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

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Abstract

Background: Amygdala and dorsal anterior cingulate cortex responses to facial emotions have shown promise in predicting treatment response in medication-free major depressive disorder (MDD). Here, we examined their role in the pathophysiology of clinical outcomes in more chronic, difficult-to-treat forms of MDD.

Methods: Forty-five people with current MDD who had not responded to ≥2 serotonergic antidepressants (n=42, meeting pre-defined fMRI minimum quality thresholds) were enrolled and followed up over four months of standard primary care. Prior to medication review, subliminal facial emotion fMRI was used to extract blood-oxygen level-dependent effects for sad vs. happy faces from two pre-registered *a priori* defined regions: bilateral amygdala and dorsal/pregenual anterior cingulate cortex. Clinical outcome was the percentage change on the self-reported Quick Inventory of Depressive Symptomatology (16-item).

Results: We corroborated our pre-registered hypothesis (NCT04342299) that lower bilateral amygdala activation for sad vs. happy faces predicted favourable clinical outcomes (r_s[38]=.40, p=.01). In contrast, there was no effect for dorsal/pregenual anterior cingulate cortex activation (r_s[38]=.18, p=.29), nor when using voxel-based whole-brain analyses (voxel-based Family-Wise Error-corrected p<.05). Predictive effects were mainly driven by the right amygdala whose response to happy faces was reduced in patients with higher anxiety levels.

Conclusions: We confirmed the prediction that a lower amygdala response to negative vs. positive facial expressions might be an adaptive neural signature, which predicts subsequent symptom improvement also in difficult-to-treat MDD. Anxiety reduced adaptive amygdala responses.

Background

Only half of patients with major depressive disorder (MDD) respond to their initial treatment and remission rates are even lower (Rush et al., 2006; Souery et al., 2007; Thomas et al., 2013). Identifying prognostic markers of poor clinical outcomes could facilitate personalised treatment algorithms and pathways, improving time to remission. In order to develop such markers, a deeper understanding of the pathophysiology of MDD is required.

As proposed by the tripartite model of anxiety and depression (Clark & Watson, 1991; Watson, Clark, & Carey, 1988), MDD patients exhibit a proneness to experience negative rather than positive emotions, which can be observed in aspects of memory, emotional perception and emotional processing (Bourke, Douglas, & Porter, 2010; Disner, Beevers, Haigh, & Beck, 2011; Krause, Linardatos, Fresco, & Moore, 2021; Roiser, Elliott, & Sahakian, 2012; Stuhrmann, Suslow, & Dannlowski, 2011). For example, people with depression tend to respond more strongly to negative facial expressions than to positive ones, i.e. show a negative perceptual bias (Bourke et al., 2010; Krause et al., 2021; Stuhrmann et al., 2011). These perceptual biases have often been linked with hyper-activation of brain regions thought to underpin initial stimulus appraisal, such as the amygdala, and hypo-activation of cortical parts of the limbic system, such as the dorsal and pregenual anterior cingulate cortex (Beck, 2008; Disner et al., 2011; Phillips, Drevets, Rauch, & Lane, 2003; Phillips, Ladouceur, & Drevets, 2008; Pizzagalli, 2011).

Antidepressant treatment and psychotherapy are thought to introduce a positive emotional processing bias, potentially through effects on the fronto-limbic neural network and modulation of initial appraisal and attentional processing of affective stimuli (Browning, Holmes, & Harmer, 2010; Harmer, 2008; Roiser et al., 2012). As both treatment approaches ameliorate distorted emotional perception, neural response at baseline may predict treatment outcome. Indeed, neural signatures of these negative biases have been associated with

prognosis and response to treatment (Dichter, Gibbs, & Smoski, 2015; Dunlop & Mayberg, 2014; Fonseka, MacQueen, & Kennedy, 2018; Fu, Steiner, & Costafreda, 2013). More specifically, baseline dorsal anterior cingulate cortex and amygdala activation, two regions thought to underpin the emotional perception biases often observed in MDD, were relatively consistently associated with clinical response across emotional processing tasks and imaging modalities (Fu et al., 2013; Pizzagalli, 2011). However, most studies investigating imaging biomarkers related to emotional perception biases have been conducted in untreated patients or in a secondary care setting.

In this pre-registered study (NCT04342299), we sought to determine whether facial emotion perception fMRI measures are prospectively associated with clinical outcomes after four months of standard treatment in difficult-to-treat depression in a primary care setting. Here, we defined difficult-to-treat depression as "depression that continues to cause significant burden despite usual treatment efforts" (McAllister-Williams et al., 2020), to reflect the absence of formal episode and treatment response metrics in primary care, as well as the more chronic nature. Of particular interest were the neural signatures of pregenual anterior cingulate cortex and amygdala activation, which have previously been shown to predict response to treatment at the individual level in medication-naïve and medication-free MDD patients (Godlewska et al., 2018; Williams et al., 2015). More specifically, we examined whether these neural signatures generalise to more chronic, difficult-to-treat forms of MDD.

Williams et al. (2015) examined whether pre-treatment amygdala activation could predict response to a range of commonly prescribed antidepressants at an individual level. Participants were shown a series of facial emotion expressions, presented either subliminally or supraliminally. While the latter did not show any prediction effects, subliminal presentation of happy faces was associated with lower activation of the bilateral amygdala in responders relative to non-responders at baseline. Moreover, they found that responders to venlafaxine had

lower activation of the left amygdala to subliminal presentation of sad faces at baseline. These findings were in keeping with a meta-analysis that linked decreased amygdala activation to more favourable clinical response (Fu et al., 2013). Therefore, we predicted (pre-registered Hypothesis 1) that decreased activation of the amygdala for subliminal sad vs. happy faces would be prospectively associated with favourable clinical outcomes after receiving four months of standard care.

Similarly, Godlewska et al. (2018) investigated whether pre-treatment pregenual anterior cingulate cortex activation could predict response after six weeks of treatment with escitalopram. Using an fMRI paradigm consisting of brief, masked presentations of facial expressions, the authors reported that responders showed increased pre-treatment pregenual anterior cingulate cortex activation to sad vs. happy faces compared with non-responders. Meta-analyses by Pizzagalli (2011) and Fu et al. (2013), which included studies that investigated implicit and explicit emotion processing and a range of neuroimaging modalities, corroborated the finding that increased pre-treatment anterior cingulate cortex activity is relatively consistently associated with a higher likelihood of treatment response to commonly used pharmacological and psychological therapies. Therefore, we predicted (pre-registered Hypothesis 2) that increased activation in the pregenual anterior cingulate cortex to subliminal sad vs. happy faces would be prospectively associated with favourable clinical outcomes after receiving four months of standard care.

Lastly, we predicted (pre-registered Hypothesis 3) that patients with anxious distress, commonly encountered in treatment-resistant and chronic MDD populations and associated with a poor prognosis (Dold et al., 2017; Domschke, Deckert, Arolt, & Baune, 2010; Fava et al., 2004; Gaspersz et al., 2017), would show increased activation of the amygdala for subliminal sad vs. happy faces. The neural response to subliminal emotional faces can be modulated by anxiety (Etkin et al., 2004; Etkin & Wager, 2007; Stein, Simmons, Feinstein, &

Paulus, 2007). Anxiety is often accompanied by irritability (Brown, DiBenedetti, Danchenko, Weiller, & Fava, 2016) and feelings of anger (Jaeckle, 2018; Jaeckle et al., 2021). Both anxiety and anger are characterised by increased arousal (Alia-Klein et al., 2020; Steimer, 2002), which can be observed as increased amygdala activation during emotion processing (Alia-Klein et al., 2018; Etkin & Wager, 2007; Stein et al., 2007). The amygdala, heavily linked to sensory perception, is thought to assess the biological significance of emotional faces and coordinate subsequent actions through its connectivity with frontal areas, like the dorsal/pregenual anterior cingulate cortex (Adolphs, 2010; Browning et al., 2010; Pessoa, 2010; Pessoa & Adolphs, 2010). Conversely, heightened arousal may predispose an individual to anxiety and/or feelings of irritability and anger, which has been associated with poorer treatment outcome (Dold et al., 2017; Domschke et al., 2010; Fava et al., 2008; Gaspersz et al., 2017; Jaeckle et al., 2021; Jha, Minhajuddin, South, Rush, & Trivedi, 2019).

Methods

Studies

This study was linked with a cluster-randomised trial, the Antidepressant Advisor trial (ADeSS; NCT03628027), whose design and clinical results have been published elsewhere (Harrison et al., 2020; Harrison et al., 2023). In short, the ADeSS trial assessed the feasibility of a novel computerised decision support algorithm to facilitate antidepressant medication choices in MDD patients in primary care. Participants enrolled in the trial were assigned to either i) use of a computerised decision-support tool by their general practitioner (GP) to assist with antidepressant choices, or ii) treatment-as-usual. Both arms involved standard care as the decision-support tool prompted GPs to follow National Institute for Health and Care Excellence guidelines.

Most participants for the current observational prospective pre-registered study

(NCT04342299), however, were recruited outside of the ADeSS main trial through online advertising and participants received standard primary care (see Supplemental Information). As part of the current study, participants were invited to attend an optional MRI scan to examine candidate biomarkers predictive of clinical outcomes after four months in primary care. We have published task-based and resting-state functional imaging results from the same cohort previously (Fennema et al., 2023, 2024), but here, we report on the facial emotion perception fMRI data for the first time. The study was approved by the NHS Health Research Authority and National Research Ethics Service London – Camberwell St Giles Committee (REC reference: 17/LO/2074). All participants provided written, informed consent and received compensation for their time and for their travel expenses. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Participants

As previously described in Fennema et al. (2023), participants aged ≥ 18 were eligible if they had a current major depressive episode (MDE) and MDD according to the Structured Clinical Interview (SCID) for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (First, Williams, Karg, & Spitzer, 2015) and had Patient Health Questionnaire (PHQ-9) scores ≥15 (moderately severe, (Spitzer, Kroenke, Williams, & 1999)). Additionally, they had not to have benefitted from at least two serotonergic antidepressants from the following list in current or previous episodes to be consistent with the ADeSS trial: citalopram, fluoxetine, sertraline, escitalopram, paroxetine, venlafaxine, or duloxetine (Harrison et al., 2020). All participants were encouraged to book an appointment with their GP to review their treatment and were followed-up after four months in primary care. Before their GP visit, participants completed an fMRI paradigm.

Age- and gender-matched control participants without a definite first-degree family history of mood disorders and without a history of major depressive episodes, with PHQ-9 scores <10, but otherwise meeting the same exclusion criteria as the MDD group were recruited through online advertising. After the initial assessment, control participants completed the same fMRI paradigm, allowing further interpretation and exploratory cross-sectional comparisons with the MDD group (not pre-registered). For more information about inclusion/exclusion criteria, recruitment, clinical assessment, and measures collected, please see Supplementary Methods.

We considered three samples for analysis. For the primary imaging analysis, we included 38 participants with current MDD. All met strict criteria for signal dropout (sufficient coverage of the bilateral amygdala, bilateral subgenual cingulate and frontopolar cortex) and pragmatic maximum movement thresholds as in our previous paper (Fennema et al., 2023) (translation <6mm; rotation <2 degrees; less than 10% censored volumes). For the secondary imaging analysis, we additionally included four participants who did not meet the strictest fMRI quality control threshold ("reserve list") to assess how results generalise to a more pragmatic sample including those with lower fMRI quality on the findings, giving a total of 42 participants. Finally, for exploratory cross-sectional analyses to help with interpretation, we compared the MDD group with 19 control participants (15 of whom met the strict criteria and four additional control participants who did not meet the strictest criteria ["reserve list"]; Supplementary Table 1).

Primary outcome

As stated in our pre-registered protocol (NCT04342299), we used a continuous measure of clinical outcome rather than categorising participants into responders and non-responders using the standard definition of a 50% reduction (Nierenberg & DeCecco, 2001) in Quick Inventory of Depressive Symptomatology – self-rated (16-item; QIDS-SR16) (Rush et al., 2003) scores,

due to an unbalanced split between the resulting groups (responders n=10; non-responders n=32). The outcome was defined as the percentage change from baseline to follow-up on our pre-registered primary outcome measure, QIDS-SR16, where negative percentages corresponded to a reduction in depressive symptoms.

fMRI acquisition

Image acquisition was carried out on an MR750 3T MR system (GE Healthcare, Chicago, USA), using a Nova Medical 32-channel head coil. Functional image acquisition was obtained parallel to the anterior commissure – posterior commissure plane, with slices running top to bottom, using a standard T2*-weighted echo-planar imaging (blood-oxygen level-dependent; BOLD) sequence (repetition time=2000ms; echo time=30ms; matrix=64x64; field-of-view=240mm; flip angle=75 degrees; slice thickness=3mm, slice gap=0.3mm, inter-slice distance=3.3mm, 41 slices, 267 volumes). Shimming was automatically applied as part of the scanner's "pre-scan" procedures, and four additional volumes were acquired and automatically discarded at the start of each fMRI run, allowing for T1 equilibration effects.

As demonstrated by measurements of the temporal signal-to-noise, i.e. "the mean of a voxel's BOLD signal over time divided by its standard deviation over time" (Welvaert & Rosseel, 2013), overall signal quality was very good (Supplementary Figure 1; Supplementary Table 2). For more details on image acquisition, please see Supplementary Methods.

fMRI paradigm

During fMRI scanning, participants completed a backward masking task based on the fMRI paradigm outlined by Godlewska et al. (2018). Participants were shown pairs of faces, with a first "target" face (expressing a sad, happy, or neutral emotion), displayed for 34 milliseconds, and then immediately "masked" by a face of neutral expression, displayed for 66 milliseconds. This set-up has been shown to interfere with the explicit perception of the first "target" face,

thus ensuring subliminal perception (Victor, Furey, Fromm, Ohman, & Drevets, 2010).

The task followed a block design, with each participant being shown four blocks with sad faces, four blocks with happy faces and nine blocks with neutral faces. Each block cycled through ten target-mask pairs of faces, with the order varying for each block. The neutral (N) blocks were interleaved with sad (S) and happy (H) blocks, in one of two orders: N-S-N-H-N-S-H-N or N-H-N-S-N-H-N-S-N. The order of blocks was determined by pseudo-randomisation, with an even split within the MDD and control groups and across the total sample. After each block, there was a 10-second block of baseline fixation. The total task time was 8 minutes and 47 seconds. For more details, please see Supplementary Methods.

Image analysis

Following standard Statistical Parametric Mapping (SPM12; http://www.fil.ion.ucl.ac.uk/spm12) pre-processing steps, additional motion correction was applied in the form of censoring, i.e. identifying outliers based on framewise displacement and regressing them from the fMRI timeseries (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Power et al., 2014), to compensate for using fairly lenient translation and rotation cut-offs given our patient population. To limit the impact of physiological noise on the BOLD signal, functional images were denoised using the MATLAB PhysIO toolbox ((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). For more details, please see Supplementary Methods. Voxel-based analyses were thresholded at an uncorrected p = .005 for displaying our results and we subsequently used peak-voxel-level-based Family-Wise Error (FWE) correction at p=.05 over the whole brain as well as using small-volume correction over our two pre-registered *a priori* defined regions-of-interest (ROIs; further described below).

To test our pre-registered hypotheses, BOLD effects were modelled for each of the

emotion blocks, i.e. sad, happy, and neutral. Baseline fixation was not modelled to avoid overspecification of the model. Nuisance regressors created by the PhysIO toolbox, i.e. physiological noise regressors and motion-related regressors, were included as covariates. Contrasts were created to examine the relative activation to sad faces (sad vs. neutral faces), happy faces (happy vs. neutral faces) and the subtraction-based difference between sad and happy faces (sad vs. happy).

We conducted a one-sample *t*-test at the second level on the sad vs. happy faces contrast maps to test whether the regression coefficient for QIDS-SR16 change, modelled as a covariate, differed from zero. The question of prognosis was restricted to the sad vs. happy contrast only, as this relative difference was thought to be more selective and relevant to the negative emotional bias observed in MDD and to avoid multiple comparisons. The two pre-registered *a priori* defined ROIs were used for extracting average regression coefficients for each individual using the MarsBaR toolbox (Brett, Anton, Valabregue, & Poline, 2002) and for small volume correction, i.e. bilateral amygdala (based on the Automated Anatomical Labelling [AAL] atlas (Rolls, Joliot, & Tzourio-Mazoyer, 2015) and used by Williams et al. (2015)), and dorsal/pregenual anterior cingulate cortex[1], kindly shared by Godlewska et al. (2018). In addition, regression coefficient averages were extracted for left and right amygdala separately, based on the AAL atlas (Rolls et al., 2015), to help with the interpretation of amygdala findings. These were further analysed in IBM SPSS Statistics 27.

Lastly, exploratory second-level BOLD analyses were conducted to examine differences in emotional facial expression processing between participants with MDD and controls, using small volume correction over our pre-registered *a priori* defined ROIs to support the interpretation of prognostic effects. For more details, please see Supplementary

[1] Upon visual inspection, the shared ROI contained both dorsal and pregenual regions of the anterior cingulate cortex.

Methods. All analyses were inclusively masked with a grey matter mask as previously described in Green, Lambon Ralph, Moll, Deakin, and Zahn (2012).

Behavioural data analysis

All data analyses were carried out using IBM SPSS Statistics 27, using a significance threshold of p=.05, two-tailed. Correlation analysis (Spearman's rho) was used to investigate the association between the pre-registered neural signatures and QIDS-SR16 percentage change, as well as standard clinical variables to investigate their role as potential confounders.

Results

Subgroup characteristics

MDD and control groups were matched on demographic variables (Supplementary Table 3), movement during fMRI, response times, and accuracy (Supplementary Table 4). Clinical characteristics of participants with MDD are shown in Table 1 (for control participants, see Supplementary Table 5). As part of the study, participants were encouraged to book an appointment with their GP to review their antidepressant medication, which often was a selective serotonin reuptake inhibitor (SSRI; 81%; Supplementary Table 6). Even though UK care guidelines would recommend changing antidepressant medications in non-responders, unexpectedly, more than half (52%) did not change their medication and some even stopped their medication (14%; Supplementary Table 7). On average, participants showed a reduction in depressive symptoms from baseline to follow-up, both self- and observer-rated (Table 2). The percentage change in QIDS-SR16 was consistent regardless of medication status (i.e., no change in medication, minimal change, or relevant change; F[2,35]=1.11, p=.34), or any of the other clinical measures at baseline (Supplementary Table 8). However, there was a positive association between current MDE duration and percentage change in QIDS-SR16 (r_s[38]=.39, p=.02), showing that those with a longer current MDE duration had less favourable clinical

outcomes. Despite using rigorous exclusion of bipolar spectrum diagnoses at baseline, two patients had developed a hypomanic episode during follow-up and so the diagnosis was switched to a bipolar II disorder.

fMRI findings

As predicted, the extracted cluster averages for the *a priori* defined bilateral amygdala ROI fMRI responses to subliminal sad vs. happy faces (Hypothesis 1) showed a positive association with QIDS-SR16 percentage change (r_s[38]=.40, p=.01; Figure 1; Supplementary Figure 2; Supplementary Findings). This effect of negative biases in amygdala response predicting poor subsequent outcomes remained when excluding potential outliers (r_s[37]=.37, p=.02) as well as when including the reserve list (r_s[42]=.45, p=.003). Additional exploratory analyses showed that there was only a trend-wise association between QIDS-SR16 percentage change and the *a priori* defined bilateral amygdala ROI fMRI responses to subliminal happy vs. neutral (r_s[38]=-.27, p=.10) and no association for subliminal sad vs. neutral faces (r_s[38]=.21, p=.20). However, using a group comparison, patients with favourable outcomes had a stronger amygdala response to subliminal perception of happy faces vs. neutral faces, when compared with patients with unfavourable outcomes (Supplementary Figure 2, Supplementary Findings). There was a significant association between the potential clinical confounder, current MDE duration, and the neural signature (r_s[38]=-.35, p=.03). However, whilst controlling for current MDE duration, the association between *a priori* bilateral amygdala ROI fMRI responses to subliminal sad vs. happy faces and QIDS-SR16 percentage change remained (r_s[35]=.35, p=.03).

Notably, the association between amygdala BOLD activation for subliminal sad vs. happy faces and QIDS-SR16 percentage change was mostly driven by the right amygdala (r_s[38]=.46, p=.003; Supplementary Figure 3; Supplementary Findings) rather than the left amygdala (r_s[38]=.27, p=.10). There was no effect for our other pre-registered ROI (Hypothesis

2), i.e. dorsal/pregenual anterior cingulate cortex (r_s[38]=.18, p=.29). A supporting voxel-based analysis over the volume of the whole brain revealed no significant associations with QIDS-SR16 percentage change (voxel-based FWE-corrected p=.05).

We were unable to determine whether patients with anxious distress showed a more pronounced increased amygdala response, and thus less favourable clinical outcomes (Hypothesis 3), due to recruiting a predominantly anxious MDD sample. However, interestingly, participants with higher baseline anxiety levels, as measured on the Generalised Anxiety Disorder (7 items) (Spitzer, Kroenke, Williams, & Lowe, 2006), displayed lower right amygdala (r_s[38]=-.32, p=.05) and dorsal/pregenual anterior cingulate cortex (r_s[38]=-.42, p=.01) responses to subliminal happy faces vs. neutral faces. Our main contrast of interest, sad vs. happy faces, did not show an association between anxiety levels and bilateral amygdala activation (r_s[38]=.11, p=.53), although there was an association between anxiety levels and dorsal/pregenual anterior cingulate cortex activation (r_s[38]=.38, p=.02; Supplementary Table 9).

The exploratory cross-sectional BOLD analysis probing group (MDD vs. control) and emotion condition effects (sad vs. happy) did not show main effects or interaction effects of group or emotion condition within our *a priori* defined ROIs or at the whole-brain level (Supplementary Findings).

Discussion

We corroborated our first pre-registered hypothesis (Hypothesis 1) that decreased activation of the amygdala for sad vs. happy faces may be prospectively associated with favourable clinical outcomes. Additional exploratory analyses suggest that this may be driven by an increased response to subliminal perception of happy faces in patients with favourable outcomes, which could point to a positive perceptual bias. It has been proposed that treatment introduces such a

positive emotional processing bias, which allows individuals to re-tune how they process socially relevant information and have a more positive day-to-day emotional perspective (Browning et al., 2010; Harmer, 2008). We speculate that traces of a positive perceptual bias while taking antidepressant medication imply that the treatment had an implicit effect and could signal a higher likelihood of subsequent symptom improvement. In contrast, the absence of a positive perceptual bias in subsequent non-responders might indicate that antidepressant treatment was less effective in restoring function, and thus predicts less favourable clinical outcomes. Moreover, chronicity of depressive episode reduced the adaptive response of the amygdala to positive faces.

Even though similar patterns of activation were observed for the right and left amygdala in response to subliminal facial emotions, the association between amygdala activation and change in depressive symptoms appeared to be mostly driven by the right amygdala. It has been proposed that amygdala function is lateralised: while the left amygdala is thought to be more active in the processing of language-related stimuli, the right amygdala appears to be more involved in the processing of non-conscious stimuli (Costafreda, Brammer, David, & Fu, 2008; Gläscher & Adolphs, 2003). Thus, subliminal presentation would be likely to result in a more prominent neural response in the right amygdala relative to the left amygdala, which might explain why the left amygdala separately was not significantly associated with clinical outcomes.

Contrary to our second pre-registered hypothesis (Hypothesis 2), we found no association between dorsal/pregenual anterior cingulate cortex activation in response to subliminal facial emotions and clinical outcomes in current MDD. The lack of association with symptom change might be explained by differences in study set-up from that of Godlewska et al. (2018), who conducted a controlled trial with treatment-free MDD participants who underwent a six-week period of escitalopram treatment. In contrast, our study was designed as

an observational study, with participants taking a range of antidepressant medications and followed up after four months. As a result, the neural signature described by Godlewska et al. (2018) may be more relevant for prognosis in early treatment-resistant MDD rather than the more chronic forms of MDD seen in our sample.

We were unable to investigate our third pre-registered hypothesis (Hypothesis 3) that patients with anxious distress showed a more pronounced increased amygdala response, and thus poorer clinical outcomes, because our sample predominantly consisted of anxious MDD. However, exploratory analyses showed that participants with higher baseline anxiety levels displayed lower amygdala reactivity to subliminal presentation of happy vs. neutral faces, but there was no effect for our main contrast of interest sad vs. happy faces, thus requiring further replication. We speculate that this reduced amygdala reactivity to subliminal facial expressions of happiness implies a reduced positive perceptual bias, which was also associated with poorer clinical outcomes. It has been suggested that anxiety symptoms might contribute more strongly to patterns of amygdala responses to facial emotions, compared with depressive symptoms (van den Bulk et al., 2014). More research is needed to determine what role (co-morbid) anxiety plays in modulating response to subliminal emotional faces and how this might inform clinical outcomes by allowing stratification of patients.

Supporting voxel-based analyses showed no significant effects between neural responses to subliminal facial emotions and symptom change. This is likely due to the reduced statistical power of voxel-based analyses because of the need for multiple comparison correction for the number of voxels within an ROI or across the whole-brain. If the activation is relatively homogeneous across the ROI, likely with small ROIs such as the amygdala, extracting the average effect from the ROI increases the statistical power of one's analysis, which is why our primary analysis approach is preferable for clinical applications and reproducibility studies.

Lastly, we found no evidence of differences in neural responses to subliminal facial expressions between the MDD group and the control group. The lack of cross-sectional findings might be explained by our small, heterogenous control group which allowed for mild anxiety or depressive symptoms, as well as anxiety disorders and subthreshold levels of PTSD. Even though this approach may have limited cross-sectional comparisons, it provides a more representative reference group for the prognostic findings in MDD. Moreover, the null finding is in keeping with other studies reporting no amygdala activation differences between MDD patients taking antidepressant medications compared with healthy controls (Almeida, Versace, Hassel, Kupfer, & Phillips, 2010; Demenescu et al., 2011; Gotlib et al., 2005).

Limitations

As expected in difficult-to-treat MDD, a high proportion of our participants had co-morbid anxiety and trauma-related disorders. It is important to note that negative emotion perception biases are not unique to MDD and are commonly reported in anxiety and trauma-related disorders (Etkin & Wager, 2007; Killgore et al., 2014; Lee, Kim, & Lee, 2016; Stein et al., 2007). Notably, some studies have reported that depression groups with and without early-life trauma may differ in their neural response to sad and neutral faces (Grant, Cannistraci, Hollon, Gore, & Shelton, 2011), as did MDD patients with or without co-morbid anxiety (Demenescu et al., 2011), which could be suggestive of distinct subtypes of depression with regard to facial emotion perception. Therefore, it is possible that the observed negative perceptual biases could have resulted from co-morbid anxiety or trauma-related disorders rather than being specific to MDD.

Another limitation is our relatively modest sample size, which limits our power for identifying significant effects, but is nevertheless sufficient for estimating effect sizes (Teare et al., 2014; Turner, Paul, Miller, & Barbey, 2018). Moreover, treatment in our observational study was not standardised and included a range of treatment approaches, which means that

treatment effects may have introduced variability in the observed neural responses. However, this reflects standard care in a primary care setting, and it allowed to test whether the previously identified neural signatures would generalise to a pragmatic sample of patients encountered in clinical settings. Non-specific beneficial effects of being enrolled in our study could in theory have improved clinical outcomes, but we think that these are unlikely to have played a significant role, given the absence of psychiatric or psychosocial advice provided.

Conclusion

Here, we confirmed the prediction that neural correlates of positive emotional perception biases may be prospectively associated with favourable clinical outcomes in difficult-to-treat MDD. We speculate that those patients with favourable clinical outcomes showed neural correlates of an antidepressant medication-mediated restoration of positive perceptual biases, potentially through implicit stimulus appraisal by the amygdala, preceding their subsequent symptom improvement. This indicates that enhancing amygdala responses to positive stimuli should be further investigated as neuromodulation treatment targets in difficult-to-treat MDD. Initial fMRI neurofeedback evidence for reinforcing amygdala responses to positive memories in MDD are promising (K. D. Young et al., 2019).

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Conflict of interest

Prof Zahn is a private psychiatrist service provider at The London Depression Institute and co-investigator on a Livanova-funded observational study of Vagus Nerve Stimulation for Depression. Prof Zahn has received honoraria for talks at medical symposia sponsored by Lundbeck as well as Janssen. Prof Zahn has collaborated with EMOTRA, EMIS PLC and Depsee Ltd. Prof Zahn is affiliated with the D'Or Institute of Research and Education, Rio de Janeiro and advises the Scients Institute, USA. Prof Barker receives honoraria for teaching from GE Healthcare. Prof Young is employed by King's College London as an honorary consultant in the South London and Maudsley Trust (NHS UK) and is a consultant to Johnson & Johnson and Livanova. Prof Young has given paid lectures and sat on advisory open access boards for the following companies with drugs used in affective and related disorders: Astrazenaca, Eli Lilly, Lundbeck, Sunovion, Servier, Livanova, Janssen, Allegan, Bionomics, Sumitomo Dainippon Pharma. Prof Young has received honoraria for attending advisory

boards and presenting talks at meetings organized by LivaNova. Prof Young is the Principal Investigator of the following studies: Restore-Life VNS registry study funded by LivaNova, ESKETINTRD3004: 'An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression', 'The Effects of Psilocybin on Cognitive Function in Healthy Participants' and 'The Safety and Efficacy of Psilocybin in Participants with Treatment-Resistant Depression (P-TRD)'. Prof Young has received grant funding (past and present) from the following: NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); MSFHR (Canada); NIHR (UK); Janssen (UK). Prof Young has no shareholdings in pharmaceutical companies. Prof Goldsmith reports grants from NIHR, Stroke association, National Institutes of Health (US) and Juvenile Diabetes Research Foundation (US) during the conduct of the study. Dr Carr reports personal fees from NIHR during the conduct of the study. None of the other authors report biomedical financial interests or potential conflicts of interest related to the subject of this paper.

Prior publication

Part of the study has been published in a PhD thesis available on the King's College London institutional repository, Pure, see Fennema (2022).

Rights Retention

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Tables

Table 1 | Clinical characteristics MDD (n=42).

MDD modified DSM-5 subtype	**No. (%)**
Anxious distress only	8 (19%)
Melancholic features only	0 (0%)
Melancholic features + anxious distress	7 (17%)
Atypical features only	2 (5%)
Atypical features + anxious distress	18 (43%)
No specific subtype	7 (17%)
Age of depression onset (in years), M ± SD; min-max	18.2 ± 9.0; 4 – 42
Current MDE duration (in months), M ± SD; min-max	25.0 ± 44.1; 1 – 176
Number of MDEs, M ± SD; min-max	6.4 ± 4.8; 1 – 20
Illness duration (in years), M ± SD; min-max	24.0 ± 15.9; 2 – 56
Number of suicide attempts, M ± SD; min-max	0.5 ± 1.3; 0 – 6
Maudsley Staging Method	
Mild	19 (45%)
Moderate	23 (55%)
Severe	0 (0%)
Life-time axis-I co-morbidity	
Posttraumatic stress disorder	18 (43%)
Other anxiety disorder	17 (40%)
Obsessive-compulsive disorder	4 (10%)
Eating disorder	14 (33%)
None	5 (12%)
Family history	
First degree relative with MDD	14 (33%)
First degree relative with bipolar disorder	2 (5%)
No family history of MDD	21 (50%)
Outcomes	
Responder[a]	10 (24%)

[a] Responder was defined as participants who showed at least a 50% reduction in depressive symptoms as measured on the QIDS-SR16.
Percentages may not add up to 100 due to rounding. QIDS-SR16 = Quick Inventory of Depressive Symptomatology – self-rated (16-item); MDD = major depressive disorder; DSM-5 = Diagnostic and Statistical Manual for Mental Disorders 5th edition; MDE = major depressive episode; M = mean; SD = standard deviation; min = minimum; max = maximum.

Table 2 | Descriptive statistics for clinical symptom measures at baseline and follow-up MDD (n=42).

	Baseline (mean ± SD; min – max)	Follow-up (mean ± SD; min – max)	Difference [95% CI]
QIDS-SR16	17.3 ± 3.5; 10 – 23	13.0 ± 5.7; 2 – 24	-4.3 [-6.1, -2.5]
MM-PHQ-9	18.7 ± 4.5; 8 – 27	13.7 ± 8.0; 0 – 27	-5.0 [-7.2, -2.7]
GAD-7 [a]	11.7 ± 4.2; 1 – 21	10.1 ± 5.9; 0 – 21	-1.6 [-3.5, 0.4]
MADRS	31.6 ± 4.8; 22 – 42	23.4 ± 11.3; 3 – 44	-8.2 [-11.3, -5.1]
SOFAS [a]	53.6 ± 5.3; 33 – 61	58.3 ± 11.0; 33 – 85	4.8 [2.0, 7.5]
YMRS [b]	1.3 ± 1.3; 0 – 5	1.1 ± 1.5; 0 – 5	-0.3 [-0.7, 0.2]

[a] Missing follow-up data for one participant. [b] Missing baseline and follow-up data for eight participants.
MDD = major depressive disorder; CI = confidence interval; QIDS-SR16 = Quick Inventory of Depressive Symptomatology – self-rated, 16 items; MM-PHQ-9 = Maudsley Modified Personal Health Questionnaire, 9 items; GAD-7 = Generalised Anxiety Disorder, 7 items; MADRS = Montgomery-Åsberg Depression Rating Scale; SOFAS = Social and Occupational Functioning Assessment Scale; YMRS = Young Mania Rating Scale; M = mean; SD = standard deviation; min = minimum; max = maximum.

Figure Legends

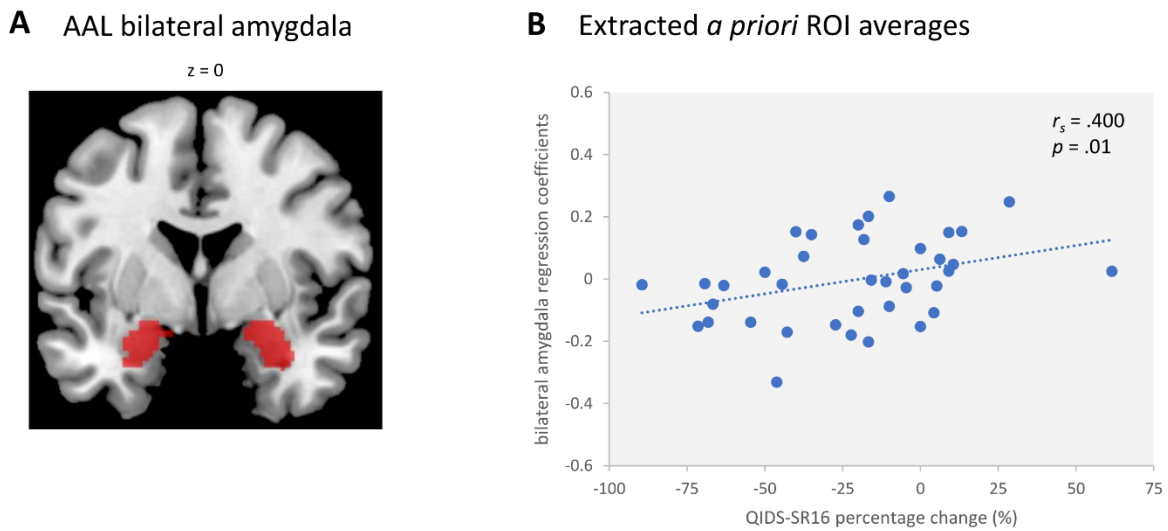

Figure 1 | Association between amygdala responses to facial emotions and change in depressive symptoms. Panel A) shows the *a priori* AAL bilateral amygdala ROI, from which the averages were extracted. **Panel B)** shows that there was a positive association between bilateral amygdala BOLD activation for sad vs. happy faces and QIDS-SR16 percentage change from baseline to follow-up, using the extracted *a priori* defined bilateral amygdala ROI averages (i.e. stronger amygdala-responses to sad vs. happy faces predicting poorer subsequent outcomes). AAL = Automated Anatomical Labelling; BOLD = blood-oxygen level-dependent; QIDS-SR16 = Quick Inventory of Depressive Symptomatology - self-rated, 16-items; r_s = Spearman correlation; ROI = region-of-interest.

Supplementary Online Content

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

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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 et al., 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 et al., 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) (R. C. 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] $$\frac{\bar{S}}{\sigma_N}$$

where $\bar{S}$ 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 et al., 2002) for our pre-registered *a priori* regions-of-interest (ROI):

1. Bilateral amygdala, as defined by the Automated Anatomical Labelling (AAL) atlas (Rolls et al., 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 ≥ 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 ≥ 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 ≥ 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 $z = \pm 2$ 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* defined ROIs 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 (r_s[38] = .46, p = .003; Supplementary Figure 3) rather than the left amygdala (r_s[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 the right 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 (r_s[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			$\chi^2(2,61) = .47$, $p = .79$
Female	n = 35 (83%)	n = 16 (84%)	
Male	n = 6 (14%)	n = 3 (16%)	
Other	n = 1 (2%)	n = 0 (0%)	
Ethnicity[a]			$\chi^2(1,60) = 2.60$, $p = .11$
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			$\chi^2(1,61) = 3.59$, $p = .06$
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 times[a] (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 health[a]	
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

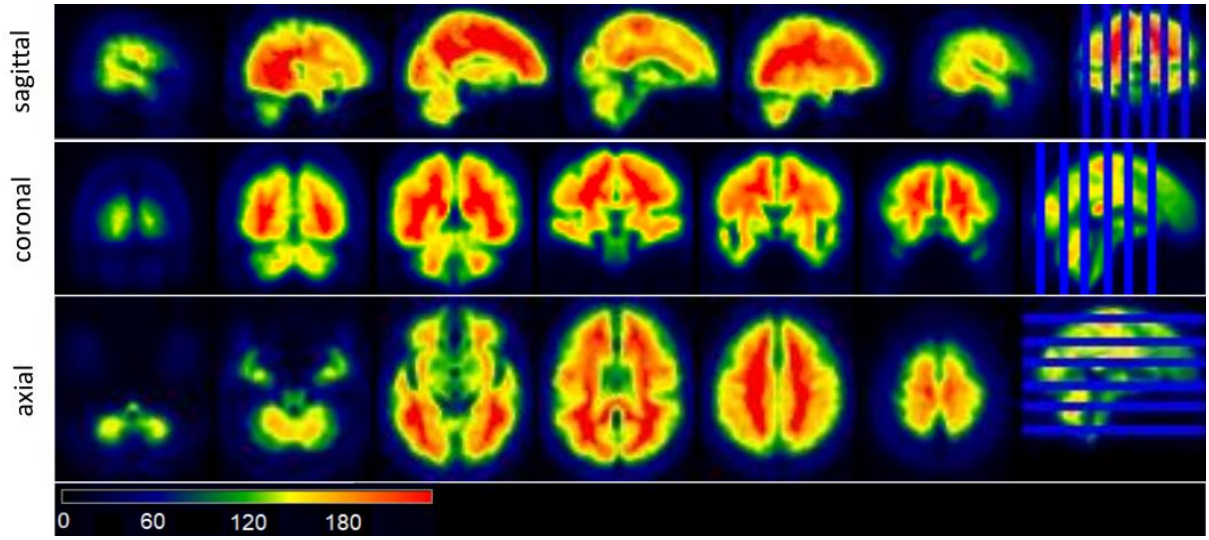
* significant at $p < .05$ threshold, two-tailed. MDD = major depressive disorder; QIDS-SR16 = Quick Inventory of Depressive Symptomatology – self-rated, 16 items; MM-PHQ-9 = Maudsley Modified Patient Health Questionnaire, 9 items; GAD-7 = Generalised Anxiety Disorder, 7 items; MDE = major depressive 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

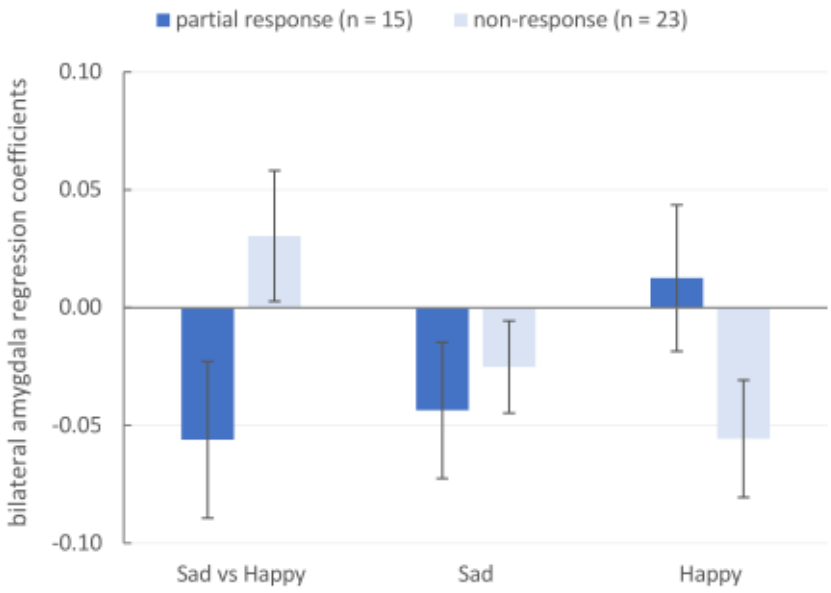
* significant at $p < .05$ threshold, two-tailed. MDD = major depressive disorder; ACC = anterior cingulate cortex; GAD-7 = Generalised Anxiety Disorder, 7 items.

Supplementary Figures



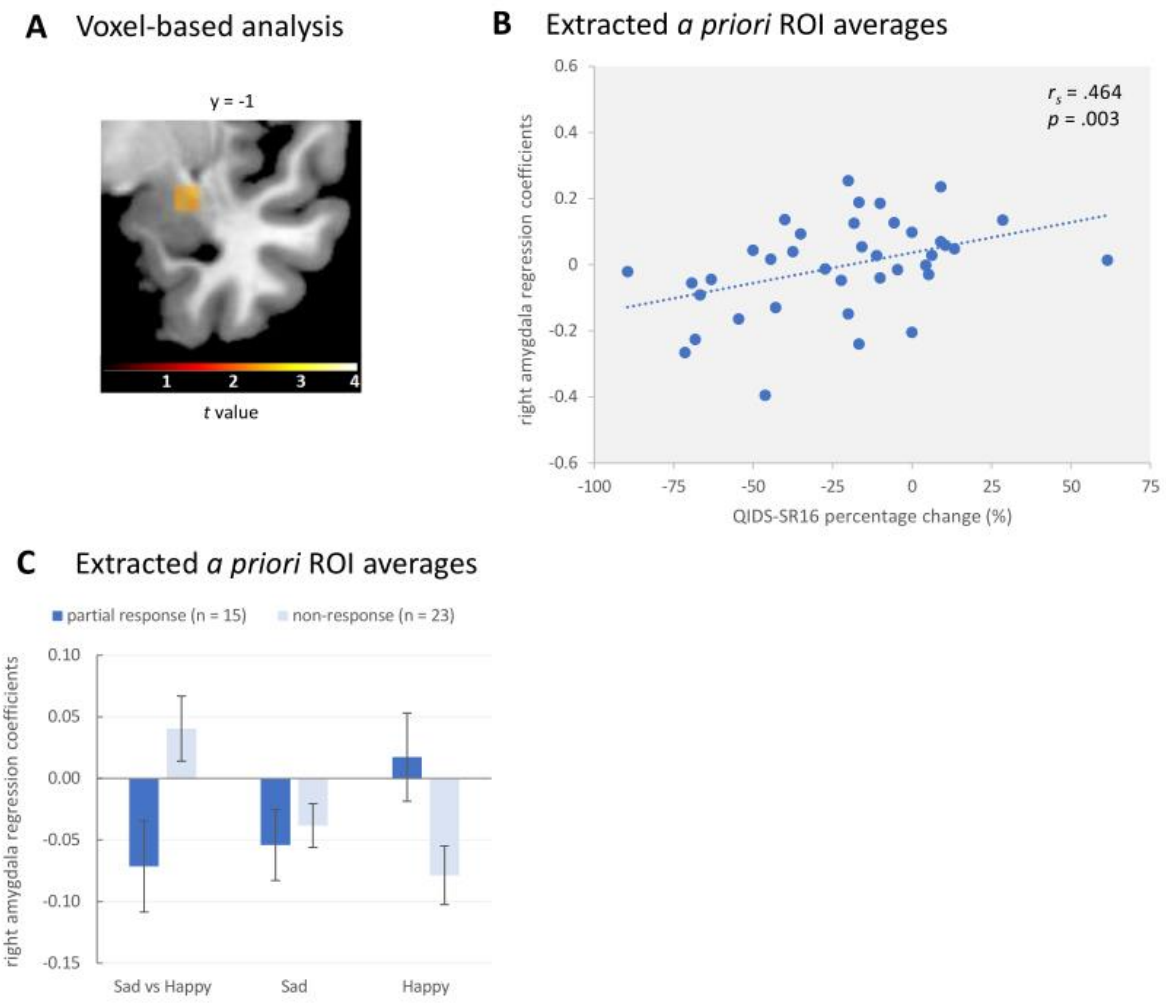
Supplementary Figure 1 | Overall mean tSNR map across participants for facial emotions fMRI paradigm.

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; r_s = Spearman correlation; ROI = region-of-interest.

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