Original Investigation

Self-blame–Selective Hyperconnectivity Between Anterior Temporal and Subgenual Cortices and Prediction of Recurrent Depressive Episodes

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IMPORTANCE Patients with remitted major depressive disorder (MDD) were previously found to display abnormal functional magnetic resonance imaging connectivity (fMRI) between the right superior anterior temporal lobe (RSATL) and the subgenual cingulate cortex and adjacent septal region (SCSR) when experiencing self-blaming emotions relative to emotions related to blaming others (eg, "indignation or anger toward others"). This finding provided the first neural signature of biases toward overgeneralized self-blaming emotions (eg, "feeling guilty for everything"), known to have a key role in cognitive vulnerability to MDD. It is unknown whether this neural signature predicts risk of recurrence, a crucial step in establishing its potential as a prognostic biomarker, which is urgently needed for stratification into pathophysiologically more homogeneous subgroups and for novel treatments.

OBJECTIVE To use fMRI in remitted MDD at baseline to test the hypothesis that RSATL-SCSR connectivity for self-blaming relative to other-blaming emotions predicts subsequent recurrence of depressive episodes.

DESIGN, SETTING, AND PARTICIPANTS A prospective cohort study from June 16, 2011, to October 10, 2014, in a clinical research facility completed by 75 psychotropic medication–free patients with remitted MDD and no relevant comorbidity. In total, 31 remained in stable remission, and 25 developed a recurring episode over the 14 months of clinical follow-up and were included in the primary analysis. Thirty-nine control participants with no personal or family history of MDD were recruited for further comparison.

MAIN OUTCOMES AND MEASURES Between-group difference (recurring vs stable MDD) in RSATL connectivity, with an a priori SCSR region of interest for self-blaming vs other-blaming emotions.

RESULTS We corroborated our hypothesis that during the experience of self-blaming vs other-blaming emotions, RSATL-SCSR connectivity predicted risk of subsequent recurrence. The recurring MDD group showed higher connectivity than the stable MDD group (familywise error–corrected $P < .05$ over the a priori SCSR region of interest) and the control group. In addition, the recurring MDD group also exhibited RSATL hyperconnectivity with the right ventral putamen and claustrum and the temporoparietal junction. Together, these regions predicted recurrence with 75% accuracy.

CONCLUSIONS AND RELEVANCE To our knowledge, this study is the first to provide a robust demonstration of an fMRI signature of recurrence risk in remitted MDD. Additional studies are needed for its further optimization and validation as a prognostic biomarker.

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Patients with remitted major depressive disorder (MDD) are at increased risk of developing further episodes over their lifetime.[1] Why some patients remain stable while others develop a recurrent episode, however, is elusive. Therefore, there is an urgent need to develop biomarkers of recurrence risk to stratify remitted MDD into pathophysiologically and prognostically more homogeneous subgroups. Mapping the neuroanatomical bases of cognitive and emotional functions using functional magnetic resonance imaging[2] (fMRI) is the most promising approach to bridge the gap between clinical symptoms and psychosocial and molecular genetic bases of MDD.[3] Such imaging biomarkers serve the development of refined disease models and of novel treatments.

One central feature of cognitive models of vulnerability to MDD is a tendency to overgenerally blame oneself for negative events occurring in one's personal life[4,5] (eg, "My relationship failed; therefore, I am a total failure"). In support of these models, self-blaming emotional biases remained detectable in remitted MDD,[6,7] and dormant self-critical attitudes are associated with recurrence risk.[8] Proneness to experience self-blaming emotions such as guilt was reproducibly associated with activation of the subgenual cingulate cortex and adjacent septal region (SCSR) in healthy individuals.[9-11] Furthermore, the SCSR exhibited abnormal metabolism in patients with current MDD,[12,13] and its normalization and its deep brain electrode-based modulation[14] were associated with remission,[15] underscoring its central pathophysiological importance. Moreover, SCSR activation predicts outcomes of cognitive therapy,[16] which tackles overgeneralized self-blame as central to depressive thinking.[5]

The SCSR, however, is only part of a brain network relevant for self-blaming emotions and MDD. Using fMRI, our group demonstrated that proneness toward self-blaming emotions in healthy individuals was associated with increased functional connectivity between the SCSR and the right superior anterior temporal cortex (RSATL),[17] which we had previously demonstrated to enable differentiated interpretations of the meaning of social behavior[18,19] (eg, differentiating actions as "impolite," or "absent-minded" rather than just overgeneralized as "bad"). A subsequent study[10] confirmed our group's hypothesis[17] that patients with remitted MDD exhibit lower functional connectivity between the RSATL and SCSR when experiencing self-blaming emotions (eg, "guilt") relative to other-blaming emotions (eg, "indignation or anger" toward others) during fMRI. These results provided a specific neural mechanism that can account for biases toward overgeneralized self-blaming emotions[20] (eg, feeling "self-disgust" or "guilty for everything") and the resulting feelings of worthlessness[4] in MDD. It is unknown, however, whether these abnormalities prospectively predict risk of recurrence. Prospective prediction of clinical outcomes from the presence of an imaging abnormality is a crucial step in establishing its potential causal role in the pathophysiology of MDD and its promise as a prognostic biomarker that could be used as a novel treatment target.[21,22]

Herein, we addressed this question by using our group's previous fMRI paradigm to investigate functional connectivity of temporo-fronto-subcortical networks at baseline in psychotropic medication–free individuals with remitted MDD to predict subsequent recurrence over 14 months of clinical follow-up. Participants were asked to make emotional judgments about sentences evocative of self-blaming emotions (eg, "Tom [participant's name] acts greedily toward Sam [best friend's name]") and emotions related to blaming others (ie, other-blame) (eg, "Sam acts greedily toward Tom"). We also recruited a closely matched control group with no personal or family history of psychiatric disorders to determine whether fMRI signatures predictive of recurrence also differed from those of the control group.

We used psychophysiological interaction (PPI) analysis, an established measure of functional connectivity,[23] to test the hypothesis that RSATL-SCSR connectivity for self-blaming relative to other-blaming emotions would predict risk of recurrence in MDD. Based on our group's previous cross-sectional study[10] in remitted MDD, our more specific prediction was to find lower connectivity in the MDD group with a recurring episode compared with the stable remission group and the control group. We further hypothesized that self-blame–selective RSATL-SCSR connectivity would show a predictive effect independent of established clinical predictors[24] such as residual symptoms as measured on the Montgomery-Åsberg Depression Rating Scale[25] (MADRS) and the number of previous episodes. This hypothesis was based on the expectation that the neural basis of vulnerability to recurrence is at least partly independent of incomplete remission and scarring effects of previous episodes.[26]

Methods

Participants

This prospective cohort study from June 16, 2011, to October 10, 2014, in a clinical research facility was approved by the South Manchester National Health Service Research Ethics Committee. All participants gave informed consent (verbal for telephone prescreening and written for all other stages) and were compensated for their time and travel costs (eMethods, eTable 1, and eTable 2 in the Supplement).

Inclusion criteria for the MDD group were MDD, according to *DSM-IV-TR*,[27] in remission for at least 6 months (eTable 3 in the Supplement). Main exclusion criteria were current Axis I disorders, including a history of substance or alcohol abuse, and past comorbid Axis I disorders being the likely cause of depressive symptoms (eMethods in the Supplement). The healthy control group had no current or past Axis I disorders and no first-degree family history[28] of MDD, bipolar disorder, or schizophrenia. Both groups were psychotropic medication free, right-handed, and native English speaking, with normal vision or vision corrected to normal.

After the initial clinical assessment (eTable 4 and eTable 5 in the Supplement), 138 eligible and available control subjects and participants with MDD underwent fMRI. Participants with MDD were subsequently followed up clinically at 3, 6, and 14 months in person or over the telephone using the well-validated Longitudinal Interval Follow-up Evaluation interview for *DSM-IV*[29] (LIFE-IV) (eMethods in the Supplement). Raters

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(K.E.L., C.I.W., and R.Z.) were blinded to the fMRI results and had received training by the developers of the LIFE-IV. Interrater reliability was excellent (eTable 6 in the Supplement).

The fMRI data from 12 participants (7 MDD and 5 control) had to be excluded before analysis because of excessive head movement or excessive signal loss (eMethods in the Supplement). Six participants with MDD were lost to follow-up. Of the included 75 psychotropic medication–free patients with remitted MDD, 37 remained in remission (ie, stable MDD group), 27 developed a recurrent major depressive episode (MDE) (ie, recurring MDD group), and 11 developed significant symptoms not meeting MDE criteria (ie, subthreshold MDD group in eMethods in the Supplement) over the 14-month clinical follow-up period. For the primary imaging analysis, we focused on the 31 stable participants, 25 recurring participants, and 39 control subjects meeting the strictest imaging quality control threshold (eMethods, eFigure, and eTable 2 in the Supplement). To probe generalization of our results to the whole sample, we extracted the SCSR cluster averages,[30] including those additional 10 MDD participants and 2 control group participants whose imaging data did not pass the strictest quality control threshold (ie, exhibiting greater movement or signal dropout outside the SCSR) and the subthreshold MDD group.

fMRI Acquisition and Paradigm

We used the same fMRI protocol (3-T Achieva; Philips) (eMethods in the Supplement) optimized for detection of ventral brain regions as described previously.[10] The T1-weighted 3-dimensional MRIs were acquired for coregistration and axial T2-weighted images to rule out vascular and inflammatory abnormalities (eMethods in the Supplement).

As in our group's previous study,[10] participants saw sentences containing social concepts (eg, "stingy" or "impatient") describing actions counter to sociomoral values. The agent was the participant (self-agency condition [n = 90]) or his or her best friend (other-agency condition [n = 90]). Self-agency and other-agency conditions contained the same social concepts. Participants were required to report how unpleasant they would feel ("mildly" or "very") by pressing a button within 5 seconds, followed by a jittered intertrial interval with a mean duration of 4 seconds. A low-level resting-state baseline condition (null condition) requiring no response (n = 90) was pseudorandomly interspersed across 3 runs whose order was counterbalanced across participants.

After the imaging session, participants rated the degree of unpleasantness on a 7-point Likert-type scale (1 is not unpleasant, and 7 is extremely unpleasant) associated with each stimulus. In addition, they were asked to "choose the feeling that they would feel most strongly" from different self-blaming and other-blaming emotions as previously reported.[7] Self-blaming and other-blaming emotion trials for the fMRI analysis were defined as those that were perceived as highly unpleasant (those rated at the individual median or above) in the respective self-agency and other-agency conditions.

Behavioral Data Analysis

Behavioral data were analyzed using 2-sided $P = .05$. A statistical software program was used (SPSS Statistics 20; IBM).

Image Analysis

Functional images were realigned, unwarped, coregistered to the participant's T1-weighted images, and normalized to the SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) template using the transformation parameters for the T1-weighted image. A smoothing kernel of 6-mm full-width at half maximum was then applied.

To measure functional connectivity, we used the well-established PPI analysis,[23] which requires the extraction of the signal from a seed region (in this case, the RSATL) and the creation of an interaction term for the psychological variable (main effect of condition) with the physiological variable (the RSATL signal time course irrespective of condition). As shown previously,[10] we used the RSATL seed region coordinates (Montreal Neurological Institute peak coordinates, 58, 0, −12; 6-mm sphere) shown to be equally activated for self-blaming and other-blaming emotions,[10,17] which is ideal for a PPI seed region by avoiding confounding coactivation and connectivity differences between conditions to be expected in the SCSR. A PPI effect is a change in the slope of the regression effect of the RSATL on another brain area for one condition (eg, self-blame) relative to another (eg, other-blame).

To investigate our main hypothesis, between-group differences on the contrast self-blaming vs other-blaming emotions were thresholded at $P = .005$ (uncorrected voxel level). They were then corrected for familywise error at cluster level or voxel level at $P = .05$ over the a priori SCSR ROI (Montreal Neurological Institute peak coordinates, −4, 23, −5; 6-mm sphere) (eMethods in the Supplement) or the whole brain.

All analyses were inclusively masked with a gray matter mask, and only regions that survived inclusive masking vs the control group at uncorrected $P = .005$ are reported to ensure the results reflected abnormalities in connectivity. Regression coefficients for the cluster averages of regions resulting from the comparisons between the recurring and stable groups were entered into a predictive linear discriminant analysis[31] in SPSS Statistics 20 (eMethods in the Supplement).

Results

Subgroup Characteristics

There were no group differences in the percentages of trials included in the self-blaming and other-blaming emotion conditions, their unpleasantness ratings, response times, or the degree of movement during fMRI (eTable 2 in the Supplement). There were also no differences in age, years of education, and sex between the recurring and stable MDD groups or the recurring MDD group and control group (eTable 7 in the Supplement). The recurring (n = 25) and stable (n = 31) MDD groups did not differ on the number of previous episodes, average length of the last MDE, or average time in remission ($t < 0.19$, $P > .85$) (eTable 4 in the Supplement). There was no difference in the MADRS scores at baseline, while the Beck Depression Inventory[32] (BDI) scores were higher and the Global Assessment of Functioning (GAF) scores were lower in the recurring MDD group (eTable 7 in the Supplement).

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Table. RSATL Psychophysiological Interaction Effects for the Recurring Episode MDD Group vs the Stable Remission MDD Group (Self-blame vs Other-Blame Emotions)[a]

Contrast	Region of Interest	Cluster Size	Cohen *d* Cluster Average	Brodmann Area	MNI Peak Coordinates			*t* Statistic	FWE-Corrected *P* Value
					x	y	z		
Recurring Episode MDD Group > Stable Remission MDD Group									
Right hemisphere	Ventrolateral putamen and claustrum	611	1.63	NA	32	8	−2	4.88	<.001[b,c]
Right hemisphere	Temporoparietal junction	467	1.22	40	64	−30	22	4.52	.002[b,c]
Right hemisphere	Posterior SCSR	56	1.07	25	2	14	−6	3.59	.03[a,d]
Stable Remission MDD Group > Recurring Episode MDD Group									
NA	No significant regions	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: FWE, familywise error; MDD, major depressive disorder; MNI, Montreal Neurological Institute; NA, not applicable; RSATL, right superior anterior temporal lobe; SCSR, subgenual cingulate cortex and adjacent septal region.

[a] Only regions that survived inclusive masking vs the healthy control group are reported, with all statistics reported for the unmasked comparisons.

[b] Region surviving inclusive masking with the recurring episode MDD group vs the control group at uncorrected $P = .005$.

[c] Region surviving inclusive masking with the control group vs stable remission MDD group at uncorrected $P = .005$, with cluster-level FWE correction over the whole brain.

[d] Region surviving voxel-based FWE correction over the a priori subgenual cingulate region of interest.

fMRI Findings

Standard blood oxygenation level-dependent (BOLD) effect analyses for self-blaming vs other-blaming emotions revealed no differences between the recurring and stable MDD groups. In contrast, when investigating our main hypothesis using the PPI analysis for self-blaming vs other-blaming emotions, patients with recurring MDD exhibited increased RSATL connectivity with the posterior SCSR, the right ventrolateral putamen (extending into the claustrum), and the right temporoparietal junction compared with patients with stable MDD (**Table** and **Figure 1**). All these regions also showed increased connectivity in the recurring MDD group relative to the control group. The reverse comparison of stable vs recurring MDD revealed no areas of increased connectivity.

The RSATL-SCSR connectivity group differences were driven by patients with recurring MDD showing higher connectivity in the self-blaming emotion condition and lower connectivity in the other-blaming emotion condition compared with patients with stable MDD. These results are shown in **Figure 2** and **Figure 3**.

The number of previous MDEs did not correlate with the RSATL-SCSR coupling coefficients in the MDD group (Spearman $\rho = 0.111$, $P = .38$), whereas there was a weak correlation with residual symptoms as measured on the MADRS (Spearman $\rho = 0.285$, $P = .02$). There were no correlations between the RSATL-SCSR coupling coefficients and the BDI or GAF scores in participants with MDD ($\rho \leq -0.202$, $P \geq .11$). The RSATL-SCSR connectivity group differences also remained unchanged when using these variables as covariates of no interest (eTable 8 in the Supplement). Finally, when comparing the physiological connectivity of the RSATL, there was no difference between the recurring and stable groups ($t_{54} = -0.90$, $P = .37$) within the SCSR cluster that showed a PPI effect.

Discussion

We found that during the experience of self-blaming relative to other-blaming emotions, connectivity of the RSATL with the SCSR predicted risk of subsequent recurring depressive episodes, as predicted. Intriguingly, contrary to our more specific hypothesis, patients with recurring MDD showed higher rather than lower connectivity compared with the stable group and the control group. In addition to RSATL hyperconnectivity with the SCSR, we also revealed similar effects with the right ventral putamen, claustrum, and the temporoparietal junction as distinctive of recurring compared with stable MDD. While residual depressive symptoms were associated with neural signatures of recurrence risk, most of the variance in RSATL-SCSR connectivity was independent of residual symptoms. Furthermore, there were no associations between RSATL-SCSR connectivity and the number of previous episodes. Together with our finding of 75% accuracy of predicting recurrence from our fMRI measures with no significant predictive value of our clinical measures (Figure 1), this result shows that the fMRI measures add information to clinical predictors and are not solely accounted for by incomplete remission or scarring effects of previous episodes.[26]

The RSATL-SCSR hyperconnectivity for self-blaming vs other-blaming emotions in the recurring MDD group relative to the other groups was confirmed when extending the analysis to patients with lower-quality MRI acquisitions, corroborating the feasibility of our fMRI measure for wider use. Furthermore, using full MDE criteria as a categorical outcome was supported in that RSATL-SCSR connectivity was comparable between stable and subthreshold MDD.

In contrast to the clear predictive effects of functional connectivity, standard BOLD analyses revealed no differences between recurring and stable MDD. This finding further corroborates the notion that functional connectivity has an important pathophysiological role in MDD[33] and may be more informative than regional BOLD[10] because it reflects the functional integration of information within networks[23] such as the "default mode network" to which both the RSATL and SCSR are contributing.[34] Two previous pilot studies[35,36] comparing recurring episode patients (N = 10 and N = 7, respectively) and stable remission

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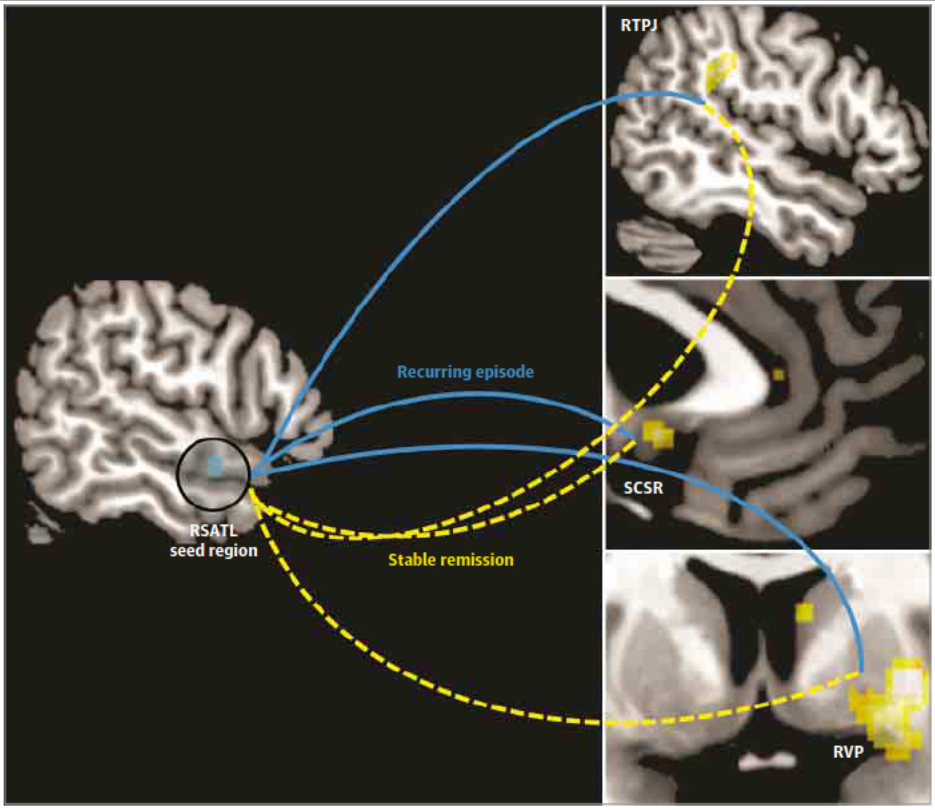
Figure 1. Regions Showing Functional Connectivity Group Differences With the Right Superior Anterior Temporal Lobe (RSATL) Seed Region for Self-blaming vs Other-Blaming Emotions Between the Recurring Episode Major Depressive Disorder (MDD) Group and the Stable Remission MDD Group



Cropped images are displayed at an uncorrected voxel-level threshold of $P = .005$, with no cluster-size threshold. A predictive linear discriminant analysis[31] using cluster average regression coefficients from the subgenual cingulate cortex and adjacent septal region (SCSR), right temporal junction (RTPJ), and right ventral putamen and claustrum (RVP), including cases with lower magnetic resonance imaging quality (n = 64), resulted in 79% correctly classified patients into recurring vs stable groups, which could be cross-validated using the well-established leave-one-out method in 75% of the cases (positive predictive value of 74%, negative predictive value of 76%, Wilks $\lambda = .681$, $P < .001$, estimating prior probabilities from subgroup sizes, 1000 bootstrap samples). In contrast, repeating this analysis only based on clinical variables (number of previous episodes, time in remission, time since stopping antidepressant medication, Beck Depression Inventory, Montgomery-Åsberg Depression Rating Scale, and Global Assessment of Functioning scores), prediction accuracy was at chance levels (61% cross-validated, Wilks $\lambda = .855$, $P = .16$). The cluster size of the SCSR effect is 56 (Table), which is large compared with the relatively small size of the anatomical region. Our statistical inference for this finding is based on the peak voxel effect size that survives voxel-based familywise error correction at $P = .05$ over our a priori region of interest. The other clusters survive familywise error correction over the whole brain. Note that some functional magnetic resonance imaging findings appear to fall on white matter; this is at least partly because of individual anatomical variability. We used a gray matter mask for inclusive masking to only retain voxels with gray matter density values on averaged segmentations of greater than 0.10. Therefore, gray matter is present in at least some participants in all the voxels of each cluster, even if the projection onto the template gives the impression of falling on white matter. The peak voxel (Cohen $d = 0.98$, corresponding to $t_{54} = 3.59$) and cluster average ($d = 1.07$) effect sizes for the subgenual region are large. They are even larger for the RTPJ ($d = 1.22$) and RVP ($d = 1.63$) cluster averages. On a cautionary note, these effect size estimates are post hoc and may therefore overestimate the true effect size, which needs to be determined in future independent studies. In contrast, the large multivariate effect size (Wilks $\lambda = 0.681$) of the linear discriminant analysis, which was independently cross-validated, provides a robust estimate that can inform power calculations for future studies. Blue line indicates relatively higher connectivity; yellow dashed line, relatively lower connectivity.

patients (N = 6 and N = 11, respectively), however, found lower[36] and higher[35] BOLD effects in medial frontal areas to be predictive of subsequent recurrence. Another study[37] found lower ventrolateral frontal BOLD to correlate with subsequent worsening on the BDI. Although interesting, difficulties in adequately controlling for confounding effects of antidepressant medication status[36,37] and randomization to different treatments,[35] together with small sample sizes, may limit the generalizability of these findings.

This study corroborates the pathophysiological importance of the RSATL for MDD.[10] The finding that self-blame–selective changes in RSATL connectivity are associated with vulnerability to MDD recurrence is in keeping with the hypothesis that deficient integration of conceptual social knowledge detail (eg, what it means to act "stingily") increases proneness to overgeneralized self-blame (eg, "I acted badly"),[17,20] described as a central cognitive feature of MDD.[4,38] This result is compatible with the view that the RSATL may implicitly enrich moral feelings such as guilt with detailed implicit social meaning (ie, social conceptual representations) even in the absence of verbalization.[39] Activation of the anterior temporal lobes for tasks probing social meaning has been corroborated independently.[40-43] Overall, this evidence is in agreement with a more general view of anterior temporal lobe

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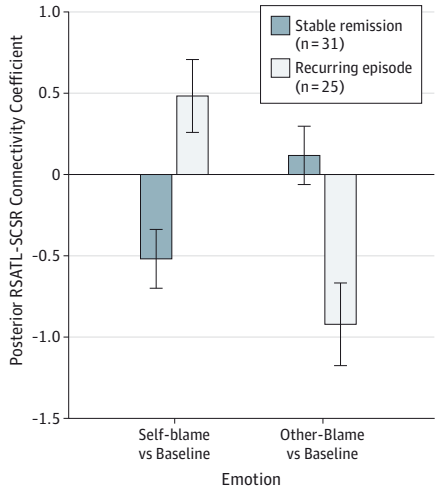
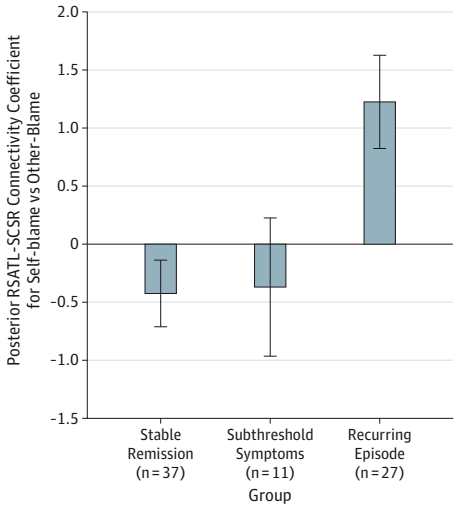
Figure 2. Connectivity Coefficients for Posterior Right Superior Anterior Temporal Lobe–Subgenual Cingulate Cortex and Adjacent Septal Region (RSATL-SCSR) for Self-blaming and Other-Blaming Emotions vs Baseline



Patients with stable major depressive disorder (MDD) and recurring MDD are shown. The RSATL-SCSR connectivity differences were driven by an interaction between emotion (self-blaming vs other-blaming) and group (recurring episode MDD [n = 25] vs stable MDD [n = 31]) ($F_{1,54}$ = 16.23, P < .001). As can be seen, the interaction arose by higher connectivity during self-blame and by lower connectivity during other-blame in the recurring episode MDD group and the opposite pattern in the stable remission MDD group. There were no significant main effects of emotion ($F_{1,54}$ = 2.303, P = .14) or group ($F_{1,54}$ = 0.016, P = .90).

Figure 3. Connectivity Coefficients for Posterior Right Superior Anterior Temporal Lobe–Subgenual Cingulate Cortex and Adjacent Septal Region (RSATL-SCSR) for Self-blaming vs Other-Blaming Emotions



Patients with stable major depressive disorder (MDD), subthreshold MDD, and recurring MDD are shown. A secondary data analysis on the extracted SCSR regression coefficients (cluster averages) in the larger data set, including the subthreshold MDD group and patients with nonoptimal quality of functional magnetic resonance imaging data, confirmed a connectivity difference for self-blaming vs other-blaming emotions between the MDD groups ($F_{2,74}$ = 6.39, P = .003). Post hoc pairwise comparisons showed increased RSATL-SCSR connectivity for self-blaming vs other-blaming emotions in the recurring episode MDD group compared with both the stable remission MDD group (mean [SE] difference, 1.65 [0.48]; 95% CI, 0.69-2.61; P = .001) and the subthreshold MDD group (mean [SE] difference, 1.59 [0.68]; 95% CI, 0.24-2.95; P = .001), with no difference between the stable remission and subthreshold MDD groups (mean [SE] difference, −0.05 [0.65]; 95% CI, −1.25 to 1.36; P = .93).

function as a "hub" representing context-independent aspects of concepts.[44,45]

Our finding of increased self-blame–selective RSATL connectivity with the ventral putamen supports previous reports of abnormal ventral striatal functional connectivity[46] and activation in response to self-negative attribution[47] in current MDD. Notably, reduced reward-related ventral striatal BOLD prospectively predicted first-onset depression in adolescents.[48] The putamen is part of a core frontal-subcortical circuit that has been implicated in hedonic abnormalities in mood disorders.[49] Dysfunction of the adjacent claustrum, which is closely connected with the lateral amygdala,[50] has also been associated with anhedonia and psychomotor symptoms in current MDD.[51]

Our result of self-blame–selective increases in RSATL connectivity with the right temporoparietal junction in the recurring MDD group relative to the stable MDD group and control group is in keeping with its proposed role in enabling internal predictions about external sensory events.[52] Such a role is needed for mental models of social agency (self vs other[52]) probed on our task.[53]

Although the direction of effects (namely, self-blame–selective increases rather than decreases in RSATL-SCSR connectivity in our recurring MDD group) is at odds with the expectation based on our group's previous cross-sectional study,[10] it is in keeping with converging findings from resting-state fMRI-based connectivity analyses in current MDD showing subgenual cingulate hyperconnectivity with the default mode network,"[54] particularly dorsomedial frontal regions,[55] previously implicated in negative self-focus in MDD.[47,56] Overall risk of recurrence in MDD samples differed between the present study (23% [13 of 56] with only one MDE) and our group's previous study[10] (56% [14 of 25] with only one MDE) and may explain the discrepancy in the direction of the results. This difference is because the MDD sample in our group's previous study may have been biased toward patients with relatively stable remission, thus preventing detection of the self-blame–selective RSATL-SCSR hyperconnectivity effects that only occurred in the recurring group of the present study. Future studies are needed to determine whether lower self-blame–selective RSATL connectivity observed in patients with stable remission relative to the control group in the present study and in our group's previous study reflects correlates of compensation mechanisms, rendering these individuals more resilient against recurrence, rather than correlates of vulnerability as previously surmised.

The following limitations of this study need to be discussed. First, we used a broader definition of self-blaming emotions in the present study compared with previous studies[10,17] specifically investigating guilt, which makes the results less comparable, and may have included negative emotions that did not entail blame. This approach, however, increased the simplicity and power of our analysis for future applications and was justified by our finding that 2 important

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self-blaming emotions (shame and guilt) showed no BOLD activation differences in the SCSR.[57] Second, although we demonstrated robust cross-validated positive and negative predictive values of self-blame–selective RSATL hyperconnectivity around 75% (Figure 1), this threshold falls short of the 80% benchmark suggested for clinically useful biomarkers.[22] Rather than using a standard approach as chosen herein to investigate regional hypotheses, this benchmark could be achieved in further analyses by using machine-learning algorithms that capture multivariate information across the whole brain and have been successfully used for predicting treatment outcomes in current MDD.[58-61]

Conclusions

We demonstrated that recurrence risk in MDD is predicted by a self-blame–selective increase in RSATL connectivity with the SCSR, right ventral putamen, claustrum, and right temporoparietal junction. Our finding supports the hypothesis that self-blame–selective changes in connectivity with the RSATL have a causal role in the pathophysiology of MDD.[10] A definitive proof of causality, however, will require showing that modulation of this neural signature by specific interventions has effects on clinical outcomes.

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Acquisition, analysis, or interpretation of data: Lythe, Moll, Gethin, Workman, Lambon Ralph, Zahn.
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Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

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eMethods. Supplemental Methods

Additional inclusion criteria for the major depressive disorder (MDD) group

At least two months duration of one past major depressive episode, a past moderate or severe depressive episode according to the International Classification of Diseases[1] .

Additional exclusion criteria for all groups

General exclusion criteria were: MRI contraindications, psychotropic medication, psychotherapy whilst taking part in the study, significant psychosocial impairment as an indicator of a possible personality disorder (assessed on the Global Assessment of Functioning scale (GAF)[2]), a Montgomery Åsberg Depression Rating Scale[3] (MADRS) score of > 10, current self-harming behaviour, clinically relevant MRI abnormalities, developmental disorders, learning disabilities, an Addenbrooke's Cognitive Exam-R score < 88 (completed in participants over 50 years of age[4]), neurological illness, or physical illnesses that significantly alter brain function or blood flow.

Recruitment and clinical assessment

Participants were recruited using online and print advertisements as part of the UK Medical Research Council-funded "Development of Cognitive and Imaging Biomarkers Predicting Risk of Self-Blaming Bias and Recurrence in Major Depression" project[5]. As in our previous study[6], initial eligibility was assessed with a phone pre-screening interview (eTable 1) to select participants to be seen by a senior psychiatrist (RZ), assessed using the Structured Clinical Interview-I (SCID-I) for DSM-IV[2] for which all investigators had received training and showed excellent inter-rater reliability[5], and to undergo urine drug screening.

The Longitudinal Interval Follow-up Evaluation interview for DSM-IV (LIFE[7], MDD module and psychosocial functioning assessment) uses a 6-point Psychiatric Status Rating (PSR) scale : no symptoms=1, mild symptoms causing no relevant impairment or distress=2, mild symptoms that cause no more than moderate distress/impairment=3, major symptoms not meeting full major depressive episode (MDE) criteria=4, symptoms meeting full MDE criteria=5, 6=most severe forms of MDE. Based on their highest PSR scale scores over the worst two weeks during the follow-up period, patients were assigned to three groups whilst remaining blinded to imaging results: 1) *Stable* remission [PSR 1-3 and not requiring treatment], 2) *Subthreshold* symptom [PSR=3 and requiring treatment or PSR=4], 3) *Recurring* episode [PSR=5-6].

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PPI analysis

In order to obtain the RSATL signal for further PPI analyses, standard Blood-Oxygenation-Level-Dependent (BOLD) effects were modelled for each participant (first level) for self-agency and other-agency conditions and modelling high (medium or above median across trials for individual) and low (below median across trials for individual) degrees of unpleasantness of the trials in each condition. Null events and realignment parameters (i.e. 6 parameters describing movement by rotation and translation in 3 dimensions each) were also included for the three runs. We modelled the temporal and spatial derivatives of the haemodynamic response function.

At the individual participant level for the PPI analysis, the psychological, physiological variable and psychophysiological interaction term for the highly unpleasant trials were entered into a general linear model in addition to the time course and realignment parameters. Single participant contrasts were created for self- versus other-blame, self-blame versus fixation, and other-blame versus fixation.

Linear discriminant analysis

Regression coefficients for the cluster averages of regions resulting from the comparisons between *Recurring* and *Stable* groups were entered into a predictive linear discriminant analysis[8], a type of machine learning, using SPSS 20 and employing cross-validation using the well-established leave-one-out method, estimating prior probabilities from subgroup sizes with 1000 boot-strap samples. The same analysis was repeated using clinical variables for comparison (Figure 1).

MRI sequences

T2*-weighted echo-planar images (3 runs of 405 volumes with 5 dummy scans) were acquired on an MRI scanner (3T Achieva, Philips) with an 8-channel head coil, 3mm section thickness, ascending continuous acquisition parallel to the anterior to posterior commissural line, 35-40 slices depending on the participant's head, repetition time=2000 milliseconds, echo time=20.5 milliseconds, field of view=220 x 220 x 120mm, acquisition matrix=80 x 80 voxels, reconstructed voxel size=2.29 x 2.29 x 3mm, and sensitivity encoding factor=2, enabling dynamic stabilisation to correct for signal drift.

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T1-weighted, magnetization-prepared, rapid-acquisition gradient-echo structural images were obtained: 160 axial slices; 0.9mm slice thickness; repetition time: 8.4ms; echo time: 3.9ms; field of view: 240 x 191 x 144mm; acquisition matrix: 256 x 163 voxels; reconstructed voxel size: 0.94 x 0.94 x 0.9mm; flip angle: 8°.

Region of interest

Our *a priori* SCSR ROI (MNI coordinates: -4, 23, -5; 6mm sphere) was identical to the one used in our previous study[6] and was based on averaging coordinates from four studies[9-12] selectively associating this region with the experience of self-blaming and prosocial emotions.

Image analysis quality control

Data from 10 participants were independently reanalysed a second time as a quality control measure. These participants were chosen pseudo-randomly to include all permutations of fMRI run orders, and an equal number of MDD and *Control* participants. All stages of the analysis were carried out, including creation of the onset vectors, image pre-processing and analysis within SPM8. Subsequently the results for the contrast of self-blaming vs. other-blaming emotions in each individual were compared against the main data analysis for that individual. All 10 analysis pairs resulted in identical clusters with identical statistical values with no discrepancies rendering analysis errors highly unlikely.

Data for the primary imaging analysis were included with movement of 2 voxels (6mm translation and 2º rotation). For the additional participants with suboptimal but acceptable data (6-8 mm translation and 2º-6º rotation) and no signal dropout in the SCSR, we extracted regression coefficients from the cluster averages resulting from the primary analysis within this region.

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eTable 1. Exclusion Reasons for Volunteers Following Phone Prescreening

Exclusion reason		*N*
	MRI contraindications	77
	Psychiatric disorders other than MDD	54
	Current antidepressants or other centrally active medications	52
	Withdrawal after telephone pre-screening	33
	Not meeting full screening criteria for MDD	30
	Family history of MDD/bipolar/schizophrenia (*Control* group)	26
	Substance or alcohol abuse	23
	Current antihypertensive or statin medications	20
	Left-handed	20
	Non-native English speaker	19
	Thyroid function problems	19
	Fulfilling criteria for current MDD	13
	History of cancer	7
	Not remitted for long enough (<6 months)	7
	Epilepsy	5
	No reason recorded	5
	Other general medical conditions	5
	Diabetes	4
	Out of age range (18 – 65 years)	4
	Excluded because of age-matching (*Control* group)	3
	Multiple sclerosis	3
	History of stroke	1
	Vitamin D deficiency	1
Total excluded after phone pre-screening		**431**

In total, 707 people participated in the phone pre-screening interview, 276 passed this screening with 184 in the remitted MDD and 92 in the *Control* group and were invited for the first study day on which a full clinical interview was administered. Of these, 202 (138 individuals pre-screened as remitted MDD and 64 pre-screened as control participants) were reachable, able and willing to be seen on the first study day after reading the participant information sheet sent to them.

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eTable 2. Movement Parameters, Ratings and Response Times for Self- and Other-Blaming Emotion Trials

	Recurring MDD (*N* = 25)	*Stable* MDD (*N* = 31)	*Control* (*N* = 39)	*Recurring* vs. *Stable* MDD comparison	*Recurring* MDD vs. *Control* comparison
Movement parameters					
RMS translation	0.35 ± 0.19	0.31 ± 0.18	0.35 ± 0.18	$t(54) = -0.83$, $p = .408$	$t(62) = -0.08$, $p = .934$
RMS rotation	0.01 ± 0.00	0.01 ± 0.00	0.01 ± 0.00	$t(54) = -0.46$, $p = .644$	$t(62) = 0.68$, $p = .496$
Frequency (%)					
Self-blaming emotion	58.84 ± 6.06	60.82 ± 8.28	59.4 ± 12.7	$t(52) = 0.96$, $p = .341$	$t(58) = -0.22$, $p = .824$
Other-blaming emotion	57.56 ± 8.59	58.10 ± 6.56	57.6 ± 7.5	$t(54) = 0.27$, $p = .789$	$t(62) = -0.01$, $p = .994$
Rated unpleasantness					
Self-blaming emotion	4.98 ± 1.13	4.60 ± 0.90	4.6 ± 1.1	$t(54) = -1.43$, $p = .158$	$t(62) = 1.48$, $p = .145$
Other-blaming emotion	4.63 ± 1.09	4.38 ± 0.78	4.3 ± 1.0	$t(54) = -1.01$, $p = .319$	$t(62) = 1.12$, $p = .265$
Response times (ms)					
Self-blaming emotion	2391 ± 535	2313 ± 426	2371± 424	$t(53) = -0.60$, $p = .551$	$t(62) = 0.17$, $p = .867$
Other-blaming emotion	2424 ± 484	2373 ± 451	2379 ± 460	$t(53) = -0.41$, $p = .687$	$t(62) = 0.38$, $p = .708$

There were no between-group differences on any of the above measures at p=0.05, 2-sided. Data for one *Stable* MDD participant for the response times were missing. Means and standard deviations are reported (*M* ± *SD*). RMS = root mean square.

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eTable 3. Exclusion Reasons for Participants Following Clinical Interview

Clinical group and exclusion reason	*N*
MDD group	
Fulfilling criteria for a bipolar disorder	6
Fulfilling criteria for current social anxiety disorder	6
Not meeting full criteria for MDD	5
Fulfilling criteria for past substance abuse	4
Not remitted for long enough (<6 months)	3
Residual symptoms of post-traumatic stress disorder	3
Probable personality disorders	2
Fulfilling criteria for current generalized anxiety disorder	1
MRI contraindications	1
Withdrawal after the clinical interview	1
Total MDD excluded after clinical interview	**32**
***Control* group**	
Probable or definite positive first degree family history of MDD	4
Fulfilling criteria for a past MDE lasting less than two months	1
Fulfilling criteria for current adjustment disorder	1
Fulfilling criteria for current MDD	1
Fulfilling criteria for current social anxiety disorder	1
Non-native English speaker	1
Past depressive episode not fulfilling criteria for a past MDE	1
Total *Control* excluded after the clinical interview	**10**

After the clinical interview on the first study day, 160 participants were enrolled in the study (106 MDD and 54 *Control* participants). 144 participants completed the second study day which included the MRI scan (10/106 MDD and 6/54 were unable to schedule the second session). fMRI data for 138/144 participants were collected, with 6/144 participants not completing the fMRI acquisitions. Of the 138 participants for which fMRI data were collected, 91 were in the MDD group and 47 in the *Control* group. Data for 4/138 participants were excluded from the fMRI analysis due to abnormal images (3 MDD, 1 *Control*). 12/134 participants (7/88 MDD and 5/46 *Control*) were excluded entirely from fMRI analysis due to excessive head movement and/or excessive signal loss. 122 participants (81 MDD and 41 *Control*) were included in a larger confirmation analysis (27/81 MDD with a recurring episode, 37/81 MDD remaining in stable remission, 11/81 MDD with sub-threshold symptoms, and 6/81 MDD without follow-up data). Data for 13/122 did not pass the strictest quality control threshold, i.e. exhibiting greater movement and/or signal dropout than the resulting main subset of participants (11 MDD and 2 *Control*). fMRI data for 109 participants (70 MDD and 39 *Control*) had good signal coverage and mild movement. Follow-up data were not available for 4/70 MDD participants. Of the remaining 66 MDD participants with excellent fMRI data quality, 25 had a recurring episode, 31 remained in stable remission, and 10 had sub-threshold symptoms. Major depressive episode, MDE.

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eTable 4. Clinical Characteristics of the Remitted MDD Groups

	Recurring MDD (*N*=25)	Stable MDD (*N*=31)
Past MDD subtype		
With melancholic features	14/25	14/31
With atypical features	2/25	5/31
No specific subtype	9/25	12/31
Number of previous MDEs		
1	2	11
2	9	7
3	4	7
4	4	1
5	4	2
6 or more	2	3
Average number of previous MDEs	3.3 ± 1.8	3.3 ± 3.9
	(range: 1-9)	(range: 1-18)
Last MDE details		
Average length of MDE (months)	14.9 ± 21.3	14.3 ± 18.4
	(range: 2-96)	(range: 1-81)
Average time in remission (months)	25.3 ± 21.1	26.6 ± 27.7
	(range: 6-72)	(range: 5-140)
Severe depressive episode*	22/25	24/31
Moderate depressive episode*	3/25	7/31
No psychotropic medication since (months)	37.32 ± 49.72	37.05 ± 70.73
	(range: 0-173)	(range: 0-372)
Previous medication		
SSRI	19/25	26/31
SNRI	1/25	2/31
Tricyclic antidepressant	0/25	1/31
Mirtazapine	0/25	1/31
Unknown class of antidepressant	4/25	1/31
No antidepressant medication	3/25	4/31
Benzodiazepines	1/25	3/31
Previous CBT	10/25	5/31
Previous counselling	8/25	8/31
Self-guided CBT using internet or books	0/25	3/31
Previous suicide attempts	0.28 ± 0.61	0.35 ± 0.84
	(range: 0-2)	(range: 0-3)
Life-time axis-I co-morbidity**		
Panic disorder with agoraphobia	1/25	0/31
Bulimia nervosa	0/25	1/31
No life-time co-morbidity	24/25	30/31
Family history		
First degree relative with MDD	14/25	18/31
No family member with history of MDD	6/25	11/31
First degree relative with schizophrenia or bipolar	5/25	2/31

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disorder		

MDD subtype classification was based on adapting the SCID-I for DSM-IV-TR to allow lifetime assessment of subtypes with excellent inter-rater reliability[5]. All participants had stopped medication well before the required washout phase. Participants in the Recurring and Stable MDD groups did not differ on number of previous episodes, average length of last MDE, average time in remission, average length since last use of psychotropic medications and number of suicide attempts (t<0.37, p>.711). Means and standard deviations (M ± SD), or number of cases are reported. CBT, cognitive behavioural therapy; MDE, major depressive episode; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inh bitor. *According to ICD-10 criteria. **All co-morbid disorders were fully remitted at the time of study and none were likely to be the primary cause of the depressive episodes.

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eTable 5. Treatment of Last Major Depressive Episode

	Recurring MDD (*N*=25)	Stable MDD (*N*=31)
Psychotropic medication		
SSRI	12/25	20/31
SNRI	1/25	1/31
Mirtazapine	0/25	1/31
Unknown class of antidepressant	4/25	1/31
Benzodiazepines	0/25	1/31
CBT	5/25	4/31

Number of cases are reported. CBT, cognitive behavioural therapy; SSRI, selective serotonin reuptake inh bitor; SNRI, serotonin norepinephrine reuptake inhibitor.

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eTable 6. Interrater Reliability on Psychiatric Status Rating (PSR) Scores at Follow-up

	Current PSR		Highest PSR during follow-up period	
Raters	ICC value	number of ratings	ICC value	number of ratings
RZ & KL	0.962	39	0.980	41
KL & CW	0.959	67	0.985	67

Reliability is given as an intra-class correlation value (ICC, two-way mixed with absolute agreement). RZ is a senior psychiatrist, KL is a postdoctoral research associate with previous experience in mental health assessments. CW is a PhD student with no previous experience in mental health assessments. KL and CW had received extensive training by RZ.

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eTable 7. Demographic and Basic Clinical Characteristics for Participants Included in the Primary Imaging Analysis

	Recurring MDD (*N* = 25)	Stable MDD (*N* = 31)	*Control* (*N* = 39)	Recurring vs Stable MDD comparison	Recurring MDD vs *Control* comparison
Age	34.3 ± 12.2	33.9 ± 12.8	33.4 ± 13.2	$t(54) = -0.13$, $p = .896$	$t(62) = 0.27$, $p = .785$
Years of education	16.52 ± 2.7	17.10 ± 2.1	17.4 ± 2.6	$t(54) = 0.94$, $p = .349$	$t(62) = -1.34$, $p = .185$
BDI score	5.84 ± 4.5	3.13 ± 3.13	1.0 ± 1.8	$t(54) = -2.66$, $p = .010$*	$t(29) = 5.17$, $p < .0001$*
Gender	6 male	13 male	15 male	x^2 (1, $N = 56$) = 1.99, $p = .159$	x^2 (1, $N = 64$) = 1.45, $p = .229$
MADRS	1.60 ± 1.83	0.9 ± 1.27	0.6 ± 1.2	$t(41) = -1.62$, $p = .113$	$t(38) = 2.37$, $p = .023$*
GAF	82.88 ± 6.34	86.94 ± 4.81	88.9 ± 2.8	$t(54) = 2.72$, $p = .009$*	$t(30) = -4.50$, $p < .0001$*

BDI, Beck Depression Inventory; MADRS, Montgomery-Åsberg Depression Rating Scale; GAF, Global Assessment of Functioning Scale. *Significant at $p < .05$ threshold, 2-tailed. Means and standard deviations are reported ($M \pm SD$).

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eTable 8. Effect of Recurrence Status on RSATL-SCSR Connectivity Adjusted for Potential Confounders

Potentially confounding covariate adjusted for	**Adjusted group effect for *Recurring* vs. *Stable***
Number of previous MDEs	$t = 3.051$, $p = .003$
MADRS	$t = 3.253$, $p = .002$
BDI	$t = 3.172$, $p = .002$
GAF	$t = 3.116$, $p = .003$
Gender	$t = 3.354$, p = .001

Linear regression models in N = 64 patients investigated the adjusted effect of recurrence status (*Recurring* vs. *Stable*) on SCSR cluster averages for the RSATL seed PPI analysis for self-blaming vs. other-blaming emotions whilst modelling each potentially confounding covariate separately. The robust group difference in PPI effects between patients with *Recurring* and *Stable* remission remained uninfluenced by potential confounders. SCSR, subgenual cingulate/septal region; RSATL, right superior anterior temporal lobe; PPI, psychophysiological interaction analysis; BDI, Beck Depression Inventory; GAF, Global Assessment of Functioning Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MDE, major depressive episode.

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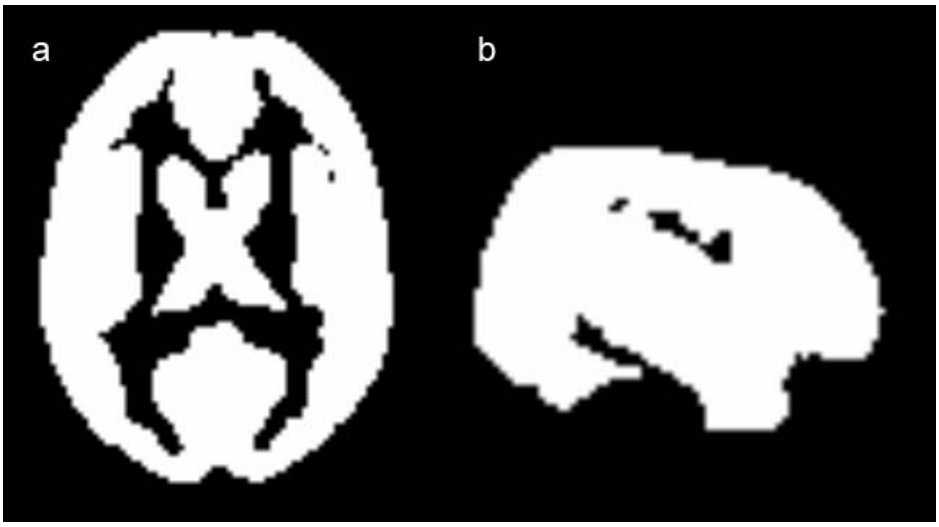

eFigure. SPM Implicit Mask

Panel a) shows an axial slice at z=14 through the implicit mask generated by SPM for the group-level analysis for 56 remitted MDD participants (*N*=25 Recurring and *N*=31 Stable). Panel b) shows a sagittal slice at x=48 through the implicit mask generated by SPM for the group-level analysis for 56 remitted MDD participants (*N*=25 Recurring and *N*=31 Stable). Coverage of the superior ATLs was complete posterior to y=13. Coverage of the posterior orbitofrontal cortex was complete superior to z=-12, and ventral coverage of the most anterior portion of ventromedial frontal cortex was complete superior to z=-16. Coverage of the most dorsal slice of the brain was up to z=42.

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