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ORIGINAL ARTICLE

Effects of electroconvulsive therapy on amygdala function in major depression – a longitudinal functional magnetic resonance imaging study

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Background. Electroconvulsive therapy (ECT) is one of the most effective treatments for severe depression. However, little is known regarding brain functional processes mediating ECT effects.

Method. In a non-randomized prospective study, functional magnetic resonance imaging data during the automatic processing of subliminally presented emotional faces were obtained twice, about 6 weeks apart, in patients with major depressive disorder (MDD) before and after treatment with ECT (ECT, $n = 24$). Additionally, a control sample of MDD patients treated solely with pharmacotherapy (MED, $n = 23$) and a healthy control sample (HC, $n = 22$) were obtained.

Results. Before therapy, both patient groups equally showed elevated amygdala reactivity to sad faces compared with HC. After treatment, a decrease in amygdala activity to negative stimuli was discerned in both patient samples indicating a normalization of amygdala function, suggesting mechanisms potentially unspecific for ECT. Moreover, a decrease in amygdala activity to sad faces was associated with symptomatic improvements in the ECT sample ($r_{spearman} = -0.48$, $p = 0.044$), and by tendency also for the MED sample ($r_{spearman} = -0.38$, $p = 0.098$). However, we did not find any significant association between pre-treatment amygdala function to emotional stimuli and individual symptom improvement, neither for the ECT sample, nor for the MED sample.

Conclusions. In sum, the present study provides first results regarding functional changes in emotion processing due to ECT treatment using a longitudinal design, thus validating and extending our knowledge gained from previous treatment studies. A limitation was that ECT patients received concurrent medication treatment.

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Key words: Amygdala, depression, electroconvulsive therapy, emotion processing, functional magnetic resonance imaging.

Introduction

Electroconvulsive therapy (ECT) is one of the most effective treatments of major depressive disorder (MDD) (Kho *et al.* 2003). Although the clinical efficacy is well documented, little is known about the mediating neurobiological effects that accompany ECT, and how they are related to the clinical symptom improvement. Though various recent studies have investigated neuro-structural effects of ECT (Tendolkar *et al.* 2013; Abbott *et al.* 2014; Dukart *et al.* 2014; Bouckaert *et al.* 2016; Redlich *et al.* 2016), very little knowledge is available at present about functional changes in the brain due to treatment.

Recent longitudinal studies show that ECT induces massive structural plasticity in humans, particularly in the hippocampus and amygdala (Tendolkar *et al.* 2013; Abbott *et al.* 2014; Dukart *et al.* 2014; Joshi *et al.* 2016). However, there is growing evidence that the extent of structural plasticity in these regions does not necessarily correlate with the extent of clinical response (Tendolkar *et al.* 2013; Dukart *et al.* 2014; Jorgensen *et al.* 2015; Bouckaert *et al.* 2016;

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Nickl-Jockschat *et al.* 2016). This suggests a possibility that these structural alterations associated with ECT might be epiphenomena – i.e. they are not essential for the therapeutic effect (Nickl-Jockschat *et al.* 2016) and might be a byproduct rather than the underlying mechanism of ECT (Jorgensen *et al.* 2015).

Therefore, the investigation of brain function and its changes during the course of ECT might be more promising for the discovery of a biomarker related to the improvement of symptoms. At present, however, little is known about functional correlates of ECT treatment in patients with MDD. Only a few recent neuroimaging studies (Abbott *et al.* 2014; Liu *et al.* 2015; Argyelan *et al.* 2016; Leaver *et al.* 2016) have investigated ECT-related changes in brain function by using resting-state functional magnetic resonance imaging (fMRI). These studies show, among other, that resting-state connectivity of the hippocampus (Abbott *et al.* 2014), the anterior cingulate gyrus (Leaver *et al.* 2016), and the subgenual cingulate cortex (Liu *et al.* 2015; Argyelan *et al.* 2016) changes due to the ECT series. Furthermore, resting-state connectivity patterns in prefrontal and cingulate cortex networks seem to be capable of predicting ECT efficacy in patients with severe unipolar depression (van Waarde *et al.* 2015). A recent study has further shown that ECT elicits robust effects on brain chemistry – including glutamate and creatine – in the subgenual anterior cingulate cortex and hippocampus, which suggests restorative and neurotrophic processes (Njau *et al.* 2016).

However, longitudinal studies probing the effects of ECT on brain function during emotion processing – a domain that is consistently reported to be impaired in MDD – are completely missing. In particular, amygdala dysfunction, including abnormally increased activation to negative (mood-congruent) stimuli and decreased activation to positive (mood-incongruent) stimuli, has been repeatedly reported for MDD, not only for supraliminal (Siegle *et al.* 2007; Groenewold *et al.* 2013), but also for subliminal stimuli associated with automatic stages of emotion processing (Sheline *et al.* 2001; Victor *et al.* 2010; Stuhrmann *et al.* 2013). These early, automatic processing stages in limbic circuits seem to play a particularly crucial role in acutely depressed patients (Stuhrmann *et al.* 2013) and, therefore, might be related to acute depressive states more directly than brain structural alterations. It has been proposed that antidepressants exert their effect partly via altering these neural emotion processing biases, thereby explaining the time lag of antidepressant action (Harmer *et al.* 2009). However, such potential mechanisms have never been investigated for ECT treatment at all.

Therefore, the present naturalistic study was designed to probe the functional neural underpinnings of emotion processing in MDD patients treated with ECT, and to investigate the following four questions:

1. Which functional changes in amygdala reactivity to rapid emotion processing accompany ECT treatment?
2. Are potential changes in amygdala reactivity specific for ECT treatment compared with pharmacotherapy alone?
3. Are these potential functional changes related to clinical response?
4. Can pre-treatment amygdala activation probed by emotion stimuli predict response to ECT?

Method

Participants and study design

The present non-randomized prospective study is comprised of 24 patients with MDD who were treated with ECT (mean age = 50.42 years, S.D. = 6.58), 23 patients with MDD who were treated solely with drugs (MED, mean age = 45.35 years, S.D. = 9.52) and 22 healthy controls (HC, mean age = 45.63 years, S.D. = 10.80). Owing to the naturalistic design of the study, the decision of treatment was only based on clinical indication and patients were not randomized into treatment groups. The MED sample was matched according to age, sex, education and depression severity (p's > 0.05).

All subjects were assessed during a subliminal affective priming paradigm at two different points of time, about 45.02 days (S.D. = 15.05) apart. Patients were recruited through the in-patient service of the Department of Psychiatry, University of Münster. HC were recruited through public notices and newspaper announcements. Diagnoses were verified employing the Structured Clinical Interview for DSM-IV (Wittchen *et al.* 1997). All patients suffered from a current major depressive episode and fulfilled the criteria of MDD. All patients in the ECT sample were treatment resistant – first-degree treatment resistance implies unresponsiveness to two successive adequate treatments with antidepressants – according to Kuhs (1995). In the MED sample 10 patients showed first-degree treatment resistance. Two patients showed psychotic symptoms and were diagnosed as severe depression with psychotic symptoms. The Beck Depression Inventory (BDI) (Hautzinger *et al.* 1994) was used as a self-evaluation questionnaire in order to assess the severity of depressive symptoms. The Hamilton Rating Scale of Depression (HAMD) (Hamilton, 1960) was additionally conducted by a clinical interviewer at both time points. In order to assess medication intake, total medication load in MDD

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patients was assessed as described earlier (Redlich *et al.* 2014). Sociodemographic, clinical, questionnaire and behavioural data were analysed, comparing the samples (see Table 1 for final sample details). Exclusion criteria for all participants were any neurological abnormalities, organic mental disorders, dementia, brain injuries or MRI contraindications. For patients, co-morbid life-time substance-related disorders, bipolar disorders, schizophrenia and other psychotic disorders were exclusion criteria. For HC, any life-time psychiatric disorder was an exclusion criterion. The study was approved by the local institutional review board, and all participants provided written informed consent before participation.

Paradigm

A frequently used paradigm (Dannlowski *et al.* 2013; Grotegerd *et al.* 2014) has been used to investigate early, automatic stages of emotion processing. Neutral, sad and happy facial expressions (Ekman & Friesen, 1976) were presented as primes for 33 ms, and subsequently masked by neutral faces. Two fixed pseudo-random sequences with 80 trials were shown: 20 each with sad, happy and neutral prime faces, as well as 20 trials with no-face stimuli as primes. Each trial lasted 9 s and proceeded according to the following pattern. A fixation cross, presented for 800 ms, preceded a prime face (for 33 ms), which was immediately followed by a picture of the same actor with a neutral expression, serving as mask and target (467 ms). A blank screen was then displayed for 7700 ms. During this period, subjects had to evaluate whether the neutral (mask) face expressed negative or positive feelings, which they indicated by pressing one of four buttons (labelled −1.5, −0.5, +0.5, and +1.5).

ECT

Brief pulse ECT was conducted three times a week using the Thymatron IV system (Somatics Inc., USA). Initially, nine to 12 sessions of ECT were given, and these were continued if they failed to achieve symptom relief (mean = 14.00, S.D. = 3.83, range: 9–24). All patients received unilateral ECT. In three patients, treatment was switched to bilateral ECT because of insufficient response to unilateral treatment. The mean stimulus intensity was 51.95% (S.D. = 18.80), the mean stimulus duration 6.98 s (S.D. = 0.50), and the mean pulse frequency 40.17 Hz (S.D. = 10.16). The mean seizure durations were 42.86 s (S.D. = 10.08; electroencephalography) and 23.98 s (S.D. = 10.64; electromyography). The mean postictal suppression index was 93.86 % (S.D. = 2.77) while the seizure generalization index was 73.27% (S.D. = 8.59). For additional details please see our previous work (Redlich *et al.* 2016).

Data acquisition and statistical analyses

Acquisition and preprocessing

Our functional MRI methods and statistical approach followed published protocols (Opel *et al.* 2015; Redlich *et al.* 2015*a*, *b*, *c*). Briefly, T2* functional data were acquired with a 3 Tesla scanner (Gyroscan Intera 3 T; Philips Medical Systems, the Netherlands) using a single-shot echoplanar sequence, with parameters selected to minimize distortion in the region of central interest, while retaining an adequate signal: noise ratio and T2* sensitivity. Volumes consisting of 34 slices were acquired (matrix 64 × 64, resolution 3.6 mm × 3.6 mm × 3.6 mm; repetition time = 2.1 s, echo time = 30 ms, flip angle = 90°). The slices were tilted by 25° from the anterior commissure/posterior commissure line in order to minimize drop-out artifacts in the mediotemporal and orbitofrontal regions. All stimuli were projected towards the rear end of the scanner (Sharp XG-PC10XE with additional high-frequency shielding). Data were analysed using statistical parametric mapping software (SPM8; Wellcome Department of Cognitive Neurology, UK; http://www.fil.ion.ucl.ac.uk/spm). Functional data were preprocessed, including realignment, unwarping and spatial normalization of each participant's functional images to the Montreal Neurological Institute International Consortium for Brain Mapping template. Nine patients with MDD (five patients from the ECT sample, four patients from the MED sample) and two HC had to be excluded due to excessive head movement (exclusion criterion 3 mm/3°). Images were smoothed with a Gaussian kernel of 6 mm full-width at half-maximum (FWHM).

First-level analyses

The onsets of the experimental conditions (positive, negative, neutral) were modelled in an event-related fashion by using a canonical haemodynamic response function in the context of a general linear model, and the model was corrected for serial correlations. A high-pass filter of 128 s was used to remove low-frequency noise. For each subject, two contrast images were generated in each individual first-level analysis (sad > neutral, happy > neutral) in order to investigate our research objective.

Second-level analyses

First, in order to investigate diagnosis and treatment-related functional changes, a 3 × 2 × 2 analysis of variance (ANOVA) was calculated using a full factorial

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Table 1. *Sociodemographic and clinical characteristics*

	ECT sample ($n = 19$)	MED sample ($n = 20$)	t Test or χ^2 test: p	HC sample ($n = 19$)	ANOVA or χ^2 test: p
Sociodemographic characteristics					
Age, years	50.42 (6.58)	45.35 (9.52)	0.06	45.36 (10.90)	0.17
Sex, *n*			0.27		0.26
Male	8	12		7	
Female	11	8		12	
Total education time, years	14.12 (2.87)	14.00 (2.15)	0.90	15.95 (2.39)	0.03
Time between measurements, days	44.10 (20.33)	49.80 (12.77)	0.34	40.84 (9.32)	0.17
Depression severity					
BDI T1	29.84 (9.28)	27.55 (7.49)	0.40	2.42 (3.25)	
BDI T2	20.23 (10.17)	22.50 (8.88)	0.48	1.58 (3.16)	
BDI change, % (1 – BDI at T2/BDI at T1)	33.39 (28.95)	15.43 (31.09)	0.07		
HAMD T1	25.00 (6.10)	23.95 (5.27)	0.57	0.68 (0.95)	
HAMD T2	13.79 (8.77)	15.58 (9.19)	0.54	0.69 (1.99)	
HAMD change, % (1 – HAMD at T2/HAMD at T1)	44.95 (34.01)	35.71 (36.48)	0.37		
Clinical characteristics					
Number of depressive episodes	5.79 (5.65)	6.65 (7.92)	0.70	N.A.	
Duration of illness, months	116.32 (100.13)	134.35 (114.89)	0.61	N.A.	
Time since first out-patient treatment, months	70.68 (77.36)	126.40 (84.75)	0.04	N.A.	
Time since first in-patient treatment, months	46.00 (54.90)	44.90 (44.91)	0.95	N.A.	
Life-time duration of in-patient treatment, weeks	18.87 (12.06)	14.05 (13.51)	0.25	N.A.	
Life-time duration of depressive state, months	39.53 (30.74)	39.83 (34.73)	0.98	N.A.	
Duration of index episode, weeks	49.05 (62.98)	24.35 (25.67)	0.11	N.A.	
Treatment resistance, *n*			<0.01		
Yes	19	10			
No	0	10			
Medical characteristics					
Medication load index	3.75 (1.28)	3.62 (1.32)	0.22	N.A.	
Antidepressants					
SSNRI	13	9	0.14		
SSRI	3	7	0.17		
SDNRI	1	2	0.58		
Tricyclic antidepressants	0	1	0.33		
Agomelantine	2	3	0.68		
Mood stabilizer	2	0	0.14		
Antipsychotics	14	6	<0.01		
Co-morbidities					
Panic disorder/agoraphobia	6	7	0.82		
Social phobia	3	5	0.48		
Specific phobia	2	2	0.96		
Generalized anxiety disorder	2	0	0.14		
Obsessive–compulsive disorder	2	1	0.52		
Post-traumatic stress disorder	2	3	0.68		
Eating disorder	2	1	0.52		

Data are given as mean (standard deviation) unless otherwise indicated. ECT, Electroconvulsive therapy; MED, medication; HC, healthy controls; ANOVA, analysis of variance; BDI, Beck Depression Inventory; HAMD, Hamilton Depression Rating Scale; N.A., not applicable; SSNRI, selective serotonin noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; SDNRI, selective dopamine noradrenaline reuptake inhibitor.

model, with group (ECT *v.* MED *v.* HC) as the between-subjects factor, as well as condition (negative *v.* neutral; positive *v.* neutral) and time (T1 *v.* T2) as within-subjects factors. To cover for the longitudinal effects, the interaction (group × condition × time) was analysed (objectives 1 and 2). Potential interactions were followed by appropriate t contrasts, including the cross-sectional comparisons of samples at T1 and

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T2, as well as the comparisons of brain functional changes across time (T1–T2), again using the above-mentioned full factorial model. To address our hypotheses on differential amygdala responsiveness to negative stimuli, region-of-interest analyses of the bilateral amygdala were carried out. The mask for the bilateral amygdala was created with the aid of the WFU PickAtlas according to the Automated Anatomical Labeling (AAL) atlas definitions (Tzourio-Mazoyer *et al.* 2002). To control for multiple statistical testing, the cluster-level false-positive detection rate was kept at $p < 0.05$, using a voxel-level threshold of $p < 0.05$ with a cluster extent (k) empirically determined by Monte-Carlo simulations ($n = 1000$ iterations). This was performed by means of the AlphaSim (Forman *et al.* 1995) procedure, implemented in the REST toolbox (http://restfmri.net/forum/index.php), as reported in previous publications (Dannlowski *et al.* 2015). The empirically determined cluster threshold was $k = 33$ voxels for the bilateral amygdala. For exploratory reasons, additional whole-brain analyses, with a cluster threshold of $k = 100$ voxels, were conducted.

Second, to determine a potential relationship between brain function changes across time (T2–T1) and the clinical response, represented by BDI percentage score changes (1 – BDI at T2/BDI at T1) in patients, the contrast values of the resulting peak voxel of the interaction analysis were extracted for both time points and further analysed by using SPSS Statistics 21 (USA). The individual functional contrast values were then correlated with the percentage of symptom relief, as represented by the changes in BDI percentage scores (objective 3).

Finally, in order to investigate pre-treatment amygdala activation of emotional stimuli as a predictor of response to ECT, pre-treatment amygdala contrast values were correlated with symptom improvement in percentage, as measured by the BDI (objective 4).

Results

Effects of treatment

Treatment response

Both groups responded significantly, while the ECT sample showed nominally higher, but not significant (p's > 0.07) percentage changes in symptoms improvement compared with the MED sample, as measured by the BDI (ECT: T1 = 29.84, S.D. = 9.28; T2 = 20.31, S.D. = 10.17, $p < 0.001$; MED: T1 = 27.56, S.D. = 7.49; T2 = 22.50, S.D. = 8.88, $p < 0.001$) and the HAMD (ECT: T1 = 25.00, S.D. = 6.10; T2 = 13.79, S.D. = 8.77, $p < 0.001$; MED: T1 = 23.95, S.D. = 5.27; T2 = 15.58, S.D. = 9.19, $p < 0.001$). Improvements in symptom severity in both patient groups did not significantly correlate with age (p's > 0.42), education (p's > 0.43), medication load index (p's > 0.20) or any other clinical parameter described in Table 1 (p's > 0.16). Furthermore, no significant difference in symptom improvement was found in both patient samples when subjects with antipsychotic treatment are compared with those with non-antipsychotic treatment (p's > 0.40). However, in the MED sample, female patients benefited significantly more than males ($p < 0.02$) while this effect was absent in the ECT group ($p > 0.28$).

Longitudinal effects on amygdala reactivity

The 3 × 2 × 2 full-factorial model yielded an interaction effect of group × condition × time within the bilateral amygdala (left: $x = -30$, $y = 0$, $z = -18$, $F_{2,220} = 6.03$, $Z = 2.77$, $k = 47$, $p = 0.003$; right: $x = 30$, $y = 2$, $z = -28$, $F_{2,220} = 5.77$, $Z = 2.77$, $k = 37$, $p = 0.004$), resulting from a decrease in amygdala activity in reaction to sad faces in both patient samples (ECT: $x = 30$, $y = 2$, $z = -20$, $Z = 2.26$, $k = 90$, $p = 0.012$; MED: right: $x = 32$, $y = 4$, $z = -20$, $Z = 3.28$, $k = 90$, $p = 0.001$; left: $x = -24$, $y = -8$, $z = -14$, $Z = 3.06$, $k = 123$, $p = 0.001$), and an increase in amygdala activity to positive faces in the MED sample ($x = 26$, $y = -8$, $z = -12$, $Z = 2.09$, $k = 33$, $p = 0.018$). However, the increase of amygdala responsiveness to positive stimuli in the ECT group failed to reach significance. An additional 2 × 2 × 2 ANOVA excluding the HC sample yielded no significant differences between both patient samples, indicating a rather non-specific effect of treatment. As one might expect, the amygdala activity of the HC sample did not change significantly over time for any emotion condition (see Fig. 1). Comparing patients receiving antipsychotic treatment with those receiving non-antipsychotic treatment by using the extracted peak voxel values of the interaction analysis yielded no significant differences in amygdala activity changes either in the ECT sample (p's > 0.67) or in the MED sample (p's > 0.42). Additionally, there was no significant association between amygdala reactivity and age – either in the ECT sample (p's > 0.38) or the MED sample (p's > 0.34). Furthermore, there were no significant associations between amygdala reactivity and ECT parameters [all p's < 0.11; mean stimulus intensity ($r = 0.39$, $p = 0.11$), mean stimulus duration ($r = -0.01$, $p = 0.97$), mean pulse frequency ($r = 0.28$, $p = 0.27$), mean seizure durations by EEG ($r = -0.13$, $p = 0.61$) and EMG ($r = -0.37$, $p = 13$), mean postictal suppression index ($r = -0.15$, $p = 0.55$) and the seizure generalization index ($r = -0.22$, $p = 0.38$)].

The whole-brain analysis indicated that no other brain area showed any significant interaction effect.

Cross-sectional effects on amygdala reactivity

Compared with HC, both patient groups showed increased amygdala activity to sad faces at T1 (ECT:

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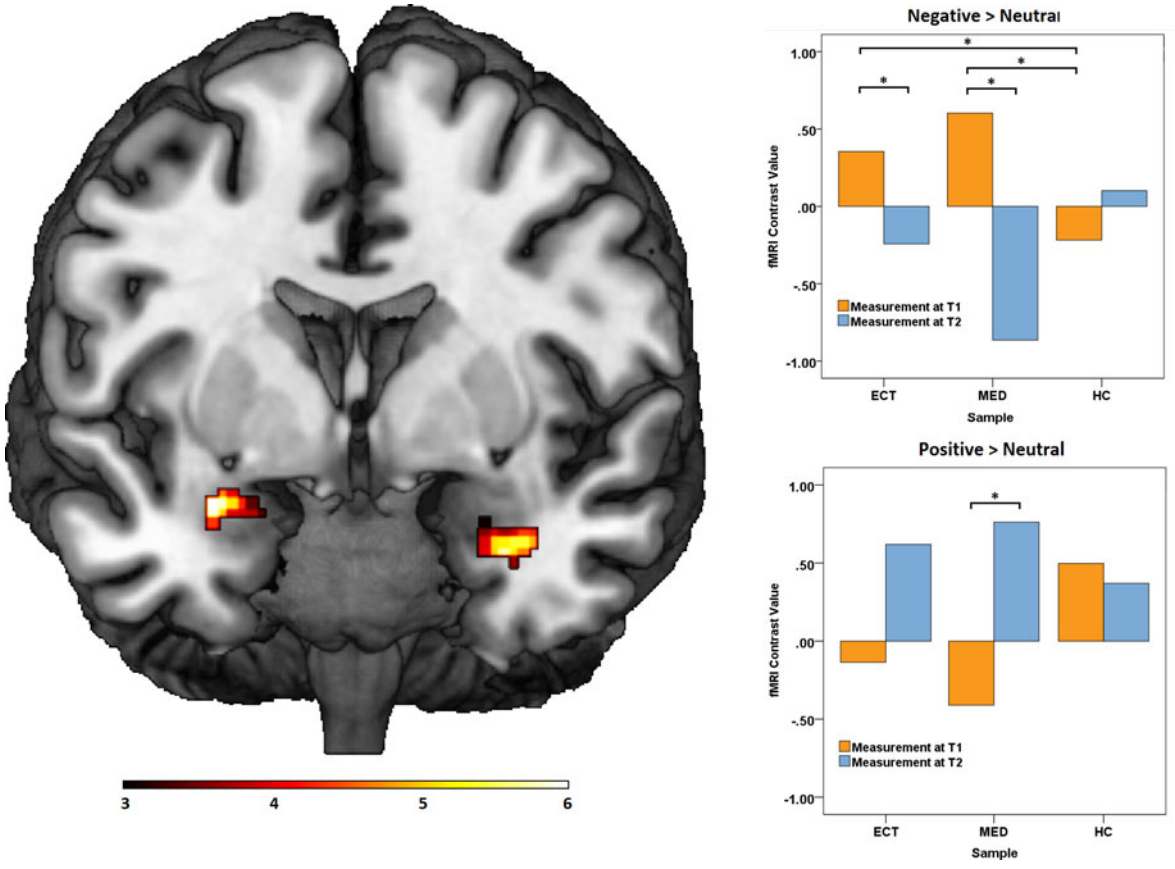

Fig. 1. Treatment effects of electroconvulsive therapy (ECT) on amygdala reactivity during emotion processing. Left: coronal view (Montreal Neurological Institute coordinates at $y = 1$) depicting the interaction effect of group × condition × time within the bilateral amygdala (left: $F_{2,220} = 6.03$, $p = 0.003$; right: $F_{2,220} = 5.77$, $p = 0.004$), resulting from a decrease in amygdala reactivity to sad faces in both patient samples [ECT: $Z = 2.26$, $p = 0.012$; medication (MED), right: $Z = 3.28$, $p = 0.001$; left: $Z = 3.06$, $p = 0.001$], and an increase in amygdala activity to positive faces in the MED sample ($Z = 2.09$, $p = 0.018$). The colour bar shows F values. Right: bar graphs depict the estimated contrast values subdivided by group [ECT, MED, healthy control HC)] at T1 (orange) and at T2 (blue) for the negative > neutral (above) and positive > neutral (below) conditions extracted from peak values of the interaction analysis. * Significant differences (Alpha-Sim corrected, voxel threshold, $p < 0.05$; minimum cluster volume threshold $k = 33$ voxels). fMRI, Functional magnetic resonance imaging.

$x = 34$, $y = -2$, $z = -28$, $Z = 2.54$, $k = 43$, $p = 0.006$; MED: $x = 28$, $y = 4$, $z = -20$, $Z = 3.14$, $k = 42$, $p = 0.001$; $x = -24$, $y = 0$, $z = -16$, $Z = 2.66$, $k = 128$, $p = 0.004$). In turn, there were no significant differences for the happy face condition. The *post-hoc* analyses of cross-sectional effects at T2 did not reveal any significant differences of amygdala activity in reaction to negative or positive faces in both patient samples compared with controls, indicating that the abnormal amygdala responsiveness pattern observed at T1 in both patient groups was entirely normalized after treatment.

Associations between brain functional changes and clinical response

The correlation analyses yielded a significant negative association between changes in amygdala activity to sad faces and symptomatic improvements in the ECT sample ($r_{spearman} = -0.48$, $p = 0.044$), and by tendency for the MED sample ($r_{spearman} = -0.38$, $p = 0.098$). In contrast, a positive association was found between amygdala activity changes to positive faces and symptomatic improvements for the ECT sample ($r_{spearman} = 0.52$, $p = 0.027$). However, this association was absent for the MED sample ($p = 0.806$, see Fig. 2). The comparison of the differences between correlation coefficients yielded marginal significance ($Z = 1.48$, $p = 0.07$) using the Fisher r-to-z transformation.

Associations between pre-treatment amygdala function and ECT response

We did not find any significant association between the pre-treatment amygdala function to emotional

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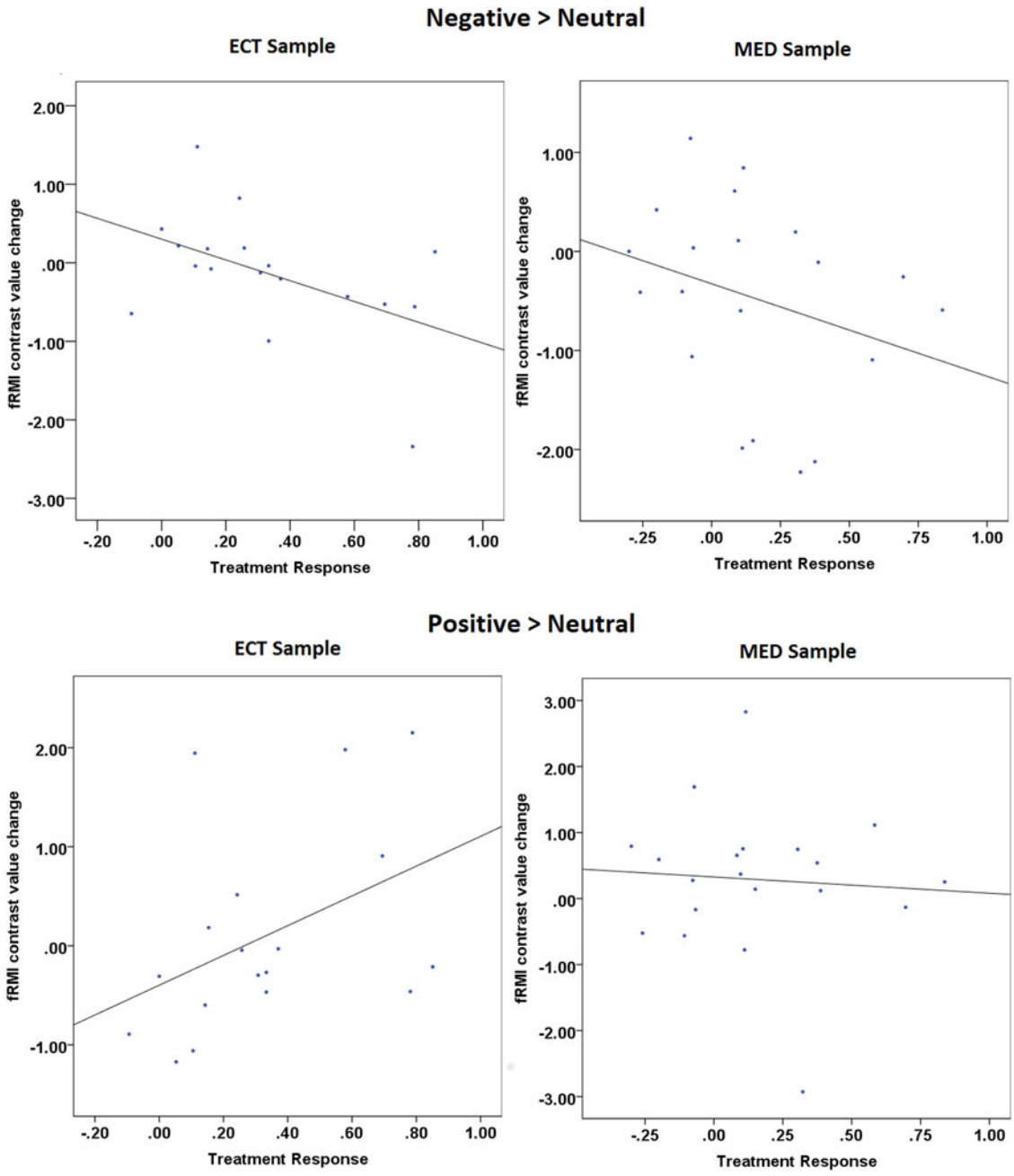

Fig. 2. Associations between functional magnetic resonance imaging (fMRI) contrast value changes in amygdala reactivity and changes in Beck Depression Inventory scores, displayed separately for the contrast negative > neutral (above) and positive > neutral (below) subdivided by treatment condition [left: electroconvulsive therapy (ECT) sample; right: medication (MED) sample]. The graphs depict a significant negative association between amygdala activity changes to sad faces and symptom relief in the ECT sample ($r_{spearman} = -0.48$, $p = 0.044$), and by tendency for the MED sample ($r_{spearman} = -0.38$, $p = 0.098$). In contrast, a positive association was found between amygdala activity changes to positive faces and symptomatic improvements for the ECT sample ($r_{spearman} = 0.52$, $p = 0.027$).

stimuli and individual symptom improvement in percentage as measured with the BDI and HAMD for either the ECT sample (p's > 0.18) or the MED sample (p's > 0.17).

Discussion

The present prospective study is the first to investigate functional changes in rapid emotion processing in the

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course of ECT in a psychiatric sample by using fMRI. The principal findings suggest pre-treatment elevated amygdala activation to subliminally presented sad faces, replicating previous reports of a mood-congruent neuronal processing bias in the amygdala (Victor *et al.* 2010; Stuhrmann *et al.* 2013; Suslow *et al.* 2013). More importantly, the present data suggest a normalization of amygdala function after a series of ECT (objective 1). However, again consistent with previous studies, this normalization of amygdala activity was also found in the MED sample, indicating a non-specific effect of treatment rather than an ECT-specific mechanism of action (objective 2). Furthermore, the findings of the regression analyses indicated that the degree of changes in amygdala reactivity to negative emotional stimuli went along with clinical symptom improvement (objective 3). However, we were not able to predict individual response to treatment through pre-treatment amygdala function (objective 4).

The present results are in line with previous studies consistently reporting functional abnormalities in implicit emotion-regulation circuitry in acutely depressed MDD patients. Abnormally elevated activity in the amygdala in response to negative, mood-congruent stimuli (Sheline *et al.* 2001; Victor *et al.* 2010; Hamilton *et al.* 2012) and, to a smaller extent, reduced activity in response to positive, mood-incongruent emotional stimuli (Suslow *et al.* 2010; Victor *et al.* 2010; Stuhrmann *et al.* 2013), for both subliminal (Suslow *et al.* 2010; Stuhrmann *et al.* 2013) as well as supraliminal emotion processing (Siegle *et al.* 2007; Groenewold *et al.* 2013) were repeatedly observed. Furthermore, consistent with longitudinal studies investigating antidepressant treatment (Sheline *et al.* 2001; Anand *et al.* 2007), both patient samples showed a decrease of amygdala reactivity to sad faces across time points. Importantly, the degree of functional changes in amygdala reactivity to 'normal' was associated with symptom improvements in both the ECT sample and the MED sample. Moreover, our results also revealed increased amygdala responses to happy facial expressions after antidepressant treatment in the MED sample as recently shown in studies investigating antidepressant treatment (Norbury *et al.* 2009; Victor *et al.* 2010; Williams *et al.* 2015). While these effects did not reach significance in the ECT sample, there was a similar tendency at an uncorrected significance level. To summarize, the present data suggest that a change in amygdala function in response to emotional stimuli seems to constitute a key factor and a general mechanism of action of therapy in depression, probably independent of the type of treatment. While recent longitudinal, structural ECT studies showed heterogeneous findings regarding the associations of structural (e.g. hippocampal) changes and clinical symptom improvements, functional changes seem to reflect a more valid state marker for symptom improvement.

However, to date, it is not finally clarified whether amygdala hyper-reactivity to negative stimuli is present before the onset of depression, and therefore represents a predisposition or trait factor for MDD, or whether these observed findings are the consequence of (acute) depression rather representing a state factor. At present, evidence exists for both interpretations. On the one hand, several neuroimaging studies are in line with our results, which provide a body of evidence proving that this pattern constitutes a state marker by reporting a normalization of abnormally elevated activity in limbic circuits in response to pharmacotherapy (Sheline *et al.* 2001; Fu *et al.* 2004; Anand *et al.* 2007). On the other hand, these abnormal amygdala activation patterns are also found in healthy subjects at genetic (Dannlowski *et al.* 2010; Joormann *et al.* 2011) or environmental risk for MDD (Dannlowski *et al.* 2013; van Harmelen *et al.* 2013), thus indicating a trait marker for the onset of depression. However, the two conclusions are not mutually exclusive. Since hyper-reactivity of the amygdala might exist before the onset of depression, constituting a trait marker, these abnormal patterns might be more pronounced in depressive states, and furthermore, might be reversed or normalized due to pharmacotherapy or ECT.

Regarding our fourth objective – to verify whether pre-treatment amygdala function might have predictive value to indicate ECT response – we were unable to detect an association between pre-treatment amygdala activity and clinical response. While some fMRI studies of treatment response prediction in depression report that a higher degree of pre-treatment amygdala activity to emotional stimuli predicts better outcome of cognitive–behavioural therapy (Siegle *et al.* 2006) and antidepressant treatment (Canli *et al.* 2005), some other studies report the opposite effects (Salvadore *et al.* 2009; Williams *et al.* 2015). Since these studies vary dramatically with respect to the form and duration of the therapy, medication types and functional paradigms, no meaningful conclusions can be drawn at present. Here, future studies with standardized paradigms and randomized clinical trials, preferably with a sham control group, are needed to prove the predictive power of the amygdala function as a pre-treatment biomarker.

Finally, despite the fact that ECT has proven efficacy for severe depression, nearly a third of patients do not benefit from ECT. For these patients, deep brain stimulation or transcranial magnetic stimulation might be alternative treatments for treatment-resistant depression (De Raedt *et al.* 2010; Taghva *et al.* 2013; Bogod

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et al. 2014). However, research on the working mechanisms of these neurostimulation techniques is necessary to develop more efficient treatment protocols.

Some limitations of this study must be acknowledged. First and foremost, patients were not randomized into treatment groups due to the naturalistic design of the study. Second, due to the naturalistic design, all ECT patients additionally received medication that might have influenced the reported effects. Therefore, a contribution of additional pharmacologically induced functional changes cannot be ruled out. Such a contribution, moreover, is very probable, particularly since similar neurobiological effects were found in the MED sample. To shed light on the specific mechanisms of actions, future studies should aim to investigate medication-naïve patients treated with ECT. Third, it should be noted that re-testing may cause habituation problems. In particular, the amygdala is known to show strong habituation effects. However, all subjects – including the HC – were measured twice and decreases in amygdala reactivity were found only for patients, but not for HC. Furthermore, it cannot be ruled out that some specific mechanisms have been missed due to power issues. While our sample size was sufficient to detect differences between the patient samples and controls, potential group differences between treatment groups might have been too weak to be detect with the current sample size. Finally, the study only allows statements about the early, automatic stages of automatic emotion processing. Future studies should focus on supraliminal emotion-processing paradigms to detect whether the observed effects are specific for automatic emotion processing or not.

In summary, despite the above-mentioned limitations, the present study provides the first results with regard to functional changes in emotion processing due to ECT treatment by using a longitudinal design, thus validating and extending our knowledge about neurobiological effects of treatment in patients with MDD. While recent longitudinal and structural ECT studies show heterogeneous results regarding the associations of often-reported structural (e.g. hippocampal) changes and clinical symptom improvements, functional changes seem be more valid state markers for acute depression and, thus, might constitute a key factor and mechanism of action in the therapy of depression.

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Declaration of Interest

V.A. is a member of the advisory board of, or has given presentations on behalf of, the following companies: Astra-Zeneca, Janssen-Organon, Lilly, Lundbeck, Servier, Pfizer, Otsuka and Trommsdorff. H.K. has received consultation fees from MR:comp GmbH, Testing Services for MR Safety. These affiliations are of no relevance to the work described in the paper. All other 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 3 years of beginning the present work that could influence or bias their work.

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