CHAPTER 1

A general introduction to the thesis
INTRODUCTION

Mrs. B was 53 years old when she was first diagnosed with a severe depressive disorder. Her husband was diagnosed with a serious medical condition having substantial impact on their lives. After a year Mrs. B was admitted to a psychiatric clinic. Her appetite disappeared and she had substantial weight loss. She was treated with antidepressant medication, to no avail. Instead, Mrs. B. developed a comorbid anxiety disorder. Due to worsening of her symptoms, Mrs. B. was transferred to a different clinic where she stayed for nearly two years. Here, Mrs. B. was treated with other antidepressant medication, but again, without achieving remission. It was only a month after her discharge from the clinic that she tried to commit suicide. Luckily, as she claims now, her attempt did not succeed. However, as Mrs. B. was still combatting a deep and severe depression, she lost the hope of recovery and decided to opt for euthanasia. In the process leading up to a possible euthanasia, Mrs. B received a second opinion from another psychiatrist. The psychiatrist concluded that yet another antidepressant was not likely to alleviate her severe depression and suggested electroconvulsive therapy (ECT) as a next, and possibly last, step. Mrs. B. agreed with this suggestion and received a total of 21 ECT sessions. After the third session her family claimed to see some improvements, and Mrs. B. herself noticed a significant change after the eighth session. After 21 sessions, her depression was fully remitted and all medication was slowly tapered off in the years following ECT. Mrs. B. now claims that ECT was a life-saving treatment for her, and she jokingly remarks that her children wonder whether 21 sessions were a few too many “because I smile more often than I used to”.

The case presented above is not an exaggeration of how deep a depression can sometimes be, nor is it a claim of a “miracle therapy” called electroconvulsive therapy (ECT). Although the case of Mrs. B. illustrates how ECT can be a viable treatment option in such cases, it also shows how for some, a depression can be a bleak time without any hope of recovery. Note that, while Mrs. B. is now medication free, the majority of ECT patients continue to need medication after ECT to prevent relapse.

The treatment of a depressive disorder usually consists of psychotherapy, pharmacotherapy or a combination of the two (Malhi & Mann, 2018; Otte et al., 2016; Spijker et al., 2013). While being effective for a considerable group of patients, a minority will not respond (as was the case for Mrs. B.). If remission does not occur, several treatment options have been tried, and pharmacotherapeutic steps (see below) have been taken, electroconvulsive therapy (ECT) can be considered as a next step (Broek, Birkenhäger, Boer, & Burggraaf, 2010). In some cases, for example in patients with severe suicidality or extreme weight loss, ECT can be an option before all pharmacotherapeutic steps are taken. ECT is one of the most effective treatments for severe and refractory major depression (Husain et al., 2004; Kellner et al., 2015; Pagnin, de Queiroz, Pini, & Cassano, 2004; UK ECT Review Group, 2003), yet its exact
working mechanism remains unclear. Uncovering its mechanism, and thereby creating a better understanding of ECT (and its side-effects), could increase refined usage of this treatment, and may even contribute to the development of new treatment strategies with similar efficacy.

This thesis therefore aims to shed light on the neural mechanism of ECT by studying the brains of depressed patients undergoing this treatment. It primarily focuses on brain structure in order to investigate whether neurogenic and neuroplastic effects found in rodent studies would translate to humans receiving ECT. Magnetic resonance images (MRI) were acquired at ultra-high field (7 tesla) in order to image the brain at a high resolution. In addition, clinical data was collected to investigate whether changes in brain structure would coincide with the antidepressant effect. Furthermore, cognitive data was collected to quantify the side effects of ECT.

To appreciate the effects of ECT in depressed patients, a general understanding of the disorder, the most common treatments of the disorder, as well as ECT itself is helpful. After providing a brief theoretical background to these topics, the outline of the thesis, the methods and the main aims of each individual study will be presented.

DEPRESSION

The World Health Organization views depression as one of the world’s leading causes of years lived with disability (Whiteford et al., 2013). The disorder is highly prevalent [affecting about one in five people at some point in their lifetime (de Graaf, ten Have, van Gool, & van Dorselaer, 2012)] and imposes substantial burden on patients, their close relatives, their social network and society.

Depression is a collective term for different types of depressive mood disorders, such as major depressive disorder (see below) and persistent depressive disorder (previously dysthymia; a long-term, at least for 2 years, form of depression). Another prevalent type of mood disorder, and relevant to ECT, is bipolar disorder (distinguishing from major depressive disorder by an alternating pattern of manic and hypomanic/depressive episodes).

The most prevalent of these and the one central to this thesis, is major depressive disorder (MDD) (de Graaf et al., 2012). MDD is usually characterized by a (combination of) depressed mood and/or anhedonia (loss of the ability to enjoy pleasurable activities), combined with neurovegetative, neurocognitive symptoms, and emotional symptoms such as feelings of worthlessness or guilt and suicidal ideation (Malhi & Mann, 2018; Otte et al., 2016). See Fig. 1 for an overview of the clusters of depressive symptoms in major depressive disorder.

PATHOGENESIS

Many theories on the pathogenesis of depression have been proposed. These theories range from psychological to environmental to biological explanations of the disorder (Otte et al., 2016). To date, no single unified theory on depression has been accepted, and it seems reasonable that a complex interplay of psychological, environmental and biological factors
In recent years, the neurogenic hypothesis of depression attracted considerable attention (Eisch & Petrik, 2012; Jacobs, van Praag, & Gage, 2000; Miller & Hen, 2015). This hypothesis states that decreased neurogenesis (the process of generating new neurons) in the dentate gyrus (DG) of the hippocampus (a laminar structure in the brain, see below and Fig. 2) leads to a depressive state, and that restoring neurogenesis would lead to remission of the depression (Anacker & Hen, 2017; Jacobs et al., 2000). Whether or not the neurogenic hypothesis holds, remains an unresolved research question. Specifically, it remains unclear if decreased neurogenesis is sufficient (and required) for causing a depressive disorder, and if restoring neurogenesis is required (and sufficient) for countering the depression. As for now, it seems more plausible that (a combination of) many factors contribute to the pathogenesis and continuation of depression (Otte et al., 2016). Most authors consider depression not to have a single underlying cellular mechanism, but largely agree that different subtypes may have different underlying mechanisms (Beijers, Wardenaar, van Loo, & Schoevers, 2019).

**Fig 1. Clustered symptoms of depression**

At the top of the figure, the two main symptoms are depicted: 1) depressed mood and 2) anhedonia. From left to right, three clusters of symptoms are presented. First, the neurovegetative symptoms: 1) in- or hypersomnia, 2) changes in weight/appetite and 3) fatigue or loss of energy. Then, neurocognitive symptoms: 1) psychomotor retardation, or agitation and 2) indecisiveness or trouble to concentrate or think. And in the last rectangle the emotional symptoms: 1) suicidal ideation, plan or attempt and 2) feelings of worthlessness or excessive guilt.

Contributes to the disease.
INTRODUCTION

TREATMENT

Just as there are likely many factors contributing to depression, there are many types of treatment which all seem to be, to some extent, effective (Otte et al., 2016). The most common types of treatment are psychotherapy, pharmacotherapy, or a combination of these two. In the Netherlands, depression is usually treated via a stepped-care model (Spijker et al., 2013). In this model, a patient presenting with depressive symptoms for the first time is offered psychoeducation, ways to (self)care, and light counseling or psychosocial interventions. When the symptoms worsen, or when/if the patient presents with a full-blown depressive disorder, psychotherapy (e.g. cognitive behavior therapy) or pharmacotherapy (e.g. a selective serotonin reuptake inhibitor), or a combination of these two is offered. If remission is not achieved multiple pharmacotherapeutic steps (see below) need to be taken before ECT will be considered.

The most common and well-studied form of psychotherapy is cognitive behavior therapy (CBT). This form of therapy proposes that psychopathology originates and perpetuates due to erroneous cognitions (e.g. “Everyone thinks I’m a loser”) and harmful (or non-helpful) behaviors such as avoidance of pleasurable activities. Accordingly, CBT focuses on changing these thoughts and behaviors in order to treat the disorder at hand. For depression, CBT is effective and seems to have favorable long-term outcomes (Butler, Chapman, Forman, & Beck, 2006; Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012; Wiles et al., 2016). However, whether CBT is more effective than other forms of psychotherapy such as interpersonal therapy (or newer forms of therapy such as acceptance and commitment therapy, and mindfulness based cognitive therapy), remains unclear (Cuijpers, Karyotaki, Reijnders, & Ebert, 2019; Cuijpers et al., 2014; Khan, Faucett, Lichtenberg, Kirsch, & Brown, 2012a; Munder et al., 2019).

Pharmacotherapy can be grouped into different classes of psychotropic drugs where selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) are the first step in the protocol. SSRIs have a slight preference over TCAs because of a more favorable side effect profile. A serotonin norepinephrine reuptake inhibitor (SNRI) can also be used. If response is not achieved, TCA is the next step and in a following step, lithium can be used as an additive. Without response to lithium addition, monoamine oxidase inhibitors (MAOIs) are considered. Pharmacotherapy is effective, yet can produce significant side effects (Otte et al., 2016). All of the traditional drugs for depression except for lithium act on the monoamine system. Newer drugs, on the other hand, that are currently being investigated act on other systems as well. Ketamine, for example, a N-methyl-D-aspartate (NMDA) receptor antagonist, is a drug that primarily targets the glutamate system in the brain and has been proven to be effective in treating depression (aan het Rot et al., 2010; Browne & Lucki, 2013; Zarate et al., 2006).

Psychotherapy and pharmacotherapy seem to be equally effective, and a combination of these two treatments seems to be slightly more effective than either of the treatments alone (Khan, Faucett, Lichtenberg, Kirsch, & Brown, 2012b). However, if the disorder worsens or relapses and all the pharmacotherapeutic options have been taken, ECT is offered.
ELECTROCONVULSIVE THERAPY

DEVELOPMENT

Electroconvulsive therapy, the process of inducing convulsions and brain activity resembling an epileptic seizure to treat psychiatric disorders, is an old practice (Payne & Prudic, 2009a). The idea of generating convulsions dates back to the 16th century when camphor (an oily substance extracted from camphor trees) was used to induce convulsions and treat “lunacy”. The treatment gained momentum in 1930s, as camphor was replaced by Cardiazol and cases of schizophrenia were successfully treated. As Cardiazol produced unpleasant side effects, direct electrical stimulation was tested as an alternative. In 1938, the Italian scientist Cerletti and his group successfully adapted the procedure of applying direct electrical stimulation to the scalps of dogs to that of humans, and treated a man with schizophrenia, observing significant improvements after 9 sessions (Accornero, 1988). And thus, ECT was born.

In the years after its discovery ECT grew in popularity, resulting in ECT being used for a multitude of indications. In these days, ECT was applied without anesthesia or muscle relaxation, making it a risky and painful intervention. However, during the period from 1950-1970 the use of ECT declined, mainly due to the discovery of psychotropic medicine (Payne & Prudic, 2009b). After disappointing results from the initially optimistic clinical trials with psychotropic drugs, ECT use began to increase again from the 1970s and onwards. Although this time, ECT was given under full anesthesia and with a muscle relaxant, it became heavily criticized and stigmatized, thus further hampering the development of ECT.

Both in the past and in the present, ECT has a bad image among the general public, including patients. The, sometimes warranted critique, stemmed from the early days of ECT when the treatment was used without muscle relaxants and/or anesthesia, without informed consent, and/or without diagnosis or indication (Payne & Prudic, 2009a). These early accounts fueled anti-ECT lobbying and together with unpleasant media depictions (e.g. in popular movies) the stigma around ECT grew.

Currently, ECT is administered (usually) twice a week under full anesthesia with muscle relaxants. The team administering ECT consists of (multiple) nurses, a psychiatrist and an anesthesiologist. It can be given bilaterally (i.e. electrodes on both sides of the head) or unilaterally (electrodes on one side). The majority of ECTs are given to treat major depressive disorder. Other indications for ECT include, but are not limited to, a depression with psychotic symptoms, bipolar depression, schizophrenia (when antipsychotics do not achieve the desired response) and patients in a catatonic state (Broek et al., 2010). ECT is associated with high effect sizes in major depression and is generally considered safe (Husain et al., 2004; Kellner et al., 2015; Pagnin et al., 2004; Tørring, Sanghani, Petrides, Kellner, & Østergaard, 2017; UK ECT Review Group, 2003). Unfortunately, ECT also causes significant short-lasting cognitive side effects and memory impairment (Prudic, Peyser, & Sackeim, 2000; Semkovska & McLoughlin, 2010). In addition, the procedure is onerous for
INTRODUCTION

To date, the mechanism of action of ECT remains undiscovered, although substantial progress has been made (see below). In addition, the exact causes of the side effects also remain unclear. This is unfortunate, since ECT is an important and effective treatment option for severe depression. Elucidating its mechanism of action, as well as the causes of its potential side effects, may reduce stigma due to misinformation. Moreover, it may lead to new and improved treatment strategies that are similarly effective but lack the side-effects of ECT.

STRUCTURAL BRAIN CHANGES

A potentially powerful way of uncovering ECT’s mechanism of action for people combating severe depression is by studying the brains of people undergoing ECT. In the past decennia, in vivo investigation of the brain has become possible with the use of magnetic resonance imaging (MRI). Using MRI, it has become clear that ECT does not induce brain damage (such as atrophy or cell necrosis) reflected in volume decreases and focal brain abnormalities. On the contrary, increases in volume of nearly all human brain structures have been observed (Gbyl & Videbech, 2018; Ousdal et al., 2020). Of particular interest is the systematically replicated result of strong volumetric increases in the hippocampus (Takamiya et al., 2018; Wilkinson, 2013). The hippocampus is a laminar structure within the brain and traditionally viewed as one of the core regions in the brain important for memory formation and consolidation. The different layers of the hippocampus have different functions and form a complex network of connections. The structure comprises the Cornu Ammonis (CA) and the DG (Duvernoy, Catrin, & Risold, 2013). The DG is folded within the CA and they both follow the characteristic hippocampal (sea horse) shape, see 3D render at the left. The dashed black line indicates the location of the coronal section of the hippocampus on the right. The CA region is further split up into three (sometimes four) distinct regions, each having its own structural and functional characteristics (Duvernoy et al., 2013; Schultz & Engelhardt, 2014). The hippocampus is accompanied by the subiculum (extending the CA1 region, altogether forming the hippocampal formation) and the entorhinal cortex (ERC), adjacent to the subiculum.
Sanacora, & Bloch, 2017). The hippocampus consists of multiple layers with different functional and structural characteristics (see Fig. 2). One of the hippocampal substructures is the dentate gyrus (DG), the only subfield of the hippocampus capable of neurogenesis. Therefore, an important question is whether these volumetric changes are limited to the DG (reflecting neurogenesis) or take place in the entire hippocampus (reflecting other processes such as angiogenesis, synaptogenesis, axonal sprouting, dendritic branching, or even edema). Accurately and reliably assessing hippocampal subfields, however, is challenging since the structure is small and has low contrast on T1-weighted scans obtained with conventional clinical MRI scanners operating at 3 tesla magnetic field strength (Yushkevich et al., 2010). Ultra-high field MRI (7 tesla) may overcome this limitation and was therefore used in this thesis.

**METHOD, AIMS AND OUTLINE**

This thesis aims to shed light on the effects of electroconvulsive therapy on cognition, depression and changes in the structure of the human brain. It has the underlying goal of creating a better understanding of ECT in general. To achieve this goal, the studies presented in this thesis follow a clear and simple design: patients were assessed clinically and cognitively at baseline (i.e. pre-ECT) and were scanned with ultra-high field MRI (7T). Then, bilateral ECT (stimulus intensity of 150% of the titrated seizure threshold, with a minimum seizure duration of 20 seconds) was given for five consecutive weeks, amounting to 10 ECT sessions. Afterwards (i.e. post-ECT), patients were assessed with the same clinical and cognitive test battery, and received an MRI scan. Six months after the tenth ECT session patients were assessed again clinically and with the same cognitive test battery. The controls were assessed cognitively and scanned with MRI twice: at baseline and after 5 weeks.

To shed light on the effects of ECT on cognition, the second chapter presents a study on the immediate (short-term) and long-term effects of bilateral ECT on cognition. Chapters three to six present the results of studies focusing on the effects of ECT on the brain and its relation to clinical measures.

Below, the aims of chapters two to six are briefly described.

**Chapter two: Immediate and long-term effects of bilateral electroconvulsive therapy on cognitive functioning in patients with a depressive disorder**

The effects of ECT on cognition have long been recognized as one of the most troubling side effects. It has been suggested that bilateral ECT has more long-term side effects compared to unilateral ECT. However, case-controlled studies on the long-term effects of bilateral ECT on cognition are scarce. This chapter presents findings from a study aiming to elucidate the short and long effects of bilateral ECT on cognition.
Chapter three: Volume increase in the dentate gyrus after electroconvulsive therapy in depressed patients as measured with 7T

Volumetric increases of the hippocampus are a robust finding in neuroimaging research in ECT. Whether these increases are due to neurogenesis, neuroplasticity in general (neurogenesis plus angiogenesis, synaptogenesis, dendritic branching etc.) or edema remains undecided. Accurate delineation of the hippocampal subfields may discriminate between neurogenic effects (limited to the dentate gyrus of the hippocampus) and neuroplastic effects or edema (reflecting more widespread changes in the entire hippocampus). This study sets out to investigate hippocampal subfields before and after ECT.

Chapter four: a collection of letters

Whether or not the findings presented in chapter three will hold in conventional 3 tesla MRI studies, and will be generalizable to other psychiatric disorders remains a subject of debate. In this chapter two letters will be presented discussing these topics.

Chapter five: Vasogenic edema versus neuroplasticity as neural correlates of hippocampal volume increase following electroconvulsive therapy

Although volumetric measurements of hippocampal subfields could reflect neuroplasticity, ruling out edema remains challenging. Furthermore, whether angiogenesis (formation of new blood vessels) occurs after ECT also remains unknown. Diffusion weighted imaging (DWI) measures the restriction of water molecules in the brain due to, for example, cells, axons and synapses. Intravoxel incoherent motion (IVIM) analysis and arterial spin labelling (ASL) are ways to study perfusion characteristics of the hippocampus. This study investigates whether ECT may cause edema (using DWI) and/or angiogenesis (using IVIM/ASL) in the hippocampus.

Chapter six: Shape and volume changes of the lateral ventricle after electroconvulsive therapy

Since bilateral ECT may have strong neurogenic effects, neurogenesis might not only be present in the dentate gyrus of the hippocampus, but also in the other neurogenic region of the brain: the subventricular zone. This study investigates whether the shape of the ventricles changes at the subventricular regions possibly reflecting neurogenesis.

Finally, Chapter seven summarizes chapters two to six and puts the results in the context of relevant literature and the overarching goal exploring the mechanism of ECT.
REFERENCES


INTRODUCTION


