDD		HC	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
BDI-II[g]	25.57	8.30	0.47	0.92	23.78	8.97	1.40	2.03	26.41	8.80	1.05	1.57
BADS-AV[g]									27.88	7.67	3.45	4.06

Clinical Diagnoses

	McLean Hospital				Harvard University				Duke/UNC			
	MDD		HC		MDD		HC		MDD		HC	
	N	%	N	%	N	%	N	%	N	%	N	%
Current MDD[g]	30/30	100	0/32	0	40/40	100*	0/57	0	30/30	100	0/20	0
Past MDD[g]	30/30	100	0/32	0	40/40	100	0/57	0	30/30	100	0/20	0
Current Dysphoria	1/30	3	0/32	0	0/40	0	0/57	0	1/30	3	0/20	0
Past Dysphoria	1/30	3	0/32	0	0/40	0	0/57	0	1/30	3	0/20	0
Current Bipolar I/II	0/30	0	0/32	0	0/40	0	0/57	0	0/30	0	0/20	0
Past Bipolar I/II	0/30	0	0/32	0	0/40	0	0/57	0	0/30	0	0/20	0
Current Psychosis	0/30	0	0/32	0	0/40	0	0/57	0	0/30	0	0/20	0
Past Psychosis	0/30	0	0/32	0	0/40	0	0/57	0	0/30	0	0/20	0
Current Substance Ab/Dep	1/30	3	0/32	0	0/39	0	0/57	0	0/30	0	0/20	0
Past Substance Ab/Dep[g]	1/30	3	0/32	0	6/39	15	0/57	0	3/30	10	0/20	0
Current Anxiety[s,g]	5/30	17	0/32	0	18/40	45	0/57	0	0/30	0	0/20	0
Past Anxiety[s,g]	9/30	30	0/32	0	21/40	48	0/57	0	3/30	10	0/20	0
Current PTSD[g]	0/30	0	0/32	0	0/40	0	0/57	0	0/30	0	0/20	0
Past PTSD[g]	0/30	0	0/32	0	0/40	0	0/57	0	1/30	3	0/20	0

Current Eating Disorder	0/30	0	0/32	0	2/40	5	0/57	0	0/30	0	0/20	0
Past Eating Disorder[g]	1/30	3	0/32	0	3/40	8	0/57	0	1/30	3	0/20	0

Note: Abbreviations include: substance abuse or dependence (Ab/Dep), Beck Depression Inventory, 2nd Ed. (BDI-II), Behavioral Activation for Depression-Avoidance Subscale (BADS-AV), healthy control (HC), major depressive disorder (MDD), medication use (Meds), Posttraumatic Stress Disorder (PTSD), University of North Carolina (UNC). [*]One participant in the MDD group recruited at Harvard University reported subthreshold depression (3 out of 5 symptoms) in the SCID, but was diagnosed as meeting DSM-IV-TR criteria for a major depressive episode based on additional query by the clinical interviewer. Chi-square or ANOVA tests were performed to identify significant differences (at $p<0.05$) in demographic or clinical variables by site[s] or clinical group[g]. Clinical groups differed on clinical variables, only. Sites differed on some demographic (age, proportion female) and clinical (past substance abuse, current/past anxiety disorder) variables; dummy-coded regressors for each site were included as covariates in all analyses, and statistically controlling for co-occurring psychiatric disorders failed to affect results.

Table S2. Imaging Procedure and Motion

	McLean Hospital	**Harvard University**	**Duke/UNC**
Scanner and Equipment	Siemens Tim Trio 3T, 32-channel head coil	Siemens Tim Trio 3T, 12-channel head coil	GE MR750 3T, 8-channel head coil

Anatomical (T1) Scan Parameters	Sequence= GRAPPA
	TR= 2200ms
	TE=4.27ms
	# slices= 144
	FOV= 230mm
	matrix= 192x192
	voxel size= 1.2x1.2x1.2mm
	flip angle= 7
		Sequence= GRAPPA
		TR= 2200ms
		TE=4.27ms
		# slices= 144
		FOV= 230mm
		matrix= 192x192
		voxel size= 1.2x1.2x1.2mm
		flip angle= 7
			Sequence=FSPGR
			TR= 7.58ms
			TE= 2.94ms
			# slices= 162
			FOV= 256mm
			matrix= 256x256
			voxel size= 1x1x1mm
			flip angle= 12

Functional (BOLD) Scan Parameters	Sequence= interleaved
	TR= 3000ms
	TE=30ms
	# slices= 47
	FOV= 216mm
	matrix= 72x72
	voxel size= 3x3x3mm
	flip angle= 85
	total duration= 372sec
	total volumes=124
		Sequence= interleaved
		TR= 3000ms
		TE=30ms
		# slices= 47
		FOV= 216mm
		matrix= 72x72
		voxel size= 3x3x3mm
		flip angle= 85
		total duration= 372sec
		total volumes=124
			Sequence=spiral-in SENSE
			TR= 1500ms
			TE= 30ms
			# slices= 34
			FOV= 240mm
			matrix= 64x64
			voxel size= 3.75x3.75x3.75mm
			flip angle= 60
			total duration= 300sec
			total volumes= 200

Timing of Resting State Scan	Approximate onset 6 minutes into total scan time; immediately after high-res anatomical scans; prior to other functional scanning.	Approximate onset 6 minutes into total scan time; immediately after high-res anatomical scans; prior to other functional scanning.	Approximate onset 25 minutes into total scan time; immediately prior to high-res anatomical scans; immediately after functional scanning of emotion picture task.
Instruction to Participants	"Rest with your eyes open"	"Rest with your eyes open"	"Rest with your eyes open"
Number of Outlier Volumes Due to Motion/Artifact	MDD Group: M=5.70, SD=6.85 HC Group: M=3.47, SD=3.57	MDD Group: M=4.38, SD=5.42 HC Group: M=4.12, SD=6.11	MDD Group: M=4.97, SD=4.80 HC Group: M=4.40, SD=5.35

Note: Abbreviations include: echo time (TE), field of view (FOV), healthy control (HC), major depressive disorder (MDD), repetition time (TR), University of North Carolina (UNC). There were no differences in number of outlier volumes due to motion or artifact between groups ($p = 0.26$) or sites ($p = 0.92$).

Table S3. Summary of Dynamic Resting-State Functional Connectivity Analysis

Processing Step	Method
General image preprocessing	Discarded first 6 seconds of functional data. Preprocessed (slice-time correction, realignment, normalization, and smoothing (6mm kernel)) in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/).
Motion and artifact detection	Outlier time points of significant head motion (>1mm from previous frame) or fluctuations in the magnetic field (global mean intensity > 3 standard deviations from mean intensity) calculated using Artifact Detection Tools (ART, www.nitrc.org/projects/artifact_detect/). Yielded a set of regressors (to be included in first-level denoising, below) including outlier vectors and motion parameters (three translation and three rotation, plus one composite).
First-level denoising	Principal component analysis performed using CompCor (Behzadi *et al*, 2007) to estimate the physiological noise from white matter and cerebrospinal fluid for each participant. Detrending, outlier sensoring and motion correction (using the output of ART, above), and physiological noise correction (using CompCor), performed simultaneously in a single first-level denoising regression model. After the above first-level regression, data band-pass filtered with a range of 0.0278-0.10 Hz. This range was selected to remove frequencies slower than the duration of a single sliding window (here, 36 seconds; see Leonardi and Van De Ville, 2015, for discussion and the formula $w \geq (1/f\text{-}min)$, where w is window duration in seconds and *f-min* is the frequency threshold). This range also removes frequencies faster than 0.10 Hz, which can include cardiac and respiratory activity (Cordes *et al*, 2001). Denoising yielded a residual time course at each voxel that was used for subsequent analyses.
First-level dynamic analyses: The sliding-window approach	Time course segmented into 36-second windows, sliding the onset of each window by 18 seconds. (Window length is consistent with recommendations for optimal duration between 30 and 60 seconds, see Leonardi and Van De Ville, 2015, or Hutchison *et al* 2013, for discussion). Computed Fisher's z-transformed Pearson's correlation coefficient for each sliding window between the seed region-of-interest in medial prefrontal cortex and all other voxels, yielding a set of beta maps (one for each window) for each participant. Computed standard deviation in beta values at each voxels across the set of beta maps for each participant, yielding a dynamic map for each participant.
Group-level dynamic analyses	First-level dynamic maps entered into a whole-brain regression analysis and group-level statistics performed at each voxel. Dummy-coded covariates for each research site were included in all group-level analyses. Group-level analyses included t-test (MDD versus control group) or correlation (with scores on the Beck Depression Inventory, 2nd Ed., Beck *et al*, 1996) at each voxel. Group level effects thresholded at a peak amplitude of $p<0.01$ (two-sided), cluster corrected at False Discovery Rate of $p<0.05$.

Table S4. Altered Static Resting-State Functional Connectivity of Medial Prefrontal Cortex as a Function of Depressive Symptom Severity

	Peak Coord	Peak *t*	Vol	Static FC of Cluster
Correlation with BDI-II				MDD
	X,Y,Z	*t*	#vx	*r*
PCC	-14, -42, 38	3.81	879	0.38

Note: Thresholding was set to $p<0.05$ (two-sided) peak amplitude of effect, cluster corrected to a False Discovery Rate of $p<0.05$. Abbreviations include: Beck Depression Inventory 2nd Ed. (BDI-II), functional connectivity (FC), major depressive disorder (MDD), and posterior cingulate cortex (PCC). Coord = coordinates in MNI standard stereotaxic space. Vol = volume of cluster of significant effect in voxels. Vx = number of 1x1x1mm voxels. Static FC was assessed by Fisher's z-transformed Pearson's correlation over the full duration of the resting scan.

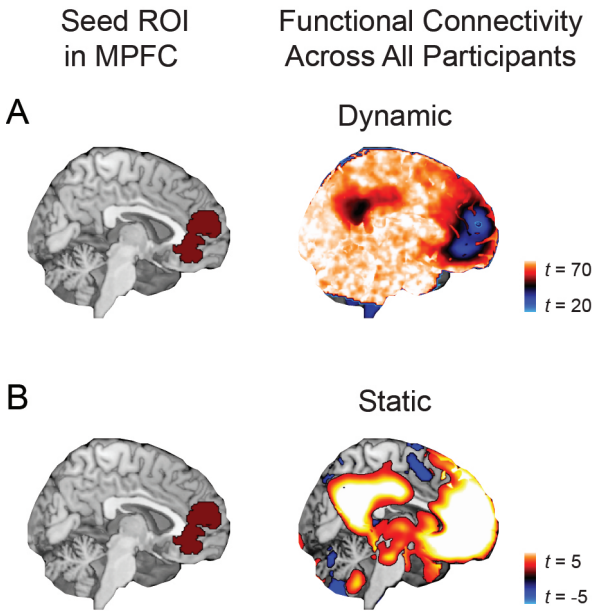

Figure S1. Average dynamic functional connectivity of a seed region of interest in medial prefrontal cortex across the sample. Across the full sample (N=209), functional connectivity of a seed region in medial prefrontal cortex (MPFC) was (A) least variable (dynamic functional connectivity), and (B) most strongly positive (static functional connectivity), with other areas of the default network including adjacent medial prefrontal regions, posterior cingulate cortex, inferior temporal cortex, and inferior parietal lobule. *Note:* Displayed is the t-map for a one-sample group t-test on average voxelwise dynamic resting-state functional connectivity (standard deviation (SD) in Fisher's z-transformed Pearson's correlations across a sequence of sliding windows) of the MPFC seed region of interest (ROI).

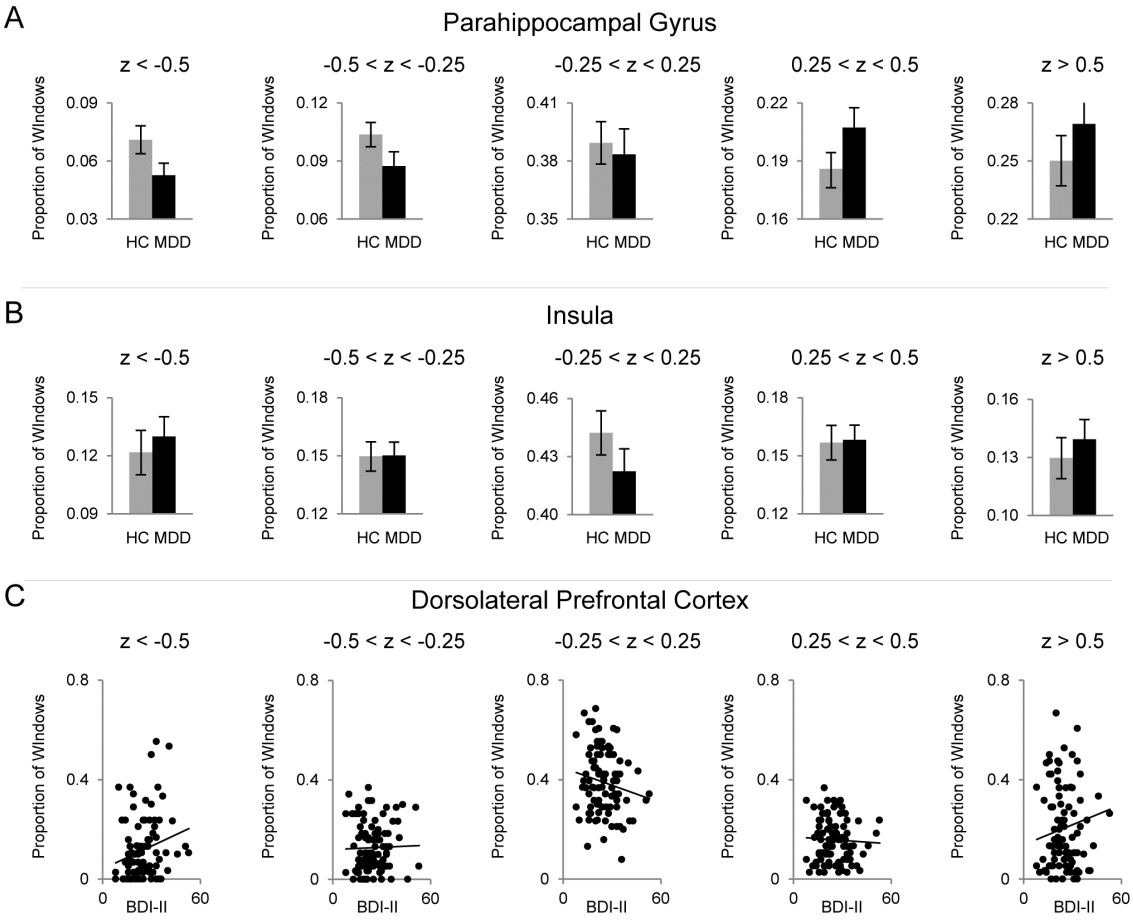

Figure S2. Descriptive statistics for proportion of sliding windows in which participants exhibited positively or negatively correlated activity between medial prefrontal cortex and other regions. For clusters of effect identified by primary analyses, and for each participant, we calculated the proportion of windows in which (Fisher's z-transformed) correlations fell within particular ranges: high negative ($z < -0.5$), moderate negative ($-0.5 \leq z < -0.25$), low/uncorrelated ($-0.25 \leq z \leq 0.25$), moderate positive ($0.25 < z \leq 0.5$), and high positive ($z > 0.5$). For the clusters in (A) parahippocampal gyrus (PHG), and (B) insula, which were implicated by group differences in dynamic resting-state functional connectivity, the proportion of windows in each range of correlation values was averaged for the group with Major Depressive Disorder (MDD) and the healthy control (HC) group. (C) For the cluster in dorsolateral prefrontal cortex, which was implicated by depressive symptom severity in the MDD group, we correlated BDI-II scores with the proportion of windows in each range of RSFC. These descriptive statistics were designed to clarify results of primary analyses by illustrating general patterns of resting-state functional connectivity among sliding windows.

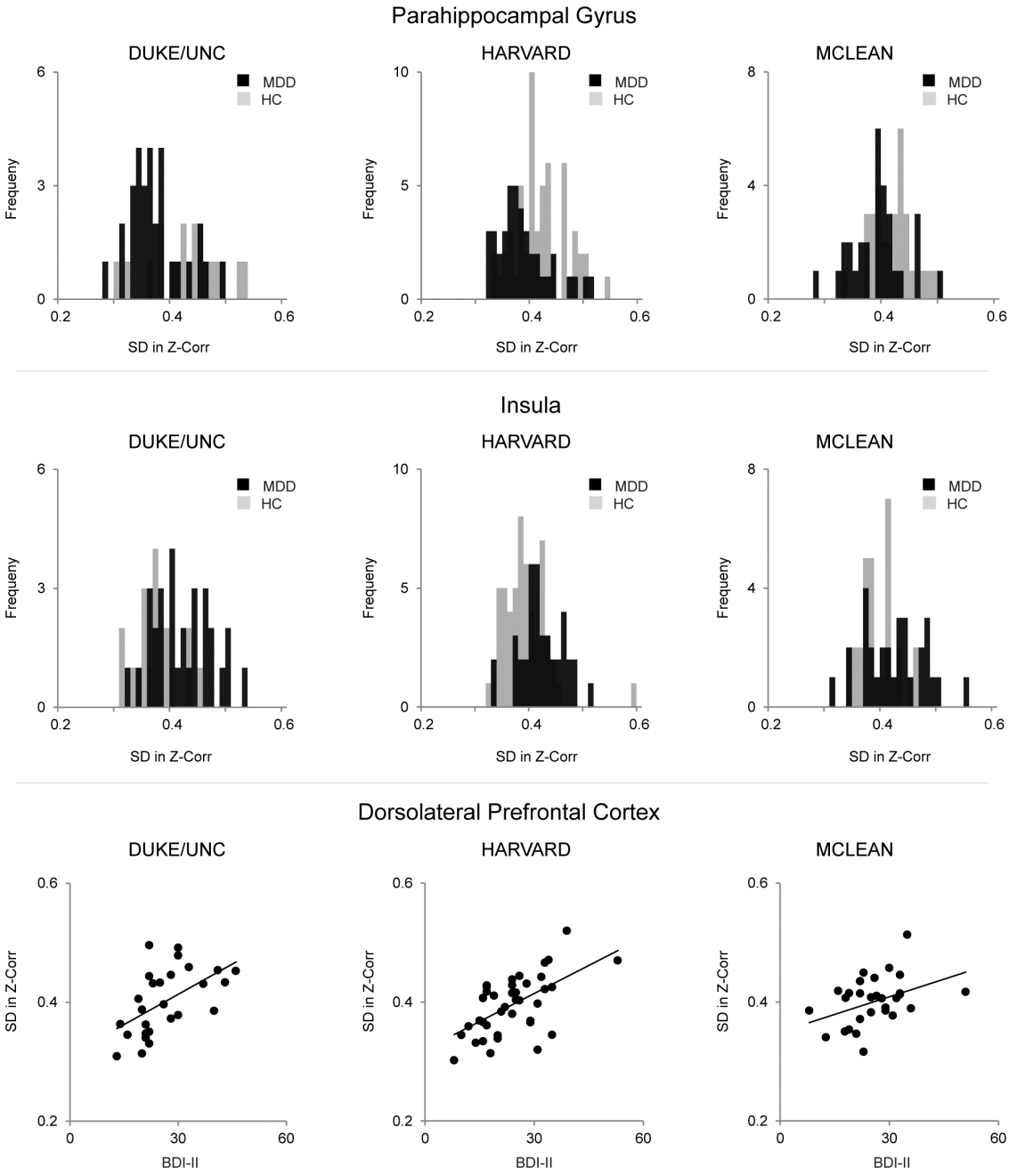

Figure S3. Dynamic resting-state functional connectivity of medial prefrontal cortex by site. Plotted, for each site, are (A-B) frequencies of dynamic functional connectivity values (standard deviation (SD) in Fisher's z-transformed Pearson's correlations across a series of sliding windows) for regions in which the Major Depressive Disorder (MDD) group differed from the healthy control (HC) group; or (C) the association between Beck Depression Inventory 2nd Ed. (BDI-II) and dynamic functional connectivity for MDD individuals in regions implicated by BDI-II. Sample sizes by site: Duke MDD n=30, HC n=20; Harvard MDD n=40, HC n=57; McLean MDD n=30, HC n=32.

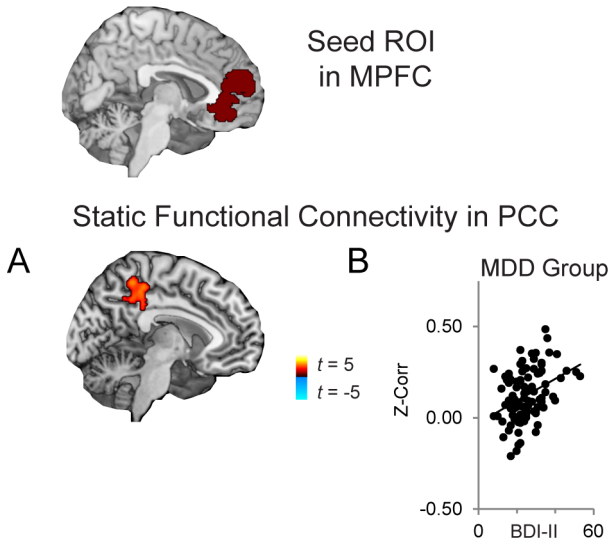

Figure S4. Altered static resting-state functional connectivity of medial prefrontal cortex as a function of depressive symptom severity. (A) For depressed individuals (n=97; three participants did not complete the Beck Depression Inventory 2nd Ed. (BDI-II)), higher BDI-II scores were associated with increased static functional connectivity between a seed region of interest (ROI) in medial prefrontal cortex (MPFC) and areas of posterior cingulate cortex (PCC). (B) Correlation between BDI-II and static functional connectivity (Fisher's z-transformed Pearson's correlation in activity over the full resting-state scan) in PCC.