

**Title:** Does a single session of ECT alter the neural response to emotional faces in depression? - a randomised sham-controlled fMRI study

**Running title:** Electroconvulsive therapy, fMRI and faces

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**Abstract**

Negative neurocognitive bias is a core feature of major depressive disorder (MDD) that is reversed by pharmacological and psychological treatments. This double-blind functional magnetic resonance imaging (fMRI) study investigated for the first time whether electroconvulsive therapy (ECT) modulates negative neurocognitive bias in MDD. Patients with MDD were randomized to one active (N=15) or sham ECT (N=12). The following day they underwent whole-brain fMRI at 3T while viewing emotional faces and performed facial expression recognition and dot-probe tasks. A single ECT had no effect on amygdala response to emotional faces. Whole-brain analysis revealed no effects of ECT vs. sham after family-wise error (FWE) correction at the cluster level, using a cluster-forming threshold of  $Z > 3.1$  ( $p < 0.001$ ) to secure  $FWE < 5\%$ . Groups showed no differences in behavioral measures, mood and medication. Exploratory cluster-corrected whole-brain analysis ( $Z > 2.3$ ;  $p < 0.01$ ) revealed ECT-induced trend changes in parahippocampal and superior frontal responses to fearful vs. happy faces as well as fear-specific functional connectivity between amygdala and occipito-temporal regions. Across all patients, greater fear-specific amygdala–occipital coupling correlated with lower fear vigilance. Despite no statistically significant shift in neural response to faces after a single ECT, the observed trend changes after a single ECT session point to an early shift in emotional processing that may contribute to antidepressant effects of ECT.

**Keywords**

**Electroconvulsive therapy, negative bias, major depressive disorder, functional magnetic resonance imaging**

## Introduction

Negative bias in the cognitive processing of emotional information is a core feature of major depressive disorder (MDD) associated with risk of depression relapse (Bouhuys et al., 1999, Mathews and MacLeod, 2005). Experimental psychology and functional magnetic resonance imaging (fMRI) studies of MDD indicate that negative bias occurs at behavioural and neural levels across several processing domains (Miskowiak and Carvalho, 2014). In particular, MDD patients display increased recognition of negative facial expressions (Harmer et al., 2009, Milders et al., 2010) and a tendency to interpret neutral or ambiguous faces as negative (Bouhuys et al., 1999, Gollan et al., 2008). This is accompanied by *hyper*-activity in the amygdala and occipito-parietal regions and prefrontal *hypo*-activity to negative faces, and limbic *hypo*-activity to positive expressions (Fu et al., 2004, 2007, 2008, Surguladze et al., 2005). In addition, reduced functional connectivity (FC) between the amygdala and anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (dlPFC) has been observed in response to negative faces (Chen et al., 2008, Kong et al., 2013) and is associated with greater illness severity (Dannlowski et al., 2009).

Aberrant neural and/or cognitive response to emotional faces is also evident during periods of remission (Miskowiak and Carvalho 2014, Norbury et al., 2010, Stuhrmann et al., 2011) and in healthy individuals at familial risk (Joormann et al., 2007, Mannie et al., 2011, Miskowiak et al., 2014), which highlights negative face processing bias as a

putative illness endophenotype — an illness biomarker associated with genetic liability for MDD (Gottesman and Gould, 2003). However, findings regarding negative face processing bias at a *behavioural* level are somewhat inconsistent, with several studies of remitted patients and high-risk groups showing no bias (Mannie et al., 2011, Norbury et al., 2010, Wolfensberger et al., 2008). In contrast, fMRI studies provide relatively robust evidence for negative bias in the *neuronal* response to emotional faces in these populations (Mannie et al., 2011, Norbury et al., 2010, Wolfensberger et al., 2008). This suggests that fMRI provides a more sensitive assay of emotion processing bias than behavioural measures; perhaps because the behavioural expression of aberrant brain responses may be prevented by compensatory or homeostatic mechanisms at a brain level (Haas et al., 2007).

Various antidepressants have been shown to rapidly modulate cognitive and neural response to emotional faces that predate symptom improvement and predict subsequent treatment efficacy (Miskowiak et al., 2007:2, Nathan et al., 2014, Tranter et al., 2009). In contrast, compounds devoid of antidepressant efficacy fail to change emotional bias (Nathan et al., 2014). Early treatment-related reversal of negative bias may therefore constitute a platform for re-learning of adaptive behaviour that again contributes to mood improvements (Harmer and Cowen, 2013). Notably, cognitive behavioural therapy (CBT) reversed limbic *hyper*-activity and dorsal anterior cingulate cortex (ACC) *hypo*-activity to sad faces in MDD (Fu et al., 2008). Reversal of imbalanced fronto-limbic response to

emotional faces may thus be a common neurocognitive mechanism of pharmacological and psychological treatments.

Electroconvulsive therapy (ECT) is the most efficient treatment of severe depression (American Psychiatric Association, 2001) but it is unclear whether ECT modulates neurocognitive response to emotional information. Key neurobiological mechanisms may be promotion of brain-derived neurotrophic factor (Altar et al., 2004) and neurogenesis (Bolwig and Madsen, 2007). In keeping with this, longitudinal MRI studies demonstrated that ECT increases hippocampal volume in MDD patients (Jorgensen et al., 2016) and increases cortical thickness within the ACC, parahippocampal gyrus and temporal regions, which correlates with symptom improvement in ECT-responders (Pirnia et al., 2016). At a *functional level*, resting-state fMRI studies found ECT-related normalization of *negative* FC between dorsal PFC and posterior regions in the default mode network (Abbott et al., 2013) and *positive* FC between the subgenual ACC (sgACC) and hippocampi, temporal and ventromedial prefrontal cortex (vmPFC) (Argyelan et al., 2016). The present fMRI study is the first to investigate the effects of ECT on the neurocognitive response to emotional information in MDD in a randomised, sham-controlled, double-blind design. We hypothesized that a single ECT session (i) reduces the neural response to fearful vs. happy faces in limbic regions including the amygdala, (ii) increases functional connectivity during negative face processing between amygdala and fronto-occipital regions, and (iii) reverses negative bias in attention to and recognition

of emotional faces. Such findings would highlight reversal of heightened neurocognitive response to negative information as a common mechanism of distinct treatments for MDD.

## **Materials and Methods**

### ***Study design and participants***

The study had a double-blind, sham-controlled, parallel-group design. Patients **aged 18-60** scheduled for ECT at Psychiatric Centre Copenhagen (Rigshospitalet and Bispebjerg) were recruited between November 2009 and July 2015. Specialists in psychiatry made the diagnoses and rated mood symptoms with the Hamilton Depression Rating Scale 17-items (HDRS-17; (Hamilton, 1960). Eligibility required a diagnosis of unipolar depression and a score  $\geq 18$  on the HDRS-17. Exclusion criteria were: substance- or alcohol abuse, pregnancy, somatic illness contraindicating ECT, having a pacemaker or other metal implants inside the body, bipolar disorder, schizoid disorder, schizophrenia or any neurological disorder. The study was approved by the local ethics committee (H-3-2009-074) and the Danish Data Protection Agency (2009-41-3676) and carried out in accordance with the Declaration of Helsinki. All patients provided written informed consent.

### ***Randomisation and Masking***

Pharma Consulting Group (Uppsala, Sweden) performed block randomisation (< or  $\geq$ 45 years and gender) and created a randomisation list and envelopes with information about treatment allocation (ECT/sham) for each patient ID number. Numbering within each stratum was consecutive and ID numbers were recorded in individual participant files. The randomisation list was kept in a locked filing cabinet in the ECT room only accessible by the caregiver administering the ECT/sham. Patients, all physicians and nurses at the ward, and outcome assessors were blinded to group assignment and blinding was maintained throughout the study and data analyses.

### ***Procedure***

Baseline mood ratings were performed during the inclusion interview (1-4 days prior to randomisation). For their *first* ECT (day 0), patients were prepared with bitemporal electrode placement, put under full anaesthesia with thiopental and given succinylcholine for muscle relaxation. Patients' primary caregiver then left the ECT room to prevent unblinding. The envelope with treatment allocation was opened, and active or sham ECT was administered accordingly **with a Thymatron IV ECT device set on X2 programme. A dosing strategy with the initial dose based on the patient's age was used (charge [per cent of 500 millicoulomb] = 50% of the age). In subsequent**

**treatments, a titration based on seizure quality (configuration and length of the EEG seizure, which should exceed 25 s) was applied with energy dosage 1.5 times above seizure threshold.**

The following day (day 1), patients underwent fMRI scanning, neurocognitive testing and ratings of mood and subjective state at the Danish Research Center for Magnetic Resonance (DRCMR). Assessments took place between 1-6 pm (to control for diurnal variation in mood symptoms) and lasted for two hours. From day 2, all patients received tri-weekly active ECT according to the standard protocol of the Capital region. Mood symptoms were rated at baseline, day 1 and after six active ECT sessions.

**The rationale for assessing treatment response after six active ECTs - rather than after completion of ECT - was to estimate a trend in treatment outcome in a standardised way. Specifically, the number of ECT sessions and end outcome after ECT completion would depend on the individual clinician's judgement and on the patient's condition. For this reason and due to lack of manpower, we did not systematically assess mood symptoms after ECT completion.**

### ***Cognitive test battery***

***fMRI paradigms.*** Neural response to fearful and happy faces was assessed with an incidental facial emotion task. Faces were displayed with E-Prime software version 1.2



(Psychology Software Tools Inc., USA) on an opaque screen at the head end of the scanner bed visible through an angled mirror. Patients indicated the gender of the faces by pressing keys on a response pad with their right middle and index fingers. Each face was shown for 200 ms followed by a fixation cross displayed for 2300 ms presented in blocks of 10 pictures (25 s per block). In-between face blocks were 16 s blocks of a central fixation cross. There were a total of four blocks for each emotion and eight in-between blocks. The total task duration was 5 min 28 s. Reaction time (RT) and accuracy were recorded.

A visual control stimulation task was employed to investigate potential confounding effects of ECT on global cerebral hemodynamic responses. Participants were instructed to look at a flashing checkerboard (frequency=8 Hz) or a fixation cross presented in alternating blocks of 14 s with a total of 20 cycles.

***Faces dot-probe and facial expression recognition tasks outside the scanner.*** The faces dot-probe and facial expression recognition tasks from the Emotional Test Battery (ETB; P1Vital Oxford) were administered on a laptop computer after the scan to assess vigilance to happy and fearful faces and recognition of emotional facial expressions, respectively. In the dot-probe task, two versions of the same face, with different expressions (one emotional and one neutral), were displayed on a vertical axis on the screen of a laptop. Three types of face pairs were presented: happy-neutral, fearful-neutral and neutral-

neutral. The face pairs were shown under two conditions: masked and unmasked for investigation of subliminal and supraliminal vigilance to emotion, respectively. In the masked condition, the face pairs were shown for 17 ms and replaced by a neutral mask for 83 ms. In the unmasked condition the face pairs were displayed for 100 ms. There were 192 trials (32 masked/unmasked happy-neutral, 32 masked/unmasked fear-neutral, 32 masked/unmasked neutral-neutral). Following the display of facial expressions, a single pair of dots appeared on either the upper or lower half of the screen. One pair of dots was vertical ( : ) while the other was horizontal ( · · ). Patients indicated the orientation of the dots by pressing one of two keys on the keyboard, and were instructed to respond as quickly as possible. The dots remained on the screen until a response had been given. The task consisted of eight blocks with unmasked stimuli and eight blocks with masked stimuli (12 trials per block) presented in balanced alternating order.

In the facial expression recognition task, participants were shown facial stimuli from Ekman & Friesen (1979) expressing either happiness, surprise, sadness, fear, anger or disgust or which were neutral, and indicate the emotion by pressing corresponding keys on a keypad as quickly and accurately as possible. The faces were shown for 500 ms and replaced by a blank screen. The facial expressions were graded at 10% intervals ranging from neutral (0%) to overt emotion (100%).

Each emotion was presented four times for each of the ten intensity levels, plus a neutral face for each emotion, for a total of 250 stimuli presentations. Response times for correct responses, accuracy and errors were recorded.

### ***Mood and subjective state***

Depressive symptoms **were** assessed with the HDRS-17 and the Beck Depression Inventory (BDI; (Beck et al., 1961)). The State Trait Anxiety Inventory (STAI; (Spielberger, 1983) and visual analogues scales (VAS) (happiness, sadness, alertness, anxiety, dizziness and nausea) were administered on the scanning day

### ***Magnetic resonance imaging***

MRI data were collected with a 3 T Siemens Trio MR scanner using an eight-channel head array coil. Blood oxygen-level dependent (BOLD)-sensitive fMRI used a T2\*-weighted gradient echo spiral echo-planar imaging (EPI) sequence with an echo time (TE) of 30 ms, repetition time (TR) of 2.49 ms and a low flip angle of 20° to minimize physiological noise (Gonzalez-Castillo et al., 2011). A total of 128 brain volumes were acquired in a single fMRI session, each consisting of 42 slices with a slice thickness of 3 mm and a field of view (FOV) of 192 × 192 mm using a 64 × 64 grid. High-resolution

3D structural T1-weighted spin echo images were obtained after the first session of BOLD fMRI (TI = 800, TE = 3.93, TR = 1540 ms, flip angle 9°; 256 × 256 FOV; 192 slices).

### *fMRI data analysis*

**Amygdala ROI.** Regions of interest (ROIs) for the left and right amygdala in standard space were obtained with mri3dX (<http://www.aston.ac.uk/lhs/staff/singhkd/mri3dX/mri3dX.jsp>), which uses a stored representation of the Talairach Daemon Database (Lancaster et al., 2000). Mean percent BOLD signal change to fearful and happy faces was computed in left and right amygdala and compared between the groups.

**Whole-brain exploratory analysis.** The FMRIB Software Library version (FSL version 6.00) ([www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)) (Smith et al., 2004) was used to pre-process and analyse fMRI data. Pre-processing included image realignment, non-brain removal, motion correction (**MCFLIRT**), spatial normalization and spatial smoothing (Gaussian kernel, 5 mm full-width-half-maximum). The time series in each session were high pass-filtered (to a maximum of 0.008 Hz). Analyses of individual subject data were computed using the general linear model with local autocorrelation correction (Woolrich et al., 2001). Two experimental conditions – ‘fearful faces’ and ‘happy faces’ – were modelled separately by convolving trials with a canonical hemodynamic response function

(Boynton et al., 1996). At the group level, all analyses employed a full mixed-effects approach (i.e., FSL FLAME1) (Woolrich et al., 2004). We chose to threshold Z (Gaussian T) statistic images at  $Z > 3.1$ ,  $p < 0.001$ , corrected for multiple comparisons at a cluster level, since this threshold has been shown to secure sufficiently low (<5%) family-wise error (FWE) rates (Eklund et al., 2016). For exploratory purposes, we also conducted whole-brain analyses with a more liberal cluster-forming threshold of  $Z > 2.3$ ,  $p < 0.01$ , to inform future studies about trend changes in brain activity and connectivity. Foci of peak cluster activation were localised using a standard anatomical atlas (Talairach and Tournoux, 1988). The face contrast determining the effects of ECT on emotional bias was fearful vs. happy. Mean percent BOLD signal change was extracted for clusters showing significant between-group interactions in the whole-brain analysis for visualization purposes.

***Right and left amygdala whole-brain PPI.*** Functional connectivity analysis was performed by extracting for each participant a deconvolved time series for (a) the emotional face blocks vs. baseline cluster identified within the anatomical right amygdala using SVC and (b) the functional cluster within the anatomical left amygdala. These time-courses were entered in two separate FSL psychophysical interaction (PPI) analyses with the functional right and left amygdala cluster as the seed region, respectively, along with the two psychological regressors (fear, happy) and the two PPI regressors (fear  $\times$  time

series, happy  $\times$  time series). These individual contrast images were entered into the group level (sham group vs. ECT) using a mixed-effects analysis across the whole brain to identify brain areas where regional activity co-varied stronger with that of the left and right amygdala in one of the two groups during fear blocks and happy blocks. For the primary analysis, Z statistic images were thresholded at  $Z > 3.1$ , with a cluster threshold of  $p < 0.001$  and family-wise error correction for multiple comparison correction was performed at the cluster level ( $p < 0.05$ , corrected). Exploratory analysis was also conducted using a more liberal cluster-forming threshold of  $Z > 2.3$ ,  $p < 0.01$ .

***Statistical analysis of behavioural data and mood ratings.*** Behavioural data from the gender discrimination and facial expression recognition tests were analysed using repeated measures analysis of variance (ANOVA) with group as the between-subjects factor, and emotional expressions as within-subjects factors (using Greenhouse-Geisser correction when appropriate). Significant interactions were followed up by simple main effect analyses ( $t$ -tests and Mann-Whitney U tests for normally and non-normally distributed data, respectively). Vigilance scores (dot-probe task) for masked and unmasked emotional faces were calculated by subtracting RTs to fearful and happy faces from RTs to neutral faces, respectively. Vigilance scores, mood and subjective state were examined with main effect analyses. Statistical significance was set to an alpha-level of

$p \leq 0.05$  (two-sided). Significant effects of ECT on behavioural measures were subjected to Bonferroni corrections for multiple comparisons.

***Exploratory correlation analyses.*** Pearson's correlations (Spearman's rho for non-normally distributed data) were conducted between clusters showing differential FC after ECT vs. sham in the whole-brain PPI analysis and (i) fear vigilance and (ii) clinical response after six ECT sessions. These correlation analyses were not adjusted for multiple comparisons due to their exploratory nature. Analyses of behavioural and mood data were performed using the Statistical Package for Social Sciences (SPSS) (version 22.0) (IBM Corporation, Armonk, New York).

## **Results**

### ***Participant characteristics and mood***

The first patient was randomised in December 2009 and the last patient assessment was completed in January 2015. A total of 29 participants were included. Data was lost for two patients; one participant (ECT) fell asleep during the fMRI scan, and for another participant the image quality for the structural scan was inadequate (sham). Functional MRI and behavioural data was thus analysed for 27 participants (ECT: N=15, sham: N=12) (Figure 1). Data for one patient (ECT) on the control visual stimulation paradigm

was lost due to technical difficulties, but the patient's other fMRI data were intact and included in the analyses. See Table 1 for demographic and clinical characteristics.

“[Insert Figure 1]”

**Table 1.** Demographic and clinical characteristics at baseline.

	Sham (N=12)	ECT (N=15)	<i>p</i> -value
Gender (N/% males)	8/67	9/60	0.7
Age, median (IQR)	36 (32)	42 (29)	0.9
Age at onset, median (IQR)	26 (23)	18 (31)	0.5
First hospitalisation, median (IQR)	27 (27)	42 (29)	0.8
Number of episodes, median (IQR)	5 (7)	10 (17)	0.5
Education (yrs.), mean (SD)	16 (2)	14 (3)	0.1
Medication <sup>a</sup> :			
Antidepressants, no. (%)	9 (75)	12 (86)	0.5
Antipsychotics, no. (%)	4 (33)	5 (36)	0.9
Anticonvulsants, no. (%)	1 (8)	1 (7)	0.9
Benzodiazepines, no. (%)	5 (42)	7 (50)	0.7
Lithium, no. (%)	2 (17)	0 (0)	0.1
Thyidea, no. (%)	0 (0)	1 (7)	0.3
Combined prescriptions, no.	1.8	1.9	0.8
STAI-trait, mean (SD) <sup>b</sup>	63 (9)	53 (13)	0.05*
<u>Baseline</u>			
HDRS-17, mean (SD)	27 (6)	26 (4)	0.7
BDI, median (IQR) <sup>c</sup>	26 (19)	28 (10)	0.5
<u>Day 1</u>			
HDRS-17, mean (SD)	26 (6)	23 (5)	0.2



BDI, median (IQR) <sup>d</sup>	18(16)	24 (10)	0.5
STAI-state, median (IQR) <sup>e</sup>	58 (22)	52 (23)	0.9
VAS <sup>f</sup>			
Happiness, median (IQR)	1 (3)	1 (3)	0.8
Sadness, mean (SD)	7 (2)	7 (3)	0.8
Alertness, mean (SD)	4 (3)	4 (3)	0.8
Anxiety, mean (SD)	5 (3)	3 (3)	0.2
Dizziness, median (IQR)	2 (4)	0 (2)	0.06
Nausea, median (IQR)	1 (3)	0 (1)	0.3

\* $p \leq 0.05$ . Abbreviations: ECT: Electroconvulsive therapy; BDI: Beck Depression Inventory; HDRS-17: Hamilton Depression Scale 17 items; STAI: State-Trait Anxiety Scale; VAS: Visual Analogue Scales; **IQR: interquartile range; SD: standard deviation.**

<sup>a</sup>Data missing for one participant (ECT).

<sup>b</sup>Data missing for three participants (sham: N=2, ECT: N=1).

<sup>c</sup>Data missing for 2 participants (sham: N=1, ECT: N=1).

<sup>d</sup>Data missing for one participant (sham).

<sup>e</sup>Data missing for two participants (sham: N=1, ECT: N=1).

<sup>f</sup>Data missing for three participants (sham: N=2, ECT: N=1).

At baseline, the two treatment groups were comparable for gender composition, age, age of onset and first hospitalisation, educational levels, number of episodes, medication and depression symptoms ( $p \geq 0.1$ ). Patients in the sham group displayed slightly more trait anxiety than ECT-treated patients ( $t=2.11$ ,  $df=22$ ,  $p=0.05$ ). However, there were no between-group differences in mood ( $p \geq 0.2$ ) or subjective state on day 1 (VAS:  $p$ -values  $\geq 0.06$ ; STAI-state:  $p=0.9$ ). **Notably, analysis of the *within-group change* in HDRS-17 scores from baseline to day 1 for each group separately showed a statistically significant improvement in the ECT group (mean  $\pm$ SD improvement:  $3.2 \pm 3.9$  points;  $t=3.17$ ,  $df=14$ ,  $p=0.007$ ) but not in the sham group (mean  $\pm$ SD**

**improvement:  $1.1 \pm 4.4$  points;  $p=0.41$ ), consistent with evidence for mood improvement after single ECT (Kellner and Knapp 2007, Lapidus et al 2013). All patients **also** showed **substantial** symptom improvement after six ECT sessions (mean $\pm$ SD **improvement**: HDRS-17:  $15 \pm 7$ ; BDI:  $13 \pm 7$ ,  $p<0.01$ ).**

### *fMRI results*

**Amygdala ROI.** Bilateral amygdalae responded significantly to fearful and happy faces vs. baseline across all patients ( $p \leq 0.01$ ). There was no effect of ECT on amygdala response to fearful faces ( $p=0.3$ ) and only a non-significant trend towards greater bilateral amygdala response to happy faces in ECT vs. sham treated patients ( $p=0.09$ ).

**Whole-brain exploratory analysis.** Emotional faces activated a broad distributed neural network including the occipital lobe, fusiform gyrus, parietal regions, dorsolateral and medial prefrontal regions and dorsal ACC (see Table 2 for peak cluster activations). Whole-brain analysis revealed no differences between ECT and sham groups at the conservative threshold ( $Z>3.1$ ,  $p<0.001$ , cluster-corrected). The exploratory whole-brain analysis ( $Z>2.3$ ,  $p<0.01$ , cluster-based) revealed ECT-associated reduction in parahippocampal activity and increase in superior frontal gyrus (SFG) and caudate

activity to fearful vs. happy faces (see clusters with effect size estimations of these exploratory findings in Figure 2; for peak cluster activations, see Table 2).

“[Insert Figure 2]”

**Right and left amygdala whole-brain PPI.** Psychophysical interaction analysis showed no significant difference between ECT and sham groups in the primary analysis using a cluster-forming threshold of  $Z > 3.1$ ,  $p < 0.001$ . Exploratory PPI analysis at a more liberal cluster-forming threshold of  $Z > 2.3$ ,  $p > 0.0,1$  indicated increased fear-specific FC between the right amygdala and cluster in the right medial temporal lobe and between the left amygdala and three clusters in occipito-temporal regions (see clusters with effect size estimations in Figure 3; for peak cluster activations see Table 2).

“[Insert Figure 3]”

**Table 2.** Peak cluster activations in brain regions with increased BOLD response during fearful and happy faces, peak cluster activations in brain areas displaying significant between-group differences in neural activity in response to fearful vs. happy faces and peak cluster activations in clusters showing significant increased negative/positive coupling with amygdala in ECT vs. sham.

	P-value	Voxel	Z max	MNI		
				x	y	Z
<i>Primary analysis using a threshold of Z&gt;3.1, p&lt;0.001, cluster-corrected</i>						
<b>Main effect of task</b>						
Right precentral gyrus (BA 4)	0.0184	101	4	54	-10	26
Right tapetum (BA 23)	0.000443	186	4.25	24	-62	8
Left medial frontal gyrus (BA 6)	4.41*10 <sup>-15</sup>	1099	6.17	-2	2	56
Right superior parietal lobe (BA 7)	1.75*10 <sup>-18</sup>	1471	5.19	32	-52	46
Right middle frontal gyrus (BA 6)	4.03*10 <sup>-31</sup>	3136	5.79	40	2	46
Left precentral gyrus (BA 4)	0	6065	5.83	-46	-12	58

Left fusiform gyrus (BA 37)	0	11958	6.88	-44	-50	-16
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**Between-group comparisons**

No significant differences between groups

**Exploratory analysis using a threshold of  $Z > 2.3$ ,  $p > 0.01$ , cluster-corrected****Whole-brain analysis****Sham > ECT**

Right middle temporal gyrus/parahippocampal gyrus (BA 20/36)	0.0189	302	3.66	36	2	-32
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**ECT > sham**

Left middle frontal gyrus (BA 6)	0.00957	337	3.76	-30	-4	56
Right occipital fasciculus (BA 29/30)	0.000928	466	4.29	18	-36	20

**Whole-brain PPI analysis**

Right amygdala functional cluster

Right superior temporal gyrus (BA 22)	0.0134	301	3.82	64	-24	-2
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Left amygdala functional cluster

Right fusiform gyrus (BA 19/37)	0.0162	281	3.62	32	-68	-10
Left lingual gyrus (BA 18)	0.0115	297	3.23	-2	-76	-12
Left lingual gyrus (BA 19)	0.000564	448	3.37	-20	-74	-18

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Abbreviations: MNI: Montreal Neurological Institute; BA: Brodmann area; PPI: psychophysical interaction.

**Occipital ROI response to visual stimulation.** No significant difference in mean percent BOLD signal change in the occipital (calcarine) ROI was observed between ECT and sham groups ( $p=0.98$ ).

**Behavioural results**

Gender discrimination during incidental emotion processing during fMRI revealed greater accuracy in ECT vs. sham groups for both happy and fearful faces ( $F(1,25)=4.97$ ,  $df=1$ ,  $p=0.04$ ; *post-hoc t*-tests:  $p\geq 0.3$ ) in the absence of differences between groups in response times ( $p\geq 0.7$ ). This difference rendered non-significant after Bonferroni correction for multiple comparisons across the behavioural measures (vigilance to emotional faces and facial expression recognition).

In the faces dot-probe task, patients showed vigilance to masked fearful faces ( $z=-2.0$ ,  $p=0.04$ ) but not to masked happy faces ( $p=0.3$ ) or unmasked emotional faces ( $p\geq 0.6$ ). There was no effect of ECT vs. sham treatment on vigilance to masked or unmasked fearful or happy faces ( $ps\geq 0.2$ ). Facial expression recognition revealed a main effect of emotion (accuracy:  $F(5,125)=8.5$ ,  $p<0.01$ ; speed:  $F(3,66)=4.4$ ,  $p<0.01$ ), reflecting generally faster and more accurate recognition of positive emotions (happy and surprise) than negative expressions (fear, anger, disgust, sad) ( $p<0.01$ ). However, there was no effect of ECT on accuracy or speed of facial expression recognition ( $p\geq 0.1$ ).

### ***Exploratory correlation analyses***

Across all patients, greater fear-specific *left* amygdala-occipital gyrus coupling correlated moderately with less supraliminal fear vigilance ( $r_s(25)=-0.40$ ,  $p=0.04$ ), which rendered non-significant in the ECT group alone, possibly due to loss of power in the smaller

sample ( $N=15$ ;  $p \geq 0.3$ ). Further, there was a trend across the entire cohort towards an association between left amygdala – fusiform coupling and less supraliminal fear vigilance ( $p=.063$ ). There were no significant correlations between *right* amygdala FC and fear vigilance ( $p \geq 0.2$ ), or between *right and left* amygdala FC and clinical response after six ECT sessions ( $p \geq 0.7$ ).

## Discussion

This study is the first randomised, double-blind, sham-controlled fMRI study of the effects of ECT on the neurocognitive response to emotional faces in MDD. Contrary to our hypothesis, a single ECT session had no effect on amygdala response to emotional faces. We also found no support for our hypothesis that ECT modulates neural response and FC during emotional face processing in the whole-brain analysis applying a cluster extent threshold that appropriately controls for family-wise errors at the cluster level (Eklund et al., 2016). However, exploratory whole-brain analysis with a liberal cluster-forming threshold indicated that ECT may reduce parahippocampal activity and increase SFG and caudate activity to fearful vs. happy faces and enhance fear-specific FC between the amygdala and temporo-occipital regions, as hypothesised. Across all patients, greater fear-specific left amygdala–occipital FC correlated with lower supraliminal fear vigilance. In contrast with our hypothesis, we observed no effects of ECT on behavioural

response to emotional faces. There were also no differences between the groups in mood symptoms, subjective state or concomitant medication.

The absence of a statistically consistent effect of a single ECT session on behavioural assays of emotional bias and neural response to fearful vs. happy faces in the primary analysis contrasts with evidence for early effects of several monoaminergic antidepressant drugs after single doses and seven days treatment in healthy individuals and patients with MDD (Harmer and Cowen, 2013). It is possible that additional ECT sessions are required to produce robust change in neurocognitive response to emotional information, consistent with more reliable change in emotional bias after repeated than single antidepressant drug administration (Harmer and Cowen, 2013). An alternative explanation for the discrepancy is our small sample size and potential confounding effects of anaesthesia, medication and variation in symptom presentation. Specifically, the cohort included a mixture of patients with treatment-resistant depression and more severely depressed individuals, which may have increased variation in the results. Indeed, *exploratory* analyses with a liberal cluster-forming threshold point to possible effects of ECT on fear-specific neural response and FC consistent with the effects of CBT, pharmacotherapy and neuromodulatory treatments (Davidson et al., 2003, Fu et al., 2004, 2008, Leyman et al., 2011, Ruhé et al., 2012).

The preliminary evidence from the exploratory analysis for reduction in parahippocampal activity and increase in SFG response to fearful vs. happy faces in ECT treated patients

are opposite to parahippocampal *hyper*-activity to negative vs. positive faces (Fu et al., 2004, 2007, Surguladze et al., 2005) and dorsal PFC *hypo*-activity to negative faces in MDD (Fu et al., 2008). Further, the increased fear-specific caudate response in ECT-treated patients is opposite to caudate *hypo*-activity in MDD during attempts to reappraise negative stimuli (Hamilton et al., 2012). Greater dorsal PFC and ACC activity to emotional—particularly negative—faces occurs in the absence of differences in amygdala activity in remitted patients with MDD (Norbury et al., 2010) and unaffected first-degree relatives (Miskowiak et al., 2014) and may represent a compensatory mechanism that limits limbic over-responsiveness (Miskowiak et al., 2014, Norbury et al., 2010). Given this, the preliminary evidence for ECT-related changes in limbic and dorsal PFC response may represent an early marker of decreased bottom-up processing of *and* stronger top-down inhibition of reactivity to fearful faces. Interestingly, modulation of limbic reactivity to negative stimuli through conscious reappraisal engages a distributed neural network of temporal, parietal and prefrontal regions (Goldin et al., 2008). The preliminary finding that ECT increases fear-specific amygdala-occipito-temporal coupling—and its correlation with reduced fear vigilance—may thus reflect increased reappraisal of negative faces.

The randomized, sham-controlled, parallel-group design was a strength of the study. Further, the investigation of the effects of *a single* ECT vs. sham session enabled insight into the *early* neuronal activity changes that precede (and potentially mediate) changes in



depression symptoms. However, the design was also a limitation since one ECT session may have been insufficient to affect behavioural assays of emotional bias and to produce robust change in neural response to emotional faces that would survive stringent FWE correction at the cluster level. Nevertheless, a longer period with repeated ECT vs. sham sessions would be unethical since patients were severely ill and 50% received sham. **Further**, the cohort was representative of patients referred to ECT and the ECT and sham groups were comparable for concomitant medication and illness presentation. **The cross-sectional study design was suboptimal, as a longitudinal study of the same patients scanned twice (before and after ECT/ sham) would have supported more robust inferences about the effects of ECT on neurocognitive response to emotional faces.** Nevertheless, the present design was chosen due to ethical concerns about time requirements of the severely depressed patients and length of period before they were able to start their ECT. Further, repeated testing would have introduced learning effects and potential desensitisation of neural response to emotional faces, as well as ceiling effects. During the six years of recruitment, about 800 patients received ECT at Psychiatric Centre Copenhagen, of whom about 25% (i.e., 200 patients) had non-psychotic unipolar depression and were aged 18-60, and were thus potentially eligible (see Hundrup et al., 2016). Key reasons for the slow recruitment were (i) lack of manpower, which led to many patients being randomly missed, and (ii) a partially competing (structural) MRI study that was conducted at the Centre

**during the same time period (Jorgensen et al., 2016). Another contributing factor to the slow recruitment was the study design, which involved** (i) 50% probability of being allocated to sham treatment for the first treatment session –potentially causing a three day delay in active ECT- and (ii) and the fact that patients scheduled for ECT often required immediate treatment. **As can be seen from the CONSORT flow chart, the latter was not the main mechanism of the slow recruitment. However, this does raise the possibility of a selection bias in the study with less acutely unwell patients being more likely to agree with the study requirements.** The small sample may explain why effects of ECT vs. sham emerged only in the analysis with a more liberal cluster-forming threshold. The findings of these analyses are therefore weak and should be considered preliminary. Although this liberal threshold was used in our original sample size estimation and is default in FSL, we decided to apply a conservative threshold in the *primary* analyses to ensure methodological stringency given the recent paper showing high FWE rates with less conservative thresholds (Eklund et al., 2016). Notwithstanding, the current sample size was relatively large compared to other ECT neuroimaging studies that included 12-29 patients in a *within-group* design (Abbott et al., 2013, Argyelan et al., 2016, Jorgensen et al., 2016, Pirnia et al., 2016). The generally small samples in neuroimaging studies of ECT are likely to reflect the challenge with conducting fMRI studies in these severely ill often suicidal or psychotic patient groups.

In conclusion, this randomised, controlled ECT study – which is the first of its kind – revealed no consistent effect of a single ECT session on behavioural or on neural response to emotional faces when applying a statistical threshold that provides good control of FWE by ensuring that the Euler characteristic is a good proxy for FWE correction at the cluster level. Likewise, there were no differences between the groups in the acute effects of ECT on mood symptoms. Exploratory analysis at a liberal cluster-forming threshold suggested that single ECT session influences fear-specific limbic and prefrontal response and functional coupling between the amygdala and occipito-temporal regions. Whether the early effects of ECT reflect a relevant therapeutic mechanism of ECT needs to be addressed in future larger studies.

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KWM reports having received consultancy fees from Lundbeck and Allergan in the past 3 years. The Lundbeck Foundation and Weimann Foundation are acknowledged for

providing half of KWM's postdoc salary between 2012-2018 for her to do full-time research in this time. OBP is a member of the board of directors of the Elsass Foundation (until 2016). CJH has received consultancy fees from P1vital ltd, Lundbeck, Servier, Eli-Lilly and is a company director of Oxford Psychologists ltd. CJH has also received grant income from GSK, UCB, Janssen Inc, Lundbeck, Servier and Astra Zeneca. HRS discloses honoraria as journal editor from Elsevier Publishers and book editor from Springer Publishing as well as honoraria as speaker from Genzyme and MerckSerono, and grant support from Biogen-idec within the past 3 years. LVK reports having been a consultant for Lundbeck, AstraZeneca and Sunovion within the last 3 years. Within the past 3 years, MBJ have received speaker fees for Lundbeck and consultant fees for Shire. All other authors report no biomedical financial interests or potential conflicts of interest.

## References

- Abbott CC, Lemke NT, Gopal S, Thoma RJ, Bustillo J, Calhoun VD and Turner JA (2013) Electroconvulsive Therapy Response in Major Depressive Disorder: A Pilot Functional Network Connectivity Resting State fMRI Investigation. *Frontiers in Psychiatry* 4. Available at: <http://journal.frontiersin.org/article/10.3389/fpsy.2013.00010/abstract> (accessed 26/09/16).
- Altar CA, Laeng P, Jurata LW, Brockman JA, Lemire A, Bullard J, Bukhman YV, Young TA, Charles V and Palfreyman MG (2004) Electroconvulsive Seizures Regulate Gene Expression of Distinct Neurotrophic Signaling Pathways. *Journal of Neuroscience* 24(11): 2667–2677.
- American Psychiatric Association (2001) *The practice of electroconvulsive therapy: recommendations for treatment, training, and privileging: a task force report of the American Psychiatric Association* (2nd ed.). Washington, D.C: American Psychiatric Association.
- Argyelan M, Lencz T, Kaliora S, Sarpal DK, Weissman N, Kingsley PB, Malhotra AK and Petrides G (2016) Subgenual cingulate cortical activity predicts the efficacy of electroconvulsive therapy. *Translational Psychiatry* 6(4): e789.
- Beck AT, Ward CH, Mendelson M, Mock J and Erbaugh J (1961) An inventory for measuring depression. *Archives of General Psychiatry* 4: 561–571.
- Bolwig TG and Madsen TM (2007) Electroconvulsive therapy in melancholia: the role of hippocampal neurogenesis. *Acta Psychiatrica Scandinavica* 115(s433): 130–135.

Bouhuys A, Geerts E and Gordijn M (1999) Depressed Patients' Perceptions of Facial Emotions in Depressed and Remitted States Are Associated with Relapse: A Longitudinal Study. 187(10): 595–602.

Boynton GM, Engel SA, Glover GH and Heeger DJ (1996) Linear systems analysis of functional magnetic resonance imaging in human V1. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 16(13): 4207–4221.

Chen C-H, Suckling J, Ooi C, Fu CHY, Williams SCR, Walsh ND, Mitterschiffthaler MT, Pich EM and Bullmore E (2008) Functional Coupling of the Amygdala in Depressed Patients Treated with Antidepressant Medication. *Neuropsychopharmacology* 33(8): 1909–1918.

Dannlowski U, Ohrmann P, Konrad C, Domschke K, Bauer J, Kugel H, Hohoff C, Schöning S, Kersting A, Baune BT, Mortensen LS, Arolt V, Zwieterlood P, Deckert J, Heindel W and Suslow T (2009) Reduced amygdala–prefrontal coupling in major depression: association with MAOA genotype and illness severity. *The International Journal of Neuropsychopharmacology* 12(01): 11.

Davidson RJ, Irwin W, Anderle MJ and Kalin NH (2003) The Neural Substrates of Affective Processing in Depressed Patients Treated With Venlafaxine. *American Journal of Psychiatry* 160(1): 64–75.

Eklund A, Nichols TE and Knutsson H (2016) Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. *Proceedings of the National Academy of Sciences* 113(28): 7900–7905.

Ekman P and Friesen W (1979) *Pictures of Facial Affect*. Palo Alto: Consulting Psychologists Press.

Fu CHY, Williams SCR, Brammer MJ, Suckling J, Kim J, Cleare AJ, Walsh ND, Mitterschiffthaler MT, Andrew CM, Pich EM and Bullmore ET (2007) Neural Responses to Happy Facial Expressions in Major Depression Following Antidepressant Treatment. *American Journal of Psychiatry* 164(4): 599–607.

Fu CHY, Williams SCR, Cleare AJ, Brammer MJ, Walsh ND, Kim J, Andrew CM, Pich EM, Williams PM, Reed LJ, Mitterschiffthaler MT, Suckling J and Bullmore ET (2004) Attenuation of the Neural Response to Sad Faces in Major Depression by Antidepressant Treatment: A Prospective, Event-Related Functional Magnetic Resonance Imaging Study. *Archives of General Psychiatry* 61(9): 877.

Fu CHY, Williams SCR, Cleare AJ, Scott J, Mitterschiffthaler MT, Walsh ND, Donaldson C, Suckling J, Andrew C, Steiner H and Murray RM (2008) Neural Responses to Sad Facial Expressions in Major Depression Following Cognitive Behavioral Therapy. *Biological Psychiatry* 64(6): 505–512.

Goldin PR, McRae K, Ramel W and Gross JJ (2008) The Neural Bases of Emotion Regulation: Reappraisal and Suppression of Negative Emotion. *Biological Psychiatry* 63(6): 577–586.

Gollan JK, Pane HT, McCloskey MS and Coccaro EF (2008) Identifying differences in biased affective information processing in major depression. *Psychiatry Research* 159(1–2): 18–24.

Gonzalez-Castillo J, Roopchansingh V, Bandettini PA and Bodurka J (2011) Physiological Noise Effects on the Flip Angle Selection in BOLD fMRI. *NeuroImage* 54(4): 2764–2778.

Gottesman II and Gould TD (2003) The Endophenotype Concept in Psychiatry: Etymology and Strategic Intentions. *American Journal of Psychiatry* 160(4): 636–645.

Haas BW, Omura K, Constable RT and Canli T (2007) Emotional conflict and neuroticism: Personality-dependent activation in the amygdala and subgenual anterior cingulate. *Behavioral Neuroscience* 121(2): 249–256.

Hamilton JP, Etkin A, Furman DJ, Lemus MG, Johnson RF and Gotlib IH (2012) Functional Neuroimaging of Major Depressive Disorder: A Meta-Analysis and New Integration of Baseline Activation and Neural Response Data. *American Journal of Psychiatry* 169(7): 693–703.

Hamilton M (1960) A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry* 23(1): 56–62.

Harmer CJ and Cowen PJ (2013) ‘It’s the way that you look at it’--a cognitive neuropsychological account of SSRI action in depression. *20120407* 368.



Harmer CJ, O'Sullivan U, Favaron E, Massey-Chase R, Ayres R, Reinecke A, Goodwin GM and Cowen PJ (2009) Effect of Acute Antidepressant Administration on Negative Affective Bias in Depressed Patients. *American Journal of Psychiatry* 166(10): 1178–1184.

**Hundrup E, Osler M and Jørgensen MB (2016) Time Trends and Variations in Electroconvulsive Treatment in Denmark 2008 to 2014: A Nationwide Register-Based Study. *The journal of ECT*.**

Joormann J, Talbot L and Gotlib IH (2007) Biased processing of emotional information in girls at risk for depression. *Journal of Abnormal Psychology* 116(1): 135–143.

Jorgensen A, Magnusson P, Hanson LG, Kirkegaard T, Benveniste H, Lee H, Svarer C, Mikkelsen JD, Fink-Jensen A, Knudsen GM, Paulson OB, Bolwig TG and Jorgensen MB (2016) Regional brain volumes, diffusivity, and metabolite changes after electroconvulsive therapy for severe depression. *Acta Psychiatrica Scandinavica* 133(2): 154–164.

**Kellner CH and Knapp RG (2007) Effect of the First Electroconvulsive Therapy in a Series: *The Journal of ECT* 23(3): 208.**

Kong L, Chen K, Tang Y, Wu F, Driesen N, Womer F, Fan G, Ren L, Jiang W, Cao Y, Blumberg H, Xu K and Wang F (2013) Functional connectivity between the amygdala and prefrontal cortex in medication-naïve individuals with major depressive disorder. *Journal of Psychiatry & Neuroscience* 38(6): 417–422.

Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, Kochunov PV, Nickerson D, Mikiten SA and Fox PT (2000) Automated Talairach atlas labels for functional brain mapping. *Human Brain Mapping* 10(3): 120–131.

**Lapidus KAB, Shin JSW, Pasculli RM, Briggs MC, Popeo DM and Kellner CH (2013) Low-Dose Right Unilateral Electroconvulsive Therapy (ECT): Effectiveness of the First Treatment. *The Journal of ECT* 29(2): 83–85.**

Leyman L, De Raedt R, Vanderhasselt M-A and Baeken C (2011) Effects of repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex on the attentional processing of emotional information in major depression: A pilot study. *Psychiatry Research* 185(1–2): 102–107.

Mannie ZN, Taylor MJ, Harmer CJ, Cowen PJ and Norbury R (2011) Frontolimbic responses to emotional faces in young people at familial risk of depression. *Journal of Affective Disorders* 130(1–2): 127–132.

Mathews A and MacLeod C (2005) Cognitive vulnerability to emotional disorders. *Annual Review of Clinical Psychology* 1: 167–195.

Milders M, Bell S, Platt J, Serrano R and Runcie O (2010) Stable expression recognition abnormalities in unipolar depression. *Psychiatry Research* 179(1): 38–42.

Miskowiak K, Papadatou-Pastou M, Cowen PJ, Goodwin GM, Norbury R and Harmer CJ (2007) Single dose antidepressant administration modulates the neural processing of self-referent personality trait words. *NeuroImage* 37(3): 904–911.

Miskowiak KW and Carvalho AF (2014) ‘Hot’ Cognition in Major Depressive Disorder: A Systematic Review. 13: 1787–1803.

Miskowiak KW, Glerup L, Vestbo C, Harmer CJ, Reinecke A, Macoveanu J, Siebner HR, Kessing LV and Vinberg M (2014) Different neural and cognitive response to emotional faces in healthy monozygotic twins at risk of depression. 45: 1447–1458.

Nathan PJ, Phan KL, Harmer CJ, Mehta MA and Bullmore ET (2014) Increasing pharmacological knowledge about human neurological and psychiatric disorders through functional neuroimaging and its application in drug discovery. *Current Opinion in Pharmacology* 14: 54–61.

Norbury R, Selvaraj S, Taylor MJ, Harmer C and Cowen PJ (2010a) Increased neural response to fear in patients recovered from depression: a 3T functional magnetic resonance imaging study. 40: 425–432.

Norbury R, Selvaraj S, Taylor MJ, Harmer C and Cowen PJ (2010b) Increased neural response to fear in patients recovered from depression: a 3T functional magnetic resonance imaging study. *Psychological Medicine* 40(03): 425.

Pirnia T, Joshi SH, Leaver AM, Vasavada M, Njau S, Woods RP, Espinoza R and Narr KL (2016) Electroconvulsive therapy and structural neuroplasticity in neocortical, limbic and paralimbic cortex. *Translational Psychiatry* 6(6): e832.

Ruhé HG, Booij J, Veltman DJ, Michel MC and Schene AH (2012) Successful Pharmacologic Treatment of Major Depressive Disorder Attenuates Amygdala Activation to Negative Facial Expressions: A Functional Magnetic Resonance Imaging Study. *The Journal of Clinical Psychiatry* 73(04): 451–459.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TEJ, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM and Matthews PM (2004) Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage* 23, Supplement 1: S208–S219.

Spielberger C (1983) *Manual for the State-Trait Anxiety Inventory*. Palo Alto: Consulting Psychologist Press.

Stuhrmann A, Suslow T and Dannlowski U (2011) Facial emotion processing in major depression: a systematic review of neuroimaging findings. *Biology of Mood & Anxiety Disorders* 1(1): 10.

Surguladze S, Brammer MJ, Keedwell P, Giampietro V, Young AW, Travis MJ, Williams SCR and Phillips ML (2005) A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. *Biological Psychiatry* 57(3): 201–209.

Talairach J and Tournoux P (1988) *Co-planar Stereotaxic Atlas of the Human Brain*. Thieme: New York.

Tranter R, Bell D, Gutting P, Harmer C, Healy D and Anderson IM (2009) The effect of serotonergic and noradrenergic antidepressants on face emotion processing in depressed patients. 118((1-3)): 87–93.

Wolfensberger SPA, Veltman DJ, Hoogendijk WJG, De Ruiter MB, Boomsma DI and de Geus EJC (2008) The neural correlates of verbal encoding and retrieval in monozygotic twins at low or high risk for depression and anxiety. *Biological Psychology* 79(1): 80–90.

Woolrich MW, Behrens TEJ, Beckmann CF, Jenkinson M and Smith SM (2004) Multilevel linear modelling for fMRI group analysis using Bayesian inference. *NeuroImage* 21(4): 1732–1747.

Woolrich MW, Ripley BD, Brady M and Smith SM (2001) Temporal autocorrelation in univariate linear modeling of fMRI data. *NeuroImage* 14(6): 1370–1386.

**Figure Captions**

**Figure 1.** CONSORT flow diagram.

**Figure 2.** Preliminary results of the *exploratory* whole-brain analysis using a statistical threshold of  $Z > 2.3$ ,  $p < 0.01$ , cluster-corrected. (a) Neural response to fearful vs. happy faces. Clusters show increased response in electroconvulsive (ECT) vs. sham groups in the superior frontal gyrus and caudate and reduced response in ECT vs. sham groups in the parahippocampal gyrus in the exploratory whole-brain analysis. Images are thresholded at  $Z > 2.3$  and  $p < 0.01$ , corrected for multiple comparisons at a cluster level. Clusters are displayed with color-coded estimated effect sizes. (b) Plot of mean percent blood-oxygen-level-dependent (BOLD) signal change in response to fearful and happy faces within these clusters. Bars show the mean; error bars show the standard error.

**Figure 3.** Preliminary results of the *exploratory* whole-brain psychophysical interaction (PPI) analysis using a statistical threshold of  $Z > 2.3$ ,  $p < 0.01$ , cluster-corrected, with right and left amygdala for fearful vs. happy faces in electroconvulsive therapy (ECT) vs. sham groups. (a) Right amygdala functional cluster (seed region) and medial temporal functional cluster showing increased functional connectivity (FC) with the right amygdala in ECT vs. sham treated patients. (b) Plot of standardized betas in the functional cluster showing greater coupling with right amygdala in ECT vs. sham groups. (c) Left amygdala functional cluster (seed region) and three functional clusters in the fusiform gyrus, occipital gyrus, and intracalcarine and lingual gyrus showing increased FC with the right amygdala in ECT vs. sham treated patients. (d) Plot of the mean standardized betas across the three functional clusters showing greater coupling with left amygdala in ECT vs. sham groups. Clusters are displayed with color-coded estimated effect sizes. Bars show the mean; error bars show the standard error.

