Current Connections
Brain Patterns in Electroconvulsive Therapy

Proefschrift

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door

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te Oss
Investigating the brain in electroconvulsive therapy for major depressive disorder: an introduction

Resting-state functional connectivity in major depressive disorder: A review

Electroconvulsive therapy for depression: Neurobiological mechanisms

Personality profiles are associated with functional brain networks related to cognition and emotion

Default mode network coherence in treatment-resistant major depressive disorder during electroconvulsive therapy

Bilateral ECT induces bilateral increases in regional cortical thickness

Structural changes induced by electroconvulsive therapy are associated with clinical outcome

Current connections: Brain patterns in electroconvulsive therapy

Summary

Dutch summary (Nederlandse samenvatting)

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During my clinical internships working at a closed ward, I was confronted with many patients suffering from severe, often even treatment resistant depression. Often they had received months, if not years, of treatment with a variety of medications and psychotherapy without any lasting effect.

I clearly remember a case of a female patient, late 50’s, who had a severe depressive episode with psychotic symptoms lasting for close to a year. Her depression was so severe and she became so nihilistic in nature that she was convinced to be deceased already as one could see by “her lack of eyes”, and that she had killed her son, which she told him repeatedly. Treatment strategies had failed up until the point where she stopped eating and drinking. She would not respond to anyone, communication was impossible and without forced intake she would die within weeks.

We admitted her and, with consent of family, started her on a course of electroconvulsive therapy. After one week she sat across from me, talking about how she was doing and in two weeks, there were no signs of depression present. She was discharged two weeks after that; her depression in full remission.

Unfortunately, not all patients have a similar recovery, but at that moment I was captivated by the potential of such a treatment. To take a person that has become the embodiment of human suffering and bring them back from the brink was, and remains, nothing short of miraculous. Understanding how, why, and when electroconvulsive therapy works became of great interest to me and is the main drive behind this thesis.

Through this thesis, I will show some of the ways in which we can understand electroconvulsive therapy’s mechanisms by investigating how it changes brain structure and function.

Peter Mulders
INVESTIGATING THE BRAIN IN ELECTROCONVULSIVE THERAPY FOR MAJOR DEPRESSIVE DISORDER: AN INTRODUCTION

Partly adapted from:

ON DEPRESSION AND ELECTROCONVULSIVE THERAPY

Major depressive disorder (MDD, depression) is a common, debilitating disorder affecting millions of people worldwide and is currently one of the disorders with the highest level of disability-adjusted life years, especially in young adults (1). It is characterized by depressed mood and/or anhedonia, accompanied by other symptoms such as weight loss/gain, psychomotor retardation, fatigue, feelings of worthlessness or guilt, problems concentrating and/or recurrent thoughts of death or suicide (see box 1). It has considerable impact both on a personal and a macro-economic level, and is one of the biggest challenges the field of mental health faces today.

Although we are fortunate that the past decade has seen an increase in societal acceptance and awareness of depression, few among the public are aware that up to a third of patients will fail to respond to multiple treatment cycles and become “treatment-resistant” (2). While the definition of treatment-resistance differs geographically, a minimum of two failed treatments (psycho- and/or pharmacotherapy) is generally required. This adds up to a significant population suffering from treatment-resistant depression, for which with each new conventional treatment cycle response rates decrease. For this group, both new and old neuromodulation strategies offer a different approach to their disorder, with electroconvulsive therapy (ECT) being the single most potent treatment for depression with response rates as high as 50-70% even in treatment-resistant samples (3).

Box 1. DSM-5 criteria for Major Depressive Episode

<table>
<thead>
<tr>
<th>Five or more of the following symptoms during the same 2-week period, including at least (1) or (2):</th>
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<tbody>
<tr>
<td>1. Depressed mood</td>
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<tr>
<td>2. Markedly diminished interest or pleasure in all, or almost all, activities</td>
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<td>3. Significant weight loss when not dieting or weight gain, or decrease or increase in appetite</td>
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<td>4. Insomnia or hypersomnia</td>
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<td>5. A slowing down of thought and a reduction of physical movement</td>
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<td>6. Fatigue or loss of energy</td>
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<td>7. Feelings of worthlessness or excessive or inappropriate guilt</td>
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<td>8. Diminished ability to think or concentrate, or indecisiveness</td>
</tr>
<tr>
<td>9. Recurrent thoughts of death, recurrent suicidal ideation, or a suicide attempt or a specific plan for committing suicide</td>
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A BRIEF HISTORY OF ECT

Electroconvulsive therapy was first introduced in the 1930’s by Ugo Cerletti and Lucio Bini as a safer alternative to elicit seizures compared to other methods of that time. In those days, there was the assumption among those working in psychiatry that a common final stage of untreated severe psychiatric disorders, the catatonic state, was the biological counterpart of epilepsy. From that hypothesis, eliciting a seizure through convulsive therapy would counteract the catatonic state and help treat patients that were otherwise untreated. The effects of ECT were remarkable, leading to significant improvement in patients’ mental health, and the method gained significant traction across Europe and the United States. As with other methods in those days, the application of the treatment widened over time and came under increasing scrutiny during the age of antipsychiatry in the 1970’s. Together with the rise of other treatment options for psychiatric disorders such as antidepressants, the perception of ECT grew more negative over the years and its use more restricted. This negative view of ECT, fueled by depictions of ECT in various media during the 70’s and 80’s, most famously in the Oscar-winning film One Flew Over the Cuckoo’s Nest, is still very much present today. Public knowledge of the current application of ECT and its remarkable clinical effects is not well known, nor the many advances the field of ECT has made over the past decades, which might contribute to its relative underuse in persistent depressive disorders (4). These advances were largely driven by the establishment of taskforces and guidelines for the proper use of ECT, as well as research paradigms aimed to establish ECT’s therapeutic effect, when to apply it, and technological progress such as the use of brief and ultra-brief stimuli and improved anesthesia. Through all these changes, ECT has found a clear position within treatment protocols as a potent treatment for various psychiatric disorders today, most significantly for treatment-resistant depression.

CURRENT APPLICATION OF ECT

ECT is currently a well-described treatment option used globally, with some small regional variations. Typically, it involves a brief or ultra-brief (0.25-1.5 ms, 10-70 Hz) electrical stimulus (0.9 A, <450 V, up to 1008 mC) being applied to the right unilateral or bitemporal window, with the goal to elicit a grand-mal seizure with a sufficient duration (Figure 1). It is common practice to start treatment right unilaterally, as this has a smaller risk of cognitive side-effects, with the option of switching to bilateral stimulation after initial non-response (~6 sessions without clinical effect). There are some alternatives such as bifrontal or left-anterior right-temporal stimulation, although these are not widely used.
months after discontinuation. This relapse can be prevented in a significant portion of patients by pharmacotherapy, for example a tricyclic antidepressant (sometimes with the addition of lithium)\(^6\), but sometimes this is insufficient and a patient needs to undergo ECT more regularly. In cases where this is a recurrent pattern, maintenance ECT with frequencies varying from once per week to once per two months, can be sufficient in preventing relapse without severe cognitive impairments.

## On Investigating Brain Structure and Function Related to Depression and ECT Treatment Using Magnetic Resonance Imaging

Understanding depression and its treatments has been an important goal of clinical neuroscience, a field that has garnered significant interest over the past decades. Understanding how symptoms and behavior relate to brain activation and mechanisms could pave the way for more targeted and patient-specific treatment options, in contrast to our current “one-size-fits-all” treatment protocol for major depressive disorder. Such advances are very promising, for example in predicting treatment response to pharmacotherapy or ECT based on neural signatures in brain structure and function\(^7\)\(^–\)\(^9\).

The current prevalent understanding in systems-level neuroscience is that no function is localized exclusively within a single brain area. Instead, each action, decision, or emotion is thought to be generated by the interaction of multiple regions across the brain. Areas that routinely cooperate to create a specific outcome are organized within “functional networks,” and there have been considerable advances in techniques that attempt to characterize these networks in terms of their organization and interactivity. Understanding how these different techniques inform us on the different aspects of brain function requires some basic understanding of both imaging acquisition and analysis, which we will briefly discuss.

### Basics of (Functional) Image Acquisition

The most commonly applied methods of network research make use of functional magnetic resonance imaging (fMRI). This type of imaging obtains a T2*-weighted blood oxygen level-dependent (BOLD) signal, which captures the shift in magnetic susceptibility that occurs when the ratio of oxygenated and deoxygenated hemoglobin changes\(^10\). Given that neuronal activity requires oxygen, the change in BOLD-signal is
strongly related to the activity of the surrounding cells, making it an indirect, yet reliable, noninvasive way to assess functional activity. Even during periods of rest, the brain is a highly active organ, accounting for approximately 20% of energy consumed, while during strong activation the increase in BOLD-signal relative to baseline is around 5%. Because this increase is small as compared to the high and subject-specific baseline activity, it is not yet feasible to use the raw BOLD-signal to evaluate disease-related patterns in a single individual. However, this type of data contains many other interesting features that bypass these limitations.

One aspect fundamental to network analysis is the fact that the BOLD-signal is far from constant. There are significant spontaneous fluctuations in signal activity during both activation and rest, and these signals can be interpreted as a combination of outputs from various signal sources, such as cardiovascular and respiratory effects and movement as well as the spontaneous fluctuations in neuronal activity. By measuring the BOLD-signal within one session at multiple points in time, a four-dimensional (4D) image is obtained, where each three-dimensional (3D) volumetric element (or “voxel,” typically of size 2x2x2 mm) in the brain has a (BOLD-signal) value for its activity at that particular time. With sufficient measurements, the signal intensity for a particular voxel over time (its “time course”) can be used to detect any similarities in temporal dynamics across the brain between voxels (Figure 2). Because of the different frequencies of the signals that are mixed within the BOLD-signal, it is important to pay attention to the different acquisition parameters when obtaining 4D fMRI. Besides the spatial resolution (which determines the size of each voxel), aspects like temporal resolution (time between each 3D image), total number of volumes, and total scanning time need to be sufficient to characterize the temporal dynamics well. As scanning systems and sequences are improved, higher spatial resolution and signal-to-noise ratio and a shorter temporal resolution will further help correctly identify even subtle variations within brain networks.

EXTRACTING NETWORKS

Initially, networks were defined based on regions that showed a significant activation pattern during a specific condition. This approach is quite similar to earlier studies using positron emission topography (PET), which used more invasive means to assess brain activity. As mentioned earlier, BOLD is a relative, i.e., non-quantitative measure of activation. This means that translating the data into discernible networks requires either a contrast when compared to baseline activity or investigation of the synchronization of the spontaneous signal fluctuations during rest. An important methodological development regarding the latter was the finding that even during rest, areas that share functionality exhibit similar temporal dynamics, leading to the discovery of the so-called “resting-state networks.” The nature of the resting state, being independent of task-based paradigms, offers an important advantage of being a method that is reproducible across different populations and study settings. While “resting-state network” is commonly used to describe the large functional networks in the brain, these networks are not exclusively tied to the resting state but instead are ever dynamic in adapting to changing environments or stimuli.

In contrast to the resting-state, task-based activation studies commonly use a block- or event-related design to assess the changes in BOLD-signal when compared to a baseline signal (rest). This contrast then represents the task-related changes within the context. Given that functional connectivity is dynamic on short time scales by nature (as opposed to structural connectivity), networks will interact to perform specific tasks, and disease-related changes in their interaction can become more apparent during a specific setting as compared to the resting state. Unfortunately, designing a task in such a way as to highlight the specific function relevant to the research question while minimizing the effect of confounds, such as variations in intelligence or cognitive deficit, can be problematic. The results obtained might not be exclusively related to the function under investigation, especially in a clinical population, where the execution of a task can be influenced by a large variety of patient-bound factors. Instead, the assumption that a task only elicits task-related responses (the principle of “pure insertion”) may not be optimal for functional neuroimaging, as it does not take...
the interactions of different cognitive components into account\textsuperscript{116}.

Although all of the methods of identifying large-scale neural networks use a similar type of imaging data, there are large differences in their base assumptions and complexity and therefore ensuing interpretations. Broadly speaking, there are two distinct approaches to analyzing resting-state fMRI data. The first uses correlations of the time series within the 4D image to create a map of functional connectivity, which can be defined as the temporal correlation of two distant neurophysiological effects. The second approach uses the fMRI image to calculate a certain connectivity-related variable for each voxel in the brain separately to inform network hypotheses. Within the first approach, similar patterns of activation and/or deactivation (similar “time courses”) in areas will lead to high correlations or high “functional connectivity.” This represents a strong functional relation and increases the likelihood of them belonging to the same network. Both seed-based correlational analysis (SCA) and independent component analysis (ICA) use this approach, each with their advantages and limitations. Other means of using the temporal dynamics in the BOLD-signal such as “regional homogeneity” (ReHo) and “amplitude of low-frequency fluctuations” (ALFF or fALFF) instead opt for the voxel-wise calculation of a derived measure to inform local coherence or the power of certain frequencies. Finally, Graph theory analysis can be seen as a more downstream technique that can be used to convert the information obtained from any method into models that describe the different aspects of a network and its nodes\textsuperscript{17,18}.

**CORRELATIONS AND CAUSALITY**

After delineating networks within a data set and testing for group effects, it is common practice to subsequently try and characterize the difference in networks and/or connectivity by correlating these changes in estimated network characteristics to a variety of patient- or disease-related variables. When describing group differences in depression, it is important to consider that any significant group difference could be either state-related, trait-related, or even just an effect of current or past treatment. Importantly, correlations in general do not imply causality from a clinical perspective, but increased connectivity also just describes a relation between two areas without further informing directionality. Some researchers have attempted to infer this directionality using methods such as “dynamic causal modelling” or “Granger causal modelling”\textsuperscript{113,120}. Unfortunately, causal inference from BOLD-fMRI data is still hindered by a number of key issues such as the indirectness of measuring BOLD as representing neural activation, variance in regions of interest between individuals, and variance in BOLD-delay across the brain\textsuperscript{121}.

**GENERAL CONSIDERATIONS**

When considering methods investigating large-scale brain networks, it is important to distinguish the key characteristics and to relate them to the actual hypothesis that is under investigation. Unfortunately, results obtained using whole-brain exploratory analyses are often presented as if answering empirical questions with a strong prior assumption. Therefore, as a reader it is important to understand if the method used fits the question. Model-free methods are suitable for those interested in either whole-brain changes or changes within the network configurations on a larger scale, while certain highly sensitive methods (SCA) may be better suited to detecting small differences in areas that have been shown to be highly relevant. Another important consideration is the reliability of the measure in question. A review investigating this showed that some analysis methods used were significantly more consistent than others\textsuperscript{122}, with SCA versus ICA comparisons being in favor of the latter in cases where large-scale network identifications are desired. One way to approach network investigations is to use model-free methods to explore large-scale changes in the first instance, while using specific sensitive measures to confirm and expand upon any relevant findings in other, similar populations.

**ON BRAIN STRUCTURE AND FUNCTION IN DEPRESSION AND ECT**

As for any type of research, it is critical to understand what has been done before and how that shapes our current understanding. While research into ECT has only really taken off in the past years, the field of neurobiological research into mechanisms underlying depression has a large body of previous work that forms an important basis to our work.

**NEUROBIOLOGY OF DEPRESSION**

Depression is heterogeneous. Considering DSM contains 9 symptoms for depression of which only 5 are requires for a diagnosis, while 3 of the symptoms (pschomotor, sleep, appetite) can be counted on both increase and decrease, a total of 945 symptom profiles exists which are all labeled “major depressive disorder”\textsuperscript{123}. That is before taking into account relevant comorbidity such as anxiety or personality disorders. Early studies on changes in brain structure reflect this heterogeneity with findings being inconsistent as a result. Several advances in recent years have enabled us to overcome this issue, most notably international collaborations to increase sample size and increased computational capabilities. These have provided us with several large (meta)
analyses that provide the strongest evidence to date if, how and where structural changes in the brain are present in depression, and how specific characteristics affect these changes.

One of the largest studies to date on depression pooling neuroimaging and clinical data is the ENIGMA-sample, which have performed analyses on more than 2 000 depressed patients and 7 000 healthy controls (24,25). They report decreased volume in bilateral frontal and temporal cortices (medial orbitofrontal, fusiform, insula, rostral anterior and posterior cingulate cortex, left middle and inferior temporal gyrus and right caudal anterior cingulate cortex). Regarding subcortical regions decreased volume in hippocampus and amygdala has been found in early onset depression (onset before age of 21). While hippocampal volume decreases were more pronounced in patients with recurrent depression, none of the decreases across cortical and subcortical areas could be related to severity. The results were supported by earlier work which had shown decreased volume in rostral anterior cingulate, dorsomedial and dorsolateral prefrontal cortex (26) when pooling data from 23 studies. Another study collecting data from 225 studies found most evidence for decreased volume in the frontal lobe and subcortical structures (caudate, putamen, pallidum, thalamus, hippocampus) (27). No large studies report areas of increased volume in depressed subjects.

Regarding function, a distinction needs to be made between task-based and resting-state fMRI. While the first is well suited to answer a specific question, due to the specificity of the paradigm comparing between studies is typically hard. Resting-state on the other hand, is easier to replicate but as we are measuring “baseline” activation, we cannot directly infer upon resting-state activity but instead we investigate spontaneous fluctuations in activity and how they correlate across the brain. Highlighting this, a recent meta-analysis on task fMRI including 57 studies relating 99 different neuroimaging experiments in cognitive and emotional processing paradigms found no consistent results or activation patterns in unipolar depression (28). Another meta-analysis did report increased response to negative stimuli in dorsal anterior cingulate cortex, amygdala and insula (29), with a decreased activation in response to negative stimuli in dorsolateral prefrontal cortex. Another meta-analysis focused on youth with depression found hyperactivation in subgenual anterior cingulate and ventrolateral prefrontal cortex and hypoactivation in the caudate nucleus (30), with more alterations relating to specific paradigms in cuneus, dorsal anterior cingulate, dorsolateral prefrontal cortex and insula. Discrepancies between meta-analyses are likely due to different inclusion criteria and the stringency of the statistics used.

As for resting-state, this method is relatively new; two recent reviews included only a limited number of studies (31) or large variation between different metrics used (32) leading them to conclude no clear evidence for consistent differences in resting-state connectivity in depression. With the increased interest in this fMRI modality in recent years an up-to-date review of all research done is overdue.

UNDERSTANDING THE ANTIDEPRESSANT EFFECTS OF ECT

With ECT being highly effective, even where other treatment options fail, the mechanisms through which it elicits such a strong response has sparked interest among clinicians and researchers for a long time. Although much is still unknown, there are multiple hypotheses on the underlying neurobiological mechanisms of ECT’s remarkable clinical effects, based on the widespread effects ECT has been found to have on the brain. These can be summarized as based on 1) monoamine changes, 2) anticonvulsive effects and 3) neurotrophic properties of ECT.

The monoamine hypothesis states that, similar to psychopharmacology, ECT works through increases in monoamine systems such as serotonin and dopamine. This hypothesis is based on both our understanding of the depressed brain, the biological effects of antidepressant medication, and the finding that ECT affects monoamine systems and receptor availability. The anticonvulsive hypothesis states that ECT, by eliciting seizures, drives the brain to become more resistant to convulsions through increasing inhibitory processes. This is supported by evidence of increases in the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) after ECT, as well as the clinical observation that some patients develop an increased seizure threshold during the course of treatment. Finally, the neurotrophic hypothesis posits that ECT works through affecting neuroplasticity. This hypothesis is supported by animal models of ECT, where electroconvulsive stimulation (ECS) has been found to increase neurogenesis in the dentate gyrus of the hippocampus and induces proliferation of glial cells. While the hippocampus was initially the primary target for research into neuroplasticity after ECS, it is increasingly found to also be present in other areas of the brain such as the frontal cortex and amygdala.

These hypotheses are not mutually exclusive and, ultimately, it is unlikely that any one hypothesis fully explains the broad effects ECT has. Instead, each of these (and likely others) may play an important role and interact to create the strong antidepressant response we see in patients. With ECT being a treatment that affects the entire brain, identifying changes in structure and function after ECT is only the first step, as it is unlikely that all changes that occur are needed or even related to its clinical effects.
Determining which of these changes relate to its antidepressant action or cognitive side effects is a crucial second step in understanding its mechanisms and a primary focus of current research on ECT.

There are major implications if we could better understand what effects of ECT relate to its clinical effects. Knowledge about regional effects could lead to adjustments to the treatment itself to further increase its effects by more targeted ECT strategies. One step further, the development of other, more targeted and less invasive neuromodulation techniques could be based on understanding what neurobiological changes have to be present for recovery. Staying closer to ECT as it is today, understanding how it is affecting the brain could provide early indicators of treatment response, or even pre-treatment selection based on a combination of clinical and neurobiological profiles, providing large benefit for the patient (who will not have to undergo invasive treatment without benefit) and society as a whole for reserving expensive treatment for those who stand to benefit from it.

**AIMS AND OUTLINE**

To summarize, depression is serious severe disease, often does not respond to treatment, and electroconvulsive therapy still works for most of those patients that do not respond to initial therapies. ECT has a clear position in treatment protocols, is well-tolerated and has manageable side-effects. Depression affects the brain both at the structural and the functional level, and there is clear evidence that specific regions and networks are involved. In addition, ECT also affects the entire brain; but how the observed changes are related to clinical outcome is still unclear.

Overall, this thesis aims to investigate how changes in the brain’s structure and function relate to depression and vulnerability to depression, and how ECT affects these changes which will further our understanding of how ECT achieves its strong clinical efficacy.

In chapter 2, we review and summarize how functional connections and large-scale brain networks are affected in the depressed patient. While structural changes have been well described, functional studies were mostly inconsistent due to large variation in paradigms used. With the introduction of resting-state fMRI, most of these limitations can now be overcome. We will gather evidence from studies using resting-state connectivity measurements in depression and propose a model of dysfunctional connectivity in the depressed brain.

In chapter 3, we review the current state of neurobiological research into changes related to ECT, by summarizing and interpreting all studies investigation brain structure and function in a longitudinal design in depressed patients.

In chapter 4, we build on our observations in chapter 2 that show how large-scale functional networks and associated regions are affected in depression; networks that are implicated in emotion and cognition on a broader scale. Within these regions we explore the resting-state dynamics of personality factors, key components in depression vulnerability and resilience, and how these factors relate to each other and key emotional and cognitive regions in the resting brain.

In chapter 5, we show how the default mode network, one of the key aberrant networks in depression as identified in chapters 2 and 3, changes after ECT and how this might be different for responders and non-responders.

In chapter 6, we explore whether we can observe changes in cortical thickness as a result of ECT treatment.

In chapter 7, we build on the work done in chapter 6, but extend that by making use of a large multi-site collaborative dataset to establish whether a specific pattern of structural changes induced by ECT is related to clinical response.

Finally, in chapter 8, we summarize and integrate our findings and propose new ways forward for understanding the biological mechanisms of ECT.
REFERENCES


RESTING-STATE FUNCTIONAL CONNECTIVITY IN MAJOR DEPRESSIVE DISORDER: A REVIEW

adapted from:

ABSTRACT

Major depressive disorder (MDD) affects multiple large-scale functional networks in the brain, which has initiated a large number of studies on resting-state functional connectivity in depression. We review these recent studies using either seed-based correlation or independent component analysis and propose a model that incorporates changes in functional connectivity within current hypotheses of network dysfunction in MDD. Although findings differ between studies, consistent findings include: (1) increased connectivity within the anterior default mode network, (2) increased connectivity between the salience network and the anterior default mode network, (3) changed connectivity between the anterior and posterior default mode network and (4) decreased connectivity between the posterior default mode network and the central executive network. These findings correspond to the current understanding of depression as a network-based disorder.

INTRODUCTION

Major depressive disorder (MDD) is one of the most prevalent psychiatric disorders and is the second leading cause of disability worldwide [1]. Despite almost 60 years of intensive neurobiological research, our current understanding of its pathophysiology is limited, which is reflected in a heterogeneous disease concept and moderate effects of treatment [2–4]. While earlier neuroimaging techniques have investigated focal structural and functional changes [5–9], depression is increasingly understood as a disorder of distributed effects of aberrant interaction in the brain [6,10,11]. Within this framework, brain regions are dynamically organized into functional networks of interconnected areas (or “nodes”) that interact to perform specific tasks [12].

With the advance of network-based research in system-level neurosciences in general, new techniques allow us to identify these large-scale brain networks, for example by looking at changes in blood-oxygen-level-dependent (BOLD) signal using functional magnetic resonance imaging (fMRI). An important methodological development in investigating these networks was the finding that they can consistently be identified during the “resting-state”, i.e. when a subject is not engaged in any particular task [13]. This independence of task-based paradigms offers the important advantage of being reproducible across different populations and study settings. Following this, many recent studies have investigated how the different nodes and networks communicate by investigating synchronous spontaneous activity in different regions of the brain. This so-called “resting-state functional connectivity” (hereafter referred to as “connectivity”) represents the temporal coherence of the BOLD-signal within or between regions or networks during rest and is an important addition to functional imaging techniques in unraveling the neurobiology of depression [14].

In MDD most findings in task-based and resting-state fMRI implicate one of three major neural networks: the default mode network (DMN), the central executive network (CEN) and the salience network (SN) [6,11–13]. Two recent papers have reviewed studies on functional connectivity in depression [14,15], but either included only a limited number of eligible studies [14] or rather divergent methods which makes comparison of results problematic [15]. Because of these limitations, and the large number of connectivity papers published in recent years, we aim to provide a coherent review of the resting-state functional connectivity literature in depression that takes into account the different methods used, and update the current concept of depression as a network-based disorder.
Our review will focus on changes within (1) the default mode network, (2) the central executive network, (3) the salience network and (4) the interactions between these networks. We will start by giving a short overview of these networks and their function. Then, we will provide a critical appraisal of all available studies on resting-state functional connectivity in MDD, taking into account different methods used as well as the relation to clinical characteristics and effects of treatment. Lastly, we will discuss the significance of these findings in the light of current depression hypotheses.

**CORE LARGE-SCALE NETWORKS IN MAJOR DEPRESSIVE DISORDER**

The default mode network (DMN), the central executive net-work (CEN) and the salience network (SN)\(^\text{15-17}\) (Fig. 1) represent the brain’s function during rest, cognition and emotional processes, all of which are essential processes that are altered in depression.

**DEFAULT MODE NETWORK (DMN)**

The default mode network (also known as the "task-negative network") was initially identified as areas that consistently showed synchronized deactivation during tasks and prominent activation during rest\(^\text{16}\). The fact that this network is related to processes that are mostly employed during rest such as self-generated thought has gained significant attention, especially in relation to depression\(^\text{15,20,21}\). The DMN is often divided into an anterior sub-network that centers on the medial prefrontal cortex (mPFC) and a posterior sub-network that centers on the posterior cingulate cortex (PCC) and the precuneus cortex (PCu)\(^\text{21,22}\). While the anterior and posterior sub-network share similar temporal dynamics, they differ in regards to their specific function\(^\text{20,22}\). In general, both the anterior and posterior parts of the DMN are related to spontaneous or self-generated cognition. The anterior DMN is more related to self-referential processing and emotion regulation, partly through its strong connections with limbic areas such as the amygdala. The posterior DMN has been implicated in both consciousness and memory processing through its relation to the hippocampal formation\(^\text{20,22,24}\).

In addition to the core regions, associated DMN areas include the inferior parietal lobule (IPL) and the lateral temporal cortex (LTC)\(^\text{21,26}\). Although not consistently reported as nodes within the DMN, the subgenual anterior cingulate cortex (sgACC) and the hippocampal formation (hippocampus and parahippocampal gyrus) also have an important functional relation to (parts of) the DMN\(^\text{21,22,26,27}\). These differences in the topography of the DMN are likely related to the variety of processes occurring during rest. Recent evidence points toward subsystems within the DMN that each attribute to different aspects of internal mentation, for instance a medial temporal lobe subsystem that covers the hippocampal formation and is mostly related to episodic memory activation during rest\(^\text{22}\). For the purpose of this review, when considering the DMN we will limit ourselves to the “core” DMN regions that are consistently identified as part of the DMN: the mPFC, the PCC/PCu and the IPL.

**CENTRAL EXECUTIVE NETWORK (CEN)**

The central executive network (CEN, also referred to as the ‘cognitive control network’...
or the 'cognitive-executive network') includes the lateral prefrontal cortex, the posterior parietal cortex (PPC), the frontal eye fields (FEF) and part of the dorsomedial prefrontal cortex (dmPFC) (24,29). Contrary to the DMN, this network is most active during cognitive tasks and is implicated in cognitive functioning including attention and working memory. The DMN and the CEN are often seen as opposing networks, and task-related inter-actions between these networks are changed in MDD (10,22). Together with some additional areas (most notably middle temporal region, supplementary motor cortex and the fronto-insular operculum) the CEN also makes up the “task-positive network” which shows strong task-related activation (32).

SALIENCE NETWORK (SN)
The salience network typically consists of the fronto-insular cortex, the dorsal ACC, the amygdala and temporal poles. It is activated in response to various salient stimuli including acute stress (17,32). It is believed to reflect paralimbic emotional processing and to play a central role in emotional control through its extensive subcortical connectivity. Moreover, it has been implicated in switching between the DMN and CEN (14,32).

METHODS

LITERATURE SEARCH
A search in PubMed/MedLine was performed to identify papers in English reporting on resting-state functional connectivity in unipolar MDD, using “major depressive disorder”, “resting state” and “functional connectivity” as search terms. Papers were selected when they (1) included patients with current MDD, (2) used fMRI, (3) made comparisons to matched healthy controls and (4) reported on measures of functional connectivity. References of the included papers were checked for citations that were not identified by our initial search. We divided papers based on the dominant network of interest, the methods used, and whether they reported on within- or between-network connectivity.

METHODS SELECTION
Given our interest in large-scale brain networks we chose to include papers using either seed-based correlation analysis (SCA) (32) or independent component analysis (ICA) (36,40). We focused on these measures because they use similar data to assess connectivity (i.e. BOLD-signal over time) and are well established in the connectivity literature. A more extensive explanation of the differences between the selected methods and their limitations can be found elsewhere (38,39). In short, SCA uses a pre-determined region of interest or ‘seed’, usually based on a clear hypothesis, and calculates correlations of its BOLD-signal fluctuations to those of all other voxels of the brain or to specific other seed regions. An increase in functional connectivity found using SCA therefore represents increased synchronization between two regions. By comparison, ICA does not require a prior selection of regions of interest, but instead uses all the data available within the fMRI image to decompose the entire fMRI dataset into temporally coherent, spatially independent “components”, which correspond to brain networks (36,40). In contrast to SCA, an increase in functional connectivity using ICA reflects the degree to which a voxel’s signal over time is correlated with a specific network or component. The “model-order” of ICA represents the (calculated or selected) number of components that the data is decomposed into, where a higher model-order can be used to identify sub-networks within larger networks (38). Another frequently used measure of functional connectivity, regional homogeneity (ReHo) was excluded for the purpose of this review as it reflects local coherence within small regions and as such is less suitable to investigate large-scale brain networks (41). Papers calculating functional connectivity based on the (fractional) amplitude of low frequency fluctuations (fALFF) were also excluded because of difficulties comparing BOLD- and frequency-based changes in connectivity (38,42). A recent review that included predominantly ReHo and fALFF papers found no consistent changes in functional connectivity in MDD (18).

RESULTS
In total 8 papers using ICA (Table 1) and 28 papers applying SCA (Table 2) were included. Papers were published between 2005 and 2014, but 34 out of 36 studies were reported in the past five years. All ICA papers have investigated the DMN, while the CEN and SN were only reported in a subset of studies. Among SCA papers, the most frequently selected seed regions are the ACC, PCC and the amygdala. 25 out of the 36 studies investigated an adult population, 6 looked at an elderly group and 5 focused on adolescents. 17 out of 36 studies included patients currently on antidepressants. Most papers demonstrate state-related changes during an episode of depression, while a few also report on longitudinal changes in the context of antidepressant treatment.

DEFAULT MODE NETWORK (DMN)
**Independent component analysis (ICA)**
All of the ICA studies investigating the DMN in MDD have found an increase in connectivity within several nodes of the anterior DMN compared to healthy controls (41–46). Greicius et al. (45) were the first to investigate the role of the DMN in (medicated)
depressed patients using ICA and reported increased connectivity within the subgenual ACC (sgACC), the orbitofrontal cortex (OFC), the precuneus (PCu) and the thalamus. Although a prominent node in the DMN of depressed patients, the sgACC was not part of the DMN in their healthy control subjects, implying that the DMN has a somewhat different configuration in MDD. Zhu et al. [42] also demonstrated increased connectivity within the anterior DMN (dorsomedial PFC (dmPFC), ventromedial PFC (vmPFC), pregenual ACC (pgACC) and medial OFC) in first-episode medication-naïve MDD patients, demonstrating that this finding is not dependent on disease course or current use of medication. Interestingly, two other papers confirmed the increased connectivity within nodes of the anterior DMN. However, instead of an increased connectivity of these areas within the full DMN they found this increase to be specific within the anterior DMN [44,45]. Together these results indicate that in depression, activity within several nodes in the medial prefrontal cortex (and especially the ACC) is more synchronized with activity of the (anterior) DMN.

Similar to the anterior DMN, connectivity in the posterior parts of the DMN is predominantly found to be increased in depression. While Greicius and colleagues reported increased connectivity in the PCu with the full DMN, the two papers that subdivide the DMN into smaller sub-networks report increased connectivity of the PCC/PCu within the posterior DMN specifically [44,45]. In contrast, Zhu et al. [42] instead report a decrease in connectivity in the PCC, the PCu and the angular gyrus. This difference could be related to characteristics of their sample, which consisted of relatively young (mean age 20 years) and mildly depressed patients. The authors suggest that the anterior and posterior DMN show a dissociation pattern during depression, which is supported by some of the other studies.

While using a high model order for ICA can reliably identify sub-networks within the DMN [44,45], Li and colleagues found this split even using a low model-order ICA (20 components). They identified an anterior and posterior sub-network that were spatially independent and showed asynchronous activity patterns [46]. This distinction was further supported by the effects of antidepressant treatment that normalized the increased connectivity in the posterior DMN, but not in the anterior DMN. The hypothesis of a dissociation within the DMN is also supported by findings of Guo et al. [42], who used ICA to identify the DMN and found that network homogeneity (defined as the mean correlation of a voxel with all other voxel’s within a network) within the DMN was increased in the anterior DMN (dmPFC), but decreased in the posterior part (inferior temporal gyrus). The final two papers exploring connectivity within the DMN using ICA found no changes in connectivity [49,50]. However, since both studies...
<table>
<thead>
<tr>
<th>Paper</th>
<th>No. patients (mean age), Population</th>
<th>Med</th>
<th>Seed regions</th>
<th>Design</th>
<th>Default mode network</th>
<th>Central executive network</th>
<th>Salience network</th>
<th>Other</th>
<th>Longitudinal effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andreescu 2009</td>
<td>47 (69.7 yr) Moderate-severe</td>
<td>PCC</td>
<td>Longitudinal</td>
<td>+ PCC - PCu</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Antidepressant treatment: + PCC - medFG, dmPCC (not significant)</td>
</tr>
<tr>
<td>Berman 2011</td>
<td>15 (52.7 yr) Moderate-severe</td>
<td>PCC, mPFC</td>
<td>Cross-sectional</td>
<td>+ PCC - sgACC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Blum 2009</td>
<td>14 (21.9 yr) Moderate</td>
<td>PCC, PCu</td>
<td>Cross-sectional</td>
<td>+ PCC, PCu</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Wu 2011</td>
<td>12 (10.5 yr) Moderate-severe</td>
<td>PCC</td>
<td>Longitudinal</td>
<td>+ PCC - dmPFC, OPC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Zhou 2010</td>
<td>18 (33.9 yr) First episode Moderate</td>
<td>PCC, PCu, dlPFC</td>
<td>Cross-sectional</td>
<td>+ sgACC and PFC (R) specific for DMN in MDD</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>van Tol 2013</td>
<td>30 (38.3 yr) MDD-moderate</td>
<td>PCC, PCu</td>
<td>Cross-sectional</td>
<td>+ dmPFC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Pannesebo 2014</td>
<td>26 (51.4 yr) Adolescent Treatment-naive MDD-moderate</td>
<td>PCC, PCu, amygdala, dlPFC</td>
<td>Cross-sectional</td>
<td>+ dmPFC - ACC (L)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Aireopulos 2012</td>
<td>16 (42.7 yr) Late-life Moderate</td>
<td>PCC, dlPFC</td>
<td>Prospective</td>
<td>+ within the DMN</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Liston 2014</td>
<td>16 (42.3 yr) Treatment-resistant MDD and bipolar II depression MDD-severe</td>
<td>PCC, dlPFC</td>
<td>Cross-sectional</td>
<td>+ sgACC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**TABLE 2. Summary of studies using seed-based correlation analysis**

**TABLE 2 continued.**

<table>
<thead>
<tr>
<th>Paper</th>
<th>No. patients (mean age), Population</th>
<th>Med</th>
<th>Seed regions</th>
<th>Design</th>
<th>Default mode network</th>
<th>Central executive network</th>
<th>Salience network</th>
<th>Other</th>
<th>Longitudinal effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>En микро 2010</td>
<td>18 (32.1 yr) Moderate-severe</td>
<td>PCC</td>
<td>Cross-sectional</td>
<td>+ sgACC, dlPFC, PCC, dlPFC (dlorsal nucleus)</td>
<td>N/A</td>
<td>+ sgACC - dorsal nexus (dmPCC)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Ye 2012</td>
<td>22 (46.7 yr) First episode Moderate</td>
<td>dlPFC</td>
<td>Cross-sectional</td>
<td>+ sgACC, dlPFC, and PCC with (dorsal nucleus) (part of dmPFC)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Liu 2011</td>
<td>28 (2.1 12/12) Responders (28) / Non-responders (27) Severe</td>
<td>13 seeds (R)</td>
<td>Prospective</td>
<td>+ ACC, thalamus, postcentral gyrus and + dPFC - precentral cortex (R)</td>
<td>N/A</td>
<td>+ within prefrontal-limbic-thalamic circuit</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Avery 2013</td>
<td>30 (26.7 yr) MDD-severe</td>
<td>dmIC</td>
<td>Cross-sectional</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Cullen 2014</td>
<td>41 (55.7 yr) Adolescent Severe</td>
<td>Amygdala</td>
<td>Cross-sectional</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Ramasubbu 2014</td>
<td>55 (66.5 yr) Moderate-severe</td>
<td>Amygdala</td>
<td>Cross-sectional</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Tang 2013</td>
<td>28 (29.1 yr) Treatment-naive Severe</td>
<td>Amygdala</td>
<td>Cross-sectional</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Yue 2013</td>
<td>22 (67.7 yr) Late-onset Severe</td>
<td>Amygdala</td>
<td>Cross-sectional</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Tehrissan 2013</td>
<td>21 (51.9 yr) Recurrent Severe</td>
<td>Amygdala, hippocampus</td>
<td>Cross-sectional</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Paper</td>
<td>No. patients (mean age)</td>
<td>Population</td>
<td>Med</td>
<td>Seed regions</td>
<td>Design</td>
<td>Default mode network</td>
<td>Central executive network</td>
<td>Salience network</td>
<td>Other</td>
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<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Horn 2010</td>
<td>28 (39.2 yr)</td>
<td>Moderate</td>
<td>Y</td>
<td>pgACC, N (l)</td>
<td>Cross-sectional</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>+ pgACC – N (l)</td>
</tr>
<tr>
<td>Anand 2005</td>
<td>15 (29 yr)</td>
<td>Moderate-severe</td>
<td>N</td>
<td>pgACC, amygdala, PST and medial thalamus</td>
<td>Cross-sectional</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>+ pgACC – PST, medial thalamus + pgACC - amygdala (not significant)</td>
</tr>
<tr>
<td>Cao 2012</td>
<td>42 (29.2 yr)</td>
<td>First episode</td>
<td>N</td>
<td>Hippocampus</td>
<td>Cross-sectional</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>reduced negative connectivity hippocampus - MTG (R), - right IPL (R), cerebellum (R)</td>
</tr>
<tr>
<td>Connolly 2013</td>
<td>23 (16 yr)</td>
<td>Adolescent</td>
<td>N</td>
<td>sgACC</td>
<td>Cross-sectional</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>+ sgACC – insula, amygdala</td>
</tr>
<tr>
<td>Cullen 2009</td>
<td>12 (16.5 yr)</td>
<td>Adolescent</td>
<td>Y</td>
<td>sgACC, pgACC, pgACC, amygdala</td>
<td>Cross-sectional</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>+ sgACC, sgACC, lateral frontal cortex, STG and insula</td>
</tr>
<tr>
<td>Davey 2012</td>
<td>18 (18.3 yr)</td>
<td>Adolescent</td>
<td>Y</td>
<td>sgACC, pgACC, aMCC, pMCC</td>
<td>Cross-sectional</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>+ sgACC – dmPFC, + pgACC – dmPFC + pgACC – caudate nucleus</td>
</tr>
<tr>
<td>de Rosas-Arenet 2013</td>
<td>18 (44.6 yr)</td>
<td>Severe</td>
<td>Y</td>
<td>sgACC</td>
<td>Cross-sectional</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>+ sgACC – amygdala, hippocampus, OFC, thalamus</td>
</tr>
<tr>
<td>de Rosas-Arenet 2013</td>
<td>21 (21.71 yr)</td>
<td>Severe</td>
<td>N</td>
<td>6 striatal seeds (B)</td>
<td>Cross-sectional</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>+ in frontostriatal circuitry</td>
</tr>
<tr>
<td>Gabbay 2013</td>
<td>21 (21.71 yr)</td>
<td>Treatment-resistant (18) / First episode (17)</td>
<td>Y</td>
<td>4 striatal seeds (B)</td>
<td>Cross-sectional</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>+ dorsal caudate – dorsal IPC + ventral striatum – vmPFC, sgACC</td>
</tr>
<tr>
<td>Furman 2011</td>
<td>21 (17.9 yr)</td>
<td>Female subjects</td>
<td>Y</td>
<td>pgACC</td>
<td>Cross-sectional</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>+ pgACC – A2 anterior insula, PST, pallidoblastrium, spACC, supragenual anterior cingulate cortex, DMACC, midcingulate cortex</td>
</tr>
</tbody>
</table>

Note: 1 Table shows changed connectivity between different nodes in the networks, organized by which network is investigated by the seed region. 2 Direct correlation of seed-regions (not whole-brain correlation) Abbreviations: ↑: increased function connectivity; ↓: decreased functional connectivity; (l) left; (r) right; (B): bilateral; Med: medication; MDD: major depressive disorder; PCC: posterior cingulate cortex; PG: precuneus medFG: medial frontal gyrus; dmACC: dorsolateral anterior cingulate cortex; mPFC: medial prefrontal cortex; sgACC: subgenual anterior cingulate cortex; dmPFC: dorsomedial prefrontal cortex; OFC: orbitofrontal cortex; dPFC: dorsolateral prefrontal cortex; PFC: parahippocampal cortex; DMN: default mode network; mOFC: medial orbitofrontal cortex; CEN: central executive network; PFC: prefrontal cortex; IPL: inferior parietal lobule; LPC: lateral parietal cortex; STG: superior temporal gyrus; mPCC: medial precingulate cortex; MCC: midcingulate cortex; FIC: fronto-insular cortex; AG: angular gyrus; MTG: middle temporal gyrus; PCU: precuneus operculum; TP: temporal pole; FP: frontal pole; pgACC: paragigantocellular nucleus; vPFC: ventrolateral prefrontal cortex; MFG: middle frontal gyrus; SFG: superior frontal gyrus; AI: anterior insula; PST: pallidoblastrium; spACC: subgenual anterior cingulate cortex; AMCC: anterior midcingulate cortex; SMG: supramarginal gyrus; FG: inferior frontal gyrus.
investigated a mixed group of mild and remitted MDD this limits a direct comparison with the above findings.

Seed-based correlation analysis (SCA)
Based on earlier work defining the DMN and results from resting-state and activation studies, the most commonly used seed regions in SCA studies investigating the DMN are either the sgACC or the PCC. Importantly though, the sgACC is not always considered part of the DMN although several authors point toward its inclusion in the DMN in depressed samples. A study by Zhou et al. on this issue found that the recruitment of the sgACC within the DMN is specific for MDD and not present in healthy controls. This is an important finding which limits the use of this area as a seed region to study the DMN as a whole when comparing different subject groups. Therefore we will focus on studies using DMN seeds in the mPFC (dorsal to the ACC) and the PCC/PCu and address the sgACC separately.

For the anterior DMN, only two papers selected seeds in the medial prefrontal cortex dorsal to the ACC. Consistent with the hypothesis of a dissociation between the anterior and posterior DMN in depression, Van Tol et al. found a decrease in connectivity of the dmPFC with the posterior DMN. Furthermore, connectivity of the dmPFC to the left anterior insula was increased, indicative of increased connectivity between the anterior DMN and the SN. Sheline et al. selected their dmPFC seed based on an overlapping increase in connectivity from three different seeds (sgACC, PCu and dlPFC). They hypothesized that this region, which they termed the ‘dorsal nexus’, is a converging point of increased connectivity and could give rise to the complex dysfunctions seen in depression. Using this area as a seed revealed a pattern of increased connectivity with medial prefrontal (ACC, ventromedial prefrontal cortex (vmPFC)), medial posterior (PCC, PCu) and lateral prefrontal (dlPFC) areas. The different findings between these two studies could be related to differences in medication status and differences in seed-selection; while van Tol and colleagues based their seed on an area of reduced cortical thickness, Sheline and colleagues defined their seed by its hyperconnectivity with other seed regions.

In addition to the papers using seeds in the anterior DMN, eight papers investigating the DMN used seed regions located in the posterior DMN (PCC or PCu). In general, these studies show inconsistent changes in connectivity between anterior and posterior nodes of the DMN.

In line with some of the ICA-papers, Alexopoulos et al. found connectivity of the PCC to be increased with both anterior (sgACC, vmPFC) and posterior (PCu) nodes of the DMN in a medicated group of late-onset depression. Berman et al. also found increased connectivity of the posterior DMN with the sgACC in a much younger (mean age 25.7 years) medicated patient group. Similarly, Zhou et al. reported increased connectivity of the PCC with other posterior DMN nodes and the mPFC and OFC. Interestingly, another study in a smaller unmedicated group of elderly depressed patients also reported increased connectivity of the PCC with the dmPFC and OFC, but connectivity of the PCC with the sgACC was decreased. This decrease in connectivity was partly restored after 12 weeks of treatment with paroxetine, which suggests that antidepressant treatment influences connectivity between anterior and posterior DMN regions. Further evidence for this hypothesis was reported in a larger group of unmedicated elderly. At baseline, they found increased connectivity of the PCC with other nodes in the posterior DMN, but decreased connectivity with the medial frontal gyrus. After 12 weeks of antidepressant treatment connectivity in both the bilateral medial frontal gyrus and the dorsal ACC (dACC, part of the SN) was increased, although these effects did not survive correction for white matter hyperintensities. The other papers investigated connectivity from the posterior DMN in young adults and adolescents and reported a decrease in connectivity with the caudate nucleus or no changes. In summary, SCA studies from the posterior DMN mainly report increased connectivity with different medial prefrontal regions, which might be related to medication status. Longitudinal studies also point toward an effect of antidepressant treatment on connectivity between the anterior and posterior DMN.

CENTRAL EXECUTIVE NETWORK (CEN)
Independent component analysis (ICA)
A limited number of papers thus far has used ICA to investigate connectivity within the CEN in depression. Manoliu and colleagues used a high model-order ICA to define three sub-networks within the CEN. They reported increased connectivity of the right angular gyrus within the left ventral CEN and of the right postcentral gyrus within the dorsal CEN. Veer et al. did report decreased connectivity of the frontal pole, but within an attentional network that only partly overlapped with the typical CEN-configuration. A study investigating the CEN in a group of mostly remitted patients found no differences in connectivity.

Seed-based correlation analysis (SCA)
SCA studies on connectivity of the CEN are consistent in using the dlPFC as a seed region and most show decreased connectivity of the dlPFC with other regions of the CEN. This hypoconnectivity within the CEN was found in medicated patients with
a first depressive episode \textsuperscript{63}, late-life depression \textsuperscript{65} and treatment-resistant depression \textsuperscript{61}. A longitudinal study by Lui et al. \textsuperscript{82} investigated a group of medication-naive depressed patients before starting antidepressant treatment. Interestingly, they report decreased connectivity of the dIPFC with the parietal cortex and PCu specifically in those patients who would later respond to antidepressant treatment, while those that failed to respond instead showed decreased connectivity of the dIPFC with several regions of the SN (insula, dACC).

Two studies also report areas of increased connectivity with the dIPFC, while one found no changes \textsuperscript{82}. Ye et al. \textsuperscript{83} found that in a first episode of depression connectivity of the dIPFC was increased with the left dACC, left parahippocampus, thalamus and precentral gyrus, while Sheline et al. \textsuperscript{85} report increased connectivity with the ‘dorsal nexus’, an area in the dmPFC with overlapping increased connectivity from different seeds.

**SALIENCE NETWORK (SN)**

*Independent component analysis (ICA)*

Networks related to emotion regulation were investigated in three papers using ICA \textsuperscript{65,69,70}. Manoliu and colleagues identified the SN and found increased connectivity within the bilateral ACC and decreased connectivity within the bilateral anterior insula. Notably, the decreased connectivity in the right anterior insula was inversely correlated with depression severity and positively correlated with decreased connectivity between the DMN and the CEN \textsuperscript{85}, which is in line with the insula’s involvement in switching between the DMN and the CEN\textsuperscript{16,24,31}. Consistent with a decreased connectivity within the SN, Veer et al. \textsuperscript{50} report a decoupling of both the insula and amygdala within a network involved in emotional processing, although this network is different from the typical SN. Sexton et al. \textsuperscript{49} found no difference within an ‘affective network’ that was centered on the sgACC and ventral mPFC in mostly remitted patients.

*Seed-based correlation analysis (SCA)*

The most investigated seed regions involved in the SN are the insular cortex \textsuperscript{62,64,65} and the amygdala \textsuperscript{58,62,66–72}. Compared to the DMN and the CEN, the SN is less well-defined during the resting-state, although many authors report changes in networks related to emotional processing. Possibly related to this, changes in the SN appear less consistent and more node-dependent in comparison to the DMN and CEN.

Consistent with the ICA-based finding of increased connectivity of the SN with the ACC \textsuperscript{45}, SCA investigating the insula found that its connectivity was increased with the pregenual ACC \textsuperscript{60} and the medial OFC \textsuperscript{64}. This increased connectivity to nodes of the anterior DMN is in line with hyperconnectivity of the anterior DMN and the insula’s hypothesized role in orchestrating network interactions\textsuperscript{16,24,31}. Another important node in the SN and highly relevant for MDD \textsuperscript{73,74}, the amygdala is typically found to have decreased connectivity with various brain regions \textsuperscript{70,72}. In line with the uncoupling of the amygdala and insula from the SN as found using ICA \textsuperscript{45,10}, two other papers also reported decreased connectivity between the amygdala and the insula \textsuperscript{87,88}. In further support of a dissociation within the SN, another study found decreased connectivity of the insula with the dACC in adolescent depression \textsuperscript{58}.

Other areas that were repeatedly found to have decreased connectivity with the amygdala include the left ventrolateral PFC (vPFC) \textsuperscript{87,88} and the ACC \textsuperscript{56,63}. Despite the majority of papers reporting decreased connectivity of the amygdala, two studies instead reported an increase in connectivity of the amygdala with the temporal pole, which was found to correlate with depression severity \textsuperscript{15–17}. Together, studies on amygdala connectivity mainly show a pattern of dissociation from the rest of the brain, and more specifically the SN, with a possible exception for the temporal pole.

**OTHER SEED-BASED CORRELATION ANALYSIS**

*Anterior cingulate cortex (ACC)*

The anterior cingulate cortex has several anatomically defined subregions that have been investigated in the context of MDD. SCA studies on the ACC mainly report increased connectivity with regions in the anterior DMN, and some show evidence for increased connectivity with regions of the SN. As discussed earlier, the sgACC is sometimes included within the DMN, although this inclusion could be specific during the depressed state \textsuperscript{27,40}.

Sheline et al. \textsuperscript{20} used the sgACC as a seed region and reported increased connectivity with the ‘dorsal nexus’, an area in the dmPFC. Consistent with these findings, Davey et al. \textsuperscript{57} also report increased connectivity from the ACC to both dorsomedial and dorsolateral prefrontal cortex. Further elaborating on these regions, Liston et al. \textsuperscript{61} investigated patients during the course of repetitive transcranial magnetic stimulation (rTMS), and found that at baseline connectivity of the sgACC with the DMN was increased, while connectivity of the sgACC with the CEN was decreased. Not only did rTMS reduce the connectivity of the sgACC with the DMN, but higher pretreatment connectivity also predicted a good response to treatment, an important finding replicated in another rTMS study \textsuperscript{74}. De Kwaasteniet et al. \textsuperscript{70} also used the sgACC as a seed region and found a pattern of increased connectivity which is remarkably similar.
to the OFC and the thalamus, in addition to increased connectivity with the hippocampus and amygdala.

Three studies used the sgACC as a seed region to investigate changes in connectivity specifically in adolescent depression. Davey et al. found connectivity increased with the dmPFC, which is in line with increased connectivity of the sgACC with the DMN in depression. Connolly et al. showed that depressed adolescents exhibit greater connectivity of the sgACC with the amygdala and the insula, but decreased connectivity with the PCu. They interpreted their findings as aberrant connectivity between the DMN and the SN, with the insula possibly driving the difficulties in network transition as proposed by others. In addition, the decrease in connectivity between the sgACC and the PCu is consistent with the studies reporting decreased connectivity between the anterior and posterior DMN. Although not discussed, the four different seeds in the sgACC did show significantly different patterns of changed connectivity, which underlines the effect of small variances in seed selection. In contrast to the majority of papers on sgACC connectivity, Cullen et al. found decreased connectivity of the sgACC within an ACC-network including the insula, although their conflicting findings can probably be attributed to the fact that subjects were listening to their own choice of music, which has been shown to influence emotional network connectivity. In summary, SCA studies confirm increased connectivity of the sgACC with the anterior DMN and nodes of the SN (amygdala and insula).

Two papers opting for direct correlations (as opposed to whole-brain SCA) used seeds placed in the pgACC. Employing direct correlation over whole-brain SCA has a trade-off in being more sensitive to node-specific effects while being less informative about large-scale networks. Anand et al. found that direct correlations between the pgACC and limbic structures (amygdala, pallidostriatum and thalamus) were decreased, explaining it as a potential decrease in ACC-mediated regulation of limbic areas. Another study by Horn et al. showed increased connectivity between pgACC and the left anterior insula. With the insula being implicated in switching between different states or networks, they too proposed that the increased assignment of the insula to the anterior DMN leads to a decrease in the ability to direct attention away from inward/self-related processing.

Hippocampus and subcortical areas
In addition to the amygdala, changes in connectivity of several other subcortical structures have been investigated in depression. Two studies report decreased connectivity of the hippocampus with the insular cortex. As the hippocampus (together with the parahippocampal gyrus) is strongly related to the posterior DMN, this could reflect a decrease in connectivity between the insula and the posterior DMN. Only one study focused on connectivity of the hippocampus specifically. Although they did not confirm any changes in connectivity with the insula, they did find impaired negative connectivity (reduced negative correlation) of the hippocampus with bilateral middle frontal gyrus, the right inferior parietal cortex and the right cerebellum. They interpreted this reduction in negative correlation as a failure of the hippocampus to segregate its function in the depressed state, which could be related to the emotional and cognitive dysfunction in MDD.

A study focusing on the connectivity of subcortical structures used seeds placed in the nucleus accumbens (NAC), caudate nucleus, and putamen. They found an increase in connectivity with the dmPFC in adolescent depression for these nodes. Another paper using a seed in the striatum instead found decreased connectivity with vmPFC and sgACC and increased connectivity with the medial frontal gyrus. Lui et al. also included seeds in the putamen and thalamus that showed decreased connectivity to regions in the lateral prefrontal cortex. In addition, the thalamus also showed decreased connectivity with the insula. Overall, their study on 13 different regions of interest concluded that there is a pattern of significantly reduced connectivity within prefrontal–limbic–thalamic areas bilaterally, which they consider to represent the loss of top-down regulation of prefrontal cortex over limbic regions in MDD. Finally, Ma et al. used seeds in the right middle temporal gyrus (MTG) and caudate nucleus based on reduction in gray matter density and found abnormal connectivity with the DMN for the MTG, but not for the caudate nucleus. Unfortunately, since they found both increased and decreased connectivity in various regions, these findings are difficult to interpret.

BETWEEN-NETWORK CONNECTIVITY
Changed connectivity between two nodes of different networks can reflect an alteration in the interaction between these networks. However, several authors also specifically addressed how connectivity between the larger networks changes in depression using ICA. The study by Manoliu et al. in addition to the above mentioned within-network connectivity, also investigated between-network connectivity for three sub-networks of the DMN (anterior, inferior–posterior, superior–posterior), three sub-networks of the CEN (left ventral, right ventral, dorsal) and the SN. They found increased connectivity between the inferior–posterior DMN and the SN, and decreased connectivity between both of the posterior DMN sub-networks and the dorsal CEN, which was related to
the decreased connectivity of the right anterior insula within the SN. Consistent with these findings, Abbott and colleagues investigated between-network connectivity in a group of treatment-resistant depressed patients prior to electroconvulsive therapy and also found decreased connectivity between posterior DMN and the CEN (dlPFC) at baseline. In line with the hypothesis of dissociation within the DMN, they also found decreased connectivity between the posterior DMN and the dmPFC. The between-network connectivity changed from negative to positive following electroconvulsive therapy, which is consistent with the SCA findings of antidepressant treatment affecting connectivity within the DMN. These findings also highlight the importance of between-network interactions in addition to the within-network findings.

**DISCUSSION**

Due to the relative ease of collecting resting-state fMRI scans and the availability of new techniques such as ICA to accommodate the large amount of information involved, a large body of investigations into resting-state functional connectivity in depression is available now. Our review of the currently available data has yielded several findings that were consistent across different methods:

1. increased connectivity within the anterior DMN,
2. increased connectivity between the anterior DMN and the SN,
3. changed connectivity between the anterior and the posterior DMN, and
4. decreased connectivity between the posterior DMN and the CEN.

A summary of these findings is represented in Fig. 2. We will discuss the support for these findings and their implications for our current understanding of MDD and its treatment.

**FIG. 2.** Within- and between-network connectivity changes in major depressive disorder. Red/blue outlines represent a within-network increase/decrease in connectivity; red/blue lines between networks represent a between-network increase/decrease in connectivity. Black ellipses represent key nodes related to connectivity. Numbers represent main findings: (1): increase in anterior DMN connectivity and inclusion of sgACC within the anterior DMN, (2): increased connectivity between anterior DMN and SN, (3): changed connectivity between anterior and posterior DMN, (4): decreased connectivity between posterior DMN and CEN.

Abbreviations: sgACC: subgenual ACC.

**Increased connectivity within the anterior DMN**

The most consistent finding across all studies is increased connectivity in the anterior DMN, both within the DMN as a whole and between the different anterior nodes. In depression, gray matter volume in this area is typically decreased, while activity is increased both during rest and in response to emotionally salient stimuli. Adding to this, the attenuation of anterior DMN activity during cognitive tasks is impaired in the depressed state. Hyperactivity in the sgACC has been a consistent finding, and activity within this node serves also as a marker of treatment response. Because of this, the change in DMN configuration to incorporate the sgACC in depression is intriguing, especially considering its extensive structural connectivity to both the DMN and the SN.
INCREASED CONNECTIVITY BETWEEN THE ANTERIOR DMN AND THE SN

Although not as often reported as the increase in anterior DMN connectivity, several papers indicate an increase in functional connectivity between the anterior DMN and the SN, which is consistent with reports of increased structural connectivity (35). Hyperactivity of the amygdala, especially in response to negative stimuli, is common in depressed patients and has been hypothesized to interact with the mPFC to underlie the negativity bias in MDD (33). The repeat finding of increased connectivity between the amygdala and sgACC, in addition to a recent report on its relation to disease onset (31), therefore further highlights the relevance of this connection in MDD. However, whether these changes in connectivity constitute an increase in top-down modulation of limbic hyperactivity, bottom-up interference of self-processing regions, or both, is unclear. Surprisingly, connectivity of the amygdala with other brain regions implicated in emotional control is decreased in MDD, which could indicate an inability to control amygdala hyperactivity by regions other than the sgACC. This is in line with a recent review by Rive et al. (70), who showed both differential functioning of ACC regions and an inability to recruit additional prefrontal resources in emotional control in depressed patients. The decreased connectivity of the amygdala with more lateral brain regions (insula and lateral PFC) is also consistent with limbic hyperactivity and lateral hypoactivity as found in resting-state activation studies in depression (91). It is also remarkably similar to the limbic–cortical dysregulation model initially hypothesized by Mayberg (41) that explains MDD as an inability to regulate hyperactive “ventral limbic” areas (including the ventral insula, amygdala, hypothalamus, hippocampus, vmPFC and sgACC) by hypoactive “dorsal limbic” areas (including dACC, PCC, inferior parietal, dorsal frontal areas). This model also implicates the rostral ACC as a key area in both MDD and treatment response.

DECREASED CONNECTIVITY BETWEEN THE POSTERIOR DMN AND THE CEN

Another interesting finding concerning the posterior DMN specifically is its decreased connectivity with the CEN. In line with the role the posterior DMN has in awareness and directed attention (14) and the role of the CEN in higher cognitive functioning (28), the change in their interaction could underline difficulty in switching from a “default-state” in which the DMN is dominant and which is directed internally, to an “executive state” in which the CEN is dominant and attention is directed toward outward stimuli (9). Several authors have implicated that the insular cortex might be crucial for this shift in network-dominance (25,34,55,45), which is supported by the increased connectivity of the insula with the anterior DMN and decreased connectivity with other networks.

CHANGED CONNECTIVITY BETWEEN THE ANTERIOR DMN AND THE POSTERIOR DMN

Connectivity between anterior and posterior nodes of the DMN has repeatedly been found to be changed in MDD. Studies using ICA and SCA with anterior DMN seeds mainly report evidence of a dissociation of the DMN, while in the SCA investigations using seeds in the posterior DMN the majority reports increased connectivity between anterior and posterior nodes. As described earlier, an anterior and posterior sub-network within the DMN has been identified in healthy subjects (17,74,76) and they were shown to contribute to different aspects of self-generated thought. However, the implications of changes in functional connectivity between the anterior and posterior sub-networks are not well understood, although a paper by Leech and Sharp (29) hypothesized that an increase in PCC connectivity with anterior DMN regions would relate to an increase in internally directed attention, which is in line with its correlation to rumination scores in depression (35). In depressed patients findings of decreased connectivity between the anterior and posterior DMN are supported by a decrease in structural connectivity in a sgACC-posterior DMN based network (30). Considering that using a higher model-order in ICA reliably splits the DMN into its sub-networks (45,47), a possible explanation for the inconsistent findings is that MDD merely accentuates a normal functional distinction already present within the DMN in healthy subjects. Regardless, it is worth noting that while findings are inconsistent, several authors have reported treatment for depression to selectively affect parts of the DMN, which underlines the relevance of the distinction between anterior and posterior sub-networks.

CLINICAL CORRELATES AND TREATMENT EFFECTS

Many authors have attempted to correlate clinical measures to changes in connectivity in MDD. In agreement with the most consistent regions of changed connectivity, nearly all findings of significant correlation between connectivity and clinical scores are either within the DMN or the interaction between the DMN and the SN. In short, severity of disease was related to connectivity of the sgACC (17,74,76), the dmPFC (51), the dACC (30), the dorsal caudate (42) and the insula (25,54,64). Connectivity of the sgACC was further related to disease duration (43) and rumination (45,55,76), while connectivity within the posterior DMN was related to overgeneralized memory (46).

Adding to this, numerous authors have reported changes in connectivity through various treatment modalities. Longitudinal studies found antidepressant medication to affect the anterior and posterior DMN differently, but whether the effect is specific for the sgACC (94), the anterior DMN (14), posterior DMN (14), their interaction (14) or the interaction between parts of the DMN and the SN (95,96) is unclear. However, as most of these changes were in subjects with a baseline difference in connectivity within the
DMN this signifies that effective antidepressant treatment restores aberrant network configuration within the DMN. Consistent with this, other treatment modalities find similar effects with TMS normalizing an increase in sgACC-DMN connectivity \(^{(61,74,55)}\) and ECT also targeting disrupted connectivity between the anterior and posterior DMN \(^{(47,51)}\) and between the DMN and the CEN \(^{(47,24,51)}\). Studies looking at differences between treatment-sensitive and treatment-unresponsive patients in a longitudinal setting also found that responders showed lower baseline connectivity of the PCC with the striatum \(^{(56)}\) and higher connectivity of the insula with DMN nodes \(^{(62)}\). Extending the clinical relevance of connectivity measures, a number of authors have been able to predict treatment response using functional connectivity. A positive response to rTMS was predicted by high baseline connectivity of the sgACC with the DMN \(^{(51,74)}\) or strong anticorrelation of the sgACC with the stimulation site in the dlPFC \(^{(100)}\). More recently, a paper by Van Waarde et al. \(^{(100)}\) showed that connectivity patterns in two networks centered on the dmPFC and ACC could identify responders to ECT with high reliability, which corresponds with our findings that the majority of consistent changes in connectivity center on networks related to the anterior DMN.

Importantly, due to the differences in methods and results there is as of yet no compelling evidence for differentiating different subtypes of depression based on connectivity measures. As subtypes of depression respond differently to treatment strategies, this is a line of research that could prove promising in the future \(^{(102–104)}\).

**METHODOLOGICAL CONSIDERATIONS AND LIMITATIONS**

Although the primary findings as presented above expand our current understanding of MDD, it is important to also address the shortcomings of current connectivity investigations. Especially for seed-based approaches even the most consistent findings are often not reproduced or connectivity changes are only found using one of the regions as a seed. For instance, a number of studies find increased connectivity for the sgACC with the amygdala when using the sgACC as a seed region, while none of the papers using the amygdala as a seed regions report increased connectivity with the sgACC. This heterogeneity in findings could reflect heterogeneity within the disorder itself, which is inherent to the symptom-based classification used to diagnose depression. However, it could also reflect the methodological difficulty in correct seed-selection and the problems introduced when correlating one or a few seeds to all other brain voxels. This is illustrated when papers use several similar seed voxels close to one another and find large differences in the emerging connectivity pattern \((38,76)\), which shows that small variation in seed selection can significantly impact the final results. In short, while seed-based approaches are very sensitive to changes in connectivity of the seed-region under investigation, this high sensitivity could also induce spurious findings with no biological meaning, for instance by merely reflecting similarity in noise within the two regions. This also limits the conclusions that we can draw from singular findings in papers using SCA. Another important methodological concern is the use of global signal regression in a number of the SCA papers, as this has repeatedly been shown to induce anti-correlations in the data \((120,126)\).

In contrast to the SCA-based papers, studies using ICA to identify networks appear much more consistent in their findings, as in fact all studies using a depressed group found increased connectivity within the anterior DMN, and nearly all report changes in the connectivity of anterior and posterior DMN regions. A limitation of ICA however is that there is no clear consensus on a “correct” number of components to identify, and this directly influences the possible outcomes. However, different model-orders could also be used to further our understanding of sub-networks within networks. For example, a limited number of components could be used to look at large-scale networks (e.g. the DMN as a whole), while a high number of components in the same data would allow us to look at decompositions into sub-networks and investigate the underlying changes in network configuration (e.g. interaction between anterior and posterior DMN). A limitation of investigating neural networks in general is that there is no consensus on the boundaries of these networks. Additionally, while key nodes are identified consistently, associated regions may vary in their connectivity to any given network. Finally, a limitation of both ICA and SCA is that there is no clear consensus on what statistical thresholds should be used to either identify networks or make claims about the reliability of certain findings. For example, papers vary between what cluster size represents a significant finding. As these statistics are also influenced by the data used and the choices made during preprocessing, one common threshold will not be suitable for all study designs. Instead, researchers should provide clear information about their methodological considerations.

**FUTURE DIRECTIONS**

Based on the current findings and methodological properties of the different techniques, there are several recommendations for future researchers. The decreased bias and increased consistency of findings using ICA over SCA leads us to propose that ICA should be used to give a model free estimation of regions of change in depression. Consequently, SCA should be used to further expand upon these significant findings by being more sensitive to specific changes less related to within network connectivity. As mentioned above, the number of components used in ICA analysis could help to delineate within-network configurations and sub-networks. Furthermore, large-scale
networks are not static, but instead change over time even during rest (107,108). More insight into these network dynamics, for instance by looking at causal interactions and directionality of influence between the different nodes or networks, could inform us how the activation of networks is coordinated and possibly how network control is changed under various conditions such as the depressed state. Finally, relating changes in connectivity to distinct symptom profiles and neurocognitive domains would help us tackle the issue of large heterogeneity within MDD and improve treatment strategies for specific depression subtypes.

CONCLUSION

Connectivity studies in MDD expand upon activation studies by reporting increased connectivity within nodes of the anterior DMN and between the anterior DMN and the SN, changed connectivity between the anterior and posterior DMN and decreased connectivity between the posterior DMN and the CEN. We propose that this reflects a state of increased interaction between self-referential and emotional networks, and the dominance of negative self-referential over cognitive processing which corresponds to the clinical symptoms of depression. The consistent differences found in the interaction between nodes and networks, as well as its clinical potential in predicting treatment response, highlights the importance of functional connectivity in furthering our understanding and treatment of depression. Future studies should focus more on model-free investigations to elucidate true underlying biology, for example using ICA, while methods with high sensitivity such as SCA could be used to confirm and expand upon the found changes. Furthermore, investigations into how large-scale networks consist of sub-networks and the interactions between different networks are important challenges for current researchers in the field.

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ELECTROCONVULSIVE THERAPY FOR DEPRESSION: NEUROBIOLOGICAL MECHANISMS

adapted from:

INTRODUCTION

Although it has been around since the 1940s, electroconvulsive therapy (ECT) is still the most potent antidepressant treatment available today. Electroconvulsive therapy is a neurostimulation technique where an electrical current is applied, usually at the temporal window, during a brief induced anesthesia with applied muscle relaxation, with the goal to elicit an epileptic seizure. A course of ECT lasts several weeks during which two or three of these sessions are performed weekly. ECT is effective for various brain disorders including bipolar disorder, schizophrenia, Parkinson’s disease, and catatonia, but is predominantly applied in patients suffering from treatment-resistant major depressive disorder (MDD). It is the single most effective treatment for depression and, even in patients who fail to respond to pharmacotherapy and/or psychotherapy, response rates are as high as 50%–70%.[2]. Due to its relative invasiveness, its high costs, and sometimes severe (although usually transient) cognitive side effects, it is typically reserved as a last-line treatment when either fast response is crucial or other treatments have proven unsuccessful. In light of both its remarkable therapeutic effect and its limitations, understanding the underlying neurobiological mechanisms of ECT has great potential in improving antidepressant treatments.

After a few decades when the use of ECT was considered questionable by both society and psychiatrists, the sheer efficacy of the treatment has renewed scientific interest in these mechanisms, which are still poorly understood. With recent advances in neuroimaging, there is a substantial body of literature investigating how ECT affects the brain and how this relates to its strong clinical effects. Early work using positron emission tomography—computed tomography (PET-CT) has indicated that ECT alters brain perfusion both during and after the seizure in various cortical and subcortical regions.[3] During ECT, perfusion increases, which is followed by a state of hypoperfusion in the postictal phase. Early work on glucose metabolism has found that, after ECT, metabolism is decreased in medial and inferior frontal regions, while being increased in the medial temporal lobe.[4] More recently, rapid advances in neuroimaging, including a variety of new methods using magnetic resonance imaging (MRI), offer us new ways to explore how ECT affects both the structure and function of the brain.

Currently, there are a number of hypotheses regarding ECT’s mechanisms of action that are important to briefly discuss.[5] (1) The monoamine hypothesis states that, similar to psychopharmacology, ECT works through increases in monoamine systems such as serotonin and dopamine. This hypothesis is based on both our understanding of the depressed brain and the finding that ECT affects monoamine systems and receptor availability. (2) The anticonvulsive hypothesis, which states that ECT, by eliciting seizures, drives the brain to become more resistant to convulsions through increasing inhibitory processes, as evidenced by increases in the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and the clinical observation that patients develop an increased seizure threshold during the course of treatment.[6] (3) The neurotrophic hypothesis, which posits that ECT works through affecting neuroplasticity. This hypothesis is supported by animal models of ECT, where electroconvulsive stimulation (ECS) has been found to increase neurogenesis in the dentate gyrus of the hippocampus and induces proliferation of glial cells, showing that these effects might not be limited to specific cell types.[7] While the hippocampus was initially the primary target for research into neuroplasticity after ECS, it is increasingly found to also be present in other areas of the brain such as the frontal cortex[8] and amygdala.[9]

These hypotheses are not mutually exclusive and, ultimately, it is unlikely that any one hypothesis fully explains the broad effects ECT has, but instead each of these (and likely others) may play an important role and interact to create the strong antidepressant response we see in patients. For the purpose of this chapter, we will provide an overview of all longitudinal studies that compare baseline to post-treatment magnetic resonance imaging and address the neuroplastic changes that occur after ECT at the human systems level. We incorporate studies investigating structure as well as function, and although these are often investigated separately, it is important to note that these are dependent entities; it is assumed that structure underlines function, at least to an extent, in a way that a decrease in volume is indicative of a decrease in function over a longer period of time. With ECT being a treatment that affects the entire brain, identifying changes in structure and function after ECT is only the first step, as it is unlikely that all changes that occur are needed or even related to its clinical effects. Determining which of these changes relate to its antidepressant action or cognitive side effects is a crucial second step in understanding its mechanisms and would inform us whether ECT restores the brain to its original non-depressed state or, instead, acts through compensatory mechanisms that help combat depression.

METHODOLOGICAL DIFFERENCES BETWEEN MRI TECHNIQUES

There is a large number of possible techniques to examine neurobiological changes induced by ECT, each with their own specific advantages and limitations. Since
considering these factors is important to interpret individual studies, we will briefly discuss the most commonly used modalities here. Very broadly, neuroimaging studies can be categorized as investigating either structural or functional changes. A recent addition to functional studies is the measurement of brain metabolites in vivo by magnetic resonance spectroscopy (MRS), which we will discuss separately.

**STRUCTURAL**
Investigations into structural changes induced by ECT significantly outnumber other types of research. These studies can be divided into either whole-brain explorative analyses (voxelwise or parcellation-based) or region-of-interest analyses that aim to test a specific hypothesis about a region, either shown to be affected by ECT in earlier (animal) work or relevant in the pathophysiology of depression. Studies on gray matter usually calculate either the density of the gray matter at each voxel (voxel-based morphometry), the thickness of the cortex, or the volume of specific regions-of-interest, either manually or using automated algorithms. These methods allow us to evaluate whether ECT leads to an increase or decrease in volume of certain regions of the brain, which is assumed to underlie a change in function and can be indicative of neuroplasticity. Notably, depression has been shown to relate to volumetric changes in the brain as well.

Investigations into white matter focus on the structural connections through which gray matter areas communicate to each other or the rest of the body. These studies typically base their results on how the diffusivity of water in the brain is restricted, as water diffuses freely along the direction of white matter tracts. The derived measures include fractional anisotropy (FA), mean diffusivity (MD), or radial diffusivity (RD), which relate to the integrity of white matter tracts and are hypothesized to indicate their ability to facilitate communication between the regions they are connecting.

**FUNCTIONAL**
Functional imaging has undergone many developments in recent years and offers a variety of different types of analyses. In its early days, the use of radioactive ligands allowed for measuring blood flow in the brain at various stages of electroconvulsive treatment by positron emission tomography (PET). More recently, functional imaging is predominantly performed by evaluating the blood-oxygen-level-dependent (BOLD) response, which is based on small changes in the magnetic field induced by changes in the amount of oxygen-saturated hemoglobin to desaturated hemoglobin. These small changes can be detected using tailored MRI-sequences, which are used to collect scans at intervals ranging from 0.4 to 3 s for a prolonged period of time (from 5 min up to an hour). These volumes can then be used to assess the evoked response in brain activation from a stimulus given during scanning (task-based fMRI) or to assess the spontaneous fluctuations that occur during rest; so-called resting-state fMRI. As the researcher obtains the activity of every voxel in the brain (typically 2–3 mm isotropic), is it also possible to calculate the correlation of signal over time between different regions. This is called functional connectivity and is often used to infer functional relationships between structures or to detect “functional networks”; networks of areas that consistently activate or deactivate in unison form a coherent functional unit. Functional networks of particular interest in the context of depression are: (1) the default mode network (DMN), which is most active during rest and related to self-referential activity and spontaneous thought; (2) the cognitive-executive network, which is related to cognitive effort such as attention, and (3) the salience network, which is related to emotional control. A commonly used hypothesis-driven approach to functional connectivity is “seed-based correlational analysis” (SCA), where a seed-region is selected a priori and the functional connectivity of that region to every other voxel in the brain is calculated to obtain a map of connectivity for the seed-region. This map can then be calculated in different groups or under different conditions (such as before vs after treatment) to detect changes in the connectivity pattern. In contrast to SCA, independent component analysis (ICA) is a method that uses all of the functional data available to estimate brain networks in a model-free way. It is more fitting for exploratory analyses, but is more difficult to interpret as changes relate to connectivity of regions to an entire network, instead of just two regions to one another.

**MRS**
A more recent addition to functional neuroimaging, and one gaining more traction over the past few years, is magnetic resonance spectroscopy (MRS). Using specific MRI-sequences, we can obtain a spectrum that reflects the presence of molecules with various weights from a region-of-interest in the brain. Since we know the molecular weight of several important substances, we can use the spectrum to determine the (relative) presence of a particular neurotransmitter or molecule, such as choline, N-acetylaspartic acid (NAA), glutamate/glutamine (Glx), and gamma-aminobutyric acid (GABA). MRS is an exciting new avenue of research with a lot of potential, for example with regard to solving the anticonvulsant hypothesis of ECT. Currently, it has some technical limitations, as it is only possible to acquire the spectrum of a single relatively large region at a time and it is very susceptible to motion during acquisition.

**ADDITIONAL CONSIDERATIONS**
In investigating neurobiological changes induced by ECT, there are other considerations...
in addition to the specific imaging modality used. Due to the heterogeneity between depressed patients, a longitudinal design is often necessary to determine effects related to ECT specifically. It is also important to consider the timing of the pre- and post-treatment measurements: a shorter time between the last ECT and the measurement could favor changes induced by ECT unrelated to its treatment efficacy, while a longer time after treatment could favor effects related to antidepressant action or side effects. A longer follow-up is often complicated by the high rate of depression relapse in patients treated with ECT. Another complicating factor is the concomitant use of medication (psychopharmacology but also anesthesia/muscle relaxants), both during ECT and after, since although patients are typically treatment-resistant, it is still likely that medication alters brain structure and function.

There is also a significant difference between explorative studies and studies with a specific hypothesis regarding a region-of-interest. While the former is useful in determining the presumably broad effects of ECT, there is a significant risk of being underpowered due to the need for large-scale correction for multiple comparisons. In contrast, a hypothesis-driven approach has a smaller chance of type I errors, but is unable to detect any effect outside of the hypothesis and has the risk of a blinkered view. Ultimately, a combination of both approaches is needed to both generate and confirm relevant findings.

**BRAIN CHANGES RELATED TO ECT**

To give context to the discussion of regions affected by ECT, we will briefly discuss structural and functional changes in the depressed brain at baseline. In contrast to several decades ago, depression is no longer understood as resulting from a single change or defect. Rather, it can be better understood as a multi-systems level disorder that arises from dysfunctional circuits that interact with one another. Disentangling these circuits, patterns, and what drives them is one of the primary goals of current neuroscience.

In depression, significant decreases in the volume of gray matter have been identified. These decreases are most pronounced in the medial prefrontal cortex (dorsolateral, orbitofrontal) and the medial temporal lobe including the hippocampus and amygdala. While some of these effects are present for depression as a whole, some regions are more affected in specific subgroups such as patients suffering from a first episode, chronically depressed patients, or those with comorbid anxiety disorders. With regard to functional studies, most find evidence for hyperactive “emotional” limbic areas such as the amygdala and ACC and hypoactive “controlling” lateral areas such as the lateral prefrontal cortex. Because of the consistent hyperactivity within the ACC, deep-brain stimulation for treatment-resistant depression also targets this area. Resting-state connectivity studies also support changes primarily within and between these core regions, with connectivity being increased between anterior parts of the default mode network (medial prefrontal cortex) and parts of the ACC and the salience network (including the amygdala), while functional connectivity between cognitive-executive regions is decreased.

Compared to other neurostimulation methods such as transcranial magnetic stimulation, electroconvulsive therapy is a relatively nonspecific treatment, with broad effects on the brain. The electrical stimulus is applied either bilaterally or unilaterally to the temporal or frontal areas of the head and is adjusted to elicit a generalized epileptic seizure that, by definition, activates the entirety of the cortex. In a sense, ECT affects the entire brain, which while possibly explaining why it is so potent also complicates attempts to pinpoint what changes specifically relate to its effects or side effects. This problem is confirmed by the number of different regions that have been shown to be affected in neuroimaging studies. However, some regions are certainly more implicated both as being relevant in the context of depression and ECT: the medial temporal lobe (MTL) and the anterior cingulate cortex (ACC). An overview of papers investigating longitudinal changes after ECT can be found in Table 1 (structural) and Table 2 (functional).
Table 1. Studies of structural changes after ECT.

<table>
<thead>
<tr>
<th>Group and Study</th>
<th>Year</th>
<th>N</th>
<th>Med</th>
<th>Bip</th>
<th>ECT</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drouvaert</td>
<td>2016</td>
<td>28</td>
<td>N</td>
<td>Y</td>
<td>BL/RUL</td>
<td>• NCaud, MedTemp, Ins, LTC</td>
<td></td>
</tr>
<tr>
<td>Bruckart</td>
<td>2017</td>
<td>12</td>
<td>Y</td>
<td>N</td>
<td>BL</td>
<td>• MTL (tpc, Amyg, ParALtPc), pFGc</td>
<td></td>
</tr>
<tr>
<td>Dukart</td>
<td>2014</td>
<td>10</td>
<td>Y</td>
<td>Y</td>
<td>RUL</td>
<td>• Hpc, Amyg, TP, sgACC</td>
<td></td>
</tr>
<tr>
<td>Nickl-Jorschat</td>
<td>2016</td>
<td>21</td>
<td>U</td>
<td>N</td>
<td>RUL/LART</td>
<td>• MedTh, Frontal, Premotor</td>
<td></td>
</tr>
<tr>
<td>Ota</td>
<td>2015</td>
<td>15</td>
<td>Y</td>
<td>N</td>
<td>BL</td>
<td>• Hpc, ParALtPc, sgCC, ACC, LTC, Thal</td>
<td></td>
</tr>
<tr>
<td>Li</td>
<td>2016</td>
<td>12</td>
<td>N</td>
<td>Y</td>
<td>BL/RUL</td>
<td>• MTL, Amyg, Amyg, Ins, Putamen, Fusi, Ins, TPI, Thal</td>
<td></td>
</tr>
<tr>
<td>Redlich</td>
<td>2016</td>
<td>23</td>
<td>Y</td>
<td>N</td>
<td>BL/RUL</td>
<td>• Hpc, Amyg</td>
<td></td>
</tr>
<tr>
<td>Sartorius</td>
<td>2016</td>
<td>18</td>
<td>Y</td>
<td>N</td>
<td>RUL</td>
<td>• MTL, ParALtPc, Amyg, Ins, Fusi, ACC, Ins, Putamen, LTC, Supramarginal/parasagittal</td>
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</tr>
<tr>
<td>Cortical thickness</td>
<td>2016</td>
<td>23</td>
<td>N</td>
<td>N</td>
<td>BL</td>
<td>• Ins, TP, LTC</td>
<td></td>
</tr>
<tr>
<td>van Eijnatten</td>
<td>2016</td>
<td>30</td>
<td>N</td>
<td>Y</td>
<td>BL/RUL</td>
<td>• ParALtPc, ACC, LTC, Prefrontal/motor</td>
<td></td>
</tr>
<tr>
<td>Sartorius</td>
<td>2016</td>
<td>18</td>
<td>Y</td>
<td>N</td>
<td>RUL</td>
<td>• Ins, TP</td>
<td></td>
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<tr>
<td>Regional volumetry</td>
<td>2016</td>
<td>23</td>
<td>N</td>
<td>N</td>
<td>BL</td>
<td>Region-of-interest</td>
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<tr>
<td>Abbott</td>
<td>2014</td>
<td>19</td>
<td>Y</td>
<td>N</td>
<td>BL/RUL</td>
<td>Hpc</td>
<td></td>
</tr>
<tr>
<td>Bruckart</td>
<td>2016</td>
<td>88</td>
<td>N</td>
<td>N</td>
<td>BL</td>
<td>Hpc</td>
<td></td>
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<tr>
<td>Depping</td>
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<td>12</td>
<td>Y</td>
<td>N</td>
<td>RUL</td>
<td>• Hpc, at follow-up</td>
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<tr>
<td>Jorgensen</td>
<td>2016</td>
<td>16</td>
<td>Y</td>
<td>Y</td>
<td>BL/RUL</td>
<td>• Cerebellum</td>
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<tr>
<td>Jorgensen</td>
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<td>42</td>
<td>Y</td>
<td>N</td>
<td>BL/RUL</td>
<td>Hpc, Amyg</td>
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<tr>
<td>Nordaschroig</td>
<td>2016</td>
<td>12</td>
<td>Y</td>
<td>Y</td>
<td>BL/RUL</td>
<td>Hpc</td>
<td></td>
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<tr>
<td>Sartorius</td>
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<td>Y</td>
<td>N</td>
<td>RUL</td>
<td>Hpc, Amyg, Habenula</td>
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<tr>
<td>Tendolkar</td>
<td>2013</td>
<td>15</td>
<td>N</td>
<td>N</td>
<td>BL</td>
<td>Putamen, Pallidum, NCaud, NAc*</td>
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<tr>
<td>Wade</td>
<td>2016</td>
<td>53</td>
<td>N</td>
<td>Y</td>
<td>BL/RUL</td>
<td>Hpc, Amyg</td>
<td></td>
</tr>
<tr>
<td>Structural connectivity</td>
<td>2016</td>
<td>16</td>
<td>Y</td>
<td>Y</td>
<td>BL/RUL</td>
<td>Hpc</td>
<td></td>
</tr>
<tr>
<td>Jorgensen</td>
<td>2014</td>
<td>20</td>
<td>N</td>
<td>N</td>
<td>BL/RUL</td>
<td>• FA/MD in Hpc, FA/ax in HThal</td>
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<tr>
<td>Wylen</td>
<td>2016</td>
<td>16</td>
<td>Y</td>
<td>Y</td>
<td>BL/RUL</td>
<td>• FA/ax in HThal</td>
<td></td>
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<tr>
<td>Nickl-Jorschat</td>
<td>2016</td>
<td>21</td>
<td>U</td>
<td>N</td>
<td>RUL/LART</td>
<td>• FA/ax in HThal</td>
<td></td>
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<tr>
<td>Zeng</td>
<td>2015</td>
<td>24</td>
<td>Y</td>
<td>N</td>
<td>BL</td>
<td>• FA/MD in Hpc, FA/ax in HThal</td>
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Table 2. Studies of functional changes after ECT.

<table>
<thead>
<tr>
<th>Group and Study</th>
<th>Year</th>
<th>N</th>
<th>Med</th>
<th>Bip</th>
<th>ECT</th>
<th>Methods</th>
<th>Regions/Networks</th>
<th>Results</th>
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<tr>
<td>Angyan</td>
<td>2016</td>
<td>16</td>
<td>N</td>
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<td>BL</td>
<td>ALFF, SCA</td>
<td>scaACC</td>
<td>ALFF: + SCACC, Ins, ACC, dPPFC, Hpc</td>
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<td>Abbott</td>
<td>2013</td>
<td>12</td>
<td>Y</td>
<td>N</td>
<td>BL/RUL</td>
<td>ICA</td>
<td>dmPFC, aDMN, pDMN, dbPFC/LH</td>
<td>scaACC</td>
</tr>
<tr>
<td>Canto</td>
<td>2017</td>
<td>12</td>
<td>N</td>
<td>Y</td>
<td>BL</td>
<td>SCA</td>
<td>Amyg</td>
<td>+ Hpc (RI, Temp)</td>
</tr>
<tr>
<td>Du</td>
<td>2016</td>
<td>13</td>
<td>N</td>
<td>N</td>
<td>BL/RUL</td>
<td>ALFF (after 1 session)</td>
<td>+ Amyg (RI) - sgACC/LH</td>
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<tr>
<td>Leaver</td>
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<td>30</td>
<td>N</td>
<td>Y</td>
<td>RUL</td>
<td>SCA</td>
<td>ICA, SCA</td>
<td>ROI-to-ROI: dACC, mlThal, PCC, Cerebellum, Hpc</td>
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<tr>
<td>Liu</td>
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<td>23</td>
<td>Y</td>
<td>N</td>
<td>BL/RUL</td>
<td>ALFF, SCA</td>
<td>sgACC</td>
<td>+ Hpc (RI, Temp)</td>
</tr>
<tr>
<td>Mulders</td>
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<td>16</td>
<td>N</td>
<td>N</td>
<td>BL/RUL</td>
<td>IC</td>
<td>DMN</td>
<td>+ Activation Putamen, pOperc, Cun, Auditory, Thal</td>
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<td>Christ</td>
<td>2008</td>
<td>20</td>
<td>Y</td>
<td>Y</td>
<td>BL/RUL</td>
<td>Auditory stimulus</td>
<td>+ Activation Amyg to negative stimulus</td>
<td></td>
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<tr>
<td>Redlich</td>
<td>2016</td>
<td>23</td>
<td>Y</td>
<td>Y</td>
<td>BL/RUL</td>
<td>Affective picture</td>
<td>+ Activation Amyg</td>
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</table>

**Magnetic Resonance Spectroscopy**

<table>
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<tr>
<th>Group and Study</th>
<th>Year</th>
<th>N</th>
<th>Med</th>
<th>Bip</th>
<th>ECT</th>
<th>Metabolites</th>
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<tr>
<td>Canto</td>
<td>2017</td>
<td>12</td>
<td>Y</td>
<td>N</td>
<td>BL</td>
<td>Cho, Cre, Glx, NAA</td>
</tr>
<tr>
<td>Endo</td>
<td>2000</td>
<td>17</td>
<td>N</td>
<td>N</td>
<td>BL/RUL</td>
<td>Cho, Cre, Naa</td>
</tr>
<tr>
<td>Pfaflereder</td>
<td>2017</td>
<td>12</td>
<td>Y</td>
<td>N</td>
<td>BL/RUL</td>
<td>Cho, Cre, Glx, Naa</td>
</tr>
<tr>
<td>Jorgensen</td>
<td>2016</td>
<td>26</td>
<td>Y</td>
<td>Y</td>
<td>BL/RUL</td>
<td>Cho, Glx, ml, Naa</td>
</tr>
<tr>
<td>Markl</td>
<td>2011</td>
<td>25</td>
<td>Y</td>
<td>Y</td>
<td>BL/RUL</td>
<td>Cho, Cre, Glx, Naa</td>
</tr>
<tr>
<td>Michael</td>
<td>2003a</td>
<td>12</td>
<td>N</td>
<td>N</td>
<td>BL/RUL</td>
<td>Cho, Cre, Glx, Naa</td>
</tr>
<tr>
<td>Michael</td>
<td>2003b</td>
<td>12</td>
<td>N</td>
<td>N</td>
<td>BL/RUL</td>
<td>Cho, Cre, Glx, Naa</td>
</tr>
<tr>
<td>Nijia</td>
<td>2016</td>
<td>50</td>
<td>N</td>
<td>Y</td>
<td>BL/RUL</td>
<td>ml</td>
</tr>
<tr>
<td>Nijia</td>
<td>2017</td>
<td>50</td>
<td>N</td>
<td>Y</td>
<td>BL/RUL</td>
<td>ml</td>
</tr>
</tbody>
</table>

**Note:** BL, bilateral; RUL, right unilateral; LART, left anterior right-temporal; ALFF, amplitude of low-frequency fluctuations; SCA, seed-based correlation analysis; ICA, independent component analysis; RSN, resting-state network; ROI, region-of-interest; SCACC, subcallosal anterior cingulate cortex; Ins, insula; ACC, anterior cingulate cortex; dPPFC, dorsoparietal prefrontal cortex; Hpc, hippocampus; SMG, supramarginal gyrus; vMPFC, ventromedial prefrontal cortex; ParHpc, parahippocampal cortex; TP, temporal pole; pc, precentral; mlThal, medial thalamus; TD, temporal cortex; PCC, posterior cingulate cortex; MTL, medial temporal lobe; AMY, amygdala; ParALtPc, paralimbic cortex; Mes, mesial cortex; PCC, posterior cingulate cortex; Thal, thalamus; AMY, amygdala; Hpc, hippocampus; ACC, anterior cingulate cortex; Hjo, hypothalamus; Ins, insula; R, right; RUL, right unilateral; BL, bilateral; VM, ventromedial prefrontal cortex; PCC, posterior cingulate cortex; VA, visual area; HPC, hippocampus; HThal, hypothalamus; OFC, orbitofrontal cortex; Thal, thalamus; AMY, amygdala; Hpc, hippocampus; ACC, anterior cingulate cortex; dPPFC, dorsoparietal prefrontal cortex; ParHpc, parahippocampal cortex; TP, temporal pole; MD, middle temporal; ACC, anterior cingulate cortex; MTL, medial temporal lobe; IMF, inferior frontal; PFC, prefrontal cortex; ICA, independent component analysis; SCA, seed-based correlation analysis; SCACC, subcallosal anterior cingulate cortex; Ins, insula; ACC, anterior cingulate cortex; dPPFC, dorsoparietal prefrontal cortex; Hpc, hippocampus; SMG, supramarginal gyrus; vMPFC, ventromedial prefrontal cortex; ParHpc, parahippocampal cortex; TP, temporal pole; mdPFC, dorsomedial prefrontal cortex; DMN, default mode network; aDMN, anterior DMN; pDMN, posterior DMN; Temp, temporal; Amyg, amygdala; dACC, dorsal anterior cingulate cortex; BG, basal ganglia; Thal, thalamus; mdThal, mediodorsal thalamus; SN, salience network; PCC, posterior cingulate cortex; aDMF, anterior mediofrontal network; pDMN, posterior mediofrontal network; dACC, subgenual anterior cingulate cortex; OFC, orbitofrontal cortex; NC, network coherence; SupOcc, superior occipital; iLTC, lateral temporal cortex; pOperc, pars opercularis; Cun, cuneus; Cre, cingulate; Glx, glutamate/glutamine; NAA, N-acetyl-aspartate; ml, myoinositol; dACC, dorsomedial anterior cingulate cortex.
MEDIAL TEMPORAL LOBE

The medial temporal lobe (MTL) contains several structures related to important cognitive and emotional functions. The hippocampus and its adjacent parahippocampal cortex, entorhinal cortex, and perirhinal cortex are the primary regions deemed responsible for the formation of memories and spatial cognition. Another core limbic structure in the medial temporal lobe is the amygdala, which drives numerous types of emotional responses and interact with other regions to encode emotional valence in various situations: e.g., with the hippocampus to couple emotions to memory and with the medial prefrontal cortex to attribute valence to environmental cues.

Regarding the effect of ECT on the brain, most evidence exists for an increase in volume of the medial temporal lobe, which is supported both by whole-brain exploratory analyses and more focused region-of-interest approaches. The extent of these changes varies between different studies and, while some report them to cover the entire MTL extending into adjacent structures, evidence is strongest for the bilateral hippocampus and, to a lesser extent, the amygdala. Whether there is a true difference in the extent of these changes between study samples or if this merely reflects a different approach to analysis and statistics is unclear. In addition, the amount of evidence for the hippocampus specifically could be explained by the focus on this region in region-of-interest analyses, which is mostly based on evidence of changes in the hippocampus in animal models of ECT. The reported increase is most consistent for both the hippocampus and amygdala, and to a lesser extent, for the insula and temporal poles. Out of all longitudinal whole-brain analyses using VBM, only one does not report a change in medial temporal lobe volume, while all of the studies investigating hippocampal volume specifically report an increase in volume, with an average increase around 5% compared to baseline. A meta-analysis on hippocampal volume increase after ECT also reports that there is sufficient evidence of a volumetric increase \(^\text{[1]}\). Potentially, these volumetric changes reflect an increase in angiogenesis, neurogenesis, and/or gliogenesis \(^\text{[8,9]}\). Interestingly, two follow-up studies report that the increase in hippocampal volume is transient and that, after 6–12 months, hippocampal volume return to baseline levels. The return to pretreatment volume did not relate to any change in clinical or cognitive symptoms \(^\text{[31,32]}\). In addition to the volumetric changes, reports also indicate changes in MTL white matter tracts, functional connectivity, and metabolite levels (creatinine, choline, NAA, glutamate/glutamine (Glx)). A study investigating white matter integrity in the hippocampus reported a decrease in both fractional anisotropy and mean diffusivity, which they hypothesized to be indicative of synaptogenesis or dendritic branching \(^\text{[2]}\). Functionally, one study finds a decrease in functional connectivity between the hippocampus and the posterior default mode network; the network that is most prominent during rest and is primarily related to self-generated and spontaneous thought, in addition to memory retrieval \(^\text{[23]}\). Region-specific studies on functional connectivity find changes in the functional relation of the hippocampus and parahippocampal gyrus to subgenual anterior cingulate cortex and the lateral temporal lobe, although reports are conflicting \(^\text{[23,24]}\). The hippocampus and the amygdala have also been the focus of studies using magnetic resonance spectroscopy. The hippocampus has been reported to exhibit an increase in choline and creatine and a decrease in Glx \(^\text{[25,26]}\), which could be indicative of increased cell turnover or neurogenesis. Overall, the functional changes could be important, but studies are too limited in number and consistency to draw any definitive conclusions from.

As evidenced by studies comparing longitudinal changes in patients undergoing ECT to baseline differences with healthy controls, the volumetric increase in the MTL is consistent with changes as reported in depression. A decreased hippocampal volume is one of the hallmark neurobiological features of depression \(^\text{[37,38]}\) and is most pronounced in patients with a long disease duration, multiple depressive episodes, or poor response to treatment \(^\text{[28–30]}\); common features in a population receiving ECT. While there is ample evidence that chronic or recurrent MDD is related to decreased volume in the medial temporal lobe and ECT leads to an increase in this volume, as well as changes in medial temporal lobe function, there is no clear connection to clinical outcome. The earlier mentioned meta-analysis on hippocampal volume changes also finds no evidence of such a relation \(^\text{[35]}\), and another study also found no evidence relating changes to cognitive side effects after ECT \(^\text{[21]}\), which might be explained by cognitive side effects on average being limited in both time and severity \(^\text{[32]}\). Interestingly, the same is true for depression where there is no evidence of a relation between decreased hippocampal volume and depression severity \(^\text{[27,29]}\) or cognitive deficits in several domains, attributed to hippocampal function that is common in depression \(^\text{[33]}\). Furthermore, the two studies available with a longer follow-up after ECT show that, after 6–12 months, hippocampal volume is similar to pretreatment volume and that this change is unrelated to changes in clinical symptoms. Although, based on the number of studies reporting on structural and functional changes in the MTL, it is tempting to think that ECT works by restoring hippocampal atrophy, it may also indicate a bias in the literature. Most studies that look outside of the hippocampus show this increase is part of a much larger increases in MTL volume, as well as in other brain regions, and its relation to clinical efficacy is not otherwise supported by the literature.
ANTERIOR CINGULATE CORTEX

The other main region with reported changes across all modalities, the anterior cingulate cortex consists of several distinct areas adjacent to the cingulum and is an important monitoring hub, contributing to attributing valence to stimuli as well as cognitive, social, and arousal processes. In the context of the pathophysiology of depression, the ACC is a major hub region and has been the focus of much research. Studies indicate a pivotal role for this structure in task-selection, based on previously learned task-reward coupling. In depression, this process is disrupted, and neuroimaging studies have found decreased activation in the ACC under both rest- and task-paradigms. These effects are likely specific to subregions within the ACC, as studies on subgenual ACC function usually report an increase in activity and connectivity. The functional segregation of subregions within the ACC is worth noting, as it also fits with regionally specific effects of ECT. A significant number of studies find evidence that ECT increases the volume of several regions within the ACC, with an emphasis on the subgenual area. This increase in volume is reported by several exploratory analyses, and after changes in the MTL, an increase in subgenual ACC volume is the most consistently reported result of ECT treatment from structural studies. As with the MTL, studies reporting on increases in volume of the ACC cover several distinct regions. As the ACC spans from the subgenual area around the cingulum to the posterior cingulate cortex, these findings are unlikely to be different representations of a single underlying mechanism. Whether changes in different parts of the ACC all attribute to ECT’s clinical effects or whether this is only true for some remains to be seen. As the ACC has such a large number of subdivisions and boundaries are less well-defined compared to structures in the MTL, ROI-analyses on the ACC are significantly less common. Interestingly, a parcellation-based study on changes in the cortical thickness did report an increase in ACC, as well as increases in temporal areas, but also found that the ACC increase specifically correlated to clinical improvement.

Functional studies support changes in the ACC, but show conflicting reports with regard to a functional increase or decrease in this region. Functional connectivity appears to change after ECT, but effects seem highly localized, with small differences in exact location leading to divergent changes in connectivity. Functional connectivity from the subgenual ACC to the temporal pole and parahippocampal cortex is increased in one study, while connectivity from the subcallosal cingulate cortex to the same areas is decreased in another study. A study using the amygdala as a seed-region reports a decrease in connectivity to the subgenual ACC. These results could indicate locally specific changes in ACC-connectivity, but also highlight the significant impact small variations in seed-region can have on connectivity patterns. Of note, a study reporting high subcallosal cingulate cortex activity at baseline (compared to healthy controls) also found that this increased activity predicted treatment efficacy. Furthermore, during treatment, connectivity decreased to several regions implicated in depression: the hippocampus, the temporal pole, and medial prefrontal cortex.

The inconsistencies in results between studies hold true for the small number of studies on metabolite changes. Studies observe an increase in Glx in the pregenual ACC and the subgenual ACC, an increase in creatine in the subgenual ACC, and an increase in myo-inositol in the dorsomedial ACC, either an increase or a decrease in creatine in the dorsal ACC, and either a decrease or an increase in NAA in the dorsal ACC. Overall, even with the limited number of studies, results are highly variable. Altogether, while a volumetric increase in the ACC seems likely, functional studies all indicate changes within the ACC after ECT, but diverging paradigms and methodologies make direct comparisons between them difficult.

To put the volumetric changes into context, in depression there is evidence of a volumetric decrease on both the macroscopic and microscopic levels in the ACC. This fits with the observation that ECT leads to a volumetric increase in several ACC subregions, indicating that ECT might reverse depression-related changes similarly to how it affects depression-related changes in the MTL. Of note, although it has received much less specific attention compared to the MTL, several studies report that changes in the ACC relate to clinical improvement or that baseline ACC activity predicts treatment response. A possible explanation for this is that while its changes are less profound, likely due to the region being less clearly defined and functionally heterogeneous, these changes are more strongly related to clinical status, both in the depressed state and as affected by treatment such as ECT. The strongest evidence for this is in the subgenual ACC, which has already been established as an important region in depression and has also been successfully targeted by deep-brain stimulation to treat treatment-resistant depression. In addition, interactions of lateral cortical regions with the ACC are assumed to be important in the antidepressant effects of repetitive transcranial magnetic stimulation. The clinical relevance of the ACC is consistent with studies showing that baseline ACC activity predicts clinical response to antidepressant treatments.

OTHER REGIONS

Although evidence is more limited, several other regions have been implicated in ECT and are potentially interesting targets of future research: the insula, temporal pole, and
striatum. While rarely the specific focus of studies, exploratory work often finds these regions to be affected by ECT. Reported changes are, therefore, mostly derived from whole-brain analyses using VBM or cortical thickness estimates. In addition, functional studies exploring large-scale brain networks, while fewer in number, indicate that ECT appears to restore aberrant functional connectivity present at baseline, and most evidence exists for effect on connectivity between regions in the anterior and posterior default mode (48–50).

Interestingly, all studies investigating cortical thickness report an increase in the temporal pole, which is mostly related to social and emotional processing (51). Functional connectivity from the ACC to the temporal pole has also been reported, although whether ECT increases or decreases the strength of this functional connection is undecided (24,52). The insula, besides its role in sensory integration and interoceptive awareness, has also been suggested as a main coordinating hub determining mental state through changing the relative dominance of cognitive vs default mode network activity (53,54). Studies report an increase in volume and cortical thickness in this area after ECT, either as an isolated finding or as an extension of the increase in MTL volume. Together with the aforementioned amygdala, the insula and temporal pole are both considered part of the salience network, which activates in response to salient stimuli including stress and reflects paralimbic emotional processing (55). A change in these regions affected through ECT might reflect changes in emotional processing when recovering from depression.

Finally, the striatum consists of several regions that govern, among others, emotion and reward processes. The nucleus accumbens, caudate nucleus, and the putamen all have been reported as being affected by ECT and, as with other regions, reports mostly indicate an increase in volume. This is further supported by increased activation in response to auditory stimuli in the putamen (56). All of these areas have been implicated in the pathophysiology of depression and may relate to changes in reward sensitivity or anhedonia (52) and are also particularly affected in treatment-resistant depression. Of note, we cannot rule out that effects on volume of lateral and temporal regions is a direct effect of the stimulation given during ECT, as these sites receive the largest stimulation (25).

CLINICAL AND METHODOLOGICAL CONSIDERATIONS

While all studies confirm strong clinical effects of ECT in their mostly treatment-resistant depressed subjects, few find significant correlations between changes in depression severity and changes in brain structure or function. For the most consistent change, an increase in volume in medial temporal lobe (including hippocampus/amygdala), only a few studies report a significant relation to response (17–19,41,58). Similarly, in single studies clinical improvement was related to structural changes in the ACC (42), subgenual ACC (59), striatum (50), insula (50), lateral temporal cortex (61), and cerebellum (62). So far, none of these findings have been replicated. In addition to studies investigating depression severity, one study found a strong correlation between caudate nucleus volume increase after ECT and a decrease in psychomotor symptoms (63).

Although more limited in number, two studies reporting changes in fronto-limbic white matter tracts also found that this relates to clinical response (63,59). In one study, response was related to increased FA and decreased MD/RD in dorsal fronto-limbic connections (61) and, in another study, to changes in the connection between the amygdala and parahippocampal gyrus (64). In functional studies, clinical improvement in responders was related to changes in functional connectivity of the right hippocampus to the medial and lateral temporal cortex (65), connectivity of the subgenual ACC to the temporal pole, and activity in the left subgenual ACC and hippocampus (measured by ALFF) (24). While most functional studies do not find clinical correlates of the longitudinal changes related to ECT, there appears to be a pattern that ECT normalizes differences to healthy controls in large-scale functional networks present at baseline (10,24,50). Finally, for MRS studies, one study reports increased Glx in subgenual ACC and decreased Glx in the hippocampus to be related to changes in depressive symptoms (71).

As only four studies use exclusively (right) unilateral ECT and the majority of studies use both unilateral and bilateral ECT, as is common in a clinical setting, there is no evidence of site-specific clinically relevant changes. Similarly, the most consistent effects are reported in studies regardless of medication status or the presence of subjects with bipolar depression, while for the less reported findings, the number of studies is too limited to detect any sample-specific effects.

There are several explanations for the lack of convergence between neurobiological changes and the strong clinical effects in depression. Primarily, the sample sizes in ECT studies are usually small and, while possibly sufficient to report longitudinal differences...
in a paired fashion, even with response rates as high as 60%–70%, studies might simply be under-powered to detect relationships between treatment and neurobiology in a robust fashion. Furthermore, this relation may be affected by differences between potential responders and nonresponders at baseline. Another explanation is that attempting to correlate clinical improvement to longitudinal changes in single structures or connections is a too simplistic approach, as depression is similarly not limited to single brain regions, but instead is linked to widespread changes in structure and function. Finally, some studies opt to include both unipolar and bipolar depression, which have been shown to exhibit different underlying neurobiology.

Although the field of ECT research has seen a sharp uptake in recent years, our understanding of its mechanisms is still bound by limitations in individual studies. As ECT is reserved for those patients with treatment-resistant depression, samples are usually limited in size and there is significant comorbidity with other psychiatric disorders. Between studies, differences in design and approach to analysis (e.g., selection of seed-regions in MRS and SCA studies) make validation or comparison between studies difficult. Similarly, differences between the ECT procedure used and medication allowed during treatment also make for additional confounding factors.

CONCLUSION

Electroconvulsive therapy may be the oldest, still widely used, neurostimulation method, but only very recently has been the focus of many neuroimaging research groups around the world. Its strong antidepressant effects warrant the efforts undertaken to uncover its mechanisms of action. Although changes happen throughout the brain in response to ECT, there are several regions that are more implicated than others (Fig. 1). The hippocampus, while most consistently reported to be increased in volume after ECT, does not seem to be strongly related to clinical outcome. The anterior cingulate cortex, on the other hand, is also a commonly reported area of change and might be more important in understanding ECT, similar to its role in other antidepressant treatments including other neurostimulation techniques. Other areas of interest are the temporal pole, the insula, and the basal ganglia, and future work is needed to confirm their relevance in depression and ECT.

Figure 1. Changes in brain structure and function after ECT. Representation of changes in brain structure and function. Red areas represent areas with volumetric increases after ECT, which are found in the amygdala (am), hippocampus, anterior cingulate cortex (ACC), insula, and lateral temporal cortex (LTC, including temporal pole). Basal ganglia also show changes across different modalities. In addition, there is some evidence for changes in the functional connectivity between the anterior and posterior default mode network (aDMN/pDMN).

Overall, although we still do not understand why ECT is so effective, converging evidence supports that ECT normalizes many of the effects depression has on brain structure and function. Which of these effects are ultimately the key to symptom reduction is still unclear. Collaborations to obtain large datasets (such as the GEMRIC consortium[66]) should help with translating neuroimaging findings back to the clinic, while consistency in methods used should help improve the reproducibility of results. Furthermore, advances in multimodal imaging, which allows us to combine different types of imaging data, and multivariate techniques such as machine learning will help us understand how structural and functional changes tie together and entangle the therapeutic mechanisms.
REFERENCES


4

PERSONALITY PROFILES ARE ASSOCIATED WITH FUNCTIONAL BRAIN NETWORKS RELATED TO COGNITION AND EMOTION

adapted from:

Personality profiles are associated with functional brain networks related to cognition and emotion.
Peter Mulders, Alberto Llera, Indira Tendolkar, Philip van Eijndhoven & Christian Beckmann
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ABSTRACT

Personality factors as defined by the “five-factor model” are some of the most investigated characteristics that underlie various types of complex behavior. These are, however, often investigated as isolated traits that are conceptually independent, yet empirically are typically strongly related to each other. We apply Independent Component Analysis to these personality factors as measured by the NEO-FFI in 471 healthy subjects from the Human Connectome Project to investigate independent personality profiles that incorporate all five original factors. Subsequently we examine how these profiles are related to patterns of resting-state brain activity in specific networks-of-interest related to cognition and emotion. We find that a personality profile of contrasting openness and agreeableness is associated with engagement of a subcortical-medial prefrontal network and the dorsolateral prefrontal cortex. Likewise, a profile of contrasting extraversion and conscientiousness is associated with activity in the precuneus. This study shows a novel approach to investigating personality and how it is related to patterns of activity in the resting brain.

INTRODUCTION

For the past decade, significant progress has been made in using functional neuroimaging to identify the neural correlates of human behavior. There has been a gradual shift from linking complex behavioral traits to single individual brain regions, to more recent attempts to understand behavior as complex interactions both within and between distributed sets of regions and ensuing large-scale brain networks. Along these lines, advances in the use of resting-state functional magnetic resonance imaging (rs-fMRI) and initiatives to collect large openly available datasets have provided the means to investigate brain patterns without strong prior assumptions. Functional imaging during rest has the benefit of being unconstrained by specific task-based paradigms, allowing for more broad comparisons of results and more convenient data-sharing between sites. Large-scale data initiatives additionally offer the increased statistical power to detect even moderate effects and to replicate results in an independent sample. Most critically, these advances together permit investigations into the neural correlates of individual traits that underlie various types of behavior.

One of the most compelling traits that influence behavior is personality, which refers to characteristic patterns of thinking, feeling and behaving. Personality is often investigated using a set of personality factors based on the “five-factor model” that includes neuroticism, extraversion, openness/intellect, agreeableness and conscientiousness. These factors are empirically defined, stable over time and together integrate different psychological mechanisms that have proven useful to explain specific types of behavior. Previous research has related these factors to structural and functional brain networks and specific related regions such as the amygdala, hippocampus and orbitofrontal cortex. The patterns of functional interaction between these networks and regions have also been consistently identified as crucial in processes related to emotion and cognition, even during rest. Of note, the personality factors themselves are broad summarizations of distinct underlying traits. While these traits can be considered conceptually independent, these personality factors are not statistically independent of one another and empirically exhibit significant correlations. Nevertheless, research usually treats them as unitary concepts and often only reports on one or a subset of the five personality factors. This complicates interpretation when a certain personality factor might result in behavior only in a particular context, for instance in the absence of another “opposing” trait.

We can overcome this problem by considering the five personality factors as observations driven by underlying and unobserved independent cognitive and
emotional processes. By applying Independent Component Analysis (ICA) in a large sample of healthy subjects from the Human Connectome Project (21), we can identify characteristic patterns of covariation between the personality traits of the “five-factor-model”. In doing so we obtain independent personality profiles that take into account all five original traits, and subject-specific loadings for each of the new profiles. We hypothesize that these profiles can be linked to the degree of co-activation within and across brain regions associated with emotion and cognition as measured by means of resting-state fMRI.

RESULTS

Personality Profiles

We investigated the personality factors in 471 healthy subjects from the Human Connectome Project (age range 22–36 years) by the NEO Five-Factor Inventory (NEO-FFI) that contains 60 questions related to five different personality domains: neuroticism, extraversion, openness/intellect, agreeableness and conscientiousness. Scores for these domains and demographics are presented in Table 1. As expected, there were strong and significant correlations between several of the domains: neuroticism was negatively correlated to agreeableness, extraversion and conscientiousness; agreeableness was positively correlated to openness, extraversion and conscientiousness; agreeableness was positively correlated to openness, extraversion and conscientiousness; extraversion was positively correlated to conscientiousness (Fig. 1).

TABLE 1. Demographics and personality factors. Personality traits and demographics of the included subjects.

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>471</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>194 / 277</td>
</tr>
<tr>
<td>Age in years</td>
<td>29.2 (± 3.51)</td>
</tr>
<tr>
<td>No twins / Twins (MZ) / Twins (DZ)</td>
<td>237 / 142 / 92</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.8 (± 1.87)</td>
</tr>
<tr>
<td>NEO – Neuroticism</td>
<td>16.4 (± 7.15)</td>
</tr>
<tr>
<td>NEO – Extraversion</td>
<td>30.6 (± 6.12)</td>
</tr>
<tr>
<td>NEO – Openness/Intellect</td>
<td>28.1 (± 6.11)</td>
</tr>
<tr>
<td>NEO – Agreeableness</td>
<td>32.1 (± 4.89)</td>
</tr>
<tr>
<td>NEO – Conscientiousness</td>
<td>34.8 (± 5.73)</td>
</tr>
</tbody>
</table>

Independent component analysis (ICA) on the normalized NEO-FFI personality scores was used to derive five distinct and uncorrelated personality profiles from the factor profiles (Fig. 1). These “personality profiles” have maximized statistical independence and optimally explain the variance in the behavioral data. Each of the five components contains a weight and a direction for each of the five original personality factors, but load significantly onto some factors and not onto others. Some profiles also highlight contrasting personality factors while others reveal a profile where the factors are positively related. Of note, all personality factors as measured by the NEO-FFI map onto multiple personality profiles, while each of the profiles also includes significant loadings of multiple NEO-factors. The first two personality profiles are loaded onto ‘extraversion’ and ‘conscientiousness’, either in synchrony (profile 1) or contrasting (profile 2). The next two profiles both incorporate ‘neuroticism’, but one profile also loads onto contrasting ‘extraversion’ and ‘conscientiousness’ (profile 3) while the other loads onto contrasting ‘openness’ and ‘agreeableness’ (profile 4). Finally, the fifth personality profile is defined by a contrast between ‘openness’ and ‘agreeableness’. Validation of these profiles using either a leave-one out or split-half approach show that these profiles are highly reproducible within our dataset (see Supplementary Table S2).

We use a linear projection to obtain values for every subject that reflect where they scale on each of the five new personality profiles. As an example: profile 5 loads positively onto openness/intellect and negatively onto agreeableness, with low loadings onto the other three personality factors. If the projection of this profile for a subject would be strongly positive, that subject exhibits this contrast very clearly and in the same direction (high openness/low agreeableness); if the projection was strongly negative the subject exhibits the opposite pattern (low openness/high agreeableness); if the projection is close to zero, the subject does not show a clear contrast between the original openness and agreeableness scores.

**RESTING STATE BRAIN ACTIVITY**

To investigate the relationship between personality domains and brain activity, we used high-quality preprocessed resting-state data from the Human Connectome Project which includes one hour of resting-state for each subject.20 We hypothesized that our personality profiles would be intrinsically driven by the functional interactions of networks and regions that are well established to be related to emotion and cognition on a broader scale. To test this hypothesis, we selected regions-of-interest based on their inclusion within the default mode network (medial prefrontal cortex, posterior cingulate cortex, precuneus), the salience network (insula, amygdala, dorsal anterior cingulate cortex), the cognitive executive network (dorsolateral prefrontal cortex) or on their strong relation with these networks (hippocampus, subgenual anterior cingulate cortex, orbitofrontal cortex), the well-established anti-correlation between dorsolateral prefrontal cortex and default mode regions24. The full time series of these selected regions from all subjects (Fig. 2) was used as the basis for a temporal ICA decomposition (Fig. 1). A multiple regions-of-interest approach, as opposed to a whole-brain analysis, increases our sensitivity to detect effects relating to our hypothesis while also decreasing the likelihood of type 1 errors. Using the Harvard-Oxford Atlas as implemented in the FSLview package, part of the FMRIB Software Library (FSL, http://www.fmrib.ox.ac.uk/fsl/), we extracted the mean time series for the selected twelve regions-of-interest. Figure 1 shows the full correlation matrix for the time series of these regions and confirms the expected strong correlations between the subcortical regions, between regions within the default mode network (medial PFC, posterior cingulate cortex, precuneus) and the well-established anti-correlation between dorsolateral prefrontal cortex and default mode regions24. The full time series of these selected regions from all subjects were used as the basis for a temporal ICA decomposition.27 This results in a set of characteristic patterns of activation (or ‘temporal modes’) that, similar to the ICA on the personality factors, have a weight and direction for each of the twelve regions-of-interest (Fig. 1). The resulting co-activation patterns reveal that some regions, such as the dorsolateral prefrontal cortex and insula, show relatively little temporal correlation with the other regions.

By comparison, the right amygdala and hippocampus are incorporated into multiple temporal modes but drive none of them exclusively. Similar to the personality profiles, a leave-one and split-half validation showed that the temporal modes were highly reproducible (see Supplementary Table S2).
The temporal modes were used to obtain subject-specific “mode time series” reflecting the engagement of each patterns of co-activation at every time point. For each subject, the variance over these “mode time series” was calculated as a measure of average engagement for a particular pattern. As an example, the variance over a subjects’ projection of temporal mode 1, which is predominantly defined by activity in the precuneus, reflects a high level of engagement of the precuneus for that subject over the full hour of resting-state data. Similarly, the variance of a subject’s representation of temporal mode 3 would reflect the average engagement of a functional network defined by synchronous activity within the medial prefrontal cortex and dorsal anterior cingulate cortex.

We applied a standard linear model for each of the five personality profiles by regressing the engagement of the 12 different temporal modes to discover how our personality profiles are associated with the engagement of temporal modes of brain activity within the selected regions, while correcting for gender. Significance was assessed by permutation testing while considering the family structure, again while correcting for gender [29]. We applied false discovery rate [29] correction to account for multiple comparisons. This analysis resulted in three personality-brain interactions. We observed that the profile defined by contrasting openness/agreeableness (profile 5) was associated with a temporal mode defined by the amygdala, right hippocampus, medial PFC and dorsal ACC (mode 2; r = 0.16; corrected p = 0.015). Additionally, this same personality profile was also associated with the temporal mode that is primarily driven by the dorsolateral PFC (mode 4; r = 0.16; corrected p = 0.024). Furthermore, the profile relating to contrasting extraversion/conscientiousness (personality profile 2) correlated with the temporal mode defined by activity in the precuneus (mode 1; r = −0.15; corrected p = 0.015).

To validate the generalization of these relationships we also performed a leave one subject out approach, where we learn the group-level temporal modes and personality profiles using the data from all other subjects, and then project the left-out sample on both of these measures independently. Correlation analyses between these projected values reproduce the above described interactions (see Supplementary Table S3). In addition, the out of sample analyses reveals an additional significant relationship, namely between profile 5 and temporal mode 2.

DISCUSSION

It is generally appreciated that complex behaviors are rarely determined by a single variable or personality factor. Instead they result from a balance of different and sometimes opposing factors within a specific context [29]. With this in mind, investigating profiles of personality instead of personality factors in isolation might capture more distinct behavioral phenotypes and opens up many possibilities for future research.

On the behavioral data alone our ICA-decomposition of personality factors as defined by the “five-factor model” gives some interesting insights into such distinct profiles of personality. The personality profiles generated by our analysis reveal how each original personality factor can be observed in the context of the other factors, which might relate to divergent types of behavior. With regards to personality, this is especially significant in cases where a clinically relevant personality factor like neuroticism results in pathological behavior (e.g. depression) specifically in the absence of a stress-resilience trait such as high conscientiousness or extraversion [2]. Of note, within our personality profiles the personality factor neuroticism is represented both in a pattern with contrasting openness and agreeableness (profile 4) and in a pattern with contrasting extraversion and conscientiousness (profile 3). The latter might be especially significant as high levels of neuroticism increases stress-sensitivity and the incidence of stress-related disorders, while extraversion and conscientiousness increase resilience to stress [3].

We further investigate how these personality profiles relate to patterns of co-activation within and between key regions related to cognition and emotion. We show that the personality profile defined by contrasting ‘openness/intellect’ and ‘agreeableness’ is associated with two distinct patterns of co-activation in the resting brain: a temporal mode defined by the dorsolateral prefrontal cortex, key node of the cognitive executive network [21,32] and a temporal mode resembling a self-referential/affective network defined by the amygdala, hippocampus, dorsal anterior cingulate and medial prefrontal cortex [13,14]. Regarding the personality profile, ‘openness/intellect’ is the personality factor that reflects creativity and intellectual curiosity and is related to cognitive ability and flexibility [14]. ‘Agreeableness’ includes items like compassion and politeness, and is related to positive affect and subjective wellbeing [25,26], while low levels of agreeableness are regarded as indicative of hostility and antagonism [27]. When taken together, the personality profile we observe reflects high openness/intellect and low agreeableness on one end, and low openness/intellect and high agreeableness on the other end. Within this profile, we observe that high openness/intellect and low agreeableness relates to high engagement of the dorsolateral prefrontal cortex, which

agrees with contrasting openness and agreeableness (profile 4) and in a pattern with contrasting extraversion and conscientiousness (profile 3). The latter might be especially significant as high levels of neuroticism increases stress-sensitivity and the incidence of stress-related disorders, while extraversion and conscientiousness increase resilience to stress [3].

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is the primary region for demanding cognitive tasks and relates to cognitive ability across a great number of experimental paradigms. Additionally, it was also related to a temporal mode defined by interaction between the amygdala, hippocampus, medial prefrontal cortex and dorsal anterior cingulate cortex. The amygdala is well established as the key node relating to various emotional processes and has strong functional and structural connections to the adjacent hippocampus. It is also a key component of the ‘salience network’ together with the dorsal anterior cingulate cortex, which has been shown to be heavily involved in emotional processing and works together with the medial prefrontal cortex in emotion regulation. In short, this temporal mode includes multiple regions related to emotional and self-referential processing.

We also observe an association of the personality mode defined by contrasting extraversion and conscientiousness by a temporal mode driven by activity in the precuneus, a central hub within the posterior default mode network. ‘Extraversion’ is essentially a measure of assertiveness and social skills, while ‘conscientiousness’ is related to orderliness and industriousness. Together, this profile of personality could be interpreted as scaling from sociable or ‘easy-going’ but disorganized, to more introverted with a strong sense of duty and self-discipline. The precuneus has been implicated in a variety of functions such as consciousness, memory retrieval and self-processing. It is also an important region within the default mode network and has been shown to adapt to changes in cognitive demand. Overall, its function is highly adaptive and as such it has been hypothesized to orchestrate brain function at a broad level. Within our model, high levels of orderliness and low extraversion relate to strong engagement of the precuneus during rest.

Although the observed association of personality patterns with temporal modes of brain activity is highly significant, the effect sizes measured are relatively small. While this is not uncommon in neuroimaging, it underlines that while mathematical models might help us understand behavior better, we are limited by our ability to quantify behavior and by how we measure activity in the brain. We are also limited by our focus on regions-of-interest as we cannot exclude the possibility that other regions might contribute to personality or the observed modes of resting-state activity. Note here that we consider “engagement” as represented by the variance over the temporal mode series. Consequently, the presented model is a simplification and does not account for stable “low” or “high” states over the full hour of rest. Those dynamics could be better understood by employing different mathematical models to take into account the time structure (i.e. Hidden-Markov Models), and is outside of the scope of this paper. Finally, although we show that our findings are reproducible within our dataset, applying a similar model to an independent dataset is needed to validate our results.

In summary, we investigate personality in a large healthy cohort and show that it is possible to capture distinct profiles of personality. These profiles have the benefit of observing the original personality factors in the context of all other traits, which could prove useful in linking personality to, for example, increased risk for psychiatric disorders. We also show that two of these ‘personality profiles’ are associated with patterns of co-activation in the brain during rest in regions that are known to be involved with cognition and emotion. These findings provide new ways for investigating patterns in behavior and how they relate to brain function which can lead to a better understanding of both normal and pathological processes.

METHODS

STUDY POPULATION

In this study, we used data from the Human Connectome Project (HCP) 500-subjects release. The HCP project (Principal Investigators: Bruce Rosen, M.D., Ph.D., Martins Center at Massachusetts General Hospital; Arthur W. Toga, Ph.D., University of Southern California, Van J. Weeden, MD, Martinos Center at Massachusetts General Hospital) is supported by the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute of Mental Health (NIMH) and the National Institute of Neurological Disorders and Stroke (NINDS). HCP is the result of efforts of co-investigators from the University of Southern California, Martinos Center for Biomedical Imaging at Massachusetts General Hospital (MGH), Washington University, and the University of Minnesota. The HCP includes data from healthy adult twins and their non-twin siblings. We included all data from subjects that had resting-state fMRI available for all four time-points and completed the NEO-FFI personality inventory. Two subjects were excluded on the basis of structural abnormalities. The considered data was gathered from 194 males and 277 females with a small age range (range 22–36 y, mean 29.2 y).

PERSONALITY SCORES

The NEO-FFI contains 60 questions divided into 12 questions relating to 5 different personality domains: ‘neuroticism’, ‘extraversion/introversion’, ‘openness to experience’, ‘agreeableness’ and ‘conscientiousness’. The NEO-FFI has shown excellent reliability and validity. The data used in this study was collected as part of the Penn Computerized Cognitive Battery within the HCP.
MRI DATA ACQUISITION
We used resting-state fMRI-data from the Human Connectome Project (HCP) [29]. This contains one hour of resting-state data for each subject (4800 time points), obtained in four 15-minute block across two visits, with each visit having separate scans for both encoding directions (left-right and right-left). Scans were obtained using a customized Siemens 3 Tesla ‘Connectome Skyra’ housed at Washington University in St. Louis, using a standard 32-channel Siemens receiver head coil. With a gradient-echo simultaneous multi-slice EPI sequence. This sequence has the following characteristics: TR 720 [ms], TE 33.1 [ms], flip angle 52 [deg], field of view 208 x 180 [mm], voxel size of 2.0 [mm3], multiband factor 8, echo spacing 0.58 [ms]. For this study, we included the 471 subjects that had all 4 scans available and completed the questionnaires on personality domains (NEO-FFI).

PERSONALITY DATA ANALYSIS
NEO-scores and demographics are presented in Table 1. We appreciate that there were significant Pearson correlations between several of the domains: neuroticism was negatively correlated to agreeableness, extraversion and conscientiousness; agreeableness was positively correlated to openness, extraversion and conscientiousness; extraversion was positively correlated to conscientiousness (Fig. 2). The NEO-scores for all 471 subjects were used as an input for ICA using the fastICA algorithm (at full rank) [27], which resulted in five independent components that represent personality profiles derived from the behavioral data. These were multiplied with the original data to obtain, for each subject, a loading for each component that represents where they scale on each of the five new personality profiles. For the personality profiles, we checked if these were related to motion and found that one (personality profile 4) showed a significant correlation to the root mean-squared of the relative displacement (r = 0.15, fdr-corrected p = 0.0495). We found no relation of motion to the personality profiles that were significantly correlated with resting-state data.

RESTING STATE fMRI DATA ASSOCIATION WITH PERSONALITY PROFILES ARE ASSOCIATED WITH FUNCTIONAL BRAIN NETWORKS RELATED TO COGNITION AND EMOTION

RESTING STATE fMRI PREPROCESSING
We used the minimally preprocessed resting-state fMRI data from the HCP. This includes gradient distortion correction, FLIRT-based motion correction [40], TOPUP-based field map preprocessing [40], distortion correction and registration of the EPI to high resolution T1-weighted image using a Boundary Based Registration algorithm [50], spline resampling from EPI to standard space and intensity normalization and bias field removal. Additional preprocessing to remove structured noise was performed using ICA-FIX [51,52].
To validate the correlations between personality profiles and temporal modes we used a leave-one-subject-out approach. For each subject, we learn the group-level temporal modes and personality profile using the data from all other subjects, and then project the left-out sample on both of these measures independently. We then correlate these projected values between the personality profiles and temporal modes. The p-values for this correlation can be found in Supplementary Table S3. The three interactions we report in the manuscript are clearly reproducible within our sample. Furthermore, we observe one significant interaction (between temporal mode 7 and profile 5) that did not survive statistical threshold before.

DATA RESOURCES AND AVAILABILITY

All personality scores and resting-state fMRI data are available at http://www.humanconnectome.org. The Harvard-Oxford atlas used to define ROIs is available as part of the FSL toolbox at http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases. Both the FastICA and PALM algorithms are available online (27,28). Any additional information or resource is available on request.

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PERSONALITY PROFILES ARE ASSOCIATED WITH FUNCTIONAL BRAIN NETWORKS RELATED TO COGNITION AND EMOTION

CHAPTER 4


**SUPPLEMENTARY**

**TABLE S1.** Statistics output. Results(\(p\)-values) for regression analysis of the five personality dimensions versus the 12 temporal modes as presented in figure 1, corrected for gender.

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<tr>
<th>TM1</th>
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<td>0.90</td>
<td>0.88</td>
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<td>0.64</td>
</tr>
<tr>
<td>0.95</td>
<td>0.45</td>
<td>0.33</td>
<td>0.58</td>
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<td>0.45</td>
<td>0.057</td>
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<td>0.84</td>
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</tr>
<tr>
<td>0.41</td>
<td>0.0039*</td>
<td>0.83</td>
<td>0.00014*</td>
<td>0.84</td>
<td>0.37</td>
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<td>0.17</td>
<td>0.40</td>
<td>0.79</td>
<td>0.06</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Abbreviations: ext: extraversion; con: conscientiousness; ope: openness/intellect; agr: agreeableness; neu: neuroticism; TM: temporal mode. * significant interactions at \(p < 0.05\) after FDR-correction. ** \(p\)-values after permutation analysis of linear models to account for family structure of the data.

**TABLE S2.** Reproducibility of personality profiles and temporal modes. Mean correlation and standard deviation for the reproducibility of the personality profiles and temporal modes. For the leave–one out approach, correlation represents the average correlation between the full ICA results and each iteration where one subject is excluded. For the split-half validation, the middle column ("Split-half") represents the correlation between the results when ICA was performed on two halves of the dataset independently, while "split-half versus full" represents the correlation between results obtained from the ICA on half the data against the original analysis on the full sample. Highlighted rows show the profiles and modes that relate to the significant brain-behavior correlations. We show here that (1) both leave–one out and split-half reproducibility is high, for both the personality profiles and the temporal modes and (2) the level of reproducibility is dependent on the amount of data used, as is apparent by the difference in reproducibility between columns 1 and 2–3.

<table>
<thead>
<tr>
<th></th>
<th>Leave–one out</th>
<th>Split-half</th>
<th>Split-half versus full</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Personality profile 1</strong></td>
<td>0.98</td>
<td>0.03</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Personality profile 2</strong></td>
<td>0.95</td>
<td>0.03</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Personality profile 3</strong></td>
<td>0.97</td>
<td>0.02</td>
<td>0.79</td>
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<tr>
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<td>0.80</td>
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<td>0.91</td>
<td>0.14</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>Temporal mode 1</strong></td>
<td>0.95</td>
<td>0.03</td>
<td>0.86</td>
</tr>
<tr>
<td><strong>Temporal mode 2</strong></td>
<td>0.99</td>
<td>0.02</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Temporal mode 3</strong></td>
<td>0.99</td>
<td>0.04</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>Temporal mode 4</strong></td>
<td>0.90</td>
<td>0.10</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>Temporal mode 5</strong></td>
<td>0.94</td>
<td>0.09</td>
<td>0.87</td>
</tr>
<tr>
<td><strong>Temporal mode 6</strong></td>
<td>0.94</td>
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<td>0.83</td>
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<tr>
<td><strong>Temporal mode 7</strong></td>
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<td>0.01</td>
<td>0.82</td>
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<tr>
<td><strong>Temporal mode 8</strong></td>
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<td>0.09</td>
<td>0.81</td>
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<td><strong>Temporal mode 9</strong></td>
<td>0.92</td>
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<td>0.81</td>
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<tr>
<td><strong>Temporal mode 10</strong></td>
<td>0.98</td>
<td>0.03</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Temporal mode 11</strong></td>
<td>0.98</td>
<td>0.02</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Abbreviations: std: standard deviation.
TABLE S3. Results for the validation. p-values from the approach used to validate the original findings. Subjects’ loading onto the personality profiles and variance over the temporal modes were predicted out of sample, and these values were correlated to validate the findings of the original analysis. Highlighted cells relate to the significant correlations from the original analysis.

<table>
<thead>
<tr>
<th>Profile 1</th>
<th>TM1</th>
<th>TM2</th>
<th>TM3</th>
<th>TM4</th>
<th>TM5</th>
<th>TM6</th>
<th>TM7</th>
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<th>TM10</th>
<th>TM11</th>
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</tr>
</thead>
<tbody>
<tr>
<td>ext &amp; con</td>
<td>0.71</td>
<td>0.25</td>
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<td>0.40</td>
<td>0.67</td>
<td>0.22</td>
<td>0.22</td>
<td>0.64</td>
<td>0.38</td>
<td>0.39</td>
<td>0.69</td>
</tr>
<tr>
<td>ext &amp; cons</td>
<td>0.53</td>
<td>0.18</td>
<td>0.22</td>
<td>0.47</td>
<td>0.89</td>
<td>0.09</td>
<td>0.15</td>
<td>0.87</td>
<td>0.96</td>
<td>0.878</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>con &amp; ope</td>
<td>0.82</td>
<td>0.65</td>
<td>0.71</td>
<td>0.53</td>
<td>0.76</td>
<td>0.52</td>
<td>0.79</td>
<td>0.94</td>
<td>0.31</td>
<td>0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ext &amp; ext</td>
<td>0.82</td>
<td>0.64</td>
<td>0.31</td>
<td>0.47</td>
<td>0.63</td>
<td>0.68</td>
<td>0.94</td>
<td>0.44</td>
<td>0.84</td>
<td>0.45</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>ext &amp; ext</td>
<td>0.19</td>
<td>0.04</td>
<td>0.18</td>
<td>0.001</td>
<td>0.96</td>
<td>0.673</td>
<td>0.0004</td>
<td>0.994</td>
<td>0.43</td>
<td>0.910</td>
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</tbody>
</table>

Abbreviations: ext: extraversion; con: conscientiousness; ope: openness/intelligence; agr: agreeableness; neu: neuroticism; TM: temporal mode. * significant interactions at p < 0.05 after FDR-correction.
DEFAULT MODE NETWORK COHERENCE IN TREATMENT-RESISTANT MAJOR DEPRESSIVE DISORDER DURING ELECTROCONVULSIVE THERAPY

adapted from:

ABSTRACT

Background: Functional connectivity in the “default mode network” (DMN) is changed in depression, and evidence suggests depression also affects the DMN’s spatial topography and might cause a dissociation between its anterior and posterior regions. As antidepressive treatment affects anterior and posterior regions of the network differently, how depression and treatment change DMN-organization is crucial for understanding their mechanisms. We present a novel way of assessing the coherence of a network’s regions to the network as a whole, and apply this to investigate treatment-resistant depression and the effects of electroconvulsive therapy (ECT).

Methods: Resting-state functional MRI was collected from 16 patients with treatment-resistant depression before and after ECT and 16 healthy controls matched for age and sex. For each subject, the mean time series of the DMN was used as a regressor for each voxel within the DMN, creating a map of “network coherence” (NC). The obtained maps were compared across groups using permutation testing. Results: NC was significantly decreased in depressed subjects in the precuneus and the angular gyrus. With ECT the NC normalized in responders (n=8), but not in non-responders (n=8).

Conclusions: We present a novel method of investigating within-network coherence and apply this to show that in depression, a large area of the DMN shows a decrease in coherence to the network as a whole. Although tentative due to the small sample size, we find that this effect is not present after ECT in those improving clinically, but persists in patients not responding to ECT.

INTRODUCTION

Major depressive disorder (MDD) is a common and disabling psychiatric disorder. For patients not responding to regular treatment (treatment-resistant) electroconvulsive therapy (ECT) is the most potent treatment option to relieve depression [2,3]. The pathophysiology of MDD is far from understood, but recent evidence indicates a key role for large-scale networks, and specifically the default mode network (DMN). The DMN is also promising as a target for the antidepressant effects of ECT [4–8].

The DMN consists of an anterior and a posterior part with the medial prefrontal cortex and the posterior cingulate cortex/precuneus as its “core” midline regions and several associated areas, such as the inferior parietal lobules and the lateral temporal cortex. Functionally the DMN is related to self-referential processing including self-generated thought, awareness and memory processing, drawing upon its connections with the extended hippocampal formation [9–11]. Alterations in activity within the cores of this network [11–13], functional connectivity between nodes in the network and between the DMN and other networks [6,7] have all been linked to symptoms of MDD. For example, increased connectivity within the anterior DMN has been related to (negative) self-generated thought (rumination) [11–13], while decreased connectivity within the posterior DMN has been related to overgeneralizing memory [31].

Changes in connectivity of the DMN differ within several of its subregions. Although functional connectivity within the anterior DMN has consistently been reported to be increased in MDD, results regarding the posterior DMN are conflicting: some studies report an increase [13,16,17], while others report a decrease [31], or even areas of both increase and decrease within the same sample [58]. Understanding the cause of these different results is important, considering that connectivity within the posterior DMN has often been identified as relevant for treatment response in MDD [58–60].

One factor that many studies do not take into account is that the DMN is not static in its spatial topography [31]. In fact, evidence supports the notion that some areas might be part of the DMN in depression, but not in non-depressed individuals [57,72]. Additionally, the anterior and posterior subnetworks of the DMN have been shown to dissociate in depressed subjects [15,21]. We hypothesize that inconsistencies in reports about functional connectivity in the posterior DMN could be mediated by differences in the coherence of regions within the DMN in patients with MDD. Exploring new ways to understand the internal organization of the DMN and how it is affected by depression and ECT treatment is therefore crucial to advance research on brain networks in MDD.
CHAPTER 5

DEFAULT MODE NETWORK COHERENCE IN TREATMENT-RESISTANT MAJOR DEPRESSIVE DISORDER DURING ELECTROCONVULSIVE THERAPY

Here, we present a novel method of investigating the internal organization of the DMN by looking at the coherence of the different DMN-regions within the network as a whole and show how this method can be used to investigate the state of the DMN in depression, both before and after ECT.

METHODS AND MATERIALS

PARTICIPANTS
Depressed subjects were recruited for this observational cohort study from a pool of patients that were referred for ECT at the Department of Psychiatry of the Radboud University Medical Centre in Nijmegen, the Netherlands. Inclusion criterion was unipolar MDD confirmed using the Structured Clinical Interview for DSM-IV (SCID). Patients were eligible to receive ECT according to the Dutch guidelines for the treatment of depression. This means that before ECT was started their depression was treatment-resistant for selective serotonin-reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants with adjuvant lithium or antiepileptics, as well as psychotherapy. This makes for a more treatment-resistant group when compared to the international literature. All psychotropic medication was discontinued for a minimum of one week prior to ECT, and three weeks for tranylcypromine due to longer washout. No patients received antidepressants with a long lasting half-life prior to the start of treatment. Low doses of promethazine and quetiapine (up to 150 mg) during the course of ECT were allowed, but not in the 24 h before MRI measurements. Depression severity was assessed using the Hamilton Rating Scale for Depression (HRSD, 17 items) before, during and after ECT [24]. Exclusion criteria were ECT in the year prior to inclusion, bipolar depression, comorbid diagnosis of schizophrenia or substance use disorder, the use of psychotropic medication with the exemption of intermittent benzodiazepine use (not in the 24 h before each ECT session), and MRI-related exclusion criteria. We also recruited healthy control subjects matched for age and sex using local advertisements. The study was approved by the local ethical committee. All subjects provided written informed consent. The treatment itself was unaltered from the standard care for patients receiving ECT.

ECT-PROCEDURE
ECT was administered twice a week bilaterally at the temporal window with a brief pulse, constant current apparatus with a maximum stimulus output of 1008 mC (200%) (Thymatron System IV, Somatics, IL, USA). Seizure threshold was determined during the first session with stimulus titration [25] and subsequently the stimulus dosage that elicited a seizure was set at 1.5 times the initial seizure threshold. Anesthesia was achieved with intravenous administration of etomidate 0.2–0.3 mg/kg followed by succinylcholine 1.0 mg/kg.

All patients were hospitalized during at least the first two weeks of their ECT course. Treatment was continued until a plateau was reached and no more improvement was seen in the last four bilateral sessions. In line with the Dutch Guidelines for ECT, a minimum of 10 adequate ECT sessions were administered before ECT was stopped in case of non-response or partial response. ECT was terminated before 10 sessions when there was complete remission of all depressive symptoms [26]. A positive response to ECT was defined as a decrease in HRSD-score of 50% or more [27].

IMAGE ACQUISITION AND PREPROCESSING
Imaging data was acquired using a SIEMENS 1.5T Avanto system. Patients were scanned within the week prior to starting ECT and within one week after their final ECT session. Healthy subjects were scanned at a single time point. T1-weighted structural images were obtained using a standard MPRAGE-sequence (T1 850 [ms], TR 2250 [ms], TE 3.68 [ms], flip angle 15 [deg], FoV 224x224x137 [mm], voxel-size 1.0 [mm] isotropic). Resting state functional MRI was acquired using an echo planar imaging (EPI) sequence (TR 1870 [ms], TE 35 [ms], flip angle 80 [deg], FoV 224x224x137 [mm], voxel-size 3.5x3.5x3.0 [mm], 266 volumes, acquisition time 8 min 20 s). During acquisition of the resting-state data subjects were instructed to lie still with their eyes open and to keep their gaze fixed on a fixation cross while surrounding lights were dimmed. This method has been shown to have the highest reliability and consistency in acquiring resting state data [28] and promotes the subjects to remain awake during acquisition.

Data was preprocessed using the FMRI Expert Analysis Tool (FEAT), which is part of the FMRIB Software Library (FSL) [29]. This step includes brain extraction, motion correction, high-pass temporal filtering with a cutoff of 100 s, spatial smoothing with a 6 mm Gaussian kernel, registration of functional images to high-resolution T1 using boundary-based registration and subsequent nonlinear registration to standard space (MNI152). The final voxel size for analysis was 2 mm isotropic. We did not apply global signal regression as this has been shown to induce anti-correlations and potentially distorts group differences [30,31]. We used ICA-based Advanced Removal of Motion Artefacts (ICA-AROMA) for further single-subject denoising [32]. As head motion is an important factor in fMRI studies, we examined head motion between groups [33,34]. Mean displacement for controls, pre-treatment patients and post-treatment patients...
was 0.33 mm, 0.24 mm and 0.35 mm, respectively. One-way ANOVA revealed no significant differences in motion between the groups (df=2; p=0.22).

INDEPENDENT COMPONENT ANALYSIS
To identify the DMN, we estimated brain networks using MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components) which uses time-concatenated Independent Component Analysis (ICA) to automatically estimate networks from the 48 sets of resting-state fMRI data[30]. We used automatic model-order estimation for selecting the number of components, which decomposed the data into 10 components.

NETWORK COHERENCE ANALYSIS
We obtained network-specific maps by thresholding the DMN map obtained from the groups ICA using a threshold of Z≥5. Higher Z-scores in the component maps obtained from ICA reflect a higher likelihood of an area belonging to the network instead of to the background (signal not explained by the network)[31]. While stringent, our high threshold was selected to limit our analysis only to those regions that are important within the DMN. Although this excludes some DMN-associated regions, a Z-score of Z≥5 ensures that our representation of the DMN and its mean time series adequately represents the DMN as reported in the literature[32,33] and is less affected by regions that are also associated with other networks. Furthermore, a threshold of Z≥5 also approximates a voxelwise Bonferroni-corrected error level of 1% for the DMN-template. Using this template as a mask, we obtained the average time series for the DMN for each individual subject by means of a weighted average of all voxels’ time series data. These network-specific time series were entered as a regressor in a general linear model to obtain values for the variance explained by the average default mode activity and the residuals for each voxel within the DMN for each subject.

Using the signal variance pre and post regression against the network specific time series we obtain variance-ratio statistic values for each voxel within the DMN. In short, this value represents the amount of variance explained by the average DMN time series in contrast to the variance unexplained (i.e. the residuals). The main difference of our method compared to other methods like network homogeneity[34] or investigating thresholded network maps using the direct ICA-output[35] is that our measure of network coherence explicitly takes into account local differences in noise or background signal. The single-subject maps of these values where tested between groups using coherence explicitly takes into account local differences in noise or background signal. The single-subject maps of these values were obtained from ICA using a threshold of Z≥5. Higher Z-scores in the component maps obtained from ICA reflect a higher likelihood of an area belonging to the network instead of to the background (signal not explained by the network)[31]. While stringent, our high threshold was selected to limit our analysis only to those regions that are important within the DMN. Although this excludes some DMN-associated regions, a Z-score of Z≥5 ensures that our representation of the DMN and its mean time series adequately represents the DMN as reported in the literature[32,33] and is less affected by regions that are also associated with other networks. Furthermore, a threshold of Z≥5 also approximates a voxelwise Bonferroni-corrected error level of 1% for the DMN-template. Using this template as a mask, we obtained the average time series for the DMN for each individual subject by means of a weighted average of all voxels’ time series data. These network-specific time series were entered as a regressor in a general linear model to obtain values for the variance explained by the average default mode activity and the residuals for each voxel within the DMN for each subject.

Using the signal variance pre and post regression against the network specific time series we obtain variance-ratio statistic values for each voxel within the DMN. In short, this value represents the amount of variance explained by the average DMN time series in contrast to the variance unexplained (i.e. the residuals). The main difference of our method compared to other methods like network homogeneity[34] or investigating thresholded network maps using the direct ICA-output[35] is that our measure of network coherence explicitly takes into account local differences in noise or background signal. The single-subject maps of these values where tested between groups using permutation testing (5000 permutations per contrast, 5 mm variance smoothing)[36]. Resulting t-statistic maps were corrected using local false-discovery rate (local-FDR) thresholding[37] and masked by gray-matter probability maps at p=0.30. The higher-level comparisons were done for both the full groups (baseline MDD versus HC, baseline MDD versus post-treatment MDD, post-treatment MDD versus HC) and, post-hoc, stratified for responders and non-responders. FDR-corrected p-values <0.05 in clusters of 20 voxels or more were considered significant. We correlated the normalized change in NC within the largest cluster (normalized per subject for NC across the DMN) with the changes in HDRS-scores using Pearson correlation.

Compared to standard Z-scores, which inform us on whether a region is part of a network, the variance-ratio test instead evaluates the level of voxel-wise synchronicity in regions within this network relative to the total network’s temporal dynamics. The variance ratio is used as a marker of Network Coherence (NC).

RESULTS
Forty-eight resting-state datasets were obtained (16 healthy controls and 16 depressed patients both before and after ECT). Demographics are presented in Table 1. There were no significant differences in age or sex between the groups. The response rate to ECT was 50% which is in line with the response rate to ECT in the Netherlands[40]. The low response rate compared to international literature is likely related to the higher level of treatment resistance before ECT is administered in the Netherlands. ECT had a significant effect on HRSD-score, with a mean decrease of 8.4 points on the 17-item scale (df=15; p<0.001). Responders and non-responders did not differ on baseline clinical variables.

<table>
<thead>
<tr>
<th>TABLE 1. Demographics.</th>
<th>Characteristic</th>
<th>healthy controls</th>
<th>patients</th>
<th>p-value</th>
<th>responders</th>
<th>non-responders</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>16</td>
<td>16</td>
<td>-</td>
<td>8</td>
<td>8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>50.3 (9.48)</td>
<td>49.6 (9.29)</td>
<td>0.837</td>
<td>48.1 (10.1)</td>
<td>52.0 (7.39)</td>
<td>0.195</td>
<td></td>
</tr>
<tr>
<td>Male/female, No. (%)</td>
<td>6 / 10 (62.5%)</td>
<td>6 / 10 (62.5%)</td>
<td>1</td>
<td>3 / 5</td>
<td>3 / 5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Right handed, No. (%)</td>
<td>15 (93.8 %)</td>
<td>14 (87.5 %)</td>
<td>0.544</td>
<td>8 (100%)</td>
<td>7 (87.5%)</td>
<td>0.302</td>
<td></td>
</tr>
<tr>
<td>Baseline HRSD, mean (SD)</td>
<td>N.a.</td>
<td>22.1 (5.7)</td>
<td>-</td>
<td>22.9 (3.7)</td>
<td>21.3 (7.4)</td>
<td>0.588</td>
<td></td>
</tr>
<tr>
<td>Post-ECT HRSD, mean (SD)</td>
<td>N.a.</td>
<td>13.7 (7.2)</td>
<td>-</td>
<td>7.9 (2.8)</td>
<td>19.6 (4.7)</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Response, No. (%)</td>
<td>8 (100%)</td>
<td>8 (100%)</td>
<td>-</td>
<td>0 (100%)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>ECT-treatments, mean (SD)</td>
<td>N.a.</td>
<td>17.8 (6.8)</td>
<td>-</td>
<td>18.1 (8.8)</td>
<td>17.5 (4.7)</td>
<td>0.861</td>
<td></td>
</tr>
<tr>
<td>Duration of current episode (months)</td>
<td>N.a.</td>
<td>18.9 (15.2)</td>
<td>-</td>
<td>14.3 (6.56)</td>
<td>23.5 (20.1)</td>
<td>0.236</td>
<td></td>
</tr>
<tr>
<td>Presence of psychotic symptoms, No. (%)</td>
<td>N.a.</td>
<td>6 (62.3%)</td>
<td>-</td>
<td>3 (37.5%)</td>
<td>3 (37.5%)</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SD: standard deviation; HRSD: Hamilton Rating Scale for Depression; ECT: electroconvulsive therapy.
INDEPENDENT COMPONENT ANALYSIS

Our ICA decomposed the data into 10 independent components that correspond to well-known large-scale networks as described broadly in the literature. The default mode network was the component explaining the most variance in the data. The DMN obtained covered (in order of maximum Z-value): the precuneus, the posterior cingulate cortex, inferior parietal lobules, medial prefrontal cortex, superior frontal gyrus and lateral temporal cortex (see Fig. 1). Associated areas with Z-values between 2.3 and 5 include the hippocampus, medial thalamus, extended lateral temporal cortex into the temporal poles and (parts of) the somatosensory cortex. All these areas have been reported as part of, or are strongly associated with, the DMN.

MAIN EFFECTS

The main findings are summarized in Table 2. In MDD-patients (before ECT), we found a large part of the precuneus (anterior dorsal) and a smaller part of the right angular gyrus to have significantly lower NC when compared to healthy matched controls (see Fig. 2). Compared to baseline the full patient group after ECT showed a decrease in coherence within the right lateral temporal cortex. Compared to healthy controls, patients after ECT still showed decreased coherence within the precuneus and angular gyrus, although the size of these areas was greatly reduced. Additionally, after ECT patients displayed a larger NC within bilateral superior-occipital cortex and the posterior cingulate cortex.
Patients who responded to ECT show a longitudinal effect of increased NC within the precuneus after treatment, while nonresponders show a decreased NC in the dorsomedial prefrontal cortex. After ECT, responders no longer showed any significant differences in NC when compared to healthy controls. Non-responders instead still showed the decreased NC in the precuneus, but larger network coherence in the posterior cingulate cortex and retrosplenial cortex. Additionally, after ECT they showed a lower NC in the dorsomedial prefrontal cortex (see Fig. 3). Correlation between the change in NC within the largest cluster (precuneus) and the change in HDRS was not significant (R² Linear 0.133, P=0.166).

**DISCUSSION**

We report alterations in network coherence within the DMN in depression and after ECT, which is an important and informative addition to the current understanding of network-pathology in MDD. Patients suffering from treatment-resistant major depressive disorder show decreased network coherence in the default mode network in comparison with healthy controls localized in the precuneus and angular gyrus. Post-hoc analyses indicate that after ECT, this decrease in network coherence is resolved for patients who also improve clinically (responders), while persisting for patients who
do not respond to ECT (non-responders). A decrease in network coherence, quantified by means of voxel-wise estimates of variance explained by the mean network time course, reflects areas within a network that are poorly integrated within the network, i.e. likely to split off said network and thereby changing its topographic organization.

Given that the precuneus (together with the posterior cingulate gyrus) is the core hub of the posterior DMN \(^{[15]}\), a decrease in its coherence to the rest of the DMN could give rise to numerous changes in the functioning of the default mode network. The precuneus has a variety of functions including visuospatial imagery, episodic memory retrieval and self-related processing which are related to subregions within the precuneus that are connected to specific other cortical areas \(^{[11,45]}\). It is of note that the region of the precuneus that showed decreased NC in MDD (anterior-dorsal) overlaps with the part of the precuneus relevant for cognitive processing through strong connections to cognitive areas such as the dorsolateral prefrontal cortex \(^{[45]}\). In this light, the decrease in network coherence of this area of the precuneus within the DMN could represent an increased functional connection to these cognitive areas; or at least a "shift" away from its function within the DMN. This also corresponds to a report that links decreased within-DMN connectivity of the precuneus to an increase in depression-related overgeneralization of memories \(^{[15]}\). Alternatively, the precuneus might instead become more isolated in general, as is evidenced by reports of decreased connectivity with other large-scale networks \(^{[21,46]}\).

The decreased NC in a core region of the posterior DMN gives insight into the many reports of altered connectivity between anterior and posterior DMN-regions with seed-based analyses. The precuneus is merely one part of the posterior DMN, and has different subregions that functionally diverge and therefore the seemingly contradictory findings of changed connectivity of the posterior DMN might reflect regionally specific effects. In this model, functional connectivity as seen from an anterior seed region might reveal decreased connectivity in the dissociated part of the posterior DMN, while connectivity to other parts of the posterior DMN might be unchanged or even increased \(^{[15,20,45]}\). A decrease in NC of a large part of the posterior DMN could also drive the dissociation between the anterior and posterior DMN as repeatedly found in MDD \(^{[20]}\).

The absence of the decreased NC after ECT in clinical responders implies that ECT restores the integration of the precuneus within the DMN. Whether ECT has its clinical effect through this restoration, or the restoration is a consequence of some other antidepressive mechanism is unclear. Regardless, this is more evidence showing that a good response to antidepressant treatment affects the DMN, and specifically the posterior DMN. Others have found similar restoration effects on aberrant functional connectivity in the posterior DMN induced by antidepressants \(^{[15,20,45]}\), transcranial magnetic stimulation \(^{[47]}\) and ECT \(^{[48]}\). We add to this that the restored functional connectivity might have its foundation in restoring the underlying coherence of the precuneus to the rest of the DMN.

In addition to the large cluster of decreased NC within the precuneus, regions in the right angular gyrus also show a decrease in NC in depression compared to healthy controls. Within the DMN, the angular gyrus has been implicated in mental representations during mindwandering and the manipulation of conceptual knowledge \(^{[48]}\). A decrease in NC within this area could indicate a lesser integration of this function within the usual repertoire of the DMN during rest. This decrease persists in patients after ECT, which could indicate a trait-related feat. Both responders and non-responders also show a longitudinal decrease in NC within a small cluster in the right lateral temporal cortex. As this area is close to the electrode placements in ECT, additional follow-up in future studies could help in clarifying whether this is a local effect of the treatment or if it is related to ECT’s efficacy.

The changes we observe in the network coherence in MDD highlight the clinical relevance of the DMN, but also the relevance of improving our understanding of the internal organization of networks in depression. To this end, the method we propose uses subject-specific representations of how strongly different areas within a network conform to the network as a whole. Instead of representing how likely it is for an area to be part of a network (as reflected in t- and Z-statistics), it represents the level of voxel-wise synchronicity in regions within this network relative to the total network’s temporal dynamics. By looking at this network coherence, we improve not only our understanding of networks in general, but also on how to interpret findings from functional connectivity analyses. In doing so, it adds to our understanding of functional patterns in depression alongside research on brain activity and functional connectivity. Our method also emphasizes that in MDD the DMN shows a distinct topological organization that differs from healthy controls, even in its core regions. Considering that the precuneus is a commonly used site for seed placement in seed-based correlational analysis, small variance in placement could lead to the seed region not representing the DMN equally in healthy controls compared to patients. Finally, furthering our understanding of within-network changes as a result of ECT-treatment might further improve our ability to predict clinical outcomes, as recent studies have highlighted the relevance of resting-state fMRI and connectivity in relation to ECT’s efficacy \(^{[50,51]}\).
There are some limitations to our study, mostly related to our limited sample size. Although our main finding (of decreased NC in the precuneus) was present in both responders and non-responders independently of one another, and the overall sample size resembled that of recent studies providing significant evidence for DMN changes [10,17,40], it is entirely possible that we were unable to detect more subtle effects. The discontinuation of medication helps to homogenize the sample regarding current effects of treatment, but we cannot exclude an effect of the discontinuation of antidepressants on our results. The findings related to treatment-response, although promising and fitting well within other reports of network restoration as a function of ECT, are preliminary and need to be replicated within a larger sample. In addition, we were unable to correlate depression severity scores to the decrease in NC. Finally, given that we examined a treatment-resistant group of patients receiving bilateral ECT, our results might not generalize to the broader class of MDD patients or patients receiving unilateral ECT. In future research, clinical variables related to symptom-specific or patient-specific factors that can affect treatment outcome (i.e. cognitive scores) could help in linking neuroimaging findings to clinical outcomes. Additional follow-up after treatment to distinguish acute effects of ECT from lasting outcome-related changes, as well as additional scans of healthy subjects to account for within-subject variability, would also be beneficial in furthering our understanding of ECT’s underlying mechanisms.

In conclusion, we have presented a new method of investigating within-network organization by means of network coherence is. This method complements existing tools for network analyses by investigating the relation of a network’s regions to the network as a whole, which inform us on its underlying organization. We show that applying this method to treatment-resistant depression reveals that the “cognitive” section of the precuneus dissociates from the DMN, and in responders to ECT this effect is no longer present after treatment while it persists in non-responders. Future research could benefit from looking at network coherence to investigate large-scale network organization on a subject-specific basis in psychiatric disorders and their treatments, which could help to interpret the complex nature of large-scale network connectivity.

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BILATERAL ECT INDUCES BILATERAL INCREASES IN REGIONAL CORTICAL THICKNESS

adapted from:

Bilateral ECT induces bilateral increases in regional cortical thickness.
ABSTRACT

Electroconvulsive therapy (ECT) is the most effective treatment for patients suffering from severe or treatment-resistant major depressive disorder (MDD). Unfortunately its underlying neurobiological mechanisms are still unclear. One line of evidence indicates that the seizures produced by ECT induce or stimulate neuroplasticity effects. Although these seizures also affect the cortex, the effect of ECT on cortical thickness is not investigated until now. We acquired structural magnetic resonance imaging data in 19 treatment-resistant MDD patients before and after a bilateral ECT course, and 16 healthy controls at 2 time points, and compared changes in cortical thickness between the groups. Our results reveal that ECT induces significant, bilateral increases in cortical thickness, including the temporal pole, inferior and middle temporal cortex and the insula. The pattern of increased cortical thickness was predominant in regions that are associated with seizure onset in ECT. Post hoc analyses showed that the increase in thickness of the insular cortex was larger in responders than in non-responders, which may point to a specific relationship of this region with treatment effects of ECT.

INTRODUCTION

Although electroconvulsive therapy (ECT) is the most effective treatment for patients suffering from severe or treatment-resistant major depressive disorder (MDD), achieving faster and higher response rates than pharmacotherapy, the underlying neurobiological mechanisms remain poorly understood. Several hypotheses, based on the effects of ECT on monoamine systems and endocrine function, have been proposed. In explanations of its superior effectiveness, the neuroplasticity effects of ECT have become dominant.

The therapeutic efficacy of ECT is related to its capacity to generate a generalized epileptic seizure. Animal models of electroconvulsive stimulation have shown that convulsions cause neuroplasticity effects. ECT-induced seizures engage both cortical and subcortical networks to varying degrees and result in increased cerebral blood flow in focal cortical areas. In line with these broad hemodynamic effects of ECT on the brain, recent research indicates that next to effects on volume of hippocampus or amygdala, ECT induces also neuroplasticity effects in the cortex. Up till now, there are no studies that have used cortical thickness analysis to investigate the effects of ECT treatment, which is a sensitive method to study longitudinal changes in the cortex.

Cortical thickness represents the thickness of the outer layer of gray matter in the brain which varies greatly between species and also between cortical subregions within subjects. Differences in cortical thickness have been observed in a variety of neuropsychiatric disorders. Emerging evidence indicates that cortical thickness is affected in MDD, primarily expressed as regional thinning in the cingulate and orbitofrontal cortex, although areas of thickening have also been found. A recent, large meta-analysis of cortical thickness in 20 depression cohorts worldwide gathered in the ENIGMA group, confirmed thinning of the orbitofrontal cortex and cingulate cortex, and also identified thinning of the insula and temporal lobes. In contrast with decreases in hippocampal volume, which was mainly associated with recurrent depression, cortical thickness changes were robustly detectable in adult patients at their first episode. Based on the fact that ECT-induced seizures affect the cortex, we hypothesize that ECT leads to regional increases in cortical thickness. A secondary goal is to identify changes in cortical thickness that may be related to treatment response.
MATERIALS AND METHODS

SUBJECTS

Twenty three patients (8 male/15 female; age 50.7 ± 8.5 years) with treatment-resistant MDD were recruited at the department of psychiatry of the Radboud University Medical Centre Nijmegen. Sample size was based on previous studies investigating the longitudinal effects of ECT on structural measures such as hippocampal gray matter volume. All patients were diagnosed with MDD using the Structural Interview for DSM disorders (SCID) and were eligible to receive ECT treatment based on treatment resistance for medication, according to the Dutch guidelines for depression and ECT. Briefly this means that patients had failed to respond to a stepwise treatment including serotonergic or serotonergic–noradrenergic–reuptake inhibitors, tricyclic antidepressants and augmentation with lithium or anti-epileptics, and in some cases MAO-inhibitors before receiving ECT. Exclusion criteria were bipolar depression, having received ECT within 1 year prior to the current course, schizophrenia or a history of alcohol or substance abuse. Twenty two sex- and age-matched healthy controls (8 male/14 female; mean age = 50.8 ± 8.8 years) were recruited from the local area by advertisement. Exclusion criterion for controls was having any life-time psychiatric disorder. Exclusion criteria for all persons included were present or past relevant somatic or neurologic comorbid disorder, and magnetic resonance imaging (MRI)-related exclusion criteria such as claustrophobia, a pacemaker or pregnancy.

Patients were tapered off from all psychotropic medication, such as antidepressants, antipsychotics, mood stabilizers and benzodiazepines at 1 week before the start of ECT. Only incidental use of benzodiazepines or promethazine was permitted during the course of ECT. During the course of ECT treatment, severity of depression was measured using the Hamilton Depression Rating Scale (HDRS-17). All participants provided written informed consent and the study protocol was approved by the review board of the Radboud University Nijmegen Medical Centre.

ECT-SERIES

ECT was administered bilaterally at the temporal window using a brief pulse, constant current apparatus with a maximum stimulus output of 1008 mC (200%) (Thymatron System IV, Somatics, Lake Bluff, IL, USA). Seizure threshold was determined during the first session with stimulus titration. The seizure threshold is defined as the minimum stimulus dosage required to generate a generalized seizure of at least 20-s duration according to the cuff method. For the second treatment session, a stimulus intensity of 1.5 times the initial seizure threshold was used. Global anesthesia was achieved by administering i.v. etomidate (0.2–0.3 mg kg−1), followed by succinylcholine 1.0 mg kg−1 to achieve muscle relaxation. Patients received treatment twice a week for as long as there was substantial improvement in symptom severity. When no improvement was measured after at least 10 adequate treatment sessions or no further improvement during the last 4 sessions, treatment was discontinued. On average, patients were treated 18 ± 7 times (range 7–32 sessions).

PROCEDURE

Patients were assessed at two time points: T1, 1 week before the first ECT treatment; and T2, within 1 week of completing the ECT series. Of the 23 patients examined at T1, 19 patients completed T2. Drop out was caused by defect scanner (two patients) and to patient-initiated discontinuation of ECT (two patients). Of the 22 healthy controls that were examined at T1, 16 were re-examined at T2, with a time interval similar to the mean of the ECT series, to control for timing and test–retest effects. The longitudinal effects of ECT were analyzed by comparing changes in cortical thickness between the patients and controls with data for both T1 and T2.

IMAGING TECHNIQUE AND CORTICAL THICKNESS MEASUREMENTS

High-resolution MPRAGE images were acquired (1.5 T Avanto, Siemens, Erlangen, Germany) for all subjects. Acquisition parameters were: T1 850 (ms), TR 2250 (ms), TE 3.68 (ms), flip angle 15 (°), FoV 256 × 256 × 176 (mm), voxel-size 1.0 × 1.0 × 1.0 (mm). The MRI data were analyzed by using FreeSurfer software version 5.3.0 (http://surfer.nmr.mgh.harvard.edu). This software package is almost completely automated and reliably computes cortical thickness. The data were motion corrected and intensity normalized. We performed segmentation of white matter and tessellation of the gray–white matter junction. Topological defects in the gray–white estimate were fixed. Then a deformable surface algorithm was applied to find the pial surface. We visually inspected the entire cortex in each subject and corrected any inaccuracies in segmentation manually. The reconstructed cortical surfaces were inflated to normalize interindividual differences in gyral or sulcal depth. Each reconstructed brain was morphed and registered to an average spherical surface representation so that sulci and gyri were optimally aligned and cortical thickness difference maps could be constructed on a common spherical coordinate system. To extract reliable thickness estimates, images of subjects were automatically processed within the longitudinal stream in FreeSurfer. Specifically an unbiased within-subject template space and image was created using robust, inverse consistent registration.
Several processing steps, such as skull stripping, Talairach transforms, atlas registration, as well as spherical surface maps and parcellations were then initialized with common information from the within-subject template, significantly increasing reliability and statistical power.\(^{27}\)

**STATISTICAL ANALYSIS**

After smoothing (full width at half maximum, 10 mm), the cortical thickness data were averaged across subjects in the spherical coordinate system, so that surface areas with significant differences of mean cortical thickness could be overlaid in statistical difference maps (using t-statistics). We addressed cross-sectional differences between the MDD patients and the healthy controls at baseline, corrected for age and sex. Longitudinal changes between the two time points for the two groups were analyzed with the general linear model functionality within QDEC, FreeSurfer’s graphical interface for analyzing group data. We estimated for the whole brain (in vertex-wise statistical difference maps) the main effect of group (ECT versus healthy controls), on symmetrized percent change of the cortical thickness corrected for age and sex. Correction for multiple comparisons was applied by clusterwise correction, based on Monte Carlo Z simulation, build into QDEC (threshold 0.005, sign absolute)\(^{29}\).

In a second step, we compared responders (n = 10) and non-responders (n = 9) to ECT by a whole-brain analysis. In addition to this exploratory whole-brain analysis looking into effects of successful treatment, we also performed a post hoc analysis with independently defined cortical parcellations (from the Desikan–Killiany Atlas), to explore whether there were effects associated with response (defined as a decrease in HDRS of >50%), within the regions that showed the longitudinal increases in the first step (that is, insula, temporal pole and temporal cortex). Changes in mean thickness of these parcellations were analyzed with SPSS (Statistic Package for the Social Sciences) software version 20.0 (Armonk, NY, USA), with independent t-tests. Further, these absolute changes in thickness were used for exploratory correlational analyses (Pearson’s correlations, P<0.05 one-tailed) with clinical variables: age, change in Hamilton depression score and parameters linked to the ECT course: that is, number of ECT sessions, change in charge between last and first session and change in seizure duration between first and last session.

**RESULTS**

Patient characteristics are summarized in Table 1. There were no significant differences between MDD patients and healthy controls in age, sex distribution, level of education or handedness. Hamilton scores after (12.6 \(\pm\) 7.1) on average 16.9 \(\pm\) 6.2 ECT sessions differed significantly from Hamilton scores (21.9 \(\pm\) 5.3) before ECT (P<0.001). HDRS based response rate was 57%. There were no differences in number of ECT sessions between responders and non-responders (P = 0.93).

**TABLE 1.** Demographical and clinical characteristics of the MDD patients and matched healthy controls.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Patients (n=23)</th>
<th>Healthy (n=23)</th>
<th>Group difference P(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (male/female)</td>
<td>50.7 (8.3)</td>
<td>50.6 (8.0)</td>
<td>0.98</td>
</tr>
<tr>
<td>Education (1=3(^\text{a}))</td>
<td>8/15</td>
<td>8/14</td>
<td>0.22(\text{b})</td>
</tr>
<tr>
<td>Handedness (right/left)</td>
<td>2 1/2</td>
<td>1 9/2</td>
<td>0.60</td>
</tr>
<tr>
<td>HDRS 17 baseline</td>
<td>21 (9.3)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>HDRS 17 after ECT</td>
<td>12.6 (7.5)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Responders (% of patients)</td>
<td>13 (57%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td>40.8 (10.9)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Number of depressive episodes</td>
<td>2.8 (1.5)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Duration current episode (months)</td>
<td>31.0 (52.7)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Psychotic features (present/not present)</td>
<td>6/17</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Melancholic features (present/not present)</td>
<td>11/8</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ECT sessions</td>
<td>16.9 (8.2)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale 17 item; MDD, major depressive disorder. Data are expressed as mean (s.d.) unless otherwise specified. \(^a\)Independent t-test. \(^b\)Pearson’s \(X^2\) for categorical variables. \(^\text{a}\)Educational level is coded level 1–5 (5=academic), according to the Dutch education system.

Additional information about the clinical characteristics of each patient, such as age at onset, number of depressive episodes, duration of the current episode, melancholic and psychotic features and details about medication history is presented in Supplementary Table 1A. Details about the ECT course of each patient are provided in Supplementary Table 1B (number of ECT sessions, pulse width, charge at start and end of ECT course, seizure duration at start and end). There was a significant difference between both charge and seizure duration at the start and end of the ECT course (mean charge start 175 mC; end 393 mC; P<0.001; mean seizure duration start = 52 s; end 36; P<0.001).

**CROSS-SECTIONAL EFFECTS**

Whole-brain comparisons for baseline cortical thickness between MDD patients and healthy controls revealed no significant differences between the two groups.
LONGITUDINAL EFFECTS OF ECT

Whole-brain comparisons revealed large bilateral clusters (left 2886 mm², right 3599 mm²) of increased thickness after ECT treatment. These clusters extended from the temporal pole, middle and superior temporal cortex to the insula and inferior temporal cortex in the left hemisphere (see Figure 1 and Table 2). There were no areas showing a significant decrease of cortical thickness in the longitudinal analysis, neither were there changes in cortical thickness in the healthy controls in the longitudinal analysis.

**FIGURE 1.** Increases in cortical thickness in MDD patients (n=19) during ECT treatment in comparison with healthy controls (n=16) on inflated brain. Shown is the statistical output of QDEC, the graphical interface of Freesurfer, with the results corrected for multiple comparisons by Monte Carlo Z simulation*. (a) Left hemisphere, with a large cluster in yellow extending from temporal pole, middle and superior temporal cortex to the insula and the inferior temporal cortex. (b) Right hemisphere, with a large cluster in yellow extending from the temporal pole to the insula.

*Monte Carlo Null-Z simulation, threshold 0.005 (absolute); MDD, major depressive disorder.

**TABLE 2.** Longitudinal changes in cortical thickness (SPC) in MDD patients during ECT treatment (n=19) in comparison with healthy controls (n=16)

<table>
<thead>
<tr>
<th></th>
<th>Size (mm²)</th>
<th>Talairach (x y z)</th>
<th>Number of vertices</th>
<th>Clusterwise P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD=healthy controls, left hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal pole</td>
<td>2086</td>
<td>−28.6−56</td>
<td>5557</td>
<td>0.0001</td>
</tr>
<tr>
<td>Middle temporal cortex</td>
<td>793</td>
<td>−56−56−2</td>
<td>7176</td>
<td>0.0001</td>
</tr>
<tr>
<td>MDD=healthy controls, right hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insula</td>
<td>3599</td>
<td>27−15−2</td>
<td>7970</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Abbreviations: ECT, electroconvulsive therapy; MDD, major depressive disorder; SPC, symmetrized percent change; *Monte Carlo null-Z simulation, threshold 0.005 (absolute).

RELATIONS BETWEEN INCREASE IN CORTICAL THICKNESS, TREATMENT RESPONSE AND CLINICAL VARIABLES

The whole-brain analysis did not give rise to significant differences in cortical thickness between responders and non-responders as a function of ECT treatment. In a next step, we took the mean thickness of predefined cortical parcellations, which were included within the bilateral cluster of increased cortical thickness, and compared responders and non-responders to ECT. Supplementary Table 2 presents the absolute increases of the predefined cortical parcellations that were identified in the second step. Independent t-tests of changes in thickness of both the left and the right insula revealed significant differences between responders and non-responders; responders showed a larger increase in cortical thickness than non-responders (left insula; P = 0.017, and right insula; P = 0.017). Changes in cortical thickness of the temporal pole and temporal cortex (inferior, middle and superior) did not differ between responders and non-responders.

Exploratory correlational analyses with clinical variables revealed that the change in HDRS score was negatively correlated with change in mean cortical thickness of the right insula (r = −0.45; P = 0.028; one-tailed). The number of ECT sessions was positively correlated with change in mean thickness of the left temporal pole (r = 0.43; P = 0.035 one-tailed), the left middle temporal cortex (r = 0.51; P = 0.013 one-tailed) and the left inferior temporal cortex (r = 0.45; P = 0.028 one-tailed). There were no significant correlations with age and change in seizure duration or change in electrical charge between the first and last ECT session.

DISCUSSION

In this study, we believe we show for the first time that ECT induces significant increases in cortical thickness in treatment resistant MDD patients. We used bilateral ECT, which induced large bilateral increases in cortical thickness, including the temporal pole, the inferior and middle temporal cortex and the insula. Post hoc analyses revealed that increased thickness of the bilateral insular cortex differentiated responders and nonresponders to ECT, which may point to a specific relationship of this region with treatment effects. Below we will discuss these findings in more detail.

The widespread increases in cortical thickness that were revealed in this study extend the existing animal and human data on neuroplastic effects of ECT, pointing to broader neuroplastic effects of ECT in MDD, beyond effects in the hippocampus and amygdala.
In contrast, right unilateral stimulation found. Although neuroimaging data do not allow us to directly investigate the exact nature of these neuroplastic effects, it can be assumed that increases in cortical thickness could reflect changes in neurons, glia cells or neuropil. Increased cortical thickness was predominant in regions such as temporal cortex that are subjected to the highest electric field strength and may therefore be associated with seizure onset. Previous research has found direct effects of ECT on cerebral blood flow and gray matter volume voxel based morphometry in these regions and this pattern suggests that the changes are a direct consequence of seizure onset that is induced by ECT.

In the course of treatment, most patients show an increase in seizure threshold and a decrease in seizure duration, pointing to additional anticonvulsant properties of ECT that may also count for its clinical effectiveness. Speculatively, the increased cortical thickness could drive these anticonvulsant properties of ECT, possibly by means of an increase in GABAergic inhibitory interneurons or glia cells, in line with the anticonvulsant mechanisms of ECT. Previous reports have found increases in cortical and serum GABA levels in patients following ECT treatment, which in turn increase the expression of neurotrophic factors such as brain-derived neurotrophic factor. Animal models of ECT have indicated that the neuroplasticity effects of ECT are mediated by increases in vascular endothelial growth factor and brain-derived neurotrophic factor. Increased GABAergic neurotransmission could also be relevant therapeutically via restoration of cortical control over hyperactive limbic structures, through a process known as cortical inhibition. ECT patients in our sample showed an increase in charge between the first and last ECT session and a decrease in seizure duration, which may point to anticonvulsive properties of ECT. Additional correlational analysis with these parameters and the changes in cortical thickness could not establish a direct relation of increases cortical thickness with anticonvulsant properties of ECT.

When comparing responders and non-responders to ECT, we found a response-related effect in the bilateral insular cortex. Though still explorative in nature, this increase could be a response marker for therapeutic effects of ECT. These findings add to the increasing amount of evidence implicating the insular region as an important structure in the pathophysiology of MDD. The insula monitors internal states and which makes it also difficult to establish differences between responders and non-responders. While this should be a clear goal of future studies, we would like to emphasize that patients were otherwise homogenous in terms of diagnosis and free of any medication that may have interfered with potential effects of ECT. We found bilateral changes in cortical thickness associated with the method of bilateral stimulation, which is in line with increases in gray matter volume in the temporal cortex that were revealed by Ota et al. In contrast, right unilateral stimulation seems to induce a different pattern of neuroplastic changes. Abbott et al. found that right unilateral ECT induced a right-sided increase in hippocampal volume and connectivity after ECT and Dukart et al. reported an increase in gray matter volume in the right anterior temporal pole and insula. At odds with these lateralization effects is the study by Joshi et al. who found bilateral increases in both hippocampal and amygdala volumes in a sample of patients who received predominantly right unilateral ECT. Possibly, not the stimulation method per se, but rather the capacity of electrical stimulation to induce a generalized seizure may determine the pattern of neuroplastic responses. Also it not clear what determines the differences between the hemispheres that are apparent in Figures 1a and b. Another limitation is that we do not know yet whether these increases in cortical thickness reflect a temporary effect, as was shown for the increase in volume of the hippocampus induced by ECT and longer follow-up studies in new line of ECT neuroimaging studies are certainly warranted.

In summary, we show that ECT does not only change the neuroplasticity of subcortical brain regions, but also leads to regional increases in cortical thickness. The localization of this increase suggests that it is related to seizure onset in ECT. Moreover, extension of this area of increase to the insula seems to be an important factor, which may determine the therapeutic response. The exact nature of these changes has to be investigated by future research in larger samples and multimodal imaging techniques including magnetic resonance spectroscopy. Further it should be established whether the ECT-induced changes in cortical thickness remain on follow-up.
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Structural changes induced by electroconvulsive therapy are associated with clinical outcome.

Adapted from:


Structural changes induced by electroconvulsive therapy are associated with clinical outcome.

*Brain Stimulation.* 2020 May-June 13 (3): 696-704
ABSTRACT

BACKGROUND
Electroconvulsive therapy (ECT) is the most effective treatment option for major depressive disorder, so understanding whether its clinical effect relates to structural brain changes is vital for current and future antidepressant research.

OBJECTIVE
To determine whether clinical response to ECT is related to structural volumetric changes in the brain as measured by structural magnetic resonance imaging (MRI) and, if so, which regions are related to this clinical effect. We also determine whether a similar model can be used to identify regions associated with electrode placement (unilateral versus bilateral ECT).

METHODS
Longitudinal MRI and clinical data (Hamilton Depression Rating Scale) was collected from 10 sites as part of the Global ECT-MRI research collaboration (GEMRIC). From 192 subjects, relative changes in 80 (sub)cortical areas were used as potential features for classifying treatment response. We used recursive feature elimination to extract relevant features, which were subsequently used to train a linear classifier. As a validation, the same was done for electrode placement. We report accuracy as well as the structural coefficients of regions included in the discriminative spatial patterns obtained.

RESULTS
A pattern of structural changes in cortical midline, striatal and lateral prefrontal areas discriminates responders from non-responders (75% accuracy, p<0.001) while left-sided mediotemporal changes discriminate unilateral from bilateral electrode placement (81% accuracy, p<0.001).

CONCLUSIONS
The identification of a multivariate discriminative pattern shows that structural change is relevant for clinical response to ECT, but this pattern does not include mediotemporal regions that have been the focus of electroconvulsive therapy research so far.

INTRODUCTION
Major depressive disorder is a leading cause of disability worldwide and one of the biggest challenges the field of mental health faces today. High prevalence and the fact that up to a third of patients suffering from depression fail to respond to conventional pharmaco- or psychotherapy has renewed scientific interest in electroconvulsive therapy (ECT), which achieves a fast antidepressant response in a majority of these treatment-resistant patients. Understanding the mechanisms through which ECT achieves its remarkably strong clinical effect could provide critical biological markers to advance both established and emerging antidepressant therapies. To this end, the Global ECT-MRI Research Collaboration (GEMRIC) was founded to pool data from multiple sites to increase power and enable analyses that cannot be performed on smaller samples.

Over the past years an emerging body of literature has investigated ECT-related changes in brain structure and, to a lesser degree, function. A recent explorative GEMRIC analysis of structural change reported volumetric increases in 79 of 84 grey matter regions, which linked to electrode placement (uni- or bilateral) and number of ECTs, but not to clinical outcome. While others have also observed widely distributed effects throughout the brain, several regions have been more consistently implicated as relevant to ECT’s antidepressant effects. Stimulated by translational studies on neurotrophic effects of ECT, medial temporal lobe structures including the hippocampus and amygdala have been subject to a number of investigations. Nearly all these studies report significant volume increases after ECT, which has been confirmed through meta-analyses. In a recent GEMRIC mega-analysis this increase in hippocampal volume after ECT was again related to both electrode placement and number of ECT sessions administered, but while translational and human studies have suggested a link between hippocampal volume and behavioral changes, no relation to treatment outcome was established. Furthermore, follow-up studies have found the increase in medial temporal lobe volume to be transient in nature. Other areas of interest reported across multiple studies are the anterior cingulate cortex (ACC), the insula, and the striatum. Critically, all of these regions are also affected in patients suffering from depression, with recurrent or treatment-resistant patients being typically more affected.

So, although ECT induces prominent and widespread structural changes, it remains unclear whether these changes are related to its antidepressant properties. A lack of reproducible links between structural changes and clinical efficacy of ECT could
indicate that either treatment response to ECT is not related to any structural changes in the brain or that samples and methods used so far have been underpowered to detect a statistically and clinically relevant relationship. An important limitation here is that most studies have employed a univariate approach, attempting to link clinical improvement to structural change in a single region, while both depression and ECT are known to affect various interacting regions and circuits throughout the brain which makes it unlikely that response depends on changes in a single region (33,34). To address this issue, we use the aforementioned GEMRIC dataset to investigate whether 1) patterns of structural changes in the brain induced by ECT are related to clinical response and 2) if so, which regions in these patterns are most relevant for treatment response. We employ multivariate discriminant analysis to test whether a model that can discriminate responders from non-responders on the basis of volumetric changes detected with structural MRI can be developed. Such a model provides both the flexibility of not needing strong prior assumptions on where clinically relevant effects happen as well as the appropriate multivariate linear framework allowing us to identify which regions contribute to ECT’s remarkable clinical effect.

METHODS

PARTICIPANTS AND NEUROIMAGING DATA

We use data from the Global ECT-MRI Research Collaboration (GEMRIC), a multi-site initiative pooling clinical and neuroimaging data of ECT patients. Informed consent was obtained from all patients. For our analysis we use data from 10 GEMRIC sites for a total of 237 depressed subjects who had received either right unilateral or bilateral ECT (or both) with available imaging and clinical data (depression severity, either 17-item Hamilton Depression Rating Scale (HAM-D) or Montgomery-Asberg Depression Rating Scale converted to HAM-D through the method described by Heo et al. [35]). For a detailed description of GEMRIC including site-specific ECT procedures, image acquisition and common data processing methods, we refer to Oltedal et al. [36]. In short, the data includes patients with a depressive episode who were eligible to receive ECT, most typically after failure to respond to conventional psycho- and pharmacotherapy. There are some regional differences in ECT procedure used among the sites in our sample, including electrode placement which varies between right unilateral only, bilateral only or initial right unilateral with a switch to bilateral after non-response. For each subject, response was defined as a decrease of 50% or more on HAM-D score.

T1-weighted MRI volumes with a minimum resolution of 1.3 mm³ were acquired before and after ECT using either a 1.5T or 3T scanner. Imaging data were analyzed using a common pipeline. Images were corrected for scanner-specific gradient nonlinearity [36], registered to a common atlas and resampled to 1mm³ resolution. FreeSurfer 5.3 was used to obtain measures of cortical and subcortical volumes [37–39]. Longitudinal change was estimated using Quarc [40], for a total of 80 longitudinal features per subject (see supplementary information for the full feature list). Due to the lack of robust clinically relevant effects found in ECT and the widespread effect ECT has on brain volume we did not select only regions-of-interest.

ANALYSIS

80 different regions were tested for association with treatment response by means of a penalized Linear Discriminant Analysis (LDA). Because of sensitivity to outliers in feature selection, we excluded patients that were extreme outliers (>3 standard deviations) on any of the 80 imaging features for a final sample of 192 subjects. A leave-one-subject out design, using volume normalization and recursive feature elimination with internal cross-validation, provided 192 model estimates of features relevant for discrimination between responders and non-responders [42].

Due to the large number of features compared to the number of subjects in the smallest group, we observed high variance in the number of relevant brain areas selected at each fold. Consequently, to get a unique set of relevant features we removed features that were selected less than ~1% of all models (2 models). To validate the quality of the set of selected brain areas, we used these remaining features to train a linear classifier (LDA, least squares fit with automatic shrinkage estimation) which provided us with the learned model accuracy The performance of this model was then evaluated by means of permutation testing (1,000 permutations, where within each iteration the labels are randomized and our model is tested against the “chance” model) [42]. Due to the large number of features in contrast to our smallest group (72 non-responders), we were unable to select features, train and test the model in independent samples. As such, while our sample is diverse and contains data from various research sites, the model accuracy is an indication of picking up relevant within-sample signal, rather than the estimated accuracy should it be applied to an out-of-sample dataset. Using both leave-one out and stratified 10-fold cross-validation gives insight into how the model accuracy changes based on a different split of the data.

Because we use a linear model, we can interpret the weights from the classifier by transforming them to structural coefficients as described by Haufe et al. [41]. This transform helps us discern weights that contribute to classification from those included
to cancel noise that obscures the underlying relevant discriminative properties. These structural coefficients are more informative for the classification of interest the further they are from zero, while their sign indicates how values are indicative of belonging to one class over the other. These coefficients together make up a discriminative map that indicates regional predictive power for clinical improvement.

We used this analysis to detect which regions are related to treatment response to answer our main research question. To assess how our model is affected by variables that are inherently linked to treatment trajectory and effect, we also test the model taking into account age, sex, number of ECT sessions and electrode placement by regressing these variables out of the imaging data before training the classifier. We also test for site-differences by training the classifier excluding each site and predicting treatment response in the site left out. Finally, as an additional validation strategy for our analysis, we apply the same method to obtain a discriminative map for regions associated with site of electrode placement (defined as having received either right unilateral treatment only (RUL) versus bilateral treatment only or unilateral followed by bilateral treatment (BL)). All analyses were performed in python using the scikit-learn toolkit\(^{(44)}\) and results were visualized using a template\(^{(45)}\).

**RESULTS**

**DEMOGRAPHICS**

Key demographics are presented in table 1. Notably, there is a clear treatment effect for ECT, which separates responders from non-responders, and these groups also differ in age (p<0.001), but not sex or baseline clinical score. As expected, non-responders have a higher likelihood of receiving bilateral ECT, as a switch from unilateral to bilateral treatment is common practice after initial non-response. Within our sample 62.5% were responders and 61% received exclusively unilateral ECT while the other 39% received only bilateral ECT (n=39) or switched to bilateral ECT after non-response to unilateral treatment (n=36).

**TABLE 1. Demographics of patients included in the data analysis.** Relevant subject demographics and comparison between responders and non-responders to treatment.

<table>
<thead>
<tr>
<th></th>
<th>full sample (n=192)</th>
<th>responders (n=120)</th>
<th>non-responders (n=72)</th>
<th>responders vs. non-responders*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>mean 16.81 std 2.4</td>
<td>mean 16.28 std 2.4</td>
<td>mean 17.26 std 2.5</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>m/f 5/189</td>
<td>m/f 35/85</td>
<td>m/f 51/27</td>
<td></td>
</tr>
<tr>
<td>Laterality (RUL/BL)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>HRSD pre</td>
<td>25.3</td>
<td>31.4</td>
<td>28.2</td>
<td></td>
</tr>
<tr>
<td>HRSD post</td>
<td>10.8</td>
<td>6.3</td>
<td>13.0</td>
<td></td>
</tr>
<tr>
<td>HRSD change</td>
<td>14.4</td>
<td>13.7</td>
<td>16.9</td>
<td></td>
</tr>
<tr>
<td>No. ECT sessions</td>
<td>74 ± 113</td>
<td>81 ± 39</td>
<td>75 ± 48</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0000079</td>
</tr>
</tbody>
</table>

---

**GENERAL EFFECTS**

In line with earlier work\(^{(3)}\), all features included in the analysis showed an average positive increase in volume, ranging from 0.2 to 5.1%. This increase is more pronounced in lateral and mediotemporal regions (amygdala, hippocampus, entorhinal cortex, temporal pole), while changes in parietal and occipital regions were relatively small (see supplementary table S1 for baseline and changes per region).

**FEATURE SELECTION AND ANALYSIS**

**Treatment response**

The feature selection procedure over 192 iterations selected on average 8.9 features (±2.4 features, median 8). 18 features were selected by more than 1% of all models (see supplementary table S2 for probabilities). Using these features, we trained a linear classifier (LDA), which performed with an accuracy of 75% to classify treatment response (sensitivity 84%, specificity 60%), which is significantly better than chance (p < 0.001; stratified 10-fold accuracy 72%, p < 0.001; split-half accuracy 66%, p < 0.001). Per-site accuracy scores are presented in supplementary table S3. The discriminative pattern remained significant after regressing out age, sex, number of ECT sessions and electrode placement (p < 0.001, supplementary table S4).

The relevant features, ranked by their structural coefficients\(^{(45)}\), are presented in figure 1 and table S5. From highest to lowest importance, the contributing regions are the right precuneus (0.27), right putamen (-0.26), left rostral ACC (-0.21), right supramarginal gyrus (0.17), left rostral middle frontal gyrus (-0.16), right caudal ACC (0.16), right rostral ACC (-0.11), right fusiform gyrus (0.11), left precuneus (0.11), left middle temporal cortex (-0.11), left supramarginal gyrus (0.09), right frontal pole (0.06), left entorhinal cortex (-0.06), right precentral cortex (-0.05), left banks of the superior temporal sulcus (-0.04),
left isthmus cingulate (-0.02), left fusiform gyrus (0.02) and right parahippocampal cortex (0.01). The signs of the coefficients indicate that larger increases in volume in the bilateral precuneus, supramarginal gyrus and right caudal ACC are more indicative of being a responder to ECT, while larger increases in right putamen, left rostral middle frontal gyrus and rostral ACC are more indicative of being a non-responder.

As is evident by the discriminative map presented, while all regions add classification accuracy, some regions are highly relevant for discriminating responders from non-responders as represented in high absolute structural coefficients (right precuneus, right putamen, right supramarginal, left rostral ACC, left rostral middle frontal gyrus, right caudal ACC), while other regions are almost exclusively cancelling noise to uncover the relevant signal (structural coefficient close to zero; left fusiform gyrus, right parahippocampal cortex, left isthmus cingulate, left banks of the superior temporal sulcus, right precentral cortex).

**Electrode placement**

Feature selection for electrode placement revealed 31 features of interest. The linear classifier trained using these features classified electrode placement with an accuracy of 81% (sensitivity 90%, specificity 68%, p < 0.001). The full set of features and their structural coefficients are presented in figure 2 (and supplementary table S6). Most notably, the obtained discriminative map shows a strong contribution of left-sided regions known to be affected differently by electrode placement: the left amygdala (0.28), left hippocampus (0.21) and left entorhinal cortex (0.24). Larger changes in these regions are indicative of having received bilateral over unilateral ECT.
DISCUSSION

Understanding the neural mechanisms underlying the most potent antidepressant treatment available is an important step towards advancing current and novel treatment strategies, as well as reducing stigma surrounding psychiatric disorders and their treatments. As such, information on whether structural changes in the brain are relevant for treatment response is a simple yet fundamental question that needs to be addressed. We show, by means of training a linear classifier, that a pattern of structural changes in the brain is associated with clinical response to ECT. Regions identified as contributing to response are located in cortical midline, striatal and lateral prefrontal areas implicated in the pathophysiology of depression. In addition, we dissociate regions related to treatment response from those related to site of electrical stimulation by showing that the type of ECT used (unilateral or bilateral) can be identified by a discriminative map that incorporates unilateral medial temporal regions that are known to be affected by ECT [4]. Below, we will discuss the significance of these findings.

To interpret our results in the light of earlier work, it is important to distinguish that our multivariate model is not directly comparable with the majority of univariate analyses; none of the regions associated with treatment response or electrode placement does so independently. Instead, multivariate analysis takes the full pattern of structural changes into account and allows us to discriminate responders from non-responders. Furthermore it is able to discriminate bilateral from unilateral ECT which, given the clinical discussion on preference of unilateral versus bilateral stimulation, could aid in uncovering neuroimaging correlates of different approaches to ECT. In addition to the multivariate interpretation, the sign of the structural coefficients as derived from the feature weights relates to increases in volume, within the pattern as a whole, being either indicative of response (bilateral precuneus, supramarginal gyrus and right caudal ACC) or non-response (right putamen, rostral ACC, left rostral middle frontal gyrus).

We observe that the predominantly bilateral regions contributing significantly to classification of treatment response are consistent with other work indicating aberrant structure and/or function in cortico-limbic and cortico-striatal systems in depression. In fact, all of the discriminative regions have previously been demonstrated to show changed (mostly decreased) volume [29,30,32,47,48] and dysconnectivity within large-scale functional networks [49–52] in depression. Several of these regions are well established in the context of depression and warrant additional consideration here.

The precuneus is part of the posterior default mode network and is associated with self-related processing and episodic memory retrieval [53,54]. There is evidence of decreased volume in the precuneus in first-episode depression [151], and altered function or functional connectivity during rest [155–158] and self-related judgment [159]. Preliminary evidence also links changes in precuneus activity or network connectivity to treatment with antidepressants [49], psychotherapy [50] and ECT [49]. The anterior cingulate cortex is a core region within the anterior default mode network [152], showing decreased volume [29,30,32] and typically increased activation during rest in depressed patients [29,32,49], which has been suggested as a biomarker for treatment response to various forms of biological treatment up to deep brain stimulation [32,49]. Importantly, activity within the anterior cingulate cortex appears to be highly context-sensitive, in line with its function in self-referential emotional processing and the attribution of valence to external stimuli [155–157]. The left rostral middle frontal cortex includes the dorsolateral prefrontal cortex and is part of the cognitive-executive network, a functional hub that exerts top-down cognitive control over cortical midline and limbic regions, a balance that has been shown to be dysfunctional in depression [158–160]. Antidepressant effects have been found in this region in response to antidepressants [29] and ECT [152], and left dorsolateral prefrontal cortex is currently the primary target for transcranial magnetic stimulation for depression. A recent study has also shown how various lesions in a brain circuit centered around the dorsolateral prefrontal cortex link to depression [29]. Finally, the discriminative relevance of the putamen is consistent with reports of reduced putamen volume in depression [152,55] and the relevance of the striatum in the context of depression and as a potential marker for treatment response [54]. Taken together our finding that these regions, which are critical to our discriminative pattern, are already established as key depression hubs, potential biomarkers of treatment response, and/or the target for other neuromodulation techniques [56], give further credence to our method detecting relevant response-related effects.

We also report that structural changes in the main regions under investigation in the context of ECT, the hippocampus and amygdala, are not included in the pattern associated with treatment response. This is in line with a lack of any reproducible findings linking volumetric changes in these regions to clinical effects in either depression or ECT [14,15]. One possible explanation is that not the hippocampus as a whole, but rather specific subfields within the hippocampus such as the dentate gyrus (or granule cell layer) are relevant for clinical response [15,75]. Medial temporal regions also appear differentially engaged by unilateral or bilateral ECT, as is evident by unilateral medial temporal changes being associated with electrode placement. Recent work within GEMRIC has shown how structural changes are affected by local electric fields [7], which could further explain differences between stimulation
methods. This is consistent with differences in cortical volume\(^{(99)}\), cerebral blood flow\(^{(96)}\) and seizure propagation\(^{(179)}\) between unilateral and bilateral ECT. More expansive engagement of medial temporal regions in bilateral ECT might be related to the higher occurrence of cognitive side-effects in bilateral versus unilateral ECT\(^{(100,101)}\). Overall, no single region was in itself predictive of treatment response or electrode placement at the level of the multivariate solution, corresponding to our current understanding of depression as a multi-systems level disorder encompassing large-scale brain networks and with the large-scale engagement of the brain in ECT\(^{(92)}\). As such, a multivariate approach appears more suitable to further conceptualize neuroimaging markers of antidepressant response.

In light of their expansiveness and the timeframe of structural changes induced by ECT, there has been much discussion on their biological nature. While some have suggested they could be attributable to edema caused by the electrical stimulus itself, this notion is not supported by studies using T2-relaxometry to detect significant fluid shifts\(^{(12,83,84)}\). A prominent hypothesis posits that ECT combats depression by inducing neurotrophic effects\(^{(85)}\), in line with volumetric increases in depression\(^{(10,12)}\). Indeed, preclinical studies of ECT have found support for neurogenesis\(^{(18,19)}\), angiogenesis\(^{(87)}\), gial cell proliferation\(^{(88)}\) and increased dendritic complexity and synaptogenesis\(^{(91)}\). Certainly, in ECT, neurogenesis is not the only factor at play as neurogenesis is slow compared to ECT-induced volume changes and is limited to the dentate gyrus and subventricular zone, while ECT-induced volume changes occur across the brain. In patients, support for neuroplastic effects are represented by increases in plasma and serum brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor after ECT\(^{(92,93)}\) but while persistent depression has been associated with decreased peripheral BDNF, its prognostic value may be limited\(^{(92–94)}\). Furthermore, while volumetric increases after ECT become more pronounced as the number of ECT sessions increases, they revert back to pre-treatment levels after 6\(^{(12,23,95)}\) and 12 months\(^{(25)}\). Consistent with the lack of a clear relation of ECT-induced volumetric changes to clinical efficacy, their return to pre-treatment levels has not been found to be related to either relapse of depression or recovery from cognitive side-effects\(^{(92,23,95)}\).

Taken together, it is likely that not one but multiple neuroplastic systems are engaged during and after ECT and operate on varying timescales to affect both short and longer-term changes in structure and function. How these neuroplastic changes can help to overcome depression is still largely unknown, but one possibility is that this forging or restoring of connections within large scale networks that are dysfunctional in depression helps to overcome depressogenic pathways. Better characterization of changes over time, as opposed to only before and after treatment, their relation to both response and relapse, and integration of structural and functional imaging could be beneficial in understanding these effects.

Despite our promising results there are some limitations that need addressing. While we use both a statistical and biological validation for the method used, we are still limited by trying to optimize covariance space of 80 features in a sample with 72 non-responders, which restricts us to selecting the relevant features and building the classifier using the same data while ideally those processes would be split. Although we validate our discriminative pattern by cross-validation and our methods by applying it to well-known unilateral effects (site of electrode placement), there is still a risk of overfitting the feature selection to our specific dataset. As such, accuracy of the model should be interpreted as indicative of within-sample performance; additional work should confirm whether this pattern holds in independent samples. Furthermore, the FreeSurfer parcellation, while robust and sufficiently validated, remains an average representation of more localized variations in structure. Finer grained parcellations could provide more insight into the areas identified in this paper here or areas whose relevance is now undervalued by their inclusion into a larger region, such as the dentate gyrus\(^{(79,80)}\). In addition, subject-specific information such as stimulation parameters other than electrode placement might also affect structural changes differently, which we were unable to take into account. Finally, while multivariate analyses are powerful in detecting relevant patterns, with an increase in the number of relevant regions their interactions become more complex to interpret.

**CONCLUSION AND FUTURE**

In conclusion, we show that structural brain changes are indicative of treatment response to ECT, but not in the regions that are typically investigated (medial temporal areas). Instead, we observe this response to be related to cortical midline, striatal and lateral prefrontal areas implicated in the etiology of depression and its treatments. We show the power of collaborative efforts to tackle questions that would otherwise remain elusive and the power of explorative multivariate approaches when linking brain and behavior. Future studies could elaborate on our work, including replication in larger or independent samples, as well as integrating structural and functional data to reach a more comprehensive understanding of the mechanisms underlying antidepressant response.
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CHAPTER 7

STRUCTURAL CHANGES INDUCED BY ELECTROCONVULSIVE THERAPY ARE ASSOCIATED WITH CLINICAL OUTCOME


162

163
FreeSurfer parcellation used as input before feature elimination. All regions were entered bilaterally for a total of 80 features per subject.

**Frontal**
- Superior Frontal
- Rostral and Caudal Middle Frontal
- Pars Opercularis, Pars Triangularis, and Pars Orbitalis
- Lateral and Medial Orbitofrontal
- Precentral
- Paracentral
- Frontal Pole

**Parietal**
- Superior Parietal
- Inferior Parietal
- Supramarginal
- Postcentral
- Precuneus

**Temporal**
- Superior, Middle, and Inferior Temporal
- Banks of the Superior Temporal Sulcus
- Fusiform
- Transverse Temporal
- Entorhinal
- Temporal Pole
- Parahippocampal

**Occipital**
- Lateral Occipital
- Lingual
- Cuneus
- Pericalcarine
### Cingulate
- Rostral Anterior (Frontal)
- Caudal Anterior (Frontal)
- Posterior (Parietal)
- Isthmus (Parietal)

### Subcortical
- Amygdala
- Hippocampus
- Nucleus Accumbens
- Putamen
- Thalamus
- Pallidum

### SUPPLEMENTARY TABLE S1. Baseline and relative changes per region

<table>
<thead>
<tr>
<th>Region</th>
<th>Base left</th>
<th>Base right</th>
<th>Change left</th>
<th>Change right</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior frontal</td>
<td>18388 (+2468)</td>
<td>17809 (+2445)</td>
<td>0.97 (+1.2)</td>
<td>1.1 (+1.3)</td>
</tr>
<tr>
<td>Rostral middle frontal</td>
<td>12349 (+1798)</td>
<td>12602 (+1830)</td>
<td>0.66 (+1.3)</td>
<td>0.77 (+1.4)</td>
</tr>
<tr>
<td>Caudal middle frontal</td>
<td>5607 (+1031)</td>
<td>5173 (+1029)</td>
<td>0.91 (+1.3)</td>
<td>0.94 (+1.3)</td>
</tr>
<tr>
<td>Pars opercularis</td>
<td>3957 (+659)</td>
<td>3551 (+649)</td>
<td>1.2 (+1.2)</td>
<td>1.1 (+1.3)</td>
</tr>
<tr>
<td>Pars triangularis</td>
<td>2877 (+444)</td>
<td>3409 (+622)</td>
<td>0.98 (+1.4)</td>
<td>1.1 (+1.4)</td>
</tr>
<tr>
<td>Pars orbitalis</td>
<td>1566 (+236)</td>
<td>1926 (+286)</td>
<td>0.66 (+1.9)</td>
<td>0.99 (+1.8)</td>
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<tr>
<td>Lateral orbitofrontal</td>
<td>6398 (+793)</td>
<td>6030 (+822)</td>
<td>0.60 (+1.3)</td>
<td>0.98 (+1.2)</td>
</tr>
<tr>
<td>Medial orbitofrontal</td>
<td>4116 (+631)</td>
<td>4035 (+528)</td>
<td>0.70 (+1.4)</td>
<td>1.1 (+1.4)</td>
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<tr>
<td>Precentral</td>
<td>11163 (+1484)</td>
<td>11121 (+1461)</td>
<td>0.63 (+1.1)</td>
<td>0.58 (+1.1)</td>
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<tr>
<td>Paracentral</td>
<td>3072 (+125)</td>
<td>3582 (+591)</td>
<td>0.97 (+1.1)</td>
<td>1.9 (+1.1)</td>
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<tr>
<td>Frontal pole</td>
<td>508 (+88)</td>
<td>679 (+121)</td>
<td>0.39 (+2.5)</td>
<td>0.73 (+2.3)</td>
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<tr>
<td>Parietal</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior parietal</td>
<td>11635 (+1547)</td>
<td>11121 (+1461)</td>
<td>0.63 (+1.1)</td>
<td>0.58 (+1.1)</td>
</tr>
<tr>
<td>Inferior parietal</td>
<td>1379 (+1419)</td>
<td>12412 (+3534)</td>
<td>0.97 (+1.3)</td>
<td>0.96 (+1.2)</td>
</tr>
<tr>
<td>Supramarginal</td>
<td>9106 (+1453)</td>
<td>8638 (+1304)</td>
<td>1.0 (+1.3)</td>
<td>1.2 (+1.3)</td>
</tr>
<tr>
<td>Postcentral</td>
<td>8324 (+1259)</td>
<td>7755 (+1033)</td>
<td>0.95 (+0.9)</td>
<td>0.99 (+1.0)</td>
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<td>Precuneus</td>
<td>8296 (+1251)</td>
<td>8747 (+1235)</td>
<td>0.43 (+0.95)</td>
<td>0.47 (+0.89)</td>
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<tr>
<td>Temporal</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Superior temporal</td>
<td>9356 (+1297)</td>
<td>9276 (+1246)</td>
<td>1.0 (+1.3)</td>
<td>1.8 (+1.4)</td>
</tr>
<tr>
<td>Middle temporal</td>
<td>7811 (+128)</td>
<td>8832 (+1337)</td>
<td>0.99 (+1.6)</td>
<td>1.4 (+1.4)</td>
</tr>
<tr>
<td>Inferior temporal</td>
<td>7952 (+1466)</td>
<td>7826 (+1441)</td>
<td>1.3 (+1.4)</td>
<td>1.8 (+1.4)</td>
</tr>
<tr>
<td>Banks superior temporal sulcus</td>
<td>2351 (+437)</td>
<td>2253 (+386)</td>
<td>0.95 (+1.3)</td>
<td>1.2 (+1.3)</td>
</tr>
<tr>
<td>Fusiform</td>
<td>7917 (+1099)</td>
<td>7555 (+1075)</td>
<td>1.2 (+1.1)</td>
<td>1.6 (+1.2)</td>
</tr>
<tr>
<td>Transverse temporal</td>
<td>1002 (+188)</td>
<td>756 (+136)</td>
<td>0.73 (+1.5)</td>
<td>1.2 (+1.5)</td>
</tr>
<tr>
<td>Entorhinal</td>
<td>1216 (+217)</td>
<td>1130 (+268)</td>
<td>2.7 (+2.5)</td>
<td>3.4 (+2.6)</td>
</tr>
<tr>
<td>Temporal pole</td>
<td>1542 (+288)</td>
<td>1481 (+230)</td>
<td>2.7 (+2.9)</td>
<td>4.2 (+2.7)</td>
</tr>
<tr>
<td>Parahippocampal</td>
<td>1722 (+289)</td>
<td>1638 (+262)</td>
<td>1.5 (+1.5)</td>
<td>2.1 (+1.5)</td>
</tr>
<tr>
<td>Occipital</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral occipital</td>
<td>9526 (+1337)</td>
<td>9369 (+1375)</td>
<td>0.67 (+1.1)</td>
<td>0.76 (+1.0)</td>
</tr>
<tr>
<td>Lingual</td>
<td>5555 (+916)</td>
<td>5747 (+869)</td>
<td>0.45 (+0.79)</td>
<td>0.57 (+0.82)</td>
</tr>
<tr>
<td>Cuneus</td>
<td>2507 (+404)</td>
<td>2601 (+416)</td>
<td>0.45 (+0.91)</td>
<td>0.51 (+0.90)</td>
</tr>
<tr>
<td>Pericalcine</td>
<td>2126 (+420)</td>
<td>2303 (+420)</td>
<td>0.39 (+0.93)</td>
<td>0.51 (+0.92)</td>
</tr>
<tr>
<td>Cingulate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rostral anterior cingulate</td>
<td>2218 (+418)</td>
<td>1831 (+392)</td>
<td>1.0 (+1.5)</td>
<td>1.9 (+1.6)</td>
</tr>
<tr>
<td>Caudal anterior cingulate</td>
<td>1677 (+409)</td>
<td>1912 (+402)</td>
<td>1.7 (+1.4)</td>
<td>1.7 (+1.4)</td>
</tr>
<tr>
<td>Posterior cingulate</td>
<td>2729 (+469)</td>
<td>2766 (+491)</td>
<td>0.48 (+1.0)</td>
<td>0.56 (+1.1)</td>
</tr>
<tr>
<td>Isthmus cingulate</td>
<td>2357 (+411)</td>
<td>2312 (+367)</td>
<td>0.20 (+1.1)</td>
<td>0.28 (+0.94)</td>
</tr>
<tr>
<td>Subcortical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amygdala</td>
<td>1464 (+250)</td>
<td>1517 (+295)</td>
<td>3.2 (+2.6)</td>
<td>5.1 (+2.7)</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>3762 (+581)</td>
<td>3862 (+595)</td>
<td>2.2 (+1.9)</td>
<td>2.9 (+1.7)</td>
</tr>
<tr>
<td>Nucleus accumbens area</td>
<td>467 (+136)</td>
<td>500 (+120)</td>
<td>1.5 (+1.9)</td>
<td>2.0 (+1.9)</td>
</tr>
<tr>
<td>Caudate</td>
<td>3608 (+481)</td>
<td>3699 (+509)</td>
<td>1.4 (+1.4)</td>
<td>1.4 (+1.4)</td>
</tr>
<tr>
<td>Putamen</td>
<td>5063 (+727)</td>
<td>4988 (+688)</td>
<td>1.0 (+0.95)</td>
<td>1.3 (+1.0)</td>
</tr>
<tr>
<td>Thalamus</td>
<td>7276 (+1069)</td>
<td>6702 (+966)</td>
<td>1.0 (+1.0)</td>
<td>1.3 (+1.0)</td>
</tr>
<tr>
<td>Pallidum</td>
<td>1446 (+290)</td>
<td>1436 (+215)</td>
<td>0.94 (+1.0)</td>
<td>1.2 (+0.95)</td>
</tr>
</tbody>
</table>
**SUPPLEMENTARY TABLE S2.** Probability of features being including in model

Results of feature selection prior to training of the model. Regions selected > 1% of models (more than 2 iteration) were included in the model (in bold). Other features were not picked up by any iteration.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Probability (%) / No. times included</th>
</tr>
</thead>
<tbody>
<tr>
<td>rostral middle frontal (L)</td>
<td>100 / 192</td>
</tr>
<tr>
<td>putamen (R)</td>
<td>100 / 192</td>
</tr>
<tr>
<td>fusiform (R)</td>
<td>98 / 188</td>
</tr>
<tr>
<td>caudal anterior cingulate (R)</td>
<td>98 / 188</td>
</tr>
<tr>
<td>precuneus (R)</td>
<td>98 / 188</td>
</tr>
<tr>
<td>rostral anterior cingulate (R)</td>
<td>98 / 188</td>
</tr>
<tr>
<td>supramarginal (L)</td>
<td>97 / 187</td>
</tr>
<tr>
<td>parahippocampal (R)</td>
<td>97 / 187</td>
</tr>
<tr>
<td>precentral (R)</td>
<td>25 / 47</td>
</tr>
<tr>
<td>supramarginal (R)</td>
<td>16 / 30</td>
</tr>
<tr>
<td>frontal pole (R)</td>
<td>15 / 28</td>
</tr>
<tr>
<td>isthmus cingulate (L)</td>
<td>10 / 19</td>
</tr>
<tr>
<td>precuneus (L)</td>
<td>10 / 19</td>
</tr>
<tr>
<td>middle temporal (L)</td>
<td>7 / 13</td>
</tr>
<tr>
<td>fusiform (L)</td>
<td>6 / 11</td>
</tr>
<tr>
<td>banks superior temporal sulcus (L)</td>
<td>3 / 6</td>
</tr>
<tr>
<td>rostral anterior cingulate (L)</td>
<td>3 / 5</td>
</tr>
<tr>
<td>entorhinal (L)</td>
<td>3 / 5</td>
</tr>
<tr>
<td>inferior parietal (L)</td>
<td>1 / 2</td>
</tr>
<tr>
<td>isthmus cingulate (R)</td>
<td>1 / 2</td>
</tr>
<tr>
<td>postcentral (L)</td>
<td>1 / 2</td>
</tr>
<tr>
<td>pallidum (L)</td>
<td>1 / 1</td>
</tr>
<tr>
<td>caudate (R)</td>
<td>1 / 1</td>
</tr>
<tr>
<td>paracentral (L)</td>
<td>1 / 1</td>
</tr>
<tr>
<td>putamen (L)</td>
<td>1 / 1</td>
</tr>
<tr>
<td>accumbens (L)</td>
<td>1 / 1</td>
</tr>
</tbody>
</table>

**SUPPLEMENTARY TABLE S3.** Linear discriminant analysis performance per site

Linear discriminant analysis performance where for each site, the model was trained on the other nine sites and then tested in the one site left out.

<table>
<thead>
<tr>
<th>site</th>
<th>n</th>
<th>accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>67%</td>
</tr>
<tr>
<td>2</td>
<td>39</td>
<td>74%</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>82%</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>71%</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>83%</td>
</tr>
<tr>
<td>6</td>
<td>18</td>
<td>67%</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>85%</td>
</tr>
<tr>
<td>8</td>
<td>13</td>
<td>54%</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>80%</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>full</td>
<td>292</td>
<td>75%</td>
</tr>
</tbody>
</table>

**SUPPLEMENTARY TABLE S4.** Linear discriminant analysis performance accounting for confounds-of-interest

Performance of the linear discriminant analysis while adding confounds known to be related to treatment response to ECT. Models were run regressing confounds out of the imaging data using linear regression, before training, then tested using leave-one-out crossvalidation with 1,000 permutations.

<table>
<thead>
<tr>
<th>model</th>
<th>accuracy (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>no confounds</td>
<td>75</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>age</td>
<td>70</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>sex</td>
<td>72</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>number of ECT sessions</td>
<td>74</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>electrode placement</td>
<td>69</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>age * sex</td>
<td>70</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>number of ECT sessions * electrode placement</td>
<td>70</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>age * sex * number of ECT sessions * electrode placement</td>
<td>68</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**SUPPLEMENTARY TABLE S5.** Regions included in discriminative pattern for treatment response and their structural coefficients

Regions included in the discriminative patterns associated with treatment response to ECT; regions are ordered by their absolute structural coefficient, which corresponds to their relevance for discriminating responders from non-responders. Positive structural coefficients indicate that volumetric increase in those areas increase likelihood of being a responder, while a volumetric increase in regions with a negative structural coefficient increase likelihood of being a non-responder.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Structural coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>precuneus (R)</td>
<td>0.27</td>
</tr>
<tr>
<td>putamen (R)</td>
<td>-0.26</td>
</tr>
<tr>
<td>rostral anterior cingulate (L)</td>
<td>-0.21</td>
</tr>
<tr>
<td>supramarginal (R)</td>
<td>0.17</td>
</tr>
<tr>
<td>rostral middle frontal (L)</td>
<td>-0.16</td>
</tr>
<tr>
<td>caudal anterior cingulate (R)</td>
<td>0.16</td>
</tr>
<tr>
<td>rostral anterior cingulate (R)</td>
<td>-0.11</td>
</tr>
<tr>
<td>fusiform (R)</td>
<td>0.11</td>
</tr>
<tr>
<td>precuneus (L)</td>
<td>0.11</td>
</tr>
<tr>
<td>middle temporal (L)</td>
<td>-0.11</td>
</tr>
<tr>
<td>supramarginal (L)</td>
<td>0.09</td>
</tr>
<tr>
<td>frontal pole (R)</td>
<td>0.06</td>
</tr>
<tr>
<td>entorhinal (L)</td>
<td>-0.06</td>
</tr>
<tr>
<td>precentral (R)</td>
<td>-0.05</td>
</tr>
<tr>
<td>banks superior temporal sulcus (L)</td>
<td>-0.04</td>
</tr>
<tr>
<td>isthmus cingulate (L)</td>
<td>-0.02</td>
</tr>
<tr>
<td>fusiform (L)</td>
<td>0.02</td>
</tr>
<tr>
<td>parahippocampal (R)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
**SUPPLEMENTARY TABLE S6.** Regions included in discriminative pattern for electrode placement and their structural coefficients

Regions included in the classifier predicting right unilateral only versus bilateral ECT; regions are ordered by their absolute structural coefficient, which corresponds to their relevance for discriminating unilateral only from bilateral treatment. Positive structural coefficients indicate that volumetric increase in those areas increase likelihood of having received bilateral ECT, while a volumetric increase in regions with a negative structural coefficient increase likelihood of having received RUL only.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Structural coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>amygdala (L)</td>
<td>0.28</td>
</tr>
<tr>
<td>entorhinal (L)</td>
<td>0.24</td>
</tr>
<tr>
<td>hippocampus (L)</td>
<td>0.21</td>
</tr>
<tr>
<td>medial orbitofrontal (L)</td>
<td>0.15</td>
</tr>
<tr>
<td>lateral orbitofrontal (L)</td>
<td>0.12</td>
</tr>
<tr>
<td>pallidum (L)</td>
<td>0.11</td>
</tr>
<tr>
<td>caudate (L)</td>
<td>0.11</td>
</tr>
<tr>
<td>pars orbitalis (L)</td>
<td>0.09</td>
</tr>
<tr>
<td>posterior cingulate (R)</td>
<td>-0.08</td>
</tr>
<tr>
<td>putamen (L)</td>
<td>0.08</td>
</tr>
<tr>
<td>hippocampus (R)</td>
<td>0.06</td>
</tr>
<tr>
<td>middle temporal (R)</td>
<td>0.06</td>
</tr>
<tr>
<td>lateral occipital (L)</td>
<td>0.06</td>
</tr>
<tr>
<td>frontal pole (L)</td>
<td>0.06</td>
</tr>
<tr>
<td>nucleus accumbens (R)</td>
<td>0.06</td>
</tr>
<tr>
<td>posterior cingulate (L)</td>
<td>-0.05</td>
</tr>
<tr>
<td>postcentral (R)</td>
<td>-0.05</td>
</tr>
<tr>
<td>pars opercularis (R)</td>
<td>0.04</td>
</tr>
<tr>
<td>fusiform (R)</td>
<td>0.04</td>
</tr>
<tr>
<td>lateral orbitofrontal (R)</td>
<td>0.04</td>
</tr>
<tr>
<td>superior frontal (L)</td>
<td>0.04</td>
</tr>
<tr>
<td>superior temporal (R)</td>
<td>0.03</td>
</tr>
<tr>
<td>rostral middle frontal (L)</td>
<td>0.03</td>
</tr>
<tr>
<td>cuneus (R)</td>
<td>-0.03</td>
</tr>
<tr>
<td>pallidum (R)</td>
<td>0.03</td>
</tr>
<tr>
<td>superior frontal (R)</td>
<td>0.03</td>
</tr>
<tr>
<td>postcentral (L)</td>
<td>-0.02</td>
</tr>
<tr>
<td>pars opercularis (L)</td>
<td>0.02</td>
</tr>
<tr>
<td>precentral (L)</td>
<td>0.02</td>
</tr>
<tr>
<td>inferior parietal (R)</td>
<td>0.01</td>
</tr>
<tr>
<td>lingual (R)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
CURRENT CONNECTIONS:
BRAIN PATTERNS IN
ELECTROCONVULSIVE THERAPY
SUMMARY OF FINDINGS

In chapter 1, we introduce the clinical concepts of depression and electroconvulsive therapy and propose how we can use neuroimaging methods to find brain-based clinical determinants. Mainly, advances in neuroimaging increase our ability to map behavior to more complex patterns of brain activity, for example by investigating functional connectivity and large-scale functional networks. In chapter 2, we outline the current state of research in the connectivity mechanisms underlying major depressive disorder. Based on our review of 36 papers that compared depressed subjects with healthy controls using resting-state fMRI (926 patients in total), we propose a model that incorporates key functional networks (such as default mode, central executive and salience) and associated regions (subgenual anterior cingulate cortex, insula). We find a large body of evidence of increased connectivity within the anterior default mode network, which changes its configuration to include the subgenual anterior cingulate cortex and increased connectivity to areas of the salience network (amygdala, insula). In addition, subnetworks within the default mode network, the anterior and posterior default mode network, appear to show locally specific changes in their co-activation, with most evidence indicating dissociative changes between the two. In other words, during depression, the anterior and posterior parts of the default mode network do not synchronize to the same degree they do in healthy individuals. Finally, the interaction between the (posterior) default mode network and the central executive network (mainly the dorsolateral prefrontal cortex) is decreased, in line with other studies reporting a decrease in the correct interplay between them and difficulties in switching from task-oriented cognitively demanding states to the default resting-state.

The proposed model fits with the hypothesized function of these large-scale networks, as well as the clinical case of our depressed patient from the first chapter: high levels of internally oriented attention and high levels of rumination (default mode network hyperconnectivity, increased connectivity with the salience network), difficulties disengaging from this mindset (difficulties switching from default mode to cognitive dominance) and difficulties in goal-directed behavior (disconnectivity to the central executive network). Overall, this model fits with other theories of increased activity and connectivity in and towards cortical midline and limbic areas, with medial prefrontal cortex acting as a main hub of increased connectivity. Other areas that relate to general orchestration of network dominance and cognitive control, such as the precuneus and dorsolateral prefrontal cortex, mainly show decreased connectivity towards these regions. Whether this constitutes a primary dysfunction of top-down control towards limbic areas, primarily increased central hyperactivity, or both, is unclear. While studies on treatment effects are sparse, in general these show that dysfunctional connectivity as presented in our model is reversed through treatment, instead of some other compensatory mechanism. Recently, additional reviews and meta-analyses have appeared that support our proposed model of changed connectivity within depression.

In chapter 3, we review all research investigating longitudinal changes in patients undergoing ECT. We find that most research so far has reported increased volume changes due to ECT in mediotemporal regions, medial prefrontal regions (mainly anterior cingulate cortex) and insula/lateral temporal cortex. Additionally, functional studies indicate that ECT can affect the functional relationship between regions in the anterior and posterior default mode network.

To build on these reviews, we were interested whether changes in the areas relevant for depression and antidepressant response could also be reflective of trait-like patterns that are pervasive throughout different types of behavior. To that end, in chapter 4 we used data from the Human Connectome Project to investigate if personality, a key factor underlying many types of disorders including depression, is reflected in patterns of spontaneous brain activity in regions associated with emotion and cognition as found in our models of depression and ECT. We propose a method of converging highly correlated behavioral measures into patterns of behavior that more appropriately reflect individuals (that typically contain more than one behavioral dimension), by means of temporal independent component analysis. This results in personality profiles that show how the five different dimensions integrate to maximally explain population variance in these dimensions. In short, the original five measure from the NEO-FFI personality inventory are used to create five new profile, that each have a loading and direction on the original five personality types. Each of these profiles has a loading onto each of the original personality factors, so for example we identify personality profiles showing strongly contrasting neuroticism and extraversion, while another profile includes contrasting openness and agreeableness. As these profiles are independent of one another (as opposed to the original factors that are strongly (anti) correlated, loading of subjects on these profiles capture more individual variation. We show that a personality profile of contrasting openness and agreeableness (reflecting high openness/intellect and low agreeableness on one end, and low openness/intellect and high agreeableness on the other end) is associated with a subcortical-medial prefrontal network and the dorsolateral prefrontal cortex, while a profile of contrasting extraversion and conscientiousness (which could be interpreted as scaling from sociable or ‘easy-going’ but disorganized, to more introverted with a strong
sense of duty and self-discipline) is associated with activity in the precuneus. In this work, we show that it is possible to map complex heterogeneous patterns of behavior, such as personality, onto the brain in a multivariate fashion. In addition, we show that when sufficiently powered, even generic behavioral phenotypes such as personality are reflected in the brain’s spontaneous activity.

Shifting towards investigating the neuroimaging correlates of ECT, we wanted to test our hypothesized model of default mode network dissociation in depression and how this is affected by ECT. In chapter 5, using a longitudinal sample of 16 ECT patients, we found that a significant portion of the precuneus, part of the posterior default mode network, is dissociated with the rest of the default mode network in depression, in line with our hypothesis. We go on to show that this dysconnectivity restores after ECT in responders but not in non-responders, in line with our hypothesis that ECT restores brain connectivity to a healthy state rather than through inducing an alternative compensatory mechanism. That this dissociation appears in the precuneus, of which the resting-state also was strongly linked to underlying personality profiles, could be indicative of this regions’ importance in both state- and trait-like characteristics. This fits with reports that the precuneus as a region is ideally situated to orchestrate functional patterns and activation throughout the brain, and also is strongly linked to awareness (8).

Moving from function to structural brain variation, in chapter 6 we show (based on a post-hoc analysis using the same sample as chapter 5) that ECT also induces marked increases in cortical thickness in bilateral temporal pole, lateral temporal cortex and insula, with this increase in the insula being significantly more pronounced in responders than in non-responders. As elaborated on in the introduction to this thesis, these results are in line with other studies showing broad effects of ECT on (medio-)temporal structures (6-8), and are likely to be related to site of stimulation, the associated induced electric field and seizure induction. Unfortunately, the sample size was too small to correct for some of the confounding effects, for example differences in the number of treatments received between responders and non-responders. As elaborated on in the introduction to this thesis, these results are in line with other studies showing broad effects of ECT on (medio-)temporal structures (6-8), and are likely to be related to site of stimulation, the associated induced electric field and seizure induction. Unfortunately, the sample size was too small to correct for some of the confounding effects, for example differences in the number of treatments received between responders and non-responders in a non-post-hoc fashion. While promising, the small sample size prevented us from making claims that could be extrapolated to a broader population of ECT-patients.

To ultimately address this common issue within ECT-research, we set out to determine whether or not structural changes are associated with treatment response to ECT. To overcome the typical limitations in ECT samples, we made use of a much larger dataset from the Global ECT-MRI Research Collaboration (GEMRIC) in chapter 7 to investigate if structural changes induced by ECT are related to treatment response and, if so, which regions are relevant in the context of response. We find, by means of multivariate discriminant analysis, that structural changes are indicative of treatment response, though not in mediotemporal regions (hippocampus, amygdala) which have been the main focus of research. Instead we find that a more widespread pattern of regions in cortical midline and lateral prefrontal areas is associated with treatment response. This pattern mostly highlights regions implicated in depressions’ etiology in line with our main model of depression; most notably it includes the precuneus, the anterior cingulate cortex, the dorsolateral prefrontal cortex and the putamen. We go on to show that electrode placement (either right unilateral only or bilateral placement) is associated with unilateral changes in volume, most profoundly in the mediotemporal regions.

**METHODOLOGICAL CONSIDERATIONS**

For this work, we make use of three different datasets: our own sample of ECT patients and healthy controls (n=36), the Human Connectome Project (n=471) and the Global ECT-MRI Research Collaboration (n=237). Regarding clinical populations, it is important to note some differences between ECT applied in our own sample compared to most of GEMRIC. In the Netherlands, ECT is typically reserved as a last-line treatment after a series of pharmacologic (SSRI, SNRI, TCA, lithium-addition, MAO-inhibitor) and psychotherapeutic therapies. This contrasts with international standards of “treatment resistance” which is most commonly defined as failure to respond to only two different pharmacologic therapies. In addition, our patients were included from an academic hospital that serves as a tertiary center for a large region. Together this adds up to our sample being more treatment resistant than is typical even for a population of ECT patients. Our patients also received exclusively bilateral ECT, while a more common strategy is to start with right unilateral ECT and switching after initial non-response when necessary. With regards to how this would affect our result: more severe cases of depression might increase the changes induced by depression in the brain which could cause us to observe relevant effects even in the relatively small sample. As a downside, effects reported here might not translate as strongly to a less severely affected population. Our sample was also part of GEMRIC, which pools data from 10 different sites with different scanners, populations, and some small differences in treatment strategies (7). The tradeoff herein is that the large sample size with a single processing pipeline allows us to power analyses that cannot be performed in smaller samples. As the sites are relatively balanced, one could consider that findings within
this sample would also be more broadly applicable to ECT populations worldwide than if it were tailored to one specific site. In contrast to these small or mixed samples, the HCP is a single dataset with both an impressive battery of demographic/behavioural and cognitive information as well as high-quality neuroimaging data.

**CURRENT CONNECTIONS**

At the onset of our work, we aimed “to investigate how changes in the brain’s structure and function relate to depression and vulnerability to depression, and how ECT affects these structures and how this can help us understand by which means ECT achieves its strong clinical efficacy”. Through our work, we have used a variety of methods, data types and different datasets to answer questions relating to this overarching theme.

Firstly, major depressive disorder is characterized by changed connectivity within the three large-scale networks highly relevant for psychiatry: the default mode network, the central executive network and the salience network. While hypothesized based on our understanding of their function, we show how these networks are changed in depression as per the literature, and go on to confirm our main hypothesis: evidence of decreased connectivity within subregions of the default mode network in depression. Secondly, we find that ECT affects the entire brain, but more specifically the functional connections within the default mode network and structure of medial prefrontal, medial temporal and lateral temporal areas. As one conclusion from our work we find that, while the analyses were performed separately, results from both functional and structural analyses show large topographical overlap. For example, functional changes we identify after ECT also indicate restoration of within-default mode network connectivity, in line with the abnormalities in depression. Finally, we reveal how, when observing structural changes, the most pronounced effects are not (the most) relevant for ECT’s clinical effects. In fact, no single region can be predictive of treatment success. Instead, a pattern of regions within the three relevant networks drives or represents clinical response.

Figure 1 shows the significant overlap between regions and networks implicated in depression, those affected by ECT and the pattern that is discriminative of response versus non-response. The pattern, which is based on structural changes, predominantly includes key regions within the networks shown to have the changed connectivity in depression. These include - amongst others - the rostral and caudal anterior cingulate cortex, the dorsolateral prefrontal cortex and the precuneus. Our observation that multiple data-driven approaches return similar regions and networks gives credence to their relevance within the depressed brain and ECT’s effects. The critical involvement of both anterior and posterior midline regions within our work also fits with one of our proposed hypotheses on ECT’s underlying effects, namely the restoration of default mode network dysfunction, which is apparent in both structural and function imaging works by us and many others.

In light of the hypotheses on ECT’s mechanisms as outlined in the introduction to this thesis, namely the monoamine, anticonvulsive and neurotrophic hypothesis, our work has mainly focused on effects that are related to neurotrophic properties. As shown by our review of the available literature on ECT, there is limited reproducible evidence for monoamine and anticonvulsant mechanisms that are supported by neuroimaging. This, however, is mostly a result of technical limitations in investigating monoamines (or GABA) in an in-vivo clinical sample. Advancements within magnetic resonance
spectrum will help us in determining the relative contribution of these systems to other models that we have been able to further develop. In contrast, most of the work on ECT, including our own, has shed light on neurotrophic effects of ETC. We, and others, have shown how the most pronounced and well-established structural volumetric increases found after ECT are not relevant for treatment response. In fact, as others have also reported, no single region can reliably explain clinical improvement. While one solution might be to push for more specific hypothesis-driven imaging, for example by investigating smaller regions such as the dentate gyrus, it seems unlikely that changes within a single region will be able to adequately explain a disorder as heterogeneous as depression. Instead, as evidenced by our and others work looking at functional and structural networks; a whole-brain (data-driven) approach that is able to capture patterns of structural and functional changes and their interaction is much more suited to tackle this question going forward. Such an approach will be able to show how interactions within and between the relevant large-scale networks change through ECT. It is very possible that certain regions, such as the dentate gyrus, play an important role within these networks. However, the brain is more than a collection of solitary regions and it will always be crucial to then also understand how this key region interacts with the rest of the brain and how changes within these interactions explain behavioral variation (e.g. clinical response). Ultimately, understanding the relevance of these nodes and networks in the context of depression and treatment response also paves the way for novel methods of neuromodulation in depression, for example by targeting key hubs of networks and evaluating how they garner their effects by modulating connectivity with other regions and networks.

**FUTURE CONNECTIONS**

It is clear from our work, and supported by both broad explorative and narrow hypothesis-driven research, that depression is linked to specific regions and neural circuits that relate to emotion and cognition. Although these regions and networks are also implicated in other psychiatric disorders and symptoms, we have shown how changes within these areas can help us understand the typical depressive phenotype. As outlined above, this thesis adds onto the existing literature by showing how these same regions are affected by ECT and how a complex pattern of changes together can link the brain to its remarkable clinical effects. Going back to the earlier models of ECT’s neural mechanism, our work supports neuroplasticity as one core feature of treatment response, although it needs to be emphasized that not all neuroplasticity is related to (measurable) clinical effects.

One important theme throughout our work is that both depression and ECT are complex in their neural basis, and that no current method available can fully capture this complexity within a single model. However, if our ultimate goal is to provide tangible benefit to the depressed patient, there are some issues that we have addressed that give guidance towards future work to be done within this field.

**TOWARDS A MULTIVARIATE UNDERSTANDING OF DEPRESSION AND ECT**

A growing body of work has shown us that even relatively simple behavioral variations cannot be properly explained by structural or functional variation within a single brain region alone. This goes even more so for explaining the complexity of individual clinical response of a multi-systems level disorder such as depression to a non-targeted therapy such as ECT. Our work supports this notion by showing how connectivity changes in the depressed brain are both widespread based on explorative work and often conflicting in strongly hypothesis-driven work. Even considering heterogeneity within major depressive disorder as a classification, this highlights how depression is not linked to any specific region exclusively. We add onto that basis that, even though the inconsistencies are prevalent, there seems to be signal within the noise, indicating the relevance of certain networks and regions over others. To reiterate, a broad pattern of changes is present in specific brain circuits that relate to emotion and cognition. Depression as a disorder of circuits is not a novel concept, but the relevance of this concept is increasing with regards to therapeutic interventions. A variety of treatment options targeting different parts of these circuits now exist, from deep-brain stimulation targeting the anterior cingulate cortex, to rTMS targeting dorsolateral prefrontal cortex, to ECT that (like pharmacotherapy and psychotherapy) doesn’t target but affects essentially the entire brain. With this complexity as a given, we believe it to be evident that, when trying to understand non-targeted treatment approaches in disorders affecting neural circuits, a univariate approach is not suitable to relate it to clinically meaningful effects. As we show in our model on structural changes, we are able to pick up on treatment-related effects in the multivariate sense, while univariate models on the same dataset have not been able to relate changes to clinical outcome. This underlines that 1) brain changes and signal are important tools for understanding depression and ECT, and 2) relating brain changes to clinically relevant effects requires incorporating data while taking into account the multitude of changes and their interactions (i.e. the multivariate model). With collaborative efforts and increasing quality and quantity of data, in general there is no reason to remain satisfied with univariate solutions to multivariate problems.

When translating these results to the clinic, having a good framework and understanding of what factors (including neuroimaging) relate to eventual treatment response, in
combination with clinical predictors, could help guide clinical decision making by presenting a likelihood of treatment response at different stages of depression. In better understanding the pattern of changes relevant for a positive response, treatment aimed specifically at these key regions could potentially decrease the likelihood or seriousness of adverse effects. Additionally, when viewing depression as a disorder of brain circuits; interventions targeting specific parts of these circuits might differentially benefit different (groups of) patients. In this regard, the concept of “biotypes” has garnered interest in using specific abnormalities within circuits to distinguish subtypes of depressed patients that will go on to respond differently to treatment [31]. While questions have been raised regarding its generalizability [32], the concept of biotypes is interesting, as it incorporates neuroimaging data in clinical decision making in a way that would be feasible. Comparing between these interventions through clinical and research programs will benefit our understanding of how to engage them in meaningful ways, and would lead to more targeted and personalized treatment options.

**TOWARDS STRUCTURAL-FUNCTIONAL INTEGRATION**

In our work we have incorporated both structural and functional neuroimaging. One important aspect herein is that effects tend to happen in similar regions regardless of whether we investigate structural or functional changes related to ECT (insula, precuneus, ACC, dorsolateral prefrontal cortex). It is important to note that structure and function are not independent; they overlap and add onto each other to explain intricate behavioral phenotypes. Within a large sample of the Human Connectome Project (n=1200), we have recently shown how, by using integrated structural information, we can find a pattern of brain variation that links to a large quantity of demographics and behavior including sex, age, education, income, cognition (memory, vocabulary) and general wellbeing (agreeableness, social support, sadness) [33]. The same pattern in demographics and behavior had previously been linked to resting-state connectivity [34]. We go on to show how brain structure explains more variation in behavior than function, and hypothesize how this might relate to analysis steps taken in processing of functional data (i.e. registration to standard space based on brain structure). In this regard, it is also important to consider the difference between structure and function when related to time. As structural changes occur over a longer period of time, it is less suitable to detect specific state-related effects (e.g. cognition or emotion within a certain context) but might function as a more stable marker of (chronic) disease or a predisposition. In contrast, functional markers relating to disease are more closely related to the current state of the individual, but that also introduces variation based on context that might not be disease-related but instead more context dependent, even contexts that are not related to the research question per se.

Based on this, it becomes clear that a distinction between structure and function is imposed and not biologically well defined. This also implies that, similar to the univariate model, only observing one while ignoring the other will lead to a simplified representation of neurobiological mechanisms. While some authors have performed analysis of structure and function within a single sample, these analyses have also remained separate, only coming together in discussing how patterns show visual overlap. As we have recently shown, while much of the information between structure and function are shared, they also carry information unique to their own modality. With increasing sample sizes, we also increase our ability to link data together (for example through linked-ICA) to find patterns that cross the boundaries of these modalities and by doing so inform us on how these modalities line up in explaining variance in both imaging and behavioral data. Whether in the context of the depressed brain and ECT it is primarily structure or function driving the disorder and/or treatment response is not clear, and this distinction is likely to be both subject- and context-dependent. Integration of multimodal data is an important step from inference to directly showing how these both explain overlapping and distinct variation in behavior.

**TOWARDS TRANSLATIONAL PSYCHIATRY**

While the previous steps are supported by our own work and there are clear examples of how each could be performed, one additional point needs addressing. On the crossroads of clinical psychiatry and neuroimaging, it is common for each part of this equation to simplify the other in order to get a more straightforward (and sufficiently powered) answer. For example, neuroimaging typically compares groups or treatment effects by reducing psychiatric disorders to yes/no conditions, or in some cases as a scale on symptom severity. As any clinician will tell you, there is no sharp biological boundary between being depressed and non-depressed, and the line we use, while useful in communicating concepts, does little to inform us on biology itself.

With bigger samples and better data, we can start to move away from these strict clinical, dichotomization and dive into more complex and meaningful patterns that can pick up on behavior that actually translates to the patient. This shift from clinical labels in research is being highlighted in approaches such as the Research Domain Criteria that tries to link brain circuitry to more general transdiagnostic conceptualizations of brain function and dysfunction. Even in the cases where disorders are clear and well-defined disorders of specific circuits, a patient’s behavior and functioning are not just explained in terms of disorders, but also in their genetics, development, personality and current contexts (such as support systems). Each of these will affect their presentation and also their response to treatments, meaning it requires an additional step to not
only link the brain to psychiatric disorders, but also to incorporate behavioral patterns or phenotypes within such a model to be applicable in medicine. In our work we have shown how, in sufficiently large samples, we can use relatively straightforward methods such as temporal ICA to detect independent patterns in behavior that incorporate scores on many different dimensions and how these are reflected in the brain. For example, with regards to ECT this could mean a combination of clinical baseline parameters (genetics, personality type, depression type, symptom severity), which can be adjusted based on early intervention results (seizure thresholds, early signs of recovery). On the neuroimaging side of this issue, new ways of capturing individual variation (e.g. through functional gradients) or interpreting data as deviations from the population mean (e.g. through normative modelling) have potential in describing individuals instead of diagnostic labels to improve translatability of research findings.

To ultimately guide us towards clinical utility requires more than better imaging sequences and more elaborate methods. Instead, we should aim towards using the increases in power from better and more data to adapt our current simplified models of depression towards models that can capture the complexity inherent in human behavior and dysfunction. Furthermore, while our theoretical models help us understand depression and ECT, it is only meaningful for the patient if it adds to the current clinical workflow, i.e. it makes the clinician better at treating patients either through better treatment options available or through optimizing treatment for a specific individual. One thing that is lacking in translational psychiatry is an integrated approach; either we investigate the brain and link it to highly simplified representations of a diagnosis, or we stick to clinical research and treat patients as a black box; looking only at the relation between input and output and not what is in between. Importantly, bridging this gap requires an integrated approach to research that includes expertise from both the clinical and the research domains. Currently, in the search for straightforward answers, both sides undergo unique and valuable information and as such are only able to find partial solutions. The goal should be to strike a true balance between all information available: the patient, those close to them, the clinician, a medical workup and neuroimaging each offer their own meaningful properties. Uncovering how they integrate will ultimately help us in pushing psychiatry forward.

REFERENCES

Major depressive disorder is one of the leading causes of disability worldwide, and up to a third of patients will fail to respond to conventional pharmaco- or psychotherapy. Electroconvulsive therapy (ECT) is the single most potent treatment available for major depressive disorder, inducing remission even in those treatment-resistant patients. Although it has been used to treat patients for close to 80 years, little is known about its mechanism of action.

ECT affects both structure and function of the brain, and these effects can be found throughout the cortex and subcortical regions. In the cortical midline, it restores connectivity within the default mode network which is changed in the depressed brain. This network has consistently been implicated in the pathophysiology of depression and relates to rumination and memory impairment as seen in depression. Structurally, cortical volume increases in most areas of the brain after ECT, with a more pronounced increase in lateral and mediotemporal regions.

No single region or change adequately explain ECT’s clinical efficacy, but these effects are strongly related to the full pattern of changes. The most important regions within this model are those that are also affected in the depressed patient, most notably the medial prefrontal cortex (including anterior cingulate cortex), dorsolateral prefrontal cortex, the precuneus and the basal ganglia. We show how both structure and function change through ECT in these depression-related regions, and how we can use novel neuroimaging and statistical methods to further our understanding of ECT’s antidepressive properties.
De depressieve stoornis is een aandoening met een zeer grote impact wereldwijd. Een derde van de patiënten met een depressieve stoornis reageert niet of onvoldoende op de standaard behandelingen zoals psychotherapie of antidepressieve medicatie. Electroconvulsitherapie (ECT) is de meest effectieve behandeling voor depressieve stoornissen, en leidt tot herstel in het merendeel van de behandelingen, zelfs in deze therapie-resistente groep. Hoewel ECT al meer dan 80 jaar wordt toegepast is er nog weinig bekend over het mechanisme dat het sterke behandeleffect verklaart.

ECT heeft invloed op zowel de structuur als de functie van de hersenen, en deze effecten worden teruggevonden in zowel corticale als subcorticale structuren. In het mediale deel van de cortex herstelt ECT functionele connectiviteit binnen het "default mode" netwerk, dat is aangedaan in depressieve patiënten. Dit netwerk staat centraal binnen de rustfunctie van de hersenen, en is herhaaldelijk aangetoond als zijnde afwijkend en relevant in het ontstaan of onderhouden van depressieve klachten. Kijkend naar veranderingen in structuur zien we dat na ECT vrijwel alle corticale en subcorticale gebieden in volume zijn toegenomen, met een nadruk op gebieden in laterale gebieden en de temporaalkwab.

Er is geen gebied waarin structurele of functionele veranderingen een afdoende verklaring bieden voor het sterke klinische effect van ECT, echter zijn deze effecten wel te verklaren door naar de veranderingen als patroon te kijken, en de interactie tussen de verschillende veranderingen die optreden. Binnen dit patroon van veranderingen zijn met name de regio’s van belang die eerder zijn aangetoond als cruciaal in de context van de depressieve stoornis. Het sterkste zijn hierin de mediale prefrontale cortex (inclusief de anterieure cortex cinguli), de dorsolaterale prefrontale cortex, de precuneus en de basale ganglia. Wij tonen aan hoe structuur en functie veranderen na ECT in deze depressie-gerelateerde gebieden, en hoe we nieuwe beeldvormings- en analysetechnieken kunnen gebruiken om beter te begrijpen hoe ECT zijn effect sorteert.
LIST OF PUBLICATIONS

PUBLICATIONS


• Alberto Llera, Thomas Wolfers, Peter Mulders, Christian Beckmann. Inter-individual differences in human brain structure and morphometry link to variation in demographics and behavior. (eLife, 2019).

• Alberto Llera, Roselyne Chauvin, Peter Mulders, Christian Beckmann. Spatial Patterns for Discriminative Estimation (SPDE) of functional MRI Connectomes (submitted).


• Robbert Duvivier, Carmen van Geel, Peter Mulders, Eveline Ackermans, Kwaliteit.
LIST OF PUBLICATIONS


• Daphne Everaerd, Marloes Henckens et al. Good vibrations: An observational study of real-life stress induced by a stage performance. Psychoneuroendocrinology 2020; April; 114 [104593].

BOOK CHAPTERS


OTHER SCIENTIFIC ACTIVITIES

• Team Lowlands Science 2017, “Lowlands got Talent”.
• Scientific posters at conferences of Biological Psychiatry 2015 (Toronto), NVvP spring conference 2016, Organization for Human Brain Mapping 2016 (Geneve).
• Workshop “Neuroimaging voor psychiaters” (“Neuroimaging for psychiatrists”) at the NVvP spring conference in 2017 and 2018.
• Presentations at the WEN-conference 2015 (Werkgroep ECT-Nederland, Arnhem) and Organization for Human Brain Mapping 2018 (Singapore).
Peter Mulders was born on June 15th 1987 in Oss, The Netherlands. He grew up with his parents and his sister Anne, and graduated from gymnasium at the Titus Brandsma Lyceum in 2005. Afterwards, he studied biomedical sciences at Radboud University for a year before switching to medicine, which he completed in 2012. During his medicine studies, he worked as a steward for the emergency department. After working as a M.D. at the department of psychiatry, in 2012 he started his medical specialty training in psychiatry at the Radboud University Medical Center under prof. Indira Tendolkar. During this training he has worked in a variety of psychiatric institutions, amongst which psychosis care (Pro Persona), acute psychiatry (Pro Persona) and an eating disorders clinic (Amarum, GGNet).

During his medicine studies Peter started his research work in psychiatry on narcolepsy and addiction, and in 2011 shifted his focus to neuromodulation and electroconvulsive therapy. Together with Indira Tendolkar, Philip van Eijndhoven and Christian Beckmann, he applied for a PhD program to focus on neural mechanisms underlying ECT. During his PhD he has been involved in other neuromodulation research (mainly repetitive transcranial magnetic stimulation) and methods development. Next to his research interests, during his medical specialty training he has been engaged in policy through the national association of psychiatry residents (subvereniging assistenten psychiatrie), of which he was a board member for 2.5 years.

Peter is married to Karin Mulders-Manders, and they have a son Tijn (2017).
During the PhD-track, several courses, conferences and workshops were attended.

**COURSES**
- FMRIB Software Library (FSL) Course, Oxford, April 2014
- Advanced Maths (Master Course, Radboud University), 2017
- Grant Writing and presenting for funding committees (Master Course, Radboud University), 2019
- ‘Leergang 3.0’, one year-course on medical leadership, 2019
- Courses as part of the psychiatrist training programme (including specific course psychopharmacology, liaison psychiatry, policy, neuropsychiatry), weekly from 2012-2020

**CONFERENCES**
- Biological psychiatry 2015 (Toronto)
- Organization for Human Brain Mapping 2016 (Geneva)
- Organization for Human Brain Mapping 2018 (Singapore)
- Organization for Human Brain Mapping 2019 (Rome)
- Spring conference for the Dutch Psychiatric Association 2012-2018
DATA MANAGEMENT

Work in this thesis was performed with three different datasets. All human studies were approved by ethical boards, when applicable, and conducted in accordance with the principles of the declaration of Helsinki.

The work in chapter 4 was done on data from the Human Connectome Project (HCP). The HCP is an international collaboration aimed at uncovering the human connectome. It collects data from healthy adults and their siblings (including twins). It is a multisite effort that collects high quality data using both structural and functional MRI in addition to extensive demographics and a task battery. The HCP is sponsored by the National Institute of Health (NIH). Data is freely accessible after acceptance of the HCP Open Access Data Use Terms through the website of the HCP (www.humanconnectome.org). A local copy of the HCP data is stored at a secure server in the Donders Center for Cognitive Neuroimaging (DCCN). This information has no identifiable information available.

The work in chapters 5 and 6 was done using data collected from patients undergoing ECT at the Radboud University Medical Center. All patients provided written informed consent and the study protocol was approved by the review board of the Radboud University Medical Center. Data was de-identified in the hospital, and only the anonymous treatment parameters relevant to the study (age, sex, medication status, depression scores) were transferred to the imaging site (the Donders Center for Cognitive Neuroimaging) for analysis. Imaging data was collected at the DCCN and stored on a server only accessible to the researchers on the project (P. van Eijndhoven and P. Mulders).

The work in chapter 7 was supported by data from the Global ECT-MRI Collaboration (GEMRIC). GEMRIC is an international collaboration of centers engaged in research into electroconvulsive therapy. Data used in this study is collected at 10 different GEMRIC sites. All sites need to have approval from their local ethical committees in order to be able to take part in GEMRIC. GEMRIC itself was approved by the Regional Ethic Committee Sout-East in Norway. In GEMRIC, data is de-identified locally, before it is uploaded to a secure server that is situated at the University of Bergen, Norway. Due to site-specific institutional review boards, data can only be accessed by approved GEMRIC collaborators, although open data sharing is a future goal. Data cannot be exported from the Data Portal, and all analyses are performed on the server through a secured connection.

All analysis, results and code used in these works is available upon request.
ACKNOWLEDGEMENTS

As is true for any PhD thesis this book is not the product of an individual but rather the combined effort of many; both on a professional and a personal level. I immensely enjoyed my time and the company of everyone I have met during my PhD training.

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Philip, you have been a mentor to me from very early on while doing my senior-internships at the department. Throughout the years we have worked together on many projects and it seems only fitting you are a part of the finalization of both my academic and medical training. I have great respect for all the work you do and who you are as a person, and look forward to working with you for many years to come. Indira, I (and others with me) consider you the “mother” of our department, taking care of all the trainees and being involved and interested in both their professional growth but also who they are as a person. I was one of many to greatly benefit from your vision and motivation and all this would not have been possible without you. Christian, thank you for all your guidance in the field. I think we worked great as a team and share a similar sense of humor. I remember asking you when we just met, just coming from the medical field, what times I was expected at work and you answering that you didn’t care as long as the work gets done. Throughout the years you have stood by this and given me complete freedom to do what I wanted in my PhD, while always being available when we needed to tackle something together.

Then to all my friends and colleagues. There is never enough room to name everyone, but at least several of you deserve special mentioning. The original office mates: Wei, Daniel and Thomas. At this point we are scattered around the world but the first few years of sharing the office was a very inspirational time and I remember it fondly. Alberto, for being a friend and always bringing great enthusiasm and excitement in every finding we do. Dori, for all the dori- and pectorino’s, sporting and just chatting. Roselyne, for being an overall amazing person and confidant. Iza, for being joyful and dependable. Jill for your great sense of humor and lots of great memories. Of course, there are many others and other groups who made this into a great experience: other members of the SIN group (and collaborators), staff, residents, nurses and fellow researchers from the department of psychiatry, GEMRIC, “Gebakken Lucht”, and clubsubzero to name a few; as well as all my other great friends and colleagues. Fortunately, I will be working and seeing most of you for years to come.
I would also like to thank my family; moms, dads, sisters, brothers and sisters- and brothers-in-law, my nephews and niece, for always being supportive, caring and/or a joy to be around.

Finally, Karin. I cannot imagine a life without you and you always know how to motivate me to do and be better. Together with Tijn our family feels complete, and having such a happy life at home makes me feel like I could take on anything the world might throw at me. Thank you for always being there.