DISSERTATION

The relationship of changes in prefrontal-limbic connectivity and distinct depressive symptoms after electroconvulsive therapy

Der Zusammenhang von Veränderungen der präfrontal-limbischen Konnektivität und spezifischen depressiven Symptomen nach Elektrokonvulsionstherapie

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III Abbreviations

ACC	Anterior cingulate cortex
AM	Amygdala
BDI-II	Beck Depression Inventory-II
BOLD signal	Blood-oxygen-level-dependent signal
dACC	Dorsal anterior cingulate cortex
DLPFC	Dorsolateral prefrontal cortex
DMPFC	Dorsomedial prefrontal cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECT	Electroconvulsive Therapy
F	Female
fALFF	Fractional amplitude of low frequency fluctuation
FC	Functional connectivity
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
FP	Frontal pole
HRSD	Hamilton Depression Rating Scale
M	Male
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major depressive disorder
MNI	Montreal Neurological Institute
ROI	Region of interest
rsFC	Resting state functional connectivity
rTMS	Repetitive transcranial magnetic stimulation
SCC	Subcallosal cingulate cortex

sgACC	Subgenual cingulate cortex
SPM	Statistical parametric mapping
SPSS	Statistical Package for the Social Sciences
T0	Pre treatment timepoint
T1	Post treatment timepoint
TE	Echo time
TR	Repetition time
TRD	Treatment resistant depression

IV Deutsche Zusammenfassung

Die Elektrokonvulsionstherapie (EKT) gilt als eines der wirksamsten Verfahren zur Behandlung therapieresistenter Depressionen. Trotz einer zunehmenden Zahl von Behandlungsstudien sind die zugrunde liegenden Wirkmechanismen jedoch noch nicht ausreichend geklärt. Durch funktionelle Magnetresonanztomographie (fMRT) besteht die Möglichkeit, spezifische Marker für die Wirkmechanismen der EKT sowie für die Prädiktion des Behandlungserfolges zu identifizieren. Die Untersuchung depressionsspezifischer Netzwerke mit fMRT im Ruhezustand insbesondere in Verbindung mit der differentiellen Symptomverbesserung liefert einen innovativen Ansatz, der neue Erkenntnisse über die der EKT zugrunde liegenden Prozesse liefern kann.

In dieser Arbeit wurde der Zusammenhang zwischen Veränderungen der funktionellen Konnektivität (rsFC) sowie der spontanen Hirnaktivität (fractional amplitude of low frequency fluctuation - fALFF) im Ruhezustand und der Symptomverbesserung nach EKT bei 21 Patienten mit behandlungsresistenter Depression untersucht.

Prä-post EKT Veränderungen von rsFC und fALFF in Relation zur Symptomreduktion wurden untersucht. Weiterhin wurde der Zusammenhang von rsFC und fALFF vor Behandlungsbeginn mit der Symptomverbesserung nach Behandlung untersucht, um neuronale Faktoren zu identifizieren, die ein individuelles klinisches Ansprechen auf EKT vorhersagen könnten. Zusätzliche Korrelationsanalysen wurden durchgeführt, um die direkte Beziehung zwischen rsFC-Veränderungen und Symptomdimensionen wie Traurigkeit, negative Gedanken, Abgeschlagenheit und neurovegetativen Symptomen zu untersuchen.

Ein Anstieg der rsFC zwischen der linken Amygdala und dem linken dorsolateralen präfrontalen Kortex nach EKT war mit einer allgemeinen Symptomreduktion assoziiert sowie mit einer Verringerung spezifischer Symptome wie Traurigkeit, negative Gedanken und Abgeschlagenheit, nicht aber mit neurovegetativen Symptomen. Darüber hinaus gab es einen Zusammenhang zwischen einer hohen rsFC zwischen der linken Amygdala und dem rechten frontalen Pol (FP) vor Behandlungsbeginn und einer stärkeren Symptomverbesserung. Die Untersuchung des Zusammenhangs zwischen Aktivität vor Behandlungsbeginn und Symptomreduktion ergab, dass eine geringere Aktivität im rechten FP, supramarginalen Gyrus und okzipitalen Pol eine höhere Symptomreduktion vorhersagte.

Es wurde kein signifikanter Zusammenhang zwischen Aktivitätsveränderung vor und nach EKT mit der Symptomverbesserung gefunden.

Die Ergebnisse deuten darauf hin, dass Veränderungen der rsFC in Regionen des limbisch-präfrontalen Netzwerks mit Symptomverbesserung, insbesondere in affektiven und kognitiven Dimensionen, verbunden sind. Zudem hat die frontal-limbische Konnektivität das Potenzial, die Verbesserung von Symptomen nach EKT vorherzusagen. Auf der Grundlage der Ergebnisse dieser Dissertation ist zu erwarten, dass weitere Forschung, die funktionelle bildgebende Biomarker mit einem symptombasierten Ansatz kombiniert, vielversprechend sein könnte.

V English Abstract

Electroconvulsive therapy (ECT) is considered one of the most effective interventions for treatment-resistant depression. Despite an increasing number of treatment studies, the underlying mechanisms of action are not yet sufficiently explained. Through functional magnetic resonance imaging (fMRI), there is the potential to evaluate specific treatment markers or predictive markers. The examination of depression-specific networks by means of fMRI in the resting state and the association with differential symptom improvement could be an innovative approach that may provide new insights into the underlying processes. In this dissertation, we investigated the relationship between changes in resting-state functional connectivity (rsFC) as well as spontaneous brain activity (fALFF) and symptom improvement after ECT in 21 patients with treatment-resistant Major depressive disorder (MDD).

The change in rsFC and fALFF before and after ECT was examined, with all analyses directly relating to symptom reduction after the end of treatment. Furthermore, effects of pretreatment rsFC and fALFF on posttreatment symptom improvement were assessed to identify neural targets that might predict individual clinical responses to ECT. Additional correlational analyses were conducted to examine the direct relationship between rsFC changes and symptom dimensions such as sadness, negative thoughts, detachment, and neurovegetative symptoms.

An increase in rsFC between the left amygdala and the left dorsolateral prefrontal cortex after ECT was associated with an overall symptom reduction as well as with a reduction in specific symptoms such as sadness, negative thoughts, and detachment, but not neurovegetative symptoms. In addition, high baseline rsFC between the left amygdala and the right frontal pole (FP) predicted treatment outcome. The investigation of the relationship between baseline activity and symptom reduction revealed that lower activity in the right FP, supramarginal gyrus, and occipital pole predicted higher symptom reduction. No significant association was found between activity change pre- and post-ECT with symptom improvement.

These results suggest that changes in FC in regions of the limbic-prefrontal network are associated with symptom improvement, particularly in affective and cognitive dimensions. Frontal-limbic connectivity has the potential to predict symptom improvement after ECT.

Based on the findings in this dissertation, it can be expected that further research combining functional imaging biomarkers with a symptom-based approach will be promising.

VI Framework for the dissertation thesis[1]

[1]The following parts of the framework are adapted with permission from my previously published article, in which I am the sole first author

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1.1 Depressive disorders 1.2 Electroconvulsive therapy for the treatment of depression 1.4 Resting-state functional alterations in MDD and changes through ECT, 2. Methods, 3. Results 4.1 Summary, 4.2 Comparison with the literature, 4.4 Limitations, 4.5 Conclusion

1 Introduction

1.1 Depressive disorders

Major depressive disorder (MDD) is one of the most diagnosed mental disorders and affects an estimated 5% of the adult population worldwide (WHO, 2020). MDD is among the leading causes of the global burden of disease, ranking third in the world and first place in middle- and high-income countries according to the World Health Organisation. The 12-month-prevalence of unipolar depression accounts for 8% in the German general population (age between 18 and 65). That corresponds to a total number of 5.3 million people who suffer from a depressive episode or a recurrent depressive disorder (Jacobi et al., 2016; Jacobi et al., 2004). Lifetime prevalence for a diagnosed MDD accounts for 12%. Women are affected almost twice as often as men (15% vs. 8%) (Busch et al., 2013). The median age of onset of MDD is approximately 25 years with a range from mid-to-late adolescence to middle adulthood (the early 40s) (Otte et al., 2016).

Even from the economic perspective, MDD bears a considerable risk. The World Health Organization's (WHO) Global Burden of Disease (GBD) Study quantified and compared the burdens imposed by diseases in terms of disability adjusted life years (DALYs) (Murray et al., 1996). They found that MDD is the illness with the greatest individual burden and that it is clearly associated with an enormous economic burden (Wang et al., 2003) due to reduction in work productivity, direct treatment costs, and economic costs from increased mortality (Greenberg et al., 1996).

MDD is very heterogeneous with varying symptom presentations. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), a depressive episode can be characterized by the following symptoms: depressed mood, loss of interest or pleasure, significant unintentional weight loss or weight gain, decrease or increase of appetite, sleep disturbances, psychomotor changes, tiredness, fatigue, or low energy, a sense of worthlessness or excessive inappropriate guilt, impaired ability to think, concentrate, or make decisions and recurrent thoughts of death, suicidal ideation, or suicide attempts. To diagnose a patient with a depressive episode, at least five of these symptoms have to persist over a period of at least two weeks, while one symptom has to be depressed mood or loss of interest. Also, symptoms have to cause clinically significant distress or impair-

ment in social, occupational, or other important areas of psychosocial functioning. Depending on the number of present symptoms and their severity, depressive episodes can be classified as mild, moderate, or severe.

MDD usually takes an episodic course. It has been estimated that 75% to 90% of patients with depression will have multiple episodes (Angst, 1992; Greden, 2001). In 15 to 25% of the cases MDD becomes a chronic phenomenon (Bschor, 2008). Resistance to treatment is another difficulty in the therapy of MDD. It must be noted that chronic MDD and treatment resistant MDD are not necessarily equivalent. A depression is defined as chronic if the symptomatology lasts longer than two years, independent from any treatment trials (Bschor, 2008). Furthermore, Bschor et al. (2014) declare that it should be distinguished whether the chronification is based on a true treatment-resistance or if it refers to a ‘pseudoresistance’ because of insufficient treatment or diagnostic errors. The European Agency for the Evaluation of Medical Products (2002) defined treatment-resistance as a failure to respond to two antidepressant trials of adequate dosage and sufficient length of time.

In various approval and efficacy trials of different antidepressants, one third to half of the patients did not respond properly to several weeks of treatment ((Bauer et al., 2007; Bauer et al., 2013; Trivedi et al., 2006). In an effectiveness study within the largest study of the treatment of MDD so far, the STAR*D trial (Sequenced Treatment Alternatives to Relieve Depression), researchers found that less than 20% of patients who failed to respond to two antidepressant treatment trials profited from a further switch to another antidepressant (Fava et al., 2006), indicating a resistance to pharmacotherapy.

However, treatment resistant MDD is not untreatable. The majority of patients can be substantially helped by rigorous treatment approaches, including somatic interventions such as Electroconvulsive therapy (ECT) and psychotherapeutic methods (Bschor, 2008).

1.2 Electroconvulsive therapy for the treatment of MDD

ECT is the most effective treatment for refractory MDD with a response rate of 50% to 85% in general and 50% to 75% in patients who did not respond to antidepressant medication (UK-ECT-Review-Group, 2003). ECT is a safe induction of a series of generalized

epileptic seizures for therapeutic purposes, using brief-pulse stimulation techniques under anaesthesia and muscle paralysis (Baghai & Möller, 2008; Seshadri & Mazi-Kotwal, 2011).

Accounting for 80%, affective disorders, especially depressive episodes, are by far the most common indication for ECT in the clinical practice, followed by psychotic disorders with 19% (Grager & Di Pauli, 2013). ECT as first-line treatment is indicated for depressive stupor and inanition as well as for catatonic or psychotic depression (Baghai & Möller, 2008), as it is associated with a fast relief of symptoms (Gangadhar et al., 1982) which is essential in cases of severe psychomotor retardation or refusal of food and drink (Weiner, 2001). Another indication is a patient's response to ECT in the past (Bauer et al., 2013). These patients are eligible for immediate ECT if a new-onset depressive episode requires treatment.

Repeated inadequate medication trials may result in a negative outcome of the MDD and may even be harmful for the patient (Bauer et al., 2013). On this account refractory MDD and other treatment resistant psychiatric disorders are an indication for ECT as second-line treatment (Baghai et al., 2005; Sackeim, 2001).

Worldwide, the average number of ECT sessions administered per patient is 8 (Leiknes et al., 2012). Despite widespread application for almost a century, the underlying antidepressant mechanisms of action are still not fully understood, which may be a contributing factor to the stigma which is still present. Different mechanisms of action have been discussed, such as changes in neurotransmission or effects on inflammatory processes, but also volumetric and functional changes in the brain. However, further longitudinal studies combining modalities such as peripheral physiological measurements, magnetic resonance imaging, and spectroscopy are needed to gain deeper insights (Stippl et al., 2020). Although overall response rates for ECT in depressed patients are relatively high (60-80%) (Baldinger et al., 2014), there are still many patients who remain symptomatic or do not respond to ECT in any way (Cinar et al., 2010). It is therefore of utmost clinical importance to better understand how ECT affects specific symptoms of MDD. In addition, a better understanding of symptom- and treatment-specific biomarkers is no less important, because with each failed treatment attempt, the burden of disease and the risk of suicide increases (Hawton et al., 2013; Phillips et al., 2015; Reutfors et al., 2021).

Recent investigations have shown that different antidepressant treatments have differential effects on specific symptom dimensions, with cognitive symptoms improving after a single subanaesthetic dose of ketamine (Stippl et al., 2021), whereas ECT specifically reduced affective symptoms (Carstens et al., 2021). In another study that examined the relationship between differentiated symptom clusters and general response to ECT, it was found that in particular the symptoms of depressed mood and anhedonia, which are considered core symptoms of MDD, improved more with ECT (Wade et al., 2020). Somatic or vegetative symptoms, on the other hand, did not change significantly. Furthermore, factors that included these symptoms (Okazaki et al., 2010; Spashett et al., 2014) had a high predictive value for ECT outcome. A recent imaging study examined the association between three dimensions of depressive symptoms (somatic disturbance, baseline mood and anhedonia, and insomnia, measured with the 17-item Hamilton Depression Rating Scale (HDRS) and volumetric changes in brain regions linked to depressive symptoms, and identified distinct structural imaging predictors (Wade et al., 2021). Another method of studying neural changes in MDD and the mechanisms of action of ECT is functional magnetic resonance imaging, which measures functional processes in the brain either while processing specific stimuli or solving tasks but also during resting-state.

1.3 Resting-state functional MRI

Since Biswal and colleagues initially discovered spatially coherent activity in the blood oxygen level dependent (BOLD) signal, resting-state functional magnetic resonance imaging (rs-fMRI) received growing interest (Biswal et al., 1995). It is feasible to evaluate the performance of regional and neural circuits at rest and in the absence of external tasks using rs-fMRI. The use of this strategy in clinical trials additionally appears rather simple (Fox & Greicius, 2010; Lui et al., 2010). In rs-fMRI research, two parameters that are calculated from the BOLD signal are typically employed. Functional connectivity (FC) and the amplitude of low frequency fluctuations (ALFF) (,0.08 Hz) are two different concepts. The resting-state ALFF reflect spontaneous neural activity (Gonçalves et al., 2006; Shmuel & Leopold, 2008; Yu-Feng et al., 2007). These spontaneous low-frequency fluctuations show numerous similarities with fluctuations of neural metabolic, hemodynamic, and neurophysiological parameters (De Luca et al., 2006; Fox & Raichle, 2007). To coun-

teract possible physiological noise, the fractional ALFF (fALFF) approach was further developed to selectively suppress artifacts from non-specific brain areas and thereby significantly improve the sensitivity and specificity of detecting spontaneous brain activity (Zou et al., 2008).

Functional connectivity has been defined as "the temporal correlation of a neurophysiological index measured in different brain areas" (Friston et al., 1993). It can measure the signal synchrony of low-frequency fluctuations of activity between different brain areas (Biswal et al., 1995), which provides information about the intrinsic network organization of the brain as well as possible dysfunctions of the network.

1.4 Resting-state functional alterations in MDD and changes through ECT

Spontaneous brain activity has been found to be altered in MDD at rest (Liu et al., 2013) as well as in response to negative stimuli (Redlich et al., 2017). Considerably reduced activity in prefrontal areas has been observed in patients which may contribute to emotional dysregulation (Liu et al., 2013; Zhang et al., 2014). Furthermore, structural and functional brain imaging studies have shown that volumetric amygdala properties might be important for the prediction (Ten Doesschate et al., 2014) and the mechanism of action (Gryglewski et al., 2021) of ECT response in addition to general MDD related amygdala activity alterations during emotion processing tasks (Drevets et al., 2002; Groenewold et al., 2013; Peluso et al., 2009). Furthermore, decreased activity in DLPFC during emotion processing tasks (Groenewold et al., 2013) or active emotion regulation (Erk et al., 2010) was found, which is in line with theoretical frameworks proposing dysfunctional modulatory effects of prefrontal regions on limbic emotion processing mechanisms (Drevets, 2000, 2001; Kaiser et al., 2015; Mayberg, 2003).

Task-based FC studies have shown reduced connectivity of the amygdala with regions of the cognitive control network, involving the DLPFC, dorsomedial PFC (DMPFC), dorsal anterior cingulate cortex (dACC), and hippocampus, while processing induced negative emotions (Chen et al., 2008; Dannlowski et al., 2009; Lu et al., 2012). It is hypothesized that bidirectional connections between the DLPFC, ACC and amygdala might be crucial for downregulation of increased amygdala activation in MDD (Erk et al., 2010; Pizzagalli, 2011) and therefore represent a possible target identifying predictors of ECT response or neural changes underlying therapeutic effects.

Previous treatment studies demonstrated that pharmacotherapy (Arce et al., 2008; Chen et al., 2008; Arnone et al., 2012, Godlweska et al., 2012; Redlich et al., 2017;), Ketamine (Loureiro, 2020), cognitive behavioral therapy (Fu et al. 2008), repetitive Transcranial magnetic stimulation (rTMS; Liston et al., 2014), and ECT (Abbott et al., 2013, Cano et al., 2016; Loureiro, 2020; Redlich et al., 2017) normalize amygdala activity and FC alterations, which could be related to emotion-processing-specific antidepressant effects. Gudayol-Ferré et al. (2015) reviewed studies that investigated changes in connectivity after different antidepressant treatments (pharmacotherapy, ECT, rTMS) and concluded that FC changes between cortical-limbic structures during rest and task performance correlate with an improvement of the core depressive symptoms. In a recent systematic review the authors state that ECT-induced resting-state FC increases seem to be the most consistent finding among fMRI measures that are used to examine depressive patients, with prefrontal regions showing the highest interaction scores with other brain regions (Porta-Casteràs et al., 2021). This finding underlines the utility of resting-state FC for detecting neural markers for treatment induced changes and points out that specifically prefrontal regions offer additional value as a biomarker for therapy success.

The results of different fMRI studies that investigated functional connectivity in the resting state came to divergent results. At one end, Perrin et al. (2012) reported a significant reduction in average global functional connectivity in and around the left dorsolateral prefrontal cortex (DLPFC) after ECT, which was associated with a significant decrease in depressive symptoms. At the other end, (Abbott et al., 2013) found a significantly increased pattern of functional network connectivity between the posterior default mode network and the left DLPFC in remitted patients compared to non-remitted patients after ECT. However, the results of these studies can only be considered preliminary, as the small sample sizes of n= 9 and n = 12, respectively, do not allow for generalization.

In another longitudinal rsFC study, (Cano et al., 2016) reported that a FC decrease between amygdala and subgenual anterior cingulate cortex (sgACC) in early ECT treatment phases (after the first ECT session) could potentially regulate a subsequent increase between right amygdala and DLPFC (after the 9th ECT session), which in turn could be associated with clinical response after the completion of ECT. With their study they emphasize the relevance of the fronto-limbic circuit for the identification of ECT specific prediction and response biomarkers. They used predefined target regions so that connections from seed regions were restricted to these targets. Whole brain analysis as a complementary approach could provide further information on how rsFC of the amygdala or

DLPFC changes after ECT. In addition, none of the studies to date has examined the relationship between rsFC changes and improvement in specific symptom dimensions, although it could provide further insight into direct treatment effects of ECT.

1.5 Research question

In summary, dysfunction in key components of the prefrontal-limbic circuitry has been associated with cognitive and emotional deficits in MDD. Restoration of dysfunctional activity and connectivity within and between these key regions might not only reflect an antidepressant response, but specific alterations prior to ECT might even serve as treatment predictors. Thus, resting-state fMRI could be a useful measure to enhance the understanding of the mechanisms underlying response to treatment. However, the clinical utility of FC of the frontal-limbic network has remained limited, and to date it has not been investigated whether there is a relationship between FC changes in that circuit and the improvement of distinct symptom dimensions.

The primary aim of this dissertation was to investigate the relationship between changes in rsFC and depression severity after ECT. For this purpose, resting-state fMRI data were collected before ECT and after completion of the intervention. A data-driven seed-based connectivity approach was used at the whole-brain level, and analyses focused on the bilateral DLPFC and bilateral amygdala, as these are important areas for emotion regulation, which may be significantly impaired in MDD. The rsFC changes after ECT, in particular, were expected to be directly associated with improvement in symptom severity. In order to identify possible predictive markers at the neural level, it was also investigated whether rsFC from bilateral amygdala and bilateral DLPFC at baseline could potentially anticipate response to ECT. Regarding spontaneous brain activity and possible treatment-related changes, change in fALFF and baseline fALFF in relation to symptom improvement after ECT were also examined at the whole brain level. The MADRS total score was used as the primary outcome measure. In addition, with regard to the heterogeneity of depressive symptoms, a four-factor structure of the MADRS proposed by Williamson et al. (2006) including sadness, negative thoughts, detachment, and neurovegetative symptoms was considered to shed further light on the relationship between neural changes and specific symptom dimensions.

2 Methods

2.1 Participants

Twenty-one patients (10 female, age M = 44.05 years, SD = ± 11.03, range = 22 - 60 years) with a current treatment-resistant depressive episode were examined for the study. They were diagnosed according to the criteria of the DSM-5. Moreover, the participating patients were treated with right-unilateral ultra-short ECT. The treatment and the examinations within the framework of the study took place at the Department of Psychiatry of the Charité - Universitätsmedizin Berlin. There was no restriction regarding the parallel use of antidepressant medication, however, it was documented which psychotropic drugs the patients received in addition to ECT. The study was conducted in accordance with the latest version of the Declaration of Helsinki and approved by the Institutional Review Board of Charité - Universitätsmedizin Berlin. Before participation, all participants gave their written informed consent.

2.2 Study design

Prior to the first ECT session, all patients underwent an initial resting-state fMRI and clinical assessment (T0). The treatment consisted of right-sided ECT with an ultrashort pulse device with a pulse length of 0.25 milliseconds (Thymatron IV System, Somatics Inc.) according to the standard protocol of the Department of Psychiatry, Charité-Universitätsmedizin Berlin, which involves three ECT sessions per week over a period of four weeks. Anesthesia comprised propofol (approximately 1.50 mg/kg) or etomidate (approximately 0.75 mg/kg). Succinylcholine (approximately 0.75 mg/kg) was used for muscle relaxation. Motor and electroencephalographic seizure duration were monitored to control for appropriate duration. During the first ECT treatment, the seizure threshold was titrated, and the voltage was adjusted only if patients did not respond clinically or showed inadequate seizures during the course of ECT (i.e., motor response < 20 s or electroencephalographic seizure activity < 30 s). See Brakemeier et al. (2014) for a more detailed description of the procedure. Resting-state fMRI examination and clinical assessment were repeated after the last ECT session (T1).

2.3 Clinical assessment

To assess the severity of depression, a standardized clinical interview was conducted by a trained professional. The interview was the German version of the MADRS (Montgomery & Åsberg, 1979). The MADRS consists of 10 items assessing the following depressive symptoms on a 7-point scale (with 0 = no abnormality and 6 = severe): apparent sadness, reported sad-ness, inner tension, decreased sleep, decreased appetite, difficulty concentrating, lassi-tude, inability to feel, pessimistic thoughts, and suicidal thoughts. In the later analyses, a four-factor model of MADRS (Quilty et al., 2013; Williamson et al., 2006) was applied to further examine the relationship between various MDD symptoms and resting-state neural correlates. The model includes the factors of sadness, negative thoughts, detachment, and neurovegetative symptoms. Table 1 shows detailed information about the factor structure. A reduction in MADRS total score of 50% or more after ECT was defined as a response, and a MADRS total score ≤10 was defined as remission (Bauer et al., 2013). Statistical procedures for demographic and clinical data were performed in IBM SPSS Statistics 28 for Windows. Statistical tests were based on a significance level of $\alpha = .05$.

Table 1 *MADRS factor structure*

Factor	MADRS Items
1 Sadness	Apparent sadness (1), reported sadness (2)
2 Negative thoughts	Pessimistic thoughts (9), suicidal thoughts (10)
3 Detachment	Concentration difficulties (6), Lassitude (7), Inability to feel (8)
4 Neurovegetative symptoms	Tension (3), reduced sleep (4), reduced appetite (5)

Notes: MADRS Montgomery-Åsberg Depression Rating Scale (reprinted from Domke et al., 2023 with permission).

2.4 FMRI acquisition and analyses

Functional imaging data were collected with a 3T Tim Trio MR scanner (Siemens, Erlangen, Germany), a standard 12-channel head coil at the Center for Cognitive Neuroscience Berlin (Freie Universität Berlin, Germany) using standard echo-planar imaging sequences. Data were collected in 8-minute runs (210 vol.) with 37 oblique axial slices of 3

mm (TE = 30 ms; field of view = 192 mm, 3×3 mm in-plane resolution, TR 2300 s, flip angle 70 °). A 3-dimensional T1-weighted anatomic scan was obtained as a structural reference. All resting-state fMRI data were analyzed in Matlab (version R2015b) using SPM12 and the CONN toolbox (version 20.b; https://www.nitrc.org/projects/conn) (Whitfield-Gabrieli & Nieto-Castanon, 2012). Preprocessing of the functional and structural data was performed using CONN's standard preprocessing pipeline for MNI space. The pipeline encompasses motion correction (realignment and unwarping), slice timing correction, structural segmentation and normalization, functional normalization, outlier detection (ART-based scrubbing), and spatial smoothing (8 mm). During the denoising step in CONN, linear regression analyses were performed for individual subjects to remove the effects of head motion (total of 12 motion covariates: 6 motion parameters plus 6 temporal derivatives), physiological artifacts (total of 10 CompCor eigenvariates: 5 each from eroded WM and CSF masks), and artifact-affected scans. The resulting residual blood oxygen level-dependent (BOLD) time series were band-pass filtered (0.01–0.1 Hz). A seed-based approach was used to assess the effects of ECT on regions of the emotional and cognitive control network. Seeds were chosen on the basis of recent published literature (Cano et al., 2016; Gärtner et al., 2019; Moreno-Ortega et al., 2019; Scheidegger et al., 2012). Seed regions of interest (ROI: x, y, z, in Montreal Neurological Institute [MNI] space) included bilateral DLPFC (±40 36 32) and bilateral amygdala (±24 -2 -20). Spherical ROI templates with a diameter of 10 mm were created using automated term-based meta-analyses on neurosynth.org. Single subject seed-to-voxel correlation maps were computed by extracting the residual blood oxygen level-dependent (BOLD) time course from the seed and calculating Pearson’s correlation coefficients between this time course and the time course of all other voxels.

Group statistical analyses were performed in two steps. First, the association of rsFC changes with symptom improvement at the end of the acute ECT phase was examined. Furthermore, the method of fractional amplitude of low frequency fluctuation (fALFF, (Zou et al., 2008)) was used to examine functional activity change across the whole brain related to the change of depressive symptoms post ECT. Linear regression analyses were conducted in CONN by defining a simple main effect of MADRS percent symptom reduction (defined as psr = (T0-T1)/T0*100) as between-subjects contrast, and time point (pre vs. post) as between-conditions contrast. These regression analyses were performed for the rsFC change in the previously defined seed regions as well as for the fALFF change at the whole-brain level. The same analyses were performed using the

baseline scans only, to investigate the predictive power of baseline rsFC and baseline fALFF. Statistical thresholds were set to $p < 0.001$ (uncorrected) at the single voxel level, and to $p < 0.05$ (FDR corrected) at the cluster level. For the connectivity results the mean FC levels of each ROI were extracted with the REX Toolbox (https://www.nitrc.org/projects/rex/) . To further explore the association between the improvement of specific symptoms and changes in rsFC post-hoc correlational analyses (Spearman's correlation coefficient, two-sided) with the four MADRS factors were performed. Bonferroni-correction was applied to all results, yet uncorrected results are exploratively reported.

3. Results

3.1 Clinical and demographic data

The data of n= 21 patients with a diagnosed depressive episode was analysed. An overview of the demographic and clinical characteristics are provided, along with additional information on treatment, response, and remission, in Table 2. In total 85.71% of patients (18/21) showed a significant reduction in depressive symptoms after completion of their individual acute ECT phase, as visualised in Figure 1. Overall, 52.38% (11/21) of patients were classified as responders. The remission rate in this sample was 19.05% (4/21). For a visual overview of the distribution of the different primary diagnoses, see Figure 2. Figure 3 and Figure 4 illustrate the frequencies of psychiatric and somatic comorbidities . For an overview of the concomitant antidepressant medication see Table 4.

Table 2 *Participants demographic and clinical characteristics*

Variable	*M*	*SD*			*n*			
Age	44.05	11.03			21			
Number of depressive episodes [a]	3.76	3.36			17			
No. of ECTs	12.62	3.22			21			
	Pre ECT		Post ECT					
	M	*SD*	*M*	*SD*	*n*	*T*	*df*	*p*
MADRS total score	31.38	5.98	19.05	10.34	21	6.76	20	<.001
MADRS symptom reduction (%)	40.89	28.63			21			
MADRS Factors								
Sadness	7.29	1.85	4.76	2.98	21	4.29	20	<.001
Neg. thoughts	5.00	2.26	3.10	2.43	21	3.99	20	<.001
Detachment	10.38	2.36	6.33	3.53	21	5.74	20	<.001
Neurovegetative Symptoms	8.57	2.96	4.81	3.30	21	4.54	20	<.001
Gender (F:M)	10:11							
Response (Y:N)	11:10							

Notes: ECT Electroconvulsive therapy, MADRS Montgomery-Åsberg Depression Rating Scale, M Mean, SD Standard Deviation, [a] n <21 due to missing data (reprinted from Domke et al., 2023 with permission).

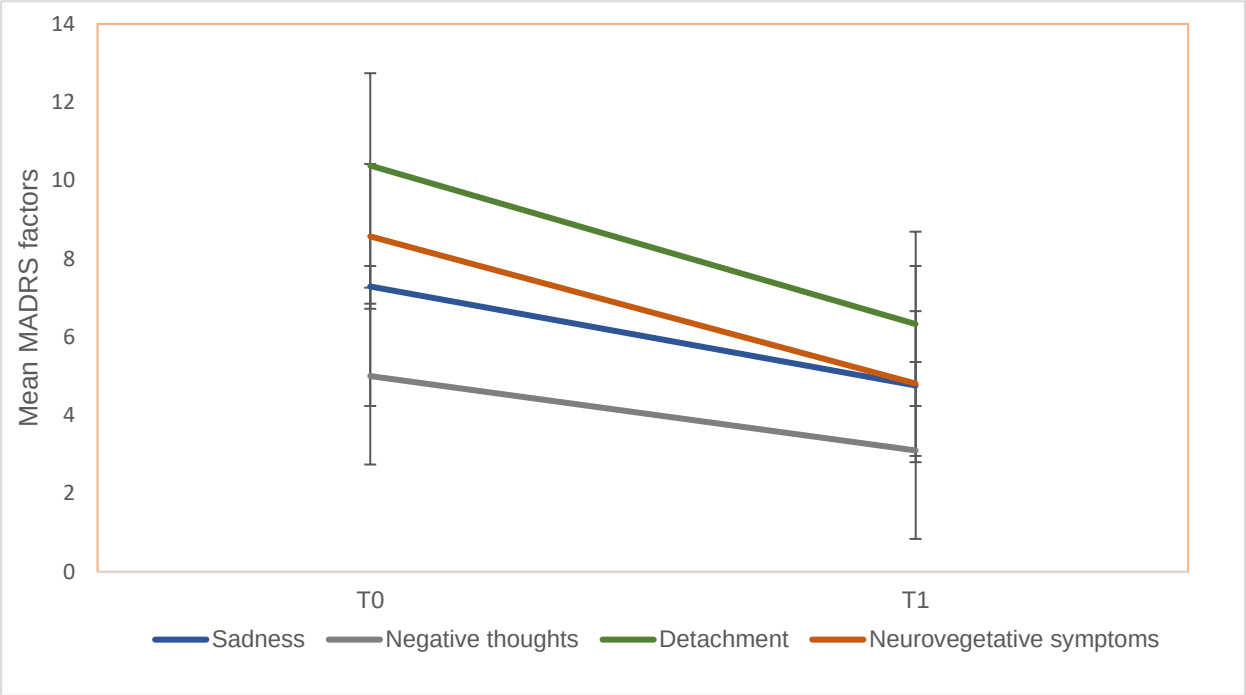

Figure 1 Symptom reduction in Montgomery-Åsberg Depression Rating Scale (MADRS) dimensions. The different lines represent the absolute change in the MADRS dimensions between baseline (T0) and post treatment with ECT (T1). Error bars represent standard deviations (reprinted from Domke et al., 2023 with permission).

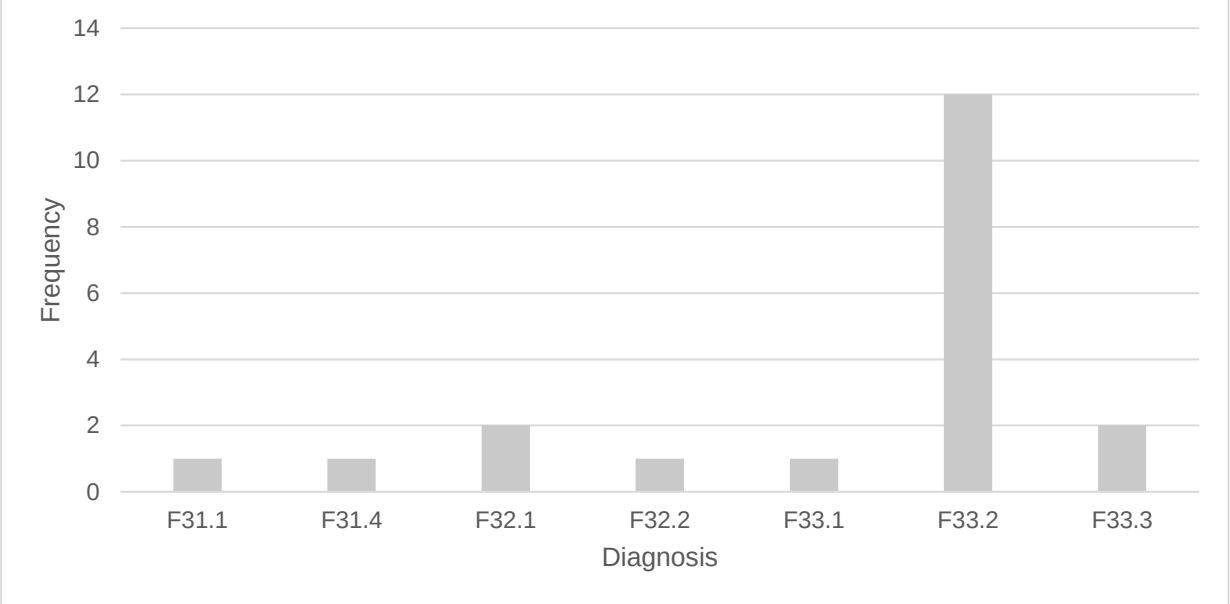

Figure 2 Frequencies of primary diagnoses. Diagnoses are classified according to ICD-10 codes. F31.3: Bipolar affective disorder, current episode mild or moderate depression, F31.4: Bipolar affective disorder, current episode severe depression with-out psychotic symptoms, F32.1: Moderate depressive episode, F32.2 Severe depressive episode without psychotic symptoms, F33.1: Recurrent depressive disorder, current episode moderate, F33.2: Recurrent depressive disorder, current episode severe without psychotic symptoms, F33.3: Recurrent depressive disorder, current episode severe with psychotic symptoms, F34.1:

Dysthymia. The y-axis shows absolute frequencies. (This figure appears only in the context of this dissertation, the copyright belongs to the author. It has not been published before).

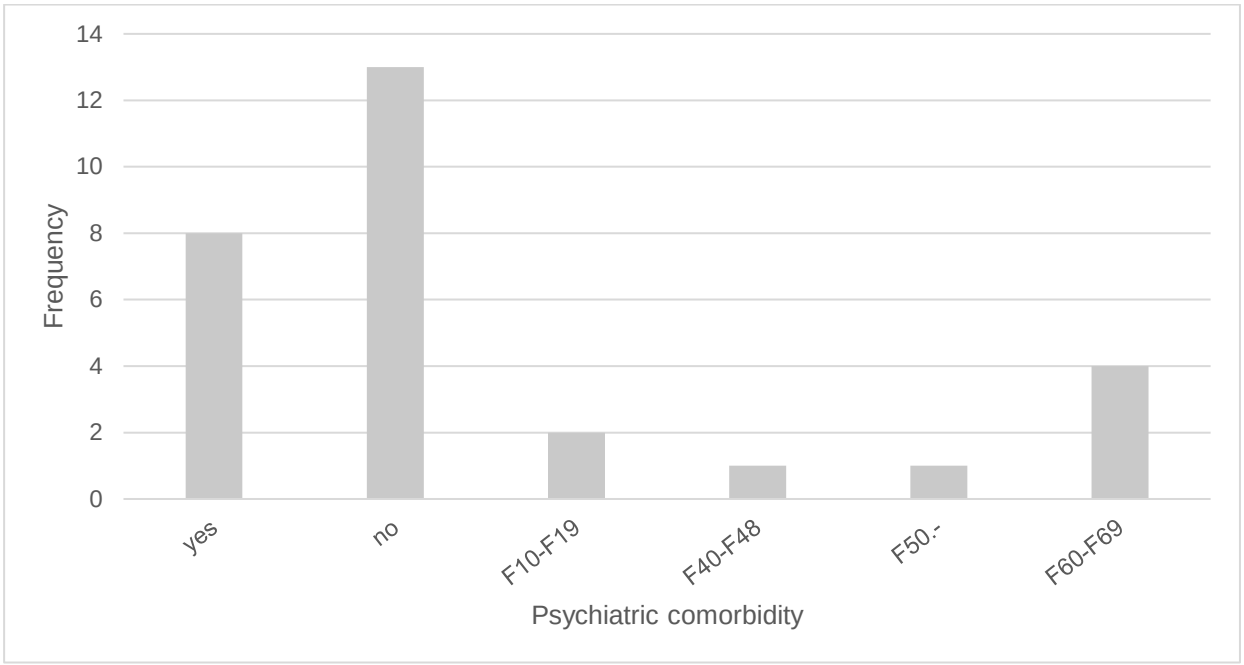

Figure 3 Frequencies of psychiatric comorbidities. Categories refer to ICD-10 codes. F10-F19: past psychoactive substance use or dependence syndrome, F40-F48: anxiety, stress-related, or somatoform disorders, F50.-: eating disorders, F60-F69: personality disorders. Not listed categories did not appear in this sample. The y-axis shows absolute frequencies. (This figure appears only in the context of this dissertation, the copyright belongs to the author. It has not been published before).

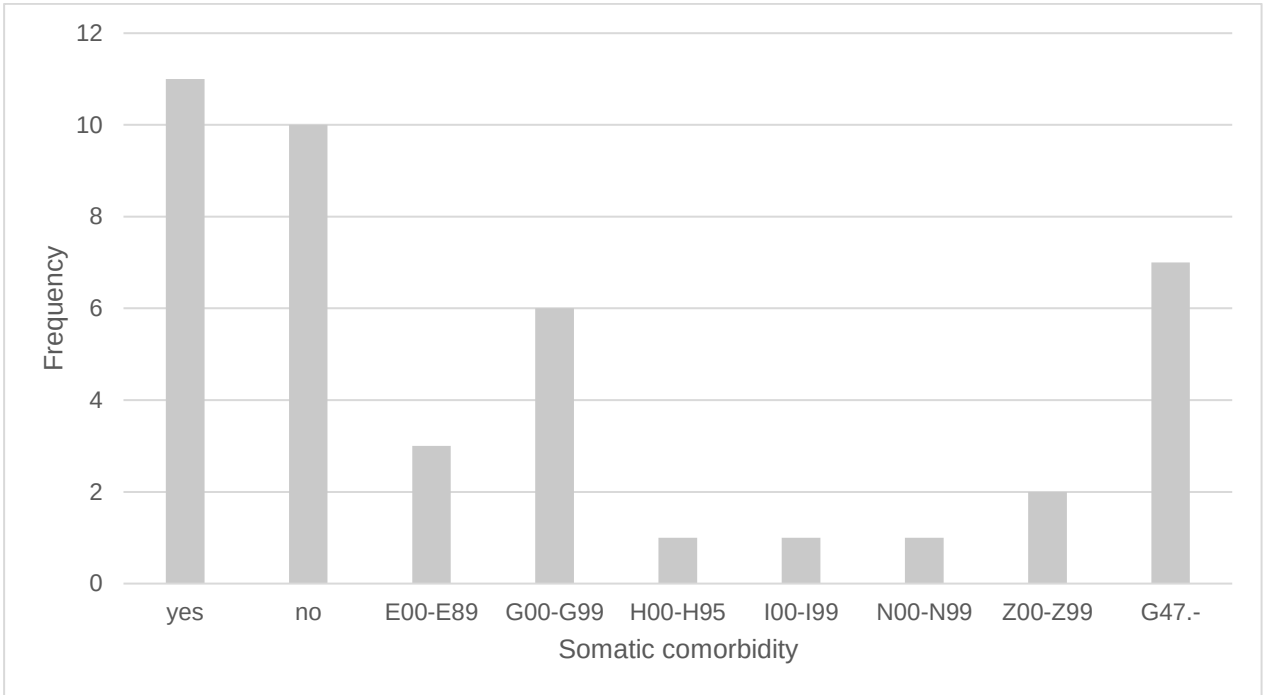

Figure 4 Frequencies of somatic comorbidities. Categories refer to ICD-10 codes. E00-E89: endocrine, nutritional or metabolic, G00-G99: of the nervous system, H00-H95: of the eye or ear or nose, I00-I99: of

the circulatory system and heart, N00-N99: of the genitourinary system, Z00-Z99: presence of factors influencing health status, G47.-: sleep disorder. Not listed categories did not appear in this sample. The y-axis shows absolute frequencies. (This figure appears only in the context of this dissertation, the copyright belongs to the author. It has not been published before).

Table 3 *Antidepressant medication use*

Variable	Frequencies
Concomitant Medication	90.5% Yes (19) 9.5% No (2)
Antidepressants	38.1% none (8) 61.9% ADs (13): 14.3% SSRIs (3) 9.5% SNRI (2) 14.3% NDRIs (3) 19.0% SARIs (4) 9.5% TCAs (2) 4.8% TeCAs (1) 4.8% MAOI (1) 4.8% NaSSA (1)
Other psychiatric medication	66.7% none (14) 33.3% others (7): 28.6% antipsychotics (6) 19.0% mood stabilizer (4) 4.8% benzodiazepines (1)

Notes. Census data in parentheses. ADs= Antidepressants. SSRIs= selective Serotonin-Reuptake-Inhibitors. SNRIs= Selective norepinephrine reuptake inhibitor. NDRIs= Norepinephrine-dopamine reuptake inhibitors. SARIs= Serotonin antagonist and reuptake inhibitors. TCAs= Tricyclic antidepressants. TeCAs= Tetracyclic antidepressants. MAOIs= Monoamine oxidase inhibitors. NaSSA= Noradrenergic and Specific Serotonergic Antidepressant. Due to participants receiving several psychiatric medications, percentage scores may not add up to exactly 100% (reprinted from Domke et al., 2023 with permission).

3.2 fMRI results

Between the left amygdala seed and a cluster in the left DLPFC (coordinates: -38, 14, 46; cluster size: 93; p = .008275, p-FDR-corrected), a regression analysis revealed a significant association between an increase in rsFC and overall symptom reduction. To counter the multiple comparisons problem, a Bonferroni-corrected alpha level of .0125 was applied. The result remained significant (p = .0331) after the correction. Figure 5 shows a

visualization of the cluster on the cortical surface as well as the location of the left amygdala seed. Gender and age were posteriorly controlled by a hierarchical multiple regression analysis. Both variables were added blockwise to the regression model, but neither showed a significant effect on the outcome variable MADRS symptom reduction. (age: β = .214, p =. 261; gender: β = -.260, p =. 155). The bilateral DLPFC seeds and the right amygdala seed revealed no significant rsFC changes related to symptom reduction. The analysis of baseline rsFC showed that the baseline rsFC of the left amygdala to the right FP (coordinates: 16 64 20; cluster size: 74; p = .038816) was positively related to symptom reduction. Thus, higher connectivity before ECT treatment predicted stronger symptom improvement after treatment was completed. No significant effects were found for the two DLPFC seeds.

The analysis of whole-brain activity changes (fALFF) did not reveal any relation to symptom improvement, but examining the relation between baseline activity and symptom reduction showed that lower baseline activity in the right frontal pole (coordinates: 18 68 20; cluster size: 154; p = .000023), right supramarginal gyrus (coordinates: 68 -32 18; cluster size: 80; p = .002230), and right occipital pole (coordinates: 28 -94 04; cluster size: 71; p = .003102) predicted a higher symptom reduction.

For the significant rsFC change between amygdala and DLPFC, additional correlation analyses were performed with the four MADRS factors. A strong positive correlation was found between the rsFC change (mean rsFC between left amygdala and left DLPFC cluster) and the change in the factors sadness, negative thoughts, and detachment, but not for the factor neurovegetative symptoms. Figure 6 shows the correlations between the amygdala-DLPFC rsFC and the four different MADRS factors. Excluding one outlier that showed a reduction in rsFC, the positive association between FC change and symptom reduction remained for the three symptom dimensions mentioned [sadness: r = .524, p = .014 (uncorrected); negative thoughts: r = .700, p = .002 (Bonferroni-corrected); detachment: r = .663, p = .004 (Bonferroni-corrected)].

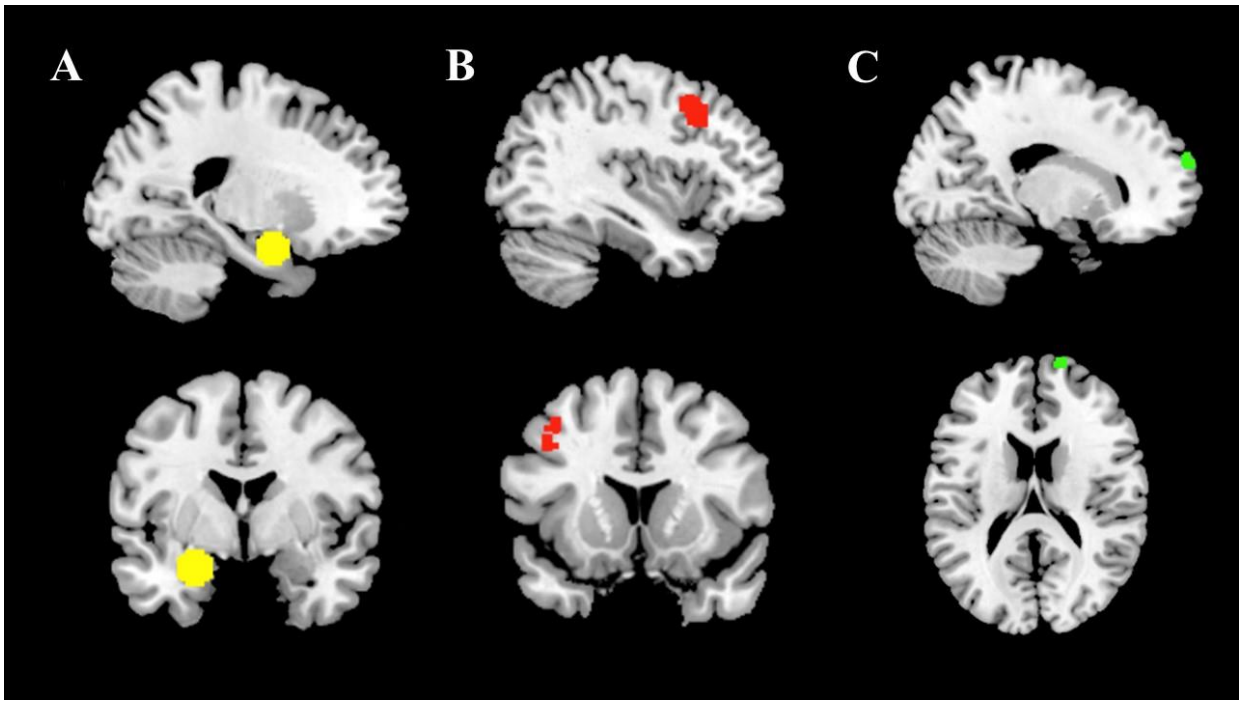

Figure 5 Resting state functional connectivity (FC) related to the reduction of depressive symptoms after completion of electroconvulsive therapy (ECT). (A) Yellow color marks the seed region in the left amygdala that was used for the seed-to-voxel analysis. (B) Red color marks the region in the left dorsolateral prefrontal cortex (DLPFC) whose FC change to the amygdala after ECT is positively related to symptom reduction (higher connectivity after ECT = higher symptom reduction). (C) Green color marks the region in the right frontal pole (FP) whose baseline FC to the left amygdala is positively related to symptom reduction (high baseline connectivity = high symptom reduction). Statistical thresholds for (B) and (C) were $p < 0.001$ at the voxel level, and $p < 0.05$ (FDR corrected) at the cluster level (reprinted from Domke et al., 2023 with permission).

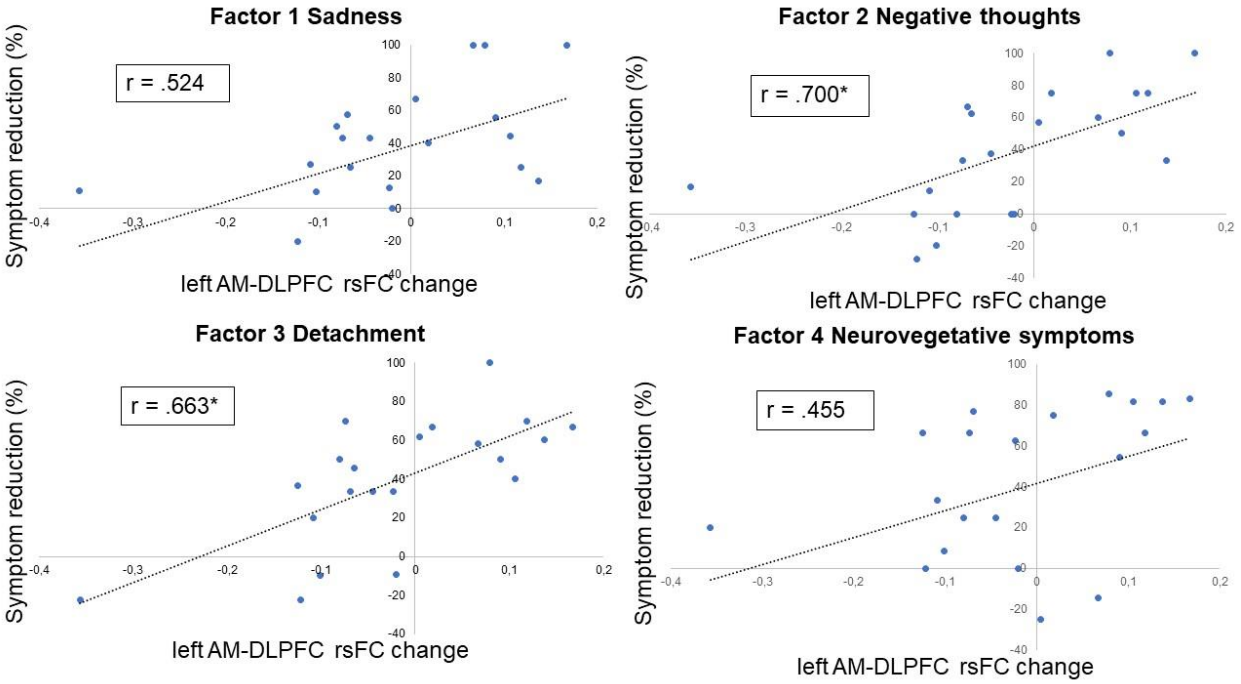

Figure 6 Post-hoc correlation analyses of resting-state functional connectivity (FC) change between left amygdala and left dorsolateral prefrontal cortex (DLPFC) related to the reduction in the different symptom dimensions. Symptoms were measured with the Montgomery-Asberg Depression Rating Scale (MADRS). The R -value depicts Spearman's Correlation Coefficient (* the corresponding P -value is < 0.05 Bonferroni-corrected) (reprinted from Domke et al., 2023 with permission).

4. Discussion

4.1 Summary

In this dissertation, the modulatory effect of ECT on resting-state functional connectivity of the amygdala and DLPFC as well as spontaneous brain activity during rest on the whole-brain level in depressed patients was investigated. In addition to the changes, it was also examined whether baseline rsFC and activity could predict clinical outcome. To gain a more detailed comprehension of clinical responses after ECT, the relationship between rsFC and the specific symptom dimensions of sadness, negative thoughts, detachment and neurovegetative symptoms was also investigated. Because significant changes in amygdala-prefrontal connectivity have been reported in MDD (Dannlowski et al., 2009) and improvement in rsFC between prefrontal-limbic regions is associated with successful treatment (Brakowski et al., 2017), changes in rsFC in these regions were expected.

4.2 Comparison with the literature

The rsFC between the left amygdala and the left DLPFC increased after ECT and these neural changes were related to overall symptom improvement (see also Domke et al., 2023). This confirms earlier findings from many treatment trials (Eshel et al., 2020; Gudayol-Ferré et al., 2015; Liu et al., 2016), which reported improved connectivity between prefrontal and limbic areas after successful therapy. The DLPFC is a component of the cognitive control network, and it modulates limbic regions like the amygdala, a crucial region involved in emotion formation, according to the theoretical framework (Berboth & Morawetz, 2021; Erk et al., 2010). Lack of DLPFC regulation has been linked to cognitive impairments and negative emotional biases in MDD (Erk et al., 2010; Groenewold et al., 2013; Kaiser et al., 2015; Siegle et al., 2007). The results of resting-state fMRI studies of amygdala changes in patients with MDD appear somewhat discrepant, but reduced rsFC of the amygdala with the prefrontal cortex and other regions involved in emotion processing and regulation have been reported (Ramasubbu et al., 2014).

Recent research has shown that the therapeutic effects of ECT depend on the regulation of FC patterns involving the DLPFC (Abbott et al., 2013; Beall et al., 2012; Perrin et al., 2012). The central finding here is consistent with the findings of Cano et al. (2016), who found that symptom improvement was also correlated with an increase in FC

between the right amygdala and the right DLPFC after the ninth ECT session as compared to baseline. Considering the conceptual context, these findings imply that ECT improves emotion regulation by restoring the DLPFC's top-down control over the limbic system. Given the conceptual background, these results suggest that ECT leads to a restoration of top-down control of the DLPFC over the limbic system, resulting in improved emotion regulation. It is notable that the finding of decreased rsFC between amygdala and sgACC could not be replicated (Cano et al., 2016). Cano and colleagues (2016) used path analysis and the DLPFC and sgACC as predefined target regions to assess the association between rsFC changes and symptom improvement, whereas in the present investigation a linear regression model at the whole brain level was used to prevent information loss due to predefined targets. So the above mentioned discrepancy, as well as the difference in lateralization, may be the result of different methodologies. Hence, it can be suggested that ECT therapy may directly impact emotion regulation via influencing prefrontal-limbic FC, resulting in a general improvement in symptoms when ECT is completed. This finding emphasizes the value of prefrontal-limbic rsFC as a biomarker of ECT response. One explanation for the improvement in rsFC might suggest an increase in synaptic plasticity through increased production of brain-derived neurotrophic factor (BDNF). In a study examining the effects of ketamine, an increase in BDNF levels after treatment was found to be related to changes in rsFC in the prefrontal cortex, possibly due to effects of synaptic plasticity (Woelfer et al., 2020). The increase in BDNF following ECT has already been shown in numerous studies and meta-analyses (Brunoni et al., 2014; Pelosof et al., 2022; Rocha et al., 2016) , therefore the possible mechanisms for the increase in rsFC may be equivalent to that of ketamine therapy.

Moreover, it has been observed that higher baseline rsFC between left amygdala and right frontal pole predicts greater symptom reduction. Recent studies have revealed different connectivity patterns and different regions involved in predicting response to ECT treatment, including the DLPFC (Moreno-Ortega et al., 2019; Van Waarde et al., 2015), the fronto-temporal (Leaver et al., 2018), and the DMN rsFC (Moreno-Ortega et al., 2019; Pang et al., 2022), but no study has yet identified rsFC between frontal pole and amygdala as a significant predictor of ECT-induced symptom reduction. The underlying neurophysiological processes of FC patterns as enhancing or attenuating factors of ECT efficacy remain unclear. It has been suggested that the placement of the electrodes may have an impact on the initial regional synchronization that is established and causes the generalized seizure (Leaver et al., 2018; Van Waarde et al., 2015). As the connection of the

regions under the electrodes predicts the response to ECT, it has been claimed that this initiation could have a significant impact on the effectiveness of ECT (Leaver et al., 2018; Van Waarde et al., 2015). The findings provided here challenge this theory because electrodes were placed in the temporo-parietal region, far from the frontal pole or amygdala. The potential arises that the effectiveness of ECT may depend on factors other than electrode location, including frontal and prefrontal circuits and, in particular, their connectivity to regions linked to MDD. Interestingly, structural and functional changes have been observed after ECT in the amygdala (Gryglewski et al., 2021; Loureiro et al., 2020) and frontal pole (Xu et al., 2018). Higher pretreatment rsFC could affect structural and functional changes in these regions and therefore be related to symptom reduction. Future studies should focus on the underlying consequences of the initially provoked seizure quality, electrode positioning, and induced neuroplastic processes in order to identify ECT responders or create specific ECT procedures.

In addition to rsFC the relationship of neural change in spontaneous brain activity (fALFF) and the predictive value of baseline fALFF for the outcome of ECT intervention were analysed. In the literature, studies have shown that ECT significantly decreases resting-state activity in patients in the subcallosal cingulate cortex (SCC) (Argyelan et al., 2016) and significantly increases it in the dorsomedial prefrontal cortex (Bai et al., 2019). These results could not be replicated in the present work. No correlation was found between neural activity change and symptom improvement. Regarding the predictive value of spontaneous brain activity, Argyelan et al. (2016) also found that a higher baseline fALFF of SCC predicted response to ECT, which contrasts with the results obtained here. In the current investigation lower baseline activity in the right frontal pole, right supramarginal gyrus, and right occipital pole was directly associated with symptom improvement at the end of the intervention. At the functional level, the frontal pole might play an integrative role in higher-order social, emotional, and cognitive processes (Burgess et al., 2007; Gilbert et al., 2010) and contribute to the development of typical symptoms associated with MDD, such as rumination (Ray et al., 2005). The supramarginal gyrus is a key region of the cognitive control network, which is also thought to be critical for higher-level cognitive performance (Beevers et al., 2010; Clasen et al., 2014). Especially the right supramarginal gyrus appears to play a central role in controlling empathy toward others (Silani et al., 2013), which may be impaired in depressed patients (Schreiter et al., 2013). Li et al. (2022) found that patients had higher spontaneous brain activity in the right supramarginal gyrus after ECT treatment than before ECT. Together with the finding from

the current investigation here, it could be suggested that lower resting-state activation prior to the intervention offers more potential for increased functional change, which could therefore also be related to stronger symptom improvement. Rather unexpected is the finding of lower baseline activity in the occipital pole. However, it is conceivable that the occipital cortex contributes to the clinical phenomena of impaired cognition in MDD (Li et al., 2013). Sensory areas may modulate attention, memory, execution, and other cognitive functions through various projections. Nevertheless, the relationship between abnormal neural activity in these areas and depressive symptomatology needs to be further elucidated.

This appears to be the first investigation of ECT treatment combined with resting-state fMRI to examine changes in various dimensions of depressive symptoms. MDD symptoms are quite heterogeneous, which may not only explain why approximately 30% of patients do not respond adequately to treatment (Bauer et al., 2013; Fried & Nesse, 2015), but also underscore the need for a better understanding of the specific effects of a given treatment on symptomatology. Affective symptoms, such as apparent sadness and reported sadness and the inability to feel, were found to improve the strongest during the course of ECT in a prior study that used a single-item approach rather than a factor-based approach (Carstens et al., 2021). All four of the MADRS symptom dimensions showed significant improvements in the current sample, and changes in the symptom dimensions of sadness, negative thoughts, and detachment were also linked to alterations in the rsFC between the amygdala and the DLPFC. There was no correlation between the change in rsFC and the change in neurovegetative symptoms found. This finding underscores that increased connectivity in the prefrontal-limbic circuit may lead to improved emotion regulation and consequently to a reduction in affective and cognitive symptoms.

4.3 Implications

The results here show that ECT effects the functional connectivity of the prefrontal-limbic system during rest and that this effect is significantly related to overall symptom improvement. However, when individual symptom dimensions are considered, it becomes apparent that these connectivity changes are particularly related to the improvement of cognitive and affective symptoms. In general, these results support the thesis that homogenised latent symptom dimensions from multi-item scales such as the HDRS or the

MADRS can improve the identification of imaging biomarkers associated with the course of specific symptom constellations (see also Wade et al., 2021). A symptom-based approach in the investigation of treatment effects in neuromodulation treatments is therefore promising and could help to make better decisions regarding complementary treatment options. One possibility, for example, would be to apply additional psychotropic medication that improves neurovegetative symptoms, as these do not seem to be affected by ECT as much as cognitive and affective symptoms.

Moreover, resting-state fMRI appears to be a method that has the potential to be used in daily clinical practice, for example to determine predictive markers prior to treatment. It is a rapid, easily applicable way of visualising functional activity and connections that does not require patients, who are usually severely distressed, to spend more than ten minutes in the scanner and possibly have to complete complex tasks. When applied prior to the intervention, it can provide valuable information about the potential success of the considered treatment. For example, as found here, higher baseline rsFC between the amygdala and frontal pole or lower baseline activity in the right frontal pole, right supramarginal gyrus and right occipital pole predict higher symptom improvement after ECT. Furthermore, there is a potential to identify neural biomarkers for treatment success. Applied during the course of the intervention, resting-state fMRI could provide guidance for the further outcome of the treatment. A study towards this end has already been conducted by Cano et al. (2016). Future studies should also consider additional time points to further explore longitudinal effects on the neural level.

4.4 Limitations

Some limitations must be acknowledged. The findings of the study should be regarded as preliminary due to the small size and the heterogeneity of the sample. Additional clinical trials with larger sample sizes and, for example, subgroup divisions (e.g., treatment-resistant depression (TRD) vs. non-TRD, with vs. without psychotic characteristics, younger vs. older age) are needed to clarify direct connections between brain features and responsiveness to ECT. Nonetheless, it could be shown using this naturalistic study design that resting-state fMRI scans can offer crucial details about ECT-induced brain alterations linked to symptom improvement in a sample that closely resembles clinical psychiatric reality. Direct evaluation of the effects of ECT was further challenging because the participants also obtained pharmacological therapy. However, medication was not

altered at any point during the ECT treatment to reduce confounding effects. It is reasonable to assume that the ECT treatment and not the pharmacological treatment seems to be accountable for the differences from baseline to the end of treatment. Moreover, concurrent use of antipsychotics and antidepressants may complement ECT in some individuals and have a comparable but less effective impact on the nervous system (Austin et al., 2001). The present study design did not include an active control group receiving alternative treatment (e.g., antidepressants only, ketamine, transcranial magnetic stimulation). Therefore, it is not possible to compare the likelihood of response to ECT versus alternatives, which would be relevant for treatment decisions in routine clinical practice. For this reason, all analyses have consequently focused on the direct association with symptom reduction. The investigation delivers limited understanding of complex network interactions because ROIs containing just bilateral amygdala and DLPFC were stringently chosen. The objective was to look for rsFC alterations following ECT in areas that are known to be altered in MDD and appear to be crucial in the emergence of cognitive and affective symptoms (Heinzel et al., 2009; Lévesque et al., 2003).

4.5 Conclusion

The results of this dissertation point to an ECT mechanism of action that may involve increased connectivity between the amygdala and prefrontal cortex, which is linked to a reduction in cognitive and affective symptoms in depressed patients. The idea that frontal-limbic rsFC may also be an important predictor of response is based on the discovery of a correlation between baseline amygdala and frontal pole rsFC and symptom improvement following completion of ECT. Overall, it can be concluded that resting-state fMRI may be a useful tool in routine clinical practice to find neural biomarkers like functional connectivity or spontaneous activity in particular core areas known to be linked to specific MDD symptoms like sadness, negative thoughts, or detachment. It has been demonstrated that imaging biomarkers for MDD can be identified in a naturalistic sample of depressed people with various primary diagnoses, comorbidities, disease durations, and age ranges who are normally encountered in psychiatric facilities. Furthermore, it might be argued that a symptom-based approach, in addition to categorically defined diagnoses and multi-item scale total scores, has significance for the investigation of an illness as diverse as MDD. Additional investigation into the underlying mechanisms of action of the

ECT response using fMRI and the use of defined symptom dimensions is promising. Additionally, it would certainly be interesting to have more scanning repetitions. Both at an earlier time point during the acute ECT phase to look for neuronal markers for an early response and as follow-up measurements to look for long-term effects of ECT-induced changes in functional connectivity.

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VII Eidesstattliche Versicherung

„Ich, Ann-Kathrin Domke, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „The relationship of changes in prefrontal-limbic connectivity and distinct depressive symptoms after electroconvulsive therapy“ / „Der Zusammenhang von Veränderungen der präfrontal-limbischen Konnektivität und spezifischen depressiven Symptomen nach Elektrokonvulsionstherapie“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.
Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.
Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.
Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.
Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

VIII Anteilserklärung an der erfolgten Publikation

Ann-Kathrin Domke ist alleinige Erstautorin der folgenden Publikation:

Domke, A. K., Hempel, M., Hartling, C., Stippl, A., Carstens, L., Gruzman, R., Herrera Melendez, A.L., Bajbouj, M., Gärtner, M. & Grimm, S. (2023). Functional connectivity changes between amygdala and prefrontal cortex after ECT are associated with improvement in distinct depressive symptoms. *European Archives of Psychiatry and Clinical Neuroscience*, 1-11.

Der Beitrag im Einzelnen:

Die Fragestellung der vorliegenden Dissertation habe ich eigenständig unter Supervision von Prof. Dr. Simone Grimm und Dr. Matti Gärtner entwickelt und habe nach umfassender Sichtung der Literatur die relevanten seed regions für die fMRT Analysen selbst ausgewählt.

Ich habe grundlegend zur Implementierung und Einhaltung der Studienabläufe und der organisatorischen Infrastruktur am Standort Charité, Campus Benjamin Franklin beigetragen. Des Weiteren war ich für die konstante Kommunikation und Studienkorrespondenz mit den Stationen 16a/b, sowie 08a/b der Psychiatrie, Charité Campus Benjamin Franklin verantwortlich. Ich übernahm einen Großteil der Patientenakquise auf den Stationen, sowie die Koordination der fMRT-Termine. Ich habe mich um den Patiententransport von den besagten Klinikstationen zum MRT-Standort im Center for Cognitive Neuroscience (CCNB) der FU gekümmert. Dort führte ich die fMRT-Messungen als „Advanced User“ durch, betreute die Proband*innen während der Erhebung der MRT-Daten und der klinischen Daten und führte die standardisierten klinischen Interviews. Darüber hinaus bestand meine Aufgabe in der analogen und digitalen Archivierung von Probandendaten, sowie der quantitaven Aufbereitung in SPSS und Excel. Die Aufarbeitung der klinischen Daten und deren statistische Auswertung habe ich komplett eigenständig übernommen. Daraus entstanden die Tabellen 1 – 3 sowie die Abbildung 1, welche alle von mir erstellt wurden.

Nachdem ich eine grundlegende Einführung in die fMRT-Datenanalyse mit SPM12 und der Conn-Toolbox durch meinen Co-Autor und Kollegen Dr. Matti Gärtner erhalten habe, führte ich die Analysen der funktionellen MRT-Daten selbstständig durch. Bei der Interpretation der daraus resultierenden Ergebnisse unterstützten mich Prof. Dr. Simone

Grimm und Dr. Matti Gärtner. Abbildung 2 erstellte ich eigenständig mithilfe des Programmes MRICron, dessen Nutzung mir ebenfalls zunächst von Dr. Matti Gärtner nähergebracht wurde.
Ich recherchierte eigenständig nach passender Literatur und ordnete die Ergebnisse der Studie in den aktuellen Forschungstand ein. Darüber hinaus bin ich die alleinige Verfasserin der ersten Version des Manuskriptes und übernahm allein die Korrespondenz im mehrstufigen Peer-Reviewprozess vor Veröffentlichung des Papers.

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ORIGINAL PAPER

Functional connectivity changes between amygdala and prefrontal cortex after ECT are associated with improvement in distinct depressive symptoms

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Abstract
Electroconvulsive therapy (ECT) is one of the most effective treatments for treatment-resistant depression. However, the underlying mechanisms of action are not yet fully understood. The investigation of depression-specific networks using resting-state fMRI and the relation to differential symptom improvement might be an innovative approach providing new insights into the underlying processes. In this naturalistic study, we investigated the relationship between changes in resting-state functional connectivity (rsFC) and symptom improvement after ECT in 21 patients with treatment-resistant depression. We investigated rsFC before and after ECT and focused our analyses on FC changes directly related to symptom reduction and on FC at baseline to identify neural targets that might predict individual clinical responses to ECT. Additional analyses were performed to identify the direct relationship between rsFC change and symptom dimensions such as sadness, negative thoughts, detachment, and neurovegetative symptoms. An increase in rsFC between the left amygdala and left dorsolateral prefrontal cortex (DLPFC) after ECT was related to overall symptom reduction (Bonferroni-corrected $p=0.033$) as well as to a reduction in specific symptoms such as sadness ($r=0.524$, uncorrected $p=0.014$), negative thoughts ($r=0.700$, Bonferroni-corrected $p=0.002$) and detachment ($r=0.663$, $p=0.004$), but not in neurovegetative symptoms. Furthermore, high baseline rsFC between the left amygdala and the right frontal pole (FP) predicted treatment outcome (uncorrected $p=0.039$). We conclude that changes in FC in regions of the limbic-prefrontal network are associated with symptom improvement, particularly in affective and cognitive dimensions. Frontal-limbic connectivity has the potential to predict symptom improvement after ECT. Further research combining functional imaging biomarkers and a symptom-based approach might be promising.

Keywords Resting-state fMRI · Functional connectivity · Electroconvulsive therapy · Major depressive disorder

Introduction

Depression is the leading mental health disorder worldwide and affects 16–20% of individuals in their lifetime. It is a very heterogeneous disorder with varying symptom presentations such as low mood, anhedonia, cognitive dysfunctions, and somatic manifestations [1]. Considering the wide range of depressive symptoms, different types of antidepressant treatment (i.e., pharmacological or psychotherapeutic) may affect distinct symptom dimensions that are associated with unique neurobiological mechanisms of response [2]. Furthermore, it is possible that patients with distinct symptom profiles or depression biotypes may benefit from different antidepressant therapies [3]. For patients suffering from depression and characterized as resistant to pharmacological and psychotherapeutic treatment, ECT is

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another promising option for relieving depressive symptoms, with response rates of up to 50–75% [4]. Nevertheless, there are still many patients who continue to suffer from specific symptoms or do not respond to treatment with ECT at all [5]. A better understanding of the specific effect of ECT on distinct symptoms, as well as of symptom and treatment-specific biomarkers, is of paramount clinical importance, as failed treatment attempts increase patients' burden of disease and are associated with an increased risk of suicide [6–8].

We previously showed that distinct antidepressant treatments have differential effects on specific symptom dimensions, with improvements in cognitive symptoms after a single sub-anaesthetic dose of ketamine [9], whereas ECT specifically reduced affective symptoms [10]. Other studies that examined the relationship between specific symptom dimensions and overall ECT response found that core symptoms such as depressed mood and anhedonia improved more with ECT than somatic or vegetative symptoms [2]. Also, factors that comprise those symptoms [11, 12] had a high predictive value for ECT outcomes. A recent imaging study investigated the relation between three depressive symptom dimensions (somatic disturbances, core mood and anhedonia, and insomnia, measured with the 17-item Hamilton Depression Rating Scale [HDRS]) and volumetric changes in brain regions that are linked to depression and reported distinct structural imaging predictors [13].

Regarding affective dimensions, dysfunctional emotion regulation has been proposed as critical for effective core symptoms of depressive disorders [14]. Further, prefrontal-limbic connectivity, as a neural substrate, is associated with both the development of emotion regulation mechanisms [15] and their alteration in depression [16–18]. Different antidepressant treatment approaches have been demonstrated to restore disturbed prefrontal-limbic balance [19–21] and abnormal activity patterns within these regions [22]. Recent studies have already shown that functional connectivity measurements can reveal differences in emotion regulation [23, 24]. Further, resting state functional connectivity (rsFC) measurements may facilitate the identification of altered prefrontal-limbic network properties following ECT [25]. A longitudinal resting-state fMRI investigation by Perrin et al. [26] identified a considerable reduction in the average global functional connectivity in and around the left dorsolateral prefrontal cortex (DLPFC) region after ECT, which was accompanied by a significant decrease in depressive symptoms. In contrast, Abbott et al. [27] identified a significantly increased pattern of functional network connectivity between the posterior default mode network and the left DLPFC in remitted vs. non-remitted patients after ECT. However, due to the small sample sizes, the results of these studies can only be considered preliminary. Cano et al. [19] proposed that an FC decrease between amygdala and subgenual anterior cingulate cortex (sgACC) in early ECT treatment phases (after the 1st ECT session) might modulate a subsequent increase between the right amygdala and DLPFC (after the 9th ECT session), that might, in turn, be associated with a clinical response after ECT completion. They used predefined target regions so that the connections from the seed regions were limited to these targets. A whole-brain analysis, as a complementary approach, might provide further information on how rsFC of the amygdala or DLPFC changes after ECT. Furthermore, even though it might shed further light on the direct treatment effects of ECT, none of the prior studies have examined the association between rsFC changes and improvement in specific symptom dimensions.

Apart from the identification of treatment-specific biomarkers, it is of great clinical relevance to identify specific predictive markers that support decision-making for treatment with ECT. Several clinical predictors, such as older age, psychotic symptoms, or higher severity of depression at baseline for treatment response have already been outlined [28–30]. Previously, we could show that especially apparent and reported sadness and inability to feel (measured with the Montgomery-Åsberg Depression Rating Scale, MADRS [31] at baseline) have predictive value for ECT outcome [10]. When considering the prognostic value of neural markers, results become more variable across studies. To date, most studies of ECT prediction have relied on structural MRI [32–35]. The sparse literature referring to FC as a predictor has been rather inconsistent. Some of the previous studies identified the DLPFC, among other regions, as a region that has predictive value for ECT treatment success [36–38]. To our knowledge, rsFC of the amygdala, unlike DLPFC, has not yet been investigated as a possible predictor for ECT treatment outcome. However, baseline connectivity of the amygdala could also add predictive value, as alterations in that region play an important role in the development of affective symptoms [39] and connectivity changes represent a biomarker for treatment success [16].

The main objective of this study was to investigate the association between rsFC changes and changes in depression severity after ECT. For this purpose, we acquired resting state fMRI data before and after a full course of ECT treatment. We used a data-driven seed-based connectivity approach at the whole-brain level and focused our analyses on bilateral DLPFC and bilateral amygdala. Specifically, we expected that rsFC changes after ECT are directly related to the improvement of symptom severity. In addition, we explored whether baseline rsFC can predict response to ECT. As a primary outcome measure, we used the MADRS total score. Moreover, with respect to the diversity of depressive symptoms we considered a four-factor structure of the MADRS proposed by Williamson et al. [40] with the factors sadness, negative thoughts, detachment, and neurovegetative

symptoms, to further elucidate the relation between neural changes and specific symptom dimensions.

Materials and methods

Study design

All patients underwent a baseline resting state fMRI scan and clinical assessment prior to ECT treatment (T0). The treatment implied right unilateral ECT with an ultra-brief pulse device with pulse lengths of 0.25 ms (Thymatron IV System, Somatics Inc.) according to the standard protocol at the Department of Psychiatry, Charité-Universitätsmedizin Berlin, which includes three ECT sessions per week over a period of 4 weeks. Anaesthesia included propofol (approximately 1.50 mg/kg) or etomidate (approximately 0.75 mg/kg) and succinylcholine (approximately 0.75 mg/kg) was used for muscular relaxation. To control for the adequate duration, motor and electroencephalogram seizure duration was monitored. During the first ECT treatment, seizure threshold was titrated, and voltage was only modified if patients did not respond clinically or showed insufficient seizures during the course of ECT (i.e., motor response < 20 s or electroencephalogram seizure activity < 30 s). For a more detailed description of the procedure see Brakemeier et al. [41]. Resting-state fMRI and clinical assessment were repeated after the last ECT session (T1).

Participants and clinical assessments

Participants were 21 patients (10 female, age $M = 44.05$ years, SD = ±11.03, range 22–60 years) diagnosed with a current treatment-resistant depressive episode in accordance with the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and treated with right-unilateral ultra-brief ECT at the Department of Psychiatry, Charité-Universitätsmedizin Berlin. Patients classified as "treatment-resistant", i.e. failed to respond to two antidepressant treatment trials of adequate dosage and sufficient length of time. Regarding antidepressant medication there were no restrictions at the time of enrolment, however, medication intake was documented. Depression severity was assessed using a German version of the MADRS (Montgomery and Åsberg, 1979) conducted by a trained professional. The MADRS consists of 10 items assessing the following depressive symptoms on a 7-point scale (with 0 = no abnormality and 6 = severe): apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts. We used a previously established four-Factor model of the MADRS [40, 42] to further explore the relation between distinct depression symptoms and neuronal correlates during resting state. The model contains the factors sadness, negative thoughts, detachment and neurovegetative symptoms (see Table S1 in the supplementary material for detailed information about the factors). Reduction of MADRS total score of 50% or more post-ECT was defined as a response, MADRS total score ≤ 10 as remission [43]. Statistical procedures for demographic and clinical data were conducted in IBM SPSS Statistics 28 for Windows. Statistical tests are based on a significance level of $\alpha = 0.05$. The study was carried out in accordance with the latest version of the Declaration of Helsinki and approved by the Institutional Review Board of Charité-Universitätsmedizin Berlin. All participants provided written informed consent before participation.

FMRI data acquisition

Functional imaging was conducted with a 3 T Tim Trio MR scanner (Siemens, Erlangen), a standard 12-channel head coil at the Center for Cognitive Neuroscience Berlin (Free University Berlin), using standard echo planar imaging sequences. Data were collected in 8-min runs (210 vol) with 37 oblique axial slices of 3 mm (TE = 30 ms; field of view = 192 mm, 3 × 3 mm in-plane resolution, TR 2300 s, flip angle 70°). A 3-dimensional T1-weighted anatomical scan was obtained for structural reference.

Brain connectivity analyses

All resting state fMRI data were analyzed in Matlab (Version R2015b) using SPM12 and the CONN toolbox (Version 20.b; https://www.nitrc.org/projects/conn [44]). Preprocessing of functional and structural data was done with CONN's default preprocessing pipeline to MNI-space. The pipeline includes motion correction (realignment and unwarping), slice-timing correction, structural segmentation and normalization, functional normalization, outlier detection (ART-based scrubbing), and spatial smoothing (8 mm). During the denoising step in CONN single-subject linear regression analyses were performed to remove the effects of head motion (12 total motion covariates: 6 motion parameters plus 6 temporal derivatives), physiological artifacts (10 total CompCor eigenvariates: 5 each from eroded WM and CSF masks), and artifactual scans. The resulting residual blood oxygen level-dependent (BOLD) time series were band-pass filtered (0.01–0.1 Hz). We followed a seed-based approach to assess ECT effects on regions of the emotional and cognitive control network. Seeds were selected based on recent literature [19, 36, 45, 46]. Seed regions of interest (ROI: x, y, z, in Montreal Neurological Institute [MNI] space) included bilateral DLPFC (±40 36 32) and bilateral amygdala (±24 − 2 − 20). Seed-based analyses were

performed using spherical ROI templates with a diameter of 10 mm, that was built according to automated term-based meta-analyses on neurosynth.org. Single-subject seed-to-voxel correlation maps were calculated by extracting the residual blood oxygen level-dependent (BOLD) time course from the seed and computing Pearson's correlation coefficients between that time course and the time course of all other voxels.

Statistical group analyses were carried out in two steps. First, we focused on the association of rsFC changes with symptom improvement at the end of the acute ECT phase. Linear regression analyses were implemented in CONN by defining a simple main effect of MADRS percent symptom reduction (defined as psr = (T0 − T1)/T0 × 100) as between-subjects contrast, and time point (pre vs. post) as between-conditions contrast. The same analyses were performed using the baseline scans only, to investigate the predictive power of baseline rsFC. Statistical thresholds were set to $p < 0.001$ (uncorrected) at the single voxel level and to $p < 0.05$ (FDR corrected) at the cluster level. The mean FC levels of each ROI were extracted with the REX Toolbox (https://www.nitrc.org/projects/rex/) [47]. To further explore the association between the improvement of specific symptoms and changes in rsFC post-hoc correlational analyses (Spearman's correlation coefficient, two-sided) with the four MADRS factors were performed. All results are Bonferroni corrected, yet we also report exploratively the uncorrected results.

Results

Clinical and demographic data

Demographic and clinical data as well as further information regarding treatment, response, and remission are shown in Table 1. For a detailed description of diagnosis type, psychiatric and somatic comorbidities, and antidepressant medication please see tables S2 and S3 in the supplemental information. 85.71% of the patients (18/21) showed a significant reduction of depressive symptoms after the completion of their individual acute ECT phase (see Fig. 1). In total 52.38% (11/21) of the patients were classified as responders. The remission rate in our sample was 19.05% (4/21).

fMRI results

The whole-brain regression analysis revealed a significant rsFC increase related to symptom reduction (MADRS total score) between the left amygdala seed and a cluster located in the left DLPFC (coordinates: − 38, 14, 46; Cluster size: 93; $p = 0.008275$, p-FDR corrected). To address the

Table 1 Participants demographic and clinical characteristics

Variable	*M*	*SD*			*n*			
Age	44.05	11.03			21			
Number of depressive episodes [a]	3.76	3.36			17			
No. of ECTs	12.62	3.22			21			
	Pre ECT		Post ECT					
	M	SD	M	SD	n	T	df	p
MADRS total score	31.38	5.98	19.05	10.34	21	6.76	20	<.001
MADRS symptom reduction (%)	40.89	28.63			21			
MADRS Factors								
Sadness	7.29	1.85	4.76	2.98	21	4.29	20	<.001
Neg. thoughts	5.00	2.26	3.10	2.43	21	3.99	20	<.001
Detachment	10.38	2.36	6.33	3.53	21	5.74	20	<.001
Neurovegetative Symptoms	8.57	2.96	4.81	3.30	21	4.54	20	<.001
Gender (F:M)	10:11							
Response (Y:N)	11:10							

Notes: ECT Electroconvulsive therapy, MADRS Montgomery Asberg Depression Rating Scale, M Mean, SD Standard Deviation, [a] n <21 due to missing data

PB, PB235 clone; RR, RRIM600 clone; +W, with weight application; −W, without weight application; Sulf, sulfuric acid coagulation; Form, formic acid coagulation; Nat, natural coagulation; Long dur", maturation duration exceeding 9 days; Short dur", maturation duration equal or shorter to 9 days

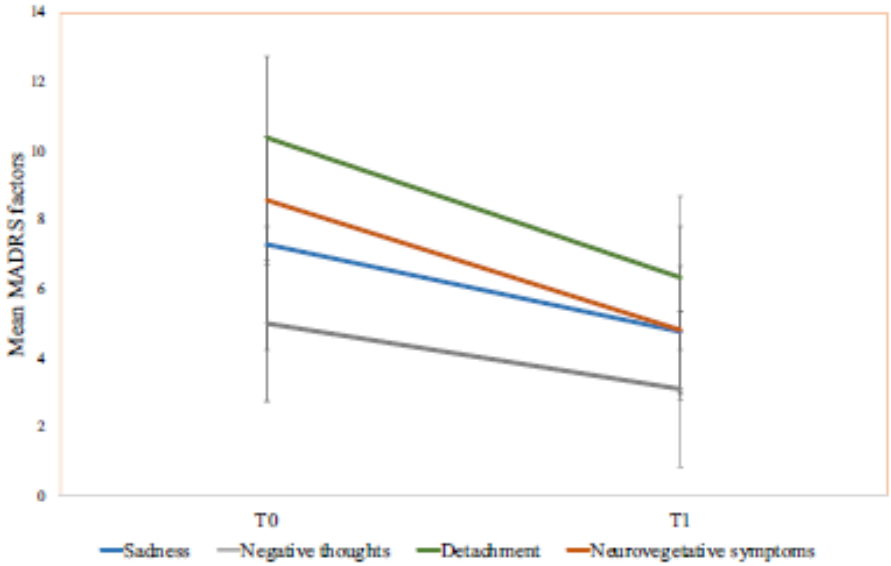

Fig. 1 Symptom reduction in MADRS dimensions. The different lines represent the absolute change in the MADRS dimensions between (T0) and post-treatment with ECT (T1). Error bars represent standard deviations

problem of multiple comparisons, we applied a Bonferroni-corrected alpha level of 0.0125. The result remained significant ($p=0.0331$). See Fig. 2b for a visualization of the cluster on the cortical surface. A post hoc hierarchical multiple regression analysis in which age and gender were added blockwise as control variables revealed that both variables had no significant effect on the outcome variable MADRS total score reduction (age: $\beta=0.214$, $p=0.261$; gender: $\beta=-0.260$, $p=0.155$). The bilateral DLPFC and right amygdala seeds did not show significant rsFC changes related to symptom reduction. The analysis of baseline rsFC revealed that baseline rsFC of the left amygdala to the right FP (coordinates: 16 64 20; Cluster size: 74; $p=0.038816$, Bonferroni-corrected $p=0.155264$) was positively related to symptom reduction, with higher levels of baseline connectivity indicating higher levels of symptom reduction. We did not find significant effects for the DLPFC seeds.

For the significant rsFC change between amygdala and DLPFC we performed additional correlation analyses with the four MADRS factors. A strong positive relationship was observed between rsFC change (mean value of the rsFC between left amygdala and left DLPFC cluster), and the change of the factors sadness, negative thoughts, and detachment but not for the factor neurovegetative symptoms (see Fig. 3). When excluding an outlier who showed a reduction in rsFC, the positive relation between FC change and symptom reduction remained for the three mentioned symptom dimensions [sadness: $r=0.524$, $p=0.059$ (Bonferroni-corrected), $p=0.014$ (uncorrected); negative thoughts: $r=0.700$, $p=0.002$ (Bonferroni-corrected); detachment: $r=0.663$, $p=0.004$ (Bonferroni-corrected)].

Discussion and conclusion

In the present study, we investigated the modulatory effect of ECT on resting-state functional connectivity of the amygdala and the DLPFC in depressive patients. In addition to FC changes, we also investigated whether baseline FC might predict clinical outcomes. For a more detailed understanding of clinical changes after ECT, we further explored the relationship between rsFC and the specific symptom dimensions of sadness, negative thoughts, detachment, and neurovegetative symptoms. Since significant alterations in amygdala-prefrontal connectivity were reported in depression [18] and enhancement of rsFC between prefrontal-limbic regions is associated with successful treatment [48], we also expected a change in rsFC in these regions.

We found that connectivity between the left amygdala (Brodmann area [BA] 28 and left DLPFC (BA 9) increased after ECT and that these neural changes were related to overall symptom improvement. Thus, our results support previous findings from various treatment studies that found increased connectivity between prefrontal and limbic areas after successful treatment [49–51]. The theoretical framework is based on the assumption that the DLPFC, as part of the cognitive control network, modulates limbic areas such as the amygdala, a key region involved in emotion generation [52, 53]. Impairments in cognitive functioning and the negative affective bias in depression have been associated with a lack of DLPFC control [53–56]. Results of resting-state fMRI studies of amygdala alterations in depression are rather inconsistent, but reduced amygdala rsFC with the prefrontal cortex and other regions involved in emotion processing and regulation has been reported [39].

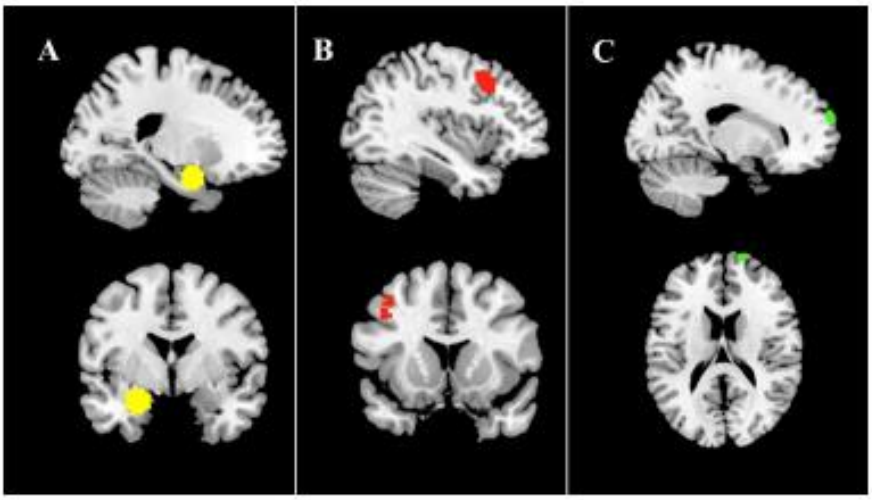

Fig. 2 Resting-state functional connectivity (FC) related to the reduction of depressive symptoms after completion of ECT. **A** Yellow color marks the seed region in the left amygdala that was used for the seed-to-voxel analysis. **B** Red color marks the region in the left DLPFC whose FC change to the amygdala after ECT is positively related to symptom reduction (higher connectivity after ECT = higher symptom reduction). **C** Green color marks the region in the right frontal pole (FP) whose baseline FC to the left amygdala is positively related to symptom reduction (high baseline connectivity = high symptom reduction). Statistical thresholds for (**B**, **C**) were $p < 0.001$ at the voxel level, and $p < 0.05$ (FDR corrected) at the cluster level

Previous studies have shown that the modulation of FC patterns involving the DLPFC is critical for the therapeutic effect of ECT [26, 27, 57]. Our key finding is in line with findings by Cano et al. [19], who observed an increase in FC between the right amygdala and right DLPFC after the ninth ECT session compared to baseline, which was also associated with symptom improvement. Based on the conceptual background, these results suggest that ECT leads to

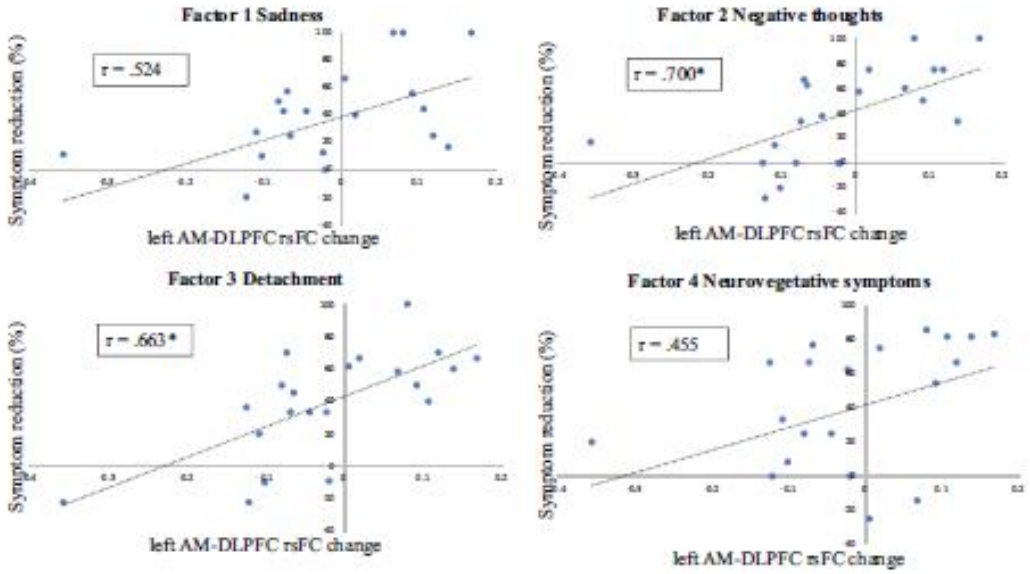

Fig. 3 Post-hoc correlation analyses of resting-state functional connectivity (FC) change between the left amygdala and left dorsolateral prefrontal cortex (DLPFC) related to the reduction in the different symptom dimensions. Symptoms were measured with the Montgomery-Asberg Depression Rating Scale (MADRS). The *R*-value depicts Spearman's Correlation Coefficient (* the corresponding *p*-value is < 0.05 Bonferroni-corrected)

the restoration of DLPFC top-down control over the limbic system, resulting in improved emotion regulation. It is notable that we were unable to replicate the finding of decreased rsFC between the amygdala and sgACC [19]. This discrepancy, as well as the difference in laterality, could be due to differences in methodology, as Cano et al. (2016) used the DLPFC and sgACC as predefined target regions and path analysis to examine the relationship between rsFC changes and symptom improvement, whereas in this study, we used a linear regression model on the whole brain-level to avoid information loss due to predefined targets. Accordingly, we argue that treatment with ECT could impact emotion regulation directly by modulation of prefrontal-limbic FC, leading to an overall symptom improvement after the completion of ECT. Our finding further highlights the importance of prefrontal-limbic rsFC as a biomarker for ECT response. One explanation for the enhancement in rsFC could be an increase in synaptic plasticity by increasing the production of the neurotrophic growth factor BDNF (brain-derived neurotrophic factor). In a study investigating the effects of ketamine, an increase in BDNF levels after treatment was shown to be related to changes in rsFC in the prefrontal cortex, possibly reflecting synaptic plasticity effects [58]. Since several studies and meta-analyses have already demonstrated the increase in BDNF after ECT [59–61], the underlying mechanism for the increase in rsFC could be similar to that of treatment with ketamine.

To the best of our knowledge, this is the first ECT study combining resting-state fMRI with the investigation of changes in distinct depressive symptom dimensions. Depressive symptoms are quite heterogeneous, which might not only explain that about 30% of patients do not respond adequately to treatment [1, 43] but also underscores the need for a better understanding of the specific effects of a particular treatment on symptomatology. In a previous study, in which we chose a single-item rather than a factor-based approach, we observed that in particular affective symptoms, such as apparent and reported sadness and inability to feel, improved most over the course of ECT [10]. In the current sample, we observed significant improvements for all four MADRS symptom dimensions, of which changes in the dimensions of sadness, negative thoughts, and detachment were also associated with the observed change in rsFC between the amygdala and DLPFC. We did not find any correlation between the rsFC change and the change in neurovegetative symptoms. This finding further underlines that increased connectivity in the prefrontal-limbic circuit may lead to improved emotion regulation and, consequently, to a reduction in affective and cognitive symptoms. Accordingly, our results support the proposition that homogenized latent symptom dimensions from multi-item scales, as the HDRS or the MADRS, can improve the detection of imaging biomarkers that are related to the trajectories of specific symptom constellations [13].

Our baseline connectivity analyses revealed that lower rsFC between the left amygdala and right FP (BA 10) predicted higher symptom improvement at the end of treatment. Because this finding was not robust to correction for multiple comparisons, it should be considered an exploratory result. Recent studies revealed distinct connectivity patterns and various involved regions for the prediction of ECT treatment response including DLPFC [36, 38], fronto-temporal [37] and DMN [36, 62] FC, but no study so far has identified FC between FP and amygdala as a significant predictor for ECT induced symptom reduction. The underlying neurophysiological processes of FC patterns as enhancing or diminishing factors of ECT effectiveness remain elusive. It has been proposed that the electrode placement may affect the initially induced regional synchronization which leads to generalized seizure [37, 38]. It has been argued that this initiation might have a crucial impact on ECT effectiveness, as the connectivity of regions beneath the electrodes predicts ECT response [37, 38]. Our results challenge this conception since we used a temporoparietal placement with electrodes distant from the FP or amygdala. We propose that frontal and prefrontal circuits and especially their connectivity to depression-associated regions may affect ECT outcomes not solely dependent on electrode placement. Interestingly, structural [63, 64] and functional [65, 66] changes following ECT have been observed within the amygdala and within the FP [67]. On a functional level, the FP may subserve an integratory role for higher-order social, emotional, and cognitive processes [68, 69] and contribute to the development of typical symptoms associated with depression e.g. rumination [70]. Higher pre-treatment FC might have an impact on the structural and functional changes within those regions and might therefore be related to symptom reduction. The underlying effects of the initially elicited seizure quality, electrode placement and induced neuroplastic processes should be addressed in further investigations to identify ECT responders or develop individual ECT protocols.

Some limitations of this study must be acknowledged. Given the relatively small and heterogenous sample, the results of the study should be considered as preliminary. Further, clinical trials with bigger sample sizes and e.g., subgroup divisions (e.g., treatment-resistant depression (TRD) vs. non-TRD, with vs. without psychotic features, younger vs. older age) are needed to clarify direct associations between neural characteristics and response to ECT. However, with our naturalistic study design, we demonstrated that resting-state fMRI measures can provide important information about neural changes induced by ECT that are associated with symptom improvement in a sample that corresponds to clinical psychiatric reality. Furthermore, subjects received pharmacological treatment, impeding a direct interpretation of ECT effects. Nevertheless, to minimize confounding effects, medication was

not modified throughout the entire ECT course. Thus, we believe that changes compared to baseline measures relate to treatment with ECT and not to pharmacological treatment. Furthermore, the simultaneous use of antidepressant and antipsychotic treatments may work in conjunction with ECT for some patients and share a similar but less effective mechanism of action [71]. Yet, future randomized controlled trials without concomitant psychopharmacological medication or the same medication for all participants in addition to ECT treatment are needed to confirm the rsFC changes shown in our naturalistic study. Our study design did not include an active control group receiving an alternative treatment (e.g., antidepressants only, ketamine, transcranial magnetic stimulation). Thus, we are unable to compare the probability of response to ECT relative to alternatives that would be relevant for making treatment decisions in clinical routine, neither can exact conclusions be derived regarding the specificity of rsFC alterations. To derive clinically relevant information from the changes in rsFC, we focused on the direct relationship between rsFC and differential symptom reduction in all our analyses. Due to the strict seed selection of ROIs with only bilateral amygdala and DLPFC, knowledge of complex network interactions is limited for this study. The aim was to highlight changes in rsFC after ECT in regions that are known to be altered in depression and that presumably play a key role in the development of cognitive and affective symptoms [72, 73].

In summary, our findings suggest that one possible mechanism of action underlying ECT may be an increased connectivity of amygdala and prefrontal cortex that is linked to the improvement of cognitive and affective symptoms in patients diagnosed with depression. We found an association between baseline amygdala and FP rsFC and symptom improvement after completion of ECT, which leads to the assumption that frontal-limbic rsFC may also be a valuable response predictor. Taken together, we propose that resting-state fMRI can be a valuable instrument in clinical routine to identify neural biomarkers such as functional connectivity in specific seed regions, that are known to be linked with specific depression symptoms such as sadness, negative thoughts, or detachment. We demonstrated that imaging biomarkers for depressive disorders can be determined in a naturalistic sample of depressed patients typically found in psychiatric units, with different primary diagnoses, comorbidities, illness durations, and from different age groups. Furthermore, we propose that a symptom-based approach, apart from categorically defined diagnoses and multi-item scale total scores, has added value for the study of a disorder as heterogeneous as depression. Further research integrating fMRI and the use of delineated symptom dimensions seems promising and may provide further insight into the underlying mechanisms of action of ECT response. Furthermore, additional scanning time points would be of great interest. Both, at an earlier time point during the acute ECT phase to investigate neuronal markers for early response, and as follow-up measurements to investigate the sustainability of ECT-induced changes in functional connectivity.

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Author contributions AD made substantial contributions to the acquisition, analysis and interpretation of data and wrote the manuscript. MH made substantial contributions to drafting the manuscript and revised it critically. CH, AS, LC, RG, and AH made substantial contributions to the acquisition of data and revised the manuscript critically. MB contributed to the funding sources and made substantial contributions to the conception and design of the study MG made substantial contributions to the analysis and interpretation of data and commented critically on the manuscript SG contributed to the funding sources and made substantial contributions to the conception and design of the study as well as analysis and interpretation of data and commented critically on the manuscript. All authors revised the work critically, approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials The data that support the findings of this study are available from the corresponding author, AD, upon reasonable request.

Declarations

Conflict of interest Malek Bajbouj has served as a consultant to GH Research, Janssen, Bayer, and Boehringer Ingelheim. Simone Grimm has served as a consultant to and received research support from Boehringer Ingelheim Pharma. No other disclosures were reported.

Ethics approval The study design was approved by the institutional review board of the Charite, performed in accordance with the Declaration of Helsinki.

Consent to participate Patients' informed consent was obtained.

Consent for publication Not applicable.

XI Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

XII Komplette Publikationsliste

Carstens L, Hartling C, Aust S, Domke AK, Stippl A, Spies J, Brakemeier EL, Bajbouj M, Grimm S. EffECTively Treating Depression: A Pilot Study Examining Manualized Group CBT as Follow-Up Treatment After ECT. Front Psychol. 2021 Sep 3;12:723977. doi: 10.3389/fpsyg.2021.723977. - *Impact Factor (2021): 4.232*

Carstens L, Hartling C, Stippl A, Domke AK, Herrera-Mendelez AL, Aust S, Gärtner M, Bajbouj M, Grimm S. A symptom-based approach in predicting ECT outcome in depressed patients employing MADRS single items. Eur Arch Psychiatry Clin Neurosci. 2021 Oct;271(7):1275-1284. doi: 10.1007/s00406-021-01301-8. *– Impact Factor (2021): 5.760*

Gruzman R, Hartling C, Domke AK, Stippl A, Carstens L, Bajbouj M, Gärtner M, Grimm S. Investigation of Neurofunctional Changes Over the Course of Electroconvulsive Therapy. Int J Neuropsychopharmacol. 2023 Jan 19;26(1):20-31. doi: 10.1093/ijnp/pyac063. *– Impact Factor (2021): 5.678*

Domke AK, Hempel M, Hartling C, Stippl A, Carstens L, Gruzman R, Herrera Melendez AL, Bajbouj M, Gärtner M, Grimm S. Functional connectivity changes between amygdala and prefrontal cortex after ECT are associated with improvement in distinct depressive symptoms. Eur Arch Psychiatry Clin Neurosci. 2023 Jan 30. doi: 10.1007/s00406-023-01552-7. *– Impact Factor (2020): 5.270*

Domke, A. K., Hartling, C., Stippl, A., Carstens, L., Gruzman, R., Bajbouj, M., ... & Grimm, S. (2023). The influence of childhood emotional maltreatment on cognitive symptoms, rumination, and hopelessness in adulthood depression. Clinical Psychology & Psychotherapy, 30(5), 1170-1178. doi: 10.1002/cpp.2872 *– Impact Factor (2022): 3.6*

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