Supplemental Information

Supplemental Methods & Materials

Remitted Patient Recruitment

Patients were recruited from a larger study on relapse prophylaxis in recurrent depression; the methods for their recruitment are published in detail as part of a larger study (1), but are also summarized below. Patients were recruited through clinical referrals, physician outreach, and media announcements describing the Mood Disorders Clinics at the Centre for Addiction and Mental Health and St. Joseph's Hospital in Toronto, Ontario, Canada. Written informed consent was obtained in accordance with the requirements of the Centre for Addiction and Mental Health, University of Toronto, and Baycrest Hospital Human Research Ethics Committees. There were 2 study phases, an acute phase in which patients were referred to the study, and a follow-up phase following successful remission of symptoms.

During the acute phase of depressed patient referral, patients were assessed for diagnostic eligibility for the study. Eligibility was determined by means of the Structured Clinical Interview for DSM-IV diagnosis (Axis I and II) (SCID), as well as the first 17 items of the Hamilton Rating Scale for Depression (HRSD).

Inclusion criteria were as follows: 1) diagnosis of MDD according to DSM-IV criteria; 2) a score of 16 or higher on the HRSD; 3) 2 or more previous episodes of MDD; 4) age between 18 and 65 years; and 5) English speaking and the ability to provide informed consent. Exclusion criteria were: 1) current diagnosis of bipolar disorder, substance abuse disorder, schizophrenia, or borderline or antisocial personality disorder; 2) a trial of electroconvulsive therapy within the past 6 months; 3) depression secondary to a concurrent medical disorder; 4) current or planned

pregnancy within 6 months of acute-phase treatment; and 5) current practice of meditation more than once per week or yoga more than twice per week. From 478 total patients considered for the study, 160 were declared eligible for participation, of which 16 were randomly recruited for participation in the current study.

Acute Phase. In the first phase of the study, all patients were treated with antidepressant medication, beginning with a default of citalopram in step 1, and switching to alternative medications in the case of drug intolerance or a documented history of serotonin reuptake inhibitor failure. In our cohort of 16 patients, 12 patients were treated with citalopram, 2 with venlafaxine hydrochloride, 1 with sertraline hydrochloride, and 1 with escitalopram.

Remission Criteria. All patients included in the study met the primary criteria for remission of treatment response (50% reduction in HRSD score) and clinical remission (HRSD score, ≤ 7 for 8 weeks), and were treated for 5 additional months to ensure full remission. Patients met with their study psychiatrist biweekly for the first 8 weeks and monthly thereafter. The actual average duration of remission before study inclusion (in which HRSD scores were < 7) was 142 days (> 20 weeks). Relapsers were in remission for slightly longer than sustained remitters (156 days on average vs. 119 days), but this difference was non-significant ($p > .10$).

Relapse Criteria. Patients who scored 16 or higher on the 17-item HRSD at a scheduled physician visit were re-interviewed in a week's time, and, if their scores were in the same range, they were then assessed with the SCID to determine whether their level of symptoms met criteria for MDD. Patients were also encouraged to call the clinic if they were concerned that depressive symptoms were reemerging, in which case an ad hoc assessment was scheduled as

soon as possible. Patients were judged to have an episode of major depression if they had a score of 16 or higher for 2 consecutive weeks at any time during the follow-up phase and they met criteria on the SCID depression module for that specific interval.

Measures

We employed two behavioral measures to index adaptive and maladaptive cognitive modes in the face of emotional challenge: acceptance and rumination. We also employed a behavioral measure of depressive severity to provide a more sensitive index of long term depressive affect than the bivariate outcome of relapse vs. sustained remission. Descriptions of the psychometric properties of these three measures are provided below.

Acceptance and Action Questionnaire (AAQ; 2). The AAQ is a 9-item, 7-point Likert scale style questionnaire measuring 'experiential avoidance', or participant tendency towards adaptive (non-judgmental) cognition during dysphoric feeling states. Scores range from 9-63, with an internal consistency of $\alpha = .70$ across both clinical and community samples. The AAQ is widely used as an index for adaptive, non-ruminative cognition in the face of stress.

Response Style Questionnaire (RSQ; 3). The short form of the RSQ is a 10 item, 7-point Likert scale style questionnaire measuring ruminative tendencies in response to negative moods. The scale has high internal consistency ($\alpha > .87$, 12), and good test-retest reliability ($r_{tt} > .5$) in both community and remitted depressed samples (4). The RSQ is positively related to neuroticism and negatively related to extraversion although it achieves discriminant validity from both of these constructs (5).

HRSD (6). The HRSD is a 17-item, 5-point Likert scale style questionnaire measuring symptoms of depression experienced over the past week. Scores range from 0 to 68; scores of 0-7 constitute the normal range, and scores of 20 or higher usually indicate at least moderate severity depression. Patient depression status was assessed through clinical interview rather than from an HRSD cutoff score, allowing HRSD scores to serve as a fluid indicator of depression symptom severity unconstrained by relapse status.

Additional Information on Experimental Design

Sets of film clips were always shown in the order neutral/sad in run 1 and sad/neutral in run 2 to limit emotional contagion between blocks and to control for confounding effects related to scanner drift. A sample run would involve presentation of the four neutral film clips (45 sec each) interleaved with reflection periods between each clip (30 sec each), followed by a resting state period for 36 seconds, then followed by 4 sad film clips interleaved with rest periods. Prior to each set of film clips a 10 second instruction screen appeared to orient the participant to the viewing task. Questionnaire data was collected in separate interviews at the Centre for Addiction and Mental Health.

Additional Information on Imaging Parameters

Setup. Imaging data were collected with a Siemens Trio 3.0-Tesla scanner operating at a slew rate of 400 T/m/s and a 12-channel asymmetric gradient head coil. The block design experiment was designed and implemented using the Visual Basic programming language (version Visual Studio 2005; Redmond, WA; Microsoft). Prior to scanning, participants were

provided with instruction and practice on the fMRI task. Low-amplitude transistor-transistor logic (TTL) pulses were monitored via a parallel port cable to synchronize slice acquisition and stimulus delivery with sub-millisecond accuracy. Stimuli were presented on a rear-mounted projection screen, set at a (native) 1024 x 768 resolution.

Structural Imaging. For each participant, a 3D magnetization prepared rapid gradient echo pulse (MP-RAGE) sequence was employed to obtain a high-resolution T1-weighted structural volume. The imaging parameters were as follows: repetition time (TR) = 2000 ms; echo time (TE) = 2.63 ms; matrix = 256 x 160; field of view (FOV) = 256 x 256; slice thickness = 1 mm; 160 axial oblique slices; total acquisition time = 6.5 minutes.

Functional Imaging. For each subject, a T2*-weighted gradient-echo echo-planar image (EPI) pulse sequence was prescribed and higher order shimmed for the functional trials. The EPI parameters were as follows: TE = 30 ms; TR = 2000 ms; flip angle = 270°; acquisition matrix = 64 x 64; FOV = 200 mm. Thirty axial oblique slices of the brain were acquired at each time point, with a voxel resolution of 3.1 x 3.1 x 5 mm, no skip between slices. In each of the two experimental runs, 404 time points were collected, of which the first 5 and last 2 were discarded (for a total of 794 reconstructed time-points).

Supplemental Results

Patient Relapse

Ten of 16 MDD history patients experienced relapse during the follow-up period. Patients relapsed, on average, 25 weeks into the 72 week (18 month) follow-up period, but with a wide deviation between patients (minimum relapse time 4 weeks, maximum 68 weeks, standard deviation = 21 weeks).

Patient Characteristics During Follow-Up

As part of the study protocols, all patients received antidepressant medication without psychotherapy up to remission, through the remission monitoring period, and at the time of neuroimaging. Following neuroimaging, patients were randomly assigned to continued antidepressant treatment (*n* = 4), antidepressant discontinuation and mindfulness-based cognitive therapy (MBCT; *n* = 8), or antidepressant discontinuation and placebo treatment (*n* = 4). However, patients did not differ in relapse risk based upon their treatment status following neuroimaging assessment, with 3, 5, and 3 patients from the antidepressant, MBCT, and placebo groups respectively relapsing, $\chi^2(2) = .2$, *n.s.* Additional analyses controlling for patient treatment did not lower the predictive power of the neural regions to predict relapse status.

Maximum HRSD as a Continuous Indicator of Relapse

HRSD scores were analyzed over the follow-up period. Since the follow-up periods were of different length for relapsing patients, i.e., follow-up was discontinued once relapse was documented, HRSD scores were divided into interview quartiles to allow for comparisons between sustained remission and relapsing subgroups of the previously depressed patient group.

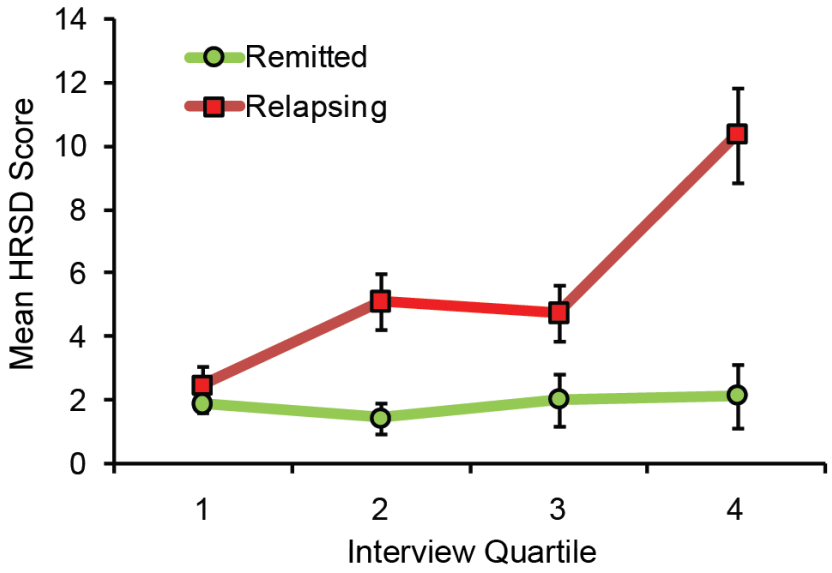

Figure S1. Hamilton Rating Scale for Depression (HRSD) as a continuous indicator of relapse.

As suggested from Figure S1, HRSD score maximums occurred in the fourth quartile of the follow-up period 100% of the time in the 10 patients who relapsed during follow-up. Furthermore, HRSD score maximum was a better predictors of relapse status (r_{14} = .73) than were initial HRSD scores (r_{14} = .00), and HRSD change scores over the follow-up period (r_{14} = .68). Maximum HRSD scores were similar, but marginally better predictors of relapse than final HRSD scores in the week preceding relapse (r_{14} = .72), as some participants demonstrated slightly lower HRSD scores than their maximum scores in the week immediately preceding relapse.

Between Groups Comparisons of the Neural Response Associated with Emotional Reactivity

Emotional reactivity (ER) blood oxygen level-dependent (BOLD) response maps were compared between the patient and control groups in a 2 (group) between x 2 (film mood)

within mixed model ANOVA. Given the powerful effects of ER (Sad – Neutral films), between groups comparisons were performed at a height threshold of $P < .001$ and a cluster corrected FDR threshold of $P < .05$.

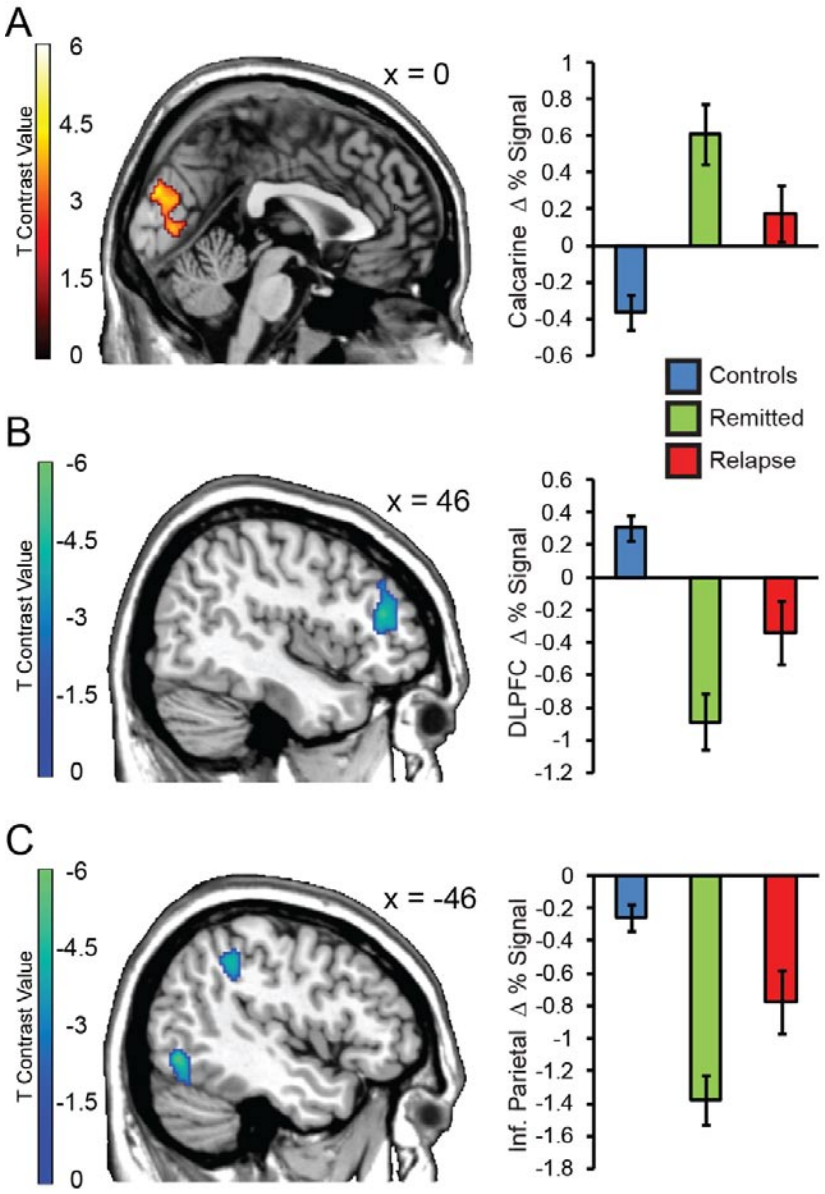

Figure S2. Between groups comparisons of emotional reactivity (ER). **(A)** The lone increased region of ER response in patients in the calcarine and surrounding visual cortex. **(B)** The right dorsolateral prefrontal cortex (DLPFC) and **(C)** the left inferior parietal and left fusiform cortex all demonstrated suppressed ER responses compared to the control group.

Four regions differed in ER BOLD responses between groups, summarized in Figure S2. Patients demonstrated heightened ER responses in the visual cortices, centered on the left calcarine gyrus (BA 17/18, at peak height: x = -6; y = -78, z = 4). Three regions of suppressed ER BOLD responses were found for the patient group as well: the right dorsolateral prefrontal cortex (BA 45, at peak height: x = 46; y = 36, z = 18), the left inferior parietal cortex (BA 40, at peak height: x = -46; y = -42, z = 42), and the left inferior occipital cortex (BA 19/37, at peak height: x = -44; y = -76, z = -8). At subthreshold levels, it should be noted that greater bilateral thalamic responses were also found for the control relative to patient groups.

Table S1. Neural Correlates of Emotional Reactivity

Anatomic Region	BA	Side	Cluster Size	Peak Z	x	y	z (mm)
Control Group							
Paralimbic Cluster		B	8393				
Caudate	-	B		6.22	14	4	18
Putamen	-	B		5.90	26	6	-6
Thalamus	-	B		5.55	2	-10	14
Frontal Operculum / Insula	47 / 48	B		5.20	34	26	-10
DLPFC	9	R		4.60	40	20	30
Middle Temporal	21	L	267	5.76	-56	-22	-16
Cerebellum (Culmen)	-	B	685	5.59	0	-50	-18
Precuneus / Post. Cingulate	31 / 23	B	2212	5.48	2	-52	24
DMPFC	32	B	2067	5.28	8	18	56
Temporal Parietal Junction	40 / 22	R	2200	4.93	60	-42	24
Temporal Parietal Junction	40 / 22	L	1143	4.84	-60	-50	20
Occipitotemporal	37	R	162	4.55	40	-46	-22
Amygdala	-	L	32	4.52	-24	-2	-24
Fuisiform (Temporal)	20	R	510	4.26	48	-28	-16
Amygdala	-	R	44	4.18	26	-4	-22
Cerebellum (Declive)	-	R	138	3.71	-40	-64	-22
DLPFC	9	R	223	3.43	-38	10	32
DMPFC	8	R	41	3.34	16	52	38
MDD Group							
Precuneus / Extrastriate	7	B	3521	5.44	-4	-54	38
Middle Temporal	39	L	802	5.41	-52	-70	28
Fusiform (Temporal)	20	R	240	4.97	50	-10	-24
DMPFC	8	B	3526	4.95	4	50	44
Operculum / Ant. Insula	47 / 48	R	639	4.87	44	28	0
Operculum / Ant. Insula	47 / 48	L	796	4.74	-40	26	-8
Cerebellum (Lingual)	-	L	443	4.43	-4	-48	-12
Caudate	-	B	939	4.29	6	10	4
Amygdala	-	R	101	4.28	34	-6	-20
Supramarginal (Inf. Parietal)	40	R	1589	4.24	58	-52	22
Middle Cingulate	23	-	290	3.82	0	-18	32
Parahippocampal	30	R	168	3.57	26	-46	10
Insula	48	L	32	3.47	-34	6	2
Thalamus / Caudate	-	R	105	3.28	12	-8	18
DLPFC	9	R	132	3.23	36	12	28
Supplementary Motor	6	-	40	3.23	4	10	54
DLPFC	9	L	30	3.13	-34	14	32
Supplementary Motor	6	R	39	3.10	48	-2	44

Ant., anterior; B, bilateral; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; Inf., inferior; L, left; Post., posterior; R, right.
In the case of bilateral activations, the peak listed is for the side with the greater peak activation.

Supplemental References

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