The anatomy of excitement

Understanding and improving the effectiveness of electroconvulsive therapy

van Doesschate, F.

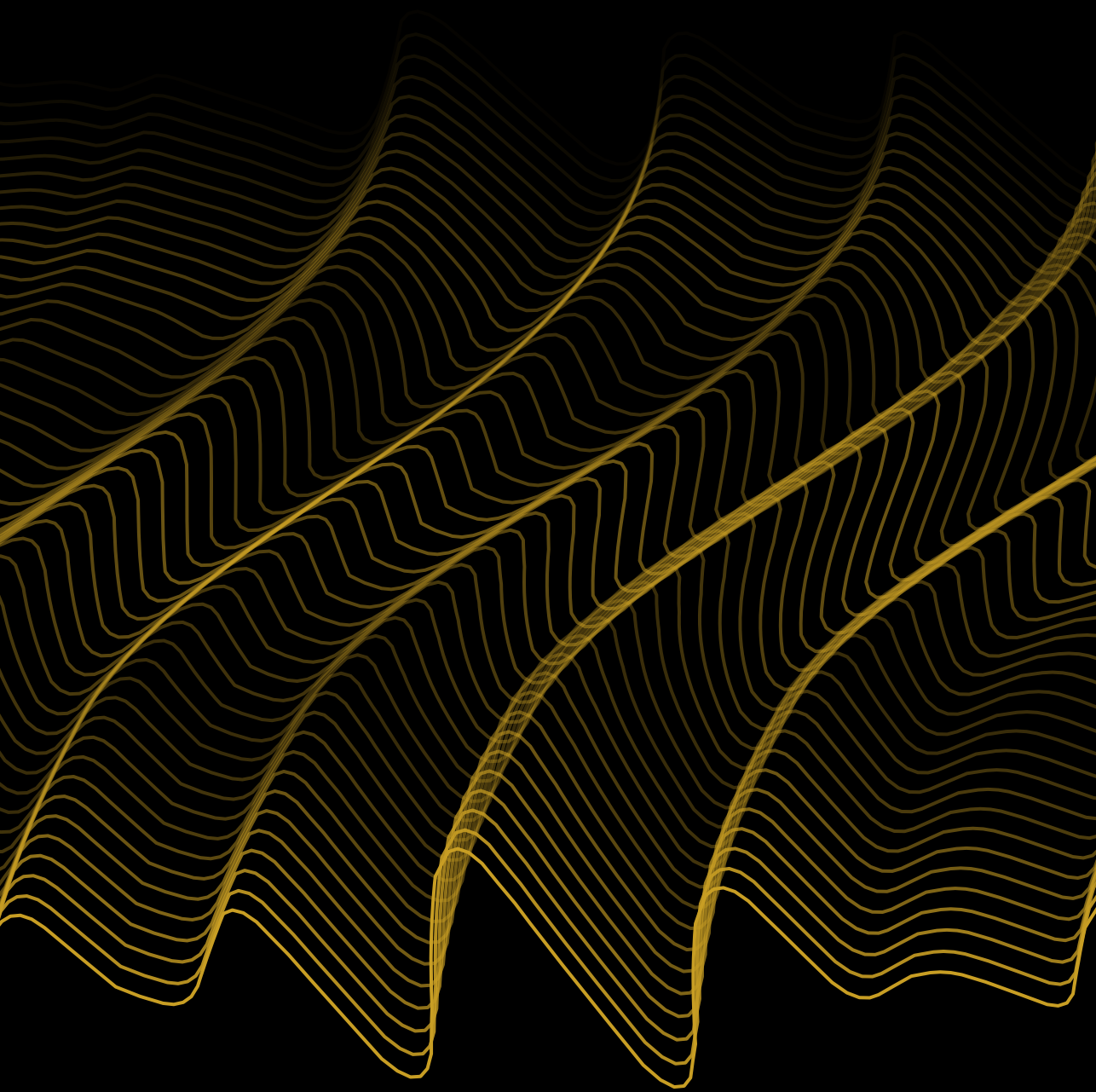
Publication date
2024

Document Version
Final published version

The Anatomy of Excitement

Understanding and improving the effectiveness of electroconvulsive therapy

Freek ten Doesschate



THE ANATOMY OF EXCITEMENT

UNDERSTANDING AND IMPROVING THE EFFECTIVENESS OF ELECTROCONVULSIVE THERAPY

Freek ten Doesschate

COLOFON

ISBN: 978-94-6473-335-8

Printed by Ipskamp Printing | proefschriften.net
Layout and design: Anna Bleeker, persoonlijkproefschrift.nl

The anatomy of excitement

Understanding and improving the effectiveness of electroconvulsive therapy

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. P.P.C.C. Verbeek
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Aula der Universiteit
op vrijdag 19 januari 2024, te 11.00 uur

door Freek ten Doesschate
geboren te NIJMEGEN

Promotiecommissie

Promotor:	prof. dr. G.A. van Wingen	AMC-UvA
Copromotor:	dr. J.A. van Waarde	Rijnstate ziekenhuis
Overige leden:	prof. dr. A.E. Goudriaan	AMC-UvA
	prof. dr. J. Hofmeijer	Universiteit Twente
	dr. L. Oltedal	University of Bergen
	dr. E. Verwijk	Universiteit van Amsterdam
	prof. dr. P.J. Lucassen	Universiteit van Amsterdam

Faculteit der Geneeskunde

INDEX

CHAPTER 1

| Introduction

Major depressive disorder (MDD) is a severe human condition leading to excessive suffering of patients and their relatives (James et al., 2018). Patients show a depressed mood and/or anhedonia for several weeks, months or sometimes years, accompanied by symptoms like severe sleep disturbances, loss of appetite and kilograms of weight lost, concentration and memory problems, low self-esteem, feelings of guilt and suicidal thoughts, and sometimes even suicidal actions (APA, 2010). About 20% of MDD-patients show psychotic features, which means that they have lost some degree of contact with reality due to delusional thoughts and sometimes hallucinations (Ohayon & Schatzberg, 2002). Because patients and their relatives may suffer intensely, there is a great urge to find adequate diagnostic tools and optimal treatments for MDD to reduce the burden, to improve the quality of life and to save lives.

Etiology of MDD. The mechanisms to explain the manifestations of MDD are not yet fully unraveled. For the individual patient, MDD can often be understood as biological as well as psychological derailments, as a result of complex interactions between current stressful events, adverse past experiences, and an inherited susceptibility for depression. Although the specific causes and conditions that precede depressive symptoms may be unique at the individual level, there does seem to be a commonality. That is, a large percentage of the human population has the capacity to react to adverse life conditions with depressive symptoms. Many attempts have been made to explain the phenomenon of depression, hypothesizing interplays with neurobiological factors (e.g., disturbed hormones, depleted neurotransmitters, neuroinflammation, altered brain networks), psychological factors (e.g., cognitive behavioral theory, psychoanalytical theory), and social factors (e.g., low socio-economic circumstances, relational problems). However, none of these mechanisms is conclusive. The manifestation, course and cessation of MDD is probably best explained by complex interactions between these domains.

Treatment of MDD. In clinical practice, treatment of MDD is often challenging because about one third of patients will not benefit the regular treatments with psychotherapy and psychopharmacology (Rush et al., 2006). In these treatment-resistant patients, electroconvulsive therapy (ECT) is a safe and effective treatment option (the UK ECT Review Group, 2003). ECT is a biological treatment in which the patients' brain is excited with electrical current, resulting in self-limiting seizure activity. In MDD-patients treated with ECT, meta-analyses show remission rates around 51%, and even higher up to 59% in the subset of psychotic depressed patients (Van Diermen et al., 2018). However, after initial remission, approximately half of the patients will relapse within two years after ECT (Jelovac et al., 2013). Additionally, a significant part of the ECT-patients will experience cognitive side-effects of varying severity, depending on the type of treatment delivery and other patient specific factors (McClintock et al., 2014). These patients may suffer anterograde and retrograde amnesia from the beginning of the treatment up until a half year after the ECT-course, and in some cases even longer.

Improving effects of ECT. It is clear that there are still major steps to be made to improve the treatment of patients with ECT. Increasing the antidepressant effectiveness and reducing

the degree of cognitive side-effects will be a great improvement in daily practice. This may be achieved by making new modifications to the treatment or by selecting patients that are more likely to benefit from ECT. Moreover, the working mechanisms of ECT are still not clear, as well as mechanisms to explain the (sometimes severe) cognitive side-effects. More insights in these biological mechanisms may improve ECT and may open the door to new treatments. Additionally, knowing these insights may help to inform individual patients and their relatives more properly about the pros' and cons' of this effective treatment.

To introduce the aims of this thesis, I will first provide a short history of ECT regarding its origins and contemporary practice. Next, I propose a taxonomy that provides an overview of ECT research up until now. This taxonomy will divide the field into studies with different objectives, the various approaches to reach these objectives, and the diversity of included measures. The studies in this thesis are placed in this proposed taxonomy. Finally, an outline of this thesis will be given with a summation of my research aims.

1.1 A SHORT HISTORY OF ECT

Since modern psychiatry developed from the beginning of the twentieth century, ECT is one of the oldest and most effective treatments in this field. However, ECT is also one of the most stigmatized treatments in medicine. From the first application of ECT to the present day, this treatment has received scientific interest. In this paragraph, the origins of ECT are described to provide some historic context to the current research and clinical practice regarding ECT, followed by a description of contemporary ECT practice to elucidate some technical aspects that were subject of some studies in this thesis.

1.1.1 ORIGINS OF ECT

In 1938, Ugo Cerletti and Lucio Bini presented ECT as a 'more simple and non-toxic way' to treat patients with severe psychiatric disorders, such as schizophrenia, catatonia and other psychotic disorders (Cerletti, 1938). These Italian clinicians noticed that pigs, who were taken to the slaughterhouse, became calm after a seizure induced by electrical shocks. In that time, it had already been noticed in psychiatric institutions that psychotic patients calmed down after having an epileptic seizure. This clinical phenomenon inspired the Hungarian psychiatrist László Meduna to experiment with inducing seizures by insuline-coma and cardiazol, to relieve psychotic and mood symptoms (Fink, 1984). In that time, patients were often locked up in large institutions without much perspective in life. Therefore, these non-electrical seizure therapies offered new perspectives for patients, although with some serious disadvantages and accidents. ECT - as a new and safer therapy with the use of electricity – appeared to be a substantial improvement in the care for chronically psychotic patients, and it was installed in many psychiatric institutions worldwide. The effects of ECT were often astonishing and severely ill patients were able to leave the institutions and their quality of life (and of their relatives) improved substantially. Since the 1950s, adequate sedation and muscle relaxation

during the ECT-procedure were offered to provide more comfort and safety to patients. In those years, ECT grew in popularity and its use expanded, also in The Netherlands.

Based on increasing amounts of scientific research, after a period of widely expanding use of ECT, the clinical indications for ECT were limited to solely the treatment of severely depressed patients, especially with psychotic and catatonic features. Although in this period, the statistical methods to analyze outcomes of patients were rather primitive, early researchers tried best to investigate ECT with scientific integrity (e.g., by using *sham*-ECT as a placebo condition). However, when the period of anti-psychiatry (1970s and 1980s) occurred and psychopharmacological drugs came on the market, a strong reduction in the use of ECT was seen, also in the Netherlands. Parallel to this, the scientific research regarding ECT was significantly reduced as well.

Since 2000, the use of ECT for pharmacotherapy-resistant depression, psychotic depression and severe suicidality was on the rise again. Use of ECT in the Netherlands, though, is still modest (i.e., only 1.2% of chronically depressed patients were treated with ECT in 2014), possibly because of a lack of knowledge in mental health care providers (Scheepens et al., 2019). Additionally, ECT is still highly stigmatized due to ongoing negative coverage in news media and fiction (McDonald & Walter, 2001). Most famous is the portrayal of ECT in 'One flew over the cuckoo's nest'. This spread of negative, most often false or outdated, information through the media is probably the cause of negative beliefs of ECT in the general population. Patients who received ECT themselves seem to have a much more positive view of the treatment compared to the lay population (Griffiths & O'Neill-Kerr, 2019).

In recent years, more - and more high-quality - research in ECT has been published. These properly performed clinical studies reveal which psychiatric disorders have (most) effectiveness of ECT and provide more basic knowledge regarding possible working mechanisms. Therewith, scientifically founded treatment guidelines are developed and new research programs are initiated.

1.1.2 CONTEMPORARY ECT

During an ECT intervention, a flow of electrical current (with a constant current of 0.9 Ampère, in bidirectional rectangular pulses of 0.25-1 milliseconds duration) is applied for a few seconds to the head of the patient using two electrodes. This is intended to induce seizure activity in the frontal parts of the patients' brain. Seizure activity will only occur when the electrical stimulus exceeds the individual seizure threshold. After evoking generalized seizure activity, which mostly will last for only 30-60 seconds and is seen in the patient as loss of consciousness and rhythmic motor jerks, unexplained negative feedback systems within the brain will actively terminate this seizure activity.

In the Netherlands, mostly two variants of electrode placement are in use, namely the right unilateral (RUL) placement according to d'Elia and the bifrontotemporal (BL) placement. ECT is administered under adequate sedation to prevent the patients' awareness and

distress, and with muscle paralysis to prevent complications (e.g., injuries, bone fractures, hematomas). During the whole procedure, patients are given 100% oxygen by a mask for optimal oxygenation of the body and brain. Also, during the procedure, patients' brain activity is monitored by using two electroencephalographic (EEG) electrodes on the forehead (i.e., Fp1 and Fp2) producing an EEG starting from the electrical stimulus until the end of the procedure.

After the seizure, normal breathing reoccurs and the patient wakes up. Treatment with ECT takes place in courses of several consecutive ECT-sessions, and in the Netherlands these sessions are usually given twice weekly. During the treatment course, concomitant pharmacological treatments (e.g., antidepressants, antipsychotics, benzodiazepines, somatic medications) are often continued. The ECT-course is discontinued when the patients' depression is in remission, or until no further improvement has been seen after two consecutive ECT-sessions, or after ten unsuccessful BL ECT-sessions.

Before and after the ECT-course, the clinical status of patients is often monitored by using standard depression severity rating scales (e.g., Hamilton Depression Rating Scale [HDRS], Montgomery-Åsberg Depression Rating Scale [MADRS]).

In this thesis, several of these described technical aspects of ECT and scores of treatment outcomes are examined in relation to brain characteristics, such as EEG measures and (structural and functional) magnetic resonance imaging (MRI) techniques.

1.2 A TAXONOMY OF ECT RESEARCH

In order to provide some context, and to appreciate the enormous scientifically efforts that have been made to improve ECT in the past and currently, I will first provide a brief overview of the field. Because a complete literature review is well beyond the scope of this Introduction, here I aim to describe some contours of this field by proposing a conceptual taxonomy of the different types of studies in ECT research (Figure 1).

In this taxonomy, one branch of the scientific field of ECT research aims to improve the clinical outcome of ECT (see paragraph 2.1 and Fig. 1a). These studies are then further subdivided into (Fig. 1c) research regarding (technical) ECT modifications and (Fig 1d) research regarding the optimal allocation of treatment with ECT. Finally, studies are further distinguished by the specific measures that are used (i.e., treatment, clinical, or biological measures).

The other branch of this taxonomy contains studies with the objective of improving our understanding of the working mechanisms of ECT (see paragraph 2.2 and Fig. 1b). These studies are further subdivided in (2.2a) research regarding the understanding of ictal effects and (2.2b) regarding the understanding of extra-ictal effects. Again, these studies are further characterized by the specific measures used. In the following paragraphs, we further elaborate on the subfields described by this taxonomy.

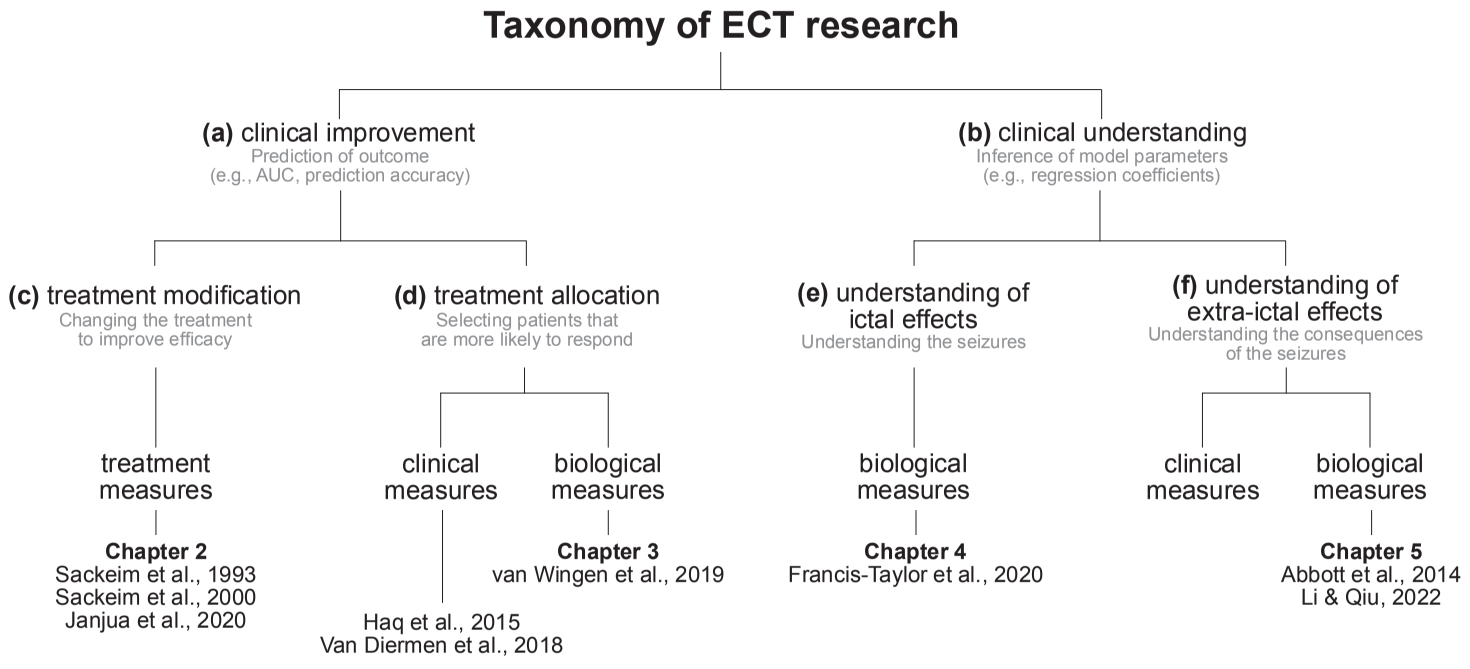


Figure 1. Tree-diagram of the proposed taxonomy regarding current and past research in electroconvulsive therapy (ECT). **(a)** and **(b)** are the main objectives in ECT research. **(c)**, **(d)**, **(e)** and **(f)** are common approaches to achieve the main objectives. Below that are the different types of measure that are typically (or could potentially be) used for these types of studies. The leaves of the tree are case-examples (i.e., reviews, seminal studies and chapters in this thesis [in bold]) of the concerning part of the taxonomy.

1.2.1 IMPROVEMENT OF CLINICAL OUTCOME

Improving treatment outcome entails a greater degree of symptom reduction, faster symptom reduction and/or a reduction of side-effects. The most important and obvious relevancy of improving the clinical outcome is to reduce the burden of patients. However, there are also other benefits of improving clinical outcome. For instance, being able to predict treatment outcome may prevent additional costs to the healthcare system by avoiding unhelpful treatments. Furthermore, the ability to provide a high likelihood for a beneficial outcome for a specific treatment could motivate patients and mental health care providers in the shared decision-making process. In ECT research, studies with the aim to improve clinical outcome (Fig. 1a) typically try to find measures acquired before or during ECT that are associated with improvement after the ECT-course. An important distinction within this line of research is whether the studied measure can be modified within an individual patient.

Research regarding treatment modification. Research on such modifiable measures can guide how ECT is performed in clinical practice (Fig. 1c). The most common modifiable measures are treatment parameters. Studies with this objective often use a randomized controlled trial (RCT) design to test whether modifications to these treatment parameters lead to improved treatment outcomes. For example, the seminal work of Sackeim *et al.* (1993; 2000) showed that modifying the stimulus dose, number of treatments per week and electrode placements may improve clinical outcome. Other treatment modifications to improve clinical ECT-outcome may be treatment additions that alter the patient's state in which ECT is delivered. For instance, altering the pharmacotherapy status (e.g., adding, reducing or discontinuing medications) changes the biological state of the patient, which may affect ECT-outcome (Janjua et al., 2020). Interestingly, non-pharmacological methods (e.g., relaxation methods, mindfulness, music, reactivation of cognitive schemas) that may alter the patient's state just before administering ECT have been largely unexplored.

Research regarding allocation of treatment. Other studies focus on clinical and biological measures that are not (easily) modifiable in treatments of an individual patient (Fig. 1d). For example, ECT-outcome is reliably associated with specific types of illness (Haq et al., 2015; Van Diermen et al., 2018) and with multiple brain measures (van Wingen et al., 2019), which are generally unmodifiable. The aim for studying such measures is typically to improve treatment allocation, i.e., to discover for *whom* ECT does or does not work. By allocating patients to treatments with a higher probability of a good clinical outcome, the number of unsuccessful treatments (and its associated burden and costs) could potentially be reduced. Recent studies that predict ECT-outcome with structural and functional brain measures are good examples of studies in this domain (Redlich et al., 2016; Van Waarde et al., 2015). This line of research dates back to 1950s, when Hobson (Hobson, 1953) aimed to predict ECT-outcome with sixteen clinical variables. Neuroimaging biomarkers of ECT-outcome appeared more recently, with the first reports in 1994 (Malaspina et al., 1994). With respect to prediction by using biomarkers, brain measures are the most common type of predictors studied in the current literature.

Methods in studies improving clinical outcome. Another issue in studying improvement of clinical ECT-outcome is the type of statistical methods that is used. Early studies used methods that yield results on the group-level (e.g., analyses of differences of group averages in biomarkers between 'responders' vs 'non-responders'). Results of such methods are not (easily) transmittable to clinical practice, since group-level results are often uninformative for decisions at the level of individual patients (Simon & Perlis, 2010). Developments in artificial intelligence enabled prediction at the level of an individual patient (e.g., Van Waarde et al., 2015; for a review on machine learning in psychiatry, see Bzdok & Meyer-Lindenberg, 2018). That is, machine learning methods can infer the probability of a particular clinical outcome for an individual patient. Although there are still major challenges in this line of research (e.g., generalizability across treatment sites and confounding factors), this is a leap forward towards biomarker-assisted treatment allocation. We will further elaborate on the use of such methods in ECT research in the *General discussion*.

1.2.2 IMPROVEMENT OF CLINICAL UNDERSTANDING

Besides treatment improvement, another objective of ECT research is improving our clinical understanding of how this treatment works. Studies with this objective aim to gain better understanding of what may cause symptom relief in depressive disorders after ECT. Insights that follow from this line of research could open the door to discovering new treatment targets and modalities, but also could help to reduce the stigma of ECT. Also, the eventual implicit goal of this research is to contribute to improving clinical outcome. However, this objective is not directly addressed in such studies.

As outlined in paragraph 1.1, the discovery of ECT has been largely serendipitous. Although some convincing hypotheses have been developed (Bolwig, 2011), the exact working mechanisms of ECT are still largely unknown. Studies on working mechanisms often compare clinical or biological patient characteristics at different times during treatment (i.e., before, during, directly after, or at follow-up). Here, we make a distinction between studies that examine measures during the ECT-induced seizure (i.e., *the ictal measures*; for a review, see Francis-Taylor et al., 2020) and studies that use measures before/after an ECT-session/course (i.e., *the extra-ictal measures*; for a review, see Abbott et al., 2014; Li & Qiu, 2022). Note that in ECT, the time a patient is actively treated is relatively short; i.e., the electrical stimuli last for 3-8 seconds and the consecutive ECT-induced seizures approximately last for 30-120 seconds, and are on average applied around sixteen times during a treatment course over multiple weeks. This adds up to an average of 8-32 minutes of active treatment (i.e., total seizure duration during an ECT-course). In between the ECT-sessions, no active treatment is necessarily given (although concomitant pharmacological treatments are often used during the course). However, while the active treatment time is short, its effects on depressive symptoms, cognitive side-effects and the brain are often found to be long-lasting (Johanson et al., 2005; Navarro et al., 2004). This line of research aims to understand both the effective mechanisms during active treatment, as well as how the (biological) consequences of treatment relate to clinical outcome.

Research regarding understanding of ictal effects. Research that focuses on ictal measures are most relevant for gaining understanding of how the active treatment phase (i.e., the actual induced seizure activity) is associated with changes in depressive symptoms, cognitive side-effects and brain characteristics. However, the use of ictal measures may also be highly relevant for studying seizure characteristics per se, since ECT is considered a human model for generalized tonic-clonic seizures observed in epilepsy (Pottkämper et al., 2021). In patients, an EEG is (almost) always measured as standard clinical practice during the ECT-procedure. Using modern analysis methods of EEG signals may improve our understanding of these ictal phenomena. The most prominent finding of the existing research using this approach is that greater post-ictal suppression (i.e., sudden inhibition that terminates seizure activity) is associated with better clinical outcome (Francis-Taylor et al., 2020). Additionally, greater EEG power and coherence in slow-wave (delta) frequencies are also associated with a greater antidepressant effect (Perera et al., 2004).

Research regarding understanding extra-ictal effects. Extra-ictal measures are defined as measures gathered before and/or after the ECT-seizure. These are used to study how short- or long-term consequences of ECT on the patients' brains (and bodies) are related to sustained symptom reduction (or absence thereof). Studies in this line of research often try to elucidate the working mechanisms of ECT by relating changes in biological or clinical measures to the effectiveness of ECT. For instance, changes in white matter tracts in the brain after ECT have been associated with clinical outcome (Lyden et al., 2014). Structural and functional changes in the hippocampus have also been related to the antidepressant effectiveness of ECT (Abbott et al., 2014). However, findings in smaller sample sizes may not generalize. That is, recent multi-center studies were not able to show significant associations between brain structure or function with ECT-outcome (Van de Mortel et al., 2022; Ousdal et al., 2021; Oltedal et al., 2018).

Methods in studies improving clinical understanding. Regarding the statistical modeling, studies with the objective to understand working mechanisms often rely on interpreting specific model parameters. That is, studies with the aim of improving outcome (see paragraph 2.1) often rely on the performance of a model on prediction out-of-sample cases. In contrast, studies on working mechanisms fit a statistical model to the data and subsequently infer conclusions based on specific parameters within this model. Very common examples are the beta-values in a linear regression model, which are interpreted as the linear association between an independent and the dependent variable (e.g., brain area volume and ECT effectiveness). However, models may be much more complicated than this, and customized models can be constructed for specific research questions. One promising approach to construct better suited statistical models for these types of studies is Bayesian modeling (see Chapter 5 for an example). This approach allows very flexible model construction and incorporating prior knowledge (e.g., from experts or earlier studies) into the used model (Wagenmakers et al., 2018). We will elaborate further on this topic in Chapter 5 and the *General discussion*.

General remarks on the taxonomy of ECT research. While the proposed taxonomy of ECT research may provide some overview over the vast scientific field, it is important to note that the subdivisions of this taxonomy are merely conceptual. In practice, the primary objectives, approaches and measures used in ECT studies often overlap. For instance, studies on outcome prediction using biomarkers may provide considerable understanding of working mechanisms of ECT. Vice versa, studies on underlying treatment mechanisms may indirectly aim to improve ECT effectiveness. Additionally, we mainly cite studies here that examined clinical improvement defined as relief from depressive symptoms. Studies on improving or understanding cognitive side-effects are relatively scarce, probably due to the difficulty of reliably measuring this type of side-effects. However, this line of research is of critical importance and is developing quickly at the moment. Additional motivations of ECT studies not explicitly mentioned here could be to reduce the anxiety in patients (and their significant others, as well as mental health caregivers) and stigma regarding this treatment option. Lastly, ECT research may increase our understanding of the treated underlying conditions (e.g., depression subtypes, psychotic features, motor features).

To conclude, multiple routes can be taken to achieve the most common objectives of ECT research, i.e., to improve ECT-outcome and to gain better understanding of the working mechanisms of ECT.

1.3 AIMS AND OUTLINE OF THIS THESIS

In this thesis, I present several studies that may serve as case-examples of existing and novel methods applied in ECT research. These studies can be roughly placed within my taxonomy of ECT research (see Figure 1), contributing to treatment modification, treatment allocation, understanding of ictal effects and understanding of extra-ictal effects, respectively.

The studies are presented in the subsequent chapters. In Chapter 2, I present the results of our randomized clinical trial in ECT-patients. With the aim of improving the antidepressant efficacy of ECT, a memory reactivation intervention was tested versus a placebo condition. The intervention supposed to activate memories that are central to the core schemas associated with depression. By reactivating these just before an ECT-induced seizure, I aimed to disrupt reconsolidation of these memories, thereby weakening the depressive schema. I expected this new method would result in improved clinical outcome. In Chapter 3, I used retrospective data to test whether pre-treatment volumes of the amygdala and hippocampus were associated with the clinical outcome of ECT. Additionally, I used leave-one-out cross validation to test whether the brain volumes of these respective regions also would predict outcome on the individual level. The goal of this study was to improve clinical outcome by uncovering pre-treatment biomarkers of ECT outcome. In Chapter 4, I studied measures acquired during the ECT-induced seizure itself. To gain more insight in the role of seizure phenomena in the working mechanism of ECT, I explored how ictal EEG coherence between the frontal poles was associated with ECT effectiveness. In particular, I tested whether changes in ictal coherence occurred over the course of treatment, and whether longitudinal effects were related to

outcome. Next, I studied the effects of ECT on effective connectivity in Chapter 5. Measures of effective connectivity provide insight in the direction of functional brain connectivity. That is, how region A affects region B and vice versa, instead of bidirectional connectivity which is typically studied using correlation-based connectivity analyses. Using this method, I aimed to provide novel insights into the functional brain mechanisms that underlie ECT effectiveness. In Chapter 6, I summarize the main findings of this thesis. Finally, in Chapter 7, these results are discussed. Also, I explore common themes between findings in the separate chapters and integrate my findings with previous research, and I discuss methodological limitation and future directions.

CHAPTER 2

Effectiveness of Emotional Memory Reactivation vs Control Memory Reactivation Before Electroconvulsive Therapy in Adult Patients With Depressive Disorder: A Randomized Clinical Trial

Scheepens DS, van Waarde JA, ten Doesschate F, Westra M, Kroes MCW, Schene AH, Bockting CLH, Schoevers RA, Denys DAJP, Ruhé HG, van Wingen GA

Published in: JAMA Network Open. 2020;3(8):e2012389. doi:10.1001/jamanetworkopen.2020.12389

ABSTRACT

IMPORTANCE

Although electroconvulsive therapy (ECT) is often effective, approximately half of patients with depression undergoing ECT do not benefit sufficiently, and relapse rates are high. ECT sessions have been shown to weaken reactivated memories. The effect of emotional memory retrieval on cognitive schemas remains unknown.

OBJECTIVE

To assess whether emotional memory retrieval just before patients receive ECT sessions weakens underlying cognitive schemas, improves ECT effectiveness, increases ECT response, and reduces relapse rates.

DESIGN, SETTING, AND PARTICIPANTS

In this multicenter randomized clinical trial conducted from 2014 to 2018 in the departments of psychiatry in 3 hospitals in the Netherlands, 72 participants were randomized 1:1 to 2 parallel groups to receive either emotional memory reactivation (EMR-ECT) or control memory reactivation (CMR-ECT) interventions before ECT sessions. The Hamilton Depression Rating Scale (HDRS [total score range: 0-52, with 0-7 indicating no depression and ≥24 indicating severe depression]) was used to measure symptoms of depression during and after ECT, with a 6-month follow-up period. Participants were between ages 18 and 70 years with a primary diagnosis of unipolar major depressive disorder (MDD) according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) and in whom ECT was indicated. Data analysis was performed from July to November 2019.

INTERVENTIONS

EMR-ECT or CMR-ECT interventions prior to ECT sessions.

MAIN OUTCOMES AND MEASURES

Depression scores and relapse rates within 6 months were assessed with the HDRS and analyzed using logistic and linear multiple regression analyses.

RESULTS

A total of 66 patients (mean [SD] age, 49.3 [12.3] years; 39 [59.1%] women) were randomized to the EMR-ECT group (n = 32) or the CMR-ECT group (n = 34). Regardless of the memory intervention, 42.4% (28 of 66) of patients responded (≥50% decrease of symptom severity on the HDRS). Of patients who responded, 39.3% (11 of 28) relapsed within 6 months. Remission rates (CMR-ECT group, 29.4% [10 of 34] vs EMR-ECT group, 25.0% [8 of 32]; $P = .58$), mean (SD) HDRS scores after the ECT course (CMR-ECT group, 14.6 [8.6] vs EMR-ECT group, 14.9 [8.8]; $P = .88$), total mean (SD) number of required ECT sessions for response (CMR-ECT group, 14.9 [7.9] vs EMR-ECT group, 15.6 [7.3]; $P = .39$), and relapse rates (CMR-ECT group, 46.7% [7 of 15] vs EMR-ECT group, 30.8% [4 of 13]; $P = .33$) were not significantly altered by the intervention.

CONCLUSIONS AND RELEVANCE

Study findings suggest that the EMR-ECT intervention just before patient receipt of ECT for depression did not improve effectiveness, increase speed of response, or reduce relapse rates after the ECT course compared with patients receiving CMR-ECT.

INTRODUCTION

Major depressive disorder (MDD) is a common mental disorder associated with substantial reductions in daily functioning. Initial treatment for MDD consists of psychotherapy and/or pharmacotherapy. A 2010 study reported that, even after receiving 4 different pharmacotherapeutic interventions, more than half of patients with depression do not recover (Pigott et al., 2010). Electroconvulsive therapy (ECT) has been reported to be beneficial in patients with MDD resistant to pharmacologic treatment (The, 2003), although half of the patients undergoing ECT will not achieve full remission (Heijnen et al., 2010). Moreover, relapse rates after successful ECT are high, as one-third of patients can be expected to relapse within 6 months (Sackeim et al., 2001). More effective targeting of specific underlying psychopathological mechanisms of MDD may help improve ECT effectiveness, be associated with more rapid ECT response times, and decrease relapse rates after successful ECT.

Cognitive schemas are relatively stable thought representations of prior knowledge and experiences. Cognitive theory holds that activated negative schemas play an important etiologic role in MDD, as activated negative schemas may be factors in information processing (Beck & Clark, 2015). Weakening of negative schemas and change from maladaptive to more adaptive schema processing have been hypothesized to underlie recovery of patients from MDD, but weakening may also lower the relapse rate after cognitive behavioral therapy (Beck & Clark, 2015; Bockting et al., 2015). Cognitive schemas are embedded in strong associative memory structures (Ghosh & Gilboa, 2014).

Research indicates that when memories are reactivated they may become temporarily labile and require restabilization processes to be maintained, a process known as reconsolidation. Pharmacologic interventions that disrupt the restabilization processes may selectively weaken the reactivated memory (Nader & Einarsson, 2010). Studies in the 1960s and 1970s reported that electroconvulsive treatment disrupted reactivated memories in rats (Misanin et al., 1968) and that reactivation of obsessive-compulsive symptoms in patients before applying ECT increased effectiveness (Rubin, 1976). In a 2014 study (Kroes et al., 2014), a single ECT session selectively impaired memory for a learned emotional story when reactivated just prior to an ECT session. If a single ECT session could weaken memory, multiple emotional memory reactivations (EMRs) in consecutive ECT sessions may improve ECT effectiveness, be associated with more rapid ECT response times, and reduce relapse rates after successful ECT.

In this randomized clinical trial (RCT), patients with MDD were randomized to receive either an autobiographical EMR or a control memory reactivation (CMR) not associated with the patients' depression just before each ECT session (EMR-ECT and CMR-ECT, respectively). We hypothesized that reactivation of patients' own emotional memories related to MDD just before receipt of ECT sessions may weaken their associated negative cognitive schemas, resulting in (1) higher remission rates and lower depression severity scores after the ECT course, (2) fewer required ECT sessions to reach a response, and (3) lower relapse rates within 6 months of the ECT course.

METHODS

STUDY SITES AND PARTICIPANTS

Patients in this multicenter study were recruited from the department of psychiatry from 3 hospitals in the Netherlands (Rijnstate Hospital, Arnhem; Amsterdam University Medical Center, Amsterdam; and University Medical Center Groningen, Groningen) from 2014 to 2018. Eligible participants were patients aged between 18 and 70 years primarily diagnosed with unipolar MDD, fulfilling all criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) (*DSM-IV-TR) (A. P. Association, 2010)*, for whom ECT was indicated. All patients had a history of insufficient response to previous treatments (pharmacotherapy and psychotherapeutic interventions), which is the primary indication for ECT in the Netherlands (Jeroen A van Waarde, van Oudheusden, Verwey, et al., 2013). Patients were willing and able to understand, to participate, and to comply with the study requirements. Exclusion criteria were the presence of psychotic features (owing to the possibility that psychotic features might worsen because of the cognitive intervention itself); bipolar disorder; schizophrenia or other primarily psychotic disorders; substance abuse; and other cognitive disorders. Psychiatric diagnoses were classified according to *DSM-IV-TR* criteria using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998)s. Participants received compensation (€40) when they completed the study. The study protocol was approved by the Medical Ethical Committee of the Amsterdam University Medical Center and registered in the Dutch Trial Register (NL4289). All patients provided written informed consent, and all procedures were carried out in accordance with the tenets of the Declaration of Helsinki (W. M. Association, 2013). This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for RCTs. The trial protocol is available in **Supplement 1**.

RANDOMIZATION AND DESIGN

Participants were randomly assigned 1:1 to 2 parallel groups, EMR-ECT or CMR-ECT, by means of a predefined randomization list, stratified for each treatment center, using blocks of 4 to ensure equal group sizes. Concealment of randomization was maintained by access to randomization lists only by study investigators who were not directly treating or assessing eligible patients. The ECT teams and clinical outcome assessors were all blinded to randomization.

Power calculation indicated a total sample size of 98 patients to detect a medium effect size (25% higher remission rate, assuming a 42% base rate in a previous trial13) with 80% power at 1-tailed α of .05. The RCT continued after an interim analysis with 38 patients that was able to detect a statistical trend ($P = .10$) with 80% power. Critical z values with O'Brien-Fleming correction were 3.11 for the interim analysis and 1.97 for the final analysis. The RCT was terminated prematurely after including 72 patients, as inclusion decreased substantially because of a change in the Dutch mental health care policy. The power to detect the same effect size (25% higher remission rate) had decreased to 69%, but the RCT still had 80% power to detect a 29% higher remission rate.

INTERVENTION

In patients receiving EMR-ECT treatment, autobiographical memories associated with maladaptive schemas were identified and reactivated according to a standardized protocol. First, an experienced psychologist, in collaboration with the patient, determined which memories to activate. Recurring maladaptive schema thoughts were identified using the Automatic Thoughts Questionnaire-Revised (Raes & Hermans, 2011). Subsequently, patients selected 6 maladaptive thoughts most central to their current depressive episode. These 6 thoughts were narrowed to 3 by determining which thoughts were most closely related to autobiographical episodes. These autobiographical episodes were then written down in short narratives as vividly as possible (ie, events written as detailed as possible including feelings, thoughts, sensory modalities, and involvement of other people).

During the ECT course, the assigned memory reactivation intervention was applied in the waiting room where the patients were prepared for ECT. In the EMR-ECT group at approximately 10 minutes before application of the ECT stimulus, a research assistant reactivated the autobiographical episode by reading 1 of the narratives slowly and carefully, providing the patient time to recall memory in detail and lasting approximately 3 minutes. Only 1 autobiographical memory was reactivated per ECT session, alternating between the 3 selected narratives.

In the CMR-ECT group, an identical procedure was followed. Instead of autobiographical EMR, the research assistant applied a 3-minute control memory intervention that was related to the importance of sleep, physical exercise, and substance use in mental health. After that process, patients received ECT sessions according to Dutch national ECT guidelines (Van den Broek et al., 2010; Jeroen A van Waarde, van Oudheusden, Verwey, et al., 2013).

PSYCHOMETRIC INSTRUMENTS

Patients were evaluated before the start of the ECT course; after 6, 12, and 18 ECT sessions; and within 2 weeks after the last ECT session. Follow-up evaluations were done at 1, 2, 4, and 6 months. At each evaluation, the Hamilton Depression Rating Scale (HDRS [total score range: 0-52, with 0-7 indicating no depression and ≥24 indicating severe depression]) was used to measure depressive symptomatology by trained research nurses blinded for treatment randomization (Hamilton, 1960; Jonghe, 1994). The HDRS is a valid observer-rated instrument consisting of 17 items with a maximum score of 52 (mean weighted sum score interrater coefficient: $\kappa = 0.92$) (Kupka et al., 1996). Remission was defined as an HDRS score less than or equal to 7, response as a 50% or more reduction in HDRS score after the ECT course compared with baseline (Frank et al., 1991), and relapse as an increase of 10 or more HDRS points on at least 1 assessment in the 1- to 6-month follow-up period.

To quantify treatment resistance at baseline, we sued the Dutch Measure for Quantification of Treatment Resistance in Depression (DM-TRD), which consists of 11 items with a maximum score of 27 and has good psychometric properties and predictive validity (Peeters et al., 2016). In addition, the Dutch version of the national adult reading test was used as a proxy for IQ.

ELECTROCONVULSIVE THERAPY

After intravenous induction of anesthesia with etomidate (0.2 mg/kg body mass), muscle paralysis with succinylcholine (0.5-1 mg/kg body mass), and application of appropriate oxygenation (100% oxygen, positive pressure) until the resumption of spontaneous respiration, ECT was administered using a constant-current (0.9 A), brief-pulse (0.5 milliseconds) device (Thymatron IV; Somatics Incorporation). Lithium was tapered before starting the ECT course; other concomitant medications were kept constant. ECT sessions were performed twice a week. Patients started with 6 right unilateral (RUL) ECT sessions unless clinicians decided to start with bifrontotemporal (BL) electrode placement because of severe clinical conditions or previous effective BL-ECT. During the first session, the seizure threshold was estimated by an internationally accepted, empirical, age-adjusted titration method, and the personalized dose was estimated as 6 or 2.5 times standard treatment for RUL or BL-ECT, respectively.13 ECT courses were discontinued when remission was achieved (HDRS score ≤7) or when no further improvement was observed over a period of 2 weeks. The total number of administered ECT sessions was registered for each patient.

STATISTICAL ANALYSIS

Baseline characteristics between both groups were analyzed using 2-sample *t* tests, $\chi 2$ tests, or Mann-Whitney tests as appropriate. For the whole study group, differences in HDRS scores before and after the ECT course were analyzed using a paired *t* test, and response and remission rates were calculated as percentages.

To investigate the relapse rates within 6 months, logistic and linear multiple regression analyses were used, with remission status (logistic) or HDRS score after the ECT course (linear) used as the dependent variable, and the intervention (EMR-ECT or CMR-ECT) as the predictor variable, with sex, age, baseline HDRS score, final electrode placement, and treatment site as covariates. This approach was different from the original analysis plan that consisted of testing only remission rates.

To explore the secondary outcomes (number of required ECT sessions to reach response and relapse rate), linear (number of ECT sessions) and logistic (relapse rate) multiple regression analyses were conducted in the patients showing response to ECT (n = 28). The number of required ECT sessions was square root transformed to reduce skewness. Because time to relapse was not recorded accurately for the intended survival analysis, we analyzed the relapse rate. In the models, the intervention was entered as the predictor variable, and sex, age, HDRS score before (number of ECT sessions) or after (relapse rate) the ECT course, final electrode placement, and treatment site were entered as covariates. All analyses were conducted using SPSS statistical software, version 25 (IBM Corp), and $P < .05$ denoted statistical significance. Data analysis was performed from July to November 2019.

RESULTS

During the study period, 72 patients were randomized. Six patients dropped out: 3 patients with anxiety about the ECT session requested not to be contacted further just before the ECT sessions, 2 patients discontinued ECT because of non–ECT related medical conditions, and 1 patient disclosed severe benzodiazepine addiction. Therefore, 66 patients (mean [SD] age, 49.3 [12.3] years; 39 [59.1%] women) were included in the final analyses (**Figure 1**). No differences appeared in age, sex, IQ, DM-TRD, and HDRS score at baseline between patients receiving EMR-ECT (n = 32) and patients receiving CMR-ECT (n = 34) (**Table 1**). Regardless of the memory intervention, the mean post-ECT HDRS score improved significantly ($t65 = 8.1$; $P < .01$; Cohen $dz = 1.00$). Twenty-eight of 66 patients (42.4%) showed response and 18 of 66 (27.3%) remission, which was lower than expected13 (**Table 2**).

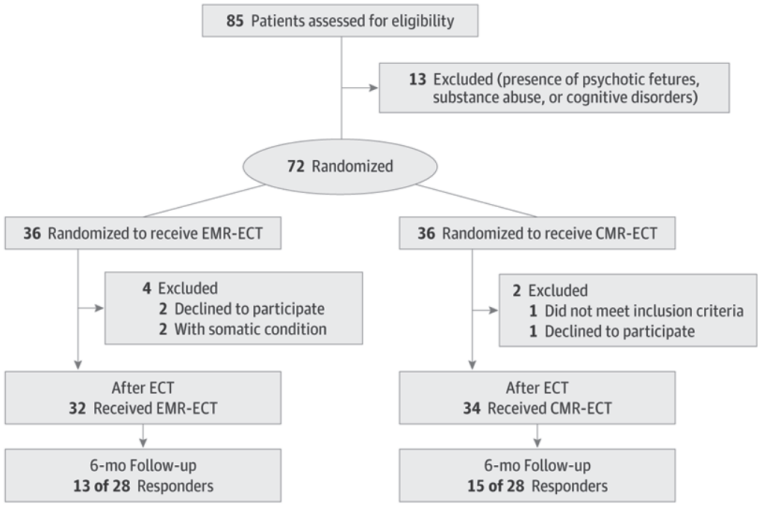


Figure 1. Patient flow diagram. CMR-ECT indicates control memory reactivation ECT; ECT, electroconvulsive therapy; and EMR-ECT, emotional memory reactivation ECT.

	Mean (SD)			
Patient characteristics	**Total sample**	**EMR-ECT**	**CMR-ECT**	**P-value**
No (%)	66 (100)	32 (48)	34 (52)	
Age	49.3 (12.3)	49.6 (11.4)	48.9 (13.2)	.78[a]
Female sex, No (%)	39 (59.1)	20 (62.5)	19 (55.9)	.59[b]
IQ	99.7 (15.9)	98.7 (14.4)	100.8 (16.6)	.62[a]
DM-TRD	15.0 (2.8)	15.1 (3.0)	14.8 (2.7)	.65[a]
HRSD score at baseline	24.9 (6.0)	26.0 (5.9)	23.9 (5.9)	.15[a]

Table 1. Patient characteristics
Abbreviations: CMR-ECT, control memory reactivation ECT; DM-TRD, Dutch Measure for quantification of Treatment Resistant Depression; ECT, electroconvulsive therapy; EMR-ECT, emotional memory reactivation ECT; HDRS, Hamilton Depression Rating Scale (total score range: 0-52, with 0-7 indicating no depression and ≥24 indicating severe depression).
[a] Two-sample t-test
[b] Chi-squared test.

	No. (%)			
Variable	**Total sample**	**EMR-ECT**	**CMR-ECT**	***P* Value[a]**
No (%)	66 (100)	32 (48)	34 (52)	
Outcome				
HDRS score after ECT course, mean (SD)	14.8 (8.6)	14.9 (8.8)	14.6 (8.6)	.89[b]
Response rate (N = 66)[c]	28 (42.4)	13 (40.6)	15 (44.1)	.77[d]
Remission rate (N = 66)	18 (27.3)	8 (25.0)	10 (29.4)	.69[d]
Relapse rate (N = 28)	11 (39.3)	4 (30.8)	7 (46.7)	.39[d]
Dropout from study (N = 72)	6 (8.3)	4 (11.1)	2 (5.5)	.39[d]
Treatment characteristic				
Final electrode placing is RUL	42 (63.6)	19 (59.4)	23 (67.6)	.49[d]
Total necessary ECT sessions during the course, mean (SD)	15.2 (7.5)	15.6 (7.3)	14.9 (7.9)	.71[e]

Table 2. Outcome and Treatment Characteristics for EMR-ECT and CMR-ECT
Abbreviations: CMR-ECT, control memory reactivation ECT; ECT, electroconvulsive therapy; EMR-ECT, emotional memory reactivation ECT; HDRS, Hamilton Depression Rating Scale (total score range: 0-52, with 0-7 indicating no depression and ≥24 indicating severe depression); RUL, right unilateral ECT.
[a] The *P* values are not corrected for covariates and therefore differ from the *P* values from the multiple regression analysis in the results.
[b] Two-sample t test
[c] Responders to ECT showed 50% or more decrease of symptom severity on the HDRS, and remitters showed an HDRS score of 7 or less after the ECT course.
[d] Chi-squared test.
[e] Mann-Whitney test.

Logistic regression analysis showed no significant effect of the memory intervention on remission rate (CMR-ECT group, 29.4% [10 of 34] vs EMR-ECT group, 25.0% [8 of 32]; β = 0.33; *P* = .58; odds ratio, 1.39). Linear regression analysis showed no significant effect of the memory intervention on post-ECT HDRS scores (CMR-ECT group, 14.6 [8.6] vs EMR-ECT group, 14.9 [8.8]; β = 0.02; *P* = .88; semipartial $r2 < 0.01$) (**Figure 2**).

Linear regression analysis showed no significant association between the memory intervention and the required total amount of ECT sessions to reach response (n = 28; CMR-ECT group, 14.9 [7.9] vs EMR-ECT group, 15.6 [7.3]; β = 0.14; *P* = .39; semipartial $r2 = 0.02$), although the covariate final electrode placement (β = 0.41; *P* = .02; semipartial $r2 = 0.12$) was significant. As expected, patients treated with BL required more ECT sessions than patients treated only with RUL, as most patients receiving BL initially received RUL-ECT as well.

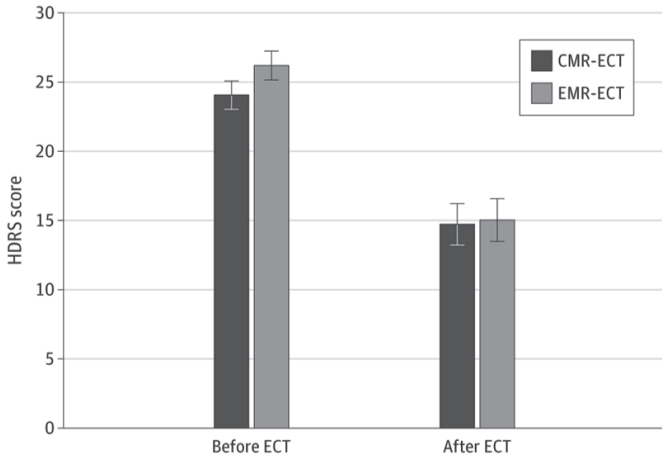


Figure 2. Hamilton Depression Rating Scale (HDRS) Score Before and After Electroconvulsive Therapy (ECT)

Twenty-eight patients showed response and 11 of those (39.3%) relapsed within 6 months. In ECT responders in the separate intervention groups, 4 of 13 patients (30.8%) receiving EMR-ECT relapsed and 7 of 15 patients (46.7%) receiving CMR-ECT relapsed. Logistic regression analysis showed no significant effect of the intervention on relapse rates within 6 months (β = 0.93; *P* = .33; odds ratio = 2.53).

DISCUSSION

In this RCT, reactivation of personalized emotional memories just prior to ECT sessions showed no better ECT outcome than a control intervention. The memory intervention neither increased the rate of the ECT response nor reduced the relapse rate within the 6-month follow-up. We aimed to translate laboratory research into our clinical MDD treatment program (Köhler et al., 2015). Therefore, as the EMR intervention was based on reconsolidation theory and only 1 ECT session already showed weakened memories in a previous clinical study (Kroes et al.,

2014), our findings were not as expected. However, several lessons may be learned from this RCT that, to our knowledge, was the first of its kind.

We attempted to weaken emotional memories with regular ECT sessions by disrupting the reconsolidation process of reactivated personalized emotional cognitive schemas. This attempt may have failed because older emotional memories were too resistant to change. Cognitive schemas underlying MDD are expected to be formed in the adolescent period. Therefore, the age and strength of these memories may have reduced the ability of our reactivation cues to induce destabilization of the very old underlying memories (Suzuki et al., 2004; Zhang et al., 2018)s. Furthermore, memories are redundantly encoded, which means that a minor disturbance does not impair its representation. However, a study from 1976 suggested that acting out obsessive-compulsive symptoms just before unmodified ECT sessions might help improve results for patients (Rubin, 1976). Administration of ECT without anesthesia is now considered unethical. But based on these results (Rubin, 1976) and insights from reconsolidation theory (Kroes et al., 2014), we considered an EMR intervention in patients undergoing ECT to be worth investigating, as new approaches are needed to further improve ECT efficacy and prevent relapse.

The type of memory that was reactivated may not have been sensitive to modulation by our chosen memory intervention. Most earlier studies on the reconsolidation theory examined pavlovian responses, but only a few studied the effect of disruption of episodic memory (Kroes et al., 2014). In our study, even forms of semantic memory were targeted, which may possibly be more rigid to modulation. Further studies are needed to examine which types of memory have utility in treatment of MDD and can be modulated.

In addition to the type of reactivated memory, the reactivation cues used in our study may not have been suitable to reactivate the underlying emotional cognitive schemas. The reactions of most patients, however, indicated that the personalized emotional memory script triggered strong emotions. Theoretically, these strong emotions could trigger negative schemas, but it was not possible to ascertain whether this mechanism actually occurred in the patients receiving EMR-ECT. Included patients had difficulty in identifying their negative schemas (eg, they overgeneralized their negative memories). Therefore, it was decided to use detailed memories, including negative emotions and cognitions, instead of more abstract underlying negative cognitive schemas. It is possible that limited destabilization of such intended abstract schemas decreased the effect of our memory intervention.

A 2017 study (Lee et al., 2017) showed that new learning might be necessary for reconsolidation to occur. As we reactivated only old memories and did not enforce new learning, destabilization of bad memories was not provoked. In future studies, other personalized cues may be invented in which the aspect of new learning for patients is taken into account. At such time, reactivation of underlying negative schemas just before an ECT session may be more beneficial.

The procedure of administering the reminders may have affected our results. In line with a rodent study, our memory reactivation paradigm was 3 to 5 minutes (Bustos et al., 2009). Other studies, however, suggest that this duration may have been too long (Eisenberg et al., 2003; Kroes et al., 2014; Lee et al., 2006; Suzuki et al., 2004). Conversely, this duration may have been too short, as a reminder duration of 10 to 30 minutes was recently found to be effective for posttraumatic stress disorder (Brunet et al., 2018). In addition, the reactivation procedure took place approximately 10 minutes before the actual ECT session so as to blind the treating physicians and to perform ECT according to regular practice. However, this delay may have been too long, as Kroes et al. (Kroes et al., 2014) reactivated the memory within a few minutes before induction of anesthesia.

In this study, the memory intervention was well tolerated by patients, and the overall dropout rate was low, suggesting similar interventions are feasible. Given the possible lessons of our RCT, future studies may consider (1) reactivation of more recent memories; (2) creation of more appropriate reminders (eg, newly learned regarding the episodic memory); (3) use of reminders of a different duration; and (4) use of a shorter duration between reactivation of the reminder and the ECT stimulus (eg, 1-5 minutes before induction of anesthesia).

LIMITATIONS

This study has limitations. From a methods standpoint, an important problem was the inability of verifying reactivation of negative memories or schemas in patients. However, our research assistants noticed emotional reactions in patients when listening to their personal negative experiences, which may indicate reactivation of negative memory. Furthermore, the control group received potentially useful psychoeducation that was necessary to maintain patient blinding but that might also have contributed to the antidepressant effects in this group and the null findings. Converesely, this psychoeducation might have been forgotten as well because of the intervention, reducing its antidepressant effects. This possible confounder of an antidepressant effect in the control condition usually affects clinical trials with psychological interventions.

In this RCT, the response rate was lower than expected, limiting the power to detect differences in relapse rates after ECT response; the power to detect differences in relapse rates was reduced at the outset, as this analysis was restricted to treatment responders. Highly selected groups of patients with treatment-resistant MDD may show ECT remission rates of 48% (Heijnen et al., 2010),whereas our 27.3% remission rate was consistent with that of a community sample (Prudic et al., 2004). Moreover, our DM-TRD scores appeared to be much higher than others in treatment-resistant MDD groups (Peeters et al., 2016), and we excluded patients with a higher chance of successful ECT (ie, age >70 years; psychotic depression), which may have contributed to the low remission rate. Conversely, the low response rate could have maximized the probability to show efficacy of the EMR-ECT.

CONCLUSIONS

In this study, personalized reactivation of emotional memories just before ECT sessions for MDD was well tolerated but did not improve ECT efficacy, decrease the time to response,

or reduce the relapse rate. This RCT highlights the difficulties of translating insights from laboratory research into clinical practice and may provide direction for future studies to further improve ECT for patients with severe MDD.

CHAPTER 3

Pre-treatment amygdala volume predicts electroconvulsive therapy response

Freek ten Doesschate, Philip van Eijndhoven, Indira Tendolkar, Guido van Wingen, Jeroen van Waarde

Published in: Frontiers in Psychiatry 2014;26:5;169. doi: 10.3389/fpsyt.2014.00169. ■

ABSTRACT

Background: Electroconvulsive therapy (ECT) is an effective treatment for patients with severe depression. Knowledge on factors predicting therapeutic response may help to identify patients who will benefit most from the intervention. Based on the neuroplasticity hypothesis, volumes of the amygdala and hippocampus are possible candidates for predicting treatment outcome. Therefore, this prospective cohort study examines the predictive value of amygdala and hippocampal volumes for the effectiveness of ECT.

Methods: Prior to ECT, 53 severely unipolar depressed patients [mean age 57 ± 14 years; 40% (*n* = 21) male] received structural magnetic resonance imaging (MRI) at 1.5 T. Normalized amygdala and hippocampal volumes were calculated based on automatic segmentation by FreeSurfer (FS). Regression analyses were used to test if the normalized volumes could predict the response to a course of ECT based on the Montgomery–Åsberg Depression Rating Scale (MADRS) scores.

Results: A larger amygdala volume independently and significantly predicted a lower post-ECT MADRS score ($\beta = -0.347$, $P = 0.013$). The left amygdala volume had greater predictive value for treatment outcome relative to the right amygdala volume. Hippocampal volume had no independent predictive value.

Conclusion: A larger pre-treatment amygdala volume predicted more effective ECT, independent of other known predictors. Almost all patients continued their medication during the study, which might have influenced the course of treatment in ways that were not taken into account.

INTRODUCTION

Electroconvulsive therapy (ECT) is an effective treatment for severely depressed patients (Fink, 2001; Pagnin et al., 2008). ECT is a safe treatment option, however, it is regarded as invasive and some cognitive adverse effects are known (Watts et al., 2011). Although ECT is widely used, factors predicting ECT outcome are largely unknown. Knowledge on such factors might help to identify patients most likely to benefit from the intervention, and allow patients and clinicians to make better-informed decisions about initiating ECT. Several clinical and treatment characteristics were associated with increased response rates to ECT, including the presence of psychotic symptoms (Loo et al., 2011; Petrides et al., 2001), previous response to ECT (Jeroen A van Waarde, van Oudheusden, Heslinga, et al., 2013), higher administered electrical stimulus intensity (Sackeim et al., 1993), bilateral electrode positioning (Sackeim et al., 2000), and higher age (O'Connor et al., 2001).

Structural neuroimaging could potentially be used to determine brain characteristics that predict ECT response, but until now structural MRI characteristics were not well established and showed contradictory results. For example, larger right hippocampal volumes predicted a poorer outcome after a course of ECT (Lekwauwa et al., 2005), whereas another study using visual rating scales to score severity of atrophy, showed that atrophy in the medial temporal lobe (MTL; a part of the brain including hippocampus and amygdala) seemed to be negatively correlated with the response to ECT (Oudega et al., 2010).

The structural volumes of specific brain areas are partly determined by regional neuroplasticity. According to the neuroplasticity hypothesis, knowledge on regional plasticity of specific brain areas gives further insight into the pathophysiology of depression and its treatment. Among other factors, regional neuroplasticity was associated with the level of brain-derived neurotrophic factor (BDNF; i.e., a factor involved in the regulation of neuronal growth) (Thoenen, 1995). Contradicting results show that, within the MTL, both increased and decreased regional brain volumes as well as BDNF levels were associated with severe depression and its treatment by ECT (Taylor, 2008; Yu & Chen, 2011).

Firstly, bidirectional alterations in plasticity of the amygdala, a brain region that bears an important function in emotional memory and fear conditioning (Yu & Chen, 2011), were suggested to be related to depression. Also, patients suffering from depression showed both larger and smaller amygdala volumes relative to healthy controls [for a review, see (Bellani et al., 2011)]. Secondly, depression was associated with relatively small volumes of the hippocampus (Cotter et al., 2001). Moreover, a study using animal models of depression showed that BDNF knock-down in specific sites of the hippocampus resulted in depression-like behavior (Taliaz et al., 2010). The hippocampus is related to the declarative memory system and seems to mediate the more cognitive aspects of depression (e.g., feelings of worthlessness and guilt) (Krishnan & Nestler, 2008).

Emphasizing the involvement of plasticity in the treatment of depression, studies on ECT and electroconvulsive shock (ECS; i.e., an animal model of ECT) showed that repeated ECT/ECS partially reverses the relatively high and low BDNF levels found in the amygdala and hippocampus, respectively, of depressed patients (Altar et al., 2003; Conti et al., 2007; Gersner et al., 2010; Jacobsen & Mørk, 2004; Maigaard et al., 2012; Nibuya et al., 1995). Also, a longitudinal pilot study showed an increase of both amygdala and hippocampal volume due to an ECT course (Tendolkar et al., 2013).

Recapitulating, according to the neuroplasticity hypothesis of depression, the hippocampus, and the amygdala seemed to be important structures in depression and the treatment with ECT. This study investigates whether individual differences in pre-treatment volumes of the amygdala and hippocampus predict the level of depression after a course of ECT.

MATERIALS AND METHODS

PATIENTS

Only severely unipolar depressed patients classified according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR), indicated for ECT at the Rijnstate Hospital (Arnhem, the Netherlands), were selected for this study. Patients were excluded if aged <18 years, if they suffered from bipolar disorder, if there were contraindications for MRI of the brain, and if they dropped out of treatment during the ECT course (Figure 1).

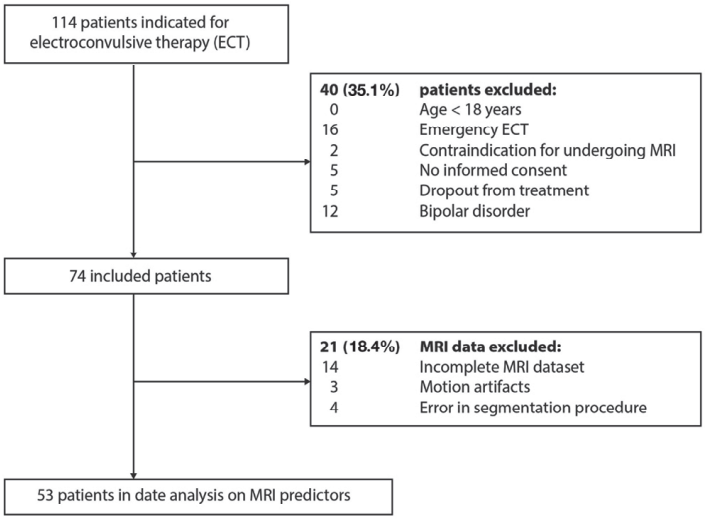


Figure 1. Flow chart of the patient selection process.

The Medical Ethical committee of the hospital approved the research protocol of this study (NL24697.091.09). Characteristics of the patients are described in more detail elsewhere

(Jeroen A van Waarde, van Oudheusden, Verwey, et al., 2013). After receiving full information about the study, written informed consent was obtained from all participants.

INSTRUMENTS

Psychometric instruments

Information on age, sex, psychiatric diagnosis, and previous ECT treatments were derived from the medical records. The severity of depression was determined with the MADRS by a trained research nurse. The MADRS consists of questions in 10 subcategories (Montgomery & Åsberg, 1979), rated 0–6, resulting in a score ranging from 0 to 60 (highest level of severity). Remission was defined as a post-ECT MADRS score of ≤10 points. Clinical raters were blind to the MRI results.

MRI and volumetric analysis

Imaging was performed within 1 week before the first ECT session on a 1.5 T MRI scanner (Philips Medical Instruments, Best, the Netherlands), using an eight-channel SENSE head coil. The scanning protocol included a high resolution T1-weighted (T1W) turbo field echo MRI (sequence parameters: repetition time = 7.6 ms; echo time = 3.5 ms; flip angle = 15°; 145 sagittal slices; voxel size = 1.1 mm isotropic). Prior to analysis, all raw MRI data were visually checked for the presence of (motion) artifacts. Regional volumes were established using the FS automatic subcortical segmentation tool, in which each voxel in the normalized brain volume is assigned one of about 40 labels, including hippocampus and amygdala[1]. Briefly, the processing stream comprises removal of the skull and dura, automated Talaraich transformation, defining the gray–white matter boundary, intensity normalization, and segmentation of subcortical gray matter. We manually corrected the cases where dura was included in the gray matter. The FS application enables automatic labeling of subcortical structures using a probabilistic algorithm. Initially, each image is a rigid body registered to a probabilistic atlas based on manually labeled image. Thereafter, the image is morphed to the atlas by a non-linear transform and a Bayesian segmentation procedure is employed. Each voxel in the MRI volume is automatically assigned to a neuro-anatomical label based on probabilistic information estimated from a manually labeled training set. The labeling procedure is not biased by anatomical variability. The segmentation procedure is based on three types of probabilities to disambiguate labels: first, the likelihood that a given structure occurs at a specific atlas location. Second, the likelihood of the image intensity given the tissue class. Third, the probability that a voxel belongs to a given tissue class based on likelihood of the spatial configuration of labels[2]. For each patient, the total volumes of the amygdala and the hippocampus were normalized by dividing each established volume by the total intracranial volume.

Treatment course and procedure

Electroconvulsive therapy was administered using a constant-current (0.9 A), brief-pulse [0.25 ms in right unilateral ECT (RUL) and 0.5 ms in bifrontotemporal (BL) ECT] device (maximum output 1008 mC; Thymatron IV; Somatics Incorporation, Lake Bluff, IL, USA), after induction

of anesthesia intravenously with etomidate (0.3 mg/kg body mass), muscle paralysis with succinylcholine (0.5–1 mg/kg body mass) intravenously, and with appropriate oxygenation (100% oxygen, positive pressure) until the resumption of spontaneous respiration. Electrode placement was started RUL, except in patients at high risk for suicidality and/or acute somatic complications of the depression, or if previous BL ECT had successfully been administered. Dosage was set at 6-times initial seizure threshold (IST) in RUL ECT and at 2.5-times IST for BL treatment. Patients were treated twice weekly. RUL electrode placement could be changed into BL electrode placement during the ECT course if the patient did not show (enough) improvement after six RUL sessions, based on the clinical decision of experienced psychiatrists. One week before starting ECT, baseline MADRS scores were determined. The course of ECT treatment was terminated when mood had not further improved in the last two ECT sessions, based on the clinical decision of the psychiatrists. Within 1 week after the last ECT session, the post-ECT MADRS score was established.

Statistical Analysis

Data are presented as means ± SD or numbers or percentages when appropriate. The statistical assumptions for the regression analyses were tested in advance. For the assumption of linearity, residuals versus predicted values plot was created and interpreted. The Durbin–Watson and the Shapiro–Wilk test were used to check for violations of independence and normality, respectively.

Regression analyses were used to test if the normalized volumes of hippocampus and amygdala predicted the effectiveness of ECT. Primarily, the post-ECT MADRS score was the dependent variable in regression analyses of covariance. The independent variables were the normalized volumes of the amygdala and hippocampus, adjusted for age, sex, baseline MADRS score, presence of psychotic symptoms, and previous ECT treatment. These last two variables were added because of their known predictive value for ECT effectiveness (Jeroen A van Waarde, van Oudheusden, Verwey, et al., 2013). To assess whether post-ECT MADRS scores could also be predicted for out-of-sample cases, we used cross-validation. We computed the correlation between leave-one-out predicted scores and the observed scores, and tested for a positive association using permutation testing with 1000 randomizations in Matlab (R2014a).

For further confirmation, binary logistic regressions were used to test if the normalized volumes were predictive of the remitted group (post-ECT MADRS score ≤ 10) relative to the non-remitters. In this analysis, remission or not served as the dependent variable, and the normalized volumes as independent variables, adjusted for age, sex, baseline MADRS score, presence of psychotic depression and previous ECT treatment. To examine whether the effect was lateralized, analyses that produced significant effects were repeated separately with the left and right area volumes as independent variables. Additionally, since both BL and RUL electrode placements were applied, the eventual electrode placement (i.e., the electrode placement that was used to complete the treatment) was included as a possible mediator in an analysis of covariance (ANCOVA) in which the same variables were included as in the regression analysis. In all tests, $P < 0.05$ denoted statistical significance; SPSS for Windows (version 20) was used for the analyses.

RESULTS

PATIENT CHARACTERISTICS

The study included 53 severely unipolar depressed patients, with a mean age of 57 ± 14 (SD) years, of which 21 (39.6%) were male. Out of 53 patients, 33 (62.3%) patients used benzodiazepines, 35 (66%) used anti-depressants, 34 (64.2%) used anti-psychotics, and 2 (3.8%) used anti-epileptics. Most patients (94.3%) suffered from longstanding, recurrent depressive disorder, and 16 (30.2%) patients were previously treated with ECT. The mean baseline MADRS score was 36.0 ± 8.1 (SD) points and psychotic symptoms were present in 12 (22.6%) patients (Table 1). The mean number of treatment sessions in a completed ECT course was 18.2 ± 7.4 (SD). At the initial session, 42 patients (79.2%) were treated with RUL ECT. Twenty (37.7%) of these patients switched from RUL to BL treatment, leaving 22 (41.5%) patients who were eventually treated with RUL treatment. After ECT, the mean MADRS score decreased significantly [$t(52) = 13.07$, $P < 0.001$] to a mean score of 13.5 ± 10 (SD). After the ECT course, 26 (49.1%) patients achieved complete remission. The patients who achieved remission did not significantly differ from the non-remitting patients in age ($P = 0.213$), sex ($P = 0.958$), total number of ECT sessions ($P = 0.151$), or use of concomitant medication [i.e., benzodiazepines ($P = 0.227$), anti-depressants ($P = 0.920$), anti-psychotics ($P = 0.344$), and anti-epileptics ($P = 0.172$)]. Also, comparison of the patients that were eventually treated with RUL and BL electrode placement revealed no differences in age ($P = 0.748$), sex ($P = 0.474$), total number of ECT sessions ($P = 0.734$), or use of concomitant medication [i.e., benzodiazepines ($P = 0.464$), anti-depressants ($P = 0.786$), anti-psychotics ($P = 0.227$), and anti-epileptics ($P = 0.233$)].

	Mean ± SD or n (%)
Patient characteristics	
Age (in years)	57.1 ± 14.3
Male gender	21 (39.6)
MADRS score at baseline	36.0 ± 8.1
Presence of psychotic features	16 (30.2)
Previously treated with ECT	12 (22.6)
Total number of sessions	18.2 ± 7.4
Concomitant medication	
Benzodiazepines	33 (62.3)
Anti-depressants	35 (66.0)
Anti-psychotics	34 (64.2)
Anti-epileptics	2 (3.8)
MRI volumes of regions of interest (in mm3)	
Bilateral amygdala	4741 ± 624
Bilateral hippocampus	6711 ± 972

Table 1. Patient and anatomical magnetic resonance imaging (MRI) descriptives at baseline of severely unipolar depressed patients (n = 53) treated with electroconvulsive therapy (ECT).
Abreviations: SD, standard deviation; MADRS, Montgomery–Åsberg Depression Rating Scale.

ECT OUTCOME RELATED TO THE VOLUME OF AMYGDALA AND HIPPOCAMPUS

Adjusted for age, sex, baseline MADRS score, presence of psychotic symptoms, previous ECT course(s), and eventual electrode placement, the linear regression analyses of covariance revealed that the normalized bilateral amygdala volume independently predicted 12.9% of the variance in the post-ECT MADRS score within this specific model. Specifically, a larger pre-ECT normalized amygdala volume predicted a lower post-ECT MADRS score (Figure 2; β = −0.347, $P = 0.013$). Moreover, as expected, the presence of psychotic depression (β = −0.406, $P = 0.014$) and previous ECT treatment(s) (β = −0.344, $P = 0.021$) showed significant predictive values for lower post-ECT MADRS scores. In this model, the normalized bilateral hippocampus volume did not predict the post-ECT MADRS score (β = −0.065, $P = 0.691$).

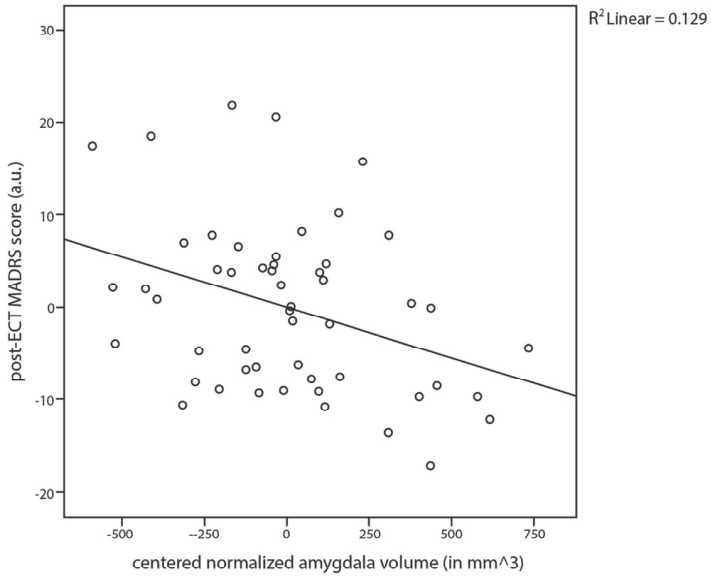


Figure 2. scatter plot and regression line for the post-electroconvulsive therapy (ECT) established montgomery–åsberg depression rating scale (MADRS) scores against the normalized amygdala volume (amygdala volume/intracranial volume).

To assess whether post-ECT MADRS scores could also be predicted for new cases on the basis of bilateral amygdala volume after correction for covariates, we calculated predicted post-ECT MADRS scores using linear regression with leave-one-out cross-validation. The correlation between predicted scores and observed scores approached significance ($r = 0.274$, $P = 0.068$), suggesting that ECT outcome can be predicted by a combination of amygdala volume and clinical variables.

Adjusted for age, sex, baseline MADRS score, presence of psychotic symptoms, previous ECT course(s), and eventual electrode placement, the binary logistic analyses confirmed our results by showing that a larger normalized amygdala volume also predicted remission after ECT ($P = 0.028$).

Identical regression analyses of the normalized left and right amygdala separately revealed a greater effect for the normalized left amygdala ($\beta = -0.346$, $P = 0.013$) compared to the normalized right amygdala ($\beta = -0.245$, $P = 0.080$).

DISCUSSION

This prospective cohort study in severely depressed patients showed that a larger pre-treatment amygdala volume predicted lower post-ECT depressive symptom score and remission after ECT. More specific, a larger left amygdala predicted better outcome of ECT. By contrast, the hippocampal volume had no predictive value for treatment outcome.

A study in elderly patients showed that more MTL atrophy correlated with less response to ECT (Oudega et al., 2010). Because this study determined atrophy on a four-point rating scale by subjective rating of a radiologist, no differentiation between amygdala and hippocampal volume could be made. Our present study showed a correlation between ECT response and pre-ECT amygdala volume and not the hippocampus volume, rather than the MTL as a whole.

Remarkably, we could not replicate a correlation between poorer treatment response and larger pre-ECT hippocampal volume (Lekwauwa et al., 2005). Several factors might have affected this discrepancy in results. For instance, this might be due to the fact that Lekwauwa and colleagues did not adjust for any confounding factors. In our analyses, age ($r = -0.463$, $P < 0.001$), sex ($r = -0.270$, $P = 0.025$), and presence of psychotic features ($r = -0.265$, $P = 0.028$) all showed significant partial correlation with the normalized hippocampal volume. Therefore, one of these factors might have confounded the previously reported correlation between hippocampal volume and ECT response (Lekwauwa et al., 2005).

To assess whether ECT outcome could also be predicted for new cases, we predicted post-ECT depressive symptom scores for individual patients on the basis of data from the rest of the group using leave-one-out cross-validation. The result approached significance and tentatively suggests that the outcome of ECT can be predicted on the basis of a combination of amygdala volume and clinical variables. This result provides further support to our recent report that ECT outcome can be predicted using neuroimaging data (J A Van Waarde et al., 2015). In that study, we analyzed functional and structural MRI data on a voxel-by-voxel basis using machine learning. However, whereas functional MRI data were predictive of ECT outcome, structural MRI data were not. Several methodological differences may have contributed to the differences in results between the current and previous study. First, we defined the amygdala on an anatomical basis and analyzed its volume in isolation in the present study, whereas we analyzed brain morphology across the entire brain on a voxel-by-voxel basis in the previous study. Second, the regression analysis accounted for the influence of clinical variables such as psychosis or previous ECT, whereas our machine learning analysis did not. Third, the required effect size to detect significant effects is different, as we had an *a priori* hypothesis for the amygdala in the current study, whereas we explored effects across the entire brain in the previous

study. Regardless of these differences, both studies suggest that the outcome of ECT can be predicted using neuroimaging data, and future studies may investigate whether combining structural and functional MRI data could provide even better predictions of ECT outcome.

To explain the prediction of a better treatment response by a larger pre-ECT amygdala volume, we will focus on the hypothesized functional role of the amygdala in recovery from depression. A study in medication-naive depressed patients showed that treatment response was dependent on the amygdala retaining its plasticity during the course of illness (Van Eijndhoven et al., 2009). In our present study, although patients suffered mostly from chronic, recurrent depressions, retaining plasticity may still be important in achieving remission after a course of ECT. Moreover, compared to pre-ECT, post-ECT activity was shown to be increased in the mediotemporal lobe (Elizagarate et al., 2001; Mervaala et al., 2001; Vangu et al., 2003), and more specifically in the amygdala (Suwa et al., 2012). At last, other studies showed relatively large mediotemporal lobe volumes (Dukart et al., 2014) and high intra-amygdalar functional amino acids (Michael et al., 2003) specifically in patients that responded positively to ECT. Thus, previous studies have shown that retaining plasticity during the course of illness and large post-ECT volumes of the amygdala correlated with a positive ECT response. We hypothesize that the pre-ECT amygdala volume is related to these findings. That is, a larger pre-ECT amygdala volume might reflect relatively higher levels of retained intra-regional plasticity and it might also facilitate larger post-ECT amygdala volumes. Thus, a large pre-ECT amygdala volume might predict positive ECT response because a larger volume reflects greater capacity for the amygdala to fulfill its functional role in the recovery of depression by ECT, suggested by previous research (Dukart et al., 2014; Michael et al., 2003; Van Eijndhoven et al., 2009). However, the data in the present study was not suited to test this hypothesis, since no post-ECT MRI data was collected.

The present study had some strengths and limitations that should be mentioned. First, the prospective nature of the study diminished the potential sources of bias and confounding factors that were associated with the retrospective design. Furthermore, compared with previous studies, the present sample size was relatively large. On the other hand, almost all patients continued their medication during the study, which might have influenced the course of treatment in ways that were not taken into account. At last, the number of treatment sessions per patient was high relative to other studies [see, for example, Ref. (Bennett et al., 2012)]. This is probably best explained by the high degree of treatment resistance of the patients who are treated with ECT in the Netherlands.

CONCLUSION

In conclusion, in this group of severely, mostly longstanding and recurrent, unipolar depressed patients, a larger amygdala volume predicted a more favorable ECT outcome. Further research, applying several MRI techniques, is needed to replicate these results and extend the findings to other groups of patients and treatments. Clinically, if replicated in other samples, pre-ECT

amygdala volume might help clinicians and patients to better predict treatment response and make better-informed decisions about initiating ECT.

FOOTNOTES

1 ^http://surfer.nmr.mgh.harvard.edu/

2 ^http://surfer.nmr.mgh.harvard.edu/fswiki

CHAPTER 4

The Longitudinal Effects of Electroconvulsive Therapy on Ictal Interhemispheric Coherence and Its Associations With Treatment Outcome: A Naturalistic Cohort Study

Freek ten Doesschate, Guido A. van Wingen, Boudewijn J.H.B. de Pont, Martijn Arns, Jeroen A. van Waarde

Published in: Clinicial EEG and Neuroscience 2019;50:44-50. doi: 10.1177/1550059418781698.

ABSTRACT

Objectives. Electroconvulsive therapy (ECT) is an effective treatment for severe depression. Electroencephalogram (EEG) measures between ECT sessions seem to be related to the antidepressant efficacy of ECT. In this naturalistic cohort study, we examine longitudinal effects of ECT on interhemispheric EEG coherence measures during seizure activity and its relation to the antidepressant efficacy.

Methods. This study included 65 patients diagnosed with severe depressive disorder. Depressive symptoms were rated according to the Montgomery-Åsberg Depression Rating Scale before and after the course of ECT. Frequency-specific ictal interhemispheric (fp1-fp2) EEG coherence measures were established during the first and each consecutive sixth treatment session. Linear mixed-effect models were used to determine longitudinal changes in ictal coherence measures during the course of ECT and its relation to treatment efficacy.

Results. Ictal interhemispheric coherence in the theta and alpha frequency bands increased over the course of treatment, whereas no significant change was found for the delta and beta frequency bands. A main effect of treatment efficacy on the interhemispheric coherence in the delta and theta band was revealed. However, the longitudinal effects of ECT were not associated with treatment efficacy.

Conclusion. The current study suggests that interhemispheric coherence during ECT-induced seizures increases over the course of treatment. Furthermore, these longitudinal effects seem to be unrelated to the antidepressant efficacy of ECT. These findings contribute to the understanding of the mechanism of action of ECT.

INTRODUCTION

Electroconvulsive therapy (ECT) is an effective treatment for severe depression (Fink, 2001; Pagnin et al., 2008). Remission rates of ECT have been shown to range from 20% to more than 80% (Lisanby, 2007). However, the mechanism by which ECT is effective are still largely unknown. During a course of ECT, series of electrical pulses are administered to the brain, thus evoking seizure activity in clusters of neurons. Propagation measures of seizure activity can be established by ictal electroencephalographic (EEG) recording. The use of ictal EEG has provided insight into the working mechanisms of ECT (Farzan et al., 2014). One measure that is often reported is the coherence of oscillations between the 2 hemispheres. Oscillatory coherence is considered to be a useful indicator of signal propagation through functional connections in the brain (Leocani & Comi, 1999). The current study explores interhemispheric seizure propagation using ictal coherence measures during ECT-induced seizures.

Previous studies have shown interictal slowing of oscillations during the course of ECT (ie, inducing oscillations in the theta and delta bands) (Heikman et al., 2001; Volavka et al., 1972; Weiner, 1982). Furthermore, the antidepressant efficacy of ECT has been correlated with increases in slow wave (theta frequency) coherence over the first 4 treatments (Jeroen A van Waarde, van Oudheusden, Verwey, et al., 2013). These studies used interictal EEGs, that is, recorded between the treatment sessions. A study that acquired EEG during the ECT-induced seizure showed that greater slow wave coherence (delta frequency) averaged over the course of treatment correlated with better antidepressant efficacy (Perera et al., 2004). Thus, previous research has shown that ECT seems to induce slow frequency oscillations, which may be correlated with antidepressant efficacy. However, the longitudinal effect of ECT on ictal coherence measures has not been established yet.

The main aim of this naturalistic cohort study was to examine the longitudinal effects of ictal interhemispheric EEG coherence during the course of ECT treatment. Furthermore, we assessed whether differences in longitudinal effects of ictal EEG coherence were related to treatment efficacy. Finally, a secondary aim of this study was to replicate a previous finding that revealed an association between treatment efficacy and the ictal EEG coherence averaged over the course of treatment (Perera et al., 2004).

MATERIALS AND METHODS

PATIENTS

Patients, indicated for ECT at the Rijnstate Hospital (Arnhem, the Netherlands), were classified according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision (*DSM-IV-TR*), with severe mood disorders and were selected for this study. Patients were excluded if aged <18 years, and if they dropped out of treatment during the ECT course. The severity of depression was determined with the Montgomery-Åsberg Depression Rating Scale (MADRS) by a trained research nurse. The MADRS consists of questions in 10 subcategories

(Montgomery & Åsberg, 1979), rated 0 to 6, resulting in a score ranging from 0 to 60 (highest level of severity). The percentage change in MADRS scores from pre- to post-ECT were established for each patient and response was defined as a decrease in MADRS score of at least 50% after the course of ECT.

The Medical Ethical Committee of the hospital approved the research protocol of this study (NL24697.091.09). After receiving full information about the study, written informed consent was obtained from all participants. Characteristics of the patients are described in more detail elsewhere (Jeroen A van Waarde, van Oudheusden, Verwey, et al., 2013).

TREATMENT COURSE AND PROCEDURE

ECT was administered using a constant-current (0.9 A), brief-pulse (0.25 ms in right unilateral [RUL] and 0.5 ms in bifrontotemporal [BL] ECT) device (maximum output 1008 mC; Thymatron IV; Somatics Incorporation, Lake Bluff, IL, USA), after induction of anesthesia intravenously with etomidate (0.3 mg/kg body mass), muscle paralysis with succinylcholine (0.5-1 mg/kg body mass) intravenously, and with appropriate oxygenation (100% oxygen, positive pressure) until the resumption of spontaneous respiration. Electrode placement was started RUL, except in patients at high risk for suicidality and/or acute somatic compromised conditions, or if BL ECT had successfully been administered previously. Dosage was set at 6 times initial seizure threshold (IST) in RUL ECT and at 2.5 times IST for BL treatment. Patients were treated twice weekly. RUL electrode placement could be changed into BL electrode placement during the ECT course if the patient did not show (enough) improvement after 6 RUL sessions, based on the clinical decision of experienced psychiatrists. One week before starting ECT, baseline MADRS scores were determined. The course of ECT treatment was terminated when mood had not further improved in the last 2 ECT sessions, based on the clinical decision of the psychiatrists. Within 1 week after the last ECT session, the post-ECT MADRS score was established.

EEG AND INTERHEMISPHERIC COHERENCE

Ictal coherence was documented by 2-channel EEG recordings as part of the standard clinical practice (using the Thymatron IV device; sampling rate = 250Hz). In this study, only EEG recordings were used that were registered after inducing a suprathreshold therapeutic seizure at the 1st, 6th, 12th, 18th, and 24th treatment session, depending of the total length of the individual course. EEG Ag/AgCl electrodes were positioned at approximately Fp1 and Fp2 and pulse artifacts were avoided by placing the reference electrodes high on the ipsilateral mastoid. An additional ground electrode was placed at the shoulder. Prelubricated and self-adhesive electrodes were used on a cleaned skin (Somatics Incorporation, Lake Bluff, IL, USA). Patients were instructed not to use any face cream or lotion on the day of treatment to increase the adherence of the electrodes. Because of the use of the Thymatron device for EEG recording, no measure of impedance could be determined.

The Thymatron device automatically calculated the interhemispheric coherences per frequency band (δ [0.7-3.5 Hz], θ [3.5-8 Hz], α [8-13 Hz], and β [13-25 Hz]). The device determined

the cross-correlation between the power spectrums of the 2 EEG electrodes for each frequency band, adjusted for possible shifts in phase, based on the following equation:

$$\text{Coherence}(f) = \frac{\left|S_{xy}(f)^2\right|}{S_{xx}(f) * S_{yy}(f)}$$

in which ||$Sxy(f)$2|| is the squared magnitude of the complex cross-spectrum function. This function is normalized by the convolution of $Sxx(f)$ and $Syy(f)$, which are the real valued power spectra of the individual left and right EEG channels, respectively. Computer-automated EEG measures established by the Thymatron IV device are shown to be reliable (Krystal & Weiner, 1995; Rosenquist et al., 1998), though precludes custom data processing and signal-to-noise optimization.

The ictal interhemispheric coherence was quantified during generalized seizures, and the pre- and post-ictal segments of the EEG were excluded from the analysis. The criteria for a generalized seizure were (*a*) visible motor tonic-clonic seizure activity at the nonparalyzed limb (≥20 seconds) and (*b*) typical peak slow-wave EEG signals at Fp1 and Fp2 (≥25 seconds). No outliers in the mean ictal interhemispheric coherence measure could be detected.

STATISTICAL ANALYSIS

Linear mixed-effect models were performed in R studio with the lme4 package (Bates et al., 2014; Team, 2013). Assumptions for homoscedasticity and normality were checked by visual inspection and did not show deviations. Separate models were run for each frequency band (as the dependent variable). First, the effect of time (ie, treatment number) on the ictal coherence measures was analyzed. Time and electrode placement were entered as fixed effects, a by-subject random slope for time and random intercepts for age and sex were included. The main effect of time was inferred from the linear mixed-effect model. Second, the effect of treatment efficacy on the ictal coherence measures was analyzed. Percentage change in MADRS scores, time, and electrode placement were entered as fixed factors, and random intercepts were included for subject, age and sex. The main effect of percentage change in MADRS scores was inferred from the linear mixed-effect model. Additional analyses were performed to assess whether the effects of treatment efficacy on the ictal interhemispheric coherence were unique for each frequency band. This was established by adding random intercepts for the frequencies that did not serve as the independent variable to the latter analysis. Third, the interaction effect of time by efficacy on the ictal coherence measures was analyzed. Time, percentage change in MADRS scores (pre- to post-ECT), electrode placement and a time by percentage change in MADRS interaction effect were entered as fixed factors, a by-subject random slope for time, and random intercepts for sex and age were also included. As additional analyses and for the purpose of visualization, the analyses on the main and interaction effects of treatment efficacy were also performed using the dichotomized treatment response score (split at 50% change in MADRS scores). Finally, to test for confounding effects, potentially confounding variables were added to the models that revealed a significant result. This was done by adding random intercepts for the following variables: length of the EEG, pre-ECT

MADRS score, use of antidepressants (yes/no), antiepileptics (yes/no), benzodiazepines (yes/no) and antipsychotics (yes/no), and the presence of a bipolar disorder (yes/no), psychosis (yes/no), or a known comorbid DSM personality disorder (yes/no). For all analyses, P-values were obtained by likelihood ratio tests of the full model with the effect of interest against the model without the effect of interest. The statistical threshold was set at $\alpha = .05$ and Cramer's *V* values were reported as a measure of effect size.

Variable	Mean (±SD) or count (%)
Age, years	57.0 (±14.5)
Sex, female	40 (62)
Pre-ECT MADRS	36.1 (±8.4)
Post-ECT MADRS	13.2 (±10.1)
Bipolar depression	12 (18)
Psychotic features present	20 (31)
Known DSM-classified personality disorder	21 (32)
Concomitant medication use during ECT	
Antidepressants	39 (60)
Benzodiazepines	42 (65)
Antipsychotics	44 (67)
Anti-epileptics	5 (8)
RUL/BL/switch RUL to BL during course	25 (35)/13 (20)/27 (42)
Total no. of ECT sessions during ECT course	17.8 (±7.0)
Initial seizure threshold (in mC)	63.4 (±34.7)
Dosis succinylcholine (in mg)	86.8 (±16.1)
Dosis etomidate (in mg)	22.1 (±5.0)

Table 1. Descriptive Statistics of the Sample's Demographic, Clinical, and Treatment Parameters. *Abbreviations: ECT, electroconvulsive therapy; MADRS, Montgomery–Åsberg Depression Rating Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; RUL, right unilateral electrode placement; BL, bifrontal electrode placement.*

RESULTS

Descriptive statistics of the sample's (n = 65) demographic, clinical, and treatment parameters are presented in Table 1.

The analyses on the effect of time revealed that the ictal interhemispheric coherence in the theta, $\chi2(1) = 7.52$, $P = .006$, $V = 0.18$, and alpha, $\chi2(1) = 13.01$, $P < .001$, $V = 0.25$, bands increased significantly over time. No effect of time was observed in the delta, $\chi2(1) = 1.54$, $P = .214$, $V = 0.08$, and beta, $\chi2(1) = 0.924$, $P = .337$, $V = 0.06$, frequencies (Figure 1). The effect of time on theta, $\chi2(1) = 6.54$, $P = .01$, $V = 0.18$, and alpha, $\chi2(1) = 12.1$, $P < .001$, $V = 0.24$, coherence remained

significant after adjusting for the effects the duration of the recorded EEG, type of depression (uni- or bipolar), comorbidity (psychosis and personality disorder) and the use of medication.

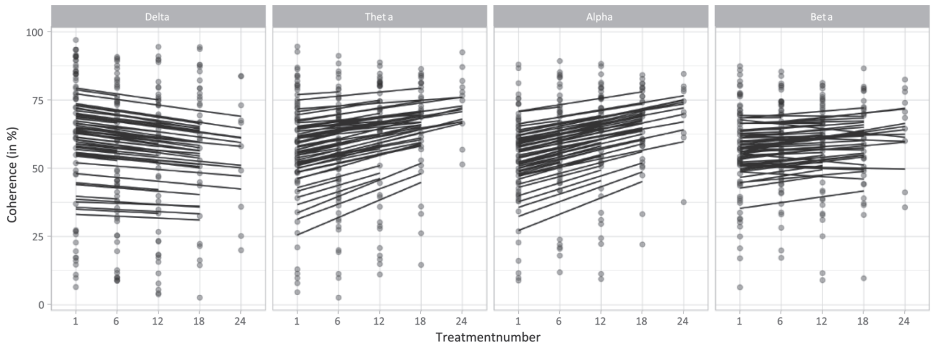


Figure 1. Regression plots for the effect of time on the ictal interhemispheric coherence for all frequency bands. Data points represent the actual measured ictal interhemispheric coherence, whereas the lines represent regression slopes for each patient as fitted by the linear mixed-effect models.

Further analyses revealed a main effect of treatment efficacy on the interhemispheric coherence in the delta and theta band. That is, a greater percentage change in MADRS scores was associated with greater ictal interhemispheric coherences in the delta, $\chi2(1) = 4.74$, $P = .029$, $V = 0.15$, and theta, $\chi2(1) = 4.11$, $P = .043$, $V = 0.14$, frequencies, whereas no significant effect was shown in the alpha, $\chi2(1) = 2.38$, $P = .123$, $V = 0.11$, and beta, $\chi2(1) = 2.72$, $P = .099$, $V = 0.11$, frequencies. Additional analyses showed that the effect of treatment response remained significant after adjusting for the coherence measures in the other frequency bands for the delta, $\chi2(1) = 4.77$, $P = .029$, $V = 0.14$, and theta, $\chi2(1) = 5.14$, $P = .023$, $V = 0.16$, frequency bands, but not for the alpha, $\chi2(1) = 2.06$, $P = .151$, $V = 0.10$, and beta, $\chi2(1) = 1.73$, $P = .188$, $V = 0.09$, frequency bands. Furthermore, the significant main effect of percentage change in MADRS scores on delta, $\chi2(1) = 5.00$, $P = .025$, $V = 0.15$, and theta, $\chi2(1) = 4.88$, $P = .027$, $V = 0.15$, coherences was not confounded by the effects of the duration of the recorded EEG, type of depression (uni- or bipolar), comorbidity (psychosis and personality disorder) and the use of psychotropic medication. Analyses on the main effects of treatment response using the dichotomized treatment response scores (split at 50% reduction) revealed similar results (Figure 2).

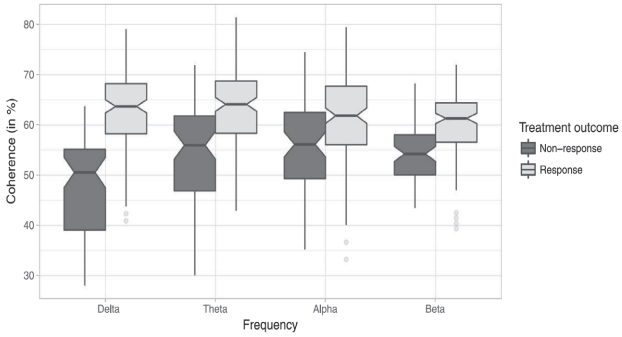


Figure 2. Notched boxplot for the effect of response on the ictal interhemispheric coherence for all frequency bands. Data predicted by the linear mixed-effect models on the effect of response were used to create the boxplots.

Finally, analyses on the interaction between time and treatment efficacy on the ictal interhemispheric coherence did not reveal a significant effect in any of the frequency bands (for delta: $\chi2(1) = 0.67$, $P = .414$, $V = 0.06$; for theta: $\chi2(1) = 0.23$, $P = .633$, $V = 0.03$; for alpha: $\chi2(1) = 0.15$, $P = .69$, $V = 0.06$; for beta: $\chi2(1) = 1.24$, $P = .266$, $V = 0.08$). In line with these results, no significant effects were revealed by analyses on the interaction effects between treatment response and time using the dichotomized treatment response scores (Figure 3).

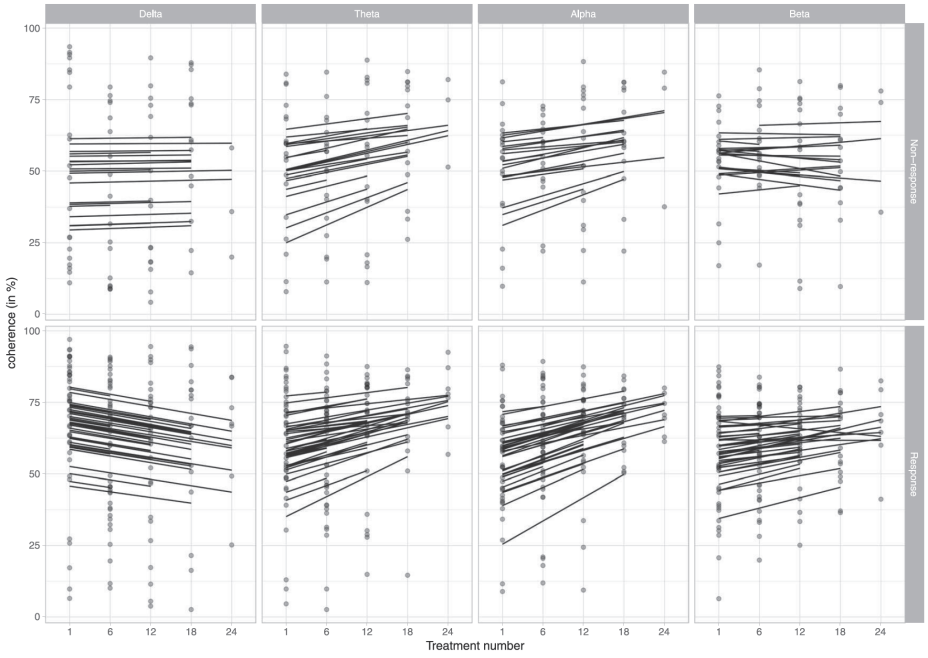


Figure 3. Regression plots for the time by treatment response interaction effect on the ictal interhemispheric coherence for all frequency bands. Data points represent the actual measured ictal interhemispheric coherence, whereas the lines represent regression slopes for each patient as fitted by the linear mixed-effect models. None of the models revealed a significant interaction effect.

DISCUSSION

This naturalistic cohort study showed that the ictal interhemispheric EEG coherence in the theta and alpha bands increased during the course of ECT, whereas no such changes over time were found for the delta and beta band frequencies. The longitudinal alterations in ictal interhemispheric coherence were not associated with the antidepressant efficacy of ECT for any of the frequency bands. Finally, a main effect of treatment efficacy on the interhemispheric coherence in the delta and theta band was revealed. That is, patients with greater reduction in MADRS scores showed greater ictal interhemispheric EEG coherence in the delta and theta bands, which confirms and extends a previous finding (Perera et al., 2004). The significant effects were independent from the duration of the recorded EEG, type of depression (uni- or bipolar), comorbidity (psychosis and personality disorder) and the use of psychotropic medication.

The current study suggests that interhemispheric EEG measures during an ECT session increase over the course of treatment. Similarly, previous studies showed an increase in slow-wave activity between ECT sessions (Heikman et al., 2001; Volavka et al., 1972; Weiner, 1982), although the increase in EEG measures was found in a slightly lower frequency range (3.5-13 Hz in our study compared with 0.5-7Hz in others). Differences in the type and time of measurements used in the studies may explain this contrast in findings. That is, previous studies used activity measures between treatment sessions whereas our current study examined coherence measures during an ECT-induced seizure. Nevertheless, these studies showed that ECT increases multiple frontal EEG measures, both during and in between treatments. These findings support the neuroplasticity hypothesis of ECT (Lyden et al., 2014; Tendolkar et al., 2013), which states that ECT induces synaptic growth, which may facilitate increased signal propagation.

In the current study, a main effect of treatment efficacy on the slow-wave ictal interhemispheric coherence during ECT-induced seizures was revealed. A previous study posed that the field has misinterpreted these associations as reflecting the therapeutic potency of ongoing treatment. Instead, we suggest that these associations derive from differences among patients in neurophysiological response to seizure provocation and that these individual differences, independent of ECT treatment parameters, are linked to therapeutic outcome (Perera et al., 2004).

In line with this hypothesis, our findings show that ictal EEG measures that depend on the amount of time in treatment (ie, the longitudinal ictal interhemispheric coherence) were not associated with treatment outcome, whereas measures independent of the amount of time in treatment (ie, the ictal slow-wave coherence averaged over the course of treatment) did correlate with efficacy of ECT. In our study, the main effect of treatment efficacy on interhemispheric coherence measures survived after adjusting for the pre-ECT symptom severity and other comorbid disorders. This further supports the hypothesis that the association between treatment efficacy and ictal interhemispheric coherence indeed reflect differences among patients in the neurophysiological response to seizure provocation, rather than preexistent states of illness. Differences in response to seizure provocation may be due to

differential brain states between patients at baseline. To test this hypothesis, future research should aim to reveal whether the treatment efficacy of ECT is also associated with pre-ECT functional connectivity measures. The association between ictal slow-wave EEG measures and treatment outcome might be explained by a possible working mechanism of ECT. That is, slow-wave ictal oscillations originate from the firing of inhibitory GABAergic interneurons (Ball et al., 1977; Steriade et al., 1990). The activation of GABAergic interneurons may underlie termination of induced seizure activity, which is proposed as a working mechanism of ECT (Sackeim et al., 1983). Thus, we suggest that the magnitude of ictal slow-wave EEG measures reflect individual differences in the strength of seizure termination processes which determine the antidepressant efficacy of ECT.

Several caveats of this naturalistic cohort study should be considered. The main limitation of this study is that the ictal interhemispheric coherence measures were automatically computed by the ECT device without visual screening for artifacts. Although computer-automated EEG measures established by the Thymatron IV device are shown to be reliable (Krystal & Weiner, 1995; Rosenquist et al., 1998), this may have reduced the signal-to-noise ratio. Second, coherence and global power measures seem to have a similar association with ECT efficacy (Perera et al., 2004). Global power measures were not included in this study and, therefore, we could not assess whether the relation between coherence and treatment efficacy may be confounded by global power measures. The reported findings should thus be interpreted in terms of EEG features in general rather than effects of coherence measures in specific. Additionally, volume conduction effects are known to increase the coherence between moderately separated electrodes (Srinivasan et al., 2007). Therefore volume conduction effects may have amplified the results in this study. Furthermore, patients did not terminate psychotropic medication treatment during treatment. The use of these medication may have influenced the ictal interhemispheric coherence measures, since antidepressants and benzodiazepines seem to affect brain oscillations (Leuchter et al., 2015). However, additional analyses revealed that medication use had no statistically significant influence on the reported results. Another potentially confounding factor is the known degradation of seizure quality over the course of treatment. Because of the lack of a valid measure of seizure quality in this study, we were not able to control for this effect which may have biased the analyses on the longitudinal effects of ECT on the interhemispheric coherence measure. Finally, the interhemispheric coherence was only determined at a limited amount of time points. Thereby, we were not able to detect subtle changes in interhemispheric coherence measures during the course of treatment.

In conclusion, the current naturalistic cohort study suggests that the interhemispheric functional connectivity during ECT-induced seizures increases over the course of treatment. Furthermore, these longitudinal effects seem to be unrelated to the antidepressant efficacy of ECT. The found ictal interhemispheric coherence increase was specific for the theta and alpha frequency bands. The findings of the current naturalistic cohort study may contribute to further understanding of the working mechanism of ECT.

CHAPTER 5

Effective resting-state connectivity in severe unipolar depression before and after electroconvulsive therapy

Freek ten Doesschate, Willem Bruin, Peter Zeidman, Christopher C. Abbott, Miklos Argyelan, Annemieke Dols, Louise Emsell, Philip F.P. van Eijndhoven, Eric van Exel, Peter C.R. Mulders, Katherine Narr, Indira Tendolkar, Didi Rhebergen, Pascal Sienaert, Mathieu Vandenbulcke, Joey Verdijk, Mike van Verseveld, Hauke Bartsch, Leif Oltedal, Jeroen A. van Waarde & Guido A. van Wingen

Published in: Brain Stimulation. 16(4), 1128-1134. doi: 10.1016/j.brs.2023.07.054

ABSTRACT

BACKGROUND

Electroconvulsive therapy (ECT) is one of the most effective treatments for severe depressive disorders. A recent multi-center study found no consistent changes in correlation-based (undirected) resting-state connectivity after ECT. Effective (directed) connectivity may provide more insight into the working mechanism of ECT.

OBJECTIVE

We investigated whether there are consistent changes in effective resting-state connectivity.

METHODS

This multi-center study included data from 189 patients suffering from severe unipolar depression and 59 healthy control participants. Longitudinal data were available for 81 patients and 24 healthy controls. We used dynamic causal modeling for resting-state functional magnetic resonance imaging to determine effective connectivity in the default mode, salience and central executive networks before and after a course of ECT. Bayesian general linear models were used to examine differences in baseline and longitudinal effective connectivity effects associated with ECT and its effectiveness.

RESULTS

Compared to controls, depressed patients showed many differences in effective connectivity at baseline, which varied according to the presence of psychotic features and later treatment outcome. Additionally, effective connectivity changed after ECT, which was related to ECT effectiveness. Notably, treatment effectiveness was associated with decreasing and increasing effective connectivity from the posterior default mode network to the left and right insula, respectively. No effects were found using correlation-based (undirected) connectivity.

CONCLUSIONS

A beneficial response to ECT may depend on how brain regions influence each other in networks important for emotion and cognition. These findings further elucidate the working mechanisms of ECT and may provide directions for future non-invasive brain stimulation research.

INTRODUCTION

With more than 250 million people affected, depression is one of the leading causes of disability worldwide (James et al., 2018). Patients suffer weeks to sometimes years of low mood, anhedonia, sleep problems, weight loss, and — in more severe cases — suicidality, motor retardation and psychotic features. Although 70% of patients show a positive response to extensive treatments with pharmacotherapy and psychotherapy (Rush et al., 2006), approximately half of them eventually relapse and experience one or more recurrent episodes in their lifetime (Eaton et al., 2008; Rush et al., 2006). Patients suffering from severe depressive episodes that are not responsive to initial treatments may benefit from electroconvulsive therapy (ECT). With a remission rate of 48-65%, ECT is currently the most effective treatment for pharmacotherapy-resistant depression (Heijnen et al., 2010). Nevertheless, it is clear that for a substantial group of depressed patients an effective treatment is still lacking. Enhancing our understanding on the neural mechanisms of depression and its treatments is indispensable to improve treatment effectiveness and to develop novel treatments.

The neural correlates of depression and its treatment with ECT have been studied extensively using structural magnetic resonance imaging (MRI) (Gbyl & Videbech, 2018; Lorenzetti et al., 2009), functional MRI (fMRI) (Mulders et al., 2015; Porta-Casteràs et al., 2021) and electroencephalography (EEG) (de Aguiar Neto & Rosa, 2019; Farzan et al., 2014). Studies using fMRI have used correlation-based connectivity measures and have focused on the default mode network (DMN), salience network (SN) and central executive network (CEN). Due to their importance in psychopathology, these networks and their modes of interaction were incorporated into a 'triple network model' of psychopathology (Menon, 2011). This model is also proposed to be of key importance for the etiology depression (Kaiser et al., 2015; Mulders et al., 2015). However, despite multiple small scale studies reporting changes in prefrontal cortex connectivity after ECT, a recent multicenter study found no evidence for changes in functional connectivity after ECT (van de Mortel et al., 2022). This suggests that functional connectivity changes are not consistent across different samples.

One drawback of correlation-based connectivity is that it assumes undirected connections between regions of interest. Alternative methods have been developed that focus on effective connectivity, a measure of the extent to which one neural system exerts influence over another (Friston, 1994). Dynamic causal modeling (DCM) is one of the most common of such methods, which uses a generative neural-mass model to infer effective (i.e., directed) connections between brain regions. Recent developments of DCM have enabled exploration of relatively large-scale networks (Razi et al., 2017) and longitudinal analyses.

Studies on effective connectivity reported widespread effective connectivity correlates associated with depression during task and resting-state fMRI (Kandilarova et al., 2018; Ray et al., 2021; Rolls et al., 2018; Schlösser et al., 2008). With respect to depressed patients treated with ECT, only a few studies have examined effective connectivity correlates. Those studies have identified increased connectivity from a cerebellar region to the subgenual anterior cingulate cortex (Wei et al., 2021),

and from the fusiform face area to the amygdala (Wang et al., 2017) following ECT. Additionally, another study found that effectiveness of ECT was associated with an increase in connectivity from the dorsolateral prefrontal cortex to the angular gyrus after ECT (Wang, Wei, et al., 2020). These studies were, however, limited to only a few regions of interest and small sample sizes.

In this present multicenter study, we used spectral DCM of resting-state fMRI (RS-fMRI) data to explore whether there are consistent differences in severe depression and healthy controls in effective connectivity between fourteen regions of the triple network model and whether there are consistent changes in effective connectivity after treatment with ECT. This study included the same samples as previous analysis (van de Mortel et al., 2022), which did not show any changes in "regular" correlation-based functional connectivity or associations with clinical effectiveness.

METHOD

PARTICIPANTS AND TREATMENT

Data were obtained from the Global ECT-MRI Research Collaboration (GEMRIC) (Oltedal et al., 2017). All patients in this study were indicated for ECT and were treated according to internationally accepted guidelines. The data used for this study were acquired at seven sites across Europe and North America. All contributing sites received ethics approval from their local ethics committee or institutional review board. In addition, approval for the centralized mega-analysis was given by the Regional Ethics Committee South-East in Norway (No. 2018/769). All patients had a clinical diagnosis of unipolar major depressive disorder, classified according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10). Two of the seven sites provided neuroimaging data for healthy controls at baseline, one site provided longitudinal neuroimaging data for healthy controls. Descriptive data on demographics (age, sex), baseline clinical (depression severity, presence of psychotic features), treatment (number of administered ECT-sessions during the course) and outcome (depression severity after the ECT-course, response [i.e., post-ECT >50% reduction of depression severity score], remission [i.e., post-ECT depression severity score <7]) variables were available. Depression severity was assessed using the Hamilton Depression Rating Scale (HAM-D) or Montgomery-Åsberg Depression Rating Scale (MADRS), depending on the sites' preferences. Ratings of the MADRS were converted to HAM-D scores (Heo et al., 2007), using the following formula:

$$HAMD = -1.58 + 0.86 * MADRS.$$

To create a more homogeneous sample, patients were excluded if bipolar disorder was present. Additionally, patients were excluded if neuroimaging data were unavailable or of insufficient quality.

FMRI ACQUISITION AND PREPROCESSING

Structural and RS-fMRI data were acquired within two weeks before the ECT-course (for scanning parameters per site, see Supplementary Table 1). The fMRI preprocessing steps were identical for each participant. First, structural and functional images were reoriented and brain extraction was performed using Advanced Normalization Tools (ANTs v2.2.0). Images were coregistered using ANTs and FMRI Software Library (FSL v5.0.10) using boundary-based registration. After discarding the first two volumes for each fMRI series, FSL's MCFLIRT was used to apply head movement correction by realigning the volumes to the middle volume using six parameters for rigid body transformations. Functional images were spatially smoothed using a Gaussian kernel with 5 mm full-width at half-maximum. For motion correction, an ICA-based strategy for Automatic Removal of Motion Artifacts (ICA-AROMA) was used. The noise components estimated by ICA-AROMA were used to compute denoised cosines for high pass filtering (f = 0.009). Furthermore, mean white matter (WM) and cerebrospinal fluid (CSF) timeseries were computed as additional nuisance variables. Temporal high-pass filtering was used to remove low-frequency drifts (< 0.01 Hz) and images were registered to 4 mm isotropic voxel size. Both the denoised cosines and WM/CSF nuisance variables were used to denoise the fMRI data and perform high pass filtering in one single step (Pruim et al., 2015). ANTs were used for normalization of transformation matrices to Montreal Neurological Institute (MNI) space using 2 mm standard templates. Finally, the quality of the preprocessed images was assessed, and images with suboptimal quality were excluded from the analysis. The procedure for quality control is described in the supplementary information. Finally, RS-fMRI of sufficient quality was available for a total of 248 participants with respect to cross-sectional baseline data. Regarding longitudinal data, RS-fMRI data of sufficient quality was available for 105 participants.

STATISTICAL ANALYSIS

Spectral DCM (spDCM) for RS-fMRI was used to estimate effective connectivity parameters (Friston et al., 2014). Analyses were conducted in Statistical Parametric Mapping (SPM12, revision 7771) with DCM12.5 (revision 7497). spDCM used a generative forward model with two components. The first one described how neuronal populations causally interact. The second component mapped neuronal activity from the first model to observed (cross-spectra of) hemodynamic responses. Thereby, spDCM was able to estimate directed connectivity between brain regions as well as regional self-connections. The construct validity of spDCM has been shown by its ability to accurately recover effective connectivity in simulated data (Friston et al., 2014; Razi et al., 2015), and specific effective connections corresponding to well-documented neural pathways in rodents (Bernal-Casas et al., 2017).

A first-level spDCM analysis was performed on 14 regions of interest (ROIs; see Figure 1), which comprise the core of the triple network model. Time series were extracted from a sphere with 5 mm radius centered around MNI coordinates extracted from previous research (Figure 1; Raichle, 2011). For analysis of baseline images, a spDCM analysis with default setting were used. For the longitudinal analysis, a multisession resting-state spDCM approach was used. For a detailed description of the first-level analysis procedure, see the supplementary information.

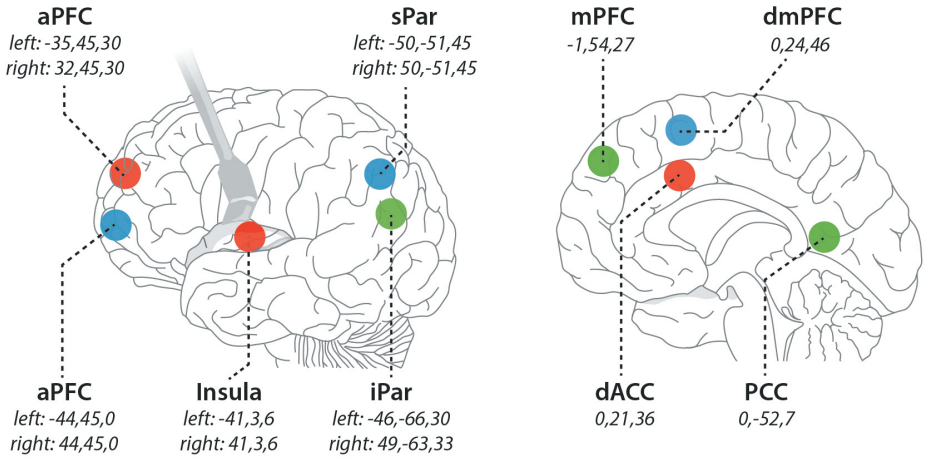


Figure 1. Overview of the regions of interest with their respective MNI coordinates. The regions belong to three networks: the central executive network (blue), salience network (red), and default mode network (green). aPFC = anterior prefrontal cortex; sPar = superior parietal cortex; mPFC = medial prefrontal cortex; dmPFC = dorsomedial pre- frontal cortex; iPar = inferior parietal cortex; dACC = dorsal anterior cingulate cortex; PCC = posterior cingulate cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Group-level effects were estimated using Parametric Empirical Bayes (PEB) models (Friston et al., 2016). A PEB general linear model (GLM) was used to infer effects at multiple levels (i.e., group effects or between-session effects) by combining the expected values and (co)variances from all individual-level spDCM parameters. PEB models were used for studying group differences at baseline, association with depression severity at baseline, and longitudinal effects associated with ECT. For each PEB model, the region-to-region effective connectivity was examined using Bayesian model reduction (BMR). This method compared model evidences for all possible reduced models (i.e., models with some connectivity parameters 'turned off' by fixing the prior probability to zero), and models with connectivity parameters that did not contribute to model evidence were iteratively discarded. This process was continued until removing parameters reduced the model evidence. Subsequently, a Bayesian model average was calculated over the 256 models with the largest model evidence in the final iteration. Using this 'pruning' and averaging approach allowed inference on the posterior probability of specific parameters. The specific PEB GLM models were adjusted for the following potentially confounding variables: age, sex, depression severity, medication use (antidepressants and benzodiazepines), psychotic features, electrode placement (only longitudinal analyses), number of ECT sessions (only longitudinal analyses), and site. A 99% posterior probability (pp) threshold was used. In order to compare effective connectivity analyses with common resting-state analyses, correlation-based connectivity was investigated with mass univariate classical GLMs. An alpha of 0.05 was used for the latter analysis, Bonferroni corrected for multiple comparison.

RESULTS

SAMPLE AND TREATMENT

In total, 248 RS-fMRI baseline scans could be included (n = 189 patients; n = 59 healthy controls) in our analyses. For 105 participants, post-ECT scans were included (n = 81 patients; n = 24 healthy controls). Patients were severely depressed at baseline (mean HDRS-score 26.2±7.2 SD). In the patient sample, 43 (23%) showed psychotic features at baseline. Most patients used concomitant pharmacotherapy during the ECT-course (61.4%), and patients without current use of pharmacotherapy did receive at least one trial of pharmacotherapy before. In the group of patients currently using antidepressants (AD), 34% used selective-serotonin reuptake inhibitors, 36% used selective-noradrenaline reuptake inhibitors, 27% used tricyclic antidepressants and 3% used monoamine oxidase inhibitors. Of the patients, 40% used concomitant benzodiazepines (BZ). Regarding used electrode placements, 126 patients received ECT with right unilateral (RUL) and 62 patients with a bilateral (BL) electrode placement. The average number of administered ECT-sessions per course was 12.4 ± 5.5 SD. For 13 patients post-ECT HDRS scores were not available. After the ECT-course, mean HDRS-score decreased significantly (post-ECT HDRS 9.9±8.1 SD; $p<0.001$), 119 (68%) patients responded and 83 (47%) patients achieved remission.

EFFECTIVE CONNECTIVITY AT BASELINE

A wide range of effective connectivity parameters showed differences between patients and healthy controls (pp > 0.99; Figure 2). Most notably, patients showed altered efferent (outgoing) connectivity from the medial prefrontal cortex (mPFC; DMN), the right insula (SN) and the left anterior PFC (aPFC; SN). Additionally, patients showed reduced excitation from all nodes of the CEN to the right aPFC (SN) compared to healthy controls. Patients showed increased connectivity from the right insula to posterior CEN regions, whereas reduced connectivity from right insula to anterior CEN. Moreover, patients showed greater self-inhibition in multiple regions of the SN compared to healthy controls, i.e., the bilateral aPFC and right insula. Analysis on effective connectivity correlates of depression severity did not yield any connections with sufficient evidence.

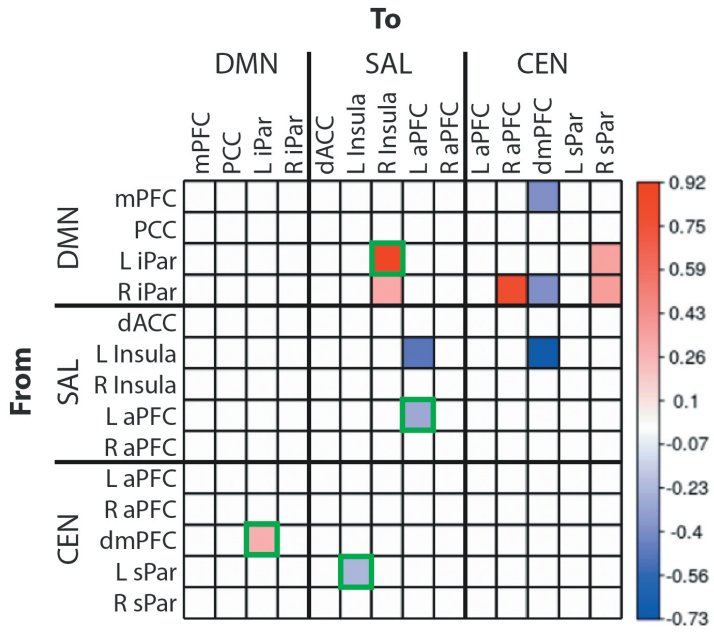


Figure 2. Effective connectivity differences between patients with severe unipolar depression and healthy controls. For off-diagonal parameters (i.e., between region connectivity), red and blue indicate increased and reduced connectivity strength in depression compared to healthy controls, respectively. The units are in Hertz. For parameters on the diagonal (self-connections), red and blue indicate stronger and weaker self-inhibition compared to healthy controls, respectively. These parameters are in arbitrary units. The variance for each connectivity parameter shown here was < 0.01. For abbreviations, see Fig. 1. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Analysis on differences between patients with and without psychotic features yielded strong evidence for group differences in 21 connectivity parameters (pp > 0.99; Supplementary Figure 1). Among other connections, the presence of psychotic features was associated with increased excitation from multiple nodes of the SN to the left aPFC (CEN). Additionally, multiple nodes throughout different networks showed reduced self-inhibition in patients with psychotic features. Psychotic features were also associated with an inter-hemispheric connectivity pattern within the SN. Specifically, patients with psychotic features showed increased excitation from the left insula to the right insula, and from the left aPFC to the right aPFC.

Analyses on baseline effective connectivity correlates of ECT effectiveness (change in HDRS; pp > 0.99; Supplementary Figure 2), response (>50% change; Supplementary Figure 3) and remission (post-ECT HDRS≤7; Supplementary Figure 4) revealed widespread associations throughout the brain. Parameters that were associated with all three of the effectiveness variables were increased connectivity from the dorsomedial PFC (dmPFC; CEN) to the dorsal anterior cingulate cortex (dACC; SN), and from the left insula (SN) to the right aPFC (SN).

The baseline models on correlation-based functional connectivity did not yield any significant results ($p > 0.05$, adjusted for multiple comparison for all connections).

EFFECTIVE CONNECTIVITY AFTER ECT

To study the general effect of ECT, we examined longitudinal differences in effective connectivity between patients and healthy controls. The analysis yielded 12 connectivity parameters with longitudinal differences between groups (pp > 0.99). However, eight of these parameters showed strong evidence for differences between time points in healthy controls only, indicating that these reflect test-retest variability in the healthy control group. The other four parameters suggested that, after the ECT-course, patients had increased connectivity from the right inferior parietal cortex (iPar; DMN) to the right insula (SN), increased connectivity from the dmPFC (CEN) to the left iPar (DMN), reduced connectivity from the left superior parietal cortex (sPar; CEN) to the left insula (SN), and reduced self-inhibition in the left aPFC (SN) (Figure 3).

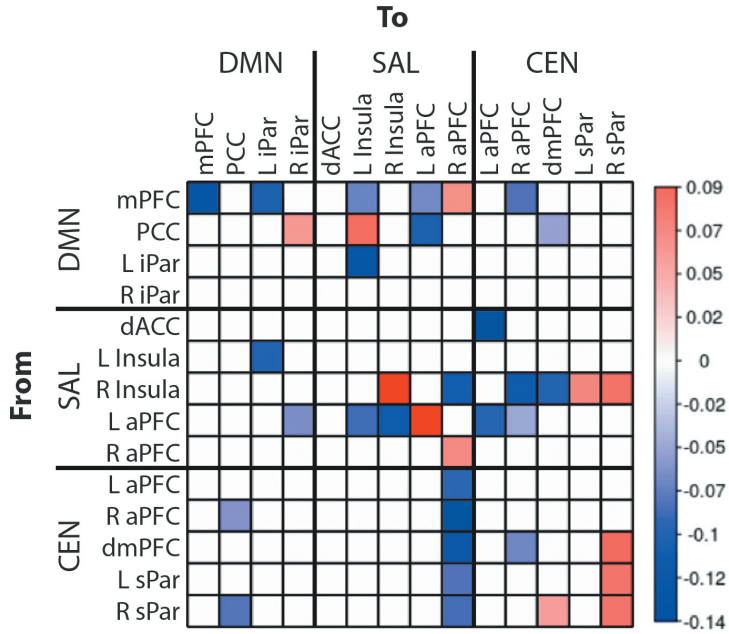


Figure 3. Longitudinal changes in effective connectivity after electrocon- vulsive therapy (ECT). For off-diagonal parameters (i.e., between region connectivity), red and blue indicate increased and reduced connectivity strength in depression after ECT compared to longitudinal data in healthy controls, respectively (thresholded at pp > 0.99). The units are in Hertz. For parameters on the diagonal (self-connections), red and blue indicate stronger and weaker self-inhibition after ECT compared to longitudinal data in healthy controls, respectively. These parameters are in arbitrary units. Green squares indicate connectivity parameters that were not due to test-retest variability in the healthy control group. The variance for each connectivity parameter shown here was < 0.1. For abbreviations, see Figure1. (For interpretation of the refer- ences to colour in this figure legend, the reader is referred to the Web version of this article.)

Analyses on longitudinal connectivity correlates of ECT effectiveness (change in HDRS) showed lateralized effects in the insula (pp > 0.99). Specifically, higher effectiveness was associated with increased connectivity after the ECT-course from the posterior parietal cortex (PCC; DMN) to the right insula (SN), and with reduced connectivity from the PCC (DMN) to the left insula (SN) (Figure 4). Effective connectivity correlates of remission and response did not overlap with correlates of the continuous effectiveness measure. Both response and remission were associated with increased connectivity from the posterior DMN to the right aPFC (CEN) (pp > 0.99; Supplementary Figures 5 and 6).

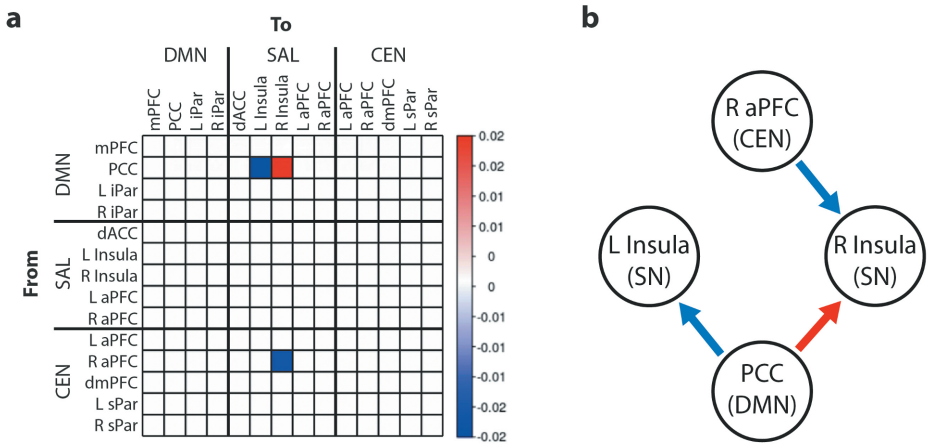


Figure 4. Changes in effective connectivity after electroconvulsive therapy (ECT) associated with treatment effectiveness. (a) Red and blue, respec- tively, indicate increased and reduced connectivity after ECT associated with treatment effectiveness (thresholded at pp > 0.99). Effectiveness is measured in change in Hamilton Depression Rating Scale (HAM-D) score. The units are in change in Hertz after ECT per points change in HAM-D. The variance for each connectivity parameter shown here was < 0.003 For abbreviations, see Fig. 1. (b) a graphical representation of the findings in (a). Red and blue arrows, respectively, indicate increased and reduced connectivity after ECT associated with treatment effective- ness (thresholded at pp > 0.99). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Finally, multiple effective connectivity parameters were correlated with the number of administered ECT-sessions during the course (pp > 0.99). Among other parameters, strong evidence was found for an association between the number of ECT-sessions and decreased self-inhibition in the left aPFC (CEN and SN) after ECT (Supplementary Figure 7).

The longitudinal models on correlation-based functional connectivity did not yield any significant results (p > 0.05, adjusted for multiple comparison for all connections).

DISCUSSION

In this multi-center cohort study, we explored the effective resting-state connectivity correlates of severe depression and its treatment with ECT. The effective connectivity analyses yielded many cross-sectional and longitudinal effective connectivity correlates throughout the triple network model. This indicates that having a depression is associated with altered effective connectivity, and that ECT changes the influence from multiple brain regions in the triple network model to other nodes of these networks. In contrast, correlation-based functional connectivity analyses did not show any significant connectivity correlates. Severe depression at baseline was associated with altered efferent effective connectivity from core regions of the SN and DMN and increased self-inhibition in multiple regions of the SN. Whereas depressed status was associated with many effective connectivity parameters, analysis on depression severity did not reveal any associated parameters. Regarding treatment with ECT, treatment effectiveness was associated with decreasing and increasing effective connectivity from the PCC (DMN) to the left and right insula (SN), respectively. Increased connectivity between the PCC and the left insula was associated with depressive status. ECT effectiveness may thus be dependent on normalization of this connection.

The results of our present study suggest that patients suffering from severe depression are characterized by increased inhibition within multiple nodes of the SN, including the right insula. This possibly reflects a general down-regulation of activity in the SN in severely depressed patients. This is in line with previous findings, that showed reduced functional connectivity (Manoliu et al., 2014) and flexibility (Wei et al., 2017) within the SN in depressed patients. The SN, and the right insula in particular, has been put forward as a critical system for switching between the CEN and DMN (Goulden et al., 2014; Sridharan et al., 2008). This is proposed to underlie appropriate responses to salient stimuli by adaptively switching between task-oriented (supported by the CEN) and self-oriented attention (supported by the DMN) (Menon, 2011). Additionally, the SN is thought to play a key role in emotion regulation, salience detection, and interoception (Menon & Uddin, 2010; Namkung et al., 2017). Excessive inhibition of the SN may therefore underlie depressive phenotypes (Avery et al., 2014; Wiebking et al., 2010).

Previous studies showed decreased connectivity between the posterior DMN and CEN in patients suffering from depression (for a review, see Mulders et al., 2015). Additionally, dynamic resting-state connectivity between the posterior DMN and the right nodes of the right CEN showed decreased variability in depression (Wang, Wang, et al., 2020). In line with this, our findings suggest reduced connectivity from the right CEN to the PCC (DMN). Interestingly, response and remission after ECT were associated with a longitudinal increase in connectivity from the posterior DMN to the right CEN after ECT. This suggests that ECT may restore dynamics between the posterior DMN and CEN.

We found dissociable lateralized associations of ECT effectiveness in connections from the PCC to the left and right insula. That is, clinical improvement after ECT was associated with decreased connectivity from the PCC to the left insula, and increased connectivity from

the PCC to the right insula. Lateralization in the insula has been associated with aberrant processing of positive emotions (Duerden et al., 2013) and a dissociation between salience detection and cognitive control processes for subsequent behavioral adaptation (Späti et al., 2014), both phenotypes that are highly disturbed in severe depression. Additionally, lateralized effects in the insula with respect to treatment effectiveness were previously reported for antidepressants (Fitzgerald et al., 2008; McGrath et al., 2013), cognitive behavioral therapy (McGrath et al., 2013), and transcranial magnetic stimulation (Kito et al., 2011). Lateralized treatment effects in the insula may thus be an interesting target for future studies on treatments for depression.

Another noticeable finding was that the analyses on ECT effectiveness (i.e., a continuous measure of treatment effect) yielded a much sparser effective connectivity pattern compared to the analyses on response and remission (i.e., binned effectiveness variables). We performed this dichotomization because it can facilitate the interpretation. Clinically relevant cut-points may increase the clinical relevancy of findings, and ease the translation of research findings to the clinical practice (MacCallum et al., 2002). However, dichotomizing variables that are originally continuous in nature usually has negative statistical effects if used in regression models. It results in a loss of power and effect size, reduced measure reliability and potentially inflated Type 1 errors (MacCallum et al., 2002; Royston et al., 2006). Also, the loss of information due to dichotomization may increase the probability that the binned variables coincide with unobserved confounds (i.e., unmeasured or unknown clinical, demographic, or treatment characteristics). In contrast to a loss of power, we actually observed more changes in effective connectivity in the dichotomous compared to the continuous analysis. We speculate that this could be the result of a nonlinear but monotonic relationship between changes in effective connectivity and symptoms, and/or the association to other unobserved clinical variables such as comorbidity and medication use.

Our findings show the added value of effective connectivity analyses using DCM. That is, whereas “regular” functional connectivity analyses did not show any effects, DCM analyses yielded strong evidence for many connectivity correlates. The absence of findings in the mass univariate correlation-based analyses may have been due to a lack of power when correcting for comparisons (i.e., the number of all tested connections, n = 196). Additionally, this contrast in findings may be explained by the different methods used to infer connectivity. Regular correlation-based analysis estimates zero-lag correlations, whereas the data features used by DCM (i.e., the cross-spectral density) is the Fourier transform of the cross-correlation function, which represents the correlation at varying lags, In other words, the data used by DCM is richer than that used by a standard correlation analysis. Additionally, Contrary to univariate correlation-based connectivity, DCM uses a neural mass model to infer multivariate directed connections. Also, shrinkage is applied in the PEB model by placing prior probabilities on the regression parameters. For future analyses, DCM analyses with PEB models may rather be compared to multivariate frequentist analyses with shrinkage for a fairer comparison. In this

study, we used mass univariate correlation-based analysis, since this is currently the most commonly used method.

Multiple limitations should be considered when interpreting these findings. First, these analyses were performed on observational data collected in a cohort study design. Controlled trials are particularly uncommon in ECT-research, due to the difficulty to design a proper control condition. Nevertheless, the current study design did not allow us to separate placebo effects from treatment effects. Second, the sample size of healthy controls (especially the longitudinal sample) was small. This resulted in considerable test-retest variability, reflected by longitudinal changes in effective connections within the healthy control group. Similarly, the number of patients with longitudinal was considerably smaller compared to the baseline sample. Third, data of different centers were retrospectively pooled. Therefore, specific study characteristics such as treatment indication and data acquisition were not standardized between centers. Fourth, data on cognitive outcomes were not available during the time of analysis. Cognitive outcomes are important in studies on ECT, since cognitive adversities are one of its most common side-effects. Finally, we studied effective connectivity in a specific subset of regions within the triple network model. Future studies could focus on including more regions of interest to capture a broader view of ECT effects on effective connectivity.

In conclusion, this multicenter cohort study yielded many effective connectivity parameters of severe depression and its treatment with ECT. This shows the added value of effective connectivity analyses for generating new hypotheses regarding psychopathology and working mechanisms of treatment. This study suggests that the connectivity from the posterior DMN to the bilateral insula is important for the effectiveness of ECT and therefore an interesting target for treatments of severe depression.

CHAPTER 6

| English summary

In this thesis, I studied electroconvulsive therapy (ECT) research with the objective to improve the clinical outcome after treatment and to gain a better understanding of its working mechanisms. In Chapter 1, I first introduced ECT and showed its relevance as a treatment option for severe depression. Then, I provided a brief history of ECT, how it has been developed from the late 1930s onwards, and described how ECT is clinically applied today. Subsequently, I proposed a taxonomy of ECT research in which studies may be classified based on their primary objective. I suggested that studies can be divided into roughly two main objectives: (1) studies that aim to improve clinical ECT-outcome by examining *treatment modification* or *treatment allocation*, and (2) studies that aim to improve clinical understanding of the working mechanisms of ECT by analyses of measured *ictal* or *extra-ictal effects*. These branches of this taxonomy may be further subdivided based on the specific measures that are used in the study. In the separate chapters of this thesis, I provided specific case-examples of these different types of studies in this taxonomy.

In Chapter 2, *treatment modification* was the primary objective. In this study, we combined a novel memory activation intervention with ECT. Recent and early studies suggested that memory reactivation just before an ECT-session may disturb reconsolidation of this reactivated memory. Therefore, as experimental intervention, we reactivated memories - that were central to the negative schemas of depressed patients - just before the ECT-sessions during the whole treatment course. Seventy-two patients were included in our randomized controlled trial (RCT) and the intervention was compared to a control condition. The findings suggest that the memory activation just prior to ECT-sessions did not improve clinical effectiveness, nor did it increase speed of response or reduce relapse rates. Several limitations are discussed which may explain the null-findings.

In Chapter 3, we examined whether pre-ECT grey matter volume of the amygdala and hippocampus could predict ECT-effectiveness, as an example of a study which more directly aims to improve the clinical outcome of ECT and to facilitate *treatment allocation*. Fifty-three patients suffering from severe unipolar depression were included in this study. Structural magnetic resonance imaging (MRI) data were acquired one week before ECT, and grey matter volumes of the hippocampus and amygdala were obtained. Regression models were used to study whether these volumes could predict ECT-effectiveness in advance. We show that a larger amygdala volume predicted lower post-ECT depression severity at group-level. Hippocampal volume did not show independent predictive value. Using leave-one-out cross-validation, we show that amygdala volumes and demographic measures may also predict ECT outcome on the individual level. These findings suggest that the amygdala volume may be (part of) a biomarker for ECT-outcome, which may lead to more proper treatment allocation.

In Chapter 4, we studied electroencephalographic (EEG) measures during the ECT-induced seizure activity and its relation to ECT-effectiveness. This study aimed to improve clinical understanding of the working mechanisms of ECT by using measures of *ictal effects*. Specifically, we explored longitudinal effects of ictal interhemispheric EEG-coherence

between the two frontal electrodes, and associated these measures with ECT-outcome. This study included 65 patients diagnosed with severe depressive disorder. Ictal interhemispheric (fp1-fp2) EEG coherence measures were established during the first and each consecutive sixth treatment session during the ECT-course. Longitudinal changes and relations to ECT-effectiveness were established using linear mixed-effects models. We show a longitudinal increase of ictal interhemispheric coherence in the theta and alpha EEG-frequency bands. Additionally, ictal EEG-coherences in the delta and theta bands averaged over the ECT-sessions were associated with antidepressant effectiveness. Thus, ECT-effectiveness seems to be related to ictal EEG-coherence that is consistent during the treatment course, rather than ictal EEG-coherence that changes over time.

In Chapter 5, we studied effective functional brain connectivity before and after ECT. This study aimed to improve clinical understanding of ECT using measures of *extra-ictal effects*. A recent multi-center study did not find consistent correlation-based functional connectivity effects after ECT across sites. Therefore, we used another type of functional connectivity, i.e., the effective connectivity, to examine whether this did show consistent effects across sites. Dynamic causal modeling (DCM) was used to obtain effective connectivity measures, which is a Bayesian method that uses a neural mass-model to infer directed (in contrast to undirected) brain connectivity. This multi-center study included data from 189 patients suffering from severe unipolar depression and 59 healthy control participants. The analyses yielded numerous effective connections that consistently changed after ECT across sites, corrected for test-retest measures in healthy controls. Also, the ECT-outcome was associated with changes in connectivity from the posterior default mode network to the bilateral insulae. Thus, effective connectivity measures between brain networks important for emotion and cognition show consistent effects across sites.

CHAPTER 7

| General discussion

In this thesis, I have explored different aspects of electroconvulsive therapy (ECT), which is used in the treatment of patients suffering major depressive disorder (MDD). In Chapter 1, I proposed a taxonomy of ECT research. In the consecutive Chapters 2-5, I provided case-examples for each leaf node in this taxonomy. The objectives of all these studies were to improve the clinical outcome of ECT as well as our clinical understanding of its working mechanisms. In the following paragraphs, I will first discuss what we have learned from this thesis about ECT by integrating the findings with each other and with previous published research. Subsequently, I will elaborate on what I have learned about the current state of methods used in ECT research and will suggest some future directions that may advance ECT research. Finally, I will provide some concluding remarks.

7.1 INTEGRATING FINDINGS WITH PREVIOUS RESEARCH

ECT AND THE AFFECTIVE BRAIN

Multiple studies in this thesis relate the effectiveness of ECT to brain regions that are associated with emotional experience and memory. In Chapter 3, larger pre-treatment amygdala volumes appeared to be associated with greater treatment effectiveness. The amygdala is a brain region of central importance to emotional memory and impulsive responses to emotional stimuli (Dalgleish, 2004; Cahill et al., 1996; Hamann et al., 1999). In Chapter 5, we showed that after ECT functional connectivity changed from the posterior cingulate cortex (PCC) to the bilateral insula, which was associated to the antidepressant effects of the ECT-course. The insula is associated with assessing subjective feeling states, based on sensory information and interoceptive (visceral) awareness (Craig 2002; 2009; Critchley et al., 2004). Thus, whereas the amygdala processes encoding of emotional memory and impulsive responses to emotional stimuli, the insula constitutes the neural basis of (more reflective) subjective feeling states.

The amygdala and insula are both suggested to be important in clinical neuroscience and psychiatry (Namkung et al., 2017). In particular, these structures have previously been implicated in MDD and its treatment with ECT. For instance, functional connectivity between the insula and amygdala has been associated with depression status and severity (Avery et al., 2014; Kandilarova et al., 2018; Ambrosi et al., 2017; Jacobs et al., 2016). Also, changes in amygdala responses to negative stimuli were related to treatment effectiveness in ECT (Redlich et al., 2017). The effects of treatment on amygdala response may not be specific to ECT, since similar changes have repeatedly been shown in the treatment of MDD with antidepressants (Delaveau et al., 2011; Ma, 2015; Godlewska et al., 2016; For a review see Arnone, 2019). A possible explanation of the importance of the amygdala in treatments of depression, may be due to its role to retrieve emotional memories (Cabeza et al., 2007). MDD is characterized by a negative autobiographical memory bias (Everaert et al., 2022; Himmelstein et al., 2018). Amygdala activity during recall of positive memories seems to be distorted in MDD (Young et al., 2016a; 2016b), and restoring amygdala activity may normalize the ability to retrieve positive memories (Young et al., 2017). This line of research provides a hypothesis that may

explain the predictive power of amygdala volume for ECT-outcome, found in Chapter 3. That is, a greater baseline amygdala volume may reflect a retained potential to restore the negative autobiographic memory bias in depression, which, in turn, may support the general alleviation of depressive symptoms.

With respect to the insula, both functional and structural abnormalities have been found in patients with MDD (Sprengelmeyer et al., 2011; Paulus et al., 2010). Similar to the amygdala, changes in insula function after ECT have been related to clinical outcome in ECT (Qi et al., 2019; Zhang et al., 2021), but also in other treatment modalities for MDD (Fischer et al., 2021; Godlewska et al., 2016). As mentioned above, the insula is implicated in processing bodily and sensory information and translating these into subjective feeling states (Craig 2002; 2009; Critchley et al., 2004). Interoceptive awareness seems to be impaired in patients suffering from MDD (Terhaar et al., 2012), and these impairments may be mediated by reduced functioning of the insula (Paulus et al., 2010). For instance, reduced activity of the insula is associated with greater depressive severity during an interoceptive attention task (Avery et al., 2014) and during rest (Wiebking et al., 2010). Notably, the same was true for the amygdala (Avery et al., 2014). A study in healthy subjects suggested that the relation between insula activity during interoception and (sub-clinical) depressive symptoms may be mediated by greater GABA-ergic concentrations (Wiebking et al., 2014). This is in line with the findings in Chapter 5, where depression status was associated with increased network inhibition in the salience network, including the right insula. In addition, treatment outcome was associated with changes in effective connectivity towards the bilateral insula. In light of previous research, a tentative hypothesis may be that a positive response to ECT may depend on changes in the capacity for interoceptive awareness, mediated by the insula.

It is important to note that findings on the relation between ECT outcome and “affective brain regions” are not conclusive. For example, a meta-analysis showed that volume changes in the amygdala after ECT were not associated with its effectiveness (Takamiya et al., 2018). Nevertheless, the studies in this thesis contribute to the growing body of work that implicate brain regions that are important to affective processing to the working mechanism of ECT. The amygdala may mediate potential effects of ECT on encoding and retrieving emotional memories, and impulsive responses to emotional stimuli. The insula may be involved in the working mechanism of ECT by changing the capacity of interoceptive awareness and subsequent subjective feeling states. These mechanisms may not be specific for ECT and may generalize to other treatment modalities for MDD. Future studies are necessary to test these hypotheses.

HEMISPHERIC ASYMMETRIES IN ECT BIOMARKERS

The results of the neuroimaging analyses in this thesis suggest that the neural biomarkers of ECT effectiveness may show hemispheric asymmetries. In Chapter 3, we show that the predictive power of the amygdala was more pronounced in the left, compared to the right hemisphere. Additionally, analyses on longitudinal effective connectivity correlates of ECT effectiveness in Chapter 5 yielded opposite effects from the PCC to the left and right insula. This

is in line with previous studies, which reported lateralized neural correlates of ECT-outcome (e.g., see Perrin et al., 2012). Thus, the antidepressant effects of ECT may depend on different neural effects in the left and right hemispheres.

Such lateralized effects of ECT may normalize hemispheric asymmetries observed in MDD. It was suggested that MDD is characterized by hyperactivity of the right hemisphere and hypoactivity in the left hemisphere (Hecht, 2010). However, while some studies found lateralized effects in MDD patients (e.g., Grimm et al., 2008; Keedwell et al., 2005), others did not show clear asymmetries (van der Vinne et al., 2017; Horato et al., 2022). Indeed, rather than a general dominance of the left or right hemisphere in the brains of MDD patients, hemispheric specialization seems to follow more localized and complex patterns (Ding et al., 2021; Fu et al., 2021). The PCC was one of the regions that showed increased asymmetries in MDD compared to healthy controls (Ding et al., 2021; Fu et al., 2021). This suggests that the opposite changes in effective connectivity from the PCC to the left and right insula (Chapter 5), respectively, may reflect normalizing effects of ECT on depression-related brain asymmetries.

An alternative hypothesis may be that asymmetries in biomarkers of ECT may be associated to the treatment itself. The ECT-stimulus is often delivered to the right hemisphere (i.e., by using a right unilateral electrode placement), which is associated with ipsilateral changes in brain volumes after ECT (Ousdal et al., 2020; Argyelan et al., 2019). Even though asymmetries in longitudinal volumetric changes induced by the ECT-stimulus were not related to the clinical outcome (Argyelan et al., 2019), asymmetries in functional changes after ECT may be (e.g., effective connectivity in Chapter 5).

Thus, although the studies in this thesis suggest that ECT-outcome may be associated with lateralized neural effects, more research is needed to confirm these findings. Additionally, if lateralization is found to be important for treatment outcome, it may be related to normalization of pre-existent brain asymmetries in patients suffering MDD or to treatment-specific factors.

NEUROPLASTICITY HYPOTHESIS

The neuroplasticity hypothesis of MDD poses that reduced levels of neuroplasticity in (specific regions of) the brain contribute to depressive symptoms (Duman et al., 1999). This hypothesis is typically supported by findings showing reduced plasticity in the hippocampus and prefrontal cortex (PFC) in animal models and post-mortem human studies, reduced levels of neurotrophic factors in depressed patients, and the reversal of neurotrophic factors and other proxies of neuroplasticity after antidepressant treatment (Serafini, 2012). Neuroplasticity-inducing effects have been observed in ECT in particular (Sartorius et al., 2022). Studies in this thesis provide some new insights into the neuroplasticity hypothesis of MDD.

In Chapter 4, we show that propagation of EEG signals in specific frequency bands (i.e., the theta and alpha bands) during ECT-induced seizures increased over the course of treatment. This increase in functional coherence suggests that ECT stimulates neuroplasticity.

Interestingly, the clinical outcome after ECT was not related to the increasing ictal propagation, but to increased measures of slow-wave ictal coherence that remained stable over the course of treatment. This finding suggests that, although ECT does stimulate neuroplasticity, its effectiveness may not depend on it. This hypothesis is supported by recent multi-center studies that showed broadly distributed changes in brain volume after ECT, but none of these changes were associated with clinical outcome (Ousdal et al., 2020; van de Mortel et al., 2022). The latter study also did not find any changes in functional connectivity after ECT (van de Mortel et al., 2022). Interestingly, using more advanced measures (i.e., effective connectivity) in Chapter 5, we were able to uncover an association between functional connectivity changes and clinical effectiveness. Thus, where recent mega-analyses provided compelling evidence against the importance of neuroplasticity in the working mechanism that explains the efficacy of ECT, our study suggests that novel measures may be needed to uncover the potential importance of neuroplasticity.

The neuroplasticity hypothesis may also provide some more insights in why the memory reactivation intervention, as examined in Chapter 2, did not result in increased ECT efficacy. This experimental intervention depended on disrupting the reconsolidation of emotional memories that were at the core of depressive schemas with an ECT-induced seizure (Kroes et al., 2014). While the initial consolidation of memories depends on the hippocampal-cortical interactions, over time the memory gets "stored" in the cortex and becomes hippocampus independent (Frankland et al., 2005; Wang et al., 2010). However, animal studies suggested that for retrieval and reconsolidation to happen, the hippocampus has to be reengaged (e.g., Grella et al., 2022; Radiske et al., 2020). In Chapter 2, we studied patients with mostly chronic depression, and hippocampal neuroplasticity seems to reduce with longer duration of illness (Yrondi et al., 2021; Sheline et al., 1999; Bell-McGinty et al., 2002; McKinnon et al., 2009). Therefore, it may be hypothesized that reduced neuroplasticity due to the chronic condition of our included patients may have distorted the recruitment of the hippocampus while retrieving the emotional memory. This may have hindered impairing the reconsolidation of these memories. In contrast, a previous study successfully impaired reconsolidation of recently learned emotional memories in a comparable chronically depressed population (Kroes et al., 2014). However, the memories we targeted in our randomized clinical trial were often formed during childhood, and reconsolidation of older memories seems to be harder compared to newly formed memories (Alberini et al., 2013). Whereas the hippocampus in chronic depression may be flexible enough to reengage in the retrieval of new memories, it may lack the capacity for reengagement in respect of old(er) memories. This line of argumentation is - of course - tentative, and other explanations are provided in the discussion of Chapter 2.

7.2 METHODS IN ECT RESEARCH: LIMITATIONS & FUTURE DIRECTIONS

Further development of research on improving the clinical outcome and understanding of ECT highly depends on methodological advancements. Here, I will reflect on the methods used

in the studies in this thesis and suggest some future directions. This discussion will roughly follow the taxonomy proposed in Chapter 1.

As previously stated, studies aiming to improve the clinical outcome of ECT often take the approach of predicting future outcome, based on baseline patient characteristics. In Chapter 3, we aimed to contribute to this line of research. We used linear regression with leave-one-out cross validation on neurobiological and clinical measures to predict the outcome of ECT. In hindsight, more complex methods may have been better suited for a prediction study. However, the small sample size made complex models less suitable. Especially nowadays, methods are far more sophisticated than I have applied. Rapid developments in the field of machine learning allows the prediction of outcomes based on highly complex multivariate patterns, as exploited by deep-learning methods (Durstewitz et al., 2019). Neuroimaging data is highly dimensional, and these models are more likely to capture the specific complexities that are important for treatment outcome. With recent efforts of pooling ECT neuroimaging data across centers (Oltedal et al., 2017), the application of such methods becomes more and more viable. Recent attempts suggest that this may be a promising path for future ECT research (Bruin et al., 2022). Nevertheless, there is probably still a long road ahead of us before these methods can be applied in clinical practice and will help individual patients.

In Chapter 4 and 5, we aimed to improve our understanding of the working mechanisms of ECT using ictal and extra-ictal measures, respectively. One interesting approach for future studies may be to combine ictal and extra-ictal measures. This may improve our understanding of how phenomena during the actual treatment procedure itself (i.e., ictal effects) may relate to pre-existent brain states and longer-term neurobiological and clinical consequences of the treatment (i.e., extra-ictal effects). I have piloted this approach by studying how pre-existent brain structure (sMRI) and function (fMRI) were associated with ictal interhemispheric EEG-coherence during ECT-seizure activity (for summaries, see ten Doesschate et al., 2015). Although these preliminary studies yielded some interesting results (e.g., larger white matter volumes in the prefrontal cortex and midbrain were associated with better propagation of delta band ictal interhemispheric EEG-coherences), it appeared difficult to publish the manuscript. One of the major issues for non-acceptance was probably the overly complex statistical analyses. I used multiple separate regression models to link ictal EEG-coherence, structural and functional pre-ECT MRI and clinical measures. In hindsight, a unified statistical model that included all associations at once may have been more promising. Additionally, I used a two-lead EEG at the two frontal poles, identical to the data used in Chapter 4. This type of EEG measure is easily acquired, since it is part of the standard clinical practice during ECT. However, the spatial resolution of two-lead EEG measurements is very low, and more fine-grained measures are desirable. However, acquiring such measures during generalized seizure activity is usually challenging. Acquiring measures with a high-spatial resolution, such as MRI, is not feasible during ECT-induced seizures. Therefore, measuring ictal EEG with more electrodes seems to be the best approach for now. Efforts for studying such measures are currently made (Miller et al., 2022; Verdijk et al., 2022).

Finally, I argue that using statistical models that are more tailored to the ECT-procedure will provide a more advanced understanding of the working mechanisms compared to out-of-the-box statistical methods. Being able to build statistical models that more closely resemble the generative process of the data acquired in ECT research allows us to ask more specific and nuanced research questions that could illuminate specific aspects of the ECT-procedure. A convenient way to build flexible statistical models is Bayesian modeling. Bayesian statistics is a statistical approach that is rooted in probability theory. Interpreting results from Bayesian models is often more intuitive compared to results produced by the more commonly used frequentist methods (Wagenmakers et al., 2018). Additionally, current Bayesian programming languages (such as Stan or PyMC) provide tools to build flexible, complex and customized models. An application of such complex model is showcased in Chapter 5. In this case, the Bayesian model was tailored to infer directed connectivity in resting-state fMRI data. Similarly, models can be customized specifically to the ECT-procedure. One example that may be applied in ECT research is the 'epileptor' model, i.e., a model that simulate epileptic seizures using ordinary differential equation (Jirsa et al., 2014). This model has recently been combined with Bayesian inference to locate brain regions in which seizures originate (i.e., the eliptogenic zones) and regions that are subsequently affected by the seizure (i.e., the propagation zones; Hashemi et al., 2020). In ECT, these kinds of models could potentially elucidate which mechanisms during the ECT-induced seizure actually affect subsequent changes in depressive symptoms (and cognitive side-effects) and brain morphology and function. These studies are still lacking today.

7.3 CONCLUSION

In this thesis, I explored various methods in ECT research. The methods varied with respect to sample selection (i.e., single- versus multi-center data), study design (i.e., observational retrospective study versus prospective RCT, controlled versus non-controlled), type of data (i.e., clinical, EEG, and [f]MRI), and the applied statistical models to analyze the data (i.e., frequentist versus Bayesian models). Additionally, I proposed a taxonomy of ECT research. The main chapters can be considered as specific case-examples of the child-nodes of this taxonomy. Thereby, this thesis contributes to improving the clinical outcome and understanding of the working mechanisms of ECT. Based on the findings in this thesis, I have discussed the methods that are commonly used in ECT research and which future directions this may take.

Although much research has to be done to improve ECT-outcome and the understanding of its working mechanisms, we cannot ignore that already much knowledge is present today. From the introduction of ECT in 1938 until now, clinicians and researchers have been impressed by the clinical results of ECT, as well as have been fascinated about its neurobiological aspects. The recent developments in methods may eventually open doors towards new and improved treatments for treating depressed patients.

LITERATURE

Abbott, C. C., Gallegos, P., Rediske, N., Lemke, N. T., & Quinn, D. K. (2014). A review of longitudinal electroconvulsive therapy: neuroimaging investigations. *Journal of Geriatric Psychiatry and Neurology*, *27*(1), 33–46.

Alberini, C. M., & LeDoux, J. E. (2013). Memory reconsolidation. *Current Biology*, *23*(17), R746–R750.

Altar, C. A., Whitehead, R. E., Chen, R., Wörtwein, G., & Madsen, T. M. (2003). Effects of electroconvulsive seizures and antidepressant drugs on brain-derived neurotrophic factor protein in rat brain. *Biological Psychiatry*, *54*(7), 703–709.

Ambrosi, E., Arciniegas, D. B., Madan, A., Curtis, K. N., Patriquin, M. A., Jorge, R. E., Spalletta, G., Fowler, J. C., Frueh, B. C., & Salas, R. (2017). Insula and amygdala resting-state functional connectivity differentiate bipolar from unipolar depression. *Acta Psychiatrica Scandinavica*, *136*(1), 129–139.

Argyelan, M., Oltedal, L., Deng, Z.-D., Wade, B., Bikson, M., Joanlanne, A., Sanghani, S., Bartsch, H., Cano, M., & Dale, A. M. (2019). Electric field causes volumetric changes in the human brain. *Elife*, *8*, e49115.

Arnaud, A., & Bonthapally, V. (2022). Zuranolone Provides a Rapid Response Without Chronic Dosing: Response to Correspondence by ten Doesschate et al. *Journal of Affective Disorders*.

Arnaud, A., Suthoff, E., Stenson, K., Werneburg, B., Hodgkins, P., Bonthapally, V., Jonas, J., Meyer, K., & O'Day, K. (2021). Number Needed to Treat and Number Needed to Harm analysis of the zuranolone phase 2 clinical trial results in major depressive disorder. *Journal of Affective Disorders*, *285*, 112–119.

Arnone, D. (2019). Functional MRI findings, pharmacological treatment in major depression and clinical response. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *91*, 28–37.

Association, A. P. (2010). *Diagnostic and statistical manual of mental disorders, text revision (DSM-IV-TR®)*.

Association, W. M. (2013). World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *Jama*, *310*(20), 2191–2194.

Avery, J. A., Drevets, W. C., Moseman, S. E., Bodurka, J., Barcalow, J. C., & Simmons, W. K. (2014). Major depressive disorder is associated with abnormal interoceptive activity and functional connectivity in the insula. *Biological Psychiatry*, *76*(3), 258–266.

Ball, G. J., Gloor, P., & Schaul, N. (1977). The cortical electromicrophysiology of pathological delta waves in the electroencephalogram of cats. *Electroencephalography and Clinical Neurophysiology*, *43*(3), 346–361.

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2014). Fitting linear mixed-effects models using lme4. *ArXiv Preprint ArXiv:1406.5823*.

Beck, A. T., & Clark, D. A. (2015). Anxiety and depression: An information processing perspective. In *Anxiety and self-focused attention* (pp. 41–54). Routledge.

Bell-McGinty, S., Butters, M. A., Meltzer, C. C., Greer, P. J., Reynolds III, C. F., & Becker, J. T. (2002). Brain morphometric abnormalities in geriatric depression: long-term neurobiological effects of illness duration. *American Journal of Psychiatry*, *159*(8), 1424–1427.

Bellani, M., Baiano, M., & Brambilla, P. (2011). Brain anatomy of major depression II. Focus on amygdala. *Epidemiology and Psychiatric Sciences*, *20*(1), 33–36.

Bennett, D. M., Perrin, J. S., Currie, J., Blacklaw, L., Kuriakose, J., Rao, A., & Reid, I. C. (2012). A comparison of ECT dosing methods using a clinical sample. *Journal of Affective Disorders*, *141*(2–3), 222–226.

Bernal-Casas, D., Lee, H. J., Weitz, A. J., & Lee, J. H. (2017). Studying brain circuit function with dynamic causal modeling for optogenetic fMRI. *Neuron*, *93*(3), 522–532.

Bockting, C. L., Hollon, S. D., Jarrett, R. B., Kuyken, W., & Dobson, K. (2015). A lifetime approach to major depressive disorder: the contributions of psychological interventions in preventing relapse and recurrence. *Clinical Psychology Review*, *41*, 16–26.

Bolwig, T. G. (2011). How does electroconvulsive therapy work? Theories on its mechanism. *The Canadian Journal of Psychiatry*, *56*(1), 13–18.

Bruin, W. B., Oltedal, L., Bartsch, H., Abbott, C. C., Argyelan, M., Barbour, T., Camprodon, J. A., Chowdhury, S., Espinoza, R., & Mulders, P. C. R. (2022). Development and validation of a multimodal neuroimaging biomarker for electroconvulsive therapy outcome in depression: a multicenter machine learning analysis. *MedRxiv*, 2007–2021.

Brunet, A., Saumier, D., & Pitman, R. K. (2018). On the use of memory update mechanisms to treat patients: response to Waits and Hoge. *American Journal of Psychiatry*, *175*(11), 1145–1146.

Bustos, S. G., Maldonado, H., & Molina, V. A. (2009). Disruptive effect of midazolam on fear memory reconsolidation: decisive influence of reactivation time span and memory age. *Neuropsychopharmacology*, *34*(2), 446–457.

Bzdok, D., & Meyer-Lindenberg, A. (2018). Machine learning for precision psychiatry: opportunities and challenges. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *3*(3), 223–230.

Cabeza, R., & St Jacques, P. (2007). Functional neuroimaging of autobiographical memory. *Trends in Cognitive Sciences*, *11*(5), 219–227.

Cahill, L., Haier, R. J., Fallon, J., Alkire, M. T., Tang, C., Keator, D., Wu, J., & Mcgaugh, J. L. (1996). Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proceedings of the National Academy of Sciences*, *93*(15), 8016–8021.

Cerletti, U. (1938). Un nuevo metode di shockterapie" L'elettro-shock". *Boll Accad Med Roma*, *64*, 136–138.

Cipriani, A., Furukawa, T. A., Salanti, G., Chaimani, A., Atkinson, L. Z., Ogawa, Y., Leucht, S., Ruhe, H. G., Turner, E. H., & Higgins, J. P. T. (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Focus*, *16*(4), 420–429.

Conti, B., Maier, R., Barr, A. M., Morale, M. C., Lu, X., Sanna, P. P., Bilbe, G., Hoyer, D., & Bartfai, T. (2007). Region-specific transcriptional changes following the three antidepressant treatments electro convulsive therapy, sleep deprivation and fluoxetine. *Molecular Psychiatry*, *12*(2), 167–189.

Cotter, D. R., Pariante, C. M., & Everall, I. P. (2001). Glial cell abnormalities in major psychiatric disorders: the evidence and implications. *Brain Research Bulletin*, *55*(5), 585–595.

Craig, A. D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nature Reviews Neuroscience*, *3*(8), 655–666.

Craig, A. D. (2009). How do you feel—now? The anterior insula and human awareness. *Nature Reviews Neuroscience*, *10*(1), 59–70.

Critchley, H. D., Wiens, S., Rotshtein, P., Öhman, A., & Dolan, R. J. (2004). Neural systems supporting interoceptive awareness. *Nature Neuroscience*, *7*(2), 189–195.

Dalgleish, T. (2004). The emotional brain. *Nature Reviews Neuroscience*, *5*(7), 583–589.

de Aguiar Neto, F. S., & Rosa, J. L. G. (2019). Depression biomarkers using non-invasive EEG: a review. *Neuroscience & Biobehavioral Reviews*, *105*, 83–93.

Delaveau, P., Jabourian, M., Lemogne, C., Guionnet, S., Bergouignan, L., & Fossati, P. (2011). Brain effects of antidepressants in major depression: a meta-analysis of emotional processing studies. *Journal of Affective Disorders*, *130*(1–2), 66–74.

Ding, Y.-D., Yang, R., Yan, C.-G., Chen, X., Bai, T.-J., Bo, Q.-J., Chen, G.-M., Chen, N.-X., Chen, T.-L., & Chen, W. (2021). Disrupted hemispheric connectivity specialization in patients with major depressive disorder: evidence from the REST-meta-MDD Project. *Journal of Affective Disorders*, *284*, 217–228.

Duerden, E. G., Arsalidou, M., Lee, M., & Taylor, M. J. (2013). Lateralization of affective processing in the insula. *Neuroimage*, *78*, 159–175.

Dukart, J., Regen, F., Kherif, F., Colla, M., Bajbouj, M., Heuser, I., Frackowiak, R. S., & Draganski, B. (2014). Electroconvulsive therapy-induced brain plasticity determines therapeutic outcome in mood disorders. *Proceedings of the National Academy of Sciences*, *111*(3), 1156–1161.

Durstewitz, D., Koppe, G., & Meyer-Lindenberg, A. (2019). Deep neural networks in psychiatry. *Molecular Psychiatry*, *24*(11), 1583–1598.

Eaton, W. W., Shao, H., Nestadt, G., Lee, B. H., Bienvenu, O. J., & Zandi, P. (2008). Population-based study of first onset and chronicity in major depressive disorder. *Archives of General Psychiatry*, *65*(5), 513–520.

Eisenberg, M., Kobilo, T., Berman, D. E., & Dudai, Y. (2003). Stability of retrieved memory: inverse correlation with trace dominance. *Science*, *301*(5636), 1102–1104.

Elizagarate, E., Cortes, J., Pinto, A. G., Gutierrez, M., Alonso, I., Alcorta, P., Ramirez, M., de Heredia, J. L. P., & Figuerido, J. L. (2001). Study of the influence of electroconvulsive therapy on the regional cerebral blood flow by HMPAO-SPECT. *Journal of Affective Disorders*, *65*(1), 55–59.

Everaert, J., Vrijsen, J. N., Martin-Willett, R., van de Kraats, L., & Joormann, J. (2022). A meta-analytic review of the relationship between explicit memory bias and depression: Depression features an explicit memory bias that persists beyond a depressive episode. *Psychological Bulletin*, *148*(5–6), 435.

Farzan, F., Boutros, N. N., Blumberger, D. M., & Daskalakis, Z. J. (2014). What does the electroencephalogram tell us about the mechanisms of action of ECT in major depressive disorders? *The Journal of ECT*, *30*(2), 98–106.

Fink, M. (1984). Meduna and the origins of convulsive therapy. *The American Journal of Psychiatry*.

Fink, M. (2001). Convulsive therapy: a review of the first 55 years. *Journal of Affective Disorders*, *63*(1–3), 1–15.

Fischer, A. S., Holt-Gosselin, B., Fleming, S. L., Hack, L. M., Ball, T. M., Schatzberg, A. F., & Williams, L. M. (2021). Intrinsic reward circuit connectivity profiles underlying symptom and quality of life outcomes following antidepressant medication: a report from the iSPOT-D trial. *Neuropsychopharmacology*, *46*(4), 809–819.

Fitzgerald, P. B., Laird, A. R., Maller, J., & Daskalakis, Z. J. (2008). A meta-analytic study of changes in brain activation in depression. *Human Brain Mapping*, *29*(6), 683–695.

Francis-Taylor, R., Ophel, G., Martin, D., & Loo, C. (2020). The ictal EEG in ECT: A systematic review of the relationships between ictal features, ECT technique, seizure threshold and outcomes. *Brain Stimulation*, *13*(6), 1644–1654.

Frank, E., Prien, R. F., Jarrett, R. B., Keller, M. B., Kupfer, D. J., Lavori, P. W., Rush, A. J., & Weissman, M. M. (1991). Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence. *Archives of General Psychiatry*, *48*(9), 851–855.

Frankland, P. W., & Bontempi, B. (2005). The organization of recent and remote memories. *Nature Reviews Neuroscience*, *6*(2), 119–130.

Friston, K. J. (1994). Functional and effective connectivity in neuroimaging: a synthesis. *Human Brain Mapping*, *2*(1-2), 56–78.

Friston, K. J., Kahan, J., Biswal, B., & Razi, A. (2014). A DCM for resting state fMRI. *Neuroimage*, *94*, 396–407.

Friston, K. J., Litvak, V., Oswal, A., Razi, A., Stephan, K. E., Van Wijk, B. C. M., Ziegler, G., & Zeidman, P. (2016). Bayesian model reduction and empirical Bayes for group (DCM) studies. *Neuroimage*, *128*, 413–431.

Fu, X., Ding, Y., Chen, J., Liu, F., Li, H., Zhao, J., & Guo, W. (2021). Altered Brain Functional Asymmetry in Patients With Major Depressive Disorder Related to Gastrointestinal Symptoms. *Frontiers in Neuroscience*, *15*.

Gbyl, K., & Videbech, P. (2018). Electroconvulsive therapy increases brain volume in major depression: a systematic review and meta-analysis. *Acta Psychiatrica Scandinavica*, *138*(3), 180–195.

Gersner, R., Toth, E., Isserles, M., & Zangen, A. (2010). Site-specific antidepressant effects of repeated subconvulsive electrical stimulation: potential role of brain-derived neurotrophic factor. *Biological Psychiatry*, *67*(2), 125–132.

Ghosh, V. E., & Gilboa, A. (2014). What is a memory schema? A historical perspective on current neuroscience literature. *Neuropsychologia*, *53*, 104–114.

Godlewska, B. R., Browning, M., Norbury, R., Cowen, P. J., & Harmer, C. J. (2016). Early changes in emotional processing as a marker of clinical response to SSRI treatment in depression. *Translational Psychiatry*, *6*(11), e957–e957.

Goulden, N., Khusnulina, A., Davis, N. J., Bracewell, R. M., Bokde, A. L., McNulty, J. P., & Mullins, P. G. (2014). The salience network is responsible for switching between the default mode network and the central executive network: replication from DCM. *Neuroimage*, *99*, 180–190.

Grella, S. L., Fortin, A. H., Ruesch, E., Bladon, J. H., Reynolds, L. F., Gross, A., Shpokayte, M., Cincotta, C., Zaki, Y., & Ramirez, S. (2022). Reactivating hippocampal-mediated memories during reconsolidation to disrupt fear. *Nature Communications*, *13*(1), 1–19.

Griffiths, C., & O'Neill-Kerr, A. (2019). Patients', carers', and the public's perspectives on electroconvulsive therapy. *Frontiers in Psychiatry*, *10*, 304.

Grimm, S., Beck, J., Schuepbach, D., Hell, D., Boesiger, P., Bermpohl, F., Niehaus, L., Boeker, H., & Northoff, G. (2008). Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. *Biological Psychiatry*, *63*(4), 369–376.

Gunduz-Bruce, H., Silber, C., Kaul, I., Rothschild, A. J., Riesenberg, R., Sankoh, A. J., Li, H., Lasser, R., Zorumski, C. F., & Rubinow, D. R. (2019). Trial of SAGE-217 in patients with major depressive disorder. *New England Journal of Medicine*, *381*(10), 903–911.

Hamann, S. B., Ely, T. D., Grafton, S. T., & Kilts, C. D. (1999). Amygdala activity related to enhanced memory for pleasant and aversive stimuli. *Nature Neuroscience*, *2*(3), 289–293.

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

Haq, A. U., Sitzmann, A. F., Goldman, M. L., Maixner, D. F., & Mickey, B. J. (2015). Response of depression to electroconvulsive therapy: a meta-analysis of clinical predictors. *The Journal of Clinical Psychiatry*, *76*(10), 18164.

Hashemi, M., Vattikonda, A. N., Sip, V., Guye, M., Bartolomei, F., Woodman, M. M., & Jirsa, V. K. (2020). The Bayesian Virtual Epileptic Patient: A probabilistic framework designed to infer the spatial map of epileptogenicity in a personalized large-scale brain model of epilepsy spread. *NeuroImage*, *217*, 116839.

Hecht, D. (2010). Depression and the hyperactive right-hemisphere. *Neuroscience Research*, *68*(2), 77–87.

Heijnen, W. T., Birkenhäger, T. K., Wierdsma, A. I., & van den Broek, W. W. (2010). Antidepressant pharmacotherapy failure and response to subsequent electroconvulsive therapy: a meta-analysis. *Journal of Clinical Psychopharmacology*, *30*(5), 616–619.

Heikman, P., Salmelin, R., Mäkelä, J. P., Hari, R., Katila, H., & Kuoppasalmi, K. (2001). Relation between frontal 3–7 Hz MEG activity and the efficacy of ECT in major depression. *The Journal of ECT*, *17*(2), 136–140.

Heo, M., Murphy, C. F., & Meyers, B. S. (2007). Relationship between the Hamilton depression rating scale and the montgomery-Åsberg depression rating scale in depressed elderly: a meta-analysis. *The American Journal of Geriatric Psychiatry*, *15*(10), 899–905.

Himmelstein, P., Barb, S., Finlayson, M. A., & Young, K. D. (2018). Linguistic analysis of the autobiographical memories of individuals with major depressive disorder. *PloS One*, *13*(11), e0207814.

Hobson, R. F. (1953). Prognostic factors in electric convulsive therapy. *Journal of Neurology, Neurosurgery, and Psychiatry*, *16*(4), 275.

Horato, N., Quagliato, L. A., & Nardi, A. E. (2022). The relationship between emotional regulation and hemispheric lateralization in depression: a systematic review and a meta-analysis. *Translational Psychiatry*, *12*(1), 1–6.

Jacobs, R. H., Barba, A., Gowins, J. R., Klumpp, H., Jenkins, L. M., Mickey, B. J., Ajilore, O., Peciña, M., Sikora, M., & Ryan, K. A. (2016). Decoupling of the amygdala to other salience network regions in adolescent-onset recurrent major depressive disorder. *Psychological Medicine*, *46*(5), 1055–1067.

Jacobsen, J. P. R., & Mørk, A. (2004). The effect of escitalopram, desipramine, electroconvulsive seizures and lithium on brain-derived neurotrophic factor mRNA and protein expression in the rat brain and the correlation to 5-HT and 5-HIAA levels. *Brain Research*, *1024*(1–2), 183–192.

James, S. L., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., & Abdelalim, A. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, *392*(10159), 1789–1858.

Janjua, A. U., Dhingra, A. L., Greenberg, R., & McDonald, W. M. (2020). The efficacy and safety of concomitant psychotropic medication and electroconvulsive therapy (ECT). *CNS Drugs*, *34*(5), 509–520.

Jelovac, A., Kolshus, E., & McLoughlin, D. M. (2013). Relapse following successful electroconvulsive therapy for major depression: a meta-analysis. *Neuropsychopharmacology*, *38*(12), 2467–2474.

Jirsa, V. K., Stacey, W. C., Quilichini, P. P., Ivanov, A. I., & Bernard, C. (2014). On the nature of seizure dynamics. *Brain*, *137*(8), 2210–2230.

Johanson, A., Gustafson, L., Risberg, J., Rosén, I., Sjöbeck, M., & Silfverskiöld, P. (2005). Long-term follow-up in depressed patients treated with electroconvulsive therapy. *The Journal of ECT*, *21*(4), 214–220.

Jonghe, F. E. R. E. R. (1994). *Leidraad voor het scoren van de Hamilton Depression Rating Scale: HDRS leidraad*. Benecke Consultants.

Kaiser, R. H., Andrews-Hanna, J. R., Wager, T. D., & Pizzagalli, D. A. (2015). Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. *JAMA Psychiatry*, *72*(6), 603–611.

Kandilarova, S., Stoyanov, D., Kostianev, S., & Specht, K. (2018). Altered resting state effective connectivity of anterior insula in depression. *Frontiers in Psychiatry*, *9*, 83.

Keedwell, P. A., Andrew, C., Williams, S. C. R., Brammer, M. J., & Phillips, M. L. (2005). The neural correlates of anhedonia in major depressive disorder. *Biological Psychiatry*, *58*(11), 843–853.

Kirsch, I., Deacon, B. J., Huedo-Medina, T. B., Scoboria, A., Moore, T. J., & Johnson, B. T. (2008). Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Medicine*, *5*(2), e45.

Kito, S., Hasegawa, T., & Koga, Y. (2011). Neuroanatomical correlates of therapeutic efficacy of low-frequency right prefrontal transcranial magnetic stimulation in treatment-resistant depression. *Psychiatry and Clinical Neurosciences*, *65*(2), 175–182.

Köhler, C. A., Carvalho, A. F., Alves, G. S., McIntyre, R. S., Hyphantis, T. N., & Cammarota, M. (2015). Autobiographical memory disturbances in depression: a novel therapeutic target? *Neural Plasticity*.

Krishnan, V., & Nestler, E. J. (2008). The molecular neurobiology of depression. *Nature*, *455*(7215), 894–902.

Kroes, M. C. W., Tendolkar, I., Van Wingen, G. A., Van Waarde, J. A., Strange, B. A., & Fernández, G. (2014). An electroconvulsive therapy procedure impairs reconsolidation of episodic memories in humans. *Nature Neuroscience*, *17*(2), 204–206.

Krystal, A. D., & Weiner, R. D. (1995). ECT seizure duration: reliability of manual and computer-automated determinations. *Convulsive Therapy*, *11*(3), 158–169.

Kupka, R. W., De Jonghe, F., Koeter, M., & Vermeulen, H. D. B. (1996). Betrouwbaarheid van een semi-gestructureerd interview voor de Hamilton-depressieschaal [Reliability of a semi-structured interview for the Hamilton Depression Rating Scale]. *Tijdschrift Voor Psychiatrie*, *38*, 759–765.

Lee, J. L. C., Milton, A. L., & Everitt, B. J. (2006). Reconsolidation and extinction of conditioned fear: inhibition and potentiation. *Journal of Neuroscience*, *26*(39), 10051–10056.

Lee, J. L. C., Nader, K., & Schiller, D. (2017). An update on memory reconsolidation updating. *Trends in Cognitive Sciences*, *21*(7), 531–545.

Lekwauwa, R. E., McQuoid, D. R., & Steffens, D. C. (2005). Hippocampal volume as a predictor of short-term ECT outcomes in older patients with depression. *The American Journal of Geriatric Psychiatry*, *13*(10), 910–913.

Leocani, L., & Comi, G. (1999). EEG coherence in pathological conditions. *Journal of Clinical Neurophysiology*, *16*(6), 548.

Leuchter, A. F., Hunter, A. M., Krantz, D. E., & Cook, I. A. (2015). Rhythms and blues: modulation of oscillatory synchrony and the mechanism of action of antidepressant treatments. *Annals of the New York Academy of Sciences*, *1344*(1), 78–91.

Li, X.-K., & Qiu, H.-T. (2022). Current progress in neuroimaging research for the treatment of major depression with electroconvulsive therapy. *World Journal of Psychiatry*, *12*(1), 128.

Lisanby, S. H. (2007). Electroconvulsive therapy for depression. *New England Journal of Medicine*, *357*(19), 1939–1945.

Loo, C. K., Mahon, M., Katalinic, N., Lyndon, B., & Hadzi-Pavlovic, D. (2011). Predictors of response to ultrabrief right unilateral electroconvulsive therapy. *Journal of Affective Disorders*, *130*(1–2), 192–197.

Lorenzetti, V., Allen, N. B., Fornito, A., & Yücel, M. (2009). Structural brain abnormalities in major depressive disorder: a selective review of recent MRI studies. *Journal of Affective Disorders*, *117*(1–2), 1–17.

Lyden, H., Espinoza, R. T., Pirnia, T., Clark, K., Joshi, S. H., Leaver, A. M., Woods, R. P., & Narr, K. L. (2014). Electroconvulsive therapy mediates neuroplasticity of white matter microstructure in major depression. *Translational Psychiatry*, *4*(4), e380–e380.

Ma, Y. (2015). Neuropsychological mechanism underlying antidepressant effect: a systematic meta-analysis. *Molecular Psychiatry*, *20*(3), 311–319.

MacCallum, R. C., Zhang, S., Preacher, K. J., & Rucker, D. D. (2002). On the practice of dichotomization of quantitative variables. *Psychological Methods*, *7*(1), 19.

Maigaard, K., Hageman, I., Jørgensen, A., Jørgensen, M. B., & Wörtwein, G. (2012). Electroconvulsive stimulations prevent chronic stress-induced increases in L-type calcium channel mRNAs in the hippocampus and basolateral amygdala. *Neuroscience Letters*, *516*(1), 24–28.

Malaspina, D., Devanand, D. P., Krueger, R. B., Prudic, J., & Sackeim, H. A. (1994). The significance of clinical EEG abnormalities in depressed patients treated with ECT. *Convulsive Therapy.*

Manoliu, A., Meng, C., Brandl, F., Doll, A., Tahmasian, M., Scherr, M., Schwerthöffer, D., Zimmer, C., Förstl, H., & Bäuml, J. (2014). Insular dysfunction within the salience network is associated with severity of symptoms and aberrant inter-network connectivity in major depressive disorder. *Frontiers in Human Neuroscience*, *7*, 930.

McClintock, S. M., Choi, J., Deng, Z.-D., Appelbaum, L. G., Krystal, A. D., & Lisanby, S. H. (2014). Multifactorial determinants of the neurocognitive effects of electroconvulsive therapy. *The Journal of ECT*, *30*(2), 165.

McDonald, A., & Walter, G. (2001). The portrayal of ECT in American movies. *The Journal of ECT*, *17*(4), 264–274.

McGrath, C. L., Kelley, M. E., Holtzheimer, P. E., Dunlop, B. W., Craighead, W. E., Franco, A. R., Craddock, R. C., & Mayberg, H. S. (2013). Toward a neuroimaging treatment selection biomarker for major depressive disorder. *JAMA Psychiatry*, *70*(8), 821–829.

McKinnon, M. C., Yucel, K., Nazarov, A., & MacQueen, G. M. (2009). A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. *Journal of Psychiatry and Neuroscience*, *34*(1), 41–54.

Menon, V. (2011). Large-scale brain networks and psychopathology: a unifying triple network model. *Trends in Cognitive Sciences*, *15*(10), 483–506.

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure and Function*, *214*(5), 655–667.

Mervaala, E., Könönen, M., Föhr, J., Husso-Saastamoinen, M., Valkonen-Korhonen, M., Kuikka, J. T., Viinamäki, H., Tammi, A.-K., Tiihonen, J., & Partanen, J. (2001). SPECT and neuropsychological performance in severe depression treated with ECT. *Journal of Affective Disorders*, *66*(1), 47–58.

Michael, N., Erfurth, A., Ohrmann, P., Arolt, V., Heindel, W., & Pfleiderer, B. (2003). Neurotrophic effects of electroconvulsive therapy: a proton magnetic resonance study of the left amygdalar region in patients with treatment-resistant depression. *Neuropsychopharmacology*, *28*(4), 720–725.

Miller, J., Jones, T., Upston, J., Deng, Z.-D., McClintock, S. M., Ryman, S., Quinn, D., & Abbott, C. C. (2022). Ictal theta power as an electroconvulsive therapy safety biomarker: a pilot study. *The Journal of ECT*, *38*(2), 88–94.

Misanin, J. R., Miller, R. R., & Lewis, D. J. (1968). Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace. *Science*, *160*(3827), 554–555.

Montgomery, S. A., & Åsberg, M. (1979). A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry*, *134*(4), 382–389.

Mulders, P. C., van Eijndhoven, P. F., Schene, A. H., Beckmann, C. F., & Tendolkar, I. (2015). Resting-state functional connectivity in major depressive disorder: a review. *Neuroscience & Biobehavioral Reviews*, *56*, 330–344.

Nader, K., & Einarsson, E. Ö. (2010). Memory reconsolidation: an update. *Annals of the New York Academy of Sciences*, *1191*(1), 27–41.

Namkung, H., Kim, S.-H., & Sawa, A. (2017). The insula: an underestimated brain area in clinical neuroscience, psychiatry, and neurology. *Trends in Neurosciences*, *40*(4), 200–207.

Navarro, V., Gastó, C., Lomeña, F., Mateos, J. J., Portella, M. J., Massana, G., Bernardo, M., & Marcos, T. (2004). Frontal cerebral perfusion after antidepressant drug treatment versus ECT in elderly patients with major depression: a 12-month follow-up control study. *Journal of Clinical Psychiatry*, *65*, 656–661.

Nibuya, M., Morinobu, S., & Duman, R. S. (1995). Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *Journal of Neuroscience*, *15*(11), 7539–7547.

O'Connor, M. K., Knapp, R., Husain, M., Rummans, T. A., Petrides, G., Smith, G., Mueller, M., Snyder, K., Bernstein, H., & Rush, A. J. (2001). The influence of age on the response of major depression to electroconvulsive therapy: a CORE Report. *The American Journal of Geriatric Psychiatry*, *9*(4), 382–390.

Ohayon, M. M., & Schatzberg, A. F. (2002). Prevalence of depressive episodes with psychotic features in the general population. *American Journal of Psychiatry*, *159*(11), 1855–1861.

Oltedal, L., Bartsch, H., Sørhaug, O. J. E., Kessler, U., Abbott, C., Dols, A., Stek, M. L., Ersland, L., Emsell, L., & van Eijndhoven, P. (2017). The Global ECT-MRI Research Collaboration (GEMRIC): Establishing a multi-site investigation of the neural mechanisms underlying response to electroconvulsive therapy. *NeuroImage: Clinical*, *14*, 422–432.

Oudega, M. L., van Exel, E., Wattjes, M. P., Comijs, H. C., Scheltens, P., Barkhof, F., Eikelenboom, P., de Craen, A. J. M., Beekman, A. T. F., & Stek, M. L. (2010). White matter hyperintensities, medial temporal lobe atrophy, cortical atrophy, and response to electroconvulsive therapy in severely depressed elderly patients. *The Journal of Clinical Psychiatry*, *71*(1), 22435.

Ousdal, O. T., Argyelan, M., Narr, K. L., Abbott, C., Wade, B., Vandenbulcke, M., Urretavizcaya, M., Tendolkar, I., Takamiya, A., & Stek, M. L. (2020). Brain changes induced by electroconvulsive therapy are broadly distributed. *Biological Psychiatry*, *87*(5), 451–461.

Pagnin, D., de Queiroz, V., Pini, S., & Cassano, G. B. (2008). Efficacy of ECT in depression: a meta-analytic review. *Focus*, *6*(1), 155–162.

Paulus, M. P., & Stein, M. B. (2010). Interoception in anxiety and depression. *Brain Structure and Function*, *214*(5), 451–463.

Peeters, F. P. M. L., Ruhe, H. G., Wichers, M., Abidi, L., Kaub, K., van der Lande, H. J., Spijker, J., Huibers, M. J. H., & Schene, A. H. (2016). The Dutch measure for quantification of treatment resistance in depression (DM-TRD): an extension of the Maudsley staging method. *Journal of Affective Disorders*, *205*, 365–371.

Perera, T. D., Luber, B., Nobler, M. S., Prudic, J., Anderson, C., & Sackeim, H. A. (2004). Seizure expression during electroconvulsive therapy: relationships with clinical outcome and cognitive side effects. *Neuropsychopharmacology*, *29*(4), 813–825.

Petrides, G., Fink, M., Husain, M. M., Knapp, R. G., Rush, A. J., Mueller, M., Rummans, T. A., O'Connor, K. M., Rasmussen Jr, K. G., & Bernstein, H. J. (2001). ECT remission rates in psychotic versus nonpsychotic depressed patients: a report from CORE. *The Journal of ECT*, *17*(4), 244–253.

Pigott, H. E., Leventhal, A. M., Alter, G. S., & Boren, J. J. (2010). Efficacy and effectiveness of antidepressants: current status of research. *Psychotherapy and Psychosomatics*, *79*(5), 267–279.

Porta-Casteràs, D., Cano, M., Camprodon, J. A., Loo, C., Palao, D., Soriano-Mas, C., & Cardoner, N. (2021). A multimetric systematic review of fMRI findings in patients with MDD receiving ECT. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *108*, 110178.

Pottkämper, J. C. M., Verdijk, J. P. A. J., Hofmeijer, J., van Waarde, J. A., & van Putten, M. J. A. M. (2021). Seizures induced in electroconvulsive therapy as a human epilepsy model: A comparative case study. *Epilepsia Open*, *6*(4), 672–684.

Prudic, J., Olfson, M., Marcus, S. C., Fuller, R. B., & Sackeim, H. A. (2004). Effectiveness of electroconvulsive therapy in community settings. *Biological Psychiatry*, *55*(3), 301–312.

Pruim, R. H. R., Mennes, M., van Rooij, D., Llera, A., Buitelaar, J. K., & Beckmann, C. F. (2015). ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. *Neuroimage*, *112*, 267–277.

Qi, S., Abbott, C. C., Narr, K. L., Jiang, R., Upston, J., McClintock, S. M., Espinoza, R., Jones, T., Zhi, D., & Sun, H. (2020). Electroconvulsive therapy treatment responsive multimodal brain networks. *Human Brain Mapping*, *41*(7), 1775–1785.

Radiske, A., Gonzalez, M. C., Conde-Ocazionez, S., Rossato, J. I., Köhler, C. A., & Cammarota, M. (2020). Cross-frequency phase-amplitude coupling between hippocampal theta and gamma oscillations during recall destabilizes memory and renders it susceptible to reconsolidation disruption. *Journal of Neuroscience*, *40*(33), 6398–6408.

Raes, F., & Hermans, D. (2011). De Nederlandstalige versie van de Automatic Thoughts Questionnaire-Revised (ATQ-R-NL). *Gedragstherapie*.

Raichle, M. E. (2011). The restless brain. *Brain Connectivity*, *1*(1), 3–12.

Ray, D., Bezmaternykh, D., Mel'nikov, M., Friston, K. J., & Das, M. (2021). Altered effective connectivity in sensorimotor cortices is a signature of severity and clinical course in depression. *Proceedings of the National Academy of Sciences*, *118*(40), e2105730118.

Razi, A., Kahan, J., Rees, G., & Friston, K. J. (2015). Construct validation of a DCM for resting state fMRI. *Neuroimage*, *106*, 1–14.

Razi, A., Seghier, M. L., Zhou, Y., McColgan, P., Zeidman, P., Park, H.-J., Sporns, O., Rees, G., & Friston, K. J. (2017). Large-scale DCMs for resting-state fMRI. *Network Neuroscience*, *1*(3), 222–241.

Redlich, R., Opel, N., Grotegerd, D., Dohm, K., Zaremba, D., Bürger, C., Münker, S., Mühlmann, L., Wahl, P., & Heindel, W. (2016). Prediction of individual response to electroconvulsive therapy via machine learning on structural magnetic resonance imaging data. *JAMA Psychiatry*, *73*(6), 557–564.

Rolls, E. T., Cheng, W., Gilson, M., Qiu, J., Hu, Z., Ruan, H., Li, Y., Huang, C.-C., Yang, A. C., & Tsai, S.-J. (2018). Effective connectivity in depression. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *3*(2), 187–197.

Rosenquist, P. B., McCall, W. V., Colenda, C. C., & Melton, B. A. (1998). A comparison of visual and computer-generated measures of" seizure quality". *The Journal of ECT*, *14*(2), 76–82.

Royston, P., Altman, D. G., & Sauerbrei, W. (2006). Dichotomizing continuous predictors in multiple regression: a bad idea. *Statistics in Medicine*, *25*(1), 127–141.

Rubin, R. D. (1976). Clinical use of retrograde amnesia produced by electroconvulsive shock: a conditioning hypothesis. *Canadian Psychiatric Association Journal*, *21*(2), 87–90.

Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., Niederehe, G., Thase, M. E., Lavori, P. W., & Lebowitz, B. D. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR* D report. *American Journal of Psychiatry*, *163*(11), 1905–1917.

Sackeim, H. A., Decina, P., Prohovnik, I., Malitz, S., & Resor, S. R. (1983). Anticonvulsant and antidepressant properties of electroconvulsive therapy: a proposed mechanism of action. *Biological Psychiatry*.

Sackeim, H. A., Haskett, R. F., Mulsant, B. H., Thase, M. E., Mann, J. J., Pettinati, H. M., Greenberg, R. M., Crowe, R. R., Cooper, T. B., & Prudic, J. (2001). Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *Jama*, *285*(10), 1299–1307.

Sackeim, H. A., Prudic, J., Devanand, D. P., Kiersky, J. E., Fitzsimons, L., Moody, B. J., McElhiney, M. C., Coleman, E. A., & Settembrino, J. M. (1993). Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *New England Journal of Medicine*, *328*(12), 839–846.

Sackeim, H. A., Prudic, J., Devanand, D. P., Nobler, M. S., Lisanby, S. H., Peyser, S., Fitzsimons, L., Moody, B. J., & Clark, J. (2000). A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Archives of General Psychiatry*, *57*(5), 425–434.

Sartorius, A., Karl, S., & Zilles-Wegner, D. (2022). Hippocampal neuroplasticity, major depression and, not to forget: ECT. *Molecular Psychiatry*, 1–2.

Scheepens, D. S., van Waarde, J. A., Lok, A., Zantvoord, J. B., de Pont, B., Ruhé, H. G., Denys, D., & van Wingen, G. A. (2019). Electroconvulsion therapy for persistent depression in the Netherlands; very low application rate. *Tijdschrift Voor Psychiatrie*, *61*(1), 16–21.

Schlösser, R. G. M., Wagner, G., Koch, K., Dahnke, R., Reichenbach, J. R., & Sauer, H. (2008). Fronto-cingulate effective connectivity in major depression: a study with fMRI and dynamic causal modeling. *Neuroimage*, *43*(3), 645–655.

Serafini, G. (2012). Neuroplasticity and major depression, the role of modern antidepressant drugs. *World Journal of Psychiatry*, *2*(3), 49.

Sheehan, D. V, Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*, *59*(20), 22–33.

Sheline, Y. I., Sanghavi, M., Mintun, M. A., & Gado, M. H. (1999). Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *Journal of Neuroscience*, *19*(12), 5034–5043.

Simon, G. E., & Perlis, R. H. (2010). Personalized medicine for depression: can we match patients with treatments? *American Journal of Psychiatry*, *167*(12), 1445–1455.

Späti, J., Chumbley, J., Brakowski, J., Dörig, N., Grosse Holtforth, M., Seifritz, E., & Spinelli, S. (2014). Functional lateralization of the anterior insula during feedback processing. *Human Brain Mapping*, *35*(9), 4428–4439.

Sprengelmeyer, R., Steele, J. D., Mwangi, B., Kumar, P., Christmas, D., Milders, M., & Matthews, K. (2011). The insular cortex and the neuroanatomy of major depression. *Journal of Affective Disorders*, *133*(1–2), 120–127.

Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences*, *105*(34), 12569–12574.

Srinivasan, R., Winter, W. R., Ding, J., & Nunez, P. L. (2007). EEG and MEG coherence: measures of functional connectivity at distinct spatial scales of neocortical dynamics. *Journal of Neuroscience Methods*, *166*(1), 41–52.

Steriade, M., Gloor, P., Llinas, R. R., Da Silva, F. H. L., & Mesulam, M.-M. (1990). Basic mechanisms of cerebral rhythmic activities. *Electroencephalography and Clinical Neurophysiology*, *76*(6), 481–508.

Suwa, T., Namiki, C., Takaya, S., Oshita, A., Ishizu, K., Fukuyama, H., Suga, H., & Murai, T. (2012). Corticolimbic balance shift of regional glucose metabolism in depressed patients treated with ECT. *Journal of Affective Disorders*, *136*(3), 1039–1046.

Suzuki, A., Josselyn, S. A., Frankland, P. W., Masushige, S., Silva, A. J., & Kida, S. (2004). Memory reconsolidation and extinction have distinct temporal and biochemical signatures. *Journal of Neuroscience*, *24*(20), 4787–4795.

Takamiya, A., Chung, J. K., Liang, K., Graff-Guerrero, A., Mimura, M., & Kishimoto, T. (2018). Effect of electroconvulsive therapy on hippocampal and amygdala volumes: systematic review and meta-analysis. *The British Journal of Psychiatry*, *212*(1), 19–26.

Taliaz, D., Stall, N., Dar, D. E., & Zangen, A. (2010). Knockdown of brain-derived neurotrophic factor in specific brain sites precipitates behaviors associated with depression and reduces neurogenesis. *Molecular Psychiatry*, *15*(1), 80–92.

Taylor, S. M. (2008). Electroconvulsive therapy, brain-derived neurotrophic factor, and possible neurorestorative benefit of the clinical application of electroconvulsive therapy. *The Journal of ECT*, *24*(2), 160–165.

Team, R. C. (2013). *R: A language and environment for statistical computing*.

ten Doesschate, F, van Waarde, J. A., & van Wingen, G. A. (2021). Non-superiority of zuranolone (SAGE-217) at the longer-term. *Journal of Affective Disorders*.

ten Doesschate, Freek, van Wingen, G. A., & van Waarde, J. A. (2015). Clinical and neural correlates of ictal interhemispheric EEG coherence during electroconvulsive therapy. *BIOLOGICAL PSYCHIATRY*, *77*(9).

Tendolkar, I., van Beek, M., van Oostrom, I., Mulder, M., Janzing, J., Voshaar, R. O., & van Eijndhoven, P. (2013). Electroconvulsive therapy increases hippocampal and amygdala volume in therapy refractory depression: a longitudinal pilot study. *Psychiatry Research: Neuroimaging*, *214*(3), 197–203.

Terhaar, J., Viola, F. C., Bär, K.-J., & Debener, S. (2012). Heartbeat evoked potentials mirror altered body perception in depressed patients. *Clinical Neurophysiology*, *123*(10), 1950–1957.

The, U. K. (2003). Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *The Lancet*, *361*(9360), 799–808.

Thoenen, H. (1995). Neurotrophins and neuronal plasticity. *Science*, *270*(5236), 593–598.

Thorlund, K., Dron, L., Park, J. J. H., & Mills, E. J. (2020). Synthetic and external controls in clinical trials–a primer for researchers. *Clinical Epidemiology*, *12*, 457.

van de Mortel, L. A., Bruin, W. B., Thomas, R. M., Abbott, C., Argyelan, M., van Eijndhoven, P., Mulders, P., Narr, K. L., Tendolkar, I., & Verdijk, J. (2022). Multimodal multi-center analysis of electroconvulsive therapy effects in depression: Brainwide gray matter increase without functional changes. *Brain Stimulation*, *15*(5), 1065–1072.

Van den Broek, W. W., Birkenhäger, T. K., De Boer, D., Burggraaf, J. P., van Gemert, B., & Groenland, T. H. N. (2010). Richtlijn elektroconvulsietherapie. *Dutch Association for Psychiatry*.

Van Der Vinne, N., Vollebregt, M. A., Van Putten, M. J. A. M., & Arns, M. (2017). Frontal alpha asymmetry as a diagnostic marker in depression: Fact or fiction? A meta-analysis. *Neuroimage: Clinical*, *16*, 79–87.

Van Diermen, L., Van Den Ameele, S., Kamperman, A. M., Sabbe, B. C. G., Vermeulen, T., Schrijvers, D., & Birkenhäger, T. K. (2018). Prediction of electroconvulsive therapy response and remission in major depression: meta-analysis. *The British Journal of Psychiatry*, *212*(2), 71–80.

Van Eijndhoven, P., van Wingen, G., van Oijen, K., Rijpkema, M., Goraj, B., Verkes, R. J., Voshaar, R. O., Fernández, G., Buitelaar, J., & Tendolkar, I. (2009). Amygdala volume marks the acute state in the early course of depression. *Biological Psychiatry*, *65*(9), 812–818.

Van Waarde, J. A., Scholte, H. S., Van Oudheusden, L. J. B., Verwey, B., Denys, D., & Van Wingen, G. A. (2015). A functional MRI marker may predict the outcome of electroconvulsive therapy in severe and treatment-resistant depression. *Molecular Psychiatry*, *20*(5), 609–614.

van Waarde, J. A, van Oudheusden, L. J. B., Heslinga, O. B., Verwey, B., van der Mast, R. C., & Giltay, E. (2013). Patient, treatment, and anatomical predictors of outcome in electroconvulsive therapy: a prospective study. *The Journal of ECT*, *29*(2), 113–121.

van Waarde, J. A, van Oudheusden, L. J. B., Verwey, B., Giltay, E. J., & van der Mast, R. C. (2013). Clinical predictors of seizure threshold in electroconvulsive therapy: a prospective study. *European Archives of Psychiatry and Clinical Neuroscience*, *263*(2), 167–175.

van Wingen, G. A., Arns, M., & van waarde, J. A. (2019). Klinische, somatische en neurale voorspellers van behandeluitkomst. In van waarde, J. A. & Verwey, B. (Eds.), *Leerboek Electroconvulsietherapie.* Boom psychologie en psychiatrie.

Vangu, M. D. T., Esser, J. D., Boyd, I. H., & Berk, M. (2003). Effects of electroconvulsive therapy on regional cerebral blood flow measured by 99mtechnetium HMPAO SPECT. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *27*(1), 15–19.

Verdijk, J. P. A. J., Pottkämper, J., Verwijk, E., van Wingen, G. A., van Putten, M. J. A. M., Hofmeijer, J., & van Waarde, J. A. (2022). Study of effect of nimodipine and acetaminophen on postictal symptoms in depressed patients after electroconvulsive therapy (SYNAPSE). *Trials*, *23*(1), 1–15.

Volavka, J., Feldstein, S., Abrams, R., Dornbush, R., & Fink, M. (1972). EEG and clinical change after bilateral and unilateral electroconvulsive therapy. *Electroencephalography and Clinical Neurophysiology*, *32*(6), 631–639.

Wagenmakers, E.-J., Marsman, M., Jamil, T., Ly, A., Verhagen, J., Love, J., Selker, R., Gronau, Q. F., Šmíra, M., & Epskamp, S. (2018). Bayesian inference for psychology. Part I: Theoretical advantages and practical ramifications. *Psychonomic Bulletin & Review*, *25*(1), 35–57.

Wang, L., Wei, Q., Wang, C., Xu, J., Wang, K., Tian, Y., & Wang, J. (2020). Altered functional connectivity patterns of insular subregions in major depressive disorder after electroconvulsive therapy. *Brain Imaging and Behavior*, *14*(3), 753–761.

Wang, S.-H., & Morris, R. G. M. (2010). Hippocampal-neocortical interactions in memory formation, consolidation, and reconsolidation. *Annual Review of Psychology*, *61*(1), 49–79.

Wang, Wang, Huang, Jia, Zheng, Zhong, Chen, G., Huang, L., & Huang, R. (2020). Abnormal dynamic functional network connectivity in unmedicated bipolar and major depressive disorders based on the triple-network model. *Psychological Medicine*, *50*(3), 465–474.

Wang, Wei, Bai, Zhou, Sun, Becker, B., Tian, Y., Wang, K., & Kendrick, K. (2017). Electroconvulsive therapy selectively enhanced feedforward connectivity from fusiform face area to amygdala in major depressive disorder. *Social Cognitive and Affective Neuroscience*, *12*(12), 1983–1992.

Watts, B. V, Groft, A., Bagian, J. P., & Mills, P. D. (2011). An examination of mortality and other adverse events related to electroconvulsive therapy using a national adverse event report system. *The Journal of ECT*, *27*(2), 105–108.

Wei, Q., Ji, Y., Bai, T., Zu, M., Guo, Y., Mo, Y., Ji, G., Wang, K., & Tian, Y. (2021). Enhanced cerebro-cerebellar functional connectivity reverses cognitive impairment following electroconvulsive therapy in major depressive disorder. *Brain Imaging and Behavior*, *15*(2), 798–806.

Wei, Qin, Yan, Bi, Liu, C., Yao, Z., & Lu, Q. (2017). Abnormal dynamic community structure of the salience network in depression. *Journal of Magnetic Resonance Imaging*, *45*(4), 1135–1143.

Weiner, R. D. (1982). Electroencephalographic correlates of ECT. *Psychopharmacology Bulletin*, *18*(2), 78–81.

Wiebking, C., Bauer, A., De Greck, M., Duncan, N. W., Tempelmann, C., & Northoff, G. (2010). Abnormal body perception and neural activity in the insula in depression: an fMRI study of the depressed "material me." *The World Journal of Biological Psychiatry*, *11*(3), 538–549.

Young, K. D., Drevets, W. C., Bodurka, J., & Preskorn, S. S. (2016a). Amygdala activity during autobiographical memory recall as a biomarker for residual symptoms in patients remitted from depression. *Psychiatry Research: Neuroimaging*, *248*, 159–161.

Young, K. D., Siegle, G. J., Bodurka, J., & Drevets, W. C. (2016b). Amygdala activity during autobiographical memory recall in depressed and vulnerable individuals: association with symptom severity and autobiographical overgenerality. *American Journal of Psychiatry*, *173*(1), 78–89.

Young, K. D., Siegle, G. J., Zotev, V., Phillips, R., Misaki, M., Yuan, H., Drevets, W. C., & Bodurka, J. (2017). Randomized clinical trial of real-time fMRI amygdala neurofeedback for major depressive disorder: effects on symptoms and autobiographical memory recall. *American Journal of Psychiatry*, *174*(8), 748–755.

Yrondi, A., Fiori, L. M., Nogovitsyn, N., Hassel, S., Théroux, J. F., Aouabed, Z., Frey, B. N., Lam, R. W., Milev, R., & Müller, D. J. (2021). Association between the expression of lncRNA BASP-AS1 and volume of right hippocampal tail moderated by episode duration in major depressive disorder: a CAN-BIND 1 report. *Translational Psychiatry*, *11*(1), 1–7.

Yu, H., & Chen, Z. (2011). The role of BDNF in depression on the basis of its location in the neural circuitry. *Acta Pharmacologica Sinica*, *32*(1), 3–11.

Zhang, J. J., Haubrich, J., Bernabo, M., Finnie, P. S. B., & Nader, K. (2018). Limits on lability: Boundaries of reconsolidation and the relationship to metaplasticity. *Neurobiology of Learning and Memory*, *154*, 78–86.

Zhang, T., Bai, T., Xie, W., Wei, Q., Lv, H., Wang, A., Guan, J., Tian, Y., & Wang, K. (2021). Abnormal connectivity of anterior-insular subdivisions and relationship with somatic symptom in depressive patients. *Brain Imaging and Behavior*, *15*(4), 1760–1768.

NEDERLANDSE SAMENVATTING

In dit proefschrift onderzoek ik elektroconvulsietherapie (ECT) met als doel om de klinische uitkomst na de behandeling te verbeteren en om de werkingsmechanismen beter te begrijpen. In Hoofdstuk 1 wordt ECT geïntroduceerd als behandeloptie voor ernstige depressie. Ik geef een korte beschrijving van de geschiedenis van ECT, hoe het is ontwikkeld vanaf het einde van de jaren 1930, en beschrijf ik hoe ECT tegenwoordig klinisch wordt toegepast. Vervolgens stel ik een taxonomie van ECT-onderzoek voor, waarin studies kunnen worden geclassificeerd op basis van hun primaire doel. Studies kunnen grofweg worden onderverdeeld in twee hoofddoelstellingen: (1) studies die gericht zijn op het verbeteren van de klinische uitkomst van ECT door behandelingsmodificatie of behandelingstoewijzing te onderzoeken, en (2) studies die gericht zijn op het verbeteren van het klinische begrip van de werkingsmechanismen van ECT door analyses van gemeten ictale of extra-ictale effecten. Deze takken van onze taxonomie kunnen verder worden onderverdeeld op basis van de specifieke maten die in het onderzoek worden gebruikt. De afzonderlijke hoofdstukken van dit proefschrift kunnen worden gezien als voorbeeld-casus van de verschillende soorten onderzoeken in deze taxonomie.

In Hoofdstuk 2 bestuderen we een behandelingsmodificatie, waarin we een nieuwe geheugenreactiveringsinterventie combineren met ECT. Recente en vroegere studies suggereerden dat geheugenreactivering vlak voor een ECT-sessie de reconsolidatie van de gereactiveerde herinnering kan verstoren. Daarom reactiveerden we, als experimentele interventie, herinneringen – die centraal stonden in de negatieve schema's van depressieve patiënten - vlak voor de ECT-sessies gedurende het hele behandeltraject. Tweeënzeventig patiënten werden geïncludeerd in de gerandomiseerde gecontroleerde studie (RCT) en de interventie werd vergeleken met een controleconditie. De bevindingen suggereren dat de geheugenreactivering net voorafgaand aan ECT-sessies de klinische effectiviteit niet verbeterde, noch de snelheid van herstel verhoogde of het terugvalpercentage verminderde. Verschillende beperkingen worden besproken die de nulbevindingen kunnen verklaren.

In Hoofdstuk 3 onderzoeken we of het pre-ECT grijze stof volume van de amygdala en hippocampus de ECT-effectiviteit kan voorspellen. Dit is een voorbeeld van een studie die meer direct gericht is op het verbeteren van de klinische uitkomst van ECT en het verbeteren van behandelingstoewijzing. Drieënvijftig patiënten die leden aan ernstige unipolaire depressie werden in deze studie opgenomen. Een week voor ECT werden structurele *magnetic resonance imaging* (MRI) gegevens verkregen en werden grijze-stof volumes van de hippocampus en amygdala bepaald. Regressiemodellen werden gebruikt om te onderzoeken of deze volumes de ECT-effectiviteit vooraf konden voorspellen. We laten zien dat een groter amygdala-volume een lagere ernst van post-ECT-depressie op groepsniveau voorspelde. Het volume van de hippocampus vertoonde geen onafhankelijke voorspellende waarde. Met behulp van *leave-one-out cross-validation* laten we zien dat amygdala-volumes tezamen met demografische maten ook ECT-uitkomsten op individueel niveau kunnen voorspellen. Deze bevindingen suggereren dat het amygdala volume (een deel van) een *biomarker* voor ECT-uitkomst kan zijn, wat kan leiden tot een betere behandelingstoewijzing.

In Hoofdstuk 4 bestuderen we elektro-encefalografische (EEG) metingen tijdens het ECT-geïnduceerde insult en de relatie met ECT-effectiviteit. Deze studie heeft tot doel het klinische begrip van de werkingsmechanismen van ECT te verbeteren door metingen van ictale effecten te gebruiken. In het bijzonder hebben we de longitudinale effecten van ictale interhemisferische EEG-coherentie tussen de twee frontale elektroden onderzocht en deze maat geassocieerd met de ECT-uitkomst. Deze studie omvatte 65 patiënten met een ernstige depressieve stoornis. Ictale interhemisferische (fp1-fp2) EEG-coherentie werd vastgesteld tijdens de eerste en elke opeenvolgende zesde behandelingssessie tijdens de ECT-kuur. Longitudinale veranderingen en associaties met ECT-effectiviteit werden vastgesteld met behulp van lineaire mixed-effects modellen. We laten een longitudinale toename zien van ictale interhemisferische coherentie in de theta en alfa EEG frequentiebanden. Bovendien waren ictale EEG-coherenties in de delta- en theta-band gemiddeld over de ECT-sessies geassocieerd met de effectiviteit van de behandeling. ECT-effectiviteit lijkt dus gerelateerd te zijn aan ictale EEG-coherentie die consistent is tijdens de behandeling, in plaats van ictale EEG-coherentie die in de loop van de tijd verandert.

In Hoofdstuk 5 bestuderen we effectieve functionele hersenconnectiviteit voor en na de ECT-kuur. Deze studie heeft tot doel het klinische begrip van ECT te verbeteren met behulp van extra-ictale maten. Een recent onderzoek in meerdere behandelcentra vond geen consistente, op correlatie gebaseerde functionele connectiviteitseffecten na ECT. Daarom hebben we een ander type functionele connectiviteit gebruikt, effectieve connectiviteit, om te onderzoeken of we met deze maat wel in staat waren om een consistent effect over verschillende behandelcentra te vinden. *Dynamic causal modeling* (DCM) werd gebruikt om effectieve connectiviteit te bepalen. Dit is een Bayesiaanse methode die een *neural mass* model gebruikt om *directed* (in tegenstelling tot *undirected*) hersenconnectiviteit af te leiden. Deze multicenter studie omvatte gegevens van 189 patiënten die leden aan ernstige unipolaire depressie en 59 gezonde controledeelnemers. De analyses leverden tal van effectieve connectiviteitsparameters op die consequent veranderden na de ECT-kuur in data van verschillende behandelcentra, gecorrigeerd voor test-hertest variabiliteit in gezonde controles. Ook was de ECT-uitkomst geassocieerd met veranderingen in connectiviteit van het posterior *default mode network* naar de bilaterale insula. Effectieve connectiviteitsmaten tussen hersennetwerken die belangrijk zijn voor emotie en cognitie vertonen dus consistente effecten tussen verschillende behandelcentra.

Ten slotte geven we in Hoofdstuk 7 eerst een korte samenvatting van onze bevindingen per hoofdstuk. Vervolgens bespreken we deze bevindingen in het licht van onze voorgestelde taxonomie van ECT-onderzoek. We bespreken mogelijke toekomstige richtingen voor onderzoeksmethoden die geschikt kunnen zijn voor de verschillende typen ECT-onderzoeken. We besluiten met enkele korte opmerkingen over de relevantie van de bevindingen in dit proefschrift. De taxonomie en casus-studies die in dit proefschrift worden gepresenteerd, kunnen ook dienen als introductie en overzicht van de momenteel beschikbare onderzoeksmethoden, die verder ECT-onderzoek kunnen stimuleren.

ACKNOWLEDGEMENTS / DANKWOORD

Dit is het dan. De laatste woorden van mijn proefschrift! Wat heb ik hier lang naar uitgekeken. Om deze lange weg, met veel pieken en dalen, af te sluiten, sta ik graag nog even stil bij wie mij in dit proces hebben bijgestaan.

Ik wil beginnen bij mijn promotor Guido van Wingen. Guido, ik wil je heel erg bedanken voor deze tweede kans die je me hebt gegeven om dit traject onder jouw begeleiding af te leggen! Ik begon ooit een eerder promotietraject bij jou. Je was erg begripvol toen ik hiermee stopte om op persoonlijk vlak stappen te zetten. En ook toen het vuur om onderzoek te doen in mij toch weer ging branden, stond jij snel open om mij weer te verwelkomen. Hiervoor ben ik je erg dankbaar! Deze onbevooroordeelde en medemenselijke blik waarmee jij, in mijn ervaring, naar de wereld kijkt heb ik gedurende het hele traject in jouw begeleiding ervaren. Daarnaast heb erg veel gehad aan jou scherpe analytische manier van denken en al jouw ervaring. Als je er nog niet zo bekend mee bent, kan de wetenschappelijke wereld soms voelen als een doolhof. Al jouw ervaring in deze wereld was cruciaal om me door dit doolhof te manoeuvreren. Bedankt!

Dan wil ik graag stilstaan bij mijn copromotor, Jeroen van Waarde. Jeroen, ik heb je inmiddels meer dan 10 jaar geleden leren kennen via mijn broer. Sindsdien hebben we samen mooie reizen gemaakt (New York en Toronto) om congressen te bezoeken. Maar, in plaats van de wetenschappelijke presentaties, zijn het vooral onze wandelingen, ontspanningsmomenten en musea bezoeken die me zijn bijgebleven, die altijd gepaard gingen met mooie gesprekken! Jouw begeleiding bij het proefschrift was van onschatbare waarde. Het immense tempo waarop jij denkt en dingen voor elkaar krijgt heeft me geïnspireerd. Soms ben ik in dit traject obstakels tegen gekomen waarvan ik niet wist wat er mee aan moest. Als ik er dan met jouw over had gesproken, bleef er van deze obstakels weinig meer over en zag ik vooral nieuwe mogelijkheden. Jeroen, zonder jou was dit proefschrift er niet geweest, was ik nu niet opgeleid tot psychotherapeut en had ik nu niet bij het Rijnstate ziekenhuis gewerkt. Ik heb me soms verbaasd waar ik al deze kansen aan verdiend heb, maar ik ben je er erg dankbaar voor!

Ik wil ook alle patiënten bedanken die aan deze onderzoeken hebben meegewerkt. Nu ik de opleiding tot psychotherapeut heb afgerond heb ik een beter beeld van wie deze patiënten zijn. Als onderzoeker was het voor mij soms makkelijk om te denken in datapunten of proefpersonen. Echter heb ik tijdens mijn werk als therapeut ontdekt dat er achter elk datapunt en proefpersoon een heel leven schuil gaat. In het geval van de studies die in dit proefschrift staan, levens waarin mensen lijden onder een vaak onverdraagbare somberheid, wanhoop en machteloosheid. Dat deze mensen, die aan het eind van hun latijn zijn, zich nog in willen spannen om deel te nemen aan onderzoek, waarmee ze toekomstige mensen in een soortgelijke situatie kunnen helpen, heb ik diep respect voor. Misschien dat deze mensen dit nooit zullen lezen, toch wil ik ze hier heel erg voor bedanken!

Daarnaast wil ik graag mijn collega's (zowel in het onderzoek als in de kliniek), werkbegeleiders, supervisoren, de psychotherapie opleidingsgroep en leertherapeuten bedanken. De afgelopen

jaren waren pittig. Er kwamen veel nieuwe dingen op me af, zowel in het onderzoek als in de psychotherapie. Leren blijkt gepaard te gaan met veel frustratie, vermoeidheid, op je bek gaan en weer opstaan. Zonder jullie inzichten, steun en aanmoedigingen om me te blijven ontwikkelen was dit niet gelukt! In het bijzonder wil ik hierbij noemen: Oscar Buno Heslinga, Boudewijn de Pont, Heidi Delcliseur en Esther Hameleers. Bedankt!

Naast alle hulp vanuit de werkgerelateerde hoek, heb ik ook veel steun ervaren vanuit persoonlijke kring. Om te beginnen van mijn vrienden. Door jullie kon ik mijn zinnen verzetten als ik weer eens diep met mijn gedachten in het onderzoek verzonken zat. Ik kon mijn struggles met jullie delen, met jullie ouwehoeren, feesten, ontspannen en mooie gesprekken over het leven voeren. Door jullie aanwezigheid ben ik altijd bewust gebleven dat er meer is dan alleen promoveren en opleiding. Het is heerlijk om met zulk mooie mensen om mij heen te mogen leven! Veel van jullie ken ik al vanaf de basisschool of middelbare school. Hierdoor weten we van elkaar wie we waren, wie we nu zijn, en ik hoop dat we nog lang met elkaar mee zullen lopen om te zien wie we gaan worden!

Als laatste wil ik de mensen die het dichtst bij me staan bedanken, mijn familie. Om te beginnen met Sam en Thijs, mijn broers en tevens mijn paranimfen. Het is een zegen om met twee oudere broers zoals jullie door het leven te gaan. Sam, jouw betrokkenheid en positieve energie hebben me steeds weer gesteund tijdens dit proces. Onze gesprekken over wie we als persoon zijn en waar we naartoe willen helpen me steeds weer opnieuw koers te houden, zowel in mijn persoonlijke leven als op professioneel vlak. Thijs, door jouw intelligentie, betrokkenheid, humor en realistische kijk op de wereld kan ik in contact met jou vaak weer een frisse blik op het leven krijgen. Het belang, maar ook de absurditeit en de humor ervan in zien. Waardevol hoe dit alles vaak weer even in perspectief zet, zeker in deze hectische jaren. Evelien, mijn schoonzus, wat fijn om jou als familie erbij te hebben. Je bent altijd betrokken en geïnteresseerd, dat is erg fijn om te merken. Ook waardeer ik het erg dat jullie deur altijd voor me open staat. En natuurlijk mijn neefje en nichtje, Lise en Pepijn! Al jullie knuffels, alle spelletjes die we samen hebben bedacht (de een nog gekker dan de ander) en al jullie grapjes geven het leven steeds weer meer kleur! En als laatste, en belangrijkste, mijn ouders, Jan Willem en Marianne, mam en pap. Jullie hebben altijd voor me klaar gestaan, in goede en in slechte tijden. Dat waardeer ik enorm. Willem, ik heb mijn sensitieve inborst van jou. Ik heb even moeten zoeken hoe daar mee om te gaan, maar nu is dit het kompas waar ik op vaar. Ook heb ik van jou geleerd om te willen weten hoe iets precies zit. Een eigenschap die het leven veel interessanter maakt en die onmisbaar is in het onderzoek. Mam, bij jou kan ik altijd met alles terecht. Ik heb van jou geleerd hoe belangrijk het is om waarachtig te zijn en trouw te blijven aan je idealen. Ook heb je me altijd laten zien hoe belangrijk het is om je in te zetten voor mensen die het minder hebben dan jijzelf. Jullie hebben me gevormd tot wie ik nu ben en daar ben ik jullie erg dankbaar voor!

CURRICULUM VITAE

Freek ten Doesschate was born on October 4th 1989 in Nijmegen, the Netherlands.

In 2009 he finished secondary school at the Nijmeegse Scholengemeenschap Groenewoud (NSG). After a short period of studying civil engineering at the Technical University Delft, he started studying Beta-Gamma at the University of Amsterdam. After the first year of his bachelor year, he started his major in psychobiology. Besides the main curriculum he attended multiple minors in various fields of research, e.g., in islamic history, thought and religion. In 2015 he earned his masters degree in Cognitive Neuroscience at the Donders Institute in Nijmegen, the Netherlands.

In 2016 he started a PhD in computational psychiatry at the Amsterdam Medical Center, the Netherlands. After one year, he took a break from science and focused on personal development for 1.5 year. In 2018, he restarted his PhD and he started his training as a psychotherapist at the Rijnstate hospital Arnhem, the Netherlands. Currently this is where he combines his clinical practice as a psychotherapist and his research endeavors.

PHD PORTFOLIO

Name PhD student: Freek ten Doesschate
Names of PhD supervisor(s) & co-supervisor(s):
Prof. dr. Guido A. van Wingen
Dr. Jeroen A. van Waarde

PhD training

		Year	ECTS
Specific courses			
1	Bayesian Cognitive Modeling: A Practical Course	2021-2022	2
2	Statistical Rethinking: A Bayesian Course with Examples in R and Stan	2022	2
3	Fast.ai: Practical deep learning for coders	2021-2022	2
Seminars, workshops and master classes			
- Meduna meeting (workgroup ECT Research Rijnstate)		2018-2022	0.5
Presentations			
4	Oral: Results Amygdala study, Working group ECT Netherlands (WEN)	2014	0.5
5	Poster: Amygdala study, SOBP	2014	0.5
6	Oral: Results sMRI-fMRI in ECT study, WEN	2015	0.5
7	Poster: Seizure coherence and white matter study, SOBP	2015	0.5
8	Poster: Seizure coherence and rs-fmri study SOBP	2015	0.5
9	Oral: Results GEMRIC DCM study, KHL-ECT meeting	2018	0.5
10	Oral: Results GEMRIC ICA study, KHL-ECT meeting	2019	0.5
11	Oral: Uniform analysis for SYNAPSE study, KHL-ECT meeting	2020	0.5
12	Oral: Results GEMRIC DCM Study, Voorjaarscongres NVVP	2022	0.2
(Inter)national conferences			
13	Society of Biological Psychiatry, meeting New York	2014	0.7
14	Society of Biological Psychiatry, meeting Toronto	2015	0.7
15	GEMRIC workshop, Bergen	2018	0.7
16	Voorjaarscongres NVVP	2022	0.7
Other			
17	Peer reviewing of articles	2018-2020	1
18	Conducting qualitative interviews for PVAD study	2018	1

Teaching

		Year	ECTS
Lecturing			
19	Attachment styles and neuroscience, Rijnstate psychiatry	2020	0.5
Tutoring, Mentoring			
20	Ouderen psychiater, scientific internship	2015	1
21	Marc van Megen, scientific internship	2017	1
22	Stef Verheesen, scientific internship	2018	1
23	Gijsbert Schuur, scientific internship	2020	1
24	Joey Verdijk, statistical assistance	2021	1
Supervising			
25	Amber Selie, MSc Thesis	2020	1.5
26	Tijn Stolk, MSc Thesis	2022	1.5

PUBLICATIONS

IN THIS THESIS

Scheepens DS, van Waarde JA, **Ten Doesschate F**, Westra M, Kroes MCW, Schene AH, Bockting CLH, Schoevers RA, Denys DAJP, Ruhé HG, van Wingen GA. Effectiveness of Emotional Memory Reactivation vs Control Memory Reactivation Before Electroconvulsive Therapy in Adult Patients With Depressive Disorder: A Randomized Clinical Trial. JAMA Netw Open. 2020 Aug 3;3(8):e2012389. doi: 10.1001/jamanetworkopen.2020.12389. PMID: 32749468; PMCID: PMC7403919.

Ten Doesschate F, van Wingen GA, de Pont BJHB, Arns M, van Waarde JA. The Longitudinal Effects of Electroconvulsive Therapy on Ictal Interhemispheric Coherence and Its Associations With Treatment Outcome: A Naturalistic Cohort Study. Clin EEG Neurosci. 2019 Jan;50(1):44-50. doi: 10.1177/1550059418781698. Epub 2018 Jun 21. PMID: 29929395.

Ten Doesschate F, van Eijndhoven P, Tendolkar I, van Wingen GA, van Waarde JA. Pre-treatment amygdala volume predicts electroconvulsive therapy response. Front Psychiatry. 2014 Nov 26;5:169. doi: 10.3389/fpsyt.2014.00169. PMID: 25505429; PMCID: PMC4244657.

Ten Doesschate F, Bruin W, Zeidman P, Abbott CC, Argyelan M, Dols A, ... van Waarde, JA & van Wingen GA (2023). Effective resting-state connectivity in severe unipolar depression before and after electroconvulsive therapy. *Brain stimulation*, *16*(4), 1128-1134.

OTHER PUBLICATIONS

Scheepens DS, van Waarde JA, **Ten Doesschate F**, Westra M, Kroes MCW, Schene AH, Schoevers RA, Denys D, Ruhé HG, van Wingen GA. Negative cognitive schema modification as mediator of symptom improvement after electroconvulsive therapy in major depressive disorder. J Affect Disord. 2022 Apr 28;310:156-161. doi: 10.1016/j.jad.2022.04.088. Epub ahead of print. PMID: 35490877.

Bruin WB, Oltedal L, Bartsch H, Abbott C, Argyelan M, Barbour T, Camprodon J, Chowdhury S, Espinoza R, Mulders P, Narr K, Oudega M, Rhebergen D, **ten Doesschate F**, Tendolkar I, van Eijndhoven P, van Exel E, van Verseveld M, Wade B, ... van Wingen G. Development and validation of a multimodal neuroimaging biomarker for electroconvulsive therapy outcome in depression: A multicenter machine learning analysis.Psychological Medicine 2023 https://doi.org/10.1017/S0033291723002040

Blanken MAJT, Oudega ML, Hoogendoorn AW, Sonnenberg CS, …, Van Wingen G, **Ten Doesschate F**, …, Dols A. Sex-specifics of ECT outcome. J Affect Disord. 2023 Jan 9;326:243-248. doi: 10.1016/j.jad.2022.12.144. Online ahead of print.

PMID: 36632848

van Verseveld M, Mocking RJT, Scheepens D, **Ten Doesschate F**, Westra M, Schoevers RA, ... & Ruhé HG. Polyunsaturated fatty acids changes during electroconvulsive therapy in major depressive disorder. *Journal of Psychiatric Research, 2023, 160*, 232-239.

Ten Doesschate F, van Waarde JA, van Wingen GA. Still no evidence for the efficacy of zuranolone beyond two weeks: Response to Arnaud and Bonthapally. J Affect Disord. 2022 Sep 15;313:149-150. doi: 10.1016/j.jad.2022.06.085. Epub 2022 Jun 30.

Schuur G, Verdijk JPAJ, **ten Doesschate F,** van Wingen GA, van Waarde JA. Severe Postictal Confusion After Electroconvulsive Therapy: A Retrospective Study. Journal of ECT: May 25, 2022 (published ahead-of-print).

Ten Doesschate F, van Waarde JA, van Wingen GA. Non-superiority of zuranolone (SAGE-217) at the longer-term. J Affect Disord. 2021 Aug 1;291:329-330. doi: 10.1016/j.jad.2021.05.015. Epub 2021 May 23. PMID: 34082218.

Verheesen SMH, **Ten Doesschate F**, van Schijndel MA, van der Gaag RJ, Cahn W, van Waarde JA. Intoxicated persons showing challenging behavior demand complexity interventions: a pilot study at the interface of the ER and the complexity intervention unit. Eur Arch Psychiatry Clin Neurosci. 2021 Aug;271(5):903-913. doi: 10.1007/s00406-020-01162-7. Epub 2020 Jul 12. PMID: 32656630; PMCID: PMC8236043.

Verdijk JP, Schuur G, Pottkämper JC, **Ten Doesschate F**, Hofmeijer J, & van Waarde JA. Medication preventing postictal hypoperfusion and cognitive side-effects in electroconvulsive therapy: A retrospective cohort study. *Frontiers in Psychiatry*, 2023, *14*, 1026014.

BOOK CHAPTER

Ten Doesschate F, van Waarde JA. Hoofdstuk 20. Voorlichting. In: Leerboek Elektroconvulsietherapie. Amsterdam: Boom Uitgevers, 2019.