Brain Stimulation 13 (2020) 1051–1058

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

# Brain functional effects of electroconvulsive therapy during emotional processing in major depressive disorder

Verena Enneking [a], Fanni Dzvonyar [a], Kerstin Dück [a], Katharina Dohm [a], Dominik Grotegerd [a], Katharina Förster [a], Susanne Meinert [a], Hannah Lemke [a], Melissa Klug [a], Lena Waltemate [a], Janik Goltermann [a], Carina Hülsmann [a], Tiana Borgers [a], Joscha Böhnlein [a], Lisa Sindermann [a], Maike Richter [a], Elisabeth J. Leehr [a], Jonathan Repple [a], Nils Opel [a], Bernhard T. Baune [a, b, c], Udo Dannlowski [a], Ronny Redlich [a, *]

[a] Department of Psychiatry, University of Münster, Germany
[b] Department of Psychiatry, Melbourne Medical School, The University of Melbourne, Melbourne, VIC, Australia
[c] The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, VIC, Australia

ARTICLE INFO

*Article history:*
Received 13 November 2019
Received in revised form
12 March 2020
Accepted 30 March 2020
Available online 7 April 2020

*Keywords:*
Electroconvulsive therapy
Depression
Functional magnetic resonance imaging
Emotional processing
Response
Biomarker

ABSTRACT

*Background:* In treatment-resistant major depressive disorder (MDD), electroconvulsive therapy (ECT) is a treatment with high efficacy. While knowledge regarding changes in brain structure following ECT is growing, the effects of ECT on brain function during emotional processing are largely unknown.
*Objective:* We investigated the effects of ECT on the activity of the anterior cingulate cortex (ACC) and amygdala during negative emotional stimuli processing and its association with clinical response.
*Methods:* In this non-randomized longitudinal study, patients with MDD ($n = 37$) were assessed before and after treatment with ECT. Healthy controls ($n = 37$) were matched regarding age and gender. Functional magnetic resonance imaging (fMRI) was obtained twice, at baseline and after six weeks using a supraliminal face-matching paradigm. In order to evaluate effects of clinical response, additional post-hoc analyses were performed comparing responders to non-responders.
*Results:* After ECT, patients with MDD showed a statistically significant increase in ACC activity during processing of negative emotional stimuli ($p_{FWE} = .039$). This effect was driven by responders ($p_{FWE} = .023$), while non-responders showed no increase. Responders also had lower pre-treatment ACC activity compared to non-responders ($p_{FWE} = .025$). No significant effects in the amygdala could be observed.
*Conclusions:* ECT leads to brain functional changes in the ACC, a relevant region for emotional regulation during processing of negative stimuli. Furthermore, baseline ACC activity might serve as a biomarker for treatment response. Findings are in accordance with recent studies highlighting properties of pre-treatment ACC to be associated with general antidepressive treatment response.


## Introduction

Electroconvulsive therapy (ECT) is a widely used therapy for severe major depressive disorder (MDD) and has been proven to be the most effective and fast-acting treatment for patients with severe depression who do not benefit from pharmacotherapy [1]. Yet, underlying neurobiological mechanisms of ECT response are still poorly understood.

An increasing body of research supports the idea of ECT-induced neuroplasticity in terms of gray matter volume increase, mainly in the hippocampus [2–4], the amygdala [3–5], as well as in the subgenual [6,7], ventral [7,8] and dorsal [7,9] anterior cingulate cortex (ACC). However, meta-analytic and mega-analytic results indicate a negative [3] or no relationship [2,10] between gray matter volume increase in the hippocampus and symptom

* Corresponding author. Department of Psychiatry, University of Münster, Albert-Schweitzer-Campus 1, Building A9 48149, Münster, Germany.
*E-mail address:* r.redlich@uni-muenster.de (R. Redlich).

https://doi.org/10.1016/j.brs.2020.03.018

improvement suggesting that these volume alterations are a possible surrogate marker of ECT rather than a real prerequisite for its antidepressant effect. In contrast, subgenual [6] and dorsal ACC [9] as well as orbitofrontal cortex [11] volume increases after ECT have been shown to be associated with clinical response.

Functional neuroimaging (fMRI) studies have provided additional insight into the effects of ECT on depression-associated biases in emotional processing — e.g. the increased activity of the limbic system, including the amygdala, during negative emotional stimuli processing [12–14] or the decreased responsiveness to positive emotional stimuli in reward related areas [15,16] compared to healthy controls. The few available task-related longitudinal fMRI studies investigating effects of ECT indicate a reduced neural response to unpleasant images in the medial prefrontal cortex after one ECT session [17], and a normalization of amygdala hyperactivity to subliminally presented sad faces that was associated with symptom improvement after an ECT series [18].

Regarding brain biomarkers associated with ECT response, especially the ACC has been highlighted. Higher pre-treatment volume [19] and resting-state activity of the subgenual ACC [20] were associated with subsequent ECT response. Furthermore, connectivity strength between subgenual ACC and prefrontal and temporal networks was predictive of ECT outcome [21].

There is a lack of longitudinal studies investigating brain functional changes of ECT and biomarkers associated with treatment response during emotional processing using paradigm-based fMRI. In our study, we aimed to investigate effects and biomarkers of ECT on conscious emotional processing. In contrast to one of our earlier studies implementing a subliminal emotional processing task [18], in the present study we employed a supraliminal face-processing task with negative emotional stimuli in patients with MDD before and after an ECT series. As we showed in the earlier study [18], ECT reduces amygdala activity during subliminal stimuli processing. Therefore, we hypothesized that amygdala activity after ECT would also be reduced during supraliminal emotional processing. Given the role of the ACC during conscious emotional stimuli processing in MDD [12,22], we further hypothesized that ACC function would as well be affected by ECT. Even if no association was found in the earlier study between pre-treatment amygdala responsiveness and symptom improvement during subliminal emotional processing [18], we aimed to investigate whether responders and non-responders differed in pre-treatment amygdala function during conscious emotional processing. Given the role of the ACC for the prediction of ECT response [19–21], we further hypothesized pre-treatment ACC activity differences between responders and non-responders. In summary, we defined the following a priori hypotheses regarding brain function during negative emotional stimuli processing:

1) At baseline, patients with MDD show higher amygdala activity and lower ACC activity in comparison to healthy controls.
2) Treatment with ECT reduces amygdala activity and increases ACC activity in patients with MDD compared to baseline.
3) ECT responders and non-responders differ in pre-treatment amygdala and ACC activity.

## Materials and methods

### *Participants and study design*

Thirty-seven patients with MDD who were treated with ECT and 37 healthy controls (HC) were included in the present study. Patients were recruited from the inpatient service of the Department of Psychiatry, University of Muenster as part of an ongoing study of the Muenster Neuroimaging Cohort (MNC) from July 9, 2010, to August 24, 2018 (see Supplementary Fig. 1). Diagnoses were verified by means of the structured clinical interview for DSM-IV (SCID-I [23]). All patients suffered from a current severe depressive episode and fulfilled the criteria of MDD. HC were recruited through public notices and newspaper announcements and matched according to age, sex, and years of education. For sample characteristics, see Table 1. Exclusion criteria for all subjects were any neurological abnormalities or previous traumatic head injury, organic mental disorders, dementia, chronic medical diseases, benzodiazepine intake or MRI contraindications. Further exclusion criteria for patients with MDD were a diagnosis of bipolar or psychotic disorder and acute substance-related disorders according to the DSM-IV. Additional exclusion criterion for HC was any lifetime psychiatric disorder according to the SCID-I [23].

All patients were defined as treatment-resistant according to Berlim and Turecki [24], as they failed to respond on at least two adequate psychopharmacological treatments. Four patients had received an ECT series in the past. The decision of treatment was based on clinical indication independent from study participation. All patients received adjuvant psychopharmacological medication during the ECT series. Type and dose of psychopharmacological treatment of the patients were recorded before and after the ECT series (see Supplementary Table 1) and a medication load index was computed as described by Hassel et al. [25].

Patients were assessed before the start of and immediately after cessation of the ECT series, HC were also assessed twice in a comparable time interval (MDD: $M = 6.51$ weeks; $SD = 2.58$ weeks; range = 2–17 weeks; HC: $M = 7.24$ weeks; $SD = 2.55$ weeks; range = 4–18 weeks). Each time, all participants completed fMRI and the Hamilton Depression Rating Scale (HDRS; [26]). The experimental procedure was approved by the local Institutional Review Board. All participants gave written informed consent prior to any study procedures and received a financial compensation.

### *Electroconvulsive therapy*

Brief pulse ECT was conducted two or three times a week using the Thymatron IV system (Somatics Inc., Lake Bluff, IL). All patients stayed at inpatient treatment for the whole duration of the ECT series. Initially, nine to twelve sessions of ECT were given, and ECT was continued if patients did not experience symptom relief ($M = 13.03$ ECT sessions; $SD = 4.18$ ECT sessions; range = 5–26 ECT sessions). All patients received unilateral ECT. In four patients, treatment was switched to bilateral ECT because of insufficient response to unilateral treatment. For details regarding ECT parameters within our sample, please see Table 2. For further information regarding ECT administration, please see our previous works [18,19].

### *Functional MRI data acquisition, paradigm and preprocessing*

Our functional MRI methods and statistical approach followed published protocols [27–30]. Briefly, T2* functional data were acquired before the first ECT session and within few days after the last ECT session of series ($M = 4.57$ days, $SD = 5.31$ days) with a 3 T scanner (Gyroscan Intera 3T, Philips Medical Systems, Best, NL). For the fMRI paradigm, a frequently used face-matching task [30–32] was used, consisting of four blocks of a face-processing task and five blocks of a sensorimotor control task. For further information on the acquisition, paradigm and preprocessing methods as well as first-level analyses of the functional MRI data, see Supplementary Methods.

**Table 1**
Sociodemographic and clinical characteristics of the sample.

| | patients with MDD $n = 37$ | | HC sample $n = 37$ | | $p$-value[1] |
|---|---|---|---|---|---|
| | mean | SD | mean | SD | |
| *Sociodemographic characteristics* | | | | | |
| Age | 47.49 | 9.83 | 45.30 | 10.35 | .354 |
| Sex (m/f)[2] | 18/19 | | 16/21 | | .641 |
| *Symptom severity* | | | | | |
| HDRS pre | 24.43 | 5.08 | 0.84 | 1.52 | <.001 |
| HDRS post | 13.68 | 8.32 | 0.84 | 1.39 | <.001 |
| *Clinical characteristics* | | | | | |
| Number of depressive episodes | 4.81 | 4.90 | – | – | – |
| Number of inpatient treatments | 3.16 | 1.76 | – | – | – |
| Life-time duration of inpatient treatment (months) | 6.00 | 4.14 | – | – | – |
| Lifetime comorbidities, no. of participants[3] | | | | | |
| None | 15 | – | – | – | – |
| Social phobia | 7 | – | – | – | – |
| Agoraphobia with or without panic disorder | 7 | – | – | – | – |
| Post-traumatic stress disorder | 5 | – | – | – | – |
| Substance abuse | 5 | – | – | – | – |
| Alcohol abuse | 4 | – | – | – | – |
| Panic disorder | 4 | – | – | – | – |
| Specific phobia | 3 | – | – | – | – |
| Bulimia nervosa | 2 | – | – | – | – |
| Obsessive-compulsive disorder | 1 | – | – | – | – |
| Eating disorder | 1 | – | – | – | – |
| *Medical treatment* | | | | | |
| Medication load index pre | 2.38 | 1.04 | – | – | – |
| Medication load index post | 2.43 | 1.30 | – | – | – |

*Abbreviations*: HC = Healthy Controls, HDRS = Hamilton Depression Rating Scale, MDD = major depressive disorder, post = second time point of measurement (for patients with major depressive disorder after series of electroconvulsive therapy), pre = first time point of measurement.[1] $p$-values were obtained using the unpaired two-tailed $t$-test except where noted.[2] $p$-values were obtained using the $X^2$-test.[3] Multiple entries per patient possible.

### *Statistical analyses*

Analyses of demographic, clinical and behavioral data were performed using SPSS Statistics (version 25.0; IBM Corporation). In order to investigate effects of ECT on depression severity, a paired $t$-test was performed comparing the baseline HDRS score with the HDRS score after ECT within the MDD group. Patients showing a reduction of at least 50% of the baseline HDRS score after ECT were defined as responders and patients showing less than 50% reduction of the baseline HDRS score were defined as non-responders. The analysis of task performance data is described in the Supplementary Methods.

*Second-level analyses:* Analyses of fMRI data were performed using statistical parametric mapping software (SPM12, Welcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm). In order to investigate baseline differences between both groups (hypothesis 1) as well as changes in brain function over time (hypothesis 2), a 2x2 ANCOVA of the contrast images (faces > shapes) was performed with group (MDD vs. HC) as a between-subjects factor and time (pre vs. post) as a within-subjects factor. Main effects of group and time as well as the group x time interaction effect were analyzed.

**Table 2**
Characteristics of electroconvulsive therapy.

| | Mean | SD |
|---|---|---|
| Stimulus intensity (%) | 52.19 | 19.95 |
| Stimulus duration (sec) | 6.93 | 0.52 |
| Pulse frequency (Hz) | 41.37 | 11.06 |
| Seizure duration EEG (sec) | 41.58 | 9.55 |
| Seizure duration EMG (sec) | 22.06 | 9.01 |
| Postictal suppression index (%) | 86.60 | 14.65 |
| Seizure generalization index (%) | 74.22 | 8.39 |

*Abbreviations*: EEG = electroencephalography, EMG = electromyography.

In order to clarify whether potential treatment effects were due to clinical response, a subsequent 2x2 ANCOVA with response (responders vs. non-responders) as between-subjects factor and time (pre vs. post) as within-subjects factor was computed. For an exploratory investigation of potential correlations of ACC activity change and further parameters, partial correlation analyses were performed with the extracted mean activity values of the significant ACC activity cluster in SPSS. Finally, for the investigation of functional biomarkers associated with ECT response (hypothesis 3), pre-treatment brain function of the responder and the non-responder group was compared using an independent $t$-test. In order to examine the predictive utility of functional brain data, a logistic regression analysis was computed with response (response = 1, non-response = 0) as dependent variable and the extracted pre ACC activity values as independent variable.

For all analyses in SPM, age and sex were included as covariates of no interest. For each of the respective analyses described previously, a region of interest (ROI) analysis of the ACC as well as a ROI analysis of the bilateral amygdala were performed separately. ROIs were created each for the bilateral amygdala and for the ACC by means of the Wake Forest University PickAtlas [33] according to the AAL-atlas [34] definitions. For a visualization of the both masks used for the respective ROI analyses, see Supplementary Fig. 2. ROIs were performed based on masked voxelwise analyses using small volume correction as implemented in the TFCE toolbox (http://dbm.neuro.uni-jena.de/tfce, version 174) in SPM. Finally, all analyses were additionally performed on the whole-brain level (voxelwise).

Significance thresholds for multiple testing were obtained at the cluster-level by threshold-free cluster (TFCE) enhancement, which is implemented in the TFCE toolbox. We established a conservative family-wise error (FWE)-corrected threshold of $p < .05$ obtained by 5000 permutations per test.

## Results

### *Clinical effects and ECT response*

Overall, ECT was effective as HDRS scores were significantly reduced within the MDD group from pre-to post-treatment (HDRS: mean difference 10.76; 95% CI 7.92 to 13.59; $p < .001$, $d = 1.26$). Improvements in symptom severity were not associated with medication load index ($p = .280$).

According to the definition of at least 50% change on the HDRS total score from pre-to post-treatment, there were 51.4% ($n = 19$) responders and 48.6% ($n = 18$) non-responders on ECT. Responders and non-responders did not differ significantly in age ($p = .582$, see Table 3). However, there were differences in sex distributions as there were more females within the responder group ($X^2 = 4.56$, $p = .033$). Responders and non-responders did not differ in course of illness variables ($p$'s > 0.137).

### *Behavioral results of task performance*

Mean percentage of correct responses and mean reaction times of the behavioral task are listed in Table 4. Results of cross-sectional and pre-post differences in task performance are described in Supplementary Results.

### *Cross-sectional effects of emotional processing of MDD vs. HC*

At baseline, MDD patients and HC did not differ in brain activity in response to negative emotional faces neither in the ROI analysis of the ACC ($p_{FWE} = .403$), nor in the ROI analysis of the amygdala ($p_{FWE} = .580$), nor on whole-brain level ($p_{FWE} = .319$).

### *Longitudinal effects of ECT on emotional processing*

The ROI analysis of the ACC showed a significant group x time interaction effect (x = −2, y = 38, z = 10, $TFCE_{(142)} = 254.41$, $k = 224$, $p_{FWE} = .009$, see Fig. 1), resulting from an increase of activity in the dorsal part of the ACC within the MDD group (x = 2, y = 36, z = 16, $TFCE_{(142)} = 194.48$, $k = 51$, $p_{FWE} = .039$), while the ACC activity of the HC sample did not change over time ($p_{FWE} = .150$). No significant main effect was found for the factor group ($p_{FWE} = .428$) nor for the factor time ($p_{FWE} = .181$) in the ROI analysis of the ACC. There were neither significant clusters in the ROI analysis of the amygdala nor at whole-brain level.

In order to clarify whether the increases in ACC activity after ECT were due to clinical response, the patient sample was separated into responders and non-responders in a subsequent analysis. Even if the ROI analysis of the ACC of this response x time interaction only showed a nominally interaction effect ($p_{FWE} = .115$), post hoc $t$-tests within the same ROI showed that responders had an increase in ACC activity (x = 4, y = 26, z = 28, $TFCE_{(68)} = 253.24$, $k = 237$, $p_{FWE} = .023$), while there was no change in ACC activity within non-responders ($p_{FWE} = .569$). The significant effect within the responder group was localized in the dorsal portion of the ACC (see Supplementary Fig. 3). A subsequent partial correlation analysis in SPSS with the extracted ACC activity values of the significant cluster revealed that there was no association of ACC activity change with symptom change (measured by HDRS change in %) within the responder group while controlling for pre ACC activity values ($p = .103$). Within the whole MDD group, changes in ACC activity values were further not associated with the number of ECT sessions ($p = .229$).

There was no significant response x time interaction neither for the ROI analysis of the amygdala ($p_{FWE} = .324$) nor at whole-brain level ($p_{FWE} = .111$).

### *Pre-treatment differences in emotional processing of responders vs. non-responders*

Within the ROI analysis of the ACC, the $t$-test comparing responders and non-responders revealed that responders had less pre-treatment activity within the ACC during emotional processing than non-responders (x = 8, y = 44, z = 28, $TFCE_{(33)} = 216.13$, $k = 25$, $p_{FWE} = .025$). MNI Coordinates show that the significant cluster was also localized in the dorsal part of the ACC, within a region similar to the significant cluster showing ACC activity increases after ECT (see Supplementary Fig. 3). The logistic regression showed that lower pre-treatment ACC activity was significantly associated with increased odds of achieving response ($b = −4.012$, Wald $X^2_{(1)} = 3.935$, Nagelkerke's $R^2 = 0.016$, $p = .047$). Based on this model, 66.7% of the non-responders (sensitivity) and 63.2% of the responders (specificity) were classified correctly, resulting in an accuracy of 64.9%. The classification table of the logistic regression is shown in Supplementary Table 2.

The ROI analysis of the amygdala showed a tendency towards significance revealing that responders had less pre-treatment amygdala activity compared to non-responders ($p_{FWE} = .088$). There were no pre-treatment differences between responders and non-responders in whole-brain activity ($p_{FWE} = .137$).

**Table 3**
Sociodemographic and clinical characteristics of responders and non-responders.

| | Responders $n = 19$ | | Non-responders $n = 18$ | | $p$-value[1] |
|---|---|---|---|---|---|
| | mean | SD | mean | SD | |
| *Sociodemographic characteristics* | | | | | |
| Age | 48.37 | 8.80 | 46.56 | 11.00 | .582 |
| Sex (m/f)[2] | 6/13 | | 12/6 | | .033 |
| *Symptom severity* | | | | | |
| HDRS pre | 24.00 | 6.01 | 24.89 | 4.00 | .602 |
| HDRS post | 6.95 | 3.73 | 20.78 | 5.29 | <.001 |
| *Clinical characteristics* | | | | | |
| Number of depressive episodes | 5.79 | 4.24 | 3.78 | 5.45 | .217 |
| Number of inpatient treatments | 3.58 | 2.12 | 2.72 | 1.18 | .137 |
| Life-time duration of inpatient treatment (months) | 6.53 | 4.44 | 5.44 | 3.84 | .430 |
| Medication load index | 2.47 | 1.02 | 2.28 | 1.07 | .573 |
| Number of ECT sessions in current series | 12.74 | 4.04 | 13.44 | 4.41 | .614 |

*Abbreviations*: HDRS = Hamilton Depression Rating Scale, post = after ECT series, pre = before ECT series.
[1] $p$-values were obtained using the unpaired two-tailed $t$-test except where noted.
[2] $p$-values were obtained using the $X^2$-test.

**Table 4**
Behavioral results of task performance: Group means (and standard deviations) of reaction time and percentage of correct responses for each time point and task condition, separated by subgroups.

| | pre[a] | | | post[b] | | |
|---|---|---|---|---|---|---|
| | HC | R | NR | HC | R | NR |
| *Reaction time (milliseconds)* | | | | | | |
| Faces | 1148.5 (214.3) | 1271.3 (211.4) | 1196.4 (242.2) | 1078.1 (162.8) | 1287.2 (117.4) | 1270.0 (296.1) |
| Shapes | 990.3 (201.2) | 1076.6 (172.1) | 1076.2 (250.9) | 944.3 (147.1) | 1066.5 (126.0) | 1117.7 (245.4) |
| *Percentage of correct responses* | | | | | | |
| Faces | 99.3 (0.02) | 99.7 (0.01) | 97.3 (0.05) | 99.6 (0.01) | 100.0 (0.0) | 98.1 (0.04) |
| Shapes | 98.4 (0.02) | 98.4 (0.02) | 96.7 (0.03) | 99.1 (0.02) | 99.2 (0.01) | 94.9 (0.10) |

*Abbreviations:* HC = healthy controls, NR = non-responders, R = responders.
[a] Performance data was available for $n = 59$ subjects ($n = 30$ HC, $n = 15$ R, $n = 14$ NR).
[b] Performance data was available for $n = 57$ subjects ($n = 33$ HC, $n = 13$ R, $n = 11$ NR).

## Discussion

This study aimed to investigate brain functional changes of ECT and biomarkers associated with treatment response during conscious emotional processing. The major finding revealed an increase in ACC activity in patients with MDD after ECT during emotional processing of negative stimuli, mainly driven by responders while non-responders did not show significant changes in ACC activity. Furthermore, ECT responders had reduced ACC activity compared to non-responders at baseline.

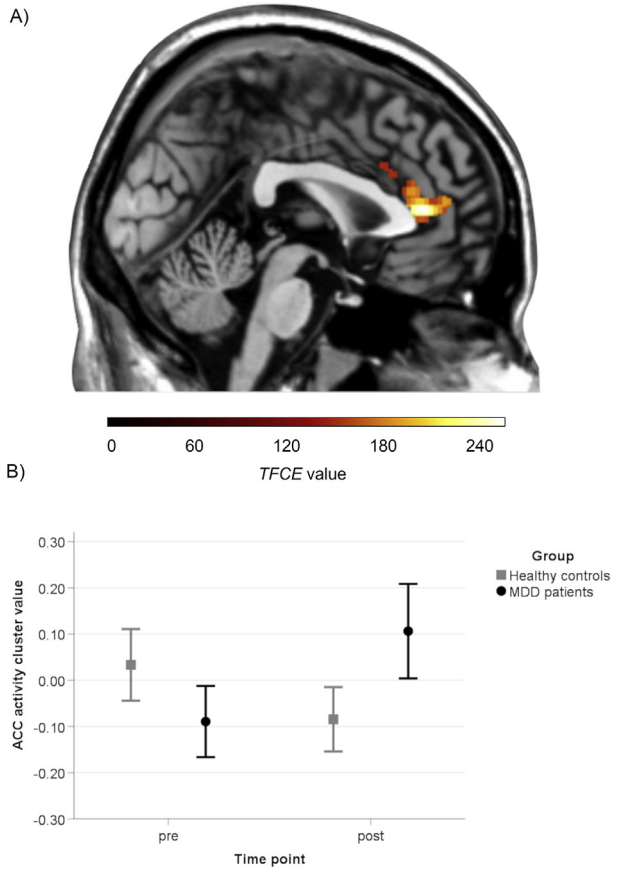


**Fig. 1.** Group x time interaction effect in the anterior cingulate cortex (ACC) during negative emotional processing (emotional faces > shapes).
A) Sagittal view of the group x time interaction (x = 2) resulting from an increase in ACC reactivity to negative stimuli in patients with major depressive disorder (MDD) after ECT (x = 2, y = 36, z = 16, $k = 51$, $p_{FWE} = .039$) and no significant changes in ACC reactivity in the healthy control group from pre to post time point ($p_{FWE} = .150$). The color bar depicts *TFCE* values.
B) Mean contrast values of the significant group x time interaction in the anterior cingulate cortex (ACC) for patients with major depressive disorder (MDD) and healthy controls at both time points. Error bars indicate 95% confidence intervals. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

The ACC is structurally strongly connected with limbic and prefrontal areas and functionally involved in emotional processing, emotion regulation as well as in attentional processes and cognitive processing [35–37]. ACC activity has been reported to be abnormal for patients with MDD during emotional processing [12,22] as well as during resting state [38]. Studies further support a functional subdivision of the ACC in a ventral, subgenual part that is highly connected with limbic structures and involved in the detection of the salience of emotional information and generation of emotional states, and into a dorsal part connected with prefrontal areas as part of the cognitive control network involved in emotional top-down regulation [37,39].

The results of the present study are mainly located in the dorsal part of the ACC, pointing out that ECT affects emotional regulation processes during conscious processing of negative stimuli. ACC activity increases were not associated with the number of ECT sessions. Instead, this effect was mainly driven by responders. Thus, ECT leads to increases in ACC activity during emotional processing, however only observed in patients who benefit from this treatment. Accordingly, studies investigating effects of ECT on brain structure revealed increases in dorsal ACC volume after ECT [7,9] that were associated with symptom improvement only within ECT responders [9]. Still, it remains unclear if the increases in dorsal ACC function are pivotal for the antidepressant mechanisms of ECT. They could as well represent either a correlate or a consequence of the antidepressant effect, independently from the specific mechanisms of ECT itself. At least, ACC activity increases do not seem to be specific for ECT, as increases in dorsal ACC activity have also been shown after treatment with antidepressants [22] or with cognitive behavioral therapy [40].

Interestingly, ECT responders showed less pre-treatment activity in dorsal parts of the ACC than non-responders. This result points to possible differences in pathophysiologies of responders and non-responders that further may drive the ACC activity increases in responders. Notably, there was no difference in ACC activity after ECT between responders and non-responders.

Pre-treatment ACC structure and function has as well been described to be associated with treatment outcome in recent studies indicating that higher pre-treatment gray matter volume of the subgenual part of the ACC [19] as well as increased baseline connectivity within networks including the subgenual ACC [21] are associated with clinical response. It seems surprising that in our study, there was no association of the subgenual part of the ACC with ECT outcome. Groenewold et al. [12] argue that subgenual ACC activation is probably not targeted by emotional perception but is

rather associated with the experience of emotions, for example during explicit emotion induction, self-referential processing or resting state as found by the study of Leaver et al. [21]. The task in our study probably did not induce the experience of the presented emotions – this may explain why subgenual ACC activity in patients with MDD was neither abnormal compared to healthy controls nor predictive for ECT response. Instead, we found dorsal parts of the ACC to be distinct between responders and non-responders at baseline. This is in line with a study reporting that lower pre-treatment activity of the dorsal ACC during negative emotional processing was associated with better response to cognitive behavioral therapy [40].

Regarding the predictive utility of pre-treatment ACC activity, the results indicate potential for predictions of ECT response or non-response – as about 65% of the patients were classified correctly. However, accuracy rates and sample size can only be a first indication of their potential usefulness in clinical practice. Multivariate methods such as machine learning may be more promising in order to reveal individual predictions that are more accurate, but require preferably independent test samples, larger sample sizes and multimodal imaging data. In summary, the results of our study support and extend the finding that pre-treatment dorsal ACC activity – reflecting the integration of cognitive and emotional processes – is to some extent associated with treatment response.

Surprisingly, there was no difference in pre-treatment ACC activity between patients with MDD and HC. Meta-analyses revealed heterogeneous results: one meta-analysis [22] showed that patients with MDD had less ventral and dorsal ACC activity compared to healthy controls during processing of negative stimuli while the other meta-analysis [12] reported the opposite effect. However, our results show that ECT led to an increased dorsal ACC activity in patients with MDD after ECT compared to healthy controls. This suggests that for patients with MDD, higher-than-average emotional regulation is needed for initiating clinical response, even if no abnormality in ACC activity was detectable at baseline. However, the lack of significance regarding baseline group differences in our study can on the other hand also be explained by problems in statistical power, regarding that patients with MDD showed at least descriptively less pre-treatment ACC activity than controls.

It was further surprising that there were no baseline differences between patients with MDD and HC in amygdala activity, standing in contrast to meta-analyses demonstrating that patients with MDD show increased amygdala activity during negative emotional stimuli processing compared to HC [12,22]. One explanation for this conflicting finding may be the previous and actual antidepressant medication intake of our MDD sample: As antidepressant medication reduces limbic hyperreactivity [41,42], multiple previous medication trials and the relatively high medication load may have influenced amygdala activity within our MDD sample.

Furthermore, in contrast to one of our earlier studies [18], there were no changes in amygdala activity within the ECT sample. In the present investigation, a supraliminal emotional processing paradigm was employed, while in the earlier study emotional stimuli were presented subliminally [18]. These heterogeneous findings may be explained by differences in types of consciousness: In automatic, unconscious processing, emotional stimuli directly evoke an autonomic emotional response represented by amygdala activation. During conscious processing though, additional emotional regulation processes are involved. As reported, ECT enhances ACC activity during conscious emotional processing and therefore might influence amygdala activation indirectly and in a more complex manner. Summing up, it is assumable that during unconscious processing, ECT might lead to a reduction of bottom-up emotional reactivity in a direct way while during conscious emotional processing ECT effects on amygdala activity are possibly masked by enhanced top-down regulation processes.

In summary, the results contribute to a more profound understanding of potential ECT effects on emotional processing – highlighting changes in ACC activity – as well as pre-treatment ACC activity as a potential biomarker for treatment response in general.

Strengths of the study comprise a relatively large sample size of $n = 37$ patients receiving ECT treatment and the investigation of effects on brain functional correlates of conscious emotion processing in a prospective approach using paradigm-based fMRI. Furthermore, as decisions for ECT were made based on clinical indication and independent from study participation, the study sample is comparable to samples in clinical practice reflecting high external validity. However, some limitations should be mentioned: First of all, most of the patients continued their antidepressant medication throughout the ECT series. Thus, the observed effects are not specifically attributable to ECT. The high previous and actual medication load might furthermore explain why there were no baseline differences in ACC and amygdala activity between patients with MDD and HC. Second, within the implemented paradigm, processing of emotions is confounded with processing of faces as the control condition to the negative emotional faces are no faces but shapes. Thus, we do not know if the effects are due to face processing or due to negative emotional processing. Third, all results are presented according to the contrast activity faces > shapes. Thus, results regarding brain activity are influenced by activity during a) negative face processing and/or b) shape processing. Specific effects regarding activity during negative emotional processing can only be disentangled if each condition was additionally compared to rest. Fourth, even if task accuracy was high in all subgroups, there were cross-sectional differences in response accuracy probably affecting fMRI activity patterns. Longitudinal changes in task accuracy and reaction time further point out practice effects of the task. However, as practice effects seem to occur quite uniformly within the different subsamples, differential changes in ACC activity over time may not be explained by changes in task performance. Fifth, even if only the subgroup of responders showed significant increases in ACC activity after ECT, the response x time interaction on ACC activity was not statistically significant. Therefore, conclusions regarding response-dependent effects of ECT on brain function should only be drawn with caution.

## Conclusions

ECT leads to increases ACC activity during negative emotional processing in patients with major depressive disorder. This effect was mainly driven by ECT responders, while non-responders did not show significant changes in ACC activity. There were no changes in amygdala activity after ECT. Responders and non-responders differed in pre-treatment ACC activity during processing of negative emotional stimuli. In summary, this study contributes to a more profound understanding of potential ECT effects on emotional processing, highlighting ACC activity as a biomarker for treatment response.

## Funding and disclosure

This work was supported by grants of the Innovative Medizinische Forschung, Münster, Germany [RE111604 and RE111722 to RR], and the German Research Foundation [DFG, grant RE4458/1-1 to RR, FOR2107 DA1151/5-1 and DA1151/5-2 to UD; SFB-TRR58, Projects C09 and Z02 to UD] and the Interdisciplinary Center for Clinical Research (IZKF) of the medical faculty of Münster [grant

Dan3/012/17 to UD]. These affiliations are of no relevance to the work described in the manuscript.

All authors state that they have no actual or potential conflict of interest to declare, including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could influence or bias their work.

## Declaration of competing interest

None.

## CRediT authorship contribution statement

**Verena Enneking:** Conceptualization, Methodology, Formal analysis, Data curation, Investigation, Writing - original draft. **Fanni Dzvonyar:** Conceptualization, Methodology, Formal analysis, Data curation, Investigation, Writing - original draft. **Kerstin Dück:** Methodology, Formal analysis, Investigation, Writing - review & editing. **Katharina Dohm:** Data curation, Investigation, Writing - review & editing. **Dominik Grotegerd:** Software, Data curation, Investigation, Writing - review & editing. **Katharina Förster:** Investigation, Writing - review & editing. **Susanne Meinert:** Investigation, Writing - review & editing. **Hannah Lemke:** Investigation, Writing - review & editing. **Melissa Klug:** Investigation, Writing - review & editing. **Lena Waltemate:** Investigation, Writing - review & editing. **Janik Goltermann:** Investigation, Writing - review & editing. **Carina Hülsmann:** Investigation, Writing - review & editing. **Tiana Borgers:** Investigation, Writing - review & editing. **Joscha Böhnlein:** Investigation, Writing - review & editing. **Lisa Sindermann:** Investigation, Writing - review & editing. **Maike Richter:** Investigation, Writing - review & editing. **Elisabeth J. Leehr:** Investigation, Writing - review & editing. **Jonathan Repple:** Investigation, Writing - review & editing. **Nils Opel:** Investigation, Writing - review & editing. **Bernhard T. Baune:** Investigation, Writing - review & editing, Supervision. **Udo Dannlowski:** Conceptualization, Investigation, Writing - review & editing, Supervision, Project administration, Funding acquisition. **Ronny Redlich:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Supervision, Project administration, Funding acquisition.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2020.03.018.

## References

[1] UK ECT Review Group. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. Lancet 2003;361:799–808. https://doi.org/10.1016/S0140-6736(03)12705-5.
[2] Wilkinson ST, Sanacora G, Bloch MH. Hippocampal volume changes following electroconvulsive therapy: a systematic review and meta-analysis. Biol Psychiatr Cogn Neurosci Neuroimaging 2017;2:327–35. https://doi.org/10.1016/j.bpsc.2017.01.011.
[3] Takamiya A, Chung JK, Liang K, Graff-Guerrero A, Mimura M, Kishimoto T. Effect of electroconvulsive therapy on hippocampal and amygdala volumes: systematic review and meta-analysis. Br J Psychiatry 2018;212:19–26. https://doi.org/10.1192/bjp.2017.11.
[4] Gbyl K, Videbech P. Electroconvulsive therapy increases brain volume in major depression: a systematic review and meta-analysis. Acta Psychiatr Scand 2018;138:180–95. https://doi.org/10.1111/acps.12884.
[5] Sartorius A, Demirakca T, Böhringer A, Clemm von Hohenberg C, Aksay SS, Bumb JM, et al. Electroconvulsive therapy increases temporal gray matter volume and cortical thickness. Eur Neuropsychopharmacol 2016;26:506–17. https://doi.org/10.1016/j.euroneuro.2015.12.036.
[6] Dukart J, Regen F, Kherif F, Colla M, Bajbouj M, Heuser I, et al. Electroconvulsive therapy-induced brain plasticity determines therapeutic outcome in mood disorders. Proc Natl Acad Sci U S A 2014;111:1156–61. https://doi.org/10.1073/pnas.1321399111.
[7] Ota M, Noda T, Sato N, Okazaki M, Ishikawa M, Hattori K, et al. Effect of electroconvulsive therapy on gray matter volume in major depressive disorder. J Affect Disord 2015;186:186–91. https://doi.org/10.1016/j.jad.2015.06.051.
[8] Cano M, Lee E, Cardoner N, Martínez-Zalacaín I, Pujol J, Makris N, et al. Brain volumetric correlates of right unilateral versus bitemporal electroconvulsive therapy for treatment-resistant depression. J Neuropsychiatry Clin Neurosci 2018;31:152–8. https://doi.org/10.1176/appi.neuropsych.18080177.
[9] Pirnia T, Joshi SH, Leaver AM, Vasavada M, Njau S, Woods RP, et al. Electroconvulsive therapy and structural neuroplasticity in neocortical, limbic and paralimbic cortex. Transl Psychiatry 2016;6:e832. https://doi.org/10.1038/tp.2016.102.
[10] Oltedal L, Narr KL, Abbott C, Anand A, Argyelan M, Bartsch H, et al. Volume of the human Hippocampus and clinical response following electroconvulsive therapy. Biol Psychiatr 2018;84:574–81. https://doi.org/10.1016/j.biopsych.2018.05.017.
[11] Gbyl K, Rostrup E, Raghava JM, Carlsen JF, Schmidt LS, Lindberg U, et al. Cortical thickness following electroconvulsive therapy in patients with depression – a longitudinal MRI study. Acta Psychiatr Scand 2019;140:205–16. https://doi.org/10.1111/acps.13068.
[12] Groenewold NA, Opmeer EM, de Jonge P, Aleman A, Costafreda SG. Emotional valence modulates brain functional abnormalities in depression: evidence from a meta-analysis of fMRI studies. Neurosci Biobehav Rev 2013;37:152–63. https://doi.org/10.1016/j.neubiorev.2012.11.015.
[13] Stuhrmann A, Dohm K, Kugel H, Zwanzger P, Redlich R, Grotegerd D, et al. Mood-congruent amygdala responses to subliminally presented facial expressions in major depression: associations with anhedonia. J Psychiatry Neurosci 2013;38:249–58. https://doi.org/10.1503/jpn.120060.
[14] Siegle GJ, Thompson WK, Carter CS, Steinhauer SR, Thase ME. Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. Biol Psychiatr 2007;61:198–209. https://doi.org/10.1016/j.biopsych.2006.05.048.
[15] Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, et al. Reduced caudate and nucleus accumbens response to rewards in unmedicated subjects with major depressive disorder. Am J Psychiatr 2009;166:702–10. https://doi.org/10.1176/appi.ajp.2008.08081201.Reduced.
[16] Zhang W-N, Chang S-H, Guo L-Y, Zhang K-L, Wang J. The neural correlates of reward-related processing in major depressive disorder: a meta-analysis of functional magnetic resonance imaging studies. J Affect Disord 2013;151:531–9. https://doi.org/10.1016/J.JAD.2013.06.039.
[17] Miskowiak KW, Macoveanu J, Jørgensen MB, Ott CV, Støttrup MM, Jensen HM, et al. Effect of electroconvulsive therapy on neural response to affective pictures: a randomized , sham-controlled fMRI study. Eur Neuropsychopharmacol 2018;28:915–24. https://doi.org/10.1016/j.euroneuro.2018.05.013.
[18] Redlich R, Bürger C, Dohm K, Grotegerd D, Opel N, Zaremba D, et al. Effects of electroconvulsive therapy on amygdala function in major depression - a longitudinal functional magnetic resonance imaging study. Psychol Med 2017;47:2166–76. https://doi.org/10.1017/S0033291717000605.
[19] Redlich R, Opel N, Grotegerd D, Dohm K, Zaremba D, Bürger C, et al. Prediction of individual response to electroconvulsive therapy via machine learning on structural magnetic resonance imaging data. JAMA Psychiatr 2016;73:557–64. https://doi.org/10.1001/jamapsychiatry.2016.0316.
[20] Argyelan M, Lencz T, Kaliora S, Sarpal DK, Weissman N, Kingsley PB, et al. Subgenual cingulate cortical activity predicts the efficacy of electroconvulsive therapy. Transl Psychiatry 2016;6:e789. https://doi.org/10.1038/tp.2016.54.
[21] Leaver AM, Wade B, Vasavada M, Hellemann G, Joshi SH, Espinoza R, et al. Fronto-temporal connectivity predicts ECT outcome in major depression. Front Psychiatr 2018;9:92. https://doi.org/10.3389/fpsyt.2018.00092.
[22] Fitzgerald PB, Laird AR, Maller J, Daskalakis ZJ. A meta-analytic study of changes in brain activation in depression. Hum Brain Mapp 2008;29:683–95. https://doi.org/10.1002/hbm.20426.
[23] Wittchen H-U, Wunderlich U, Gruschwitz S, Zaudig M. Strukturiertes Klinisches Interview für DSM-IV. Achse I: psychische Störungen. Interviewheft und Beurteilungsheft. Eine deutschsprachige, erweiterte Bearbeitung der amerikanischen Originalversion des SKID I. 1997. Göttingen: Hogrefe.
[24] Berlim MT, Turecki G. Definition, assessment, and staging of treatment—resistant refractory major depression: a review of current concepts and methods. Can J Psychiatr 2007;52:46–54. https://doi.org/10.1177/070674370705200108.
[25] Hassel S, Almeida JRC, Kerr N, Nau S, Ladouceur CD, Fissell K, et al. Elevated striatal and decreased dorsolateral prefrontal cortical activity in response to emotional stimuli in euthymic bipolar disorder: no associations with psychotropic medication load. Bipolar Disord 2008;10:916–27. https://doi.org/10.1111/j.1399-5618.2008.00641.x.
[26] Hamilton M. A rating Scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.
[27] Opel N, Redlich R, Grotegerd D, Dohm K, Haupenthal C, Heindel W, et al. Enhanced neural responsiveness to reward associated with obesity in the absence of food-related stimuli. Hum Brain Mapp 2015;36:2330–7. https://doi.org/10.1002/hbm.22773.
[28] Redlich R, Stacey D, Opel N, Grotegerd D, Dohm K, Kugel H, et al. Evidence of an IFN-gamma by early life stress interaction in the regulation of amygdala

reactivity to emotional stimuli. Psychoneuroendocrinology 2015;62:166–73. https://doi.org/10.1016/j.psyneuen.2015.08.008.
[29] Redlich R, Dohm K, Grotegerd D, Opel N, Zwitserlood P, Heindel W, et al. Reward processing in unipolar and bipolar depression: a functional MRI study. Neuropsychopharmacology 2015;40:2623–31. https://doi.org/10.1038/npp.2015.110.
[30] Redlich R, Grotegerd D, Opel N, Kaufmann C, Zwitserlood P, Kugel H, et al. Are you gonna leave me? Separation Anxiety is associated with increased amygdala responsiveness and volume. Soc Cognit Affect Neurosci 2015;10:278–84. https://doi.org/10.1093/scan/nsu055.
[31] Dannlowski U, Stuhrmann A, Beutelmann V, Zwanzger P, Lenzen T, Grotegerd D, et al. Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. Biol Psychiatr 2012;71:286–93. https://doi.org/10.1016/j.biopsych.2011.10.021.
[32] Redlich R, Schneider I, Kerkenberg N, Opel N, Bauhaus J, Enneking V, et al. The role of BDNF methylation and Val66 Met in amygdala reactivity during emotion processing. Hum Brain Mapp 2020;41:594–604. https://doi.org/10.1002/hbm.24825.
[33] Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage 2003;19:1233–9. https://doi.org/10.1016/S1053-8119(03)00169-1.
[34] Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 2002;15:273–89. https://doi.org/10.1006/nimg.2001.0978.
[35] Franklin G, Carson AJ, Welch KA. Cognitive behavioural therapy for depression: systematic review of imaging studies. Acta Neuropsychiatr 2016;28:61–74. https://doi.org/10.1017/neu.2015.41.
[36] Willner P, Scheel-Krüger J, Belzung C. The neurobiology of depression and antidepressant action. Neurosci Biobehav Rev 2013;37:2331–71. https://doi.org/10.1016/j.neubiorev.2012.12.007.
[37] Bush G, Luu P, Posner M, Ochsner KN, Gross JJ. Cognitive and emotional influences in anterior cingulate cortex. Trends Cognit Sci 2005;4:215–22. https://doi.org/10.1016/S1364-6613(00)01483-2.
[38] Zhu X, Wang X, Xiao J, Liao J, Zhong M, Wang W, et al. Evidence of a dissociation pattern in resting-state default mode network connectivity in first-episode, treatment-naive major depression patients. Biol Psychiatr 2012;71:611–7. https://doi.org/10.1016/j.biopsych.2011.10.035.
[39] Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. J Neuropsychiatry Clin Neurosci 1997;9:471–81. https://doi.org/10.1176/jnp.9.3.471.
[40] Fu CHY, Williams SCR, Cleare AJ, Scott J, Mitterschiffthaler MT, Walsh ND, et al. Neural responses to sad facial expressions in major depression following cognitive behavioral therapy. Biol Psychiatr 2008;64:505–12. https://doi.org/10.1016/j.biopsych.2008.04.033.
[41] Atkinson L, Sankar A, Adams TM, Fu CHY. Recent advances in neuroimaging of mood disorders: structural and functional neural correlates of depression, changes with therapy, and potential for clinical biomarkers. Curr Treat Opt Psychiatr 2014;1:278–93. https://doi.org/10.1007/s40501-014-0022-5.
[42] Delaveau P, Jabourian M, Lemogne C, Guionnet S, Bergouignan L, Fossati P. Brain effects of antidepressants in major depression: a meta-analysis of emotional processing studies. J Affect Disord 2011;130:66–74. https://doi.org/10.1016/j.jad.2010.09.032.