Electrically induced neuroplasticity

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ELECTRICALLY INDUCED NEUROPLASTICITY

Exploring the effects of electroconvulsive therapy for depression using high field MRI

Jasper Olivier Nuninga

Colofon

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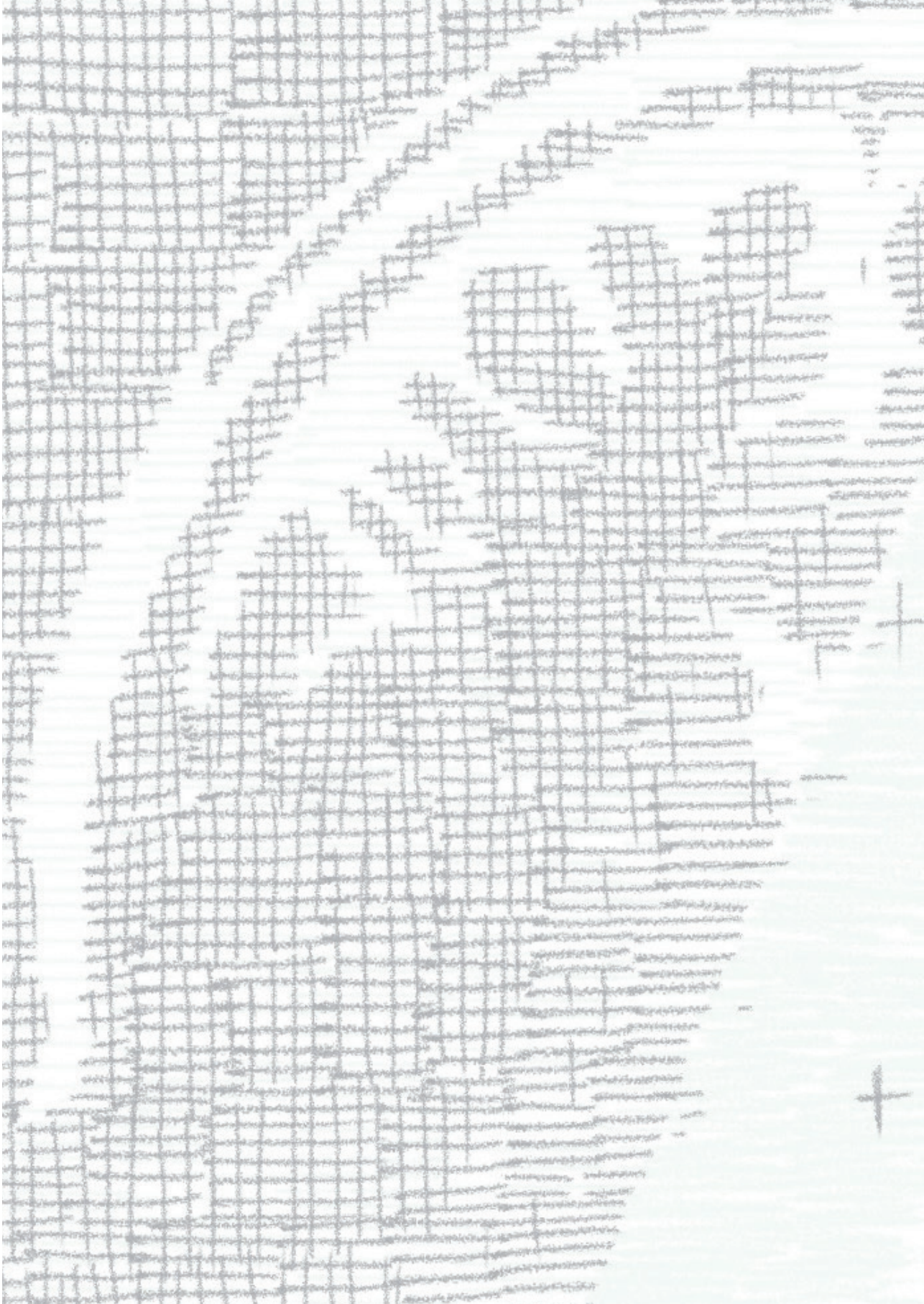

CHAPTER 1

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 Dorsselaer, 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

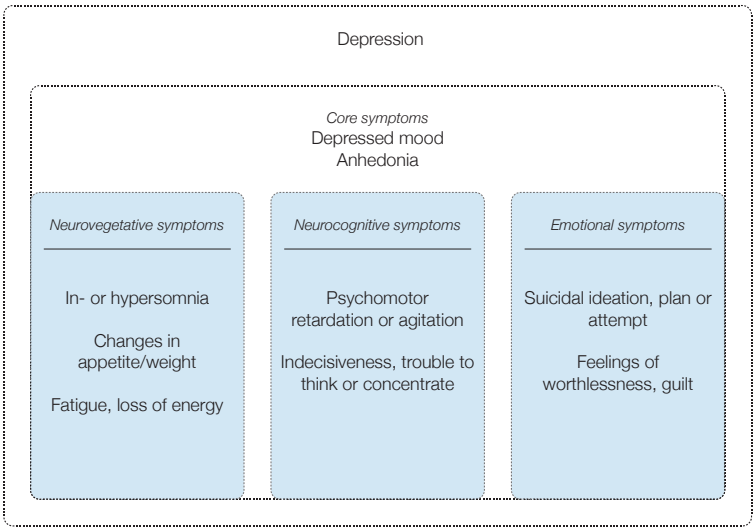

Fig 1. Clustered symptoms of depression
At the top of the figure, the two main symptoms are depicted: 1) depressed mood and 2) anhedonia. From left to right, three clusters of symptoms are presented. First, the neurovegetative symptoms: 1) in- or hypersomnia, 2) changes in weight/appetite and 3) fatigue 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.

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). The hypothesis originated from the observation that patients with depression have smaller hippocampi, decreased neurogenesis in rodents stimulates depressive behavior, and that antidepressants restore neurogenesis in animals (Anacker & Hen, 2017; Jacobs et al., 2000; Kempton et al., 2011; Malberg, Eisch, Nestler, & Duman, 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 counteracting 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).

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 depresive 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

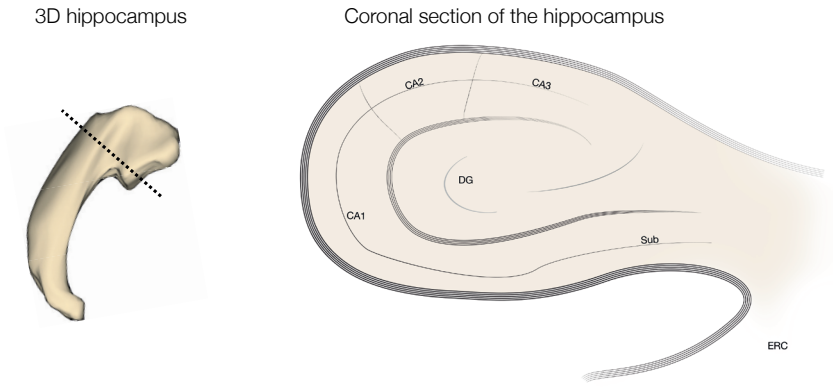

Fig. 2. The hippocampus is a laminar structure within the brain and traditionally viewed as one of the core regions in the brain important for memory formation and consolidation. The different layers of the hippocampus have different functions and form a complex network of connections. The structure comprises the Cornu Ammonis (CA) and the DG (Duvernoy, Cattin, & 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.

patients, limiting its use.

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 ECTs mechanism of action for people combatting 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,

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.

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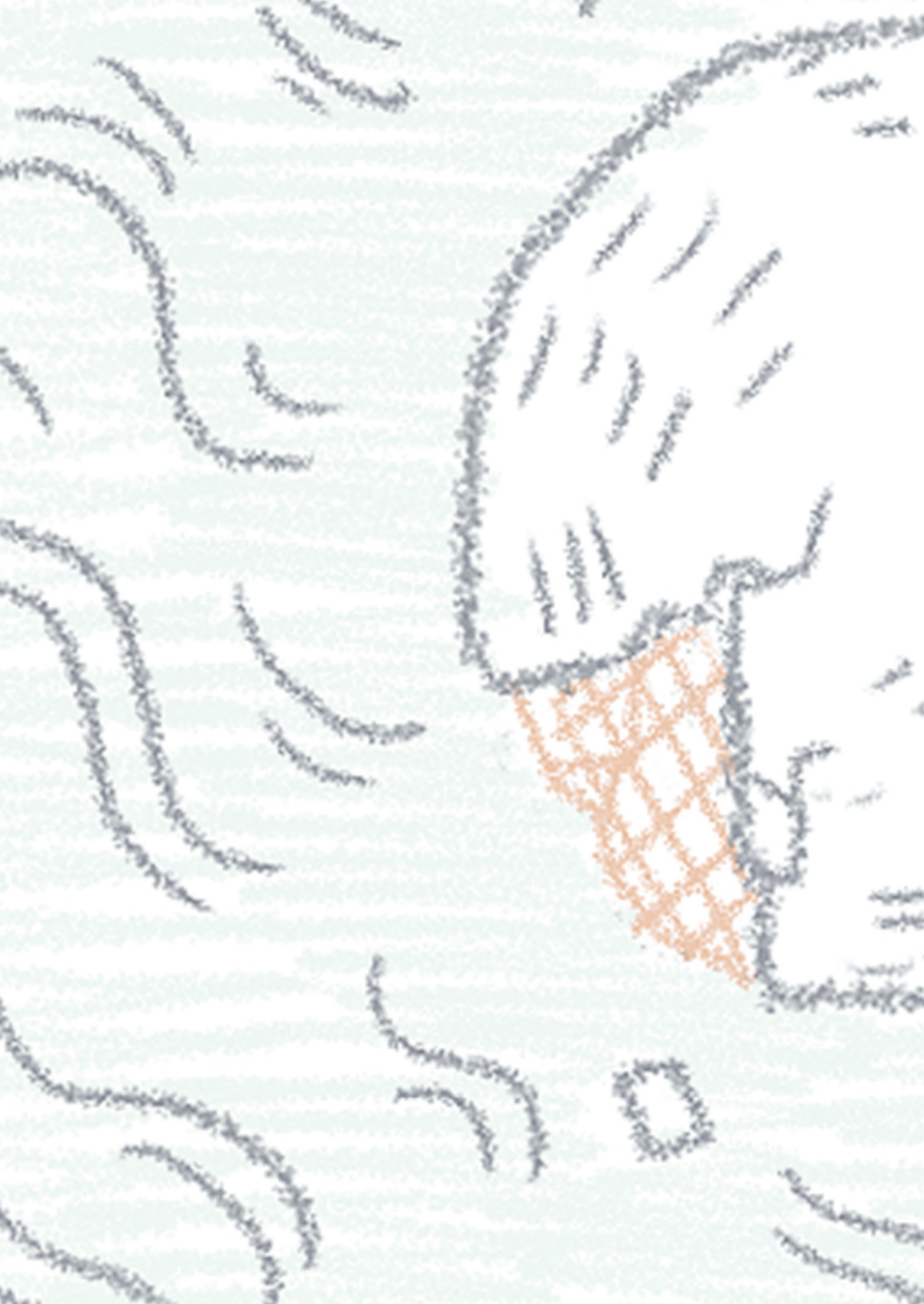

CHAPTER 2

Immediate and long-term effects of bilateral electro-convulsive therapy on cognitive functioning in patients with a depressive disorder

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ABSTRACT

Background: Electroconvulsive therapy (ECT) is the most effective treatment for patients suffering from major depression. However, its use is limited due to concerns about negative effects on cognition. Unilateral ECT is associated with transient cognitive side-effects, while case-controlled studies investigating the effect of bilateral ECT on cognition remain scarce. We investigate the effects of bilateral ECT on cognition in depression in a longitudinal case-controlled study. We hypothesize that adverse cognitive effects of bilateral ECT are transient rather than long-term.

Methods: A total of 48 depressed patients and 19 controls were included in the study and assessed with a battery of cognitive tests, including tests of: working memory, verbal fluency, visuospatial abilities, verbal/visual memory and learning, processing speed, inhibition, attention and task-switching, and premorbid IQ. Patients underwent three cognitive assessments: at baseline (n = 43), after ten ECT sessions (post-treatment; n = 39) and six months after the tenth ECT session (follow-up; n = 25). Healthy controls underwent the same cognitive assessment at baseline and after five-weeks.

Results: Within the patient group, transient adverse cognitive side-effects were observed for verbal memory and learning, and verbal fuency. None of the cognitive domains tested in this study showed persisting impairments.

Limitations: A relatively high attrition rate is observed and autobiographical memory was not assessed.

Conclusion: This study shows that bilateral ECT has negative cognitive effects on short-term. These effects could be explained by a decrease in cognitive performance, a lack of learning effects or a combination. However, the decrease in cognitive functioning appears to recover after six months.

INTRODUCTION

To date, electroconvulsive therapy (ECT) is the most effective therapy for patients suffering from a depressive disorder (Dierckx, Heijnen, van den Broek, & Birkenhäger, 2012; Kho, van Vreeswijk, Simpson, & Zwinderman, 2003; UK ECT Review Group, 2003). Next to its efficacy in reducing symptoms of depression, it has been shown that ECT is safe (Tørring, Sanghani, Petrides, Kellner, & Østergaard, 2017; UK ECT Review Group, 2003).

Despite the fact that treatment with ECT is safe and effcacious, its use in clinical practice is limited. It has been proposed that the presence of possible adverse effects on cognition resulting from treatment with ECT might negatively influence a patient's perception of ECT (Brown, Nowlin, Sartorelli, Smith, & Johnson, 2018; Calev, Gaudino, Squires, Zervas, & Fink, 1995; Case et al., 2013; Payne & Prudic, 2009; Semkovska & McLoughlin, 2010). Early studies reported that ECT causes irreversible cognitive side-effects (Squire, Slater, & Chace, 1975), although more recent studies show that cognitive side effects may be transient (Ingram, Saling, & Schweitzer, 2008; Semkovska & McLoughlin, 2010; Vasavada et al., 2017). The severity of cognitive adverse side effects seems to be affected by the number and frequency of treatment sessions, stimulus intensity and waveform (Ingram et al., 2008; Kellner et al., 2010; Sackeim et al., 2000, 1993, 2008; Tor et al., 2015), although the precise neurobiological mechanisms underlying adverse cognitive effects of ECT remain unclear (Nobler & Sackeim, 2008). Additionally, it has been reported that bilateral ECT produces more pronounced cognitive side effects compared to unilateral ECT while the therapeutic effect of both forms of ECT is comparable (Kolshus, Jelovac, & McLoughlin, 2017; Semkovska et al., 2016).

To date, case-controlled studies on the immediate and long-term effects of bilateral ECT on cognition are limited (Kessler et al., 2014; Semkovska & McLoughlin, 2010). Recently, a study investigated the short- and long-term effects of right unilateral (RUL; 61%) and mixed unilateral/bilateral (39%) ECT for depression on cognition (Vasavada et al., 2017). None of the patients exclusively received bilateral ECT. Therefore, in an effort to provide additional research into the short- and long-term effects of bilateral ECT on cognition, we conducted a longitudinal study assessing pre-treatment cognitive functioning, post-treatment cognitive functioning, including a 6-month follow up and a control group. With this study design, not only increases or decreases of cognitive functioning in patients receiving ECT treatment can be examined, but also the learning effect can be reviewed, by comparing patients to controls. We hypothesized that ECT will have negative short-term effects on cognition and that these negative cognitive effects will recover at 6-month follow-up.

MATERIALS AND METHODS

SAMPLE

Patients were recruited at the department of psychiatry in the University Medical Center (UMC) Utrecht, a tertiary hospital in the Netherlands. Inclusion criteria for patients were an

age over 18 years, a diagnosis of unipolar or bipolar depression [as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*, 2000] and an indication for ECT treatment [according to the Dutch Guidelines on Electroconvulsive Therapy (Broek, Birkenhäger, Boer, & Burggraaf, 2010)]. All patients voluntarily opted for bilateral ECT treatment. Healthy controls were included on the basis of demographic characteristics (age, gender and years of education) of the patient sample, in order to obtain a matched control sample. Exclusion criteria for both patients and controls were brain pathology, history of strokes, pregnancy and/or lactation, or any major medical condition (e.g. coronary heart disease, chronic obstructive pulmonary disease, diabetes). An exclusion criterion for patients was treatment with ECT in the preceding 6 months. An additional exclusion criterion for controls was any psychiatric illness [assessed using the MINI interview, Dutch translation (Sheehan et al., 1998; van Vliet & de Beurs, 2007)]. All participants provided written informed consent and the study was reviewed and approved by a local research ethics board (Medical Ethical Board of the UMC Utrecht).

Forty-eight patients met the inclusion/exclusion criteria and provided written informed consent. Five patients decided not participate in the examination at baseline and were excluded from the analysis. Four patients were lost to follow-up between baseline and the post-treatment measurements. Between the post-treatment and follow-up measurements, 14 more patients were lost to follow-up. As a result, a total of 25 patients completed all three measurements. Nineteen healthy individuals were included in the control group.

ECT PROCEDURE

Electroconvulsive therapy (using a Thymatron IV ECT machine, 900 mA current, bifronto-temporal electrode, stimulus intensity 150% of empirically calibrated seizure threshold), was given twice a week, for five consecutive weeks. To be included in the analysis at post-treatment and follow-up, patients needed to complete 10 ECT sessions. This was to ensure that all patients compared at post-treatment would have received the same amount of ECT-sessions. As a result, in some patients, the duration of treatment was longer than five weeks. Patients

Table 1. Tests and abbreviations used in this study.

Test	Abbreviation	Versions[a]	Reference
Rey Complex Figure Test	RCF	1	Meyers & Meyers, (1995)
Dutch Rey Auditory Verbal Learning Test	D–RAVLT	2	Van der Elst et al., (2005)
Verbal Fluency Test	VF	1	Mulder et al., (2006)
Stroop color Word Inference Test	Stroop	1	Delis et al., (2001)
Digit Span Test	DS	1	Wechsler, (2008)
Trail Making Test (A & B)	TMT	1	Delis et al., (2001)
National Adult Reading Test	PIQ	1	Schmand et al., (1992)

[a] = versions available in order to minimize learning effects.

with an indication for less than 10 ECT sessions were excluded. Patients with an indication for more ECT sessions received additional ECT after the posttreatment measurement.

Prior to treatment, etomidate (1.5 mg/kg, anaesthetic) and succinylcholine (0.5–1.0 mg/kg, muscle relaxant) were administered. Prior to administering the muscle relaxant, a blood pressure cuff was placed on the left or right lower arm to keep the muscle relaxant from entering, in order to clinically observe the provoked seizure. During treatment, blood pressure, heart rate and pulse oximetry were monitored. A two leaded electromyogram was recorded in the cuffed lower arm to observe the length of the motor seizure. An electroencephalographical (EEG) recording was obtained from a single channel using right frontomastoid placements. To be considered adequate, minimum motor seizure duration was 20 seconds, following recommendations from the literature (Abrams, 2002) and the Dutch Guidelines on Electroconvulsive Therapy (Broek et al., 2010). When a seizure of less than 20 seconds was observed, a new seizure was provoked with energy increase of 5–10%. No more than 3 attempts to induce a seizure were made.

VARIABLES

Patients were examined three times; prior to the first ECT treatment session (baseline), after ten ECT treatment sessions (post treatment) and six months after the tenth ECT treatment sessions (follow-up). Controls were examined twice: at baseline and five weeks after the first measurement occasion, yielding a comparable interval of a minimum of five weeks as in the patient group.

A neuropsychological test battery was used to determine cognitive functioning (see Table 1). The Rey Complex Figure test (RCF) was used to examine visuospatial abilities, learning and memory, including four subtests: a copy trial, immediate recall, delayed recall and recognition trial (Meyers & Meyers, 1995). The Dutch adaptation of the Rey Auditory Verbal Learning Test (D-RAVLT) was used to assess verbal memory and learning, including three subtests: immediate recall, delayed recall and recognition. (Van der Elst et al., 2005). For this test, two versions were used to minimize learning effects. The Verbal Fluency (VF) test (Dutch version) measured both semantic (responses to the letters "N" and "A") and categorical verbal fluency [responses to "profession" and "animals" (Mulder et al., 2006)]. The Stroop Colour-Word Interference Test was included to evaluate processing speed (Stroop 1) and verbal inhibition [Stroop 3 (Delis et al., 2001)]. The Digit Span (DS) test, taken from the Wechsler Adult Intelligence Scale IV, was used to measure working memory (Wechsler, 2008). The Trail Making Test was used to measure visual attention (TMT A) and task-switching [TMT B (Delis et al., 2001)]. A Dutch adaptation of the National Adult Reading Test ('Nederlandse Leestest voor Volwassenen') was used to estimate premorbid IQ [PIQ (Schmand et al., 1992)]. Trained researchers or clinicians conducted all examinations. For premorbid IQ, RCF, Verbal Fluency, Digit Span and Trail Making tests no parallel versions were available. Raw scores were converted into z-scores (see Fig. 1).

To assess the severity of the depressive symptoms in patients, the 17-item version of

Table 2. Descriptive statistics.

		Patients	Controls		Comparison	
		N (%)	N (%)		X^2	p
Total N		43	19		–	–
Sex	Male	15 (34.9)	6 (31.6)		0.064	0.8
	Female	28 (65.1)	13 (68.4)			
Handedness	Right	38 (88.4)	15 (78.9)		0.943	0.331
	Left	5 (11.6)	4 (21.1)			
Depression current		43 (100)				
Depression recurrent		26 (60.5)				
Unipolar depression		40 (93)				
Bipolar depression		3 (7)				
		M (SD)	M (SD)		t-test	p
Age		51.1 (14.48)	48.37 (10.87)		0.739	0.463
Years of education		12.1 (1.74)	12.63 (1.5)		1.222	0.227
ECT sessions		20.64 (8.57)[a]	–	–	–	–
		M (SD)	Min.	Max.	Responders N (%)	
Hamilton baseline		23.16 (7.85)	10	37	–	
Hamilton post-treatment		15.36 (7.86)	3	34	11 (28.9%)	
Hamilton follow-up		14.80 (8.06)	5	37	10 (43.5%)	

[a] = Only computed for patients receiving more than ten ECT session and thus were included in the analysis at post-treatment and follow-up; N = number; X^2= chi-square statistic; p = p-value; M = mean; SD = standard deviation; Min = minimum; Max = maximum; Response is classified as a 50% decrease in HDRS score compared to baseline

the Hamilton Depression Rating Scale (HDRS) was used (Hamilton, 1960). Clinical response was defined as a 50% reduction in depression scores compared to baseline. Relapse at follow-up e defined as 50% increase in scores from post-treatment to follow-up. Controls were not examined with the HDRS.

STATISTICAL ANALYSES

Statistical analyses were performed using SPSS software (IBM Corp. version 22). First, baseline characteristics were compared between patients and controls, using X^2-tests for dichotomized variables, and independent single t-tests for continuous variables. The group that was lost to follow-up was compared to the group with complete follow-up data, using the same tests.

To evaluate the overall effects of ECT on cognition a multivariate mixed model for repeated measures (Gueorguieva & Krystal, 2004) including all 15 cognitive variables (excluding

premorbid IQ) was performed with time as fixed factor and subject as random factor [similar to the analysis in (Vasavada et al., 2017)]. To investigate the effect of ECT on each of the cognitive variables separately, a univariate mixed model was used with time as within-subjects factor and subject as random factor. Post-hoc testing was performed when a significant result was obtained in order to determine between which measure moments the change occurred. This analysis was performed for both the controls and patients separately. Since premorbid IQ has been linked to cognitive outcome in ECT [although findings are mixed and conflicting results have been reported (Martin et al., 2013; Sackeim et al., 2007)], a post-hoc analysis was conducted with premorbid IQ as covariate in the model. Additionally, concomitant medications were allowed during the study. Therefore, to investigate whether medication status affected the results, a post-hoc analysis was conducted with four binary variables reflecting whether or not the patient was on anxiolytic, antidepressant, antipsychotic or mood stabilizing medications.

To examine whether alleviation of depression following ECT treatment influenced cognitive scores, we conducted an additional mixed analysis model including HDRS score as covariate. To further look into the effect of response to ECT on cognition, independent samples t-tests were conducted testing for the difference in absolute cognitive scores between responders (defined as a 50% reduction in depression scores) and non-responders at post-treatment and follow-up. Furthermore, to be more sensitive to change, an independent samples t-test was conducted to test for the difference between responders and non-responders in change in cognition. For example, at post-treatment, patients who responded were compared to non-responders in change in cognitive scores between baseline and post-treatment. Additionally, correlation analyses were run to see if change in cognitive test scores and change in HDRS score were related (for both baseline to posttreatment, and post-treatment to follow-up).

To compare changes between patients and controls, a mixed model was used. Post-hoc t-testing was used to assess possible significant effects seen in the mixed model for repeated measures. To correct for multiple comparisons, p-values were adjusted via the false discovery rate (FDR) procedure by Benjamini and Hochberg [1995 (as implemented in R version 3.1.1)]. In this procedure a p-value is considered significant when the FDR value $p.adjust_i$ is smaller than or equal to 0.05, where $p.adjust_i$ is determined by the rank (R_i) of the p-value (p_i) and the number of tests (n): $p.adjust_i = p_i * (n/R_i)$.

RESULTS

The demographic, clinical and baseline characteristics are displayed in Table 2. No significant differences were found between patients and controls for sex, handedness, age, and years of education. No significant differences were observed between patients who were lost to follow-up and patients who completed follow-up for sex, handedness, uni- or bipolarity, depression severity, age and years of education (*all $p > 0.05$*; supplementary S5).

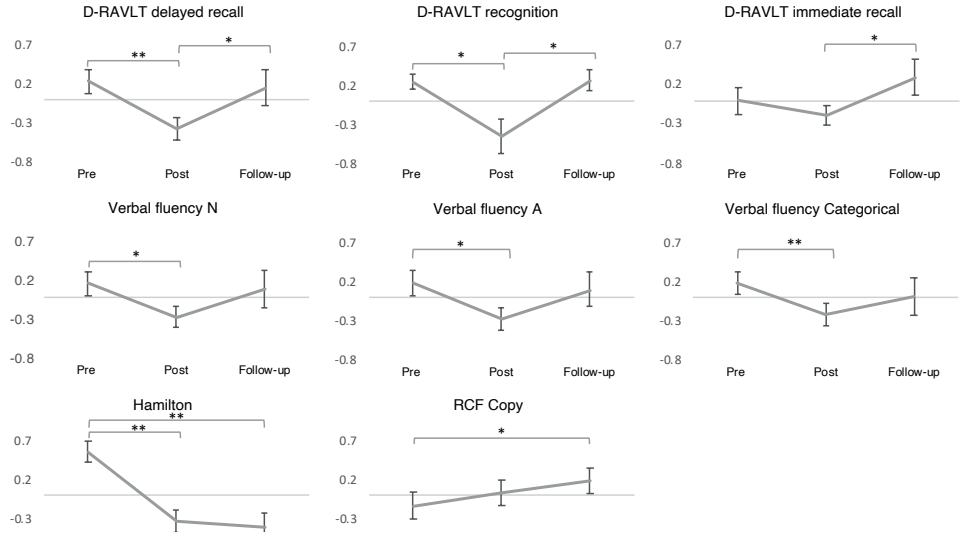

Figure 1. Representation of cognitive test results at baseline (Pre) post-measurement (Post) and follow-up (only significant results are shown). y-axes represent z-scores; x-axes represent time; * = $p < 0.001$; error bars represent standard error of the mean.

A global significant interaction effect was observed between time and cognitive test in the multivariate mixed model ($F = 14.08$, $p < 0.001$), indicating that ECT has different effects over time on different cognitive variables. Using univariate mixed models, significant changes in test scores over time were observed for the RCF copy, all subtests of the D-RAVLT, and all subtests of the VF test (Fig. 1; supplementary S1). See Fig. 1 for a visual representation of significant changes in each cognitive domain (and supplementary figure S2 for the remaining non-significant tests). For the RCF copy significant improvement in test scores was observed between baseline and follow-up (supplementary S3, $p = 0.026$). The immediate recall subtest of the DRAVLT differed significantly between post-treatment and follow-up (supplementary S3, $p = 0.009$) where follow-up scores showed improvement compared to post-treatment scores. No significant changes were observed between baseline and post-treatment, and between baseline and follow-up. For the delayed recall subtest of the D-RAVLT significant changes were seen between baseline scores and post treatment scores (supplementary S1, $p<0.001$) and between post-treatment and follow-up (supplementary S3, $p = 0.023$), where post-treatment scores were significantly impaired compared to baseline and follow-up. For the recognition part of the D-RAVLT, the same pattern was observed (supplementary S3): post-treatment scores were significantly impaired compared to baseline scores ($p = 0.012$) and follow-up scores ($p = 0.031$). The verbal-fluency task indicated a similar pattern for all three subtests (supplementary S3): performance on post-treatment scores was significantly decreased compared to baseline scores for the N, A and categorical subtest ($p = 0.001$, $p = 0.005$, $p < 0.001$, respectively). For results at an individual level, see Table 3 for the number of patients showing a decrease in cognitive test

Table 3. N patients showing decrease at post-treatment and subsequent improvement at follow-up.

Variable	n(%) decrease at exit	n(%) improvement at follow-up	n 50% decrease at follow-up
- RCF copy	17(44.7%)	9(37.5%)	–
- RCF immediate recall	23(60.5%)	11(78.6%)	–
- RCF delayed recall	15(39.5%)	9(100%)	–
- RCF recognition	17(45.9%)	7(70%)	–
- D-RAVLT immediate	25(69.4%)	14(87.5%)	–
- D-RAVLT delayed	32(88.9%)	14(66.7%)	5
- D-RAVLT recognition	30(83.3%)	15(70%)	–
- VF - N	29(74.4%)	11(64.7%)	2
- VF - A	37(63.8%)	6(46.2)	–
-VF - Categorical	31(79.5%)	13(68.4%)	2
- Stroop 1	23(57.5%)	11(78.6%)	–
- Stroop 3	13(34.2%)	5(71.4%)	–
- Digit span	15(62.5%)	7(70%)	–
- TMT A	22(59.5%)	13(81.3%)	3
- TMT B	16(42.1%)	7(70%)	2

RCF = Rey complex figure test; D-RAVLT = Dutch adaptation of the Rey auditory verbal learning test; VF = Verbal fluency; TMT = Trail Making Test; n 50% = patients showing a 50% decrease in test scores from baseline to follow-up.

scores from baseline to post-treatment, and subsequent improvement from posttreatment to follow-up. In addition, see Table 3 for the number of patients showing a 50% decrease in cognitive test scores at follow-up compared to baseline.

Adding premorbid IQ to the model did not affect the results. Adding medication status to the model did slightly affect the results. The mixed model now showed a significant effect of time on RCF immediate recall ($F = 4.82$, $p = 0.031$, reflecting a borderline significant increase in performance from post-treatment to follow-up ($p = 0.053$). For the delayed subtest of the RCF a similar pattern was observed: the mixed model indicated a significant effect of time ($F = 4.25$, $p = 0.32$) reflecting a borderline significant increase in test scores from post-treatment to follow-up ($p = 0.056$). All the other results remained the same.

ECT also showed a significant effect on depression scores (Fig. 1 and supplementary S1): significant decreases in depression score were seen between baseline and post treatment, and baseline and follow-up (supplementary S3, both $p<0.001$). No changes in HDRS score were seen between post-treatment and follow-up. At post-treatment 11 responders were identified, and at follow-up 10 responders were identified (see Table 2). One patient who responded at post-treatment relapsed at follow-up. To look into the effect of depression (and

Table 4. Mixed model patients vs. controls; baseline vs. post-treatment.

Domain		F	F-value	p
Spatial abilities	- RCF copy	F(1,51.0)	0.27	0.609
Spatial memory	- RCF immediate recall	F(1,54.8)	28.18	<0.001
	- RCF delayed recall	F(1,54.9)	27.95	<0.001
	- RCF recognition	F(1,54.9)	0.11	0.742
Verbal memory	- D-RAVLT immediate	F(1,54.8)	0.70	0.406
	- D-RAVLT delayed	F(1,530)	28.98	<0.001
	- D-RAVLT recognition	F(1,53.9)	5.54	0.022
Verbal fluency	- VF – N	F(1,58.6)	15.07	<0.001
	- VF – A	F(1,58.2)	24.21	<0.001
	- VF – Categorical	F(1,56.9)	12.49	0.001
Processing speed	- Stroop 1	F(1,56.4)	0.61	0.440
Verbal inhibition	- Stroop 3	F(1,52.6)	0.20	0.660
Working memory	- Digit span	F(1,43.1)	0.01	0.993
Visual attention	- TMT A	F(1,55.9)	0.04	0.845
Task switching	- TMT B	F(1,54.9)	.279	0.600
Intelligence	- Premorbid IQ	F(1,50.8)	2.687	0.108

RCF = Rey complex figure test; D-RAVLT = Dutch adaptation of the Rey auditory verbal learning test; VF = Verbal fluency; TMT = Trail Making Test.

treatment effect) on cognition, HDRS score was included in the model. Including HDRS score as a covariate did not affect the results. Furthermore, no differences were observed between responders and non-responders at post-treatment in any of the cognitive measures (all $p>0.05$). When looking at the differences between responders and non-responders in change in cognitive scores from baseline to exit, a greater decrease in test score was observed for responders compared to non-responders for the N subtest of the verbal fluency test ($t=-3.76$, $df=33$, $p<0.001$, FDR corrected $p=0.009$). At follow-up, no differences were observed between responders and non-responders in any of the cognitive test scores, nor in the difference between post-treatment and follow-up (all $p>0.05$). In addition, no correlation was observed between change in HDRS score and change in cognitive scores from baseline to posttreatment (all $p > 0.05$) and post-treatment to follow-up (all $p > 0.05$; see supplementary S6).

In controls, significant improvements (see supplementary S1) were seen on the RCF (immediate recall, $p < 0.001$; delayed recall, $p < 0.001$; and recognition, $p = 0.009$), delayed recall for the D-RAVLT ($p = 0.011$; BC), all of the subtests of the VF test (N: $p = 0.041$; A: $p = 0.002$; both BC), and Stroop card 3 ($p < 0.001$). When patients were compared to controls using independent samples t-tests, a significantly higher score for controls was seen at baseline for all tests, except for the RCF recognition and premorbid IQ (FDR corrected; see supplementary

S4 for p-values). At post-treatment, the controls scored significantly better on all tests except the RCF recognition, premorbid IQ and D-RAVLT recognition (FDR corrected; see supplementary S4 for p-values).

The results of the mixed design repeated measures comparing patients and controls are shown in Table 4. This test shows significant differences in the RCF, both the immediate and delayed recall (both $p < 0.001$, Table 4). Post-hoc t-tests (supplementary S1 and S3) show that the results are driven by a significant increase in the group of controls, while no significant difference was observed in patients. A significant difference is seen in the D-RAVLT – delayed and recognition subtest ($p < 0.001$ & $p = 0.022$, respectively; see Table 4). For the DRAVLT delayed subtest this result is driven by a significant decrease in scores in patients, while a significant increase is seen in controls (see supplementary S1 and S3). For the D-RAVLT recognition, this result is driven by a significant decrease in scores for patients (supplementary S1 and S3). Significant differences are seen in all subtests of the VF test (all $p \leq 0.001$; see Table 4). Post-hoc t-tests show significant decreases in scores for patients in all 3 subtests, and significant increase in the semantic verbal fluency in controls (supplementary S1 and S3).

DISCUSSION

We investigated the effect of ECT for depression on several cognitive domains and depression severity in a longitudinal study with a measurement at baseline, post-treatment (directly after the tenth ECT session) and at follow-up (6 months after the tenth ECT session). In addition, we included a control group for the baseline and post-treatment measurement. Our results showed that for patients, post-treatment scores were significantly impaired compared to baseline scores for verbal memory and learning, and verbal fluency. Importantly, for all cognitive domains tested, follow-up scores did not differ significantly compared to baseline scores, indicating that for all cognitive domains test scores returned to baseline levels after six months (except for the copy test of the RCF, even showing a slight increase in scores from baseline to follow-up). This finding supports our hypothesis that initial negative cognitive side-effects from bilateral ECT are restored to baseline levels at the long-term.

Specifically, post treatment scores were significantly lower than baseline scores for the delayed and recognition task of the D-RAVLT, and all three subtests of the verbal fluency task. For all subtests of the D-RAVLT a significant increase was seen in follow-up scores compared to post-treatment scores. In addition, for all cognitive tests, no significant decreases between baseline and follow-up scores were seen. This indicates that ECT treatment does not cause a decrease in neurocognitive functioning on long-term. The HDRS score was significantly decreased from baseline to post treatment and from baseline to follow-up. Baseline depression, and subsequent improvement in HDRS score following ECT could influence cognitive test scores. However, including HDRS score in the repeated measures mixed model, did not affect the results. In addition, cognitive scores at baseline did not correlate

with depression severity at baseline. Furthermore, when comparing responders and non-responders (at post-treatment or follow-up) on any of the cognitive measures, no significant differences were observed (except for the N subtest of the Verbal Fluency test, where patients who responded (at post-treatment) showed a greater decrease in test scores between baseline and post-treatment). Also, a change in depression severity did not correlate with a change in cognitive test scores (from baseline to post-treatment, and post-treatment to follow-up). These results suggest that the acute negative effects of ECT and subsequent recovery at follow-up are not due to depression severity, response or treatment effect.

In addition, adding premorbid IQ to the model did not change the results, suggesting no modulation of premorbid IQ functioning on negative side effects of ECT nor on recovery at follow-up. Furthermore, concomitant medications were allowed in the study at all time points. To test for the effect of medication use we included medication status per class of drugs (antidepressants, mood stabilizers, anxiolytics, and antipsychotics) in the analysis. This slightly affected our results. Specifically, the model showed significant effects of time on the RCF delayed and immediate subtest. This effect is reflected in a slight increase from post-treatment to follow-up. The other results were unaffected, suggesting that medication use could not explain our findings of the initial model.

In the group of controls, significant improvement was seen in the immediate recall, delayed recall and recognition part of the RCF, the delayed recall of the D-RAVLT, the semantic part of the verbal fluency task, and for inhibition scores of the Stroop test. The comparison between patients and controls indicates that in the patient group significant increases in performance (as quantified in the control group and most likely due to learning effects) are absent. This could mean that the absence of learning effects from baseline to post treatment in patients is, in fact, a negative cognitive side effect of ECT. Nevertheless, as our results show, follow-up scores returned to the level of baseline for patients indicating that the initial adverse side effects (i.e. a decrease in test results) are transient.

In line with the literature, this study reports short-term cognitive adverse effects of treatment with ECT in verbal fluency and verbal memory (Calev et al., 1995; Semkovska & McLoughlin, 2010). Importantly, no long-term cognitive adverse effects were seen. Early literature on this matter stated that there is a long-term negative effect on cognitive functioning (Squire et al., 1975). However, this negative effect was only observed using subjective measures, and could not be objectified with neuropsychological testing. More recent research reports that subjective cognitive functioning improves, and that it may be due to improved modern practice of ECT (Prudic, Peyser, & Sackeim, 2000). Conversely, it is recently reported that autobiographical memory might be more permanently impaired and affected by bilateral ECT (Sackeim, 2014; Semkovska et al., 2016; Verwijk, Obbels, Spaans, & Sienaert, 2017). Although this study did not include measures for autobiographical memory, it adds to the observation that ECT treatment does not have adverse cognitive effects on the long-term on other cognitive domains.

In the current study, baseline scores of patients are significantly lower compared

to controls for all cognitive domains (except for premorbid IQ and the RCF recognition; supplementary S4), indicating an effect of depression on these cognitive domains (Lee, Hermens, Porter, & Redoblado-Hodge, 2012; Millan et al., 2012; Trivedi & Greer, 2014). Although the scores of patients returned to baseline level at follow-up, the scores did not reach the level of controls, yet a significant effect of ECT on depression is observed in this study. Moreover, (change in) depression scores were not associated with (a change in) cognitive scores. This could mean that although patients recover at follow-up, ECT has an additional negative effect on cognition since patients do not show improvements in follow-up scores compared to baseline. Likewise, recently, a study investigating the short- and long-term effects of unilateral/mixed ECT on cognition also reported that although the effects of ECT on cognition recover to baseline levels, no normalization to the level of controls was observed (Vasavada et al., 2017). Moreover, impaired cognition in remitted depression is commonly reported in the literature as a residual symptom (Bora, Harrison, Yücel, & Pantelis, 2013; Hasselbalch, Knorr, & Kessing, 2011; Rock, Roiser, Riedel, & Blackwell, 2014).

Our study has several limitations. First, a relatively high loss to follow-up (41.9%) is observed. This could have influenced our findings. For example, patients experiencing the most prominent adverse side effects might have dropped out (possibly due to these side effects), therefore biasing our results. In the current study, however, this is unlikely. Cognitive scores and HDRS at post-treatment did not significantly differ between patients who dropped out at follow-up compared to patients who were not lost to follow-up (see supplementary S5). This would be expected if those who were lost to follow up had worse cognitive side effects. One possible explanation for the rate of loss to follow-up is the fact that patients received ECT treatment and the questionnaires for this research in a tertiary psychiatric hospital. After ECT treatment, they received treatment elsewhere, and were often no longer in a position to visit our centre. Second, our study did not include measures of retrograde amnesia in autobiographical memory. In recent years, retrograde amnesia and impairments in autobiographical memory have been a topic of interest in ECT research (Kolshus et al., 2017; Sackeim, 2014; Semkovska & McLoughlin, 2013). Impairments in autobiographical memory resulting from ECT have been reported to be greater in bilateral ECT compared to unilateral ECT (Kolshus et al., 2017). Future studies should further investigate the role of autobiographical memory in the cognitive side-effect profile of bilateral ECT. Third, due to logistic reasons controls were assessed only twice, whereas the patient group was assessed three times. As a result, we could not quantify the practice and learning effects in controls over a time-period of six months. As several studies indicate, practice effects could still be present at six month follow up (Bartels, Wegrzyn, Wiedl, Ackermann, & Ehrenreich, 2010; McCaffrey, Ortega, Orsillo, Nelles, & Haase, 1992). However, at 6 months follow up, these effects are usually only found after a period of high-frequency testing (Bartels et al., 2010), which is not the case in the current study. Fourth, although patients were tested after exactly 10 ECT sessions at posttreatment, a difference in number of ECT sessions was present at follow-up. At follow-up the mean number of ECT sessions was 20 (Table 2).

This could mean that our results at follow-up were negatively influenced by the number of ECT-sessions: patients receiving ECT after posttreatment or near follow-up might still experience the negative effect of ECT on cognition. However, at follow-up none of the test scores correlated significantly with the number of additional ECT sessions (supplementary S6), indicating that a negative effect of additional ECT sessions on cognition and our results is limited.

Our study has several strengths. First, we employed a large battery of neurocognitive tests in order to measure a broad spectrum of objectively quantifiable aspects of cognition. Second, we included a demographically matched control sample to see if absence of learning effect could also constitute negative effects of bilateral ECT. Third, our longitudinal design allowed us to quantify effects of bilateral ECT within subjects instead of relying on cross-sectional data. Fourth, we analysed the sample with a mixed effects model, therefore permitting the inclusion of subjects with missing data instead of deleting these data listwise. This ensured that all the available data was included in the analyses.

In conclusion, this study showed that cognitive adverse effects as a result of bilateral ECT in patients are transient. In addition, we report that negative side effects not only consist of a decrease of functioning but can also consist of a lack of increase. On long term, however, no negative effects were seen compared to baseline cognitive functioning. These results might reduce the reluctance in some patients and practitioners to consider bilateral ECT as a safe and effective treatment for refractory depression.

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SUPPLEMENTARY MATERIAL

Supplement S1. Cognitive results patients & controls; tested with a mixed model

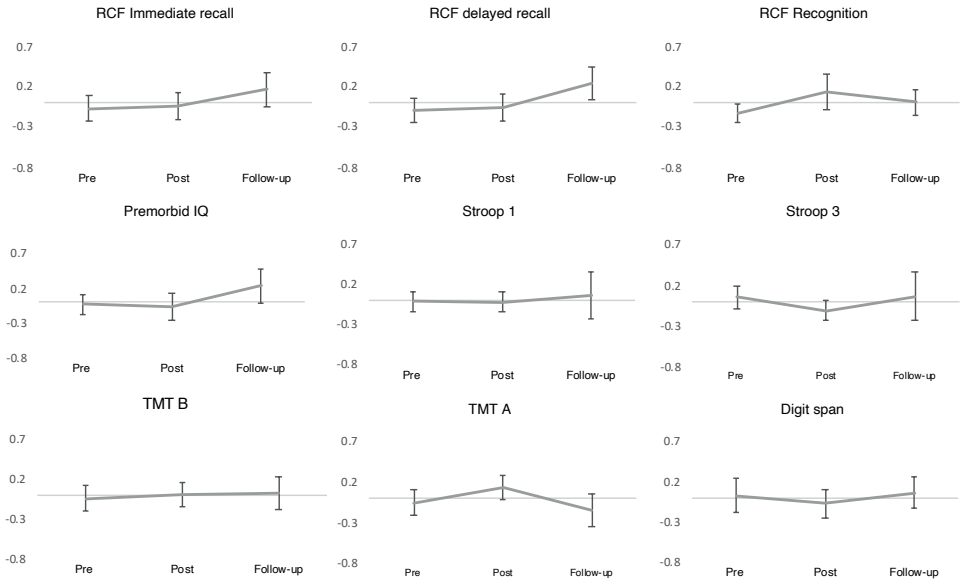
Domain	Test	Group	Baseline*	Post*	Follow-up*	F(df)	p-value
Depression	HDRS	Patient	23.16	15.48	15.53	23.99(2,32.13)	<0.001
		Control	-	-	-		
Visuo-spatial abilities	RCF Copy	Patient	31.41	32.03	33.03	3.97(2,31.05)	0.029
		Control	35.58	35.74	-	0.72(1,19)	0.407
Visuo-spatial memory & learning	RCF – IR	Patient	16.01	16.05	17.85	2.74(2,29.59)	0.081
		Control	21.89	28.34	-	49.05(1,19)	<0.001
	RCF – DR	Patient	15.42	15.51	17.49	1.91(2,29.19)	0.166
		Control	21.74	27.89	-	55.51(1,19)	<0.001
	RCF Rec.	Patient	19.26	20.05	19.49	0.82(2, 37.29)	0.447
		Control	20.32	21.42	-	8.52(1,19)	0.009
Verbal memory & learning	D-RAVLT - IM	Patient	36.39	33.75	40.61	5.22(2,30.92)	0.011
		Control	51.42	51.26	-	0.01(1,19)	0.946
	D-RAVLT - DR	Patient	7.17	4.91	6.70	17.24(2,30.58)	<0.001
		Control	10.95	11.95	-	7.85(1,19)	0.011
	D-RAVLT Rec.	Patient	.92	.83	.91	4.94(2,18.25)	0.019
		Control	.983	.991	-	2.58(1,19)	0.125
Verbal Fluency	VF – N	Patient	11.9	9.97	11.63	7.86(2,31.73)	0.002
		Control	16.11	17.89	-	4.79(1,19)	0.041
	VF – A	Patient	11.23	9.29	10.93	6.81(2,32.91)	0.004
		Control	15.11	18.53	-	12.48(1,19)	0.002
	VF – Cat.	Patient	56.42	48.82	52.09	9.28(2,30.84)	0.001
		Control	79.84	82.89	-	1.97(1,19)	0.176
Processing speed	Stroop – 1	Patient	57.07	57.46	57.29	0.03(2,30.28)	0.972
		Control	45.63	44.00	-	1.74(1,19)	0.203
Inhibition	Stroop – 3	Patient	125.64	115.95	127.303	1.82(2,32.78)	0.177
		Control	84.58	78.44	-	21.48(1,19)	<0.001

*=estimated marginal means; HDRS = Hamilton Depression Rating Scale; Rec.= recognition; IR= immediate recall; DR= delayed recall; Cat. = categorical; RCF= Rey complex figure test; D-RAVLT= Dutch adaptation of the Rey auditory verbal learning test; VF= Verbal fluency; DS= digit span; TMT= Trail Making Test; PIQ= premorbid IQ.

Supplement S1. Continued

Domain	Test	Group	Baseline*	Post*	Follow-up*	F(df)	p-value
Working memory	DS	Patient	14.18	13.94	14.31	0.18(2,24.81)	0.837
		Control	17.32	16.95	-	.42(1,19)	0.524
Visual attention	TMT A	Patient	9.46	10.30	9.33	2.37(2,33.19)	0.109
		Control	13.32	14.00		4.01(1,19)	0.06
Task switching	TMT B	Patient	8.10	8.45	8.97	1.19(2,28.40)	0.319
		Control	11.32	12.08	-	2.38(1,16.94)	0.142
Intelligence	PIQ	Patient	104.51	104.21	106.41	2.05(2,22.91)	0.152
		Control	107.84	109.63	-	3.26(1,19)	0.087

*=estimated marginal means; HDRS = Hamilton Depression Rating Scale; Rec.= recognition; IR= immediate recall; DR= delayed recall; Cat. = categorical; RCF= Rey complex figure test; D-RAVLT= Dutch adaptation of the Rey auditory verbal learning test; VF= Verbal fluency; DS= digit span; TMT= Trail Making Test; PIQ= premorbid IQ.



Supplementary figure S2. Representation of non-significant cognitive test results at baseline (Pre), post-measurement (Post), and follow-up. All scores are presented as z-scores on the y-axes; error bars represent standard error of the mean.

Supplement S3. Post-hoc test between baseline, post and follow-up (post-hoc)

Test	Time	Means*	Post-hoc test	p-values
HDRS	Baseline	23.16	baseline vs post	<0.001
	Post	15.48	baseline vs follow-up	<0.001
	Follow-up	15.53	post vs follow-up	1
RCF Copy	Baseline	31.24	baseline vs post	0.899
	Post	32.03	baseline vs follow-up	0.026
	Follow-up	33.03	post vs follow-up	0.388
D-RAVLT – IM	Baseline	36.39	baseline vs post	0.389
	Post	33.75	baseline vs follow-up	0.138
	Follow-up	40.61	post vs follow-up	0.009
D-RAVLT – DR	Baseline	7.17	baseline vs post	<0.001
	Post	4.91	baseline vs follow-up	1
	Follow-up	6.70	post vs follow-up	0.023
D-RAVLT – Rec.	Baseline	.92	baseline vs post	0.012
	Post	.83	baseline vs follow-up	1
	Follow-up	.91	post vs follow-up	0.031
VF – N	Baseline	11.9	baseline vs post	0.001
	Post	9.97	baseline vs follow-up	1
	Follow-up	11.63	post vs follow-up	0.184
VF – A	Baseline	11.23	baseline vs post	0.005
	Post	9.29	baseline vs follow-up	1
	Follow-up	10.93	post vs follow-up	0.07
VF – Cat.	Baseline	56.42	baseline vs post	<0.001
	Post	48.82	baseline vs follow-up	0.377
	Follow-up	52.09	post vs follow-up	0.761

*=estimated marginal means; HDRS = Hamilton Depression Rating Scale; Rec.= recognition; IR= immediate recall; DR= delayed recall; Cat. = categorical; RCF= Rey complex figure test; D-RAVLT= Dutch adaptation of the Rey auditory verbal learning test; VF= verbal fluency

Supplement S4. Independent samples t-tests controls vs. patients

Test	Measurement	t	df	sig	FDR cor.	Mean diff	std error
RCF - IR	Baseline	-3.205	59	.002	.0306	-5.6328	1.7573
RCF - DR	Baseline	-3.452	59	.001	.0200	-6.0345	1.748
RCF - Rec.	Baseline	-1.829	59	.072	.072	-1.0539	0.5762
RCF - Copy	Baseline	-3.156	59	.003	.0323	-3.7932	1.2018
Premorbid IQ	Baseline	-1.382	57	.172	.172	-3.553	2.571
VF - Categorical	Baseline	-4.598	60	.000023	.0114	-23.424	5.094
VF - N	Baseline	-3.059	60	.003	.0341	-4.198	1.373
VF - A	Baseline	-3.066	60	.003	.0359	-3.873	1.263
DS	Baseline	-2.902	45	.006	.0376	-2.994	1.032
D-RAVLT - IR	Baseline	-4.384	57	.000051	.0148	-15.096	3.4437
D-RAVLT - DR	Baseline	-4.556	57	.000028	.0131	-3.7974	0.8335
D-RAVLT - Rec.	Baseline	-3.462	57	.001	.0218	-0.0635	0.0183
Stroop 1	Baseline	2.694	60	.009	.0415	11.438	4.2462
Stroop 3	Baseline	3.666	58	.001	.0235	41.958	11.444
TMT A	Baseline	-3.647	58	.001	.0253	-3.6573	1.003
TMT B	Baseline	-3.914	58	<.001	.0002	-3.643	0.930
RCF - IR	Exit	-6.594	55	<.00001	.008	-11.868	1.7999
RCF - DR	Exit	-6.656	55	<.00001	.0063	-11.987	1.8008
RCF - Rec.	Exit	-1.384	54	.172	.172	-1.34	0.9681
RCF - Copy	Exit	-2.835	55	.006	.0039	-3.1316	1.1044
Premorbid IQ	Exit	-2.003	50	.051	.051	-5.389	2.69
VF - Categorical	Exit	-7.152	56	<.00001	.0003	-34.69	4.85
VF - N	Exit	-6.726	56	<.00001	.0047	-7.997	1.189
VF - A	Exit	-8.494	56	<.00001	.0035	-9.27	1.091
DS	Exit	-3.382	45	.001	.0270	-2.947	0.872
D-RAVLT - IR	Exit	-5.513	54	.00001	.0097	-17.371	3.1511
D-RAVLT - DR	Exit	-8.634	54	<.00001	.0018	-6.9474	0.8047
D-RAVLT - Rec.	Exit	0.923	54	.36	.36	1.2841	1.3907
Stroop 1	Exit	3.435	57	.001	.0288	15.055	4.3826
Stroop 3	Exit	3.927	57	.000235	.0018	35.171	8.9571
TMT A	Exit	-4.031	55	.000173	.0165	-3.579	0.888
TMT B	Exit	-4.618	55	<.0001	.0019	-4.289	0.929

Rec.= recognition; IR= immediate recall; DR= delayed recall; Cat. = categorical; RCF= Rey complex figure test; D-RAVLT= Dutch adaptation of the Rey auditory verbal learning test; VF= verbal fluency; DS= digit span; TMT= Trail Making Test.

Supplement S5. Differences at post-treatment lost to follow-up vs. no drop-out

Test	t	df	sig	Mean diff	Std error
HDRS	.721	31	.476	2.100	2.911
RCF – IM	-.915	30	.367	-2.833	3.095
RCF – DR	-.682	30	.500	-2.104	3.083
RCF - Rec.	-1.633	29	.113	-2.826	1.730
RCF - Copy	-1.377	30	.179	-2.791	2.027
Premorbid IQ	-.460	25	.650	-2.421	5.266
VF - Categorical	-.870	31	.391	-6.82	7.838
VF - N	-.025	31	.980	-0.045	1.785
VF - A	.170	31	.866	0.26	1.531
DS	-.820	21	.421	-1.289	1.572
D-RAVLT - IM	-1.085	29	.287	-4.547	4.189
D-RAVLT - DR	-1.462	29	.154	-1.940	1.326
D-RAVLT - Rec.	-1.723	29	.096	-0.080	0.046
Stroop 1	1.439	32	.160	10.222	7.105
Stroop 3	.226	32	.822	3.445	15.227
TMT A	-1.412	30	.168	-2.083	1.475
TMT B	-.536	30	.596	-.833	1.556

HDRS = Hamilton Depression Rating Scale; Rec.= recognition; IR= immediate recall; DR= delayed recall; Cat. = categorical; RCF= Rey complex figure test; D-RAVLT= Dutch adaptation of the Rey auditory verbal learning test; VF= verbal fluency; DS= digit span; TMT= Trail Making Test.

Supplement S6. Correlation coefficients of number of additional ECT sessions and cognitive scores

Test	n	r	p
RCF Immediate	25	0.061	0.772
RCF Delayed	25	0.138	0.511
RCF Recognition	25	0.265	0.201
RCF copy	25	0.182	0.384
Premorbid IQ	25	0.013	0.961
Verbal fluency cat.	25	-0.024	0.910
Verbal fluency N	25	-0.100	0.635
Verbal fluency A	25	-0.039	0.855
Digit span	25	-0.055	0.803
D-RAVLT immediate	25	0.180	0.388
D-RAVLT delayed	25	0.234	0.259
D-RAVLT recognition	25	0.320	0.119
Stroop 1	25	-0.025	0.907
Stroop 3	25	-0.149	0.477
TMT A	25	-0.068	0.746
TMT B	25	0.042	0.841

RCF= Rey complex figure test; D-RAVLT= Dutch adaptation of the Rey auditory verbal learning test; VF= verbal fluency; DS= digit span; TMT= Trail Making Test; cat. = categorical;

Supplement S7. Correlation coefficients between change in Hamilton score and change in cognitive scores

Baseline - Post-treatment	r	p	Post-treatment to Follow-up	r	p
RCF - IR	0.247	0.134	RCF - IR	-0.13	0.545
RCF - DR	0.263	0.111	RCF - DR	-0.166	0.439
RCF - Copy	0.171	0.306	RCF - Copy	-0.223	0.295
RCF - Rec.	0.141	0.406	RCF - Rec.	-0.182	0.406
VF - N	0.1	0.543	VF - N	0.043	0.838
VF - A	0.132	0.423	VF - A	-0.224	0.283
VF - Cat.	0.051	0.757	VF - Cat.	0.102	0.635
DS	0.227	0.287	DS	0.035	0.892
D-RAVLT-IM	-0.025	0.883	D-RAVLT-IM	0.14	0.513
D-RAVLT-DR	-0.063	0.714	D-RAVLT-DR	0.25	0.239
D-RAVLT-Rec.	-0.224	0.189	D-RAVLT-Rec.	-0.077	0.721
Stroop 1	0.065	0.695	Stroop 1	0.18	0.389
Stroop 3	-0.163	0.334	Stroop 3	0.246	0.236
TMT A	-0.092	0.588	TMT A	0.063	0.769
TMT B	-0.102	0.554	TMT B	-0.258	0.223

Rec.= recognition; IR= immediate recall; DR= delayed recall; Cat. = categorical; RCF= Rey complex figure test; D-RAVLT= Dutch adaptation of the Rey auditory verbal learning test; VF= verbal fluency; DS= digit span; TMT= Trail Making Test.

CHAPTER 3

Volume increase in the dentate gyrus after electroconvulsive therapy in depressed patients as measured with 7T

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ABSTRACT

Electroconvulsive therapy (ECT) is the most effective treatment for depression, yet its working mechanism remains unclear. In the animal analog of ECT, neurogenesis in the dentate gyrus (DG) of the hippocampus is observed. In humans, volume increase of the hippocampus has been reported, but accurately measuring the volume of subfields is limited with common MRI protocols. If the volume increase of the hippocampus in humans is attributable to neurogenesis, it is expected to be exclusively present in the DG, whereas other processes (angiogenesis, synaptogenesis) also affect other subfields. Therefore, we acquired an optimized MRI scan at 7-tesla field strength allowing sensitive investigation of hippocampal subfields. A further increase in sensitivity of the within-subjects measurements is gained by automatic placement of the field of view. Patients receive two MRI scans: at baseline and after ten bilateral ECT sessions (corresponding to a 5-week interval). Matched controls are also scanned twice, with a similar 5-week interval. A total of 31 participants (23 patients, 8 controls) completed the study. A large and significant increase in DG volume was observed after ECT ($M = 75.44$ mm^3, std error = 9.65, $p < 0.001$), while other hippocampal subfields were unaffected. We note that possible type II errors may be present due to the small sample size. In controls no changes in volume were found. Furthermore, an increase in DG volume was related to a decrease in depression scores, and baseline DG volume predicted clinical response. These findings suggest that the volume change of the DG is related to the antidepressant properties of ECT, and may reflect neurogenesis.

INTRODUCTION

Electroconvulsive therapy (ECT) is the most potent psychiatric treatment (Dierckx, Heijnen, van den Broek, & Birkenhäger, 2012; Husain et al., 2004; Kellner et al., 2015; Pagnin, de Queiroz, Pini, & Cassano, 2004; UK ECT Review Group, 2003), with effect sizes of 1–1.5 for severe and refractory unipolar and bipolar depression (Dierckx et al., 2012; Kellner et al., 2015; Pagnin et al., 2004; Tor et al., 2015; UK ECT Review Group, 2003). ECT convincingly outperforms pharmacotherapy such as tricyclic antidepressants and monoamine oxidase inhibitors, and any form of psychotherapy (Kellner et al., 2015; Pagnin et al., 2004; UK ECT Review Group, 2003).

Despite its outstanding performance in reducing depressive symptoms up to the point of full remission, the working mechanism of ECT remains partly unknown. In preclinical studies, electroconvulsive seizure (ECS; the animal analog of ECT) has been used to study the underlying neurochemical and neurobiological effects of ECT, with the hippocampus as the main focus (Inta et al., 2013; Kyeremanteng et al., 2014; Nakamura et al., 2013; Perera et al., 2007). Both in rodents and in non-human primates, neurogenesis in the dentate gyrus (DG; but not in any of the other hippocampal subfields) following ECS has been reported as a robust effect (Ito et al., 2010; Nakamura et al., 2013; Olesen, Wörtwein, Folke, & Pakkenberg, 2017; Parent, 2007; Perera et al., 2007; Rotheneichner et al., 2014). In addition to neurogenesis, angiogenesis, gliogenesis, mossy fiber sprouting, dendritic arborization, and synaptogenesis have also been observed as a result of ECS (Hellsten et al., 2005; Madsen et al., 2000; Rotheneichner et al., 2014; Vaidya, Siuciak, Du, & Duman, 1999; Wennström, Hellsten, Ekdahl, & Tingström, 2003). These processes can be observed in several regions of the adult mammalian brain, within and outside the hippocampus (Hickmott & Ethell, 2006; Ming & Song, 2011; Plate, 1999; Rusznák, Henskens, Schofield, Kim, & Fu, 2016).

Several neuroimaging studies in patients undergoing ECT for unipolar or bipolar depression have investigated hippocampal volume (Abbott et al., 2014; Bouckaert et al., 2016; Cao et al., 2018; Nordanskog, Larsson, Larsson, & Johanson, 2014; Pia Nordanskog et al., 2010; Oltedal et al., 2018; Ota et al., 2015; Redlich et al., 2016; Sartorius et al., 2016; Tendolkar et al., 2013). Recent meta-analytic and literature reviews summarizing these studies report significant increases in volume of both the left and right hippocampus and both amygdala (Gbyl & Videbech, 2018; Takamiya et al., 2018; Wilkinson, Sanacora, & Bloch, 2017). Recently, the Global ECT-MRI Research Collaboration (GEMRIC) (Oltedal et al., 2017), including a large sample of depressed patients, replicated these results (Oltedal et al., 2018). While this finding supports a possible role for neurogenesis in the clinical effects of ECT, other functional recovery processes of the hippocampus, such as angiogenesis or gliogenesis could also account for the increase in hippocampal volume. It therefore remains unclear if ECT in (human) depression elicits the same effect as in animal models, and especially if neurogenesis in the DG plays the same crucial role. A recent study in healthy humans showed that neurogenesis was not present in the adult brain (Sorrells et al., 2018). This finding has been debated (Boldrini et

al., 2018) and as for now, it remains undecided whether or not the adult human brain is at all capable of neurogenesis.

Accurate volumetric information from subfields of the hippocampus could help to differentiate between effects caused by neurogenesis (restricted to the DG) and effects of other processes, such as angiogenesis and synaptogenesis (affecting all hippocampal subfields). Therefore, accurately delineating the hippocampal subfields is of utmost importance to identify specific ECT-induced volumetric changes and decipher whether or not neurogenesis takes place in humans during ECT. This is an important missing link, as neurogenesis may be a crucial mediating factor of the antidepressant effects. However, the hippocampus is a small structure and a very high-resolution scan is needed in order to accurately delineate its different subfields (Giuliano et al., 2017; Wisse et al., 2016; Wisse, Biessels, & Geerlings, 2014). So far, effects of ECT have been studied on MRI scanners operating at 1.5- or 3-tesla magnetic field strength, restricting the maximum image resolution that can be achieved and therefore the level of precision for the segmentation of the hippocampal subfields (Gbyl & Videbech, 2018; Giuliano et al., 2017; van der Kolk, Hendrikse, Zwanenburg, Visser, & Luijten, 2013; Wisse et al., 2014; Yushkevich et al., 2010). A possibility to increase image resolution is to scan at ultra-high magnetic field strength (e.g., 7 tesla). For repeated measurements a further increase in sensitivity can be achieved by ensuring that the positioning of the scan with respect to the brain is kept constant for each scan session. In the current study, we therefore used a 7-tesla scan sequence that was designed for optimal measurement of the hippocampal subfields and employed fully automatic scan planning to ensure that the positioning of the scan within each subject was performed in the same way before and after ECT treatment.

We hypothesize that volume changes will pertain specifically to the DG as this structure has consistently been linked to neurogenesis in animal models of ECT. In addition, we hypothesize that the change in volume of the DG is positively related to the clinical effect (i.e., a greater increase in volume of the DG is associated with the beneficial therapeutic effects of ECT).

MATERIALS AND METHODS

SAMPLE

Patients and controls were recruited at the Department of Psychiatry in the University Medical Centre (UMC) Utrecht, the Netherlands. For patients the following inclusion criteria were used: (1) age over 18 years, (2) a diagnosis of unipolar or bipolar depression [as defined by the DSM-IV-TR criteria (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), 2000)], and (3) an indication for ECT treatment [according to the Dutch Guidelines on Electroconvulsive Therapy (Broek, Birkenhäger, Boer, & Burggraaf, 2010)]. Exclusion criteria for patients were treatment with ECT in 6 months prior to inclusion, contraindications for MRI (e.g., a pacemaker, claustrophobia, metallic implants), brain pathology, history of stroke, pregnancy and/or lactation, or any major medical condition (e.g.,

coronary heart disease, chronic obstructive pulmonary disease).

For healthy controls, an age over 18 years and absence of any psychiatric diagnosis constituted the inclusion criterion. In addition, we aimed to include controls with similar demographic characteristics (age, gender, years of education) as the patients. Exclusion criteria for controls were a (history of a) psychiatric illness [as assessed using the MINI interview, Dutch translation (Sheehan et al., 1998; van Vliet & de Beurs, 2007)], contraindications for MRI, brain pathology, history of stroke, pregnancy and/or lactation, or any major medical condition. We note that the purpose of including healthy controls was to determine whether possible volume changes could be attributed to systematic variation in scanner characteristics (e.g., scanner drift).

Written informed consent was obtained from all participants. This study was reviewed and approved by the local Medical Ethics Board at the UMC Utrecht. In total, 38 participants (26 patients, 12 healthy controls) met inclusion/ exclusion criteria. Due to personal reasons (two patients and four controls), anxiety in the scanner (one patient, one control), less than ten ECT sessions (one patient), scanning artefacts (two patients, two controls at baseline, two patients at exit), a total of 30 participants (22 patients, 8 controls) were analyzed. This corresponds to 21 complete scan sets (16 patients and five controls) and a total of 51 scans that were included in the analysis (including the scans of participants for which only a baseline or exit scan was available).

TREATMENT PROCEDURE

Using a Thymatron IV ECT machine (bifrontotemporal electrode positioning, with a stimulus intensity of 150% of the titrated seizure threshold), electroconvulsive therapy was given twice a week, for five consecutive weeks. After exactly ten sessions, patients were included in the exit assessment. This was to minimize variability of treatment duration between patients at exit. Afterward, when clinically indicated, some patients received additional ECT. One patient received less than ten ECT sessions and was excluded from the analysis.

Prior to delivering the electrical current, an anesthetic drug (etomidate/methohexital) and a muscle relaxant (succinylcholine) were administered. A blood pressure cuff was placed on the left or right arm to prevent the muscle relaxant from entering, allowing the length of the provoked seizure to be observed visually and by an electromyogram. Licensed anesthesiologists and nurses monitored the patients' vital signs during the entire session. A trained psychiatrist (or resident) administered the electrical current. Using a single channel (right frontomastoid placement) an electroencephalographical (EEG) recording was recorded. Following the Dutch Guidelines on Electroconvulsive Therapy (Broek et al., 2010) and international literature (Abrams, 2002), a minimum motor seizure duration of 20 s had to be observed. If the motor seizure duration was <20 s, a new current was delivered with an energy increase of 5–10%. No more than three attempts per session were made. All patients had seizures of >20 s on each ECT session.

Table 1. Demographics of the sample

Variable		Patients	Controls	Diff	Statistic (test)	p
Total N		23	8	–	–	–
Age		50.3	49.25	1.054	0.165 (t)	0.87
Gender	Female	18	5	–	0.770 (x^2)	0.38
	Male	5	3			
IQ		105.32	111.17	5.848	1.143 (t)	0.26
Handedness[a]	Left	2	1	–	Fisher's exact	1
	Right	21	6			
	Baseline (mean, SD)	Exit (mean, SD)	t (df)[b]	p	ES[c]	
HAM-D	22.59 (7.39)	15.48 (8.15)	4.6 (22)	<0.001	0.958	

x^2 = chi-square test statistic; diff = difference; N = number; IQ = intelligent quotient; p = p-value; [a] n=30; [b] paired t-test; ceffect size d for paired observations.

MRI DATA ACQUISITION AND PROCESSING

MRI data was acquired using a 7T magnetic resonance imaging (MRI) machine (Philips Healthcare, Best, the Netherlands) and a 32-channel head coil (Nova Medical, Wilmington, MA, USA). First, a 3D T1-weighted TFE scan was acquired (voxel size 1 mm isotropic; TR/TE 5.5/2.04 ms; flip angle 6°; FOV 256 × 256 × 190; number of slices 190; total scan duration 125 s). Next, a 3D T2-weighted TSE scan was acquired (voxel size 0.286 × 0.286 mm in plane resolution, 2 mm slice thickness; TR/TE 3800/60 ms; flip angle 90°; FOV 60 × 220 × 220; number of slices 30; total scan duration 494 s). Note that the voxels of this scan are highly anisotropic. For repeated measurements it is therefore crucial that the placement of the field of view (FOV) is planned for each measurement in the same way. To ensure this, we used so-called SmartExam planning. This is a fully automatic planning method to place the FOV on the brain based on a number of anatomical characteristics of the head extracted from a short T1-weighted scan acquired before each scan (see supplementary figure S1 for an example of two scans from the same subject scanned 5 weeks apart).

All processing was done with the Automated Segmentation of Hippocampal Subfields (ASHS) pipeline, FSL (5.0.9), and ANTs tools (Avants, Epstein, Grossman, & Gee, 2008; Smith et al., 2004; Tustison et al., 2014; Yushkevich et al., 2015). For a detailed outline of this pipeline, see Yushkevich et al. (Wang et al., 2011, 2013; Yushkevich et al., 2015). In short, the T2-weighted scan is aligned to the T1-weighted scan (rigid registration), then the T1-weighted scan is registered to the atlas template [implemented in ASHS (Yushkevich et al., 2015)]. These registrations are applied to the T1- and T2-weighted scans to resample both scans into the template space of the regions of interest (ROIs; left and right). Then, the segmentations in the atlas package are registered to subject space. Afterward, multi-atlas joint label fusion (Wang et al., 2013) and voxel-wise corrective learning methods (Wang et al., 2011) are used to segment the hippocampus (Yushkevich et al., 2015). This automated procedure resulted in reduced observer

bias. After the segmentation process, each segmentation was inspected visually and rerun or excluded if artefacts were present. Subfields included in the atlas were the DG, Cornu Ammonis 1–3 (CA1-3), entorhinal cortex (ERC), Subiculum (Subi), Collateral sulcus (CS), and Brodmann area 35 and 36 (B35, B36). Volumetric data for each subfield was subsequently exported and imported into R (version 3.4) and SPSS (IBM Corp., version 24).

CLINICAL EFFECT (HAM-D)

To quantify the effect of ECT on depression within the patient group, the 17-item version of the Hamilton Rating Scale for Depression (HAM-D) was administered at baseline and exit (Hamilton, 1960). The HAM-D is widely used in clinical practice and scientific research to assess (changes in) depression severity (Hamilton, 1960; Moran & Lambert, 1983).

STATISTICAL ANALYSES

For each subfield separately, interaction effects between time (pre/post) and group (patients/controls) were tested with R [package lmerTest (Kuznetsova, Brockhoff, & Christensen, 2017), R version 3.4.3 (R Core Team, 2013)] using a linear mixed model for repeated measures with time*group, age, and gender as fixed factors and hemisphere (left/ right; modeled as slope for different subjects) and subject as random factors [modeled as intercept (Bates, Mächler, Bolker, & Walker, 2015; Kuznetsova et al., 2017)]. Linear mixed models with significant effects for time*group were further split up into two models for patients and controls separately, to test which group drives the effect. If the patient and/or control group showed significant effects for time in this latter analysis, a linear mixed model was conducted for the left and right DG separately to see which subfield drives the effect. To test whether the volume change of the DG significantly differed from the volume change in the largest other subfield (i.e., the CA1 region), we conducted a paired t-test on the percentage increase for both the DG and CA1 region.

Additionally, we have run a repeated measures correlation analysis (Bakdash & Marusich, 2017) to assess the relationship between Hamilton score and DG volume after regressing out the effects of age, gender, baseline hippocampal volume, and baseline depression scores. Also, we performed a linear regression with decrease in HAM-D (exit–baseline) scores as dependent variable and baseline volumes of the significant subfields in the linear mixed model as predictor and age (in years) and gender as covariates. Post hoc paired t-test were conducted as an additional analysis (see supplementary S2).

Effect sizes for change in volume for patients and controls separately are calculated as Cohen's d for paired observations for each subfield (left and right together). In addition, Cohen's d for paired observations is used to calculate the effect size of the mean change in Hamilton score.

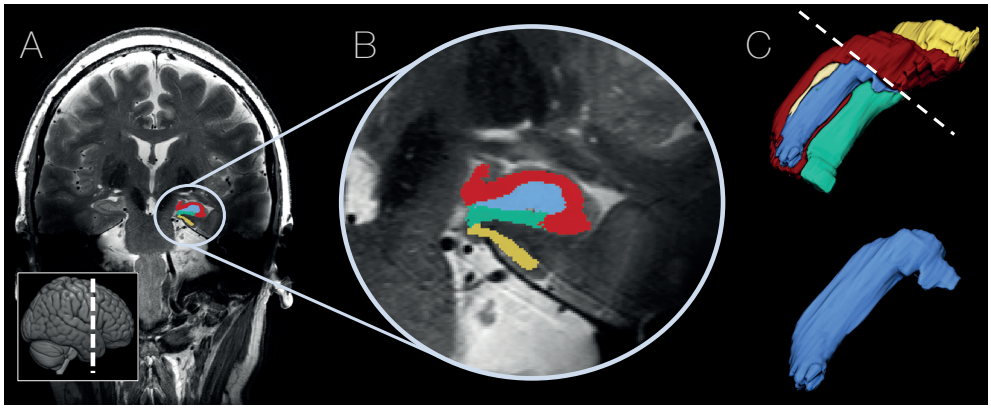


Fig. 1. Hippocampal subfield (left) segmentation and 3D rendering of the hippocampus and dentate gyrus. Panel (a) displays a whole brain T2-weighted scan showing the location of the hippocampus in a coronal slice. The location of the slice is presented in the left corner of the figure. Panel (b) displays the hippocampus subfield segmentation at the same position as panel (a) and is color coded: red = CA1; blue = DG; turquoise = subiculum, and desert = ERC. Panel (c) displays a 3D rendering of the hippocampus (upper) and the DG (lower). The dashed white line shows the positioning of the 3D hippocampus relative to panel (b). The same color coding as panel (b) is used for panel (c)

RESULTS

SAMPLE

In total, 31 participants (23 patients, 8 controls) were included in the study (see Table 1). At baseline, the patients did not differ statistically from the controls in terms of age, gender, handedness, and IQ (Table 1). Due to dropout and scanning artefacts (see Materials and methods, section 'Sample') we obtained a total of 21 complete pairs (baseline/ exit; 16 patients, 5 controls) and a total of 51 scans (26 baseline-scans, 25 exit scans). Hamilton score significantly decreased between baseline and exit ($t = 4.6$, $p < 0.001$, effect size = 0.958), see Table 1.

SEGMENTATIONS

In 51 scans the left and right hippocampus were automatically segmented. A segmentation is shown in Fig. 1 for the left hippocampus. The linear mixed model indicated a significant time*group effect for the DG ($t = -2.57$, $p = 0.0138$). None of the other subfields showed

Table 2. Estimated marginal means for baseline vs. exit patients (n = 22) and controls (n = 8) (LMM)

	Group	Baseline[a]	Exita	Diff	95% CI	t	df	Sig	ES[b]
DG	Patients	792.59	868.03	75.44	56.5–94.3	7.82	30.88	<0.001	1.489
	Controls	869.77	892.45	22.69	−7.0–52.3	1.5	15.27	.154	0.521

LMM = linear mixed model, Diff = difference between estimated marginal means for baseline and exit based on linear mixed model, 95% CI = confidence interval for difference between baseline and exit, t = t-statistic, df = estimated degrees of freedom (Satterthwait's method), Sig = p-value; [a] = Estimated marginal means for left and right DG together (i.e., average); [b] = Effect size d for paired observations based on 16 available pairs

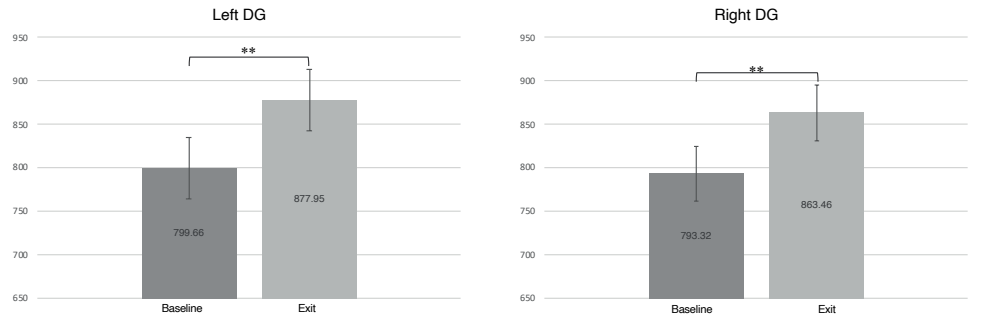
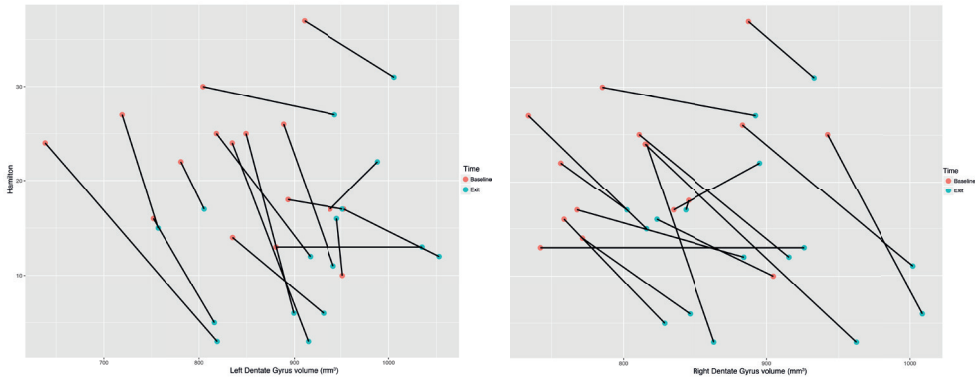


Fig. 2. Bar graphs of the estimated marginal means of the volume of the left and right DG for patients. Volume is displayed in mm^3; error bars represent standard error; ** = $p < 0.001$; estimated marginal means based on the linear mixed model for patients (left and right separately modeled)

significant time*group effects (all $p > 0.05$, see supplementary S3). For patients, the DG showed a significant increase in volume from baseline to exit (mean change = 75.44 mm^3, 95% CI [56.5–94.3], std error = 9.65, t = 7.82, $p < 0.001$). For controls, the DG showed no increase or decrease in volume from baseline to exit (mean change = 22.69 mm^3, 95% CI [–7.0–52.3], std error = 15.13, t = 1.5, p = 0.154; see Table 2). Both left (mean change = 78.30 mm^3, 95% CI [54.3–102.3], std error = 12.25, t = 6.39, $p < 0.001$) and right DG (mean change = 70.14 mm^3, 95% CI [39.9– 100.4], std error = 15.45, t = 4.54, $p < 0.001$) were significantly increased in the patient group from baseline to exit. See Fig. 2 for a visual representation of the estimated marginal means for the left and right DG in the patient group. See supplementary S6 for the output of the models referred to above. Paired samples t-tests indicated that the volume change in the DG was significantly greater than the volume change in the CA1 regions, for both the left DG (paired difference = 8.07%, t(df) = 6.15(15), $p < 0.001$, 95% CI [5.28–10.87]) and the right DG (paired difference = 7.54%, t(df) = 4.46, $p < 0.001$, 95% CI [3.94–11.15]). A 3D rendering of the DG scanned at ultra-high field and its embedding in the hippocampus is shown in Fig. 1 (BA 35 and 36 are not shown). See supplementary materials (S5) for plots showing individual scores from baseline to exit for the DG. See supplementary S2 and S4 for results of the post hoc paired samples t-tests. Effect sizes for the mean change in DG volume are 1.49 (Table 2) for left and right together and 1.63 for the left DG and 1.22 for the right DG for patients (see supplementary S4 for all subfields for patients and controls).

CLINICAL VARIABLES

The repeated measures correlation analysis indicated a significant negative relationship (after regressing out the effects of age, gender, baseline Hamilton score and baseline DG volume) between Hamilton score and right DG (r = –0.71, p = 0.001, 95% CI [–0.90 to –0.31]) and the left DG (r = –0.70, p = 0.002, 95% CI [–0.89 to –0.28]). The negative relationship indicates that an increase in DG volume is associated to a decrease in Hamilton score. See Figs. 3 and 4 for a visual representation of this relationship with raw data points. See supplementary S7 and S8 for plots of the difference (baseline–exit) in Hamilton scores and DG volume change



Figs. 3 and 4. Relationship between Hamilton and the left DG (left; Fig. 4) and right DG (right; Fig. 3) volume within subjects. Each line represents a single participant with each dot corresponding to two time points. The red dots represent the baseline measurement, the turquoise dots represent the exit measurement. A negative slope indicates that an increase in left/right DG volume is related to a decrease in Hamilton score. In other words, it displays the relationship between DG volume and Hamilton score within each individual. Volume (raw) is displayed in mm^3; Hamilton score is displayed as raw scores.

(exit–baseline). The linear regression model predicting decrease in depression scores with baseline volumes of the left and right DG, gender and age was significant ($F(4,14) = 3.382$, $p = 0.039$) explaining 49.2% of the variance (see Table 3). Baseline hippocampal volume did not predict clinical effect ($p > 0.05$).

DISCUSSION

We investigated the effect of electroconvulsive therapy on subfields of the hippocampus using ultra-high field MRI. Volume increases in the hippocampus during ECT were only found in the left and right DG, while other subfields were not affected. In addition, we showed that the increase in DG volume was related to the decrease in depression scores within individuals. These findings confirm our hypothesis that ECT increases the volume of the left and right DG in depression and point to neurogenesis as the mediating factor of anti-depressive effects. Indeed, baseline volume of the DG (together with age and gender) was a significant predictor of ECT effects, while total hippocampal volume at baseline was not. These findings suggest that the antidepressant effect of ECT is possibly mediated by neurogenesis and not by other physiological effects, such as angiogenesis, synaptogenesis, and sprouting, which would affect other hippocampal subfields as well.

Our results extend and complement clinical research into the effect of ECT on the hippocampus. Previous research has consistently shown volume increases in the left and right hippocampus (Gbyl & Videbech, 2018; Oltedal et al., 2018; Takamiya et al., 2018; Wilkinson et al., 2017). We extend this finding by showing that these volume changes pertain to the DG. A possible reason why earlier neuroimaging studies found global increases (Gbyl & Videbech,

Table 3. Linear regression predicting change in HAM-D score

Predictors	Beta	t	p
Left DG	−0.847	−3.43	0.004
Right DG	0.739	2.66	0.019
Gender	−0.346	−1.73	0.105
Age	0.103	0.496	0.628

Beta standardized coefficients, t statistic, p two-tailed p-value

2018; Takamiya et al., 2018; Wilkinson et al., 2017) or in multiple subfields (Abbott et al., 2014; Cao et al., 2018), may be that these studies were performed on 3T MRI machines without employing automatic volume selection planning, potentially blurring findings on subfield volumes. Indeed, the ability of a 3T MRI machine to accurately measure and segment subfields of the hippocampus has been questioned (Giuliano et al., 2017; Wisse et al., 2014; Yushkevich et al., 2010).

Recent meta-analyses reported that ECT-induced increases in total hippocampus volume are not correlated with clinical improvement (Gbyl & Videbech, 2018; Oltedal et al., 2018; Takamiya et al., 2018; Wilkinson et al., 2017). This finding is also observed in a recent study using a large sample (Oltedal et al., 2018). We show, however, that volume changes in the DG are significantly associated with a decrease in depression scores (correcting for the effects of age and gender, baseline depression scores, and baseline hippocampal volume). Moreover, we show that baseline DG volume significantly predicted clinical effect, while baseline total hippocampal volume did not.

To date, the animal analog of ECT, ECS, has yielded substantial information regarding the possible underlying neurochemical mechanism of ECT in humans. Most notably, neurogenesis in the granular layer of the DG has been reported as a robust effect of ECS in rodents and nonhuman primates (Ito et al., 2010; Madsen et al., 2000; Nakamura et al., 2013; Olesen et al., 2017; Perera et al., 2007; Rotheneichner et al., 2014). However, the link between neurogenesis and the antidepressant effects of ECT remains unclear (Olesen et al., 2017). In the present study we could not investigate the granular layer of the DG directly, however, our results corroborate these preclinical findings by showing a strong increase in volume, exclusively in the DG.

In addition to neurogenesis, ECS induces dendritic spine maturation of newly generated granular cells, and increases in dendritic spine density of mature granular cells (Zhao, Warner-Schmidt, Duman, & Gage, 2012). Furthermore, ECS stimulates an increase of granular cell mossy fiber sprouting to the CA3 region (Gombos, Spiller, Cottrell, Racine, & McIntyre Burnham, 1999; Lamont, Paulls, & Stewart, 2001; Vaidya et al., 1999). ECS has been shown to give rise to synaptogenesis and dendritic branching in the CA1 region of the rat hippocampus (Chen, Madsen, Wegener, & Nyengaard, 2009; Smitha, Roopa, Khaleel, Kutty, & Andrade,

2014). Another effect associated with ECS in rodents is angiogenesis and vascular remodeling in the DG and in the stratum lacunosum moleculare of the hippocampus (Ekstrand, Hellsten, Wennström, & Tingström, 2008; Girgenti, Collier, Sathyanesan, Su, & Newton, 2011; Hellsten et al., 2005; Newton, Girgenti, Collier, & Duman, 2006). Interestingly, although angiogenesis and neurogenesis in the DG often coincide and have been proposed as being dependent (Palmer, Willhoite, & Gage, 2000; Parent, 2007), research has shown that ECS can induce neurogenesis even in the absence of angiogenesis in the DG (Ekstrand et al., 2008). Last, ECS is able to induce gliogenesis in the molecular layer, granular layer, and hillus of the hippocampus (Kaae, Chen, Wegener, Madsen, & Nyengaard, 2012; Wennström, Hellsten, Ekstrand, Lindgren, & Tingström, 2006). Our results are partly in line with these preclinical studies, confirming the possibility of neurogenesis in both the left and right DG, but not of other processes such as gliogenesis or synaptogenesis in other parts of the hippocampus. Nevertheless, the absence of volume increase in the CA regions cannot be taken as proof to exclude other processes, since subtle, non-significant increases may be missed in this small sample. In addition, the increase in volume in the DG could also comprise of different processes (including, but not limited to, neurogenesis). However, given the large volume increases of both DG and its association to clinical recovery, we interpret these findings as an indication of neurogenesis.

Interestingly, neurogenesis in the hippocampus in animals has also been linked to several memory functions (Lieberwirth, Pan, Liu, Zhang, & Wang, 2016). In humans, neurogenesis in infancy underlies the effect of forgetting [e.g., in the process of infantile amnesia (Akers et al., 2014)]. The integration of new neurons into the hippocampal circuitry, which changes and remodels this circuitry, might disrupt previously stored memories (Akers et al., 2014; Frankland, Köhler, & Josselyn, 2013; Toda, Parylak, Linker, & Gage, 2018; Weisz & Argibay, 2012)]. Interestingly, ECT has also been shown to induce transient cognitive impairment (Nuninga et al., 2018; Semkovska & McLoughlin, 2010; Vasavada et al., 2017) and retrograde (autobiographical) amnesia (Sackeim, 2014). Based on the observation that ECT induces neurogenesis in preclinical studies and induced a specific increase in volume of the DG in the present study, it could be hypothesized that the formation of new neurons and their subsequent integration in hippocampal circuitry might underlie memory-specific adverse side effects of ECT. If this hypothesis is true, then the anti-depressive effect of ECT should be coupled to memory deficits induced, which can be tested in larger cohorts, such as the GEMRIC database.

The observation that (1) adults with depression have smaller hippocampi (Koolschijn, van Haren, Lensvelt-Mulders, Hulshoff Pol, & Kahn, 2009; Small, Schobel, Buxton, Witter, & Barnes, 2011) and (2) antidepressants increase neurogenesis in the dentate gyrus of the hippocampus (Malberg, Eisch, Nestler, & Duman, 2000; Santarelli, 2003) with a time gap corresponding to the delay between administration of antidepressants and clinical efficacy (Eisch & Petrik, 2012; Santarelli, 2003), led to the formation of the neurogenic hypothesis of depression. While the link between neurogenesis and antidepressants has been clearly established

(Eisch & Petrik, 2012; Eliwa, Belzung, & Surget, 2017; Santarelli, 2003), the question whether or not neurogenesis is responsible for the mechanism of action of antidepressant drugs remains under debate with some reports showing that antidepressants induce effects independent of neurogenesis, or neurogenesis independent of the antidepressant effect (David et al., 2009; Eisch & Petrik, 2012; Eliwa et al., 2017; Olesen et al., 2017). In the current study we show that baseline DG volume could predict antidepressant efficacy, and that change in DG volume is associated to clinical efficacy. Since these findings are correlative in nature, future studies using high field MRI and larger cohorts should investigate whether neurogenesis resulting from ECT is causative or necessary for the antidepressant effect or if it is an epiphenomenon.

Our study has several limitations which limit the generalizability of the results. First of all, the sample size is relatively small (resulting in possible type II errors). In total, 51 observations were made, resulting in 21 baseline–exit pairs (16 patients, 5 controls). To obtain as much information as possible from the data we employed linear mixed modeling for repeated measures to test for the effect of ECT on hippocampal subfields. However, large scale MRI studies, such as coordinated and recently published by the Global ECT-MRI Research Collaboration (GEMRIC) remain warranted (Oltedal et al., 2017, 2018). Second, 65% of the patient sample received antidepressant medication at baseline and exit. Antidepressant treatment (e.g., pharmacotherapy with Selective Serotonin Reuptake Inhibitors but also other classes of drugs such as tricyclic antidepressants) is able to induce neurogenesis in rodents and non-human primates (Malberg et al., 2000; Perera et al., 2011; Santarelli, 2003; Serafini et al., 2014; Tanti & Belzung, 2013). However, in our sample, antidepressants had been started many months (often years) before ECT and the dose of anti-depressive drugs was kept stable during ECT. Furthermore, patients who received antidepressant drugs at baseline did not differ in baseline DG volume from those who did not, neither did patients receiving antidepressant drugs at exit differ significantly in exit DG volume nor in the difference between baseline and exit volumes (all $p > 0.05$).

In conclusion, we report that ECT induces volume increases in the left and right hippocampus, observed exclusively in the DG. In addition, we show that the increase in DG volume is positively associated to clinical improvement, while volumes of other subfields were not associated with outcome. Finally, we report that baseline DG volumes (together with age and gender) significantly predict a decline in depression scores, yet baseline total hippocampal volume did not. This suggests that the DG, and probably neurogenesis which takes place exclusively in the DG, play an important role in the antidepressant effect of ECT.

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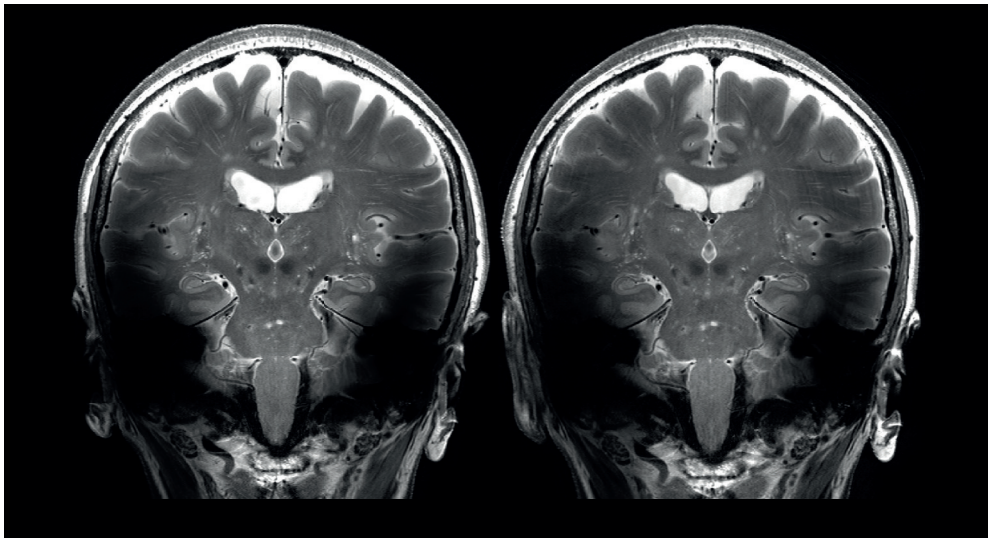
Supplementary materials



Supplementary figure S1. Two scans at the exact same slice of the same participant at baseline (left) and exit (right).

SUPPLEMENTARY S2. POST-HOC ANALYSES

As a post-hoc analysis, we compared baseline with exit scores for each subfield separately for controls and patients with a paired t-test. To control for multiple testing, for significant p-values ($p < .05$, two-sided), we calculated false discovery rates (Benjamini-Hochberg procedure as implemented in R; Benjamini and Hochberg, 1995) where a p-value is considered as significant if $p.adjust_i \leq .05$, where $p.adjust_i$ is determined by the rank (R_i) of the p-value (p_i) and the number of tests (n): $p.adjust_i = pi*(n/R_i)$. Using post hoc paired sample t-tests, assessing the difference between baseline and post treatment in all the hippocampal subfields, the same results were obtained (see supplementary S4). Specifically, volume increases were observed in the DG ($p < .001$), and in the left ($p < .001$) and right DG ($p < .001$) in the patient group. None of the other subfields in the patient group differed significantly between baseline and exit (all $p > .05$). Also, none of the subfields differed significantly between baseline and exit in the healthy control group (all $p > .05$; see supplementary S4).

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Supplementary S3. LMM for patients (22) and controls (8)

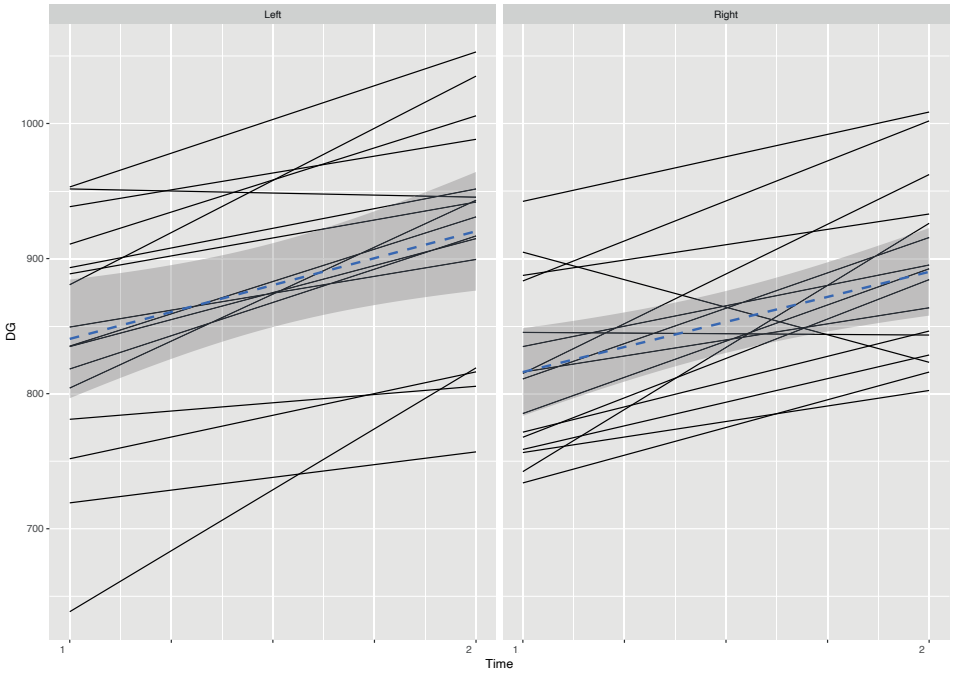
Subfield	Group	Contrast	SE	t	df	sig
DG	Patient	75.22	9.55	-2.57	41.23	0.01
	Control	25.10	17.04			
CA1	Patient	20.90	14.01	-0.09	41.02	0.93
	Control	18.43	25.02			
CA2	Patient	22.25	34.84	0.88	76.71	0.38
	Control	82.35	59.47			
CA3	Patient	73.40	47.55	-1.33	70.66	0.18
	Control	-51.44	82.00			
ERC	Patient	11.86	12.82	0.33	34.93	0.74
	Control	20.44	22.61			
SUBI	Patient	17.02	7.26	-0.32	45.22	0.75
	Control	12.37	12.88			
CS	Patient	31.79	48.70	1.23	76.63	0.22
	Control	149.96	84.42			
B35	Patient	-4.56	25.29	-1.37	56.99	0.18
	Control	-72.62	43.49			
B36	Patient	56.04	29.64	-1.52	44.09	0.14
	Control	-35.18	52.66			

Contrast = contrast exit – baseline based on estimated marginal means from the model; standard error; t = t-statistic for interaction group*time; df = estimated degrees of freedom (Satterthwait's method); sig = p-value for interaction term.

Supplementary S4. Paired samples t-test patients (16) and controls (5)

Subfield	Group	Diff.	ES	t	p	Fdr corrected p*
DG	Patients	153.86	1.49	5.95	0.000026	0.000468
	Controls	50.38	0.52	1.164	0.309	
Left DG	Patients	79.68	1.63	6.52	0.00001	0.00036
	Controls	34.20	0.51	1.15	0.315	
Right DG	Patients	74.18	1.22	4.86	0.00021	0.0038
	Controls	16.182	0.39	0.877	0.43	
CA1	Patients	45.38	0.41	1.64	0.122	
	Controls	32.17	0.19	0.42	0.694	
CA2	Patients	60.66	0.15	0.58	0.559	
	Controls	203.60	0.48	1.08	0.343	
CA3	Patients	210.09	0.42	1.70	0.110	
	Controls	-228.94	0.40	-0.90	0.418	
ERC	Patients	22.28	0.17	0.69	0.500	
	Controls	28.10	0.25	0.56	0.606	
Subi	Patients	36.94	0.50	1.99	0.065	
	Controls	18.64	0.39	0.88	0.429	
CS	Patients	119.74	0.29	1.18	.258	
	Controls	264.00	0.72	1.61	0.183	
B35	Patients	-11.21	0.08	-0.33	0.791	
	Controls	-168.58	0.54	-1.20	0.296	
B36	Patients	116.17	0.43	1.73	0.104	
	Controls	-53.27	0.30	-0.67	0.539	

*= only shown for significant results and corrected for 36 comparisons (9 subfields, left and right, patients and controls = 36 comparisons) and 18 for 9 subfields and patients and controls; diff = difference between baseline and exit; p = p-value; t = t-statistic with df 15 for patients and 4 for controls; ES = effect size d for paired observations.



Supplementary 5. Spaghetti plots showing raw volumetric data for time point 1 (baseline) and time point 2 (exit) for the DG. All but one participant show an increase in volume.

Supplementary S6 – full model output of models referred to in the main manuscript

Model 1: Volume of DG given by Time, Type (patient/control), Age and Gender

Predictors	Estimates	95% CI	Statistic	p
(Intercept)	896.57	758.18 – 1034.97	12.70	<0.001
Time	-25.08	-34.63 – -15.53	-5.15	<0.001
Type	-18.89	-64.37 – 26.59	-0.81	0.423
Age	-1.15	-3.76 – 1.47	-0.86	0.399
Gender	3.32	-42.03 – 48.66	0.14	0.887
Time*Type	-12.53	-22.08 – -2.98	-2.57	0.014
ICC ID	0.94			
Observations	102			
Subjects	30			
Conditional R2	0.947			

ICC = interclass correlation coefficient; Time = baseline/exit; Type = patients/controls; CI = 95% confidence interval; Statistic = t-statistic

Model 2a: Volume of DG in patients given by Time, Age and Gender.

Predictors	Estimates	95% CI	Statistic	p
(Intercept)	766.50	597.56 – 935.43	8.89	<0.001
Time	75.44	56.5 – 94.3	7.82	<0.001
Age	-0.98	-4.14 – 2.18	-0.61	0.549
Gender	-17.61	-77.74 – 42.51	-0.57	0.573
ICC ID	0.91			
Observations	76			
Subjects	22			
Conditional R2	0.915			

ICC = interclass correlation coefficient; Time = baseline/exit; CI = 95% confidence interval; Statistic = t-statistic;

Model 2b: Volume of DG in controls given by Time, Age and Gender.

Predictors	Estimates	95% CI	Statistic	p
(Intercept)	971.14	796.59 – 1145.69	10.90	<0.001
Time	22.69	-6.96 – 52.33	1.50	0.154
Age	-2.58	-5.87 – 0.71	-1.53	0.184

Continues on next page

Model 2b (continued)

Predictors	Estimates	95% CI	Statistic	p
Gender	42.41	-1.67 – 86.50	1.89	0.114
ICC ID	0.49			
Observations	26			
Subjects	8			
Conditional R2	0.882			

ICC = interclass correlation coefficient; Time = baseline/exit; CI = 95% confidence interval; Statistic = t-statistic;

Model 3a: Volume of left DG in patients given by Time, Age and Gender

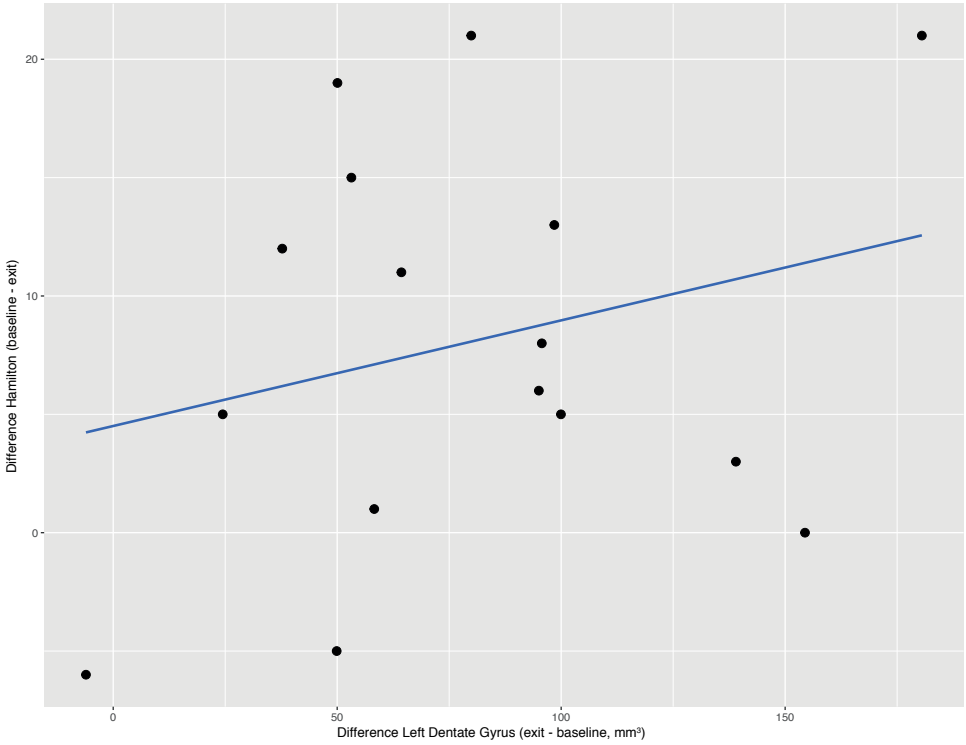
Predictors	Estimates	95% CI	Statistic	p
(Intercept)	841.64	652.65 – 1030.63	8.73	<0.001
Time	78.30	54.28 – 102.31	6.39	<0.001
Age	-0.92	-4.46 – 2.63	-0.51	0.617
Gender	8.28	-126.60 – 143.15	0.12	0.906
ICC ID	0.94			
Observations	38			
Subjects	22			
Conditional R2	0.941			

ICC = interclass correlation coefficient; Time = baseline/exit; CI = 95% confidence interval; Statistic = t-statistic;

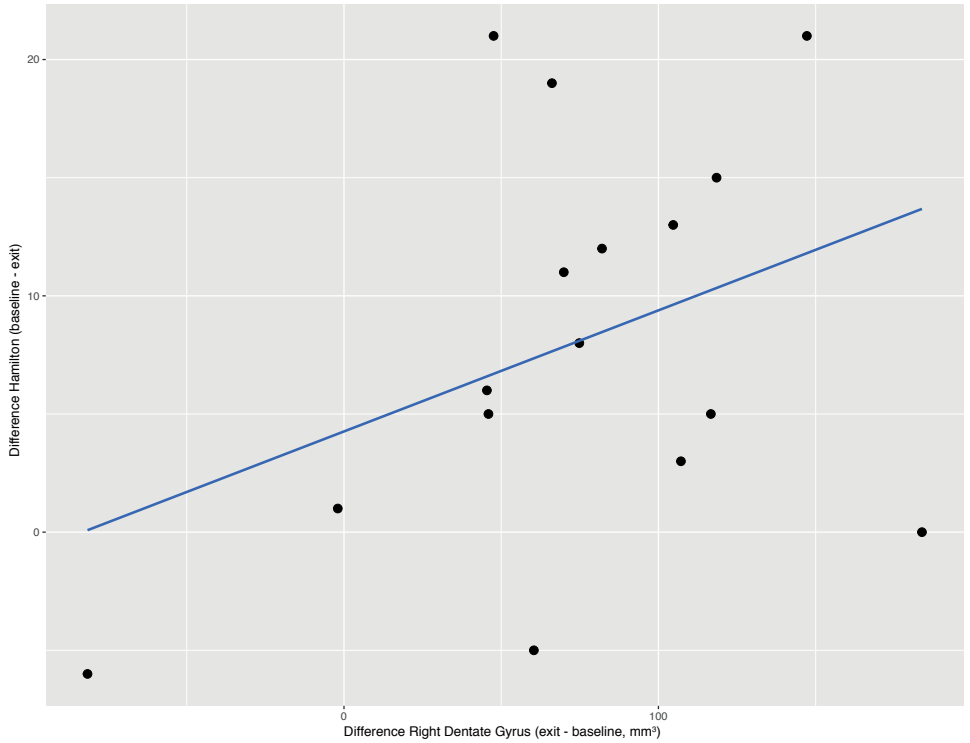
Model 3b: Volume of left DG in patients given by Time, Age and Gender

Predictors	Estimates	95% CI	Statistic	p
(Intercept)	818.80	648.77 – 988.83	9.44	<0.001
Time	70.14	39.87 – 100.42	4.54	<0.001
Age	-0.97	-4.16 – 2.22	-0.60	0.551
Gender	46.61	-74.71 – 167.93	0.75	0.451
ICC ID	0.87			
Observations	38			
Subjects	22			
Conditional R2	0.887			

ICC = interclass correlation coefficient; Time = baseline/exit; CI = 95% confidence interval; Statistic = t-statistic;



Supplementary S7. Plot showing the difference in Hamilton score (baseline – exit) on the y-axis and difference in volume of the left DG (in mm3) on the x-axis. The blue line indicates a simple linear regression line on these values.



Supplementary S8. Plot showing the difference in Hamilton score (baseline – exit) on the y-axis and difference in volume of the right DG (in mm3) on the x-axis. The blue line indicates a simple linear regression line on these values.

CHAPTER 4

A collection of letters

LETTER 1

Volume Increase of the Dentate Gyrus Induced by Electroconvulsive Therapy: Shedding Light on the Clinical Relevance of Plasticity in the Hippocampus

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Journal of ECT, 2019, 35(4), e57-e58

DEAR EDITOR:

While the underlying mechanisms of electroconvulsive therapy (ECT) remain unknown, volume increase in the hippocampus has been consistently reported (Nuninga et al., 2019; Oltedal et al., 2018; Takamiya et al., 2018, 2019) since the first study by Nordanskog et al in the Journal of ECT (Nordanskog et al., 2010). To date, the role of this volume increase, as well as whether it contributes to or is responsible for the effectiveness of ECT, is unclear. In this letter, we reanalyzed the data from a previous study (Takamiya et al., 2019), replicating a recent finding (Nuninga et al., 2019), showing that an increase in volume of the dentate gyrus (DG) is related to improvement in depressive symptoms. This replication sheds light on the relationship between volume increase and the clinical effect of ECT. Furthermore, we briefly discuss the importance of using sensitive statistical techniques to investigate the effectiveness of ECT.

The finding of ECT-induced hippocampal volume increase is consistent with multiple lines of evidence from animal studies, which have shown that electroconvulsive stimulation induced neuroplasticity in the hippocampus, including neurogenesis, synaptogenesis, gliogenesis, and angiogenesis, of which neurogenesis is the most robust finding (Bouckaert et al., 2014) . Surprisingly, previous studies found no significant correlation between hippocampal volume change and clinical improvement (Oltedal et al., 2018; Takamiya et al., 2018), yet the number of ECTs, electrode placement (Oltedal et al., 2018), or even cognitive changes resulting from ECT (Bouckaert et al., 2014) have been put forward as possible explanations of ECT-related hippocampal volume change. However, the hippocampus is a multilayer structure with each substructure comprising different functions. Therefore, analyzing the whole hippocampus might not be accurate to detect a relationship between volume change and clinical improvement. Recent technological advances in neuroimage (post)processing enabled us to calculate volumes of each hippocampal subfield. Given the strong and robust finding of neurogenesis in the DG (possibly the only neurogenic region of adult human brain) after electroconvulsive stimulation in preclinical studies, several authors suggested that the volume increase of the hippocampus will selectively pertain to the DG (Nuninga et al., 2019; Takamiya et al., 2018).

In our original study (Takamiya et al., 2018), we reported that hippocampal volume increase induced by bilateral ECT was mostly driven from volume increase in the DG and that remitters showed larger volume increase in the right DG than nonremitters. However, we did not find a linear correlation between volume change in the right DG and change in Hamilton Depression Rating Scale (HAM-D) scores. Nuninga et al. (2019), however, showed that the effect of ECT was specific to the DG by using a 7-T magnetic resonance imaging (MRI) and that volume changes in the DG were significantly correlated with change in HAM-D scores. One major difference between these 2 studies is the field strength (i.e., 3 T vs 7 T) ofMRI (increasing the accuracy of subfield delineation). In addition, Nuninga et al. (2019), investigated the relationship between volume change of the DG and clinical effect with a repeated measures correlation (rmcorr) (Bakdash & Marusich, 2017), whereas we used a simple linear

correlation. Rmcorr accounts for nonindependence among observation and adjust for interindividual variability. Moreover, it evaluates intraindividual association between 2 measures, and parallel lines are fit to the data from each participant. The benefits of rmcorr include higher statistical power than simple correlation. Because of these advantages, rmcorr seems more suitable than simple linear correlation for data from a pre-ECT/post- ECT design. Therefore, we reanalyzed our data in collaboration with Nuninga et al. (2019), using the statistical package R (version 3.4.3) and rmcorr.

As a result, we now found a statistically significant negative correlation between HAM-D score and the right DG volume ($r = -0.46$; $P = 0.018$; 95% confidence interval, −0.72 to −0.07), but no significant result in the left DG ($r = -0.35$; $P = 0.076$; 95% confidence interval, −0.66 to 0.06). The negative correlation indicates that an increase in the DG volume is associated with a decrease in HAM-D score. We did not find any correlations between HAM-D score and the other subfields. Even though our data were from 3 T MRI scanner, our reanalyzed results are consistent with the previous study (Nuninga et al., 2019) and also support the hypothesis that neuroplasticity underlies the efficacy of ECT.

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LETTER 2

The dentate gyrus in depression: directions for future research

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TO THE EDITOR:

Koch et al. (2019) discuss our results regarding volume increases in the dentate gyrus (DG) (Nuninga et al., 2019) in the interesting context of research into stress-related disorders and fear generalization in combination with neurogenesis. While our research included severely depressed patients, Koch et al. (2019) raise the possibility that findings may be generalized to wider diagnostic groups, including trauma patients (i.e., PTSD) and patients with an anxiety disorder. In the following we would like to discuss this wider interpretation of our results and shed light on the further steps needed to be taken in years to come. We recognize that our work serves as a next step into understanding the molecular mechanisms behind severe depression (and perhaps other stress-related disorders) and the development of new therapies aiming to correct pathophysiological mechanisms.

In short, using 7-tesla magnetic resonance imaging (MRI) we found that after ten sessions of electroconvulsive therapy (ECT) the volume of the DG was significantly increased in severely depressed patients, leaving the other subfields of the hippocampus unaffected. These findings point in the direction of increased neurogenesis after ECT, although other functional recovery processes (such as synaptogenesis, axonal sprouting, and angiogenesis) may also contribute to the increase in volume. In healthy controls (n = 8), this increase was not present. In addition, we found that baseline DG volume could predict clinical response (measured with the 17-item Hamilton Depression Rating scale; HAM-D, where higher scores indicate more severely depressed patients) in a regression model. Furthermore, we found that the change in volume was associated to a change in HAM-D score (i.e., larger treatment responses were associated to greater increases in volume). Importantly, our technical equipment has two major advantages:

- We used ultra-high field MRI (7 tesla), which enabled us to focus on the hippocampal area with resolution of 0.286 × 0.286 × 2 mm, a considerable higher image resolution than previous work.

- We used automatic scan planning, which enabled us to rescan the exact same location using the exact same angulation on both occasions, which substantially increases sensitivity to volume changes.

As we included severely ill patients (mean baseline Hamilton score of 22.59) it was extremely challenging to motivate and engage participants to complete both scan sessions, which resulted in a small sample size (N = 23 patients). Our findings trigger other questions and together with Koch and other authors in the field, we can now design a path to further answer remaining questions in order to come to rapid, new, and better tolerated treatment options for severely ill patients.

In answer to the first point raised by Koch et al. (2019), regarding the difference of

DG baseline volume between patients and controls, we did not find a significant difference of baseline DG volumes (left and right) between patients and controls (difference left DG patients – controls = –33.03 mm^3, Cohen's d = –0.32, difference test t = –0.69, p = 0.51; difference right DG patients – controls = –19.90 mm^3, Cohen's d = –0.26, difference test t = –0.5, p = 0.63). The volumes at post treatment of the left and right DG of patients are not statistically different from that of the controls (difference left DG patients – controls = –1.38 mm^3, Cohen's d = –0.012, difference test t = –0.03, p = 0.97; difference right DG patients – controls = –0.45 mm3, Cohen's d = –0.004, difference test t = –0.01, p = 0.99). A second question raised by Koch et al. (2019), concerns the association between DG volumes and depression severity at baseline. Koch et al. state that baseline volumes of the DG could be associated to depression severity and that this association could explain the predictive effect of DG volumes. However, we do not find an association between left or right DG and depression severity at baseline in the patient group (left r = –0.21, p = 0.37, right r = 0.28 p = 0.24). Moreover, including depression severity at baseline in our regression model predicting clinical change, did not change our results: baseline DG volume (left/right) still predict treatment response (in the patient group). Therefore, predicting treatment response based on baseline DG volumes cannot be explained by depression severity at baseline in our sample (although the effect of depression severity could be missed due to possible type II errors). Further, left and right DG have opposite effects in the linear regression model predicting clinical response. At baseline a smaller left DG is associated with better response, while for the right DG the inverse seems true. Interestingly, when computing the widely used asymmetry index ((left – right)/ (left + right) (Kurth, Gaser, & Luders, 2015; Postema et al., 2019) for the DG, the index is able to predict the response of ECT (t = –3.44, p = 0.004). This prediction model, with age and gender as covariates, is significant and explains 45.8% of the variance ($F(3,15) = 4.23$, p = 0.02). Again, inclusion of baseline Hamilton scores does not significantly change the results (the asymmetry index remains a significant predictor: t = –2.68, p = 0.018). Whether this observation will hold in larger samples, and especially at conventional (3 tesla) MRI, will be a valuable clinical question. Specifically, when this observation holds at 3 tesla MRI it could be more easily implemented in the clinic to help predict clinical response for individual patients (in combination with the help of other predictors, e.g., DG related tasks such as pattern separation).

For further research, a first important question is to answer whether or not the findings (i.e., a significant increase in volume of the DG after ECT in severely depressed patients) from our previous study (Nuninga et al., 2019) using ultra-high field MRI can be replicated with standard clinical MRI scanners operating at 3 tesla. To answer this first question, we collaborated with a group from Tokyo University. Together with Takamiya et al. we reanalyzed their previously published data (Takamiya, Plitman, et al., 2019), now reporting a significant correlation between changes in DG volume and clinical response after bilateral ECT in an independent sample using 3 tesla MRI (Takamiya, Nuninga, et al., 2019). In the aforementioned previously published study (Takamiya, Plitman, et al., 2019), Takamiya et al. reported

volume changes in DG volumes but did not find a simple linear correlation between difference scores in DG volume and HAM-D. However, when they implemented the same repeated measures correlation (Bakdash & Marusich, 2017) we used in our study (Nuninga et al., 2019), a significant correlation was found between a decrease in HAM-D score and an increase in right DG volume [yet not significant in left DG (Takamiya, Nuninga, et al., 2019)]. This finding again highlights the importance of the DG and neuroplastic changes in the DG in response to ECT treatment and suggests feasibility of replicating our findings using conventional 3 tesla MRI.

The next questions to answer regards the generalizability of our findings as well as a confirmation that they are related to neurogenesis. Now that we have a replicable method to assess DG volume and changes in that volume during recovery, we and others can set out to assess whether volumetric changes are related to plastic changes of the DG during remission. Second, animal research using both MRI and post-mortem quantification of neurogenesis is needed to confirm our theory that DG changes are caused by neurogenesis. If volumetric changes reflect plastic changes of the DG during recovery and if decreased plasticity of the DG can be confirmed to underlie the broader category of stress related disorders, this would be a major aid to develop new treatments targeting this mechanism.

In terms of treatment, while ECT is highly effective, its tolerability is low, which restricts it use. Previous animal research has delivered a wealth of information regarding processes that can positively impact neurogenesis, which include: fasting for at least 24 h (Lee, Duan, & Mattson, 2002) physical exercise [especially running (van Praag, Kempermann, & Gage, 1999)], sleep (Hairston et al., 2005) and demanding cognitive tasks (Shohayeb, Diab, Ahmed, & Ng, 2018). We envision a treatment with intensive use of these four elements as an effective and noninvasive new treatment for depression and perhaps other stress-related disorders. An extra challenge will be the motivation of patients for such a combined intervention. To this end, we may use knowledge from the gaming industry to develop an attractive and engaging program that motivates even apathic participants to continue their practice in order to stimulate neurogenesis and help patients overcome

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CHAPTER 5

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

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ABSTRACT

Background: Volume increases of the hippocampus after electroconvulsive therapy (ECT) are a robust finding, pointing into the direction of neurogenesis. However, such volumetric increases could also be explained by edema and/or neuroplastic changes (such as angiogenesis).
Objectives: If edema explains the volume increase of the hippocampus we hypothesize it would lead to increased mean diffusivity (MD). If neuroplastic would explain the volume increase, it would lead to decreased MD. To investigate angiogenesis as explanation we studied the perfusion fraction f and the pseudodiffusion component D* obtained from intravoxel incoherent motion (IVIM) data, and relative perfusion changes obtained from arterial spin labelling (ASL) data.
Methods: Using ultra-high field (7 tesla) MRI we acquired IVIM and ASL data. We compared MD, *f*, D* and ASL values for both hippocampi in 21 patients (before and after 10 ECT sessions) and 8 healthy controls (without ECT) in a linear mixed model adjusting for age and gender.
Results: We found a significant decrease in MD (which was absent in the healthy controls) in the left and right hippocampus ($t = 3.98$, $p < 0.001$). In addition, a decrease in *f* ($t = 4.61$, $p < 0.001$, but not in controls) and no differences in D* or ASL perfusion values (both $p > 0.05$) were found.
Conclusions: The decrease in MD and in perfusion fraction f suggest that formation of edema nor angiogenesis are responsible for the ECT-induced volume increases in the hippocampus. Also, it supports the hypothesis that hippocampal volume increases might be due to neuroplastic changes.

INTRODUCTION

Originated in the 1930s, electroconvulsive therapy (ECT) is the most effective treatment for severe major depression (Dierckx, Heijnen, van den Broek, & Birkenhäger, 2012; Kellner et al., 2015; Pagnin, de Queiroz, Pini, & Cassano, 2004; UK ECT Review Group, 2003), and is still widely used today to treat refractory depressive disorders. Research over the past decades focused on elucidating the mechanism by which ECT exerts its beneficial effects. These efforts, benefitting from technological advancements of studying the brain in vivo and drawing from preclinical studies, yielded several important insights (Gbyl & Videbech, 2018; Payne & Prudic, 2009).

Compelling evidence suggest that a series of ECT treatments increases the volume of the hippocampus (Nuninga et al., 2019; Oltedal et al., 2018; Takamiya et al., 2018). Interestingly, this increase selectively pertains to the dentate gyrus [DG (Nuninga et al., 2019; Takamiya et al., 2019], the primary neurogenic region of the human adult brain [alongside the subventricular zone (Ming & Song, 2011; Toda, Parylak, Linker, & Gage, 2018)]. The observation of DG volume increase adds to the plasticity hypothesis of the working mechanism of ECT (Bouckaert et al., 2014; Koch, Morey, & Roelofs, 2019), suggesting that neurogenesis in the DG is related to the anti-depressive effect of ECT. However, other processes could also contribute to the volume increase seen in the DG. For example, preclinical evidence suggests that plastic changes such as angiogenesis or synaptogenesis, might contribute to volume increases in the DG (Chen, Madsen, Wegener, & Nyengaard, 2009; Hellsten et al., 2005; Newton, Girgenti, Collier, & Duman, 2006). But, less beneficial processes such as the formation of edema could also contribute to volume increases.

In a previous study we used ultra-high field (7 T) magnetic resonance imaging (MRI) to measure changes in volume of the hippocampal subfields after ECT and reported a significant increase in volume exclusively for the DG (Nuninga et al., 2019). To investigate whether this observed increase of DG volume could be explained by either angiogenesis or edema we now investigate the hippocampus using diffusion weighted imaging (DWI; specifically, we acquired intravoxel incoherent motion (IVIM) data) and arterial spin labelling (ASL) in the same patient group receiving ECT. We also included a control group to assess whether changes found after ECT were due to systematic MRI scanner artifacts (such as scanner drift).

To investigate whether edema contributes to the increase in DG volume we compared the mean diffusivity (MD) of water molecules pre and post ECT. The restriction of diffusion of water molecules in the brain can be measured via diffusion weighted imaging and expressed in MD values, where low MD values reflect high restriction of water molecules (e.g. restriction due to cells, axons, dendrites etc.). In the human brain, three major types of cerebral edema can be observed: vasogenic (i.e. accumulation of extracellular fluids due to impairments of the blood-brain-barrier), cytotoxic (i.e. cell swelling due to cellular injury), and interstitial (caused by cerebrospinal fluid (CSF) entering the brain via the ependymal

lining in the case of obstructive hydrocephalus) edema (Ho, Rojas, & Eisenberg, 2012; Qureshi & Suarez, 2000; Unterberg, Stover, Kress, & Kiening, 2004). Since interstitial edema is associated to hydrocephalus, it is not expected to explain the volumetric increase in the DG/hippocampus. Vasogenic edema constitutes the accumulation of extracellular fluid, and therefore, it may be reflected as an increase in MD in the hippocampus (Barzó, Marmarou, Fatouros, Hayasaki, & Corwin, 1997). In contrast, for cytotoxic edema a decrease in MD will be expected since the influx of extracellular fluids into the cells will cause swelling at the expense of the extracellular space (Barzó et al., 1997). However, cytotoxic edema does not result in tissue swelling (only cell swelling), since there is a redistribution of fluids from outside the cells to inside the cells and no new fluids are added to the tissue involved, making this option less likely to explain the growth in volume of the hippocampus (Stokum, Gerzanich, & Simard, 2016). If the increase in volume could be explained by neuroplasticity a decrease in MD will be expected since the extracellular space will be filled with newborn cells, axons, synapses, dendrites, thus decreasing the MD (i.e. diffusion will be restricted by new tissue). In clinical and preclinical ECT literature to date, no cases of cytotoxic edema have been reported. In contrast, increased permeability of the blood brain barrier (BBB) with mild vasogenic edema has been reported as an effect of ECT (Andrade & Bolwig, 2014).

To study perfusion characteristics of the hippocampus we acquired IVIM and ASL data (Le Bihan et al., 1988; Le Bihan, 2017). The IVIM framework builds upon the observation that at low b-values (e.g. 0-200 s/mm2) the observed MR signal is not only influenced by apparent diffusion, but also by the perfusion of tissue (Le Bihan, 2017; Paschoal, Leoni, dos Santos, & Paiva, 2018). Within the IVIM framework, the effects of perfusion can be disentangled from that of diffusion at low b-values, commonly resulting in two perfusion parameters: the perfusion fraction *f* and the pseudo diffusion component D* (Le Bihan, 2017; Paschoal et al., 2018). These IVIM parameters have been shown to reflect angiogenesis and correlate with the density of microvessels in biological tissue (Lee et al., 2014). Next to IVIM imaging, non-invasive, and more direct MRI measurements of perfusion can be obtained by arterial spin labelling (ASL). We employed IVIM and ASL in the hippocampus to see whether perfusion in the hippocampus increases after a series of ECT treatments. If ECT stimulates angiogenesis, this would lead to an increase in perfusion in the hippocampus that could potentially be measured with both IVIM and ASL. We hypothesize that if edema takes place after ECT this will be reflected in increased MD, while a decrease in MD will reflect restricted diffusion due to neuroplastic changes of the hippocampus including but not limited to neurogenesis (exclusively in the DG), synaptogenesis and angiogenesis. Furthermore, based on preclinical literature suggesting angiogenesis in the hippocampus after electroconvulsive seizure (ECS), we hypothesize that if angiogenesis takes place in the hippocampus, this will be reflected in an increase in perfusion.

METHODS

SAMPLE

All patients and controls were recruited at the University Medical Centre (UMC) Utrecht (The Netherlands) as part of a larger study into the effects of ECT on depression, cognition and brain measurements. For patients we used the following inclusion criteria: 1) age over 18 years, 2) a diagnosis of uni- or bipolar depression [as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), 2000 criteria], 3) an indication for electroconvulsive therapy (based on the Dutch guidelines for ECT). Exclusion criteria constituted: 1) treatment with ECT in previous 6 months, 2) contraindication for MRI (e.g. a pacemaker), 3) brain pathology, 4) major medical conditions (e.g. coronary heart disease), 5) pregnancy and/or lactation.

Healthy controls were included based on the demographic characteristics of the patients' sample and matched for age, sex and education. The only inclusion criterion constituted: an age over 18 years. The exclusion criteria were: 1) a (history of a) psychiatric disorder [as assessed with the MINI interview (van Vliet & de Beurs, 2007), Dutch version], 2) contraindication for MRI (e.g. a pacemaker), 3) other brain pathology, 4) major medical conditions (e.g. coronary heart disease), 5) pregnancy and/or lactation. Controls were included for the purpose of assessing whether brain changes found are due to systematic variations between the scan sessions (e.g. scanner drift).

Written informed consent was obtained from every participant prior to participation. The study was approved by the local Medical Ethics Board of the UMC Utrecht. In total, 38 participants were included based on the in- and exclusion criteria (26 patients, 12 controls).

ECT TREATMENT

Electroconvulsive therapy treatment was carried out with a Thymatron IV ECT machine (bifrontotemporal electrode positioning, stimulus intensity of 150% of the titrated seizure threshold). ECT was given twice a week, for five consecutive weeks, leading up to a total of 10 ECT sessions. Patients were excluded from the analysis when they received less than 10 ECT sessions (one patient in the current study). The baseline MRI measurement was planned in the week prior to the first ECT session (usually the day before). To minimize variability, patients were scanned in the exit assessment in the week after the tenth ECT session (usually one day after the tenth session). Patients received extra ECT sessions after the exit assessment if clinically indicated.

An anaesthetic drug (etomidate/methohexital) and a muscle relaxant (succinylcholine) was administered prior to delivering the electrical current. A trained psychiatrist (or resident) delivered the electrical current while an anesthesiologist and licensed nurse monitored the patients' vital signs. An electroencephalogram was recorded from a single channel (right frontomastoid placement). A motor seizure duration of at least 20s had to be observed for an ECT session to be considered successful (based on the Dutch guidelines on ECT; Broek,

Birkenhäger, Boer, & Burggraaf, 2010). If a motor seizure duration of <20s was observed, a new current was delivered with an energy increase of 5-10% (with a maximum of three attempts). For all patients, seizure duration of >20s was observed on every ECT session.

MAGNETIC RESONANCE IMAGING ACQUISITION

All magnetic resonance imaging (MRI) data was acquired using a 7T magnetic resonance imaging scanner (MRI; Philips Healthcare, Best, the Netherlands) with a 32-channel head coil (Nova Medical, Wilmington, MA, USA). A 3D T1-weighted TFE scan was acquired (voxel size 1mmisotropic; TR/TE 5.5/2.04 ms; flip-angle 6°; field of view (FOV) 256 × 256 × 190; number of slices 190). Also, a 3D T2- weighted TSE scan was acquired (voxel size = 0.286 × 0.286 mm^2 in plane resolution, 2 mm slice thickness; TR/TE 3800/60 ms; flip angle 90°; FOV = 60 × 220 × 220; number of slices 30). Given that the voxel size is highly anisotropic, it is important that the FOV of the pre and post scan are placed exactly the same. To this end, we used automatic scan planning (SmartExam planning) automatically placing the FOV based on a number of anatomical characteristics of the head (extracted from a T1-weighted scan acquired before each T2-weighted scan). An IVIM scan (1.5 mm isotropic voxel size; FOV 160 × 160 × 30; EPI factor = 55; TR/TE: 3605/60.25 ms; flip angle 90°; no gap; no cardiac gating) was acquired with 46 volumes consisting of one b = 0 s/mm2 volume and 15 b-weighted volumes (3 volumes with orthogonal directions per b-value: 2, 4, 6, 8, 10, 25, 50, 75, 100, 200, 300, 400, 600, 800, 1000 s/mm^2). A single slice flow sensitive alternating recovery (FAIR) ASL scan was acquired (voxel size = 1.875 × 1.875 × 3mm; TR/TE = 1400/13.1 ms; FOV 128 × 128 × 1mm; flip angle 90°). Additionally, an Mo image (voxel size = 1.875 × 1875 × 3mm; TR/TE = 2000/13.1 ms; FOV 128 × 128 × 1mm3; flip angle 90°) was acquired to internally scale the perfusion images. The purpose of including an ASL scan was solely to confirm a possible increase in perfusion in the hippocampus as measured with IVIM.

MAGNETIC RESONANCE IMAGING PROCESSING

All data was processed using FSL, MRtrix3, ANTs, R (version 3.5.0) and MATLAB tools (Avants et al., 2011; "MATLAB R2017b" 2017; R Core Team, 2013; Smith et al., 2004; Tournier, Calamante, & Connelly, 2012). For a detailed outline of the processing of the T1-weighted and T2-weighted data and segmentation of the hippocampus please see Nuninga et al., (2019). In short, T2-weighted images were processed via the Automated Segmentation of Hippocampal Subfields (ASHS) pipeline, and ANTs tools (Avants et al., 2011; Wisse et al., 2016; Yushkevich et al., 2015). Given that the voxel resolution of the IVIM scan is relatively large (1.5 mm, isotropic) the hippocampus was chosen as a region of interest (ROI) and not the hippocampus subfields.

IVIM datasets were preprocessed using FSL [version 5.0.9 (Smith et al., 2004)] and MRtrix3 tools (Tournier et al., 2012) and MATLAB ("MATLAB R2017b," 2017) functions. First, the data was denoised, using dwidenoise (Veraart et al., 2016). Afterwards, the data was corrected for eddy currents, subject motion and bias of the main magnetic field using

various FSL and MRtrix tools (Andersson & Sotiropoulos, 2015; Smith et al., 2004; Tournier et al., 2012). The IVIM model was fitted to the preprocessed data with a segmented fit [provided in the package IVIM Model fitting (Jalnefjord et al., 2018) for MATLAB] estimating D for all b > 120 s/mm^2. We note that for IVIM parameter estimation D was estimated at b > 120 s/mm2, however the MD is computed from a subset of the IVIM volumes with stronger diffusion weightings (500 s/mm^2 < b < 1100s/mm^2), which renders it sensitive to diffusion of water in the extracellular space (Fornasa, 2011; Le Bihan et al., 1988; Le Bihan, 2017). IVIM maps were computed for the perfusion fraction *f*, and the pseudo diffusion component D*. The diffusion unweighted (b = 0) volume was extracted from the IVIM data and registered to the T2-weighted scan using affine registration, this registration was applied consecutively to the IVIM maps (Avants et al., 2011). The hippocampal segment yielded by ASHS (see previous paper (Nuninga et al., 2019)) was used as a ROI to extract the f and D* values from the IVIM maps. These values were subsequently imported into R for statistical analyses (see 'Statistical analyses' below).

To assess the diffusivity characteristics of tissue in the hippocampus, the mean diffusivity (MD) was calculated at each voxel using FSL's dtifit on high b-values 600-1000 s/mm^2 from our dataset (preprocessed as stated above; high b-values were chosen to minimize effects of perfusion influencing the MD values). Using the previously computed affine transformation the MD maps were registered to high resolution T2-space, where the hippocampal segments were available for data extraction. MD values for the hippocampus were subsequently extracted and imported into R for further analysis.

ASL datasets were processed with in-house developed functions for MATLAB. Because the only purpose of including ASL data was to see if ASL results corroborated the IVIM findings (and absolute quantification of ASL 7T FAIR data is not straightforward) no quantification of the ASL data was done. Instead, we computed the average difference between the control and the tag images (both part of the ASL scan) and divided this by the Mo-image. Differences between the pre and post ECT scan reflect possible changes in perfusion. ANTS tools were used to compute the affine transformation between the Mo-scan and the corresponding T2- weighted scan to register the resulting ASL maps into the space of hippocampus segments. For each subject, the hippocampus segmentation was then used to extract ASL values, which were subsequently imported into R for statistical analyses.

To check whether possible changes in perfusion or diffusion are due to overall systematic differences between the pre- and post-scan (e.g. scanner drift) an extra analysis was conducted with values from the pons as regressor in the model. To ensure that the ROI in the pons showed 100% overlap between the patients, a sphere was placed in the pons comprising of 1342 voxels on the 1 mm T1-weighted MNI152 template [available in FSL; see supplementary figure A (Smith et al., 2004)]. The T2-weighted scan was registered to the T1-scan using affine registration with ANTS (Avants et al., 2011). The T1- weighted scan was subsequently nonlinearly registered to the 1 mm MNI152-template image (Smith et al., 2004). The inverse of both

Table 1. Demographics of the sample.

Variable		Patients	Controls	diff	Statistic(test)	p
Total N		21	8	–	–	–
Age		48.9	49.25	0.33	0.05 (t)	0.96
Gender	Female	16	5	–	.54 (x^2)	0.46
	Male	5	3			
IQ*		106.8	109.17	2.37	0.50 (t)	0.62
Handedness*	left	3	0	–	Fisher's exact	1
	right	20	5			
		Baseline (mean, SD)	Exit (mean, SD)	t(df)†	p	ES‡
HAM-D		21.8(6.47)	15.25(7.56)	6.55 (19)	<0.001	0.9

*n = 26; x^2 = chi-square test statistic; diff = difference; N = number; IQ = intelligence quotient; p = p-value; † = paired t-test; ‡ = effect size d for paired observations.

registrations was then used to map the pons ROI back into native space. Subsequently, values for the pons were extracted and imported in R for statistical analyses.

CLINICAL EFFECT

To quantify the clinical effect of ECT, the 17-item version of the Hamilton Depression Rating Scale (HAM-D) was used (Hamilton, 1960). The HAM-D is widely used to assess the clinical effect of treatments for depression (Hamilton, 1960; Moran & Lambert, 1983).

STATISTICAL ANALYSES

To assess changes in diffusion and perfusion between pre and post ECT, linear mixed models (with unstructured covariance structures) were used (p-values < 0.05 were considered significant from a two-sided test) (Bates, Mächler, Bolker, & Walker, 2015). For each parameter map (MD, *f*, D* and the ASL map) separately, a linear mixed model was used with time (pre/post ECT)*type(patients/controls) as fixed effect, and age, sex as covariates and subject and hemisphere (left/right) as random factors. Subsequently, the models were (again for each parameter map separately), further split up into two models testing for controls and patients separately. If one of these latter models showed significant effects for time, the model was further split up into separate models for left and right hippocampus, to see whether the effects are driven by the left and/or right hippocampus. To examine whether the effects were specific to the hippocampus (and not due to an overall decrease in MD in the brain) and/or could be explained by the increase in volume of the hippocampus, models with significant effects for the left or right hippocampus were re-run with volumetric measurements of the hippocampus and parameter values in the pons as covariates (serving as an internal control measure). Effect sizes (Cohen's d) are computed for paired observations for patients and controls separately.

Table 2. Correlation coefficients parameter maps and Hamilton score.

Parameter map**	left/right	r	P
MD	left	0.581	0.061
	right	0.065	0.850
F	left	0.490	0.126
	right	–0.0001	0.999
D*	left	0.097	0.776
	right	0.086	0.798

r = repeated measures correlation coefficient; p = p-value; ** = all *df* = 9.

For each parameter map and for the left and right hippocampus separately, repeated measures correlations (Bakdash & Marusich, 2017) were computed to see if a difference over time would significantly be associated to change in depression scores (after regressing out the effects of age and sex on parameter scores and depression scores). Afterwards, a regression analysis was run with baseline values of the parameter maps (only parameters that had significant effects for time in the linear mixed model) as predictor and age, sex and baseline hippocampal volume as covariates, and difference in depression scores (baseline e exit) as dependent variable.

RESULTS

SAMPLE

In total, 28 participants (20 patients and 8 controls) were analyzed (totaling 44 scan sets). See Table 1 for demographics. At baseline, patients did not differ significantly from the controls in terms of age, sex, handedness and IQ (Table 1). In the patient group, the Hamilton score decreased significantly from pre to post ECT ($t = 6.55$, $p < 0.001$, effect size = 0.9). Due to personal reasons (two patients, four controls), anxiety in the scanner (one patient, one control), less than 10 ECT sessions (one patient) and scanning artifacts (six patients, two controls), we obtained 16 (11 patients, 5 controls) complete datasets for the IVIM measurements and 13 (10 patients, 3 controls) for the ASL measurements. However, when the data is missing completely at random linear mixed modelling is robust to missing values allowing inclusion of participants with either the baseline or exit measurement, which resulted in 28 participants (20 patients, 8 controls) for the IVIM measurements and 25 for the ASL measurements (17 patients, 8 controls). The reasons for the missing data are believed to be completely at random (e.g. scanning artifacts).

CLINICAL EFFICACY

Patients significantly improved in depression scores ($t = 6.55$, $p < 0.001$, effect size = 0.9). No significant correlations were found between any of the parameter maps and a change in Hamilton score (all $p > 0.05$; see Table 2). Baseline MD and *f* values were not related to the

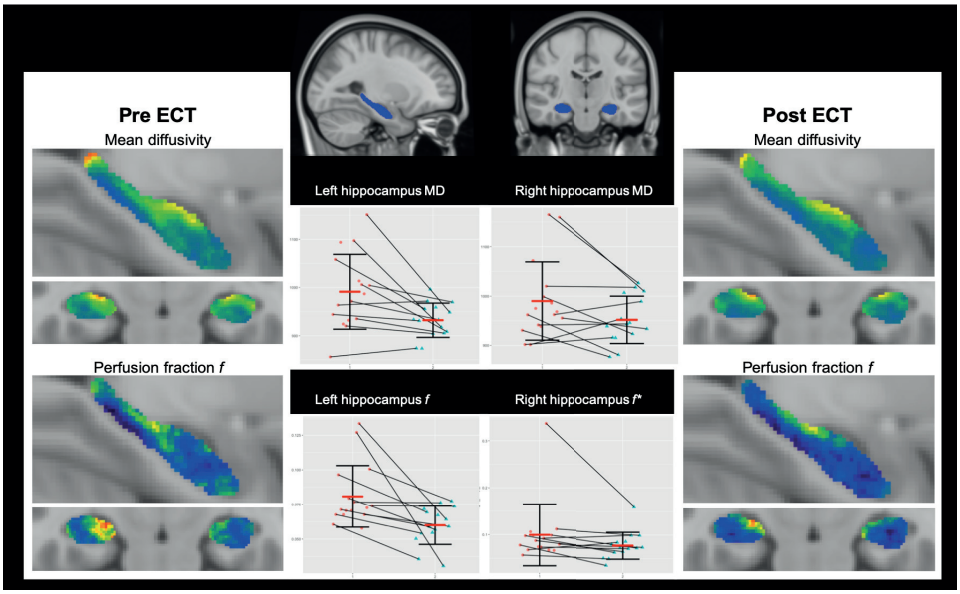

Figure 1. Perfusion fraction *f* and mean diffusivity in the hippocampus, pre and post ECT
This figure shows individual data points (red horizontal bar indicates averages) of MD and perfusion fraction *f* in the left and right hippocampus, before (red dot) and after ECT (blue triangle) for patients. Panel A shows the location of the hippocampus in the MNI152 1mm template. Panel B shows the averages for the MD and f before ECT. Panel C shows the averages of MD and *f* after ECT. The colour scale shows low values as blue colours and high values in red. The plots show individual datapoints with standard deviation (black error bar) and average (red horizontal bar). All averages differ significantly except for right *f*; * = p > 0.05; ECT = electroconvulsive therapy; MD = mean diffusivity.

change in depressions scores using (p > 0.05).

MEAN DIFFUSIVITY, IVIM *F*, D*, AND ASL PERFUSION VALUES

The first model for mean diffusivity (MD) indicated a significant reduction for MD over time (t = -4.005, p < 0.001), yet no significant effect for time*group (t = 1.533, p = 0.132) was found. When split up for patients and controls, the model for patients indicated a significant effect for time (t = -3.962, p < 0.001) but not for controls (t = -0.939, p = 0.359). To see whether the effect in patients was driven by either the left or right hippocampus, the models were further split up in two separate models for left and right hippocampus. Both for the left (t = -2.805, p = 0.012) and right (t = -2.219, p = 0.035) hippocampus, significant effects for time were found (see Fig. 1). For the left hippocampus an effect size of the paired difference of 0.85 was found, and for the right hippocampus the effect size was 0.59. When including volumetric measurements of the hippocampus and MD values of the pons in the last two models, the model for the left hippocampus showed a significant effect for time (t = -3.083, p = 0.008). For the model of the right hippocampus, the significant effect for time disappeared (t = -2.073, p = 0.06).

For the *f* parameter of the IVIM fit, a significant effect for time (t = -4.162, p < 0.001) was found, and nonsignificant for time*group (t = 1.901, p = 0.0621). When the models

were split up for patients and controls separately, the model for the patients indicated a significant effect for time (t= -3.797, p < 0.001), but not for controls (t = -0.491, p = 0.633). To check if the left or right hippocampus showed different effects for time, the models for patients were re-run for the left and right hippocampus separately. The left hippocampus (t = -3.520, p = 0.002) indicated a significant effect for time, whereas the right hippocampus did not (t = 11.871, p = 0.079; see Figure 1). For the left and right hippocampus effect sizes for the paired difference between pre and post ECT of 0.92 and 0.53 were found, respectively. Including volumetric measurements of the hippocampus and the *f* values for the pons in the model, the effect for time in the left hippocampus (t = -5.147, p < 0.001) remained significant, whereas the effect for time in the right hippocampus changed to significant (t = -2.818, p = 0.0125).

The first model for the D* parameter of the IVIM fit indicated no significant effect for time (t = -0.817, p = 0.416), yet a significant effect for time*group was found (t = 2.295, p = 0.024). To see if the effects for time in either the patient or control group was significant, the models were split up for each of these groups separately. Neither the patients (t = -1.343, p = 0.186) or the controls (t = 1.619, p = 0.121) showed significant effects for time.

The first model for the ASL maps indicated no significant effects for time (t = -0.442, p = 0.662), nor group*time effects (t = 0.142, p = 0.888). When split up for patients and controls, no significant effects for time were found (t = -0.332, p = 0.734; t = 0.061, p = 0.963; see supplementary B for bar plots of the estimated marginal means).

DISCUSSION

Using high field magnetic resonance imaging we investigated the effect of ECT on parameters of diffusivity and perfusion in the hippocampus. We found that a series of 10 ECT sessions significantly decreased MD in both the left and the right hippocampus. This effect could not be explained by a general decrease in MD nor by the volume increase of the hippocampus for the left hippocampus. In addition, the IVIM perfusion fraction *f* in the left hippocampus significantly decreased after ECT (and could not be explained by a general decrease in f or by a volume increase in the hippocampus), whereas *f* in the right hippocampus did not significantly decrease. However, after adjusting for *f* values in the pons and the increase in volume in the right hippocampus (making sure that the effects found were not due overall decreases in MD, see methods), the perfusion did significantly decrease in the right hippocampus after ECT. The pseudo-diffusion component D* did not change significantly over time, nor did the ASL perfusion values.

The decrease in MD, which is in line with recent studies looking into the effects of ECT on DTI measurements (Jorgensen et al., 2016; Yrondi et al., 2019), indicates that the formation of edema is a very unlikely explanation for the volumetric increase in the hippocampus. As vasogenic edema would increase the water content in the extracellular space, this could be reflected in an increase in MD or at least a no detectable change in MD (depending on the sensitivity of the IVIM framework and IVIM scan), as opposed to a decrease in

MD. Cytotoxic edema, in contrast, could be reflected by a decrease in MD, since water of the extracellular space traverses to the intracellular space restricting diffusion in the extracellular space. However, since water of the extracellular space moves into the intracellular space, and thus reflects a redistribution of the water content, tissue swelling does not occur (Stokum et al., 2016), making it therefore highly unlikely that cytotoxic edema explains the volume increase of the hippocampus.

An explanation of the decrease in MD could be that the extracellular space in the hippocampus becomes more occupied (e.g. due to neurogenesis in the DG, or the formation of synapses and axons in the other subfields of the hippocampus), leaving less space for free water diffusion. Indeed, it has been shown that the diffusion decreases when the cell density of tissue increases (Luo, Zhou, Zhang, Luo, & Bian, 2019). Interestingly, in animal models of ECT (ECS) widespread neuroplastic changes have been observed in the hippocampus. For example, dendritic spine formation, maturation and branching, mossy fiber sprouting, synaptogenesis and even gliogenesis have been observed after ECS (Chen et al., 2009; Gombos, Spiller, Cottrell, Racine, & McIntyre Burnham, 1999; Kaae, Chen, Wegener, Madsen, & Nyengaard, 2012; Lamont, Paulls, & Stewart, 2001; Smitha, Roopa, Khaleel, Kutty, & Andrade, 2014; Vaidya, Siuciak, Du, & Duman, 1999; Wennström, Hellsten, Ekdahl, & Tingström, 2003; Wennström, Hellsten, Ekstrand, Lindgren, & Tingström, 2006; Zhao, Warner-Schmidt, S. Duman, & Gage, 2012). It can be expected that all of these processes would take up the extracellular space in the hippocampus, thereby restricting diffusion and leading to the observed decrease in MD.

Animal research has also shown that ECS is capable of inducing angiogenesis in the hippocampus (Ekstrand, Hellsten, Wennström, & Tingström, 2008; Hellsten et al., 2005; Newton et al., 2006). However, in the current study we did not find evidence of angiogenesis in the hippocampus after ECT. Instead, we found a decrease in perfusion fraction *f* and no change in D* and ASL perfusion values. The perfusion fraction *f* can be interpreted to reflect the volume of blood flowing into the capillaries (Le Bihan et al., 1988; Le Bihan, 2017; Lee et al., 2014). In addition, the perfusion fraction *f* has been shown to correlate with microvessel density, an important marker for angiogenesis (Lee et al., 2014). Therefore, observing a decrease in *f* does not suggest an increase in angiogenesis in the hippocampus after ECT. It could be, however, that the relative density of microvessels declines due to the fact that the absolute amount of microvessels remains the same yet the volume increases, therefore decreasing the fraction of microvessels. However, as this is highly speculative, future research replicating our finding of decreased perfusion fraction *f* while subsequently investigating the biological basis of this decline is warranted. In the current study we report no CBF changes in the hippocampus, as measured by ASL. Recently, however, several studies showed CBF increases in the hippocampus after ECT (Leaver et al., 2019, 2020). Moreover, these changes seemed to precede grey matter structural changes (Leaver et al., 2019). Our results are not in line with these studies. However, as noted below, the absence of an effect could indicate that our ASL data was underpowered. Future studies remain, therefore, warranted to investigate the link between structural and

functional plasticity in the hippocampus.

Our study has several limitations. First, the sample size is small resulting in possible type II errors. We note, however, that we were able to detect significant decreases in MD showing that power to detect changes was sufficient and effectively ruling out increases in MD. However, the current study remains preliminary and replication with larger datasets is needed to confirm the current results. Additionally, we have not corrected the results for multiple comparisons in order to be sensitive enough to pick up effects in the current small sample. However, this might introduce Type I errors. Therefore, we have, using the Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995), corrected the p-values reported in the manuscript. The results indicate that only the effect of ECT for the MD values in the right hippocampus did not survive multiple comparisons correction. The other effects remained significant (FDR corrected $p < 0.05$). Another limitation is that we only acquired a single slice for the ASL measurements resulting in that we could only image a section of the hippocampus. Consequently, we could have missed perfusion effects, possibly explaining why we did find a decrease in perfusion fraction *f* from the IVIM data with a larger coverage but not in the ASL measurements (albeit that IVIM and ASL do not necessarily need to correlate). Another restriction is the limited resolution of the IVIM data (i.e. 1.5 mm isotropic voxel size). Therefore, we could not adequately investigate subfields of the hippocampus. Investigating the subfields of the hippocampus could be an interesting focus of future research since our previous work showed a significant volume increase solely in the dentate gyrus of the hippocampus. In addition, we are unable to directly study cytotoxic edema. Although it is not likely that cytotoxic edema explains volume increases, definitively ruling out this process is not possible. Lastly, because patients were scanned after exactly ten ECT sessions in order to minimize variability introduced by differences in numbers of ECT sessions, we were not able to investigate the association of remission and hippocampal changes. Future studies could focus on studying which effects of ECT are necessary for remission.

In conclusion, we studied the effects of ECT on diffusion and perfusion related measurements by using ultra high field (7T) MRI in patients with severe depression.We found a significant decrease in MD and perfusion fraction *f* after a series of 10 ECT sessions. This decrease was not present in healthy controls nor in ASL perfusion values or the pseudo-diffusion component D*. There were no correlations between any of the parameters studied and decreased depression severity. These findings question the notion that ECT induces vasogenic edema or strong angiogenesis in the hippocampus, and strengthen our previous suggestion that neuroplastic changes are responsible for the previously reported volumetric increase of the hippocampus DG.

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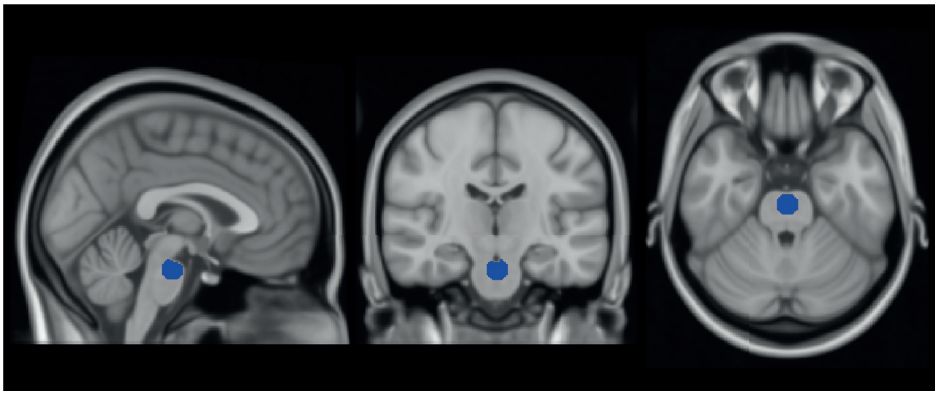
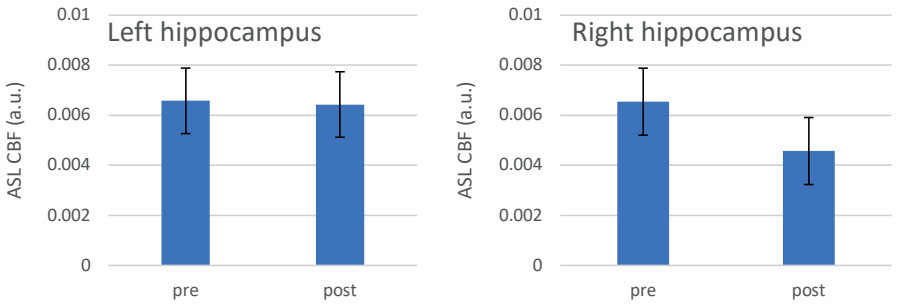
SUPPLEMENTARY MATERIAL



Supplementary figure A.
Three slices in the MNI152 1mm template showing the ROI in the pons. This region had 100% overlap in each of the subjects' individual parameters maps (MD, f, D*). Voxel location (x,y,z): 91, 107,47.



Supplementary figure B.
Barplots for the ASL data. The plots show the estimated marginal means (based on the LMM) of the ASL data, the error bars show the standard error. ASL CBF (a.u.) = arterial spin labelling, cerebral blood flow (arbitrary units).

CHAPTER 6

Shape and volume changes of the superior lateral ventricle after electroconvulsive therapy

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ABSTRACT

Background: The subventricular zone (SVZ) of the lateral ventricles harbors neuronal stem cells in adult mammals. Rodent studies report neurogenic effects in the SVZ after electroconvulsive stimulation. The present study sets out to investigate if this finding translates to depressed patients undergoing electroconvulsive therapy (ECT). We hypothesize that if ECT induces strong neurogenic effects in the SVZ, this would be reflected in shape changes at the SVZ.

Methods: Using T1-weighted MR images acquired at ultra-high field strength (7T), the shape and volume of the ventricles were compared from pre to post ECT after 10 ECT sessions (in patients, n = 22) or 5 weeks apart (controls, n = 8), using linear mixed modelling with age and gender as covariates.

Results: Ventricle shape and volume significantly decreased over time in patients for the left ($p = 0.027$, Cohen's $d = 0.61$) and right ($p = 0.0263$, Cohen's $d = 0.62$) ventricle, but not in controls. The decrease in volume of the ventricles was associated to a decrease in depression scores (left: $r = 0.522$, $p = 0.032$; right: $r = 0.509$, $p = 0.037$), and an increase in the left dentate gyrus ($r = -0.595$, $p = 0.019$).

Conclusion: The ventricles significantly changed in volume and shape after a series of ECT and this decrease correlates to the antidepressant effect of ECT. However, the shape changes of the ventricles were not restricted to the neurogenic niche in the lateral walls of the ventricles, providing no clear evidence for neurogenesis as sole explanation of volume changes in the ventricles after ECT.

INTRODUCTION

Depression is a highly prevalent psychiatric disorder (Kessler et al., 2003, 2005), posing substantial burden on patients' daily lives and their relatives (Saarni et al., 2007; Vos et al., 2012; Whiteford et al., 2013). While being a highly effective treatment for a depressive disorder, the exact working mechanism of electroconvulsive therapy (ECT) remains unknown (Pagnin, de Queiroz, Pini, & Cassano, 2004; UK ECT Review Group, 2003). In recent years substantial progress has been made in uncovering the effects of ECT on the brain, indicating widespread volumetric changes on MRI after ECT (Gbyl & Videbech, 2018; Nuninga et al., 2019; Ousdal, Argyelan, et al., 2020). Yet, whether these changes are necessary or related to the antidepressant response of ECT remains subject of debate (Nuninga, Mandl, & Sommer, 2020b, 2020a; Ousdal, Argyelan, et al., 2020; Ousdal, Gjestad, & Oltedal, 2020; Takamiya, Nuninga, et al., 2019). Also, the cellular mechanism underlying these volume changes remains unknown.

Substantial research into the mechanism of ECT has been directed towards the hippocampus. The hippocampus is a laminar structure and harbors the dentate gyrus (DG), a region where neurogenesis is thought to be possible throughout adulthood (Boldrini et al., 2018; Sahay & Hen, 2007; van Praag et al., 2002). The hippocampus, and in particular the process of neurogenesis within the DG, has been implicated in both the pathogenesis and the treatment of depression (Eisch & Petrik, 2012; Malberg & Schechter, 2005; Sahay & Hen, 2007). In preclinical studies, electroconvulsive stimulation (ECS), has been shown to induce strong neurogenesis in the dentate gyrus of rodents and nonhuman primates (Ito et al., 2010; Lamont, Paulls, & Stewart, 2001; Madsen et al., 2000; Nakamura et al., 2013; Perera et al., 2007), together with other neuroplastic effects [such as dendritic spine maturation, sprouting, synaptogenesis and angiogenesis (Ekstrand, Hellsten, Wennström, & Tingström, 2008; Hellsten et al., 2005; Vaidya, Siuciak, Du, & Duman, 1999; Wennström, Hellsten, Ekdahl, & Tingström, 2003)] In patients, specific increases in volume in the dentate gyrus have been found, suggesting that neurogenesis (and other neuroplastic processes) may also take place in humans after ECT (Nuninga et al., 2019; Takamiya, Plitman, et al., 2019). Interestingly, these volumetric changes were related to the antidepressant response of ECT (Nuninga et al., 2019; Takamiya, Nuninga, et al., 2019).

Given that ECT induces a generalized seizure and that it is associated with widespread changes in the brain, it is likely that neuroplastic effects are not limited to the hippocampus. With respect to neurogenesis, the lateral walls of the ventricles (subventricular zone; SVZ) are also capable of generating new cells, although it is unclear whether this is possible throughout adulthood in humans (Alvarez-Buylla & García-Verdugo, 2002; Hansen, Lui, Parker, & Kriegstein, 2010; Lim & Alvarez-Buylla, 2016; Quiñones-Hinojosa et al., 2006). To investigate whether ECT stimulates neurogenesis in the SVZ, we analyzed the shape of the ventricles in a group of patients with a depressive disorder undergoing ECT. A small control group was also scanned twice to test whether any changes found were due to scanner drift. In

the present study, we explore changes in the volume and shape of the ventricles and hypothesize that if neurogenesis takes place in the SVZ, this would be reflected in a change in the shape of the lateral walls of the ventricle; the location of the SVZ.

METHODS

SAMPLE

Patients and controls were recruited at the University Medical Center Utrecht. Patients were included with the following inclusion criteria: 1) age over 18 years, 2) a diagnosis of a depressive disorder [as defined by the DM-IV(Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), 2000)], 3) an indication for ECT treatment [based on the Dutch guidelines on ECT (Broek, Birkenhäger, Boer, & Burggraaf, 2010)]. Exclusion criteria were: 1) treatment with ECT six months prior to the study, 2) contraindication for MRI (e.g. metallic implants), 3) history of stroke, 4) brain pathology, 5) pregnancy and/or lactation, 6) any major medical disease (e.g. coronary heart disease). Controls were included when they were over 18 years of age and had no (history) of a psychiatric disease [assessed by the MINI interview (Pangman, Sloan, & Guse, 2000)]. Controls were matched to the patient group based on demographic characteristics. All patients and controls provided written informed consent and the study was approved by the local ethics committee.

TREATMENT PROCEDURE

ECT was given twice a week with a Thymatron IV ECT machine (bifrontotemporal electrode positioning, delivering a current at 150% of the titrated seizure threshold). As the patients were included in this study were part of a study investigating hippocampal subfields, see Nuninga et al. (2019), for a detailed description of the ECT procedure. Patients were scanned before the first ECT sessions and after exactly 10 ECT sessions (i.e. after 5 weeks) to minimize variability due to different numbers of ECT sessions. Controls were scanned twice, with a similar 5-week interval yet without ECT.

SCANNING PROCEDURE AND DATA ANALYSIS

A T1-weighted 3D turbo field echo (TFE) multishot acquisition (voxel size 1 mm isotropic; TR/TE 5.5/2.1 ms; flip angle 6°; FOV 250 x 250 mm^2; number of slices 190; total scan duration 149 s; TFE factor = 400, shot interval 3500ms, inversion time = 1200ms) was acquired using a 7 tesla (7T) MRI scanner (Philips Healthcare, Best, The Netherlands) and a 32-channel head coil (Nova Medical, Wilmington, MA, USA).

The T1-weighted scans were automatically segmented using FreeSurfers' automated pipeline for longitudinal studies, implemented in version 6.0 (Fischl & Dale, 2000; Fischl et al., 2004; Fischl, Sereno, Tootell, & Dale, 1999; Reuter, Rosas, & Fischl, 2010; Reuter, Schmansky, Rosas, & Fischl, 2012). The longitudinal pipeline of FreeSurfer creates an unbiased within subjects template, subsequently initializing processing for the individual timepoints using the information from the within subjects template (Reuter et al., 2010, 2012). This procedure results

Table 1. Demographics of the sample.

Variable		Patients	Controls	diff	Statistic(test)	p
Total N		22	8	–	–	–
Age		50.1	49.4	0.88636	0.149 (t)	0.88
Gender	Female	16	5	–	0.008 (X^2)	0.93
	Male	6	3			
IQ*		104.59	110.8	6.24	1.92 (t)	0.06
		Baseline (mean, SD)	Exit (mean, SD)	t(df)†	p	ES‡
HAM-D		21(7.09)	15(7.4)	3.57 (15)	0.003	0.89

*n = 26; X^2 = chi-square test statistic; diff = difference; N = number; IQ = intelligence quotient; p = p-value; † = paired t-test; ‡ = effect size d for paired observations.

in increased sensitivity for subtle changes within subjects. All images and parcellations of the ventricles were inspected visually to detect and correct errors if needed. After segmentation, the volumes of the lateral ventricles were extracted and imported in R [version 3.4.3 (R Core Team, 2013)]. To investigate whether the volume of the ventricles changed from pre to post ECT we employed linear mixed modelling [package lmerTest within R (Kuznetsova, Brockhoff, & Christensen, 2017)]. The first model (left and right ventricle were analyzed separately), contained time (pre/post ECT), group (patients/controls), the interaction term group*time, age and gender as fixed factors and subject as random factor (intercept). Afterwards, the models were split up to analyze patients and controls separately. This model included time (pre/post), gender, and age as fixed factors, and subjects as random factor (intercept). To see if possible volumetric increases would coincide with the antidepressant effect of ECT, we computed repeated measures correlation between ventricle volume and Hamilton scores (Bakdash & Marusich, 2017). Repeated measures correlation were also run to see if changes in ventricle volume were associated to changes in dentate gyrus volume [see (Nuninga et al., 2019) for the method for obtaining dentate gyrus volume, the patients included in the present study also participated in Nuninga et al., 2019].

Ventricle shapes were extracted from the FreeSurfer output and imported into SlicerSALT (version 3.0) for shape analysis. SlicerSALT [salt.slicer.org (Vicory et al., 2018)] is a project within the freely available software package slicer (www.slicer.org). To analyze the shape of the ventricle, spherical harmonic based point distribution models (PDM) were first computed and aligned to the standard brain (within FreeSurfer) using Procrustes alignment. After aligning all ventricles, the mean shape for both the pre and post measurements were computed.

The mean ventricle shape was also used to output the results of the statistical comparison between the pre and post-ECT shapes. Statistical comparison was done using Multivariate Functional Shape Data Analysis (MFDSA) (Vicory et al., 2018). We analyzed six

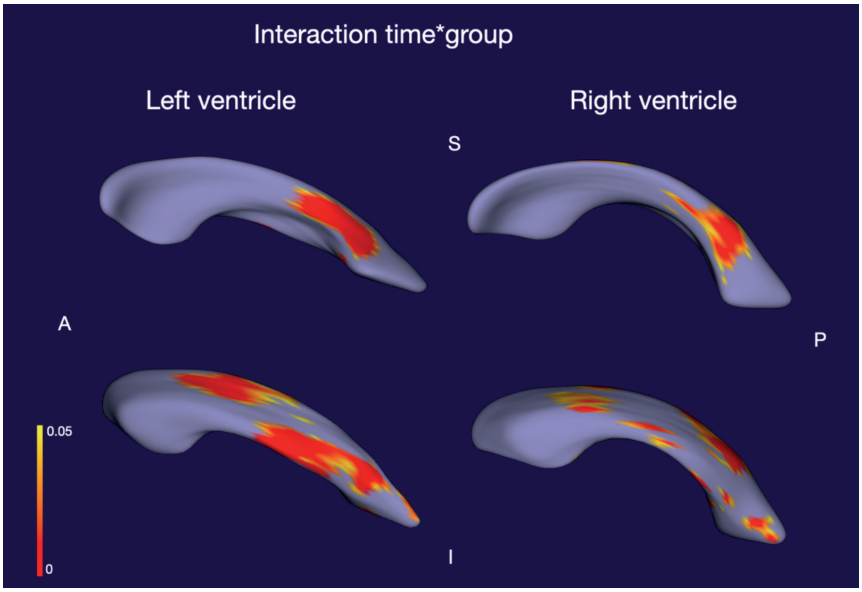

Figure 1. On the left, two views of the left ventricle showing areas where the interaction effect between time and group (i.e. patients/controls) is significant. On the right, two views of the right ventricles showing areas where the interaction effect of time is significant. Color scale: yellow, p = 0.05, red. p < 0.001; A = anterior; P = posterior; S = superior; I = inferior.

models, the first two models (left and right ventricle separately) included time, group, group*-time, age and gender as regressors. Then, the ventricles of the patients were analyzed with a separate model for left and right ventricle including, time, age and gender as regressors. To test whether shape changes associate to Hamilton scores, two additional models (for the left and right ventricles separately) were run including Hamilton scores. P-values lower than 0.05 were considered statistically significant. P-values were FDR corrected.

RESULTS

SAMPLE

In total, we included 22 patients and 8 controls for this study. Due to scanning artefacts, and dropout we were able to include complete pairs (i.e. a scan pre ECT and post ECT) of 16 patients and five controls. Patients and controls did not differ in baseline demographics (age, gender and IQ; see table 1). ECT significantly decreased depression scores ($p < 0.003$, Cohen's $d = 0.893$).

VENTRICLE VOLUME

The first two linear models showed a significant time*group effect for the volume of the right ventricle ($t = 2.31$, $p = 0.0328$), but not for the left ventricle ($t = 0.784$, $p = 0.443$). Both models showed significant effects for time for the volume of the ventricles (right, $t = -2.573$, $p = 0.0191$; left, $t = -2.658$, $p = 0.016$). When split up for patients/controls separately, the model indicated

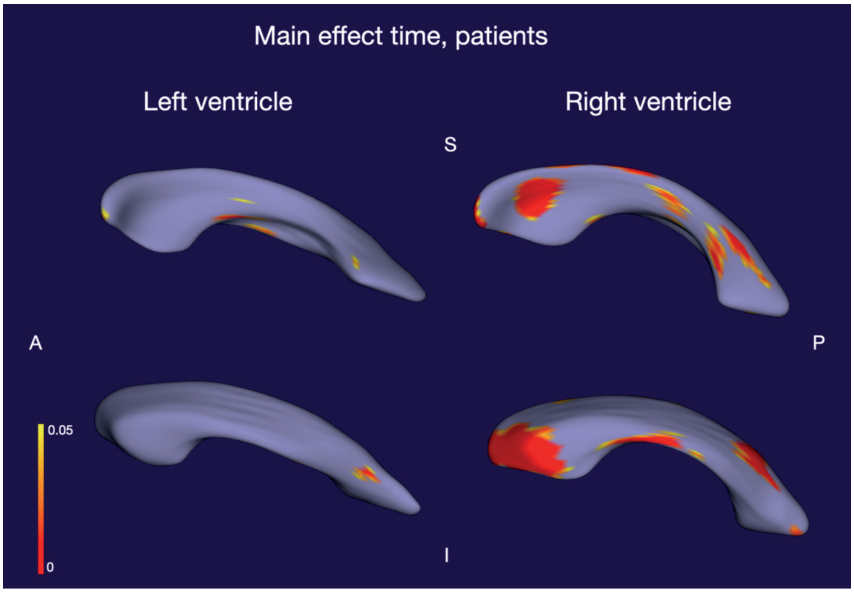

Figure 2. On the left, two views of the left ventricle showing areas where the effect of time (for patients) is significant. On the right, two views of the right ventricles showing areas where the effect of time is significant. Color scale: yellow, p = 0.05, red. p < 0.001; A = anterior; P = posterior; S = superior; I = inferior.

a significant effect of time on the volume of the right ventricle for patients (t = -2.464, p = 0.0263, effect size = 0.62), but not for controls (t = 1.749, p = 0.178, effect size = 0.88). For the volume of the left ventricle, a significant effect of time was found for patients (t = -2.455, p = 0.027, effect size = 0.61), but not for controls (t = -0.929, p = 0.421, 0.47). The repeated measures correlation indicated a significant and positive relationship between change in Hamilton score and volume for the left (r = 0.522, p = 0.032) and right ventricle (r = 0.509, p = 0.037), indicating that, within subjects, Hamilton scores decrease as ventricle volumes do. Additionally, a significant within subjects negative correlation was found between volumetric changes in the left dentate gyrus and the left ventricle (r = -0.595, p = 0.019), but not in the right dentate gyrus and the right ventricle (r = -0.49, p = 0.061).

SHAPE ANALYSIS

The first two analyses showed a significant global interaction effect for the left and right ventricles. Fig. 1 shows areas on the ventricles that significantly changed in shape for this interaction effect. Supplementary figures S1 (left) and S2 (right) show the beta coefficients for the interaction effect of the linear model for the x, y and z axes plotted for the significant areas on the ventricles. When patients were analyzed separately, global significant changes in shape pre to post ECT were also found for the left and right ventricle. See Fig. 2 for the areas where the ventricle significantly changed in shape over time in patients. Supplementary figures S3 (left) and S4 (right) show the beta coefficients of the linear model for the effect of time for three

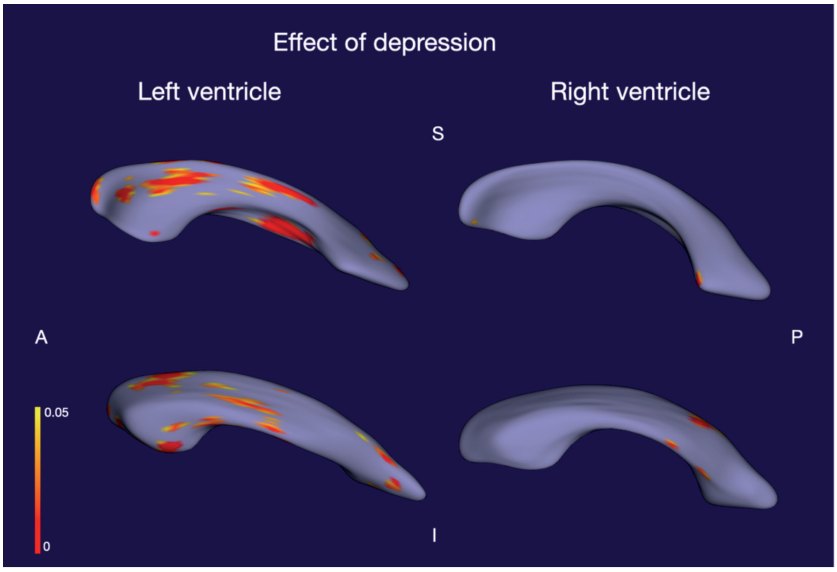

Figure 3. On the left, two views of the left ventricle showing areas where the effect of depression (for patients) is significant. On the right, two views of the right ventricles showing areas where the effect of depression is significant. Color scale: yellow, p = 0.05, red. p < 0.001; A = anterior; P = posterior; S = superior; I = inferior.

axes along x, y and z, again plotted for the significant areas. A global significant change along the ventricles was also found when looking at Hamilton scores, for the left and right ventricles. Figure 3 shows the location of areas on the ventricles that were significantly associated with Hamilton scores. See supplementary figures S5 (left) and S6 (right) for the beta coefficients along x, y, and z for the significant areas along the ventricles.

DISCUSSION

We investigated the effects of ECT on the volume and shape of the lateral ventricles. The main finding is that both the volume of the ventricle and its shape significantly change over time within individuals receiving ECT, but not in controls. The volume decrease in both right and left ventricle correlated with the decrease in severity of depression within subjects. The changes in shape did not pertain solely to the areas containing the subventricular zone (SVZ), making neurogenesis as the sole explanation of volumetric changes in the ventricle unlikely.

The working mechanism behind electroconvulsive therapy remains elusive. Recent efforts have been directed at investigating whether neuroplasticity, and especially neurogenesis could explain (parts of) the effect of ECT. In animal research, it has been robustly shown that electroconvulsive seizures (ECS) stimulate neurogenesis (Ito et al., 2010; Madsen et al., 2000; Nakamura et al., 2013; Perera et al., 2007), and other neuroplastic processes such as synaptogenesis, angiogenesis and mossy fiber sprouting (Chen, Madsen, Wegener, & Nyengaard, 2009;

Ekstrand et al., 2008; Gombos, Spiller, Cottrell, Racine, & McIntyre Burnham, 1999; Hellsten et al., 2005). Whether these processes also happen in humans, and if so, if they are contributing to the antidepressant effects of ECT is an open question. Clinical studies directed at answering this question show widespread volumetric increases in the brain, and most consistently in the hippocampus (Gbyl & Videbech, 2018; Ousdal, Argyelan, et al., 2020; Takamiya et al., 2018). More specifically, a strong increase in volume of the dentate gyrus (DG) of the hippocampus (the only region of this structure capable of neurogenesis) is observed, which could not be explained by edema (Nuninga et al., 2019; Nuninga, et al., 2020; Takamiya, Plitman, et al., 2019). Interestingly, this increase in volume of the DG, but not in the other subfields, is associated with the decrease in depression severity within subjects (Nuninga et al., 2019; Takamiya, Nuninga, et al., 2019). Here, changes in volume of the left dentate gyrus were associated to changes in the left ventricles within subjects.

Next to the DG, the subventricular zone of the lateral ventricles harbors neurogenic capacities in mammals (Conover & Todd, 2017; Quiñones-Hinojosa et al., 2006). In rodents, the neurogenic niches of the ventricles are well studied and defined, while in humans some questions remain unanswered (Akkermann, Beyer, & Küry, 2017; Conover & Todd, 2017; Quiñones-Hinojosa et al., 2006). Studies show that in normal human development, neurogenesis in the SVZ is ablated after two years of age (Coletti et al., 2018; Quiñones-Hinojosa et al., 2006). However, other studies report the existence (quiescent) neural stem cells up until later in adulthood (Donega et al., 2019; Quiñones-Hinojosa et al., 2006; Van Den Berge et al., 2010). Additionally, neuroblasts have been found in both the lateral wall of the ventricles, and the adjacent striatal areas. Considering ECT as a possible neurogenesis stimulating treatment, it could be hypothesized that ECT stimulates previously ablated neurogenesis in the SVZ. In rodent studies, seizure therapy increased neurogenesis in the SVZ both chemically (Parent, Valentin, & Lowenstein, 2002) and electrically (Inta et al., 2013; Suzuki et al., 2007). Our results show that volumetric changes, and associated changes in shape, do not limit to the lateral wall of the ventricles. These findings do not strengthen the hypothesis that the effects of ECT on ventricle size are largely due to neurogenesis in the SVZ, yet we cannot rule out that this process takes place and contributes to volume reduction and the antidepressant effect. A recent study showed that nearly all grey matter regions in the brain were increased in volume after ECT (Ousdal, et al., 2020), which may contribute to the ventricle volume decrease and associated shape changes found in the current study. Future studies could set out to investigate this question.

This study has limitations. The limited sample size is reducing the power to detect significant changes. Multi-site studies, such as coordinated by the Global ECT-MRI Consortium [GEMRIC (Oltedal et al., 2017)], are especially suited in overcoming this limitation. Increasing sample size is challenging at 7T MRI. While this is advantageous when imaging small structures demanding accurate delineation (such as the hippocampus), the ventricles are equally reliably imaged at 3T. Imaging at 3T is more feasible (both for the patients' tolerability,

and cost effectiveness), and thus could be used in future studies to maximize sample size.

In conclusion, in this study we report volumetric decreases of the lateral ventricles after ECT which correlate with the antidepressant effect. Ventricle size reductions were not reflected in site-specific alterations in shape. Our findings do not support the hypothesis of strong neurogenesis in the subventricular zone to underlie antidepressant effects of ECT.

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SUPPLEMENTARY MATERIAL

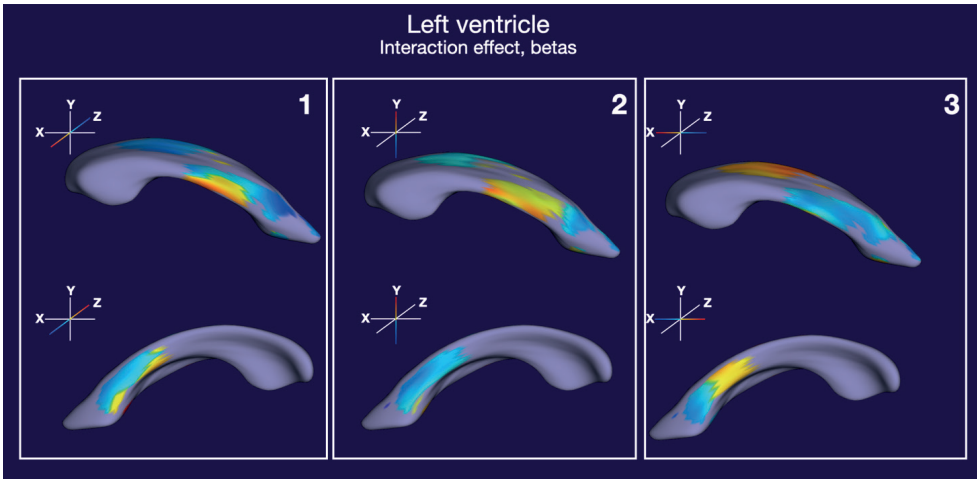


Figure S1. Beta values in 3 directions for the left ventricle, plotted for the differences in shapes in the significant areas. Panel 1 shows betavalues along the left/right axes (z); panel 2 show betavalues along the superior/inferior axis (y); panel 3 shows betavalues along the posterior/anterior axis. The color scale indicates the value of the beta's ranging from -4.5 (blue) to 4.5 (red).

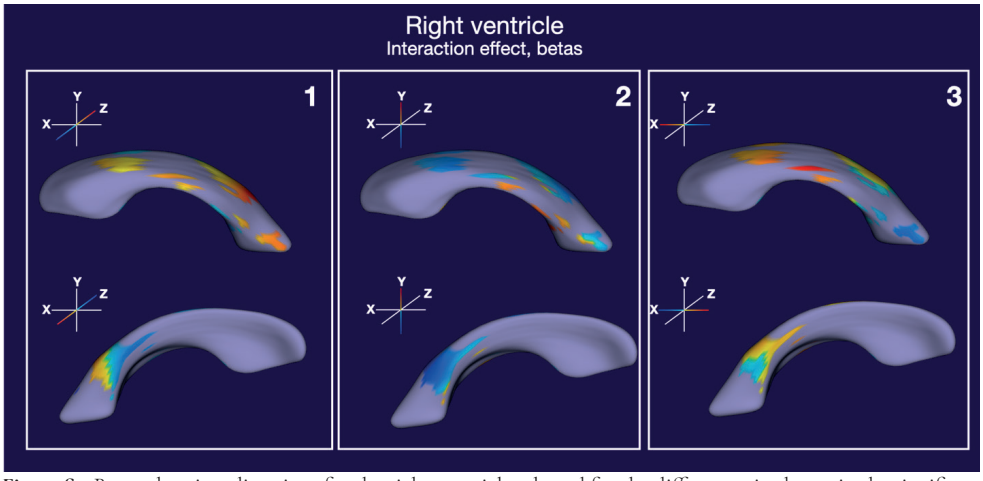


Figure S2. Beta values in 3 directions for the right ventricle, plotted for the differences in shapes in the significant areas. Panel 1 shows betavalues along the left/right axes (z); panel 2 show betavalues along the superior/inferior axis (y); panel 3 shows betavalues along the posterior/anterior axis. The color scale indicates the value of the beta's ranging from -4.5 (blue) to 4.5 (red).

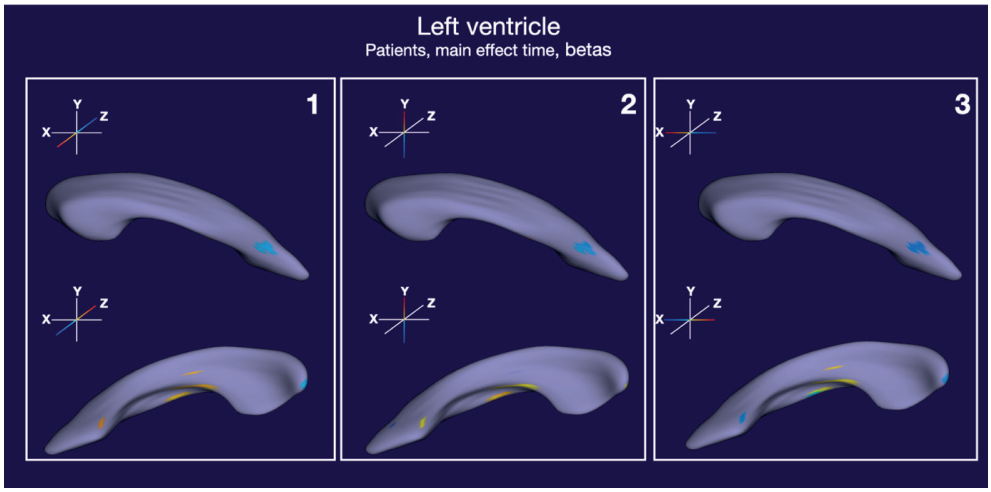


Figure S3. Beta values in 3 directions for the left ventricle, plotted for the differences in shapes in the significant areas. Panel 1 shows betavalues along the left/right axes (z); panel 2 show betavalues along the superior/inferior axis (y); panel 3 shows betavalues along the posterior/anterior axis. The color scale indicates the value of the beta's ranging from -0.5 (blue) to 0.5 (red).

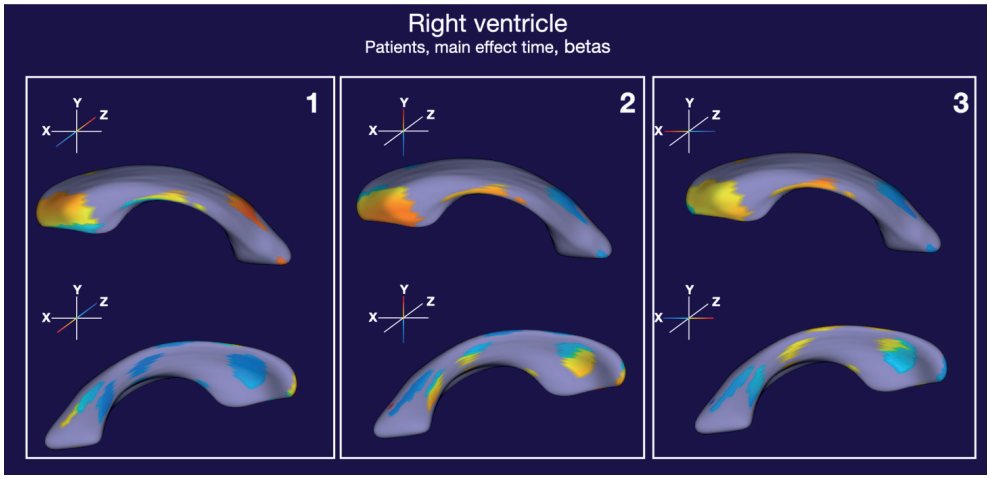


Figure S4. Beta values in 3 directions for the right ventricle, plotted for the differences in shapes in the significant areas. Panel 1 shows betavalues along the left/right axes (z); panel 2 show betavalues along the superior/inferior axis (y); panel 3 shows betavalues along the posterior/anterior axis. The color scale indicates the value of the beta's ranging from -0.5 (blue) to 0.5 (red).

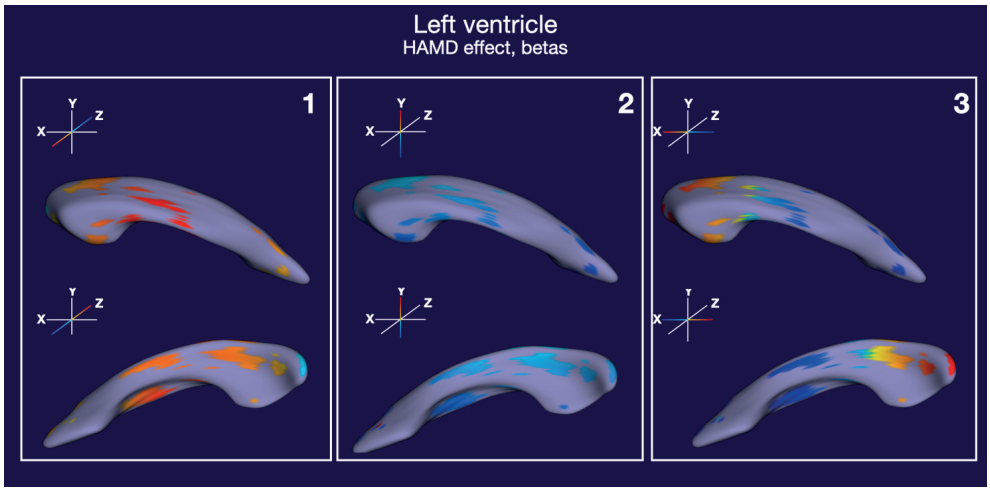


Figure S5. Beta values in 3 directions for the left ventricle, plotted for the differences in shapes in the significant areas. Panel 1 shows betavalues along the left/right axes (z); panel 2 show betavalues along the superior/inferior axis (y); panel 3 shows betavalues along the posterior/anterior axis. The color scale indicates the value of the beta's ranging from -17.5 (blue) to 17.5 (red).

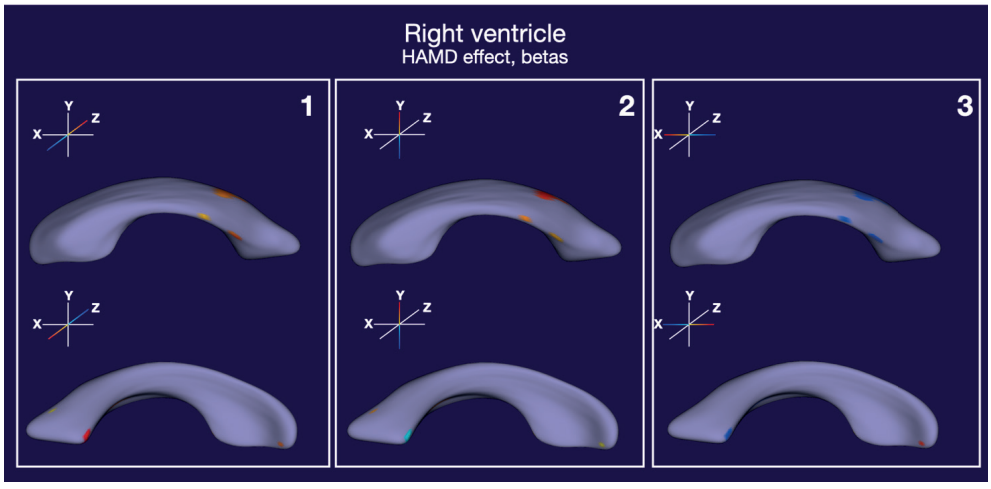
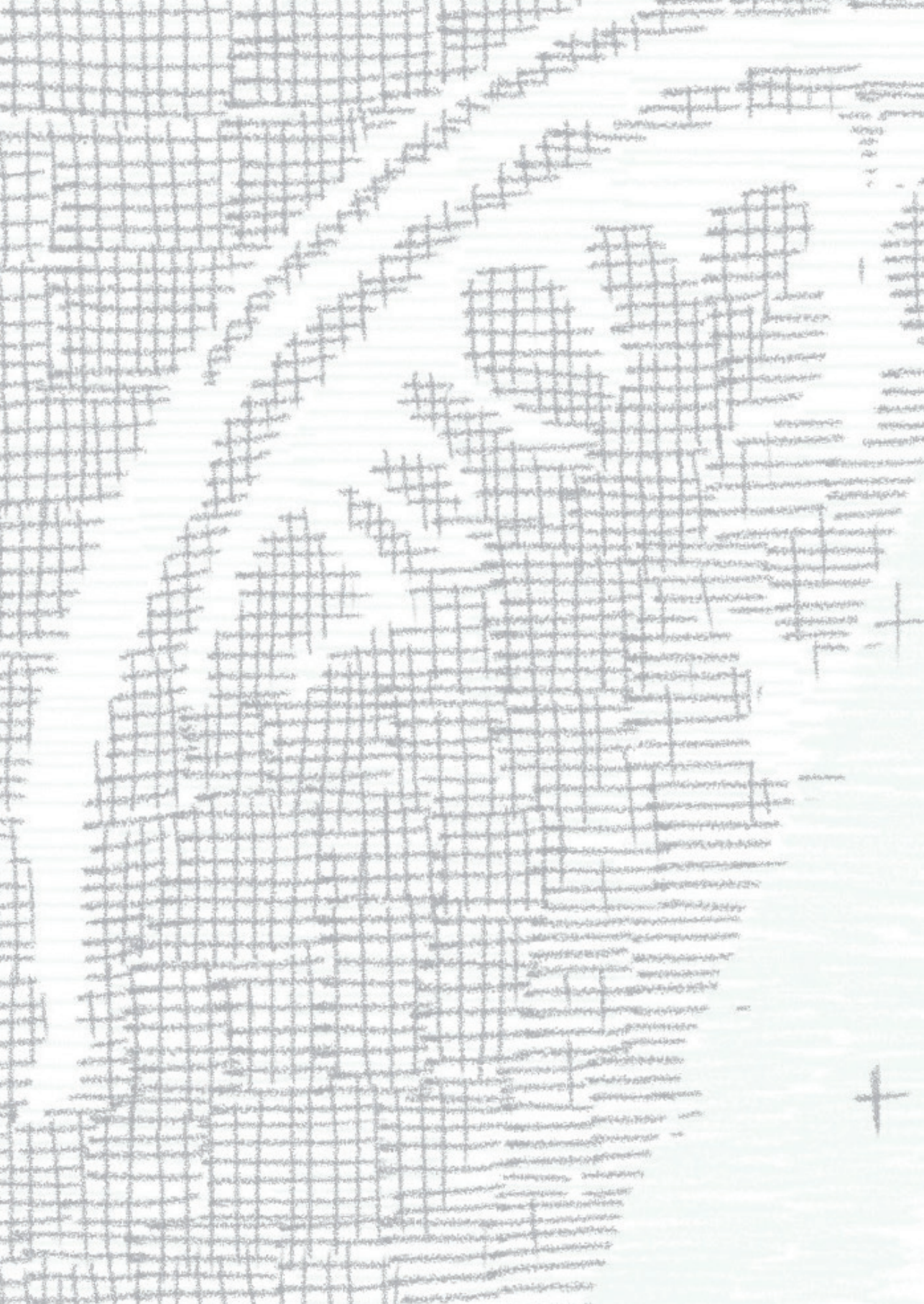


Figure S6. Beta values in 3 directions for the right ventricle, plotted for the differences in shapes in the significant areas. Panel 1 shows betavalues along the left/right axes (z); panel 2 show betavalues along the superior/inferior axis (y); panel 3 shows betavalues along the posterior/anterior axis. The color scale indicates the value of the beta's ranging from -17.5 (blue) to 17.5 (red).



CHAPTER 7

A general discussion and summary of the thesis

DISCUSSION

The research presented in this thesis was directed at elucidating the effects of electroconvulsive therapy on the brains and cognitive abilities of patients with a severe depressive disorder. This chapter summarizes the main findings of each study presented, and provides a general discussion regarding relevant literature, (methodological) considerations, clinical applications and future directions.

COGNITION

Impairment in cognitive abilities is one of the main side effects of ECT. These cognitive impairments have long been recognized as troubling and are experienced as quite daunting by patients and their families. In **Chapter 2**, research into the effects of bilateral ECT is presented. The main finding was that ECT caused significant cognitive side effects in the short-term. In the long-term, however, the patients recuperated.

Specifically, cognitive impairment was measured after ten ECT sessions for verbal memory and learning, as well as for word fluency. For all cognitive tests, the scores returned to baseline levels six months after treatment, indicating no long-term cognitive impairment. For visuospatial abilities, an improvement in test scores was seen from pre-treatment to follow-up. Improvement in depression scores was not related to a change in cognitive scores. This suggests that cognitive impairment develops independent of the antidepressant properties of ECT (although responders showed a greater decrease than non-responders in one subtest of verbal fluency at post-treatment, but not at follow-up). Note that these results pertain to averages. When looking at an individual level, a decrease in test scores at follow-up was observed for five patients on a test for verbal memory, two patients for verbal fluency, three for visual attention, and two for visual attention and task switching. Additionally, in spite of the positive effect on depression, cognition scores were not improved at end of treatment or follow-up, except for in one subtest measuring visuospatial abilities. As depression is associated with cognitive impairment (Rock, Roiser, Riedel, & Blackwell, 2014) it would be expected that when the depression remits, cognition scores will improve as well. Given that cognition scores did not increase beyond pre-ECT levels, it is not possible to fully exclude more persisting cognitive deficits caused by ECT. However, it should be noted that cognition is impaired even in remitted patients who have never had ECT (Semkovska et al., 2019).

Together these results suggest that bilateral ECT causes short term cognitive impairment in the verbal domain, and that patients recuperate six months after treatment.

DENTATE GYRUS VOLUME

In recent years, increased volume of the hippocampus after electroconvulsive therapy has been a robust and consistent finding. The exact nature of this increase remains unknown. In animals, the analogue of ECT known as electroconvulsive stimulation (ECS) strongly stimulates neurogenesis in the dentate gyrus. In **Chapter 3**, findings are presented from an ultra-high

field MRI study into the effects of ECT on the subfields of the hippocampus. We found that ECT has specific effects on the dentate gyrus, leaving the other subfields unaffected.

Specifically, after ten ECT sessions a strong increase in volume of the dentate gyrus was found. This effect pertained to the dentate gyrus (DG) specifically (i.e. no effects were found in the other hippocampal subfields). No volumetric changes were found in controls who were also scanned twice, five weeks apart. The increase in DG volume was significantly greater than the increase in volume in the largest other subfield (CA1). Interestingly, there was a strong negative correlation (within-subjects) between an increase in volume in the left and right DG and a decrease in depression scores, suggesting that the larger the increase in volume, the greater the effect of ECT on depression. Furthermore, baseline volume of the left and right DG predicted the antidepressant effect of ECT post-treatment.

The exact mechanism and nature of this volumetric increase remains unclear. As preclinical literature shows a strong and robust increase in neurogenesis after ECS in the dentate gyri of animals (Madsen et al., 2000; Nakamura et al., 2013; Perera et al., 2007), the present finding could reflect neurogenesis as well. Other functional recovery processes, such as synaptogenesis, dendritic arborization, and angiogenesis may also contribute to the volume increase, yet these processes cannot explain why growth only pertained to the DG. Less beneficial processes, such as the formation of edema, may also explain the effect, although (again) these would be expected to affect al subfields equally.

COLLECTION OF LETTERS

While the finding of volume increases in the DG of the hippocampus on 7T MRI points into the direction of neuroplasticity (and in particular, neurogenesis) as being the effect of ECT, a lot of questions remain. For example, do we really need ultra-high field MRI to measure these effects? Are DG volume increases also found on conventional 3T MRI scanners? **Chapter 4** discusses these and other questions in two letters.

The first letter concerns the question whether the volume increases in the DG and its association to the decrease in depression scores will hold when measured with a conventional, more readily available, 3T MRI scanner. To address this question, we collaborated with a group from Keio University (Tokyo, Japan), and reanalyzed their data set that was acquired using 3T MRI using similar methods as presented in Chapter 3. This reanalysis indeed revealed that a significant increase in the DG (and only the DG), is related to a decrease in depression score within subjects. Future studies can thus adopt these methods to further investigate the role of the DG in ECT using 3T MRI. This makes it easier to study larger samples to investigate whether these volume changes are necessary and sufficient for the antidepressant response.

The second letter addresses a commentary written by Koch and colleagues concerning Chapter 3 (Koch, Morey, & Roelofs, 2019). Koch et al., raised the possibility that neurogenesis plays a role in all stress-related disorders (not limited to depression). Pertaining to our study, they questioned whether pretreatment DG volume differs between patients and controls. In response we reanalyzed our data and did not find a significant difference between

patients and controls for the left or right DG. Furthermore, Koch et al., suggested that the association between baseline volume and treatment severity could explain the predictive effect of the DG, but such an association was not found when reanalyzing the data. Furthermore, including treatment severity at baseline did not change the results of the regression model predicting the antidepressant effect of ECT.

EDEMA, ANGIOGENESIS, NEUROPLASTICITY

The volumetric increases of the dentate gyrus presented in this thesis, and the robust finding of volume increases after ECT in the entire hippocampus reported by others, raise the question whether the biological basis of this volume increase can be found in beneficial processes (e.g. neuroplasticity, angiogenesis) or less beneficial processes (e.g. edema). **Chapter 5** sets out to investigate this question by employing diffusion weighted imaging to study edema or broad neuroplastic effects, and intravoxel incoherent motion analysis (IVIM) and arterial spin labelling (ASL) to study perfusion. If vasogenic edema is responsible for the volume increase seen in the hippocampus, one would expect that the mean diffusivity (MD) value increases (i.e. due to the accumulation of fluid in the extracellular space), yet when neuroplastic effects are implicated it will decrease the MD (i.e. due to the decrease in extracellular space as an effect of new cells/axons/dendrites/synapses). Additionally, an increase in perfusion parameters would be expected when angiogenesis takes place after ECT.

In the current study we found decreased MD after ECT in the left and right hippocampus in patients, but not in controls. Within the IVIM framework, the perfusion fraction *f* also decreased significantly after ECT in the left hippocampus, but not in the right (no differences were found in controls). The pseudo-diffusion component D* (estimated from IVIM data) and the ASL maps did not change significantly after ECT. Together, albeit preliminary, these results suggest that cell density increased and thus imply that neuroplastic effects (and not vasogenic edema) play a role in the volume increases of the dentate gyrus.

THE LATERAL VENTRICLES

In adult rodents, neurogenesis also takes place in the subventricular zone of the lateral ventricles. Whether this happens in humans is an open question with contrasting findings and views. Studies report ablation of neurogenesis in the lateral walls of the ventricles after two years of age while others report neuroblasts and (quiescent) stem cells up until later in adulthood. Given the neurogenesis enhancing potential of ECT, **Chapter 6** sets out to investigate if shape changes of the lateral ventricles occur in the neurogenic niches (suggesting neurogenesis), or along the entire ventricle.

We found a significant decrease in volume of the ventricles in patients, but not in controls. The decrease in ventricle volume was associated within subjects to the increase in DG volume (reported in Chapter 3), and to a decrease in Hamilton score. Shape analysis showed significant shape changes over time along the entire ventricle, not restricted at the lateral wall of the lateral ventricles. In addition, shape changes associated to the antidepressant

properties of ECT were also not restricted to the subventricular zone. These findings suggest that although the ventricles decrease in volume, this will likely not be entirely due to neurogenesis is the SVZ.

GENERAL DISCUSSION

In the following, a brief general discussion will be presented regarding literature relevant to the studies included in this thesis.

NEUROPLASTICITY

Two studies presented in this thesis suggest that neuroplasticity (and possibly neurogenesis) in the dentate gyrus of the hippocampus (but not in the subventricular zone) plays a role in the antidepressant effects of ECT. In animal research ECS has been shown to induce neurogenesis in the dentate gyrus of the hippocampus (Ito et al., 2010; Madsen et al., 2000; Nakamura et al., 2013; Olesen, Wörtwein, Folke, & Pakkenberg, 2017; Parent, 2007; Perera et al., 2007), together with other neuroplastic effects outside the dentate gyrus such as angiogenesis, synaptogenesis and dendritic arborization (Chen, Madsen, Wegener, & Nyengaard, 2009; Ekstrand, Hellsten, Wennström, & Tingström, 2008; Newton, Girgenti, Collier, & Duman, 2006; Vaidya, Siuciak, Du, & Duman, 1999; Wennström, Hellsten, Ekdahl, & Tingström, 2003). The volumetric increases of the dentate gyrus (Chapter 3), together with the absence of an indication of vasogenic edema (Chapter 5), indicate that ECT also has neuroplastic effects in the human brain, which in turn are associated with the antidepressant effects of ECT. In Chapter 6, no clear evidence was found that ECT stimulates neurogenesis in the other neurogenic region of the brain: the subventricular zone.

Although correlative in nature, these findings are in line with the neurogenic hypothesis of depression. In its simplest form the neurogenic hypothesis states that 1) decreased neurogenesis in the hippocampus is at least partially responsible for depression and that 2) reversing this decrease (by stimulating neurogenesis) would lead to remission of depressive symptoms (Eisch & Petrik, 2012; Miller & Hen, 2015; Petrik, Lagace, & Eisch, 2012). Especially studies testing if decreased neurogenesis is responsible for depression have yielded conflicting results (Anacker & Hen, 2017; Petrik et al., 2012) and therefore it is not likely that the neurogenic hypothesis will hold in its current form. However, the idea that neuroplasticity contributes to the antidepressant action of various therapies receives support. Studies show that some antidepressant effects do rely on neurogenesis (i.e. preventing neurogenesis prevents antidepressant response), but not all (Anacker & Hen, 2017). For ECT, it may also be the case that only some of the effects are explained by neurogenesis.

Acknowledging that depression is a heterogenous disorder with (most likely) a complex interplay of causal mechanisms, it could be that some (if not all) forms of depression will (in part) be due to decreased neurogenesis (or hippocampal/DG dysfunction) and that especially these types of depression will benefit from neurogenesis enhancing treatments. If

this is true, it would be important to study which patients fall in this category, and provide them with treatments that are potent neurogenesis enhancers. A possible way to find out if patients have dentate gyrus dysfunction resulting from aberrant neurogenesis is to test for DG-dependent cognitive processes. The DG has been identified to be of crucial importance in pattern separation (a process enabling the ability to discriminate between highly similar events) and cognitive flexibility in the context of learning and memory (Bakker, Kirwan, Miller, & Stark, 2008; Epp, Silva Mera, Köhler, Josselyn, & Frankland, 2016; Leutgeb, Leutgeb, Moser, & Moser, 2007). Neurogenesis, in turn, has also been identified to play a key role in regulating and mediating these processes (Anacker & Hen, 2017; Clelland et al., 2009; Epp et al., 2016). Consequently, difficulties in tasks relying on pattern separation and/or cognitive flexibility, such as the Mnemonic Similarity Task or the Picture Recognition task, might reflect DG dysfunction and aberrant neurogenesis (Anacker & Hen, 2017; Bakker et al., 2008; Brock Kirwan et al., 2012; Das, Ivleva, Wagner, Stark, & Tamminga, 2014; Déry et al., 2013; Kirwan & Stark, 2007; Stark, Yassa, Lacy, & Stark, 2013; Wesnes, Annas, Basun, Edgar, & Blennow, 2014; Yassa & Stark, 2011). If true, research could set out to assess the possible predictive properties of these processes for the antidepressant response in neurogenesis enhancing treatments. In effect, ECT might be targeted to patients showing DG-dependent cognitive impairment without having them to be scanned with an MRI scanner. Being able to predict which patients will respond to treatment will reduce the risk of administering ECT without results. This will not only prevent people from being exposed to the risk of developing cognitive side effects without a beneficiary effect of the ECT treatment, it will also prevent the huge disappointment experienced by patients who did not respond to ECT. In addition, it will also be cost-effective.

When considering ECT as a potent neurogenesis enhancing treatment, it should be noted that a time-gap is observed between the antidepressant effects of ECT (which begin to emerge after just a few sessions, i.e. within a few weeks), and for the newborn neurons to become functionally integrated in the hippocampal circuitry. For example, it takes 2-3 weeks for newborn neurons to be integrated in the rodent hippocampus, yet more than 8 weeks for them to be fully matured (Anacker & Hen, 2017). Patients, on the other hand, may report significant changes in mood before the moment that the new born neurons are fully matured. Therefore, the antidepressant effects of ECT are likely not fully attributable to matured newborn neurons. Other neuroplastic processes (such synaptogenesis, gliogenesis, dendritic arborization, spine formation and maturation), might also contribute to the working mechanism of ECT. In future work it will be important to disentangle the effects caused by neurogenesis from the effects caused by different (neuroplastic) processes in order to create a better understanding of ECT as an antidepressant treatment.

SIDE EFFECTS

Cognitive impairment after ECT is temporary for most people (Chapter 2; Vasavada et al., 2017). However, at the individual level, some people may experience more lasting side effects (Chapter 2; Hebbrecht et al., 2020). Cognitive side effects, together with memory impairment

are disturbing side effects for patients, causing anticipatory fear before, and ruminative stress, after ECT (Frank Koopowitz, Chur-Hansen, Reid, & Blashki, 2003; Griffiths & O'Neill-Kerr, 2019; Rush, McCarron, & Lucey, 2007; Vann Jones & McCollum, 2019). Alleviating and/or preventing these side effects [(for example with the use of acetylcholinesterase inhibitors (Henstra et al., 2017; van Buel et al., 2017)] will greatly improve the tolerability of ECT and improve patients' perception of ECT.

Retrograde amnesia (amnesia for previously stored memories) is one of the most troubling and hard-to-study side effects of ECT (Fraser, O'Carroll, & Ebmeier, 2008; Prudic, Peyser, & Sackeim, 2000; Sackeim, 2014; Semkovska & McLoughlin, 2013, 2014). Patients suffering from this type of amnesia have trouble recalling personal events, which can be distressing. Several groups found that objective memory performance on autobiographical memory measures was impaired up until six months after ECT, yet performance on subjective memory measures showed impairments that were more persistent (Fraser et al., 2008). However, these findings have been contradicted showing also improvements in subjective memory (Vann Jones & McCollum, 2019).

The exact causes of these memory impairments remain unknown. Given that much of the ECT related anxiety and worry is related to memory and cognitive impairment (Obbels, Verwijk, Bouckaert, & Sienaert, 2017), it is important to get a better understanding of the causes of, and ways to counteract or prevent, memory impairment. Considering ECT as a potent neurogenesis enhancing treatment it could be that neurogenesis might play a role in this side effect (Akers et al., 2014; Anacker & Hen, 2017). New neurons that are added to the existing hippocampal circuits, remodel these circuits, compete with existing neurons, form new synaptic connections and may even replace previously formed synaptic connections of 'old' neurons (Akers et al., 2014; Toni et al., 2008, 2007; Yasuda et al., 2011). Memory engrams [populations of cells that become active during formation and recall of memories (Tonegawa, Liu, Ramirez, & Redondo, 2015)] may therefore also be disturbed by the addition of new neurons to these engrams (Anacker & Hen, 2017). This is also predicted by computational models of memory and neurogenesis (Weisz & Argibay, 2012) and believed to be the underlying mechanism of infantile amnesia [the natural process of forgetting memory from infancy (Akers et al., 2014)]. Corroborating these results, it has been shown that increasing neurogenesis in adult mice promotes forgetting of newly learned memories (Akers et al., 2014). Given that ECT may increase neurogenesis in humans, it could be that these newly formed neurons integrate in memory engrams and thereby induce retrograde amnesia. Although speculative, future studies are warranted to investigate this possibility.

CONSIDERATIONS

The studies presented in this thesis have some inherent methodological limitations that deserve attention. First, the sample size used in the analyses conducted in this thesis (Chapters 2, 3, 5 and 6) is relatively small. Therefore, the results presented in this thesis should function

as a stepping stone for future more adequately powered studies, rather than as confirmatory studies that can easily be generalized. In addition, although the use of an ultra-high-field MRI scanner enabled us to delineate the hippocampus with increased resolution (Chapter 3), the imaging technique remains suboptimal when it comes to studying direct neurochemical and neuroplastic effects. Ultra-high field MRI, while cutting edge, precludes us from directly observing cells, synapses and axons. Positron Emission Tomography may provide a mean to elucidate the effects of ECT on synaptic density, but a tracer for neurogenesis is not yet available. At present, only post-mortem research can provide direct information on all these cellular mechanisms, but this type of research has limitations of its own. Therefore, although volumetric increases (Chapter 3) and diffusivity decreases (Chapter 5) point into direction of neuroplasticity, it is important to keep in mind that directly observing these processes remain challenging in humans.

Another limitation is that the findings in the current thesis are based on two (Chapter 3, 5 and 6) or three (Chapter 2) measurement points. Given that ECT causes very rapid changes in mood and changes in brain structure and function, a time interval of 5 weeks (i.e. 10 ECT sessions) may be too coarse for us to portray a detailed timeline implying causation. This leaves an important question unanswered: do volumetric increases precede improvements in mood, or vice versa? If the structural changes in the brain precede the antidepressant effects, causality would be implied. However, the sparsity of measurement point prevents us to draw definitive conclusions regarding the causal link between brain changes and mood improvements.

As alluded to in previous paragraphs, (major) depression is a heterogenous disorder. Given that a major depressive disorder (as classified by the DSM-5), consist of a combination of either depressed mood or anhedonia, together with at least four other symptoms (as depicted in Fig. 1, Chapter 1), it could be that the etiology of this disorder varies considerably. Differences in the pathogenesis of depression might also call for different treatment strategies, and possibly more importantly, it may be that the effects of ECT differ when different etiologies are present, which may be the case in our sample. Elucidating which clusters of symptoms have shared etiology (or the other way around: grouping etiological similarities regardless of the phenotype), may result in the opportunity to more effectively target treatments to patients.

CLINICAL IMPLICATIONS

Since the findings presented in this thesis come from a small sample and warrant replication, the direct clinical implication of this work is limited. However, the results do give rise to some potential clinical implications. In Chapter 3, we showed that the volume of the DG increased after ECT, that this increase correlated with symptom improvement and that baseline DG (specifically, the asymmetry index of the left and right DG) could predict clinical effect. If these effects hold in larger samples, and especially if the predictive effect of the DG asymmetry index holds when measured using more readily available clinical MRI scanners, it could

be used as a potential marker to give a better estimation of who is likely to respond and who is not.

Another scientifically interesting way forward is to see whether DG volume (for example relative to the total intracranial volume) at baseline is correlated with certain cognitive tasks that rely on adequate DG functioning [such as pattern separation and cognitive flexibility (Anacker & Hen, 2017; Bakker et al., 2008)]. If so, do impairments in DG related cognitive tasks also predict ECT efficacy? Clinically, this will make prediction of ECT efficacy more feasible and cost-effective compared to using an MRI scanner.

Together with other predictors still being investigated, a more informed advice can be given to the patient opting for ECT. Additionally, when prediction (of both the antidepressant effect, but also the side effects) is more accurate, ECT could be used earlier in the process of treating depression with a reduced risk of administering it without beneficial and/or with severe side effects.

Finally, if neurogenesis indeed plays an important role in the high efficacy of ECT, as this thesis suggests, it would be key to develop new interventions that stimulate neurogenesis but lack the necessity for anesthesia. Examples are sustained physical activity, intermitted fasting, cognitive training, or, better yet, a combination of these three methods.

GENERAL CONCLUSION

Electroconvulsive therapy is a treatment with a long history. It is effective, safe and used in severe and persisting depressive disorders. The exact effects of ECT on the brain, and more specifically, its mechanism in alleviating depression remain not fully understood. In this thesis, research is presented aiming to elucidate some of the effects of ECT on the brain while simultaneously investigating the relevance of these effects for the efficacy of ECT. The studies presented in this thesis show that ECT is associated with short term cognitive deficits, and that brain changes suggest neuroplasticity occurring after ECT. Important next steps would be to test whether the findings hold in larger samples using more feasible techniques (i.e. 3T MRI). Furthermore, the neurobiological correlates of brain volumetric changes should be further investigated, together with their relevance to ECT's positive effect on mood and adverse effects on cognition and memory.

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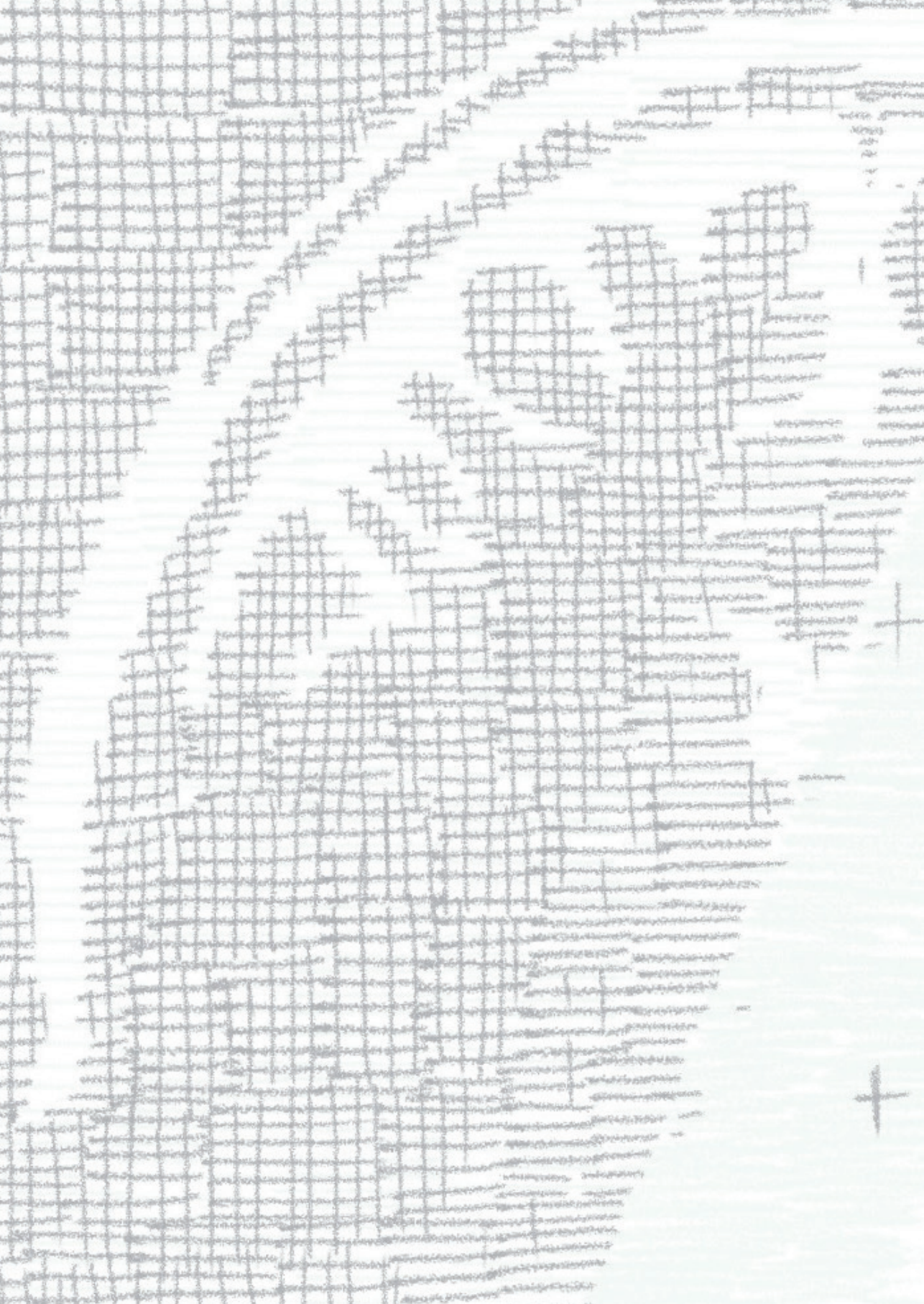

APPENDIX

PROPOSITIONS

- While ECT has a negative short-term impact on cognition, on the long-term these effects will, on average, subside.

- Disentangling the epiphenomenal effects of ECT from those that are required to establish the antidepressant response is a necessary next step in depression research.

- Understanding the mechanism of ECT enables the development of better tolerable therapies with similar high efficacy.

- Results show that electroconvulsive therapy stimulates plasticity in the brain.

- Future work should focus on elucidating the timeline of volume increases, diffusivity changes, mood improvements and cognitive/memory impairment to assess causality in the effects of ECT.

- Neurogenic effects of ECT appear to be limited to the dentate gyrus of the hippocampus.

NEDERLANDSE SAMENVATTING

Electroconvulsietherapie (ECT) is een behandeling voor (ernstige) depressie. Bij ECT wordt er (vaak 2 keer per week) stroom toegediend aan het brein via op de schedel geplaatste electroden zodat er een convulsie ontstaat die lijkt op een epileptische aanval.

De therapie is zeer effectief bij ernstige depressie (UK ECT Review Group, 2003), al blijft het werkingsmechanisme onduidelijk. Daarnaast kan ECT cognitieve bijwerkingen als gevolg hebben. Dit proefschrift is een bundeling van studies naar de cognitieve bijwerkingen van ECT en de effecten van ECT op het brein. Hieronder volgt een korte samenvatting van hoofdstukken twee tot en met zes, gevolgd door een algemene discussie en conclusie.

COGNITIE

In hoofdstuk 2 wordt een onderzoek gepresenteerd naar de effecten van bilaterale (electroden aan weerszijden van het hoofd) ECT op verschillende aspecten van het cognitieve vermogen van patiënten met een (zware) depressie. De hoofdbevinding is dat ECT op de korte termijn (na 5 weken) bijwerkingen gaf, maar dat deze bijwerking op de lange termijn (na 6 maanden) verdwenen waren.

Kijkend naar de verschillende cognitieve domeinen, bleek dat ECT op de korte termijn een significant negatief effect had op het verbale leer- en geheugenvermogen, en op een woordproductietest. Bij het visuospatiële vermogen van de participanten werd een kleine verbetering gevonden op de lange termijn. De effecten op het cognitieve vermogen werden niet verklaard door een verandering in de depressiescores. De resultaten gevonden in deze studie hebben betrekking op gemiddelde scores in de groep. Op individueel niveau lieten vijf patiënten een verslechtering zien in verbaal geheugen ten opzichte van het begin van de studie. Voor de woordproductietest waren dit er twee, drie voor visuele aandacht, en twee voor visuele flexibiliteit.

Het hebben van een depressieve stoornis is geassocieerd met een verminderd cognitief vermogen (Semkovska et al., 2019). Ondanks dat in deze studie ECT de depressie verlichtte, werden er op de lange termijn geen duidelijke verbeteringen gevonden in cognitieve vermogen. Hierdoor is een eventueel verborgen effect van ECT op cognitie niet geheel uit te sluiten.

GYRUS DENTATUS

Uit preklinisch onderzoek blijkt dat ECT neurogenese (het toevoegen van nieuwe neuronen) stimuleert in de gyrus dentatus (DG) van de hippocampus (Madsen et al., 2000; Perera et al., 2007). Uit studies met mensen blijkt dat de hippocampus in volume toeneemt (Takamiya et al., 2018). Of deze toename exclusief gedreven wordt door de gyrus dentatus (wat zou wijzen op neurogenese) of dat andere subvelden van de hippocampus ook bijdragen aan deze toename in volume (wat zou wijzen op een ander mechanisme), werd in hoofdstuk 3 onderzocht. De resultaten laten zien dat, na de ECT behandeling, de DG bilateraal toenam in volume. Deze toename

in volume hing samen met de afname in depressiescores (binnen personen), en het volume van de gyrus dentatus op baseline had een voorspellende waarde voor het antidepressieve effect van ECT. In de andere subvelden en in de controlegroep werd geen volumetoename gevonden. Deze resultaten suggereren dat neurogenese een rol heeft bij de volumetoename van de hippocampus door ECT. Echter, dat andere plastische processen zoals angiogenese (het vormen van nieuwe bloedvaten) en synaptogenese (het vormen van nieuwe synapsen) of schadelijke processen zoals oedeemvorming (ophoping van vocht) ook bijdragen, is niet uit te sluiten. Of dit het geval is wordt in hoofdstuk 5 verder onderzocht.

EEN COLLECTIE AAN BRIEVEN

In hoofdstuk 4 worden twee brieven gepresenteerd die de bevindingen in hoofdstuk 3 in een bredere context zetten. De eerste brief gaat over de vraag of de bevindingen uit hoofdstuk 3 gerepliceerd kunnen worden in een onafhankelijke steekproef op een conventionele 3T MRI scanner. Om deze vraag te beantwoorden hebben we samengewerkt met een groep van de Keio Universiteit, te Japan. In een her-analyse waarin we de methode uit hoofdstuk 3 toepasten op de data uit Japan, bleek de volume toename in de gyrus dentatus (en alleen de gyrus dentatus) ook samen te hangen met het verminderen van de depressieve symptomen.

De tweede brief is een antwoord op een commentaar geschreven door Koch en collega's (Koch, Morey, & Roelofs, 2019). Koch et al., opperen de mogelijkheid dat neurogenese een grote rol speelt in een variëteit aan stress-gerelateerde stoornissen. Met betrekking tot onze studie (hoofdstuk 3) stellen zij de vraag of het gemiddelde volume van de gyrus dentatus aan het begin van de studie verschilt tussen patiënten en controles. In een her-analyse vonden we geen statistisch significant verschil in gyrus dentatus volume tussen patiënten en controles. Daarnaast suggereren zij dat een eventuele associatie tussen het volume van de gyrus dentatus en de ernst van de depressie aan het begin van de studie een verklaring zou kunnen zijn voor de voorspellende waarde van de gyrus dentatus (zie hoofdstuk 3). Wij vonden geen associatie tussen het volume en de ernst van de depressie. Verder, wanneer we de ernst van de depressie aan het begin van de studie meenemen in het model, veranderen de resultaten niet.

PLASTICITEIT, PERFUSIE EN OEDEEM

In hoofdstuk 5, werd gekeken naar processen die mogelijk kunnen bijdragen aan de volume verandering van de gyrus dentatus. Naast neurogenese, kunnen namelijk ook andere neuroplastische processen zoals synaptogenese of oedeemvorming bijdragen aan de volume vergroting in de hippocampus. In deze studie keken we naar het verschil in diffusie en perfusie in de hippocampus voor en na ECT. We maakten gebruik van de mean diffusivity (MD; gemiddelde diffusiviteit) berekent op diffusion-weighted imaging (DWI) data om naar oedeemvorming en plasticiteit te kijken. Om naar perfusie te kijken, maakten we gebruik van de perfusie fractie *f*, en D* met behulp van intravoxel incoherent motion (IVIM) en arterial spin labelling (ASL). Het IVIM model meet de perfusie van de hippocampus op basis van DWI data. De

hypothese luidde als volgt: als vasogene oedeemvorming bijdraagt aan de volume toename na ECT dan zal de MD stijgen, maar de MD zal dalen als neuroplasticiteit bijdraagt aan dit effect. Verder, als ECT angiogenese bewerkstelligt, dan zullen de perfusie parameters geschat vanuit het IVIM model en de ASL data stijgen.

De resultaten laten een daling van de MD na ECT zien in de linker en rechter hippocampus. Verder daalde de perfusie fractie f in de linker hippocampus. Deze resultaten suggereren dat ECT niet is geassocieerd met vasogene oedeemvorming, maar mogelijk wel met neuroplastische effecten.

VORMVERANDERINGEN VAN HET LATERALE VENTRIKEL

Naast de gyrus dentatus (zie hoofdstuk 3) vindt neurogenese ook plaats in de subventriculaire zone (SVZ) van het laterale ventrikel in volwassen zoogdieren (Alvarez-Buylla & García-Verdugo, 2002). Aangezien ECT de potentie heeft om neurogenese te stimuleren in mens en dier, is de vraag of dit ook gebeurt in de SVZ. Studies bij knaagdieren suggereren dat het opwekken van convulsies (zowel chemisch als elektrisch) inderdaad neurogenese in de SVZ stimuleert (Inta et al., 2013; Parent, Valentin, & Lowenstein, 2002; Suzuki et al., 2007). Of dit ook in mensen gebeurt is niet duidelijk.

In deze studie onderzochten we of de vorm van de ventrikels verandert op de locatie van de subventriculaire zone. De resultaten laten zien dat het volume van de ventrikels significant afnam na behandeling met ECT. Vormveranderingen werden echter over het gehele ventrikel gevonden, en niet specifiek ter hoogte van de subventriculaire ruimte.

ALGEMENE DISCUSSIE

De resultaten uit hoofdstuk 3 en hoofdstuk 5 wijzen erop dat ECT neuroplastische (en neurogene) effecten heeft in de hippocampus. Ook suggereren de bevindingen dat deze processen van belang zijn voor de antidepressieve effecten van ECT. Deze resultaten zijn in lijn met een deel van de neurogene hypothese van depressie: het stimuleren van neurogenese doet de depressie weer afnemen (Eisch & Petrik, 2012; Miller & Hen, 2015; Petrik, Lagace, & Eisch, 2012). De gehele hypothese luidt: verminderde of verstoorde neurogenese in de DG is een oorzaak van depressie, en het herstellen of verhogen van neurogenese heeft een antidepressief effect. Vanuit de literatuur is er bewijs dat deze hypothese ondersteund, maar ook bewijs dat deze hypothese tegenspreekt. Voor nu lijkt het erop dat sommige vormen/symptomen van depressie samenhangen met verminderde neurogenese, en dat sommige antidepressieve effecten komen door neurogenese. Ervanuit gaande dat ECT een potente neurogene/neuroplastische stimulator is, zou het kunnen dat de vormen van depressie die samenhangen met neurogenese het meeste baat hebben bij ECT. Verminderde of verstoorde neurogenese in de DG en de functionaliteit van de DG zou terug te zien kunnen zijn in cognitieve processen die berusten op de DG en neurogenese. Patroon onderscheiding (pattern separation) is een voorbeeld van zo'n proces (Bakker, Kirwan, Miller, & Stark, 2008; Brock Kirwan et al., 2012; Stark, Yassa, Lacy, & Stark,

2013). Pattern separation is het vermogen om gebeurtenissen/plaatsen/patronen die zeer gelijkend aan elkaar zijn toch in het geheugen van elkaar te kunnen onderscheiden (Stark et al., 2013). Als het inderdaad zo is dat verminderde DG-functie en neurogenese hierop van invloed zou zijn, zou onderzocht kunnen worden wat de voorspellende waarde is van moeite met pattern separation op de effectiviteit van ECT. Als deze predictieve waarde hoog blijkt te zijn, dan zouden mensen die veel DG-dysfunctie laten zien (eerder) met ECT behandeld kunnen worden. Dit kan grote teleurstelling voorkomen wanneer mensen geen baat hebben bij ECT, maar eventueel wel last hebben van cognitieve bijwerkingen. Echter, of neurogenese inderdaad het werkingsmechanisme van ECT verklaart, blijft onzeker. Het antidepressieve effect van ECT kan soms al na een paar behandelingen optreden (na een paar weken), terwijl pasgeboren neuronen vaak meerdere (8+) weken nodig hebben om volledig volwassen te worden (Anacker & Hen, 2017). Hoe neurogenese en snellere neuroplastische processen een rol spelen bij de antidepressieve effecten (maar ook de bijwerkingen) van ECT, moet dus verder onderzocht worden.

Naast onderzoek naar de causale mechanismen van de positieve effecten van ECT is het beperken van de bijwerkingen van ECT een belangrijk doel. Ondanks de hoge effectiviteit van ECT heeft een deel van de mensen die deze behandeling ondergaat (tijdelijk, maar ook blijvend) last van cognitieve en geheugenproblemen (Hoofdstuk 2; Vasavada et al., 2017). Het verminderen van deze bijwerkingen zal de verdraagzaamheid van de behandeling verhogen en zal ECT gerelateerde angst (Obbels, Verwijk, Bouckaert, & Sienaert, 2017) doen afnemen. Net als bij de positieve effecten van ECT geldt dat het causale mechanisme van de bijwerkingen onduidelijk is. In het kader van neurogenese en neuroplasticiteit als werkingsmechanisme onderliggend aan het antidepressieve effect van ECT, is het ook van belang te noemen dat het eveneens een rol kan spelen in de bijwerkingen van ECT. Nieuwe neuronen die worden geboren in de DG integreren in bestaande hippocampale circuits, vervangen reeds gevormde connecties met 'oude' neuronen en her-modeleren daarmee de bestaande circuits (Akers et al., 2014; Toni et al., 2008; Yasuda et al., 2011). Memory engrams [collecties van neuronen die coderen voor een bepaalde herinnering (Tonegawa, Liu, Ramirez, & Redondo, 2015)] kunnen verstoord raken door het toevoegen van nieuwe neuronen (Anacker & Hen, 2017), met eventueel amnesie als gevolg. Dit wordt inderdaad voorspeld door computationele modellen van neurogenese en geheugen (Weisz & Argibay, 2012), en wordt beschouwd als het proces onderliggend aan infantiele amnesie [het vergeten van herinneringen uit de kindertijd (Akers et al., 2014)]. Vervolgonderzoek is daarom nodig om deze mogelijke verklaring, en mogelijke processen onderliggend aan cognitieve bijwerkingen, verder te bestuderen.

ALGEMENE CONCLUSIE

In deze thesis stond de vraag centraal wat de effecten van electroconvulsietherapie (ECT) zijn op het brein en de cognitieve vermogens van mensen met een depressie. De eerste studie laat zien dat ECT op de korte termijn cognitieve bijwerkingen gaf, die op de lange termijn

gemiddeld genomen verdwenen. De andere studies laten zien dat na een serie ECTs de gyrus dentatus van de hippocampus in volume toenam, en dat dit niet te verklaren was vanuit oedeemvorming. Ook bleek het volume van de laterale ventrikels te zijn afgenomen, maar dat dit niet specifiek te maken had met vormveranderingen rondom de neurogene subventriculaire zone. Samenvattend wijzen de studies erop dat ECT de neuroplasticiteit (waaronder neurogenese) in de hippocampus stimuleert bij patiënten met een depressie. Een belangrijke volgende stap is het onderzoeken welke processen precies ten grondslag liggen aan de volume veranderingen in het brein. Daarnaast kan onderzocht worden of de functie van de gyrus dentatus een voorspellende waarde heeft voor het effect van ECT en hoe deze en andere veranderingen in het brein zich verhouden tot de positieve en negatieve effecten van ECT. Ook is het belangrijk een antwoord te vinden op de vraag of en hoe we de cognitieve bijwerkingen van ECT kunnen beperken. Laten we hopen dat we deze vraagstukken snel oplossen!

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LIST OF PUBLICATIONS

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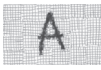
CURRICULUM VITAE

Jasper Olivier Nuninga was born on January 15th 1994 in Rotterdam, the Netherlands. After graduating from the Rudolf Steiner College in Rotterdam, he started studying Psychology at the University of Leiden. In 2015, he obtained his Bachelor of Science degree in Psychology (cum laude). Due to an increasing interest in the brain, he decided to start the Research Master Neuroscience and Cognition at the University of Utrecht and in 2017 he obtained his Master of Science degree in Clinical Neuroscience (cum laude). During this Master program he started an internship at the lab of prof. dr. Iris Sommer, studying white matter structure in the brains of people with the 22q11.2 deletion syndrome. For his second internship he had the opportunity to go to the University of Tokyo, Japan, at the lab of prof. dr. Kiyoto Kasai and dr. Shinsuke Koike, studying white matter structure in relation to auditory verbal hallucinations. During both internships (Utrecht and Tokyo) he saw colleagues combining work as health care professionals and scientists and realized the value of such a combination for the field. Filled with enthusiasm to pursue such a career path, he started a Master in in Clinical Psychology at the University of Leiden and obtained his Master of Science degree (cum laude) in 2018. In the same year, he started his PhD project under the supervision of prof. dr. Iris Sommer and dr. René Mandl focusing on the effects of electroconvulsive therapy (ECT) on the brain. During this PhD project he had the opportunity to revisit the lab of dr. Koike at the University of Tokyo and to work as a psychologist in mental health care in the Netherlands. As of January 2021, he will continue his academic career as a post-doctoral researcher at the lab of prof. dr. Iris Sommer supervising a randomized controlled trial directed at ameliorating the cognitive and memory side effects of ECT, while simultaneously working as a psychologist and therapist in clinical practice.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