Amygdala response to self-critical stimuli and symptom improvement in psychotherapy for depression

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Background
Cognitive–behavioural therapy is efficacious in the treatment of major depressive disorder but response rates are still far from satisfactory.

Aims
To better understand brain responses to individualised emotional stimuli and their association with outcome, to enhance treatment.

Method
Functional magnetic resonance imaging data were collected prior to individual psychotherapy. Differences in brain activity during passive viewing of individualised self-critical material in 23 unmedicated out-patients with depression and 28 healthy controls were assessed. The associations between brain activity, cognitive and emotional change, and outcome were analysed in 21 patients.

Results
Patients showed enhanced activity in the amygdala and ventral striatum compared with the control group. Non-response to therapy was associated with enhanced activity in the right amygdala compared with those who responded, and activity in this region was negatively associated with outcome. Emotional but not cognitive changes mediated this association.

Conclusions
Amygdala hyperactivity may lessen symptom improvement in psychotherapy for depression through attenuating emotional skill acquisition.

Declaration of interest
None.

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Harsh self-criticism not only triggers strong negative emotional responses but also is a symptom of depression itself. Accordingly, pervasive self-critical thinking is considered to be a risk factor for the development and maintenance of depression, and is consequently an important psychotherapeutic target.

Cognitive–behavioural therapy (CBT) is an empirically supported psychological strategy that is efficacious in the acute treatment of major depressive disorder in 40–60% of patients. Hence, depending on patient and therapy characteristics, a large proportion of patients still fail to achieve an adequate response.

The identification of neural abnormalities in depression during self-critical processing and the search for related neurophysiological markers of outcome prediction might advance differential treatment selection. In this study we examine the potential psychological mechanisms linking neural markers to psychotherapy outcomes. This integrative neurophysiological–psychological strategy might help to optimise individualised treatment strategies for patients with depression. Major depressive disorder is characterised by disturbances in emotional processing. In processing emotional stimuli, the amygdala functions by mediating attention, assigning an evaluation to the emotional stimulus and storing emotionally significant events in long-term memory. Additionally, the amygdala has numerous connections with other brain regions, such as the ventral striatum, which further process and integrate emotional information.

Prevalent studies have reported depression-related hyperactivity in the amygdala as well as the ventral striatum, probably causing negatively biased emotion processing, for instance in the evaluation and judgement of emotional stimuli. The majority of related functional magnetic resonance imaging (fMRI) studies have used standardised emotional pictures, masked or unmasked facial stimuli or personally relevant rating tasks for examining neural responses to emotional stimuli. However, using standardised emotional paradigms, several authors also reported no difference in amygdala activity between patients with depression and a control group (see Townsend et al for an overview). In contrast, the few studies using specific and personally relevant emotional stimuli have reported robust enhanced activation of striatal regions and the amygdala in people with acute depression, as well as in patients with a history of depression confronted with critical comments about their own mothers. Moreover, passive processing of emotional visual stimuli is associated with a higher probability of amygdala activation than processing accompanied by active task instructions. A previous study has shown enhanced amygdala activity during confrontation with individualised self-critical stimuli compared with neutral stimuli in a healthy sample. Accordingly, methodological heterogeneity regarding individualisation of stimuli and mode of presentation may explain some of the mixed findings, in addition to sample differences in symptom profiles, medication status, levels of depression severity or comorbid anxiety disorders. Consequently, the method chosen in our study – examining abnormal responses of the amygdala and ventral striatum to individualised, painful self-critical stimuli in an unmedicated patient sample with depression using the technique of passive exposure to stimuli – promises to yield more ecologically valid and robust results.

Functional magnetic resonance imaging assessment has been suggested as a powerful strategy for identifying prognostic markers of clinical response. Using a meta-analytic approach, Fu et al found enhanced activity in the right striatum and anterior insula to be associated with a lower likelihood of clinical benefit from treatment including CBT and medication. However, previous studies of amygdala response have yielded heterogeneous results regarding outcome prediction. Related findings have
indicated increased baseline amygdala activation in those who subsequently responded to therapy but have also shown the reverse relationship, with increased amygdala activity associated with poor outcomes during the treatment of depression and post-traumatic stress disorder (PTSD). Moreover, several studies have reported no significant relationship between amygdala activity and outcome (see Fu et al for an overview). In accordance with the results of studies using individualised emotional stimuli, we predicted enhanced response in the amygdala and ventral striatum in patients with depression compared with a matched healthy control group. In addition, we explored differences between those who did and did not respond to therapy, as well as the potential prediction of treatment outcome by differences in amygdala and striatal activity. If such predictions were verified we aimed to explore the associated psychological change mechanisms, defined as therapeutic processes that have the potential to ameliorate psychopathological disorder. Among other factors, change in dysfunctional cognition as well as the acquisition of emotional skills have been identified as psychological change mechanisms that are associated with better CBT outcomes. Consequently, we set out to examine whether the potentially identified biomarker–outcome relationships would be mediated by changes in dysfunctional cognitions and/or by acquisition of emotional skills.

**Method**

We investigated a sample of patients with a current major depressive episode (MDE; \( n = 23 \)) and a control group of healthy individuals (\( n = 28 \)). All participants were right-handed, native German speakers and showed no contraindication to MRI. The study procedure was approved by the local ethics committee, and all participants provided advance written informed consent. Treatment was free of charge, and participation in the fMRI assessment was reimbursed according to local standards. Patients were recruited from a larger study of cognitive–emotional assessment was reimbursed according to local standards. Patients and all participants provided advance written informed consent.

To qualify for the study, patients were required to have a minimum score of 14 on the Beck Depression Inventory II (BDI-II) at screening. Average depression severity at baseline was moderate, with a mean BDI-II score of 26.6 (s.d. = 9.3). Diagnoses of MDE were confirmed with the Structured Clinical Interview for DSM-IV. Exclusion criteria included a history of post-traumatic stress disorder (PTSD). Moreover, several studies indicated increased baseline amygdala activation in those who previously responded to therapy but have also shown the reverse relationship, with increased amygdala activity associated with poor outcomes during the treatment of depression and PTSD. Furthermore, a validation study of response and remission criteria reported that response best corresponded to a BDI change of 47%, showing a sensitivity of 80% and a specificity of 67%. Moreover, among self-report measures, the BDI-II has achieved wide acceptance and is sensitive to change. Assessments with the ERSQ and the DAS took place both immediately prior to and after treatment. Trait anxiety was assessed at baseline.

**Psychometric measures**

Symptom severity in the group with depression was measured using the German version of the 21-item BDI-II. For the assessment of emotion regulation skills we used the total score of the 27-item German version of the Emotion Regulation Skills Questionnaire (ERSQ). Dysfunctional cognitions were assessed using the 40-item German version of the Dysfunctional Attitude Scale (DAS). To control for trait anxiety we used the 20-item trait form of the State–Trait Anxiety Inventory (STAI).

**Procedure**

Psychotherapy was offered as a research therapy separate from routine care in the out-patient clinic of the University of Zurich’s psychology department. In total, 15 different therapists (2 men, 13 women) conducted the treatments, each treating one or two patients. All patients were scanned before the onset of their 22 weekly individual CBT sessions. Depressive symptoms were assessed before therapy at baseline (pre-treatment), directly after therapy ended (post-treatment) and 3 months later (follow-up). We defined response to treatment as a decrease of 50% in BDI-II scores, on the basis of a previous study comparing pre-treatment brain response to fearful and neutral facial expressions and response to CBT in PTSD. Furthermore, a validation study of response and remission criteria reported that response best corresponded to a BDI change of 47%, showing a sensitivity of 80% and a specificity of 67%. Moreover, among self-report measures, the BDI-II has achieved wide acceptance and is sensitive to change. Assessments with the ERSQ and the DAS took place both immediately prior to and after treatment. Trait anxiety was assessed at baseline.

**Stimuli and task**

During the fMRI measurement, participants were presented with three different types of adjectives in six 29 s blocks of four adjectives each: neutral adjectives, individualised self-critical adjectives and individualised negative adjectives that were not self-critical. Furthermore, six 29 s blocks of rest (looking at a fixation cross) were inserted randomly. Each block contained an introduction indicating the condition (neutral, negative, self-critical) followed by the presentation of the four adjectives and a request to press a button. In this paper we show only analyses of the neutral and self-critical conditions. Figure 1 shows the presentation times for a self-critical and a neutral block. For each person we ran one session lasting approximately 12 min. The
order of presentation was completely randomised and differed between participants. Neutral adjectives were the same for all participants and were pre-selected by the authors from 100 potentially neutral words. Forty-two volunteers (21 women and 21 men) rated the valence of all adjectives using a scale ranging from −2 (very negative) to +2 (very positive). Twenty-four adjectives were selected with modal values of 0 and mean values between −0.2 and 0.2. Individualised self-critical and negative non-self-critical blocks consisted of prototypes (e.g. fat, boring, jealous) that participants chose individually from a list of 52 negative attributes. During the imaging experiment prototypes were presented interspersed with their three respective synonyms (e.g. fat, fatty, obesity) that were chosen based on a German word database (http://wortschatz.uni-leipzig.de) and assumed to activate the same self-schema. All stimuli consisted of one to three syllables and at least 12 letters. We made sure that all adjectives reached a frequency level of at least 20 according to the Leipzig Word Database (frequency level based on Zipf’s law, which states that the reference word ‘the’ (‘der’) is 2^20 times more frequent than the respective word, ensuring common use in everyday language). Participants were instructed to read the adjectives silently and focus on their meaning as well as on the triggered emotional reactions. For more details about the stimuli and their assessment see our previous study.15

Imaging

The fMRI scanning took place at a university psychiatric hospital in Switzerland using a 3 T Philips Intera whole-body MR unit equipped with an 8-channel Philips sensitivity-encoding (SENSE) head coil (www.healthcare.philips.com). Functional time series were acquired with a SENSE single-shot echoplanar imaging sequence.28 Thirty-six contiguous axial slices were placed along the anterior–posterior commissure plane covering the entire brain. A total of 247 T2*-weighted echoplanar image volumes with blood oxygen level-dependent (BOLD) contrast (repetition time 3000 ms, echo time 35 ms, 8080 voxel matrix, interpolated to 128 × 128, voxel size 2.75 × 2.75 × 4 mm³, SENSE acceleration factor R = 2.0) were acquired. The first four scans were discarded owing to T1 saturation effects. For each participant a T1-weighted high-resolution image was acquired.

Data preprocessing and statistical analysis

The functional image data were preprocessed and analysed in SPM8 (www.fil.ion.ucl.ac.uk/spm) and implemented in MATLAB R2011a (Mathworks, Natick, Massachusetts, USA) using standard preprocessing steps.29 First-level analysis (fixed effects) was performed on each participant’s data including the six movement regressors and the three condition regressors. The BOLD data were modelled with a block design convolved with the standardised canonical haemodynamic response function and its temporal derivative. Estimated beta parameters and t-contrast images were brought to the second-level analysis (random effects). For both fMRI data group analyses (patients vs. controls; response vs. non-response), images of the contrast of interest (self-critical vs. neutral) were analysed using two-sample t-tests. A voxel-wise threshold of P < 0.001, requiring more than 10 contiguous voxels, was applied. According to our a priori hypotheses, we reported amygdala and striatal structures significant at P < 0.05 family-wise error corrected at the cluster level after small volume correction (SVC) in SPM using the bilateral anatomical masks created with the WFU Pickatlas toolbox (www.fil.ion.ucl.ac.uk/spm/ext/). All coordinates are reported in Montreal Neurological Institute (MNI) space and peak activations were labelled according to the Anatomical Automated Labeling atlas implemented in SPM (www.fil.ion.ucl.ac.uk/spm/ext/). Analyses of sociodemographic data (χ²-tests) were performed to ascertain comparability of the two respective groups. Furthermore, as structural volume differences of the amygdala might affect the findings of the cross-sectional analyses, we further ran SVC analysis integrating grey-matter volumes for each participant as a covariate vector of the left and right amygdala separately (see online supplement DS1 for the structural MRI data acquisition and voxel-based morphometry).

To examine change in depressive symptoms independent of initial severity, residual gain scores were calculated from a regression of pre-treatment BDI-II scores on post-treatment and follow-up scores.17 Associations of possible predictors and outcome were analysed using Pearson correlations (two-tailed) between the BOLD signal extracted from 6 mm radius spheres around peak voxels from the responder-analysis and residual BDI-II gain scores at post-treatment and follow-up. Mean beta parameter estimates were extracted using a MATLAB script programmed in-house.

Mediation analyses were calculated using the PROCESS script by Preacher & Hayes.30 The total effect (c) of an independent variable on a dependent variable is composed of a direct effect (c') and an indirect effect through a proposed mediator. The indirect effect was computed by bootstrapping re-sampling with 1000 samples. We considered point estimates of the indirect effects as significant in case zero was not included in the 95% confidence interval. We used residual BDI-II gain scores at post-treatment and follow-up as dependent variables. Potential mediator variables were residual DAS and ERSQ gain scores, reflecting changes in

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**Fig. 1** Example of a self-critical and a neutral block including presentation times in seconds for a participant choosing the prototype ‘unattractive’ as self-critical. FC, fixation cross.
cognitive and emotional processes during therapy. Correlation and mediation analyses were performed in PASW Statistics version 18.0 (IBM, Switzerland).

Results

Cross-sectional analyses

In accordance with our hypotheses, participants with major depressive disorder showed enhanced activity in the left amygdala (coordinates: −22, −6, 16; t(49) = 4.05, k = 21), the bilateral putamen (right: coordinates 36, 0, −4; t(49) = 4.13, k = 31; left: coordinates −32, −10, 4; t(49) = 3.93, k = 20) and two clusters in the right caudate nucleus (coordinates 6, 12, −2; t(49) = 4.63, k = 80; coordinates 20, 26, 0; t(49) = 4.09, k = 14), surviving SVC at P<0.05. Significant voxels in the right amygdala (coordinates 30, 7, 7; t(49) = 4) did not reach our predefined cluster size (k > 10). Moreover, separate SCA analyses for each hemisphere including the mean amygdala grey matter volumes of the respective hemispheres as covariates were performed. As described in online supplement DS1, we had to exclude three healthy individuals from these analyses because of the poor quality of the structural data. Small volume correction analyses resulted in significant differences for the left (r = 4.74, P = 0.004, k = 54) and right hemispheres (r = 4.16, P = 0.014, k = 13). Cortical group differences at the whole-brain level are reported in online Table DS1.

Prediction analyses

Clinical response

We divided those who completed therapy (n = 21) into two groups: those who responded to treatment (n = 13) and those who did not (n = 8) (Table 1). Figure 2 shows the distribution of the patients as well as assignments to the respective groups. At baseline there was no statistically significant difference between the two groups regarding gender distribution (P = 0.86), age (P = 0.98), marital status (P = 0.63), highest educational level (P = 0.22), single or recurrent episodes (P = 0.75), chronicity (P = 0.92) or comorbid anxiety disorder (P = 0.60). There was no significant difference on any of the assessed measures at baseline between the groups, but there were significant differences at post-treatment for the BDI-II and the ERSQ (Table 1).

Differences in brain activity

The non-responder and responder groups differed only in the right amygdala (coordinates 26, 2, −20; t(49) = 3.30, k = 19), with the non-responder group showing enhanced activity, surviving SVC at P < 0.05 (Fig. 2a,b)). Because amygdala activity might be related to depression severity or to anxiety,31,32 we included in a further step BDI-II pre-treatment score, trait anxiety or comorbid anxiety as covariates of interest in the between-group analysis. This affected the results only slightly (online Table DS2). No difference in the activation of striatal regions was detected. Moreover, the responder group did not show higher activity in any region compared with the non-responder group.

Baseline neural activity and treatment response

The BOLD response in the right amygdala during confrontation with self-critical material correlated positively with residual BDI-II gain scores at post-treatment (r = 0.52, P = 0.02) (Fig. 2c)) and follow-up (r = 0.53, P = 0.02). Therefore, poor response to CBT was significantly associated with increased right amygdala recruitment during the processing of self-critical material.

Table 1 Psychometric data for the sample before receiving cognitive–behavioural therapy and at post-treatment and 3-month follow-up

<table>
<thead>
<tr>
<th>Score, mean (s.d.)</th>
<th>Responder group (n = 13)</th>
<th>Non-responder group (n = 8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI-II Pre-treatment</td>
<td>27.85 (8.44)</td>
<td>26.13 (10.39)</td>
<td>0.68</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>6.23 (5.54)</td>
<td>21.25 (7.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Follow-up</td>
<td>8.30 (7.62)^b</td>
<td>19.75 (15.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>ERSQ Pre-treatment</td>
<td>79.36 (12.38)</td>
<td>71.13 (13.30)</td>
<td>0.16</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>109.12 (12.54)</td>
<td>75.88 (14.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DAS Pre-treatment</td>
<td>148.36 (24.13)</td>
<td>131.25 (31.04)</td>
<td>0.17</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>128.64 (28.60)^b</td>
<td>137.20 (23.81)</td>
<td>0.50</td>
</tr>
<tr>
<td>STAI Trait Pre-treatment</td>
<td>60.01 (9.62)</td>
<td>56.131 (12.63)</td>
<td>0.42</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>60.01 (9.62)</td>
<td>56.131 (12.63)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

BDI-II, Beck Depression Inventory II; DAS, Dysfunctional Attitude Scale; ERSQ, Emotion Regulation Skills Questionnaire; STAI, State–Trait Anxiety Inventory.

Mediation analysis

To explain the association between amygdala activity and negative outcome in CBT, we evaluated the change in dysfunctional cognition and in emotional skills as theoretically derived and empirically supported mechanisms of change that might be compromised by amygdala hyperactivity. In the related mediation analysis, the association between right amygdala activity before therapy and residualised depression scores post-therapy was mediated by emotional skill acquisition. After controlling for this acquisition the relation between amygdala activity and outcome was no longer significant, indicating full mediation (Table 2). This effect survived introduction of comorbid anxiety and/or trait anxiety as covariates. Furthermore, we found similar mediation effects when the residual BDI-II gain score at follow-up was the dependent variable (n = 18). The replacement of missing data at follow-up using a last observation carried forward approach by integrating post-treatment measurement data for three patients revealed comparable effects (online Table DS3). In contrast, there was no mediation by change of dysfunctional attitudes at post-treatment and follow-up (Table 2). Online Fig. DS1 shows the mediation path model.

Discussion

We examined the role of amygdala and striatal response after confrontation with individualised self-critical stimuli in unmedicated patients with depression and healthy control participants. Additionally, the potential of these subcortical activations as biomarkers of CBT outcome prediction in concert with likely psychological change mechanisms was investigated.

Patients v. healthy participants

In accordance with our hypothesis and with previous findings, patients showed enhanced activity compared with control participants in the amygdala and the bilateral ventral striatum (bilateral putamen and caudate nucleus) after emotional activation, which potentially indicates an altered neural circuitry involved in emotion processing.3,8 Our results therefore further support the use of more ecologically valid task designs using individualised stimuli for the study of abnormal subcortical
responses in people with an MDE. At the cortical level we found enhanced activity in patients with an MDE in a distributed network of the bilateral occipital cortex, mainly in higher-order visual areas, extending to the bilateral fusiform gyrus. In the left hemisphere, activations expanded into the temporal cortex. Converging evidence from both animal and human research suggests emotion- and attention-related modulation of visual processing. Emotional induction using visual stimuli probably activates the occipital cortex and enhanced activity in these regions might be driven by hyperactivity of the amygdala, which has strong anatomical connections to visual areas.\(^\text{33,34}\)

**Response v. non-response**

Participants who did not respond to therapy showed increased neural activity in the right amygdala during confrontation with self-critical material when compared with those who did respond. In addition, brain activity in this region correlated negatively with

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**Table 2** Summary of mediation analyses

<table>
<thead>
<tr>
<th>Independent variable(^a)</th>
<th>Mediating variable(^b)</th>
<th>Dependent variable(^b)</th>
<th>Effect of IV on MV (a)</th>
<th>Effect of MV on DV (b)</th>
<th>Direct effect (c)</th>
<th>Indirect effect (ab)</th>
<th>Total effect (c)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amygdala activity</td>
<td>ERSQ</td>
<td>BDI-II post</td>
<td>-0.54**</td>
<td>-0.56*</td>
<td>0.19</td>
<td>0.30*</td>
<td>0.52*</td>
<td>21</td>
</tr>
<tr>
<td>Amygdala activity</td>
<td>ERSQ</td>
<td>BDI-II follow-up</td>
<td>-0.55*</td>
<td>-0.62**</td>
<td>0.16</td>
<td>0.34*</td>
<td>0.53*</td>
<td>18</td>
</tr>
<tr>
<td>Amygdala activity</td>
<td>DAS</td>
<td>BDI-II post</td>
<td>-0.01</td>
<td>0.61**</td>
<td>0.31**</td>
<td>-0.006</td>
<td>0.50*</td>
<td>20</td>
</tr>
<tr>
<td>Amygdala activity</td>
<td>DAS</td>
<td>BDI-II follow-up</td>
<td>0.10</td>
<td>0.35</td>
<td>0.44</td>
<td>0.04</td>
<td>0.50</td>
<td>17</td>
</tr>
</tbody>
</table>

BDI-II, Beck Depression Inventory II; DAS, Dysfunctional Attitude Scale; DV, dependent variable; ERSQ, Emotion Regulation Skills Questionnaire; IV, independent variable; MV, mediating variable.

\(^a\) Amygdala activity: mean beta values of 6-mm right amygdala sphere.

\(^b\) Residualised gain scores.

\(^c\) Significant point estimate (P<0.05).

\(\ast\) P<0.05, \(\ast\ast\) P<0.01.
CBT outcome. These results indicate that there might be a subgroup of patients with MDE with enhanced amygdala activity in response to emotional stimuli, predicting poorer CBT outcome. Ruling out alternative explanations of the observed differences between the responder and non-responder groups, these groups did not differ in terms of gender distribution, age, marital status, highest educational level, single or recurrent episode, chronicity, comorbid anxiety disorder or baseline symptom severity. The last suggests that amygdala hyperactivity may be more than a marker of severe depression. Therefore, future research should examine the risk factors of insufficient treatment response such as depression subtypes, personality factors or genetics that are associated with elevated amygdala response in more detail. Remarkably, Bryant et al reported a similar association between amygdala activity at baseline and insufficient treatment response in patients with PTSD,\textsuperscript{17} raising the question whether amygdala hyperreactivity may be a transdiagnostic risk factor for therapy non-response. In support of this notion, a recent meta-analysis reported an association between increased activation in the right amygdala, striatum and insula and an increased likelihood of poor response to antidepressant medication.\textsuperscript{18}

Mechanisms of change

Mediation analyses showed that the negative relationship between right amygdala activation and change in depressive symptoms during therapy might be explained by improvement of emotion regulation skills. Given that there was no mediation for change in dysfunctional attitudes, the specificity of this finding for emotional changes is highlighted.\textsuperscript{15} Considering these results, we propose that high levels of amygdala activation by individualised self-critical stimuli at baseline may hamper patients’ readiness to learn new emotion regulation skills. In support of this hypothesis, a recent study demonstrated that adding emotion regulation training to CBT for depression given as an in-patient treatment improved treatment outcome.\textsuperscript{36}

Study implications and limitations

To our knowledge this is the first study to examine the potential change mechanisms underlying a biomarker–outcome association. At this point it would be premature to derive clinical consequences from these results, as replication of the findings will be necessary. However, the findings may add to the quest for tailored treatment strategies by uncovering a subgroup of patients with depression with amygdala hyperactivity possibly benefiting from initial training in emotion regulation skills before engaging in emotionally challenging interventions in the course of psychotherapy. As an alternative to compensating for skill deficits, therapists might additionally search for individual strengths to build on when dealing with challenging emotions, such as memories of previously mastered challenges or interpersonal resources. Along these lines, a study has reported better outcomes in personalising treatment to patients’ relative strengths than to their relative deficits.\textsuperscript{27} Whereas our study identified a possible link between neural activity at baseline and a psychological mechanism of change, it is still unclear exactly how amygdala hyperactivity might impede the development of emotion regulation skills. One explanation might be that overly strong emotions are experienced as disturbing and overwhelming, and consequent avoidance of displeasing emotions might impede or even prevent emotional change. In any case, before deducing practical implications it would be necessary to gain more information about factors potentially interconnecting amygdala hyperreactivity, impeded development of emotional skills and treatment outcome.

A main limitation of our study was the lack of a no-treatment control group. As a consequence, we were not able to exclude the possibility that the observed correlation of amygdala hyperactivity and non-response might have resulted from more general effects occurring in psychotherapy as well as in drug treatment, such as time- and/or placebo effects. Another important limitation of the study is its small sample size; our results must therefore be regarded as strictly preliminary. An additional limitation may be that we did not systematically assess negativity ratings of the neutral words during or after the scan. Given the negativity bias of people with depression, this might have had an influence on the self-critical v. neutral contrast that we could not control. Optimally, negativity ratings should be assessed immediately after presentation during the scan. However, as this would imply introducing a significant cognitive component potentially interfering and decreasing activation in limbic regions, we refrained from this option. Future studies might assess negativity bias using post-scan ratings. Methodologically, we recommend the use of in-session assessments of emotion processing and emotional change in psychotherapy to clarify further the associations between process–outcome relationships and neural predictors. Nevertheless, this interdisciplinary research strategy holds great promise for tailoring the treatment of patients with depression in the service of better outcomes.

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References


DS1 Structural MRI data acquisition and voxel-based morphometry

Structural MRI data acquisition

Images were acquired on a Philips Achieva 3 Tesla whole-body MRI unit equipped with an eight-channel head coil using a sensitivity encoded single shot echo-planar sequence (SENSE, acceleration factor R=2). A T1-weighted gradient echo sequence (turbo field echo) with a spatial resolution of 0.94×0.94×1.00 mm³ (matrix: 240×240 pixels; 160 slices), field of view=240×240 mm², echo time (TE)=3.7 ms, repetition time (TR)=8.06 ms, flip angle=8° was applied.

Voxel-based morphometry

Structural images were analyzed using voxel-based morphometry (VBM 8) toolbox (http://dbm.neuro.uni-jena.de/vbm8/) using default parameters and employing a Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra approach (DARTEL), from the statistical parametric mapping software (SPM8; http://www.fil.ion.ucl.ac.uk). Images were bias-corrected, tissue classified, and normalized to MNI space using linear (12-parameter affine) and nonlinear transformations, within a unified model, including high-dimensional DARTEL normalization. GM and WM segments were modulated only by the nonlinear components to preserve actual GM and WM values locally (modulated GM and WM volumes). Homogeneity of GM and WM images was checked using the covariance structure of each image with all other images, as implemented in the check data quality function. Based on these results, three healthy subjects were excluded from the group analysis because mean covariance for data was below 2 standard deviations. Patient and control groups did not differ in age (P=.54), sex distribution (P=.10), marital status (P=.46), or highest level of education (P=.20). The modulated GM images were smoothed with a Gaussian kernel of 8-mm full-width-at-half-maximum. The left and right amygdala masks were defined from the wfupickatlas/aal from the SPM toolbox and mean GM volumes across these masks were calculated using MarsBaR (http://marsbar.sourceforge.net/) from the SPM toolbox.

References

Table DS1: Cortical brain areas with enhanced activity in MDE patients compared to control participants for the contrast self-critical>neutral

<table>
<thead>
<tr>
<th>Anatomical region</th>
<th>Hemisphere</th>
<th>Cluster size (voxel)</th>
<th>t (df 49)</th>
<th>P corrected Cluster-level</th>
<th>MNI coordinates x y z (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusiform</td>
<td>Right</td>
<td>236</td>
<td>4.47</td>
<td>0.040</td>
<td>40 -54 -18</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>4.46</td>
<td></td>
<td></td>
<td>40 -44 -18</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>3.62</td>
<td></td>
<td></td>
<td>30 -62 -16</td>
</tr>
<tr>
<td>Occipital inferior</td>
<td>Left</td>
<td>1632</td>
<td>5.98</td>
<td>&lt;0.001</td>
<td>-28 -76 -6</td>
</tr>
<tr>
<td>Fusiform</td>
<td>Left</td>
<td>5.70</td>
<td></td>
<td></td>
<td>-36 -58 -16</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>4.72</td>
<td></td>
<td></td>
<td>-36 -44 -12</td>
</tr>
<tr>
<td>Precentral</td>
<td>Right</td>
<td>246</td>
<td>4.74</td>
<td>0.027</td>
<td>46 -6 42</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>3.32</td>
<td></td>
<td></td>
<td>42 -2 56</td>
</tr>
<tr>
<td>Cuneus</td>
<td>Right</td>
<td>412</td>
<td>4.29</td>
<td>0.004</td>
<td>20 -68 36</td>
</tr>
<tr>
<td>Occipital superior</td>
<td>Right</td>
<td>3.69</td>
<td></td>
<td></td>
<td>28 -78 20</td>
</tr>
<tr>
<td>Occipital middle</td>
<td>Right</td>
<td>3.67</td>
<td></td>
<td></td>
<td>32 -68 16</td>
</tr>
</tbody>
</table>

**Note.** Clusters significant at $P<0.001$ (κ>10) on whole brain level after statistical correction (FWE correction at cluster level, $P<0.05$) are reported. Multiple peaks within the same label are shown on subsequent lines. Regions are labeled according to the AAL-atlas.

Table DS2: Details of the responder analysis including covariates

<table>
<thead>
<tr>
<th>Covariate (pre)</th>
<th>Anatomical region</th>
<th>MNI coordinates x y z (mm)</th>
<th>t (df 18)</th>
<th>Cluster size (voxel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI-II</td>
<td>Right Amygdala</td>
<td>24, 2, -20</td>
<td>4.12</td>
<td>22</td>
</tr>
<tr>
<td>STAI trait</td>
<td>Right Amygdala</td>
<td>26, 0, -22</td>
<td>4.65</td>
<td>40</td>
</tr>
<tr>
<td>Comorbid anxiety</td>
<td>Right Amygdala</td>
<td>26, 0, -22</td>
<td>4.80</td>
<td>38</td>
</tr>
</tbody>
</table>

**Note.** Clusters significant at $P<0.001$ unc. (κ>10). Regions are labeled according to the AAL-atlas.

Table DS3: Mediation analyses (last observation carried forward).

<table>
<thead>
<tr>
<th>Independent variable (IV)</th>
<th>Mediating variable (M)</th>
<th>Dependent variable (DV)</th>
<th>Effect of IV on M (a)</th>
<th>Effect of M on DV (b)</th>
<th>Direct effect ($c'$)</th>
<th>Indirect effect (ab)</th>
<th>Total effect (c)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amygdala activity</td>
<td>ERSQ</td>
<td>BDI-II follow-up</td>
<td>$\beta = -.54^{**}$</td>
<td>$\beta = -.80^{**}$</td>
<td>$\beta = -.05$</td>
<td>$\beta = .43^{*}$</td>
<td>$\beta = .53^{*}$</td>
<td>21</td>
</tr>
<tr>
<td>Amygdala activity</td>
<td>DAS</td>
<td>BDI-II follow-up</td>
<td>$\beta = -.01$</td>
<td>$\beta = .37$</td>
<td>$\beta = .51^{*}$</td>
<td>$\beta = .004$</td>
<td>$\beta = .51^{*}$</td>
<td>20</td>
</tr>
</tbody>
</table>

**Note.** Amygdala activity = mean beta values of 6 mm right amygdala sphere, M and DV = residualized gain scores. $\beta$ = standardized regression coefficients. $^{*}P<.05$, $^{**}P<.01$. $^{*}$ Significant point estimate ($P<.05$). BDI-II data of three patients at follow-up replaced with data at post using last observation carried forward technique.
Fig. DS1: Mediation path model.

Figure DS1. Mediation path model of right amygdala activity (mean beta values), residual symptom severity post and emotional-skill acquisition. Standardized regression coefficients (β) for the direct (A) and the indirect (B) paths are given.

*P<.05. **P<.01.
Amygdala response to self-critical stimuli and symptom improvement in psychotherapy for depression

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