SUPPLEMENT

Functional Connectivity of the Subcallosal Cingulate Cortex Identifies Differential Outcomes to Treatment with Cognitive Behavior Therapy or Antidepressant Medication for Major Depressive Disorder

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Figure S1. Functional connectivity of subcallosal cingulate cortex for remitters and treatment failures with escitalopram and duloxetine individually versus cognitive behavior therapy

Resting state functional connectivity analyses by outcome for patients treated with either escitalopram or duloxetine versus CBT identified functional connectivity differences in the same regions as found through the analysis using both drugs combined (see Figure 1). Escitalopram vs CBT contrasts are displayed on the left (panels A, C, E); duloxetine vs CBT contrasts are displayed on the right (panels B, D, F).

R: Remitter; TF: Treatment Failure

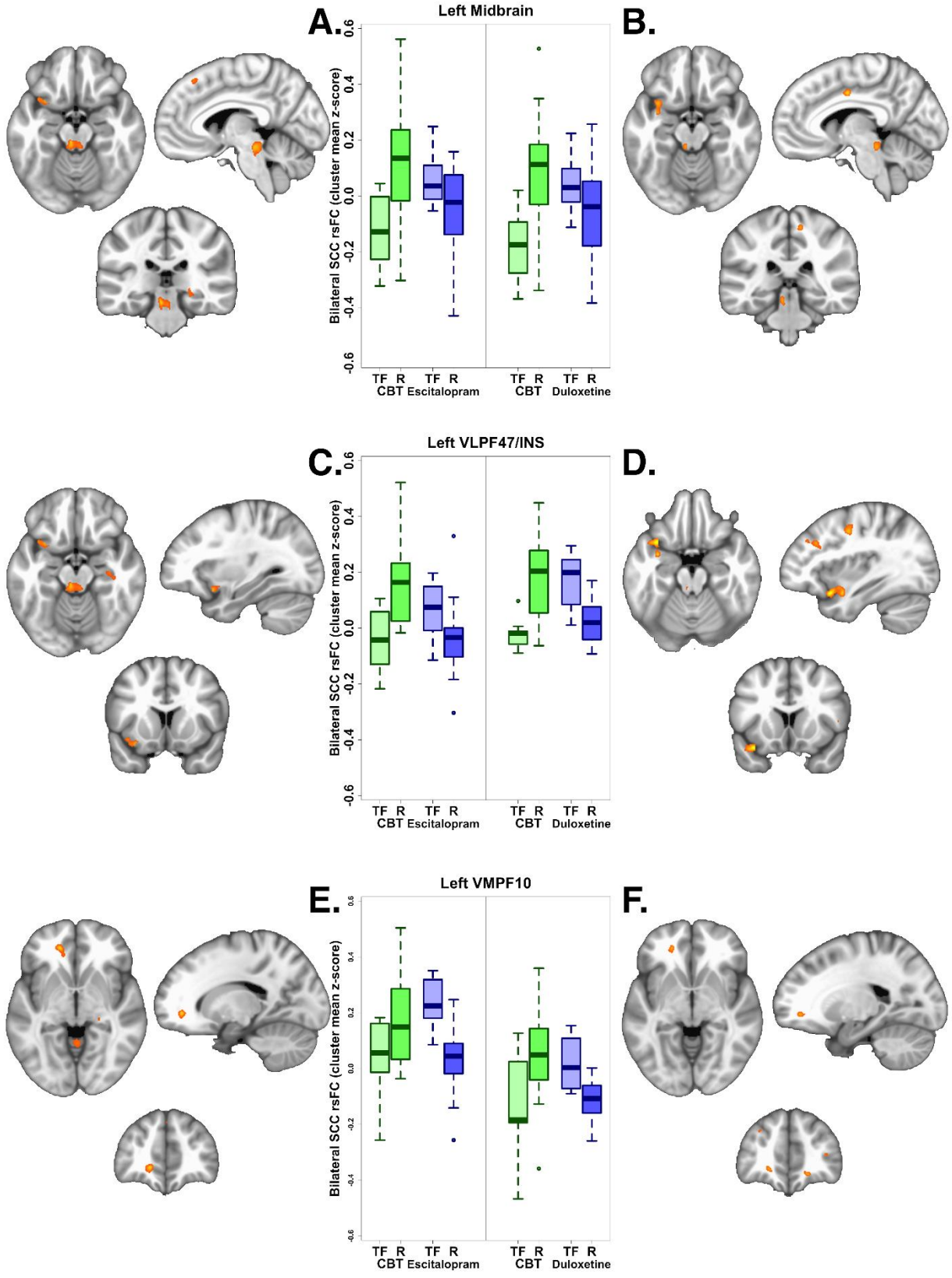
A.
Left Midbrain
B.
C.
Left VLPF47/INS
D.
E.
Left VMPF10
F.
Bilateral SCC rsFC (cluster mean z-score)
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
TF R TF R
CBT Escitalopram
TF R TF R
CBT Duloxetine

Figure S2. Prediction of Outcome to Phase 2 Combination Treatment among Phase 1 Treatment Failures

Patients who did not remit to their initial Phase 1 treatment could enter another 12 weeks of care (Phase 2) in which they received combination treatment. Patients who received CBT in Phase 1 started escitalopram while receiving CBT booster sessions, and those who received medication in Phase 1 continued on their medication (either escitalopram or duloxetine) and started the 16-session course of CBT. Too few patients with usable baseline MRIs completed combination treatment to permit statistical testing, but they are plotted here to visually represent the outcomes. Symbols representing Phase 2 combination treatment outcomes are placed within the triangles that reflect the subjects' Phase 1 treatment outcomes. Among the Phase 1 treatment failure patients, diamonds represent remission with combination treatment, Xs represent treatment failure, squares represent intermediate response between treatment failure and remission, and triangles without symbols represent patients who did not complete Phase 2 combination treatment. Patients achieving remission after addition of the second treatment tended to have summed functional connectivity scores further from the 0.1 z-score cut-point (i.e., had scores more strongly predictive of remission to CBT or medication) than non-remitters, who tended to cluster near the cut-point.

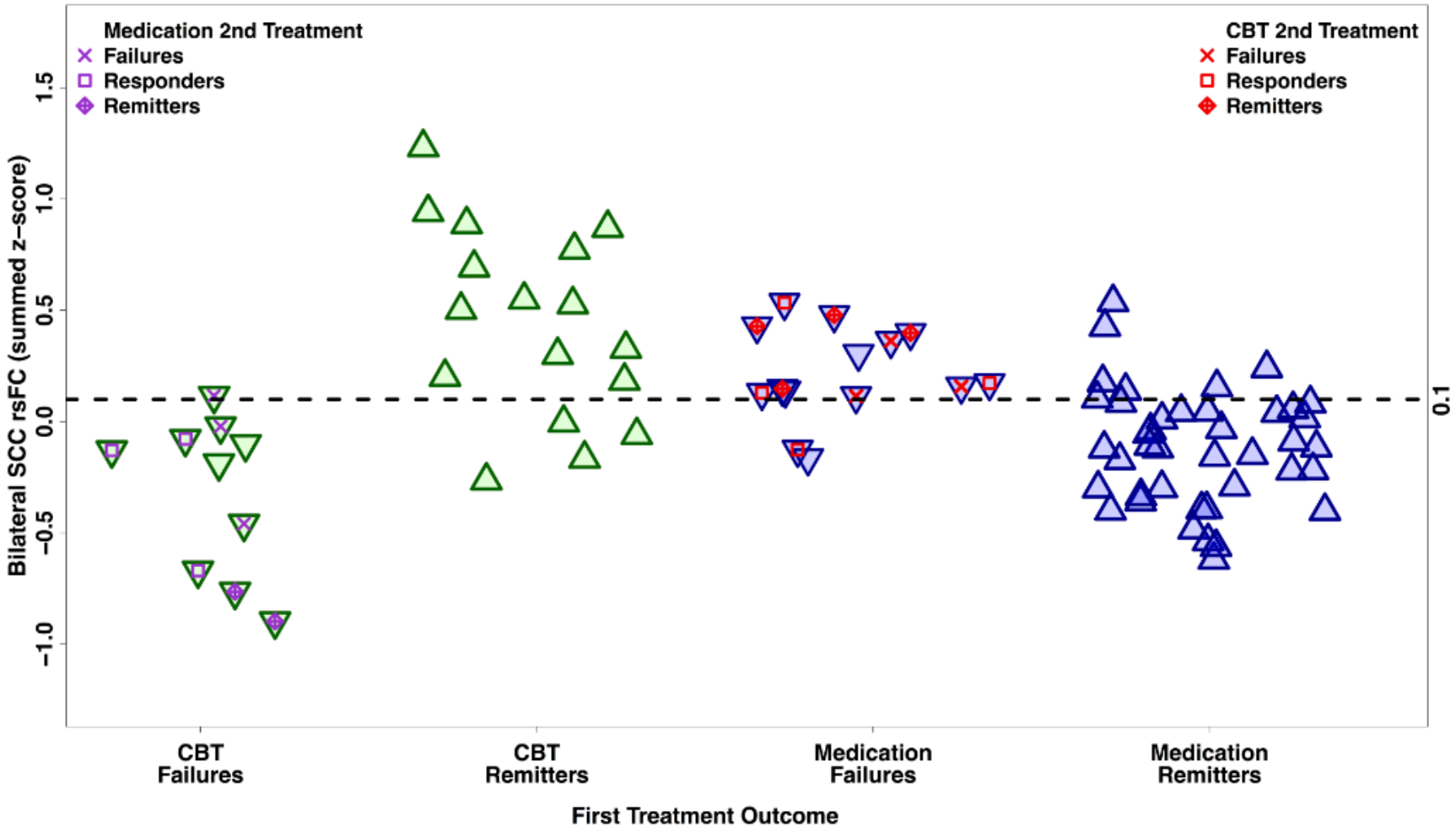
Medication 2nd Treatment
Failures
Responders
Remitters
CBT 2nd Treatment
Failures
Responders
Remitters
Bilateral SCC rsFC (summed z−score)
1.5
1.0
0.5
0.0
−0.5
−1.0
0.1
CBT Failures
CBT Remitters
Medication Failures
Medication Remitters
First Treatment Outcome

Table S1. Overall prediction of outcomes across all Phase 1 treatments

In order to facilitate comparison of the PReDICT sample with prior imaging studies that examined response/non-response outcomes to single or multiple treatments, we performed a similar analysis on all patients with usable fMRI scans (N = 122). Patients were categorized in two groups based on whether they achieved response, defined as ≥ 50% reduction in HDRS score from baseline to week 12, regardless of treatment. Note, in this analysis, "non-response" is defined in the traditional manner of clinical trials, (i.e., < 50% decrease from baseline), which is broader than the definition of treatment failure (< 30% decrease from baseline) used in the primary analysis. We also compared all remitters versus all treatment failures across both treatments. For these contrasts, we compared the resting state functional connectivity of the bilateral SCC seeds using whole-brain t-tests, using a threshold of $p < 0.001$ to identify functionally connected regions. We report significant clusters that exceeded the 300 voxel minimum.

In the responder versus non-responder analysis, responders showed significantly greater SCC functional connectivity with the post-central gyrus, and significantly lower functional connectivity with the superior frontal gyrus.

In the remitter versus treatment failure analysis, remitters showed significantly lower SCC functional connectivity with both the right pre-central gyrus and posterior putamen.

All Responders (n=81) vs Non-Responders (n=41)

		MNI Coordinates, Peak					
Region	**BA**	**X**	**Y**	**Z**	**Side**	**Cluster Size (1 mm voxels)**	**Peak Voxel p-value**
Post-central gyrus	3	36	-36	62	R	483	0.00069
Superior frontal gyrus	9	24	41	39	R	317	0.00166

All Remitters (n=58) vs All Treatment Failures (n=24)

		MNI Coordinates, Peak					
Region	**BA**	**X**	**Y**	**Z**	**Side**	**Cluster Size (1 mm voxels)**	**Peak Voxel p-value**
Pre-central gyrus	6	51	-8	23	R	903	0.00106
Posterior putamen	--	32	-9	11	R	686	0.00056

BA: Brodmann Area