Data supplement for Dunlop et al., Shared and Unique Changes in Brain Connectivity Among Depressed Patients After Remission With Pharmacotherapy Versus Psychotherapy. Am J Psychiatry (doi: 10.1176/appi.ajp.21070727)

CONTENTS

Supplementary Text

A. Inclusion and Exclusion Criteria for the Emory PReDICT study (Dunlop et al. 2012)

Inclusion Criteria

1. Male or female outpatients between 18 and 65 years old.
2. Primary psychiatric diagnosis of DSM-IV defined Major Depressive Disorder
3. Total 17-item Hamilton Depression Rating Scale (HAMD) score ≥ 18 at screening visit, and ≥ 15 at randomization visit
4. Never previously treated for MDD or dysthymia, defined as:
    a. Four or more consecutive weeks of an antidepressant at minimally effective dose, OR
    b. Four or more sessions of an established structured psychotherapy for depression, i.e. CBT, BT, IPT or Behavioral marital therapy
5. Able to independently understand and provide written informed consent
6. Able to communicate fluently in either English or Spanish

Exclusion Criteria

1. Current DSM-IV defined psychotic disorder, eating disorder, dissociative disorder, obsessive compulsive disorder, or dementia.
2. Any current primary DSM-IV disorder other than major depressive disorder
3. Lifetime history of DSM-IV defined bipolar disorder or schizophrenia
4. Current significant suicidal ideation requiring rapid initiation of treatment
5. Meeting DSM-IV criteria for alcohol or drug dependence within 12 months, or substance abuse within 3 months of randomization visit (excluding nicotine and caffeine)
6. Urine drug screen positive for drugs of abuse at screening visit
7. Any lifetime prior exposure to citalopram, escitalopram or duloxetine
8. Any lifetime adequate medication treatment (≥4 weeks at minimal effective dose) for major depression or dysthymia
9. Any (lifetime) prior treatment with Cognitive Behavioral Therapy (CBT), Interpersonal Therapy (IPT) or Behavioral Marital Therapy for depressive symptoms for ≥4 sessions
10. Treatment with any dose (including less than minimally effective dose) of an antidepressant for any reason for > 4 weeks for during the current episode.
11. Use of any psychotropic medication (except hypnotics) within 1 week of the screening visit.
12. Any use of fluoxetine within 8 weeks of the screening visit
13. Need for concurrent neuroleptic or mood stabilizer therapy
14. Currently pregnant or breast-feeding women
15. Any current acute or chronic medical disorder that would likely affect or preclude completion of the study
16. Clinically significant neurological, inflammatory, autoimmune, endocrine or other medical illness that could interfere with the conduct of the study or interfere with interpretation of study results, including clinically significant abnormal screening laboratory results.
17. Medical contraindications which would preclude treatment with escitalopram or duloxetine
18. Presence of any factors that would likely prevent the patient from completing 12 weeks of the study
19. Contraindications for MRI, such as pacemaker, aneurysm clips, or other implants
20. Unlikely to comply with the study protocol, as determined by a study psychiatrist

B. PReDICT Study Clinical Outcomes (Dunlop et al., 2017a)

B1. Mean Change in Hamilton Depression Rating Scale Score

A linear-mixed model using time as a continuous predictor and individual-level random effects for both intercept (initial depression severity) and slope (change in depression severity) was used to evaluate change in 17-item Hamilton Depression Rating Scale (HAMD) score in the intent-to-treat sample. Group-by-treatment interactions were tested.

Estimated overall reduction in HAMD scores in intent-to-treat sample:
Whole sample (N=344): -10.9 points
CBT (n=115): -10.2 points
Escitalopram (n=114): -11.1 points
Duloxetine (n=115): -11.2 points

Test for interaction: F=0.53, df=2, 257, p=0.589

Estimated overall reduction in HAMD scores in completer sample:
Whole sample (N=234): -10.5 points
CBT (n=69): - 9.8 points
Escitalopram (n=86): -11.1 points
Duloxetine (n=79): -10.7 points

Test for interaction: F=0.88, df=2, 231, p=0.415

B2. Remission Rates Among All Study Completers

- All completers: 109/234 (46.6%)
- CBT: 30/69 (42.5%)
- Escitalopram: 38/86 (44.2%)
- Duloxetine: 41/79 (51.9%)

Remission was defined as HAMD ≤7 at both week 10 and week 12 visits.

Note: The neuroimaging analyses were based on the 131 of the 234 study completers who had usable MRI scans at both baseline and week 12.

C. Functional MRI Acquisition and Preprocessing

The methods and results of the RSFC moderator analyses for acute treatment outcomes from PReDICT using the SCC seed have been published (Dunlop et al., 2017b). Resting state fMRI (rs-fMRI) scans were performed during the week prior to baseline (randomization) visit and repeated 1-4 days prior to the week 12 (final outcome) visit. Eyes-open scanning was performed for 7.4 minutes in a 3-T Siemens TIM Trio (Siemens Medical Systems, Erlangen, Germany). Image analysis was conducted using AFNI (Analysis of Functional NeuroImages) software package (Cox, 1996; Cox and Hyde, 1997). The standard preprocessing pipeline implemented in AFNI package was used for processing RSFC data. The rs-fMRI time series data were despiked and corrected for motion and slice-time acquisition. In our prior publication evaluating baseline scans for prediction of outcome (Dunlop et al., 2017b), scans with head motion >2 mm in any direction were excluded; for this analysis; the head motion threshold was increased to >3 mm in any direction to minimize the loss of subjects for the pre-post change analyses. Unusable scans were determined by head motion >3mm in any direction, signal drop or severe distortion artifact, as determined by visual inspection of the raw data, or head-coil artifacts, determined by visual inspection in each individual subject correlation map.

The residual head motion inferences were estimated from the result of the previous motion correction procedure. There were rigid-body 6-motion parameters including x-,y-,and z-transformation and roll, pitch, and yaw rotation. These 6-motion parameter estimates were intended to model any residual effects of movement after volume registration. The mean framewise displacement (FD) was used to evaluate the patient's head motion (Power et al., 2012). The 2-way ANOVA including interactions was tested and was not significant ($F=0.0159$, $p=0.9$). In addition, the mean FD was quite acceptable across the patients, 0.189 ± 0.115, using the >3mm criteria for maximum displacement.

The remaining effects of the noise signal, including residual head motion inferences, signal from the CSF and local white matter, were also removed and the data were simultaneously band pass filtered at 0.01 Hz–0.1 Hz to remove frequencies not implicated in RSFC. 3dBlurToFWHM in AFNI was applied for spatial smoothing up to 8 mm full-width at half-maximum. The anatomical and functional data sets were co-registered and normalized to standard Montreal Neurological Institute (MNI) 1-mm voxel space using a combination of linear and nonlinear registration.

D. Functional MRI Analysis

We applied bilateral 5mm radius spheres as seeds for each network based on seeds used in prior literature (**Figure S1**). The DMN was seeded with the PCC (MNI coordinates: ±7, -43, +33) (Sridharan et al., 2008); ECN with the DLPFC (±36, +27, +29) (Sheline et al., 2010); and SN with the anterior insula (±36, +18, +4) (Menon et al, 2015). For the Affective Network we used the same SCC seed as in our prior publications (±6, 24, –11) a volume of 485 mL each (Dunlop et al., 2017b).

Utilizing 3dNetCorr (Taylor and Saad, 2013), the mean time course of the bilateral seed was correlated voxel-wise with the rest of the brain. The voxel-wise correlation coefficients were z-scored by calculating the inverse hyperbolic tangent, yielding the seed-based RSFC maps for analysis.

We used the 17-network atlas of Yeo and colleagues (2011) to interpret the RSFC analyses. Each cluster identified as significantly correlated with one of the four seeds was mapped to Yeo's atlas to determine the network with which the cluster was associated.

Supplementary Tables

Tables S1-S4 report the within-treatment, permuted RSFC change for remitters to CBT and ADM for each of the four seeds. Each model utilized an alpha threshold of $p<0.005$, and a beta of 0.80 was chosen to keep voxels with a minimum of 80% power. Permutation consisted of whole brain voxel-wise subsampling run 1,000 times with 70% random subsamples.

Table S1. Significant changes in resting state whole brain functional connectivity using the Subcallosal Cingulate Cortex seed in remitters to CBT or ADM

Region (Seed: SCC)	MNI coordinates (Center of Mass)			Cluster size (mm^3)
	x	*y*	*z*	
CBT-specific changes				
Increased FC				
Posterior Insula	+34.5	-30.2	+13.9	88
Brainstem	+3.5	-21.3	-33.2	58
Cerebellum	-7.6	-63.3	-6.5	47
V1	+13.0	-96.3	+8.8	46
Superior Occipital	-21.1	-74.1	+24.8	34
Brainstem	-4.5	-15.8	-41.5	24
V2	+13.3	-47.8	-6.7	19
Entorhinal Cortex	+24.0	+5.1	-34.6	17
Nucleus Accumbens	+33.9	-7.5	-11.0	10
Postcentral	-53.2	-14.5	+25.9	8
V3	+26.8	-96.0	+6.2	4
Ventral Diencephalon	+12.3	-7.7	-6.7	3
Decreased FC				
mM1	**-7.6**	**-40.8**	**+68.1**	**8**
Inferior Temporal	-54.9	-11.9	-37.6	7
Postcentral / Area1	+44.7	-31.0	+58.8	6
V1	+2.4	-97.8	-11.6	5
ADM-specific changes				
Increased FC				
Brainstem	-9.1	-32.5	-42.3	31
Cerebellum	+38.8	-85.2	-25.8	18
Cerebellum	+50.8	-72.9	-28.3	17
Caudate Nucleus	+22.5	+18.8	+9.9	13
Decreased FC				
mM1	**-6.0**	**-38.3**	**+66.5**	**226**
mM1	+8.0	-41.0	+69.0	86
Superior Temporal	-50.7	-2.3	-9.5	31
mM1	-1.6	-30.4	+50.9	30
Postcentral/Area1	-40.2	-35.7	+65.4	28
Inferior Temporal	+57.5	-9.8	-27.6	22
mM1	+5.4	-26.8	+64.0	13
Postcentral/Area1	-34.8	-36.4	+70.8	11
Postcentral/Area1	-26.7	-36.3	+74.0	3

FC: functional connectivity, mM1: medial primary motor cortex, SCC: subcallosal cingulate cortex, V1: primary visual cortex, V2: second visual area, V3: third visual area.

Bold indicates regions with shared voxels in CBT and ADM remitting patients.

Table S2. Significant changes in resting state whole brain functional connectivity using the Posterior Cingulate Cortex seed in remitters to CBT or ADM

Region (Seed: PCC)	MNI coordinates (Center of Mass)			Cluster size (mm^3)
	x	*y*	*z*	
CBT-specific changes				
Increased FC				
Middle Frontal / Area46	-20.9	+55.7	+9.3	334
Posterior Putamen	-29.9	-16.1	+8.2	49
Inferior Frontal / Area44	-47.6	+19.2	-6.7	20
V1	+9.2	-70.3	+12.3	9
Posterior Insula	-36.9	-40.9	+18.4	8
V1	-3.0	-69.0	+7.5	2
Decreased FC				
Superior Frontal / Area6	-19.8	-3.8	+48.9	39
Inferior Frontal / Area11	-28.5	+30.2	-18.1	31
Superior Frontal / Area6	-18.8	+3.5	+48.2	4
Amygdala	-22.0	-2.0	-20.0	3
Lateral Occipital	+47.0	-81.5	-19.0	2
Postcentral	+69.0	-15.0	+21.5	2
ADM-specific changes				
Increased FC				
S1	+6.9	-34.5	+78.9	40
Putamen	-24.5	-13.9	+8.5	11
Cerebellum	-19.9	-65.2	-36.2	9
Postcentral	+43.0	-20.0	+37.7	7
Cerebellum	-39.4	-38.6	-38.0	5
Cerebellum	-17.2	-66.4	-34.6	5
Cerebellum	-41.5	-42.0	-39.0	2
Decreased FC				
Superior Frontal / Area9	+26.8	+67.2	+13.2	152
Inferior Temporal	-51.5	-33.7	-19.4	102
SCC	-6.9	+19.7	-10.4	34
V1	+24.1	-100.0	-12.7	33
Brainstem	+4.1	-19.8	-26.5	28
PCC	+6.5	-28.1	+37.3	16
Orbital Frontal	+9.0	+24.9	-27.2	14
Medial Frontal BA 10	-9.0	+56.0	+3.5	2

Table S3. Significant changes in resting state whole brain functional connectivity using the Dorsolateral Prefrontal Cortex seed in remitters to CBT or ADM

Region (Seed: DLPFC)	MNI coordinates (Center of Mass)			Cluster size (mm^3)
	x	*y*	*z*	
CBT-specific changes				
Increased FC				
Inferior Parietal Lobule	-39.7	-39.1	+40.6	230
Anterior Insula	-26.5	+18.4	+8.7	99
Inferior Parietal Lobule	-48.1	-39.5	+46.0	97
Superior Parietal Lobule	-23.5	-68.6	+52.2	34
Cerebellum	-20.5	-52.9	-19.3	26
S1	-35.1	-27.9	+65.7	15
Hippocampus	+35.7	-13.0	-14.7	7
Inferior Frontal	-32.0	+3.0	+29.5	2
Precuneus	-15.0	-54.0	+56.5	2
Superior Parietal Lobule	-29.0	-64.5	+58.0	2
Decreased FC				
Superior Frontal / Area9	-9.5	+53.8	+30.4	14
Orbital Frontal / Area47	+47.9	+48.2	-8.4	11
Hippocampus	+22.8	-24.3	-19.2	6
ADM-specific changes				
Increased FC				
Superior Frontal /Area8	-17.3	+22.0	+41.9	7
Decreased FC				
Inferior Temporal	+61.2	-44.6	-24.4	5
Superior Orbital	-13.3	+47.3	-21.0	3
Superior Orbital	+8.3	+65.7	-19.0	3

Table S4. Significant changes in resting state whole brain functional connectivity using the Anterior Insula seed in remitters to CBT or ADM

Region (Seed: Ant. Insula)	MNI coordinates (Center of Mass)			Cluster size (mm^3)
	x	*y*	*z*	
CBT-specific changes				
Increased FC				
Angular gyrus	-30.2	-52.8	+37.4	81
Fusiform gyrus	+38.4	-59.7	-10.1	49
Angular gyrus	+41.8	-52.5	+35.8	22
Angular gyrus	+34.9	-53.1	+35.0	22
Cerebellum	+27.4	-82.9	-21.9	16
Middle Temporal	+62.0	-17.3	-15.9	15
Putamen	-31.0	-15.7	+7.3	3
Decreased FC				
Precuneus	-6.7	-51.1	+63.4	143
Precuneus	-12.2	-58.4	+72.1	87
Thalamus	-14.8	-12.9	+11.7	30
Insula	+33.6	+0.2	+8.9	12
Cerebellum	-45.2	-53.7	-34.8	6
Thalamus	-11.0	-2.5	+4.0	2
ADM-specific changes				
No Findings				

Table S5. Changes in resting state functional connectivity of the six significant interactions identified in remitters (Figure 1C) using all completers across clinical outcome groups.

	1. DLPFC-L. Inferior Parietal Lobule			**2. DLPFC-R. Superior Parietal Lobule**			**3. DLPFC-L. Superior Parietal Lobule**		
	t value	p value	Cohen's d	t value	p value	Cohen's d	t value	p value	Cohen's d
CBT									
Remitter	**-5.65**	**<.001**	**-1.295**	**-3.94**	**<.001**	**-0.903**	**-3.72**	**0.002**	**-0.854**
Responder	-0.43	0.686	-0.175	0.46	0.668	0.186	0.123	0.907	0.050
Non-responder	-0.89	0.390	-0.229	0.63	0.539	0.163	1.247	0.233	0.322
ADM									
Remitter	**3.43**	**0.001**	**0.511**	**3.49**	**0.001**	**0.520**	**2.23**	**0.031**	**0.333**
Responder	**3.53**	**0.002**	**0.753**	**3.55**	**0.002**	**0.757**	**2.29**	**0.032**	**0.489**
Non-responder	1.40	0.176	0.285	0.18	0.860	0.036	0.11	0.917	0.022
	4. SCC-Posterior Insula			**5. Anterior Insula-Precuneus**			**6. Anterior Insula-V1**		
	t value	p value	Cohen's d	t value	p value	Cohen's d	t value	p value	Cohen's d
CBT									
Remitter	**-5.03**	**<.001**	**-1.155**	**-6.86**	**<.001**	**-1.573**	**-3.34**	**0.004**	**-0.765**
Responder	0.43	0.685	0.176	-0.16	0.882	-0.064	**4.01**	**0.010**	**1.636**
Non-responder	-0.32	0.752	-0.083	-0.82	0.424	-0.213	-1.39	0.186	-0.359
ADM									
Remitter	1.61	0.116	0.239	**2.52**	**0.016**	**0.375**	**2.70**	**0.010**	**0.402**
Responder	0.60	0.554	0.128	-1.23	0.234	-0.261	**3.36**	**0.003**	**0.716**
Non-responder	0.13	0.902	0.025	-0.89	0.383	-0.182	-0.32	0.751	-0.066

Table S5 evaluates the six connectivity patterns that emerged in the treatment-interaction effects among remitters shown in Figure 1C. The results indicate that the changes are generally specific to remitters (and, in a few cases, also responders) but are not found in non-responders.

Bold indicates significant at p<.05

Supplementary Figures

Figure S1. Seeds used for the four resting state networks

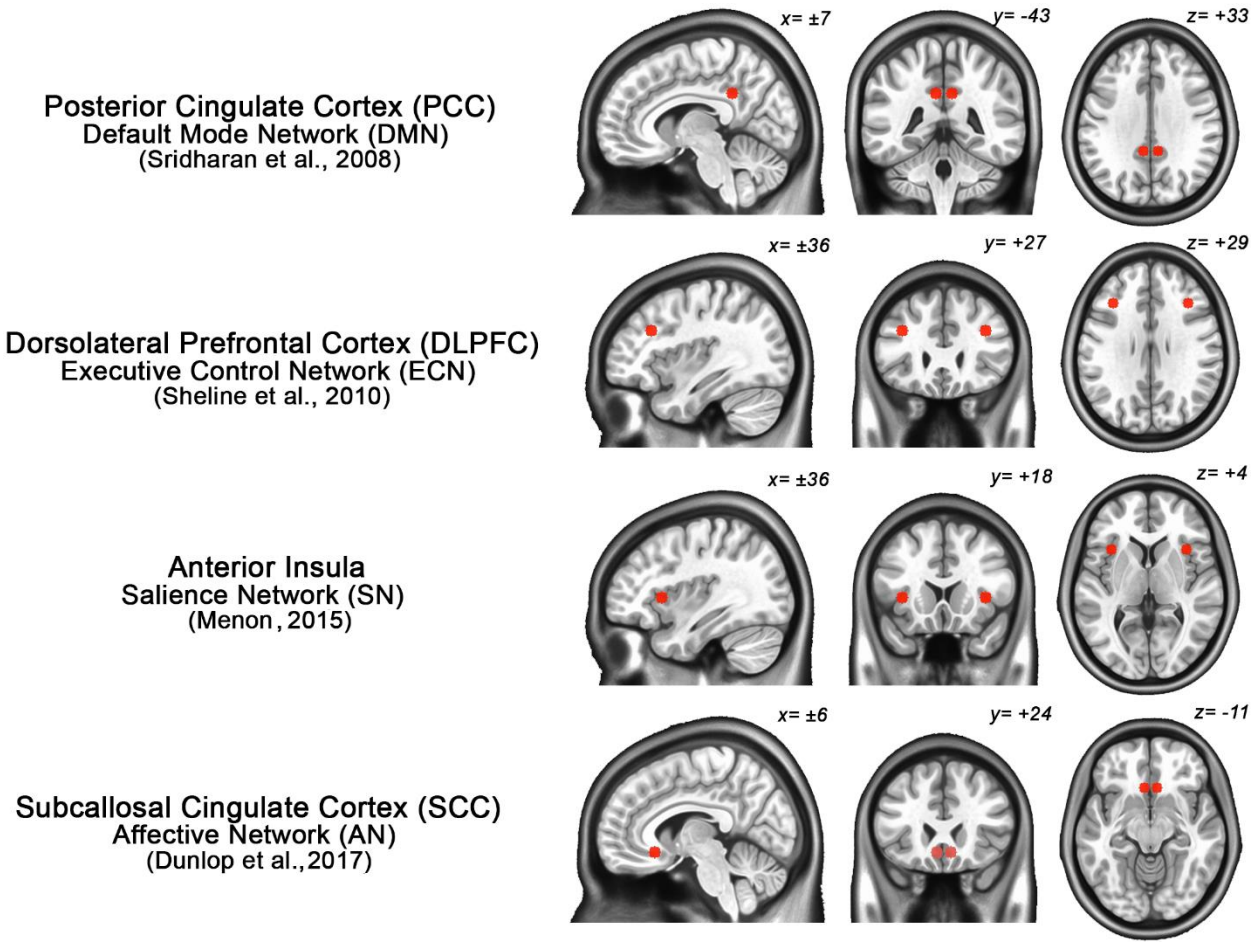


Figure S2. Changes in functional connectivity and changes in symptom severity across all study completers

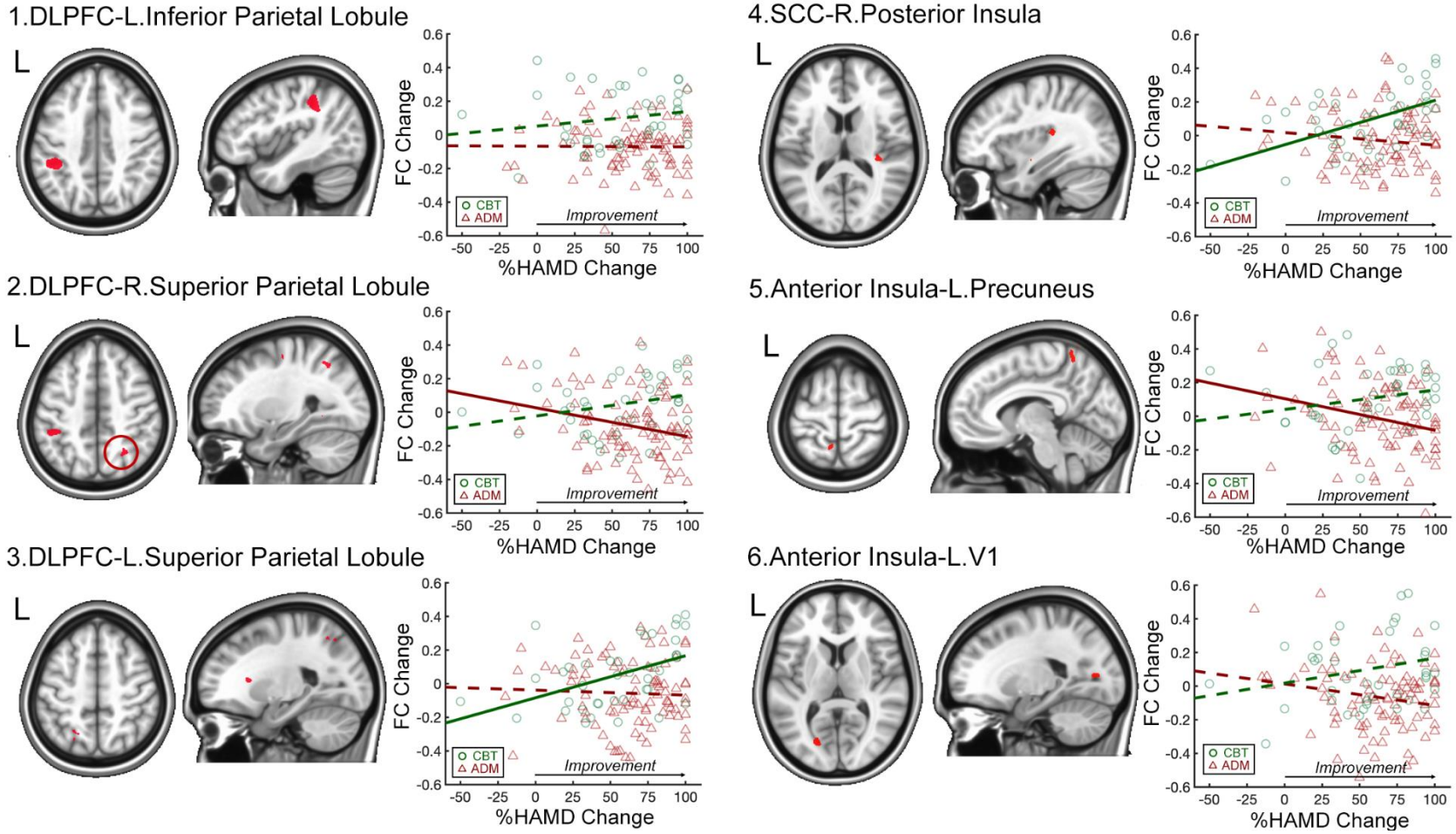


Figure S2 Legend

All-completers analysis of percent changes in HAMD score plotted against changes in RSFC in the six regions identified as having differential change in functional connectivity between ADM- and CBT-treated remitters, shown in Figure 1C.

Green circles indicate individual CBT-treated patients and red triangles indicated individual ADM-treated patients. Solid lines indicate a significant ($p<.05$) association between percent HAMD score change and RSFC change within a treatment group; dashed lines indicate this association is not statistically significant ($p>.05$).

1. For DLPFC-left inferior parietal lobule RSFC, there was no significant interaction between treatments ($F=.96$, $p=.328$) or association within patients treated with CBT ($R^2=.030$, $p=.283$) or ADM ($R^2=.000$, $p=.946$).
2. For DLPFC-right superior parietal lobule RSFC, the interaction between treatments was significant ($F=7.75$, $p=.006$), with a significant association in the ADM patients ($R^2=.065$, $p=.014$) but not the CBT patients ($R^2=.064$, $p=.114$).
3. For DLPFC-left superior parietal lobule RSFC, the interaction between treatments was significant ($F=6.53$, $p=.012$), with a significant association in the CBT patients ($R^2=.211$, $p=.003$) but not the ADM patients ($R^2=.002$, $p=.679$).
4. For SCC-right posterior insula RSFC, the interaction between treatments was significant ($F=10.88$, $p=.001$), with a significant association in the CBT patients ($R^2=.276$, $p<.001$) but not the ADM patients ($R^2=.014$, $p=.273$).
5. For anterior insula-left precuneus RSFC, the interaction between treatments was significant ($F=6.60$, $p=.011$), with a significant association in the ADM patients ($R^2=.063$, $p=.016$) but not the CBT patients ($R^2=.047$, $p=.178$).
6. For anterior insula-left V1 RSFC, the interaction between treatments was significant ($F=5.29$, $p=.023$) but not significant associations in the ADM patients ($R^2=.053$, $p=.155$) and CBT patients ($R^2=.034$, $p=.080$).

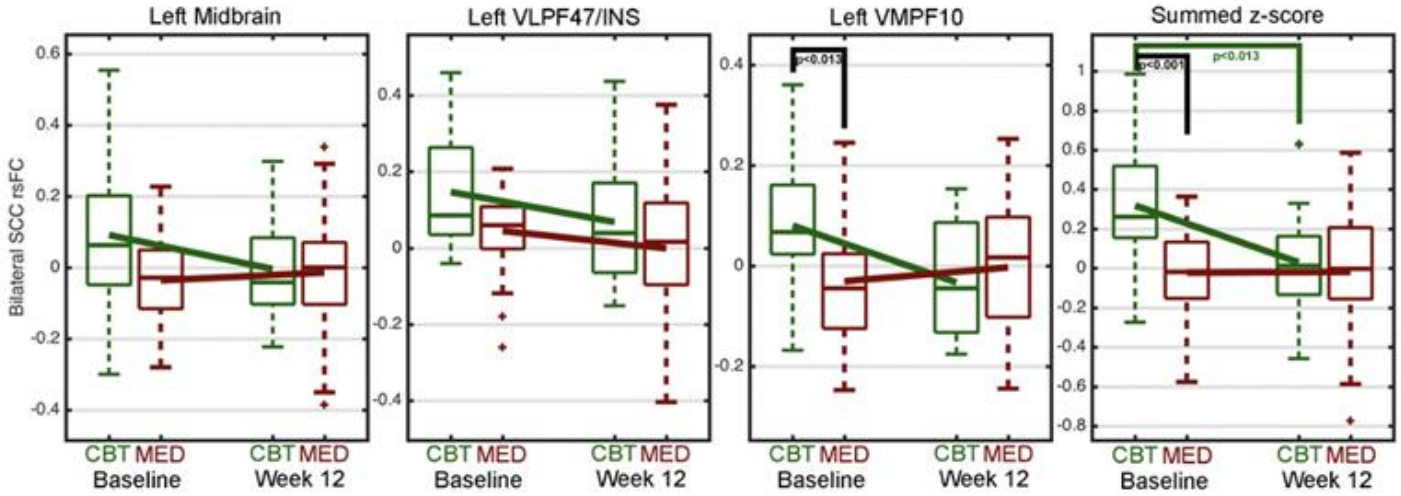
ADM, antidepressant medication; CBT, Cognitive behavior therapy; DLPFC, dorsolateral prefrontal cortex; RSFC, Resting state functional connectivity; SCC, subcallosal cingulate cortex.

Figure S3. Change in SCC Functional Connectivity Treatment Prediction Biomarker from Dunlop et al., 2017b

A. Effect of Time among all remitters

	Left Midbrain	Left VLPF47/INS	Left VMPF10	Summed z-score
p-value	0.637	0.100	0.994	0.276
Cohen's d	-0.059	-0.208	0.001	-0.137

B. Time by Treatment interaction among remitters



A. Lack of significant effect of time among all remitters (n=64) on components of the pre-treatment baseline RSFC biomarker for predicting remission or treatment failure to CBT (n=19) or antidepressant medication (MED, n=45).

B. Remitters to treatment with follow-up scans at week 12 demonstrated significant time by treatment interaction in VMPF10 (p<.014) and the summed z-score (p<.003), which was driven by the significant reduction in CBT remitters and minimal change in MED remitters.

Summed z-score was the total SCC-FC to the three significant regions, as described in Dunlop et al., 2017b.

CBT: Cognitive behavior therapy; MED: Antidepressant medication; SCC: Subcallosal cingulate cortex; VLPF47/INS: Ventrolateral prefrontal cortex Brodmann Area 47/Anterior insula; VMPF10: Ventromedial prefrontal cortex, Brodmann Area 10.

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