**Supplementary Online Content**

**Neural responses to facial emotions and subsequent clinical outcomes in difficult-to-treat depression**

Diede Fennema1, Gareth J. Barker2, Owen O’Daly2, Suqian Duan1, Beata R. Godlewska3,4, Kimberley Goldsmith5, Allan H. Young1,6, Jorge Moll7 & Roland Zahn1,6,7\*

*1 Centre of Affective Disorders, Institute of Psychiatry, Psychology & Neuroscience, Centre for Affective Disorders, King’s College London, London, UK*

*2 Department of Neuroimaging, Institute of Psychiatry, Psychology & Neuroscience, King’s College London, London, UK*

*3 Psychopharmacology Research Unit, University Department of Psychiatry, University of Oxford, Oxford, UK*

*4 Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK*

*5 Department of Biostatics and Health Informatics, Institute of Psychiatry, Psychology & Neuroscience, King’s College London, London, UK*

*6 National Service for Affective Disorders, South London and Maudsley NHS Foundation Trust, London, UK*

*7 Cognitive and Behavioural Neuroscience Unit, D’Or Institute for Research and Education (IDOR), Pioneer Science Program, Rio de Janeiro, Brazil*

\* Corresponding author

Professor Roland Zahn (see address above)

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

Phone: 0044-(0)20 7848 0348

Fax: 0044-(0)20 7848 0298

Keywords: *fMRI; amygdala; depression; biomarker; prognosis; emotional faces; treatment-resistant depression*

**Parts of this Supplementary Online Content have been adapted from a previously published one in Neuroimage:Clinical (doi: 10.1016/j.nicl.2023.103453).**

# Supplementary Methods

## *Exclusion criteria*

In addition to the criteria mentioned in the main manuscript, participants were excluded if they met any of the following: previous prescription of mirtazapine or vortioxetine at therapeutic dose, MRI contraindications, currently receiving specialist psychiatric treatment, high suicide risk on the Mini International Neuropsychiatric Interview (MINI) suicidality screen (Sheehan et al., 1998), past diagnosis of schizophrenia or schizo-affective disorder, psychotic symptoms using clinical screening questions, bipolar disorder (including otherwise specified) using the World Health Organisation Composite International Diagnostic Interview screening scale (Kessler et al., 2006) at pre-screening or Structured Clinical Interview (SCID) for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (First, Williams, Karg, & Spitzer, 2015) at baseline, at risk of being violent, drug or alcohol abuse over the last six months, suspected neurological condition, pregnancy or insufficient contraception in women of childbearing age and breastfeeding or within six months of giving birth.

## *Recruitment and clinical assessment*

We recruited participants from September 2018 to March 2020 partly through a cluster-randomised feasibility clinical trial, the Antidepressant Advisor Study (ADeSS; NCT03628027). Recruitment was halted due to the COVID-19 pandemic and recommenced in October 2020, using online advertising only, and was completed in August 2021.

As described in the trial protocol (Harrison et al., 2020), GP practices screened for patients with a history of treatment-resistance to antidepressant medications within their practice, i.e. non-responders to at least two serotonergic antidepressants in the current or previous episodes. Potential participants were approached for consent and, if given, asked to fill in a pre-screening questionnaire. Potentially eligible participants were invited for an in-depth assessment by the study team, which included a clinical assessment using the SCID (DSM-5) to establish a current major depressive disorder (MDD) (First et al., 2015), a history of participants’ depressive episodes, their current and past antidepressant medications, and completing various clinical, behavioural and experimental measures.

A follow-up assessment was conducted to establish whether any changes in baseline measures had occurred. This visit took place around 14-18 weeks after enrolling in the study, which should allow observation of any treatment effect if there is one. The assessment included questions related to medications taken in the study period as well as various clinical and behavioural measures. The main clinical measures collected at baseline and follow-up were the Quick Inventory of Depressive Symptomology (16 items, self-rated; QIDS-SR16) (Rush et al., 2003), Maudsley Modified Patient Health Questionnaire (9 items; MM-PHQ-9) (Harrison et al., 2021), Generalised Anxiety Disorder (7 items; GAD-7) (Spitzer, Kroenke, Williams, & Lowe, 2006), Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979), Social and Occupational Functioning Assessment Scale (SOFAS, part of SCID) (First et al., 2015), and the Young Mania Rating Score (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978). Please refer to the ADeSS trial protocol for more details regarding these procedures (Fennema, 2022; Harrison et al., 2020).

 As the ADeSS trial was stopped due to the COVID-19 pandemic, an alternative recruitment route was employed to continue recruitment for the observational fMRI study. Trial adverts were posted online, with further dissemination of study adverts via university and institutional recruitment circulars. Interested participants were asked to complete a similar pre-screening questionnaire as those approached for the ADeSS trial. If potentially eligible, participants were invited for an in-depth assessment to confirm their eligibility. For more details, please see Fennema (2022).

 A total of 1,755 participants with a history of MDD showed interest in participating and completed a pre-screening questionnaire. Potentially eligible MDD participants (n = 89) for the ADeSS trial and the fMRI study were invited to attend an in-depth assessment. Of those, 45 participants enrolled in the fMRI study, attended their MRI session and completed the study. Of those 45 participants, ten participants were also part of the ADeSS trial (support tool arm: n = 4; treatment-as-usual arm: n = 6).

Upon study completion, participants in the MDD group were asked to refer partners or friends who might be interested in serving as control participants. Moreover, trial adverts were posted online, with further dissemination of study adverts via university and institutional recruitment circulars. Interested participants were asked to complete a pre-screening questionnaire targeted to control participants. If potentially eligible, participants were invited for an in-depth assessment to confirm their eligibility and they completed a similar battery of clinical, behavioural and experimental measures as the MDD group.

 A total of 350 control participants completed a pre-screening questionnaire, with n = 113 meeting the initial eligibility criteria. Twenty-four control participants were invited for the initial baseline. Following the assessment, n = 22 control participants were enrolled in the study (n = 3 referred by a participant in the MDD group) and n = 20 control participants attended their MRI session.

## *Sample size*

A formal power calculation was difficult, with no previous study from which effect sizes could be drawn. As such, this study should be considered as a proof-of-concept for using fMRI to prospectively predict prognosis in MDD. If the neural signatures have at least 70% accuracy, a minimum of n = 44 MDD patients is required to achieve 85% power for a significant prediction of response (*p* = .05) compared to chance (50%) using a binomial test. Even though a clinically relevant biomarker should show at least 80% accuracy (Savitz, Rauch, & Drevets, 2013), the proposed sample size is sufficient to determine the feasibility in a subsequent larger sample.

## *Temporal signal-to-noise ratio*

Temporal signal-to-noise ratio (tSNR) was calculated using the following formula [1]:

[1] $\frac{\overbar{S}}{σ\_{N}}$

where $\overbar{S}$ is the mean activation signal of the fMRI time series and $σ\_{N}$ the standard deviation of the noise in the time series. Raw values were extracted using the MarsBaR toolbox (Brett, Anton, Valabregue, & Poline, 2002) for our pre-registered *a priori* regions-of-interest (ROI):

1. Bilateral amygdala, as defined by the Automated Anatomical Labelling (AAL) atlas (Rolls, Joliot, & Tzourio-Mazoyer, 2015) and used in Williams et al. (2015). Raw values were also extracted separately for the right and left amygdala.
2. Dorsal / pregenual anterior cingulate cortex, kindly provided by Godlewska et al. (2018) and based on the AAL atlas (Rolls et al., 2015). Please note the change in terminology for the latter ROI relative to that originally used at pre-registration: upon visual inspection, the ROI contained both dorsal and pregenual regions of the anterior cingulate cortex.

***Image acquisition***

High-resolution anatomical images were acquired with a 3D Inversion Recovery prepared Spoiled Gradient Echo (IR-SPGR) sequence (repetition time (TR) = 7.3 ms; echo time (TE) = 3.02 ms; inversion time (TI) = 400 ms; matrix = 256 x 256; excitation flip angle = 11 degrees; field-of-view (FOV) = 270 mm; slice thickness = 1.2 mm, 196 slices). Images for incidental findings review were acquired using a 2D Fast-Recovery Fast Spin-Echo (FRFSE; TR = 4380 ms; TE = 64.85 ms; matrix = 320 x 256; refocusing flip angle = 111 degrees; FOV = 240; 2 mm contiguous slices, 72 slices) and 2D Fluid Attenuated Inversion Recovery (FLAIR) sequence (TR = 8000 ms; TE = 128.41 ms; matrix = 256 x 128; refocusing flip angle = 111 degrees; FOV = 220; 4 mm continuous slices, 36 slices) and checked for brain abnormalities by a neuroradiologist at King’s College London Hospital, independent of additional, internal checks by the study team.

 While in the MRI scanner, the participant’s head motion was restricted using padding, and heart rate and respiration rate measurements were recorded via a manufacturer-supplied finger pulse sensor (peripheral plethysmograph) and respiratory belt, respectively. A mirror fitted to the head coil allowed participants to view visual stimuli presented during image acquisition, as stimuli were projected onto a screen located behind the participant’s head. Verbal instructions were communicated via the MRI intercom, using a pre-defined script to ensure consistency between participants.

## *fMRI paradigm*

The subliminal faces fMRI paradigm was based on the methodology outlined by Godlewska et al. (2018). However, we used different timings as initial testing of the fMRI paradigm revealed that the very short timings resulted in monitors dropping frames, i.e. no guarantee that the monitor would display the image and therefore no guarantee that there was in fact a stimulus. To account for this, we chose to display the target faces for longer (34 vs. 30 ms) and, to keep the total duration of each pair of faces at 100 ms, we shortened the masked face time by a corresponding amount (66 vs. 70 ms).

 Participants were asked to report the gender as fast as possible, via a button box, with the target and mask faces within the pair being of the same gender. Participants were debriefed after the fMRI session to explain the concept of subliminal presentation of emotional faces and how it can be used to detect emotional perception bias.

## *Image analysis*

Statistical Parametric Mapping (SPM12; http://www.fil.ion.ucl.ac.uk/spm12) was used for pre-processing steps and standard blood-oxygen level-dependent (BOLD) effect analysis. Functional images were realigned, unwarped and co-registered to the participant’s T1 images. These images were normalised to the co-registered T1 image and resliced at a voxel size of 3 x 3 x 3 mm. A smoothing kernel of full-width half-maximum equal to 6 mm was used. No slice timing correction was applied.

 Following the pre-processing steps, framewise displacement was calculated using Brain and Mind Lab (BRAMILA) tools (https://github.com/spunt/bspm/blob/master

/thirdparty/bramila/bramila\_framewiseDisplacement.m) to identify outliers regarding motion. Any framewise displacement of $\geq $1 mm was marked as a spike in movement and participants with spikes in more than 10% of the functional images were deemed to have moved too much and were excluded from all analyses. There is no fixed rule for proportion of spikes, but the combination of a relatively high movement threshold of $\geq $1 mm and a lower proportion of images affected by spikes, allowed for a trade-off between retaining patient data with reasonable quality and avoiding overfitting with too many scan-nulling regressors.

In addition, the MATLAB PhysIO toolbox was used to partially mitigate the impact of physiological noise (Kasper et al., 2017) (version R2021a-v8.0.0, open-source code available as part of the Translational Algorithms for Psychiatry-Advancing Science [TAPAS] software collection (Frassle et al., 2021): https://www. translationalneuromodeling.org/tapas). Heart rate and respiration rate measurements were used in a retrospective image correction (RETROICOR) model, using Fourier expansions of different orders for the estimated phases of cardiac pulsation (third order), respiration (fourth order) and cardio-respiratory interactions (first order) (Harvey et al., 2008). Moreover, the PhysIO toolbox created nuisance regressors related to motion, i.e. the standard six motion parameters describing movement by rotation and translation, and scan nulling regressors based on a framewise displacement threshold of $\geq $1 mm (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Power et al., 2014; Siegel et al., 2014).

## *Exploratory image analysis*

Exploratory analyses were conducted to examine differences in facial emotion perception processing between participants with MDD and controls, using a factorial model with two factors: group (MDD vs. control) and emotion (sad vs. happy). Within the model set-up, no assumption of independence was made for emotion, because both sad and happy faces were measured within the same participant. F-contrasts for main effects of group, emotion and their interaction were thresholded at *p* = .001 (uncorrected voxel-level) and corrected for Family-Wise Error (FWE) at the voxel-level at *p* = .05 over the *a priori* defined ROIs, i.e. bilateral amygdala and dorsal/pregenual anterior cingulate cortex, and the volume of the whole brain.

## *Behavioural data analysis*

Data were checked for outliers using standardised scores (outside *z* = ± 2 standard deviations from the mean) for the MDD group and the control group separately. Results with outliers were confirmed by supplementary analyses replacing the outlying value by the nearest occurring value in the rest of the sample that was not an outlier. Moreover, data were screened for normal distribution within each group with Kolmogorov-Smirnov tests and if the assumption of normality was violated, non-parametric Mann-Whitney-*U* tests instead of independent sample t-tests were used to investigate between-group differences (MDD vs. controls).

# Supplementary Results

## *Exploratory cross-sectional fMRI findings*

The two-way factorial SPM model probing group (MDD vs. controls) and emotion effects (sad vs. happy) on fMRI activation (BOLD) did not show any main effect of group or emotion or an interaction effect at the whole brain level. Small-volume correction with the *a priori* definedROIs also did not uncover any effects. These null findings were confirmed for the extracted cluster averages for the *a priori* dorsal/pregenual anterior cingulate cortex ROI (main effect of group: *F*[1,51] = .90, *p* = .35; main effect of emotion: *F*[1,51] = 1.06, *p* = .31; interaction effect: *F*[1,51] = .05, *p* = .83) and the *a priori* bilateral amygdala ROI (main effect of group: *F*[1,51] = .08, *p* = .77; main effect of emotion: *F*[1,51] = .001, *p* = .98; interaction effect: *F*[1,51] = .02, *p* = .88). The findings did not change when including the reserve list, i.e. those participants who did not meet the strictest quality threshold criteria.

## *Exploratory prognostic fMRI findings*

When categorising the participants into partial responders (i.e. participants who showed at least a 25% reduction in depressive symptoms as measured on the QIDS-SR16, n = 15) and non-responders (n = 23), there was a trend-wise interaction effect for the extracted *a priori* bilateral amygdala ROI cluster averages between emotion (sad vs happy faces) and group (partial responders vs. non-responders; *F*[1,36] = 3.94, *p =* .06), but no main effect of emotion (*F*[1,36] = .35, *p* = .56) or group (*F*[1,36] = .70, *p* = .41). This trend-wise interaction effect was driven by partial responders showing higher bilateral amygdala activation during happy vs. neutral faces (M = .01, SD = .12) relative to sad vs. neutral faces (M = -.04, SD = .11), resulting in a negative difference for sad vs. happy faces (M = -.06, SE = .03, *t* = -1.69, df = 14, *p* = .11; Supplementary Figure 2). In contrast, non-responders did not show a difference in bilateral amygdala activation during happy vs. neutral faces (M = -.06, SD = .12) relative to sad vs. neutral faces (M = -.03, SD = .09; difference for sad vs. happy faces: M =.03, SE = .03, *t* = 1.10, df = 22, *p* = .29). There was a trend-wise difference between the groups on relative activation of sad vs. happy faces (mean difference = -.09, SE = .04, *t* = -1.99, df = 36, *p* = .06), which was identified by the observed trend-wise interaction effect. With the inclusion of the reserve list, the interaction effect was significant (*F*[1,40] = 5.76, *p* = .02).

The association between amygdala BOLD activation for sad vs. happy faces and QIDS-SR16 percentage change was mostly driven by the right amygdala (*rs*[38] = .46, *p* = .003; Supplementary Figure 3) rather than the left amygdala (*rs*[38] = .27, *p* = .10). The extracted cluster averages for the *a priori* defined right amygdala ROI showed an interaction effect between emotion (sad vs. happy faces) and group (partial responders vs. non-responders; *F*[1,36] = 6.34, *p* = .02), but not a main effect of emotion (*F*[1,36] = .49, *p* = .49) or group (*F*[1,36] = 1.85, *p* = .18). In contrast, the extracted cluster averages for the *a priori* left amygdala ROI did not show a main effect of emotion (*F*[1,36] = .15, *p* = .70), a main effect of group (*F*[1,36] = .08, *p* = .78) or an interaction effect (*F*[1,36] = 1.37, *p* = .25).

 Similar to bilateral amygdala BOLD activation, the observed interaction effect for theright amygdala was driven by partial responders showing higher BOLD activation during happy vs. neutral faces (M = .02, SD = .14) relative to sad vs. neutral faces (M = -.05, SD = .11), resulting in a negative difference for sad vs. happy faces (M = -.07, SE = .04, *t* = -1.93, df = 14, *p* = .08; Supplementary Figure 3). Non-responders, on the other hand, did not show a significant difference in right amygdala activation during happy vs. neutral faces (M = -.08, SD = .11) relative to sad vs. neutral faces (M = -.04, SD = .09; difference for sad vs. happy faces: M =.04, SE = .03, *t* = 1.53, df = 22, *p* = .14). As a result, the groups differed on relative activation for sad vs. happy faces (mean difference = -.11, SE = .04, *t* = -2.52, df = 36, *p* = .02), which was identified by the observed interaction effect.

 When including the reserve list, the positive association between the right amygdala and QIDS-SR16 percentage change remained (*rs*[42] = .49, *p* = .001) as did the interaction effect (*F*[1,40] = 8.21, *p* = .007). However, it did not change the null findings for the left amygdala.

**Supplementary Tables**

**Supplementary Table 1 | Overview of inclusion / exclusion for imaging analysis.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | MDD | Control | *Total* |
| Total: | 45 | 20 | *65* |
| Included in main analysis: | 38 | 15 | *53* |
| * Reserve list, applying less stringent movement criteria (translation < 8 mm; rotation < 6 degrees) and suboptimal physiological input
 | 4 | 4 | *8* |
| Excluded: | 3 | 1 | *4* |
| * Excluded – abnormal images with functional implications
 | 0 | 0 | *0* |
| * Excluded – excessive movement, but OK coverage
 | 3 | 0 | *3* |
| * Excluded – excessive dropout, but OK movement
 | 0 | 1 | *1* |
| MDD = major depressive disorder. |  |

**Supplementary Table 2 | Mean tSNR for regions-of-interest (n=61).**

|  |  |  |  |
| --- | --- | --- | --- |
| Bilateral amygdala | Left amygdala | Right amygdala | Dorsal/pregenual anterior cingulate cortex |
| 132.0 | 123.2 | 139.7 | 133.9 |
| tSNR = temporal signal-to-noise ratio. |

**Supplementary Table 3 | Baseline demographic characteristics by group.**

**This table has been adapted from a previously published one in Neuroimage:Clinical (doi: 10.1016/j.nicl.2023.103453)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | MDD | Control | Comparison |
|  | n = 42 | n = 19 |  |
| Age | 41.5 ± 14.5; 19 - 66 | 40.2 ± 13.2; 20 - 66 | *t*(59) = .34, *p* = .74 |
| Gender |  |  | χ2 (2,61) = .47, *p* = .79 |
| Female | n = 35 (83%) | n = 16 (84%) |  |
| Male | n = 6 (14%) | n = 3 (16%) |  |
| Other | n = 1 (2%) | n = 0 (0%) |  |
| Ethnicitya |  |  | χ2 (1,60) = 2.60, *p* = .11 |
| Asian | n = 5 (12%) | n = 0 (0%) |  |
| Black | n = 2 (5%) | n = 0 (0%) |  |
| Other | n = 2 (5%) | n = 1 (5%) |  |
| White | n = 32 (78%) | n = 18 (95%) |  |
| Native first language  |  |  | χ2 (1,61) = 3.59, *p* = .06 |
| English | n = 34 (81%) | n = 11 (58%) |  |
| Non-English | n = 8 (19%) | n = 8 (42%) |  |
| Years of education | 16.8 ± 3.5; 10 - 24 | 16.6 ± 3.1; 9 - 22 | *t*(59) = .21, *p* = .83 |
| a Missing data for one MDD; categories have been merged into White vs. non-White for chi-square test. Means, standard deviations and range are reported (*M ± SD; minimum – maximum).* Percentages may not add up to 100 due to rounding. \* significant at *p* < .05, two-tailed. MDD = major depressive disorder. |

**Supplementary Table 4 | Movement parameters and response times for sad, happy, and neutral blocks by group.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | MDD | Control | Comparison |
|  | n = 42 | n = 19 |  |
| Movement parameters |  |  |  |
| RMS translation | .07 ± .03 | .10 ± .09 | *U*(61) = 383.0, *z* = -.25, *p* = .80 |
| RMS rotation | .07 ± .03 | .08 ± .05 | *U*(61) = 359.0, *z* = -.62, *p* = .53 |
| Response timesa (ms) |  |  |  |
| Sad faces | 596 ± 81 | 617 ± 72 | *t*(58) = -.96, *p* = .34 |
| Happy faces | 594 ± 77 | 613 ± 69 | *t*(58) = -.92, *p* = .36 |
| Neutral faces | 590 ± 81 | 615 ± 72 | *t*(58) = -1.13, *p* = .26 |
| Accuracy (%)b | 92.3 ± 10.8 | 93.6 ± 5.0 | *t*(58) = -.51, *p* = .61 |
| a One MDD participant had a faulty button box, so no behavioural measures were recorded.b Accuracy was defined as percentage of correctly identifying the gender of the pair of faces. Means and standard deviations are reported (*M ± SD).* \* significant at *p < .*05 threshold, two-tailed. MDD = major depressive disorder; RMS = root mean square. |

**Supplementary Table 5 | Baseline clinical characteristics control participants (n=19).**

**This table has been adapted from a previously published one in Neuroimage:Clinical (doi: 10.1016/j.nicl.2023.103453)**

|  |  |
| --- | --- |
| Past depressive symptoms not meeting MDE criteria | 4 (21%) |
| Life-time axis-I disorder using DSM-5 criteria |  |
| Anxiety disorder | 6 (32%) |
| Subthreshold past posttraumatic stress disorder | 2 (11%) |
| None | 12 (63%) |
| Family history |  |
| First degree relative with probable MDD | 2 (11%) |
| No family history of MDD | 17 (90%) |
| Percentages may not add up to 100 due to rounding. MDD = major depressive disorder; MDE = major depressive episode; DSM-5 = Diagnostic and Statistical Manual for Mental Disorders 5th edition. |

**Supplementary Table 6 | Current and past MDD treatment (n=42).**

**This table has been adapted from a previously published one in Neuroimage:Clinical (doi: 10.1016/j.nicl.2023.103453)**

|  |  |
| --- | --- |
| Treatment at baseline |  |
| SSRI | 34 (81%) |
| *Sertraline* | 12 (29%) |
| *Citalopram* | 9 (21%) |
| *Escitalopram* | 3 (7%) |
| *Fluoxetine* | 5 (12%) |
| *Venlafaxine (≤ 150mg)* | 5 (12%) |
| SNRI | 5 (12%) |
| *Duloxetine* | 2 (5%) |
| *Venlafaxine (> 150mg)* | 3 (7%) |
| Tricyclic antidepressant | 2 (5%) |
| Other antidepressant | 1 (2%) |
| Add-on treatment | 4 (10%) |
| Non-pharmacological treatment | 12 (29%) |
| Past treatment |  |
| 1 – 2 medications | 29 (69%) |
| 3 – 4 medications  | 9 (21%) |
| 5 – 6 medications  | 4 (10%) |
| SSRI |  |
| *Sertraline* | 13 (31%) |
| *Citalopram* | 21 (50%) |
| *Escitalopram* | 5 (12%) |
| *Fluoxetine* | 23 (55%) |
| *Paroxetine* | 5 (12%) |
| *Venlafaxine (≤ 150mg)* | 5 (12%) |
| SNRI |  |
| *Duloxetine* | 2 (5%) |
| *Venlafaxine (> 150mg)* | 1 (2%) |
| Tricyclic antidepressant | 4 (10%) |
| Other antidepressant | 8 (19%) |
| Add-on treatment | 6 (14%) |
| Lifetime mental health/psychotherapy service use | 40 (95%) |
| *Of which past secondary care use* | 9 (21%) |
| Percentages may not add up to 100 due to rounding. MDD = major depressive disorder; SSRI = selective serotonin reuptake inhibitor; SNRI = selective norepinephrine reuptake inhibitor. |

**Supplementary Table 7 | MDD treatment during follow-up period (n=42).**

**This table has been adapted from a previously published one in Neuroimage:Clinical (doi: 10.1016/j.nicl.2023.103453)**

|  |  |
| --- | --- |
| Main change |  |
| No change in antidepressant | 22 (52%) |
| Stopped antidepressant  | 6 (14%) |
| Lowered dose of antidepressant | 0 (0%) |
| Increase from effective dose to higher effective dose | 8 (19%) |
| Increase from ineffective dose to effective dose | 0 (0%) |
| Change to another antidepressant at effective dose | 4 (10%) |
| Change to another antidepressant at ineffective dose | 2 (5%) |
| Main antidepressant |  |
| SSRI | 28 (67%) |
| *Sertraline* | 9 (21%) |
| *Citalopram* | 6 (14%) |
| *Escitalopram* | 4 (10%) |
| *Fluoxetine* | 3 (7%) |
| *Venlafaxine (≤ 150mg)* | 6 (14%) |
| SNRI | 5 (12%) |
| *Duloxetine* | 2 (5%) |
| *Venlafaxine (> 150mg)* | 3 (7%) |
| Mirtazapine | 3 (7%) |
| Tricyclic antidepressant | 1 (2%) |
| Other antidepressant | 0 (%) |
| Add-on treatment | 5 (12%) |
| Change in mental health service use |  |
| Started accessing mental health service | 8 (19%) |
| Continued care in mental health service  | 9 (21%) |
| Stopped mental health treatment  | 2 (5%) |
| Type of mental health service use |  |
| *CBT* | 3 (7%) |
| *Psychotherapy* | 5 (12%) |
| *Psychoanalysis* | 2 (5%) |
| *Counselling* | 2 (5%) |
| *Other* | 5 (12%) |
| GP appointments related to mental healtha |  |
| None | 10 (24%) |
| 1 | 9 (21%) |
| 2 | 11 (26%) |
| 3 | 8 (19%) |
| More than 3 | 3 (7%) |
| a Missing data for one participant.Percentages may not add up to 100 due to rounding. MDD = major depressive disorder; SSRI = selective serotonin reuptake inhibitor; SNRI = selective norepinephrine reuptake inhibitor; CBT = cognitive behavioural therapy; GP = general practitioner. |

**Supplementary Table 8 | Association between potential clinical confounders and percentage change for primary analysis MDD group (n=38).**

**This table has been adapted from a previously published one in Neuroimage:Clinical (doi: 10.1016/j.nicl.2023.103453)**

|  |  |  |
| --- | --- | --- |
|  |  | QIDS-SR16 percentage change |
| MM-PHQ-9 (baseline) | rho | .15 |
| *p*-value | .38 |
| GAD-7 (baseline) | rho | .08 |
| *p*-value | .63 |
| Current MDE duration (months) | rho | .39\* |
| *p*-value | .02 |
| Age of onset first MDE (years) | rho | -.15 |
| *p*-value | .36 |
| Number of MDE in lifetime | rho | -.12 |
| *p*-value | .47 |
| Total duration depression from onset (years) | rho | .05 |
| *p­*-value | .79 |
| Number of suicide attempts | rho | .11 |
|  | *p­*-value | .53 |
| \* significant at *p* < .05 threshold, two-tailed. MDD = major depressive disorder; QIDS-SR16 = Quick Inventory of Depressive Symptomatology – self-rated, 16 items; MM-PHQ-9 = Maudsley Modified Patient Health Questionnaire, 9 items; GAD-7 = Generalised Anxiety Disorder, 7 items; MDE = major depressive episode. |

**Supplementary Table 9 | Association between baseline anxiety and neural measures for primary analysis MDD group (n=38).**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Dorsal/pregenual ACC | Left amygdala | Right amygdala | Bilateral amygdala |
|  |  | Happy | Sad | Sad vs. happy | Happy | Sad | Sad vs. happy | Happy | Sad | Sad vs. happy | Happy | Sad | Sad vs. happy |
| GAD-7 (baseline) | rho | -.42\* | .10 | .38\* | -.18 | -.16 | .04 | -.32\* | -.06 | .24 | -.27 | -.09 | .11 |
| *p*-value | .01 | .54 | .02 | .28 | .34 | .81 | .05 | .71 | .15 | .10 | .59 | .53 |
| \* significant at *p* < .05 threshold, two-tailed. MDD = major depressive disorder; ACC = anterior cingulate cortex; GAD-7 = Generalised Anxiety Disorder, 7 items. |

**Supplementary Figures**

**Supplementary Figure 1 | Overall mean tSNR map across participants for facial emotions fMRI paradigm.**

Mean tSNR values for each participant (n = 61) were combined into one overall mean tSNR across participants. The tSNR exceeds the minimum threshold of 40, as proposed by Murphy, Bodurka, and Bandettini (2007), for most regions. Displayed using MRIcron (Rorden & Brett, 2000). tSNR = temporal signal-to-noise ratio.

**Supplementary Figure 2 | Comparison between partial responders and non-responders for bilateral amygdala neural responses to facial emotions.**

There was a trend-wise interaction effect between group (partial responders vs. non-responders, where partial responder was defined as participants who showed at least a 25% reduction in depressive symptoms as measured on the QIDS-SR16) and emotion (sad vs. happy) for bilateral amygdala activation, using the extracted *a priori* defined bilateral amygdala ROI averages. This interaction effect was driven by higher bilateral amygdala activation during happy faces in the partial response group compared to the non-response group, and lower bilateral amygdala activation during sad faces in the partial response group compared to the non-response group. There was a trend-wise significant difference between groups on relative activation of sad vs. happy faces, which was identified by the observed interaction effect. QIDS-SR16 = Quick Inventory of Depressive Symptomatology - self-rated, 16-items; ROI = region-of-interest.

**Supplementary Figure 3 | Association between right amygdala neural responses to facial emotions and change in depressive symptoms.**

**Panel A)** shows a cropped section through the right amygdala, displayed using MRIcron (Rorden & Brett, 2000) at an uncorrected voxel-level threshold of *p* = .005, with no cluster-size threshold (the color bar represents *t* values; the numbers above the brain slices stand for coordinates of the Montreal Neurological Institute coordinate system). **Panel B)** shows that there was a positive association between right amygdala BOLD activation for sad vs. happy faces and QIDS-SR16 percentage change from baseline to follow-up, using the extracted *a priori* right amygdala ROI averages. **Panel C)** shows that there was an interaction effect between group (partial responders vs. non-responders, where partial responder was defined as participants who showed at least a 25% reduction in depressive symptoms as measured on the QIDS-SR16) and emotion (sad vs. happy) for right amygdala activation, using the extracted *a priori* right amygdala ROI averages. This interaction effect was driven by higher right amygdala activation during happy faces in the partial response group compared to the non-response group, and lower right amygdala activation during sad faces in the partial response group compared to the non-response group. There was a significant difference between groups on relative activation of sad vs. happy faces, which was identified by the observed interaction effect. BOLD = blood-oxygen level-dependent; QIDS-SR16 = Quick Inventory of Depressive Symptomatology - self-rated, 16-items; *rs* = Spearman correlation; ROI = region-of-interest.

# References

Brett, M., Anton, J.-L., Valabregue, R., & Poline, J.-B. (2002). *Region of interest analysis using an SPM toolbox.* Paper presented at the 8th International Conference on Functional Mapping of the Human Brain, Sendai, Japan.

Fennema, D. (2022). *Neural signatures of emotional biases and prognosis in treatment-resistant depression.* (PhD). King's College London, London.

First, M. B., Williams, J. B. W., Karg, R. S., & Spitzer, R. L. (2015). *Structured Clinical Interview for DSM-5 - Research Version (SCID-5 for DSM-5, Research Version; SCID-5-RV, Version 1.0.0)*. Arlington, VA: American Psychiatric Association.

Frassle, S., Aponte, E. A., Bollmann, S., Brodersen, K. H., Do, C. T., Harrison, O. K., . . . Stephan, K. E. (2021). TAPAS: An open-source software package for translational neuromodeling and computational psychiatry. *Frontiers in Psychiatry, 12*, 680811. doi:10.3389/fpsyt.2021.680811

Godlewska, B. R., Browning, M., Norbury, R., Igoumenou, A., Cowen, P. J., & Harmer, C. J. (2018). Predicting treatment response in depression: the role of anterior cingulate cortex. *International Journal of Neuropsychopharmacology, 21*(11), 988-996. doi:10.1093/ijnp/pyy069

Harrison, P., Carr, E., Goldsmith, K., Young, A. H., Ashworth, M., Fennema, D., . . . Zahn, R. (2020). Study protocol for the antidepressant advisor (ADeSS): a decision support system for antidepressant treatment for depression in UK primary care: a feasibility study. *BMJ Open, 10*(5), e035905. doi:10.1136/bmjopen-2019-035905

Harrison, P., Walton, S., Fennema, D., Duan, S., Jaeckle, T., Goldsmith, K., . . . Zahn, R. (2021). Development and validation of the Maudsley Modified Patient Health Questionnaire (MM-PHQ-9). *BJPsych Open, 7*(4), e123. doi:10.1192/bjo.2021.953

Harvey, A. K., Pattinson, K. T., Brooks, J. C., Mayhew, S. D., Jenkinson, M., & Wise, R. G. (2008). Brainstem functional magnetic resonance imaging: disentangling signal from physiological noise. *Journal of Magnetic Resonance Imaging, 28*(6), 1337-1344. doi:10.1002/jmri.21623

Kasper, L., Bollmann, S., Diaconescu, A. O., Hutton, C., Heinzle, J., Iglesias, S., . . . Stephan, K. E. (2017). The PhysIO toolbox for modeling physiological noise in fMRI data. *Journal of Neuroscience Methods, 276*, 56-72. doi:10.1016/j.jneumeth.2016.10.019

Kessler, R. C., Akiskal, H. S., Angst, J., Guyer, M., Hirschfeld, R. M., Merikangas, K. R., & Stang, P. E. (2006). Validity of the assessment of bipolar spectrum disorders in the WHO CIDI 3.0. *Journal of Affective Disorders, 96*(3), 259-269. doi:10.1016/j.jad.2006.08.018

Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry, 134*, 382-389. doi:10.1192/bjp.134.4.382

Murphy, K., Bodurka, J., & Bandettini, P. A. (2007). How long to scan? The relationship between fMRI temporal signal to noise ratio and necessary scan duration. *Neuroimage, 34*(2), 565-574. doi:10.1016/j.neuroimage.2006.09.032

Rolls, E. T., Joliot, M., & Tzourio-Mazoyer, N. (2015). Implementation of a new parcellation of the orbitofrontal cortex in the automated anatomical labeling atlas. *Neuroimage, 122*, 1-5. doi:10.1016/j.neuroimage.2015.07.075

Rorden, C., & Brett, M. (2000). Stereotaxic display of brain lesions. *Behavioural Neurology, 12*(4), 191-200. doi:10.1155/2000/421719

Rush, A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N., . . . Keller, M. B. (2003). The 16-item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biological Psychiatry, 54*(5), 573-583. doi:10.1016/s0006-3223(02)01866-8

Savitz, J. B., Rauch, S. L., & Drevets, W. C. (2013). Clinical application of brain imaging for the diagnosis of mood disorders: the current state of play. *Molecular Psychiatry, 18*(5), 528-539. doi:10.1038/mp.2013.25

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., . . . Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59*, 22-33.

Spitzer, R. L., Kroenke, K., Williams, J. B. W., & Lowe, B. (2006). A brief measure for assessing generalised anxiety disorder: the GAD-7. *Archives of Internal Medicine, 166*(10), 1092-1097. doi:10.1001/archinte.166.10.1092

Williams, L. M., Korgaonkar, M. S., Song, Y. C., Paton, R., Eagles, S., Goldstein-Piekarski, A., . . . Etkin, A. (2015). Amygdala reactivity to emotional faces in the prediction of general and medication-specific responses to antidepressant treatment in the randomized iSPOT-D trial. *Neuropsychopharmacology, 40*(10), 2398-2408. doi:10.1038/npp.2015.89

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: reliability, validity and sensitivity. *British Journal of Psychiatry, 133*, 429-435. doi:10.1192/bjp.133.5.429