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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 *v.* 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 *v.* happy faces predicted favorable clinical outcomes ($r_s[38] = 0.40$, $p = 0.01$). In contrast, there was no effect for dorsal/pregenual anterior cingulate cortex activation ($r_s[38] = 0.18$, $p = 0.29$), nor when using voxel-based whole-brain analyses (voxel-based Family-Wise Error-corrected $p < 0.05$). 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 *v.* 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 personalized 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

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(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 generalize 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 a more favorable clinical response (Fu et al., 2013). Therefore, we predicted (pre-registered Hypothesis 1) that decreased activation of the amygdala for subliminal sad *v.* happy faces would be prospectively associated with favorable 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 *v.* 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 *v.* happy faces would be prospectively associated with favorable 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 *v.* 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 characterized 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 outcomes (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-randomized 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 computerized 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 computerized 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

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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 <6 mm; 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 generalize 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']; online Supplementary Table S1).

Primary outcome

As stated in our pre-registered protocol (NCT04342299), we used a continuous measure of clinical outcome rather than categorizing 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 3 T 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 = 2000 ms; echo time = 30 ms; matrix = 64 × 64; field-of-view = 240 mm; flip angle = 75 degrees; slice thickness = 3 mm, slice gap = 0.3 mm, inter-slice distance = 3.3 mm, 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 (online Supplementary Fig. S1; Supplementary Table S2). 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 10 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-randomization, with an even split within the MDD and control groups and across the total sample. After each block, there was a 10-s block of baseline fixation. The total task time was 8 min and 47 s. 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,

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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 et al., 2014; Power, Barnes, Snyder, Schlaggar, & Petersen, 2012), 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 $p = 0.005$ for displaying our results and we subsequently used peak-voxel-level-based Family-Wise Error (FWE) correction at $p = 0.05$ 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 modeled for each of the emotion blocks, i.e. sad, happy, and neutral. Baseline fixation was not modeled 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 of sad faces (sad *v.* neutral faces), happy faces (happy *v.* neutral faces), and the subtraction-based difference between sad and happy faces (sad *v.* happy).

We conducted a one-sample *t* test at the second level on the sad *v.* happy faces contrast maps to test whether the regression coefficient for QIDS-SR16 change, modeled as a covariate, differed from zero. The question of prognosis was restricted to the sad *v.* 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, kindly shared by Godlewska et al. (2018) (please note that upon visual inspection, this shared ROI contained both dorsal and pregenual regions of the anterior cingulate cortex). 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 analyzed 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 Methods. All analyses were inclusively masked with a grey matter mask as previously described in Green, Lambon Ralph, Moll, Deakin, & Zahn (2012).

Behavioral data analysis

All data analyses were carried out using IBM SPSS Statistics 27, using a significance threshold of $p = 0.05$, 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 (online Supplementary Table S3), movement during fMRI, response times, and accuracy (online Supplementary Table S4). Clinical characteristics of participants with MDD are shown in Table 1 (for control participants, see online Supplementary Table S5). 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%; online Supplementary Table S6). 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%; online Supplementary Table S7). 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; $F[2,35] = 1.11$, $p = 0.34$), or any of the other clinical measures at baseline (online Supplementary Table S8). However, there was a positive association between current MDE duration and percentage change in QIDS-SR16 ($r_s[38] = 0.39$, $p = 0.02$), showing that those with a longer current MDE duration had less favorable 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 *v.* happy faces (Hypothesis 1) showed a positive association with QIDS-SR16 percentage change ($r_s[38] = 0.40$, $p = 0.01$; Figure 1; online Supplementary Fig. S2; Supplementary Findings). This effect of negative biases in amygdala response predicting poor subsequent outcomes remained when excluding potential outliers ($r_s[37] = 0.37$, $p = 0.02$) as well as when including the reserve list ($r_s[42] = 0.45$, $p = 0.003$). 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 *v.* neutral ($r_s[38] = -0.27$, $p = 0.10$) and no association for subliminal sad *v.* neutral faces ($r_s[38] = 0.21$, $p = 0.20$). However, using a group comparison, patients with favorable outcomes had a stronger amygdala response to subliminal perception of happy faces *v.* neutral faces, when compared with patients with unfavorable outcomes (online Supplementary Fig. 2, Supplementary Findings). There was a significant association between the potential clinical confounder, current MDE duration, and the neural signature ($r_s[38] = -0.35$, $p = 0.03$). However, whilst controlling for current MDE duration, the association between *a priori* bilateral amygdala ROI fMRI responses to subliminal sad *v.* happy faces and QIDS-SR16 percentage change remained ($r_s[35] = 0.35$, $p = 0.03$).

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

Characteristic	n (%) or mean ± s.d; range
MDD modified DSM-5 subtype	
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)	18.2 ± 9.0; 4–42
Current MDE duration (in months)	25.0 ± 44.1; 1–176
Number of MDEs	6.4 ± 4.8; 1–20
Illness duration (in years)	24.0 ± 15.9; 2–56
Number of suicide attempts	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%)

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; s.d., standard deviation.
[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.

Notably, the association between amygdala BOLD activation for subliminal sad *v.* happy faces and QIDS-SR16 percentage change was mostly driven by the right amygdala ($r_s[38] = 0.46$, $p = 0.003$; online Supplementary Fig. S3; Supplementary Findings) rather than the left amygdala ($r_s[38] = 0.27$, $p = 0.10$). There was no effect for our other pre-registered ROI (Hypothesis 2), i.e. dorsal/pregenual anterior cingulate cortex ($r_s[38] = 0.18$, $p = 0.29$). 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 $p = 0.05$).

We were unable to determine whether patients with anxious distress showed a more pronounced increased amygdala response, and thus less favorable clinical outcomes (Hypothesis 3), due to recruiting a predominantly anxious MDD sample. However, interestingly, participants with higher baseline anxiety levels, as measured on the Generalized Anxiety Disorder (7 items) (Spitzer, Kroenke, Williams, & Lowe, 2006), displayed lower right amygdala ($r_s[38] = -0.32$, $p = 0.05$) and dorsal/pregenual anterior cingulate cortex ($r_s[38] = -0.42$, $p = 0.01$) responses to subliminal happy faces *v.* neutral faces. Our main contrast of interest, sad *v.* happy faces, did not show an association between anxiety levels and bilateral amygdala activation ($r_s[38] = 0.11$, $p = 0.53$), although there was an association between anxiety levels and dorsal/pregenual anterior cingulate cortex activation ($r_s[38] = 0.38$, $p = 0.02$; online Supplementary Table S9).

The exploratory cross-sectional BOLD analysis probing group (MDD *v.* control) and emotion condition effects (sad *v.* 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 *v.* happy faces may be prospectively associated with favorable clinical outcomes. Additional exploratory analyses suggest that this may be driven by an increased response to subliminal perception of happy faces in patients with favorable 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 favorable clinical outcomes. Moreover, chronicity of depressive episodes reduces 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 lateralized: 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

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

	Baseline (mean ± s.d.; min – max)	Follow-up (mean ± s.d.; min – max)	Difference (95% CI)
QIDS-SR16	17.3 ± 3.5; 10–23	13.0 ± 5.7; 2–24	−4.3 (−6.1 to −2.5)
MM-PHQ-9	18.7 ± 4.5; 8–27	13.7 ± 8.0; 0–27	−5.0 (−7.2 to −2.7)
GAD-7[a]	11.7 ± 4.2; 1–21	10.1 ± 5.9; 0–21	−1.6 (−3.5 to 0.4)
MADRS	31.6 ± 4.8; 22–42	23.4 ± 11.3; 3–44	−8.2 (−11.3 to −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 to 0.2)

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, Generalized Anxiety Disorder, 7 items; MADRS, Montgomery-Åsberg Depression Rating Scale; SOFAS, Social and Occupational Functioning Assessment Scale; YMRS, Young Mania Rating Scale; M, mean; s.d., standard deviation; min, minimum; max, maximum.
[a]Missing follow-up data for one participant.
[b]Missing baseline and follow-up data for eight participants.

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 *v.* neutral faces, but there was no effect for our main contrast of interest sad *v.* 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

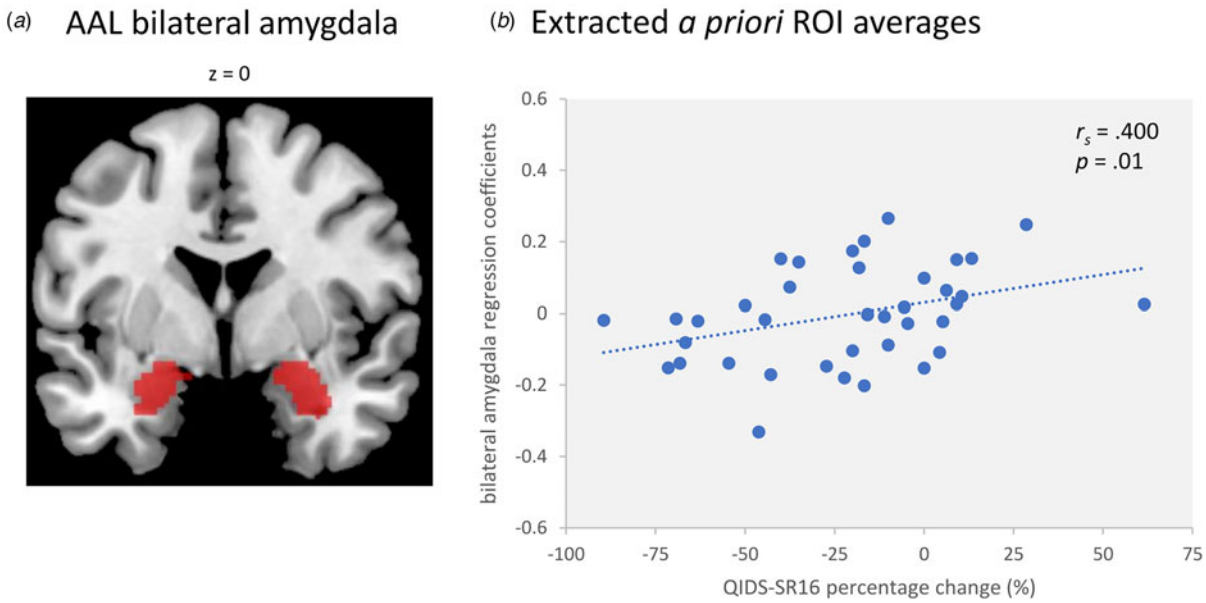

Figure 1. Association between amygdala responses to facial emotions and change in depressive symptoms. (a) shows the *a priori* AAL bilateral amygdala ROI, from which the averages were extracted. (b) shows that there was a positive association between bilateral amygdala BOLD activation for sad v. happy 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 v. happy faces predicting poorer subsequent outcomes). AAL, Automated Anatomical Labeling; 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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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 standardized 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 generalize 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 favorable clinical outcomes in difficult-to-treat MDD. We speculate that those patients with favorable 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 is promising (Young et al., 2019).

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291724001144.

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Competing interests. 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): https://kclpure.kcl.ac.uk/portal/en/studentTheses/neural-signatures-of-emotional-biases-and-prognosisin-treatment-.

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