# Supplementary Online Content

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

**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].

***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.

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.

## 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.

**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.

**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.

**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 |

| | | |
|---|---|---|
| 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 inhibitor. *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.

**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 inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor.

**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.

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

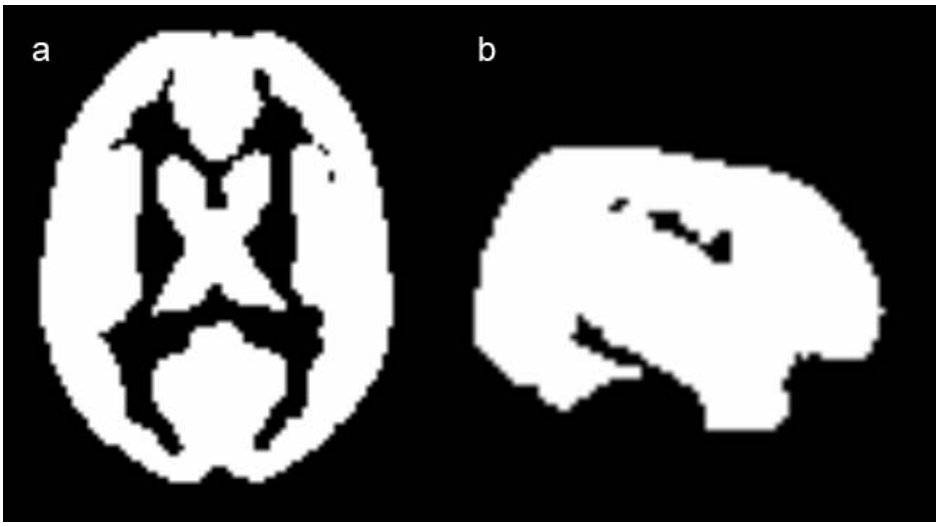
| | Recurring MDD (*N* = 25) | Stable MDD (*N* = 31) | *Control* (*N* = 39) | Recurring vs Stable MDD comparison | Recurring MDD vs *Control* comparison |
|---|---|---|---|---|---|
| Age | 34.3 ± 12.2 | 33.9 ± 12.8 | 33.4 ± 13.2 | $t(54) = -0.13$, $p = .896$ | $t(62) = 0.27$, $p = .785$ |
| Years of 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 ($M \pm SD$).

**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.




**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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