**SUPPLEMENTARY MATERIAL**

**Subgenual activation and the finger of blame: individual differences and depression vulnerability**

Karen E Lythe, Ph.D.1, Jennifer A Gethin, Ph.D..1, Clifford I Workman, Ph.D.1,2, Matthew A. Lambon Ralph, FRSLT, Ph.D.1, 3, John F.W. Deakin, F.R.C.Psych., Ph.D.2, Jorge Moll, M.D. Ph.D.4,

Roland Zahn, M.D.1,4,5,6

*1The University of Manchester & Manchester Academic Health Sciences Centre, School of*

*Psychological Sciences, Neuroscience and Aphasia Research Unit, Manchester, M13 9PL,UK*

*2The University of Manchester & Manchester Academic Health Sciences Centre,*

*Institute of Brain, Behaviour and Mental Health, Neuroscience & Psychiatry Unit,*

*Manchester, M13 9PL, UK*

*3MRC Cognition and Brain Sciences Unit, University of Cambridge, 15 Chaucer Road, Cambridge, CB2 7EF, UK*

*4Cognitive and Behavioral Neuroscience Unit, D’Or Institute for Research and Education*

*(IDOR), 22280-080 - Rio de Janeiro, RJ, Brazil*

*5Institute of Psychiatry, Psychology & Neuroscience, Department of Psychological Medicine, Centre for Affective Disorders, King’s College London, London, SE5 8AZ, UK*

*6National Service for Affective Disorders, South London and Maudsley NHS Foundation Trust, London SE5 8AZ*

\*Corresponding author

Dr Roland Zahn (see address above)

E-mail: roland.zahn@kcl.ac.uk

Phone: 0044-(0)20 7848 0348

Fax: 0044-(0)20 7848 0298

**Supplementary Methods**

**Image acquisition details**

An fMRI protocol optimised for detection of ventral brain regions was used as described previously (Green, Lambon Ralph, Moll, Deakin, & Zahn, 2012). 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=220x220x120mm, acquisition matrix=80 x 80 voxels, reconstructed voxel size=2.29x2.29x3mm, 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 using 160 axial slices; 9mm slice thickness; repetition time=8.4ms; echo time=3.9ms; field of view=240x191x144mm; acquisition matrix=256x163 voxels; reconstructed voxel size=.94 x.94x.9mm; flip angle: 8°.

**fMRI stimulus design details**

As previously described (Green et al., 2012; Lythe et al., 2015; R. Zahn et al., 2015), participants were shown written descriptions of negative interactions between themselves and their best friends in which either they (self-agency condition, n = 90) or their best friend (other-agency condition, n = 90) acted counter to social and moral values. Statements read as ‘‘[participant’s best friend’s name] does act e.g. tactlessly towards [participant’s name]’’ (other-agency condition, 90 items), ‘‘[participant’s name] does act e.g. tactlessly towards [participant’s best friend’s name]’’ (self-agency condition, 90 items). The same social concepts (e.g. ‘tactless’, ‘generous’) were used in the self- and other-agency conditions, and 50% of the stimuli used negative concepts (e.g. ‘tactless’) while 50% used negated positive concepts (e.g. ‘not generously’). After the scan, participants were shown the stimuli again in a fully randomised order, but required to select the feeling that they felt was the best label for the emotion that they would experience most strongly in response to the social violation. The choice of feelings included shame, guilt, indignation/anger towards oneself, indignation/anger towards best friend, contempt/disgust towards oneself, contempt/disgust towards best friend, no feeling, or other feeling. Participants also rated how strongly they would experience unpleasant feelings as a result of the behaviour using a 1–7 visual analogue Likert scale (1 = not unpleasant, 7 = extremely unpleasant). This “Value-related Moral Sentiment Task” was based on an earlier version and details about the stimulus selection and design have also been described in (Green, Moll, Deakin, Hulleman, & Zahn, 2013; R. Zahn et al., 2007; Roland Zahn et al., 2009).

For the fMRI analysis, as explained in (Lythe et al., 2015), we used a broader definition of self-blaming and other-blaming emotions in the present study compared with our previous studies specifically investigating self-agency-related guilt vs. other-agency-related indignation/anger towards others (Green et al., 2012; Roland Zahn et al., 2009), which makes the results not directly comparable. The approach in the current study, however, increased the simplicity and power of our analysis for future applications and was justified by our finding that two important self-blaming emotions (shame and guilt) showed no BOLD activation differences in the SCC in a secondary data analysis (Pulcu et al., 2014). The change in approach was also to avoid large individual differences in the number of trials underpinning the computation of the BOLD response for self-blaming and other-blaming emotions, which may have confounded our previous analyses (Green et al., 2012; Roland Zahn et al., 2009).

**Supplementary Results**

There were also no correlations between the SCC coefficients for self- versus other-blame in the MDD group for rated unpleasantness or negative affectivity as measured on the Positive and Negative Affect scale (Watson, Clark, & Tellegen, 1988) in the self-blame (unpleasantness: ρ=-.05, *p*=.68; negative affectivity: ρ=-.09, *p*=.36) and other-blame conditions (unpleasantness: ρ=-.15, *p*=.21; negative affectivity: ρ=-.03, *p*=.78).

**Supplementary Table 1. Exclusion reasons for volunteers following phone pre-screening. This table has previously been published in JAMA Psychiatry (doi:10.1001/jamapsychiatry.2015.1813)**

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

**Supplementary Table 2. Exclusion reasons for participants following clinical interview.**

**This table has been adapted from a previously published one in JAMA Psychiatry (doi:10.1001/jamapsychiatry.2015.1813)**

|  |  |  |
| --- | --- | --- |
| 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). 25/134 participants (18/88 MDD and 7/46 Control) were excluded entirely from fMRI analysis due to head movement and/or signal loss. fMRI data for 109 participants (70 MDD and 39 Control) had good signal coverage and mild movement (movement of up to 6mm translation and 2ºrotation) and were included in the analyses.

**Supplementary Table 3. Demographic variables and basic clinical characteristics**

|  |  |  |  |
| --- | --- | --- | --- |
|  | MDD (*n*=70) | Control (*n*=39) | MDD vs Control  comparison |
| Age | 34.1 ± 12.0 | 33.4 ± 13.2 | *t*(107) = .32, *p* = .75 |
| Years of education | 16.7 ± 2.4 | 17.4 ± 2.6 | *t*(107) = -1.33, *p* = .19 |
| Sex | 20 male | 15 male | *x2* (1, *N* = 109) = 1.12, *p* = .29 |
| BDI score\* | 4.4 ± 4.2 | 1.0 ± 1.8 | *t*(101) = 5.87, *p* < .0001 |
| MADRS\* | 1.2 ± 1.5 | .6 ± 1.2 | *t*(94) = 2.17, *p* = .03 |
| GAF\* | 85.0 ± 5.8 | 88.9 ± 2.8 | *t*(105) = -4.73, *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* ± *SD*).

**Supplementary Table 4. Clinical characteristics of the remitted MDD group**

**This table has been adapted from a previously published one in JAMA Psychiatry (doi:10.1001/jamapsychiatry.2015.1813)**

|  |  |
| --- | --- |
|  | MDD *(N*=70) |
| **Past MDD subtype** |  |
| With melancholic features | 35/70 |
| With atypical features | 8/70 |
| No specific subtype | 27/70 |
| **Number of previous MDEs** |  |
| 1 | 16 |
| 2 | 21 |
| 3 | 14 |
| 4 | 6 |
| 5 | 7 |
| 6 or more | 6 |
| Average number of previous MDEs | 3.24 ± 3.02 (range: 1-18) |
| **Last MDE details** |  |
| Average length of MDE (months) | 14.38 ± 17.93 (range: 1-96) |
| Average time in remission (months) | 27.30 ± 23.95 (range: 5.5-140) |
| Severe depressive episode\* | 56/70 |
| Moderate depressive episode\* | 14/70 |
| **No psychotropic medication since (months)** | 36.99 ± 57.94 (range: 0-372) |
| **Previous medication** |  |
| SSRI antidepressant | 54/70 |
| SNRI antidepressant | 3/70 |
| Tricyclic antidepressant | 3/70 |
| Mirtazapine | 1/70 |
| Unknown class of antidepressant | 6/70 |
| No antidepressant medication | 12/70 |
| Benzodiazepines | 2/70 |
| Quetiapine | 1/70 |
| **Previous CBT** | 12/70 |
| **Previous counselling** | 26/70 |
| **Self-guided CBT using internet or books** | 4/70 |
| **Previous suicide attempts** | 0.19 ± 0.39 (range: 0-1) |
| **Life-time axis-I co-morbidity\*\*** |  |
| Panic disorder with agoraphobia | 1/70 |
| Bulimia nervosa | 1/70 |
| Posttraumatic Stress Disorder | 1/70 |
| No life-time co-morbidity | 67/70 |
| **Family history** |  |
| First degree relative with MDD | 41/70 |
| No family member with history of MDD | 21/70 |
| First degree relative with schizophrenia or bipolar disorder | 7/70 |
| Unknown | 1/70 |

\*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. MDD subtype classification was based on adapting the SCID-I for DSM-IV-TR to allow lifetime assessment of subtypes. All participants had stopped medication well before the required washout phase. Means and standard deviations are reported (M ± SD), or number of cases. CBT, cognitive behavioural therapy; MDE, major depressive episode; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor.

**Supplementary Table 5. Ratings and response times for highly unpleasant self- and other-blaming emotion trials**

|  |  |  |  |
| --- | --- | --- | --- |
|  | MDD (*n*=70) | Control (*n*=39) | MDD vs Control  comparison |
| **Frequency (% trials)** |  |  |  |
| Self-blaming emotion | 59.6 ± 7.5 | 59.4 ± 12.7 | *t*(53) = 0.09, *p* = .93 |
| Other-blaming emotion | 57.4 ± 6.8 | 57.6 ± 13.6 | *t*(49) = -0.08, *p* = .93 |
| **Rated unpleasantness** |  |  |  |
| Self-blaming emotion | 4.9 ± 1.0 | 4.3 ± 1.0 | *t*(107) = 1.57, *p* = .12 |
| Other-blaming emotion | 4.6 ± 0.9 | 4.3 ± 1.0 | *t*(107) = 1.42, *p* = .16 |
| **Response times (ms)** |  |  |  |
| Self-blaming emotion | 2342 ± 476 | 2371 ± 424 | *t*(106) = -0.31, *p* = .76 |
| Other-blaming emotion | 2383 ± 461 | 2379 ± 460 | *t*(106) = 0.04, *p* = .97 |

There were no between-group differences on any of the above measures at p=0.05, 2-sided. Response time data were missing for one MDD participant. Means and standard deviations are reported (M ± SD).

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