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„Meta-analysis of hippocampal volume changes following electroconvulsive therapy in major depression“

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ABSTRACT (english)

Major depressive disorder (MDD) is one of the most frequent psychiatric disorders and the number one cause of disability worldwide. Depressive symptoms typically encompass clouded mood, avolition and a loss of interests as well as multiple psychophysiological changes. The most powerful treatment option for depression is electroconvulsive therapy (ECT), whereby an electrical stimulation of the brain triggers a generalized seizure. Although the first ECT was already conducted in the 1930s, the mechanisms of action of this treatment option are still not fully decoded. One potential target to explain both the emergence of depression and ECT's antidepressant effects is adult neurogenesis. As demonstrated in various investigations, ECT seems to counteract alterations of neurogenesis mirrored in hippocampal shrinkage observed in depressed patients. Based on these findings, the thesis at hands aims at determining the real effect size of ECT on hippocampal volume in patients suffering from MDD by combining the outcomes of multiple magnetic resonance imaging (MRI) studies in a meta-analysis.

Following a thorough literature search, 11 MRI studies including a total of 235 patients with depression were used in this meta-analysis. The primary outcome was the standardized change score of hippocampal volume before and after ECT.

The total hippocampal volume increased significantly following a course of ECT (0.86, 95% confidence interval (CI): [0.59, 1.13]; $p < 0.0001$; $n = 11$). Similarly, the left (0.71, 95% CI: [0.38, 1.03]; $p < 0.0001$; $n = 9$) and right (0.84; 95% CI: [0.54, 1.14]; $p < 0.0001$; $n = 9$) hippocampus showed a significant volume increase after administration of ECT. Alterations in hippocampal volume and changes in depressive symptom scores were not correlated.

The present meta-analysis demonstrated a strong effect of ECT on bilateral hippocampal volume in patients with MDD. The relationship between hippocampal volume alterations and changes in depressive symptomatology should be evaluated in more homogeneous studies in the future.

ABSTRACT (Deutsch)

Major depressive disorder (MDD) ist eine der häufigsten psychiatrischen Erkrankungen, die weltweit die Hauptursache für Erwerbsunfähigkeit darstellt. Typischerweise umfasst die depressive Symptomatik getrübte Stimmung, Antriebslosigkeit und Interessenverlust sowie vielfältige psychophysiologische Veränderungen. Die effektivste Methode zur Behandlung der Depression ist die Elektrokonvulsionstherapie (Elektrokrampftherapie, EKT), bei der eine elektrische Stimulation des Gehirns einen generalisierten Krampfanfall auslöst. Obwohl die erste EKT bereits in den 1930er Jahren durchgeführt wurde, ist die Funktionsweise bislang nicht vollständig entschlüsselt. Ein möglicher Mechanismus, um sowohl das Auftreten der MDD als auch die antidepressiven Effekte der EKT zu erklären, ist die adulte Neurogenese. Viele Studien veranschaulichen, dass die bei depressiven PatientInnen gestörte Neurogenese und das bei dieser Erkrankung beschriebene verringerte Hippocampusvolumen durch EKT normalisiert werden kann. Das Ziel der vorliegenden Arbeit ist es, auf Grundlage dieser Evidenz die tatsächliche Effektgröße der EKT auf das Hippocampusvolumen von MDD PatientInnen zu ermitteln, indem die Ergebnisse zahlreicher Magnetresonanztomographie (MRT)-Studien in einer Meta-Analyse zusammengefasst werden.

Nach einer gründlichen Literatursuche wurden 11 MRT-Studien mit insgesamt 235 depressiven PatientInnen in die Analyse eingeschlossen. Der primäre Endpunkt ist der standardisierte Änderungswert des Hippocampusvolumens vor und nach der EKT.

Nach Durchführung einer EKT-Serie zeigte sich ein signifikant erhöhtes Volumen des gesamten Hippocampuses (0.86, 95% confidence interval (CI): [0.59, 1.13]; $p < 0.0001$; $n = 11$). Ebenfalls wies der linke (0.71, 95% CI: [0.38, 1.03]; $p < 0.0001$; $n = 9$) und rechte (0.84; 95% CI: [0.54, 1.14]; $p < 0.0001$; $n = 9$) Hippocampus eine signifikante Volumenzunahme nach der EKT auf. Veränderungen des Hippocampusvolumens und der depressiven Symptomatik berechnet anhand entsprechender Skalen zeigten keine Korrelation.

Die vorliegende Meta-Analyse veranschaulicht einen ausgeprägten Effekt der EKT auf das bilaterale Hippocampusvolumen. Der Zusammenhang zwischen Volumen- und Symptomveränderungen sollte in zukünftigen, homogeneren Studien untersucht werden.

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5-HT	serotonin
$5\text{-HT}_{1A,\ 1B}$	serotonin-1A, serotonin-1B
5-HTTLPR	serotonin-transporter-linked polymorphic region
AC	adenylat cyclase
ACTH	adrenocorticotropic hormone
AD	antidepressant
BD	bipolar disorder
BDNF	brain-derived neurotrophic factor
BL	bilateral
cAMP	cyclic adenosine monophosphate
CI	confidence interval
COMP	catechol-O-methyltransferase
CPRS	The Comprehensive Psychopathological Rating Scale
CREB	cAMP response element-binding protein
CRH	corticotropin releasing hormone
D	train duration
DA	dopamine
DAG	diacylglycerol
DG	dentate gyrus
DNA	deoxyribonucleic acid
DRD2, 3	dopamine 2 receptor gene, dopamine 3 receptor gene
DSM	Diagnostic and Statistical Manual of Mental Disorders
DWI	diffusion weighted imaging
ECG	electrocardiogram
ECS	electroconvulsive shock
ECT	electroconvulsive therapy
EEG	electroencephalogram
EMG	electromyogram
F	pulse frequency
FHIT	fragile histidine triad gen
GABA	γ-aminobutyric acid
GCL	granule cell layer
G-protein	guanine nucleotide triphosphate-binding protein
GMV	gray matter volume
GWAS	genome-wide association study

HAM-D, HDRS	Hamilton Depression Rating Scale
HPA	hypothalamic-pituitary-adrenal
I	current
ICD-10	International Statistical Classification of Diseases and Related Health Problems (tenth revision)
IP_3	inositol triphosphate
MADRS	Montgomery-Åsberg Depression Rating Scale
MAO-A	monoamine oxidase A
MDD	major depressive disorder
Met	methionine
ML	molecular layer
MRI	magnetic resonance imaging
N	number of patients
n	number of studies
n.a.	not available
NE	norepinephrin
NET	norepinephrine transporter
PET	positron-emission tomography
PI	phosphatidylinositol
PKA	protein kinase A
PKC	protein kinase C
PLC	phospholipase C
PW	pulse width
Q	stimulus dosage, total delivered charge
ROI	region of interest
RUL	right unilateral
SD	standard deviation
SERT	serotonin transporter
SGZ	subgranular zone
SNP	single-nucleotide polymorphism
TRD	treatment-resistant depression
UL	unilateral
V	volume
Val	valine
WHO	World Health Organization

1 INTRODUCTION

“Studies indicate that approximately half of the general public is convinced that people with depression are weak, responsible for their own condition and unpredictable; and nearly a quarter considers them to be dangerous.” (Kohls et al., 2017). This statement seems surprising since depression was already characterized by Hippocrates ~2500 years ago with symptoms of deep sadness as well as multiple other psychophysiological alterations comparable to those described in recent diagnostic manuals (Horwitz, Wakefield, & Lorenzo-Luaces, 2017). Therefore one would think that depression is accepted as a serious disease. However, the statement mentioned above is still up-to-date. One consequence of that stigmatization is the poor treatment rate meaning that about 56% of patients with major depressive disorder (MDD) receive no adequate therapy although various options are available (Fernandez et al., 2007; Kohn, Saxena, Levav, & Saraceno, 2004). The most effective treatment for MDD, which achieves response rates between 75% and 95%, is electroconvulsive therapy (ECT) (Kasper et al., 2017; Kho, van Vreeswijk, Simpson, & Zwinderman, 2003; UK ECT Review Group, 2003). “Despite this, ECT continues to be the most stigmatized treatment available in psychiatry, resulting in restrictions on and reduced accessibility to a helpful and potentially life-saving treatment.” (Payne & Prudic, 2009). Due to the massive stigmatization, research has a major responsibility to enlighten people by decoding the underlying biological mechanism of MDD and ECT. Only with a better understanding of these basic principles, a wider acceptance of that treatment option and depression can be achieved.

Concerning multiple published preclinical and clinical investigations, one potential target to explain both the emergence of depression and the antidepressant effect of ECT is neurogenesis (for an overview see Bambico and Belzung (2013) or Dranovsky and Hen (2006)). In brief, it was shown that patients suffering from depression had decreased hippocampal volumes in comparison to healthy persons (Bremner et al., 2000; Dukart et al., 2014; Joshi et al., 2016; Wolf et al., 2016). The observed reductions in hippocampal volumes normalized following a course of ECT and were associated with increased neurogenesis induced by the current administration (Abbott et al., 2014; Jorgensen et al., 2016; Joshi et al., 2016; Nordanskog, Larsson, Larsson, & Johanson, 2014; Oltedal et al., 2015; Sartorius et al., 2016; Tendolkar et al., 2013).

The primary goal of the thesis at hands is to figure out the real effect size of ECT on hippocampal volume in patients suffering from major depression. For this purpose, the outcomes of multiple magnetic resonance imaging (MRI) studies

measuring hippocampal volume pre and post ECT were integrated in a meta-analysis. Additionally, particular attention was paid to the depressive symptomatology and its relationship with hippocampal volume changes.

2 THEORETICAL BACKGROUND

2.1 Major depressive disorder

Major depressive disorder (MDD) is a widespread mental or mood disorder, which can occur during the entire lifespan independently of sex, age, social class, culture and nationality. Nowadays about 322 million people worldwide are affected and depression is the number one cause of disability around the world (Friedrich, 2017; Kasper et al., 2012; World Health Organization, 2017, 2018). Although both sexes can suffer from MDD, women twice as often experience that disease (Ebmeier, Donaghey, & Steele, 2006; Kupfer, Frank, & Phillips, 2012). People passing through depression undergo a tremendous psychological strain and mostly cannot accomplish their daily tasks at home, school or business. As the worst consequence, the disease can give rise to suicide. The World Health Organization (WHO) published in 2018 that approximately 800 000 people worldwide die annually as a consequence of suicidal actions (World Health Organization, 2018).

Characteristics, psychometrical scales for the evaluation of depression as well as the possible underlying mechanisms and therapies are explained in more detail in the following sections.

2.1.1 Characteristics

According to the International Statistical Classification of Diseases and Related Health Problems (ICD, up-to-date version: tenth revision), MDD can be assigned to the affective and mood disorders (World Health Organization, 1992). Corresponding to the three leading symptoms patients typically experience clouded mood, avolition and a loss of interests. Furthermore, in the majority of cases the patient goes through a variety of psychophysiological changes, which impair their normal way of life (Belmaker & Agam, 2008; Butcher, Mineka, & Hooley, 2009; Ebmeier et al., 2006; World Health Organization, 1992).

2.1.1.1 Progress of disease

The progress of depression is very diverse in respect of symptoms, severity and duration. Consequently, the symptoms of different patients can vary massively and each one can develop a very individual symptomatology. Common to all is the aforementioned change of mood and the mostly occurring psychophysiological alterations. These modifications comprise different levels of symptoms like cognitive,

behavioral or somatic ones. Cognitive aspects contain for example feelings of guilt or worthlessness, the feeling of inferiority, which can heat up in suicidal thoughts. Moreover, difficulties in concentration and motivational problems as well as restraints in memory can be observed. Fatigue, agitation or the slowing of speech and action are typical for behavioral symptoms. In addition, somatic signs of depression include but are not limited to the interruption of sleep like problems falling asleep or waking up very early in the morning. Also appetite both eating more and less and the libido may be changed. The different alterations have to persist for at least two weeks and restrict ones person's life to reach the diagnosis of depression (Belmaker & Agam, 2008; Butcher et al., 2009; World Health Organization, 1992).

2.1.1.2 Assessment

The degree of the disorder can be categorized as mild, moderate or severe. This rating depends on the appearance of symptoms where quantity and quality are relevant. The more symptoms a person has and the more serious the single ones are, the more severe the depression (World Health Organization, 1992, 2018).

Another relevant aspect in view of diagnosis and the characterization of the personal disease process is the actual presence and the duration of the disorder. The ICD-10 discriminates between a single depressive episode and recurrent depressive episodes both at mild, moderate or severe level, respectively. Additionally, there are persistent affective disorders like cyclothymia or dysthymia. In general, they are characterized by depressive symptoms, which are not intense enough to reach the criteria for a mild single or recurrent depressive episode. Since only the severe form of depression (MDD) plays a key role in the work at hands, the other forms are not to be described more precisely (World Health Organization, 1992).

2.1.1.3 Etiology

In the same way as every patient develops another set of symptoms, etiology can vary a lot from person to person. There are different components that may influence the presence and the manifestation of the disorder as well as a possible therapy. The factors can be classified as biological, psychosocial and cognitive-behavioral ones. Biological components contain for example genetic factors, disturbance of neurotransmission and neurohormonal regulation (e.g., hypothalamic-pituitary-adrenal axis) as well as an impairment of adult neurogenesis. Psychosocial perspectives assume that former experiences of loss or death of an affiliated person,

grave imminence of a relationship or employment in common with problems in finances or health are highly associated with the development of MDD. It should be noted that these conditions are mostly correlated with high stress levels. Additionally, there are cognitive-behavioral components. At present models like the Lewinsohn's depression model and the learned-helplessness model are proposed, which try to explain the emergence of MDD in different persons. (Belmaker & Agam, 2008; Butcher et al., 2009; Kasper et al., 2012; Lewinsohn, 1974; Monroe & Hadjiyannakis, 2002).

2.1.1.4 Challenges

As a result of the before mentioned heterogeneity of the disease and the high comorbidity with other psychiatric disorders (e.g., anxiety disorders) or somatic diseases, the diagnosis, evaluation and treatment of depression remain a challenge (Leitliniengruppe Unipolare Depression, 2015). For the majority of the population, the first contact point when seeking help is the general practitioner. A meta-analysis by Mitchell, Vaze, and Rao (2009) showed that general practitioners are mostly able to exclude depression in patients, which are not suffering from that disease. Additionally, on the one hand, physicians tend to over-detect depression, meaning that people get the diagnosis although they do not have that disorder. On the other hand, physicians do not recognize actual cases of illness. These identification errors, false positive as well as false negative, could be avoided by a more precise evaluation of the patients whose assessment in common practice is not satisfactorily (Kupfer et al., 2012; Mitchell et al., 2009; Tyrer, 2009; Wancata, Windhaber, Bach, & Meise, 2000). With this in view, psychometrical scales may be helpful tools to give direction to a diagnose and to assess the course of the disease - not only in terms of research but also in daily primary care (U.S. Preventive Services Task Force, 2002; Wancata & Friedrich, 2011).

2.1.2 Psychometrical scales

"Literally, the term [psychometrics] refers to psychological measurement. Generally, it refers to the field in psychology […] that is devoted to testing, measurement, assessment, and related activities." (National Council on Measurement in Education, 2017). Based on that definition, psychometrical scales in the field of clinical psychiatry give physicians and researchers the opportunity to relative objectively test, measure and assess the emotional state as well as the severity of a patients' disease.

Furthermore, it is possible to evaluate whether a person is responsive to a treatment (e.g., pharmacotherapy) or not (Dyer, Hooke, & Page, 2014). Especially in research, it is necessary to receive impartial information to ensure the comparability and reproducibility.

For this purpose, a lot of different psychometrical rating scales have been developed over the last decades. In general, all scales or tests are based on structured questionnaires. This implies that the questions as well as the answers are pre-formulated and the physician or the patient itself has only to read and choose the most appropriate option. The most convincing tests are those, which do not only offer yes or no answers, but rather gradations of a specific mood, behavior or any further psychophysiological symptom (Butcher et al., 2009). What all rating scales have in common is that the higher the total score at the end the more severe the disease. Unfortunately, institutions or medical centers use different cut-off-values for the categorization in mild, moderate or severe. To this end, guidelines can be useful tools to maintain comparability. Hereafter, the most frequently used rating scales, which are essential for the current thesis, are introduced.

2.1.2.1 Hamilton Depression Rating Scale

The Hamilton Depression Rating Scale (HAM-D or HDRS) was developed by Max Hamilton in 1960. The original version includes 17 items about widespread symptoms of depression, which has to be rated by a physician or another interviewer (e.g., psychologist). The ranking is based either on a five- or a three-point scale related to severity. Hamilton chose two different grading scales because some items are hard to judge. Consequently, the items containing for example depressed mood, guilt, suicide or work and interests were categorized in five nuances: zero characterize the absence, one to three a fluent passage from mild to moderate and four reveal the most severe form of a feature. As opposed to this, symptoms such as insomnia, agitation as well as the loss of insight are based on three different classifications from zero meaning absent to two indicating clearly present. The rater has to take both severity and frequency into consideration to get a satisfying insight into a patient's disease process (Hamilton, 1960; Williams, 1988).

Because there is no standardized evaluation of the HAM-D score, the guidelines of a German committee of researchers and physicians are presented. Correspondingly, a total score up to eight is clinical inconspicuous, whereas a value upon 25 is a severe depression. In between the mild (9-16 points) as well as the

moderate (17-24 points) form of the disease are located (Leitliniengruppe Unipolare Depression, 2015).

Nowadays, different versions of the HAM-D are available, which contain various numbers of items like ones with 21 or 24 items. By way of example, questions about hopelessness or helplessness are added (Williams, 2001). Because of the numerous available versions, the exact applied one should be named in any case.

2.1.2.2 Montgomery-Åsberg Depression Rating Scale

The Montgomery-Åsberg Depression Rating Scale (MADRS) was released in 1979. The questionnaire arose from another scale, The Comprehensive Psychopathological Rating Scale (CPRS) with 65 items. To get more accurate in the detection of depression and to exclude other mental disorders, questions with less sensitivity were eliminated based on a pharmacological study. Finally, the ten most sensitive items for the assessment of MDD and the responsiveness to an antidepressant treatment were added to the MADRS (Asberg, Montgomery, Perris, Schalling, & Sedvall, 1978; Montgomery & Asberg, 1979).

Typically, the patient is rated by a physician by means of ten different categories including, for example, inner tension or the inability to feel as well as psychophysiological aspects like reduced sleep or appetite. The different items should be ranked on a zero to six scale indicating an increasing level of severity, with zero showing the absence of a symptom and six the most severe form (Montgomery & Asberg, 1979).

In view of the appraisal of the total score, there are some guidelines helping to standardize the outcome: a total score above 35 points indicates a severe depression, whereas 20-34 points may show a moderate depressive symptomatology. A mild depressive disease can be assumed between seven and nineteen points and the absence of depression may be reflected by values less than six (Leitliniengruppe Unipolare Depression, 2015).

2.1.3 Biological mechanisms

The exact mechanisms, which underlie the development of MDD are still not decoded. As briefly mentioned before, there are various biological, psychosocial and cognitive-behavioral basic approaches trying to explain the disease. Hereafter, the most commonly accepted biological theories concerning genetics, neurotransmission as well as neurohormonal regulation in respect of stress are explained in more detail

(Belmaker & Agam, 2008; Kasper et al., 2012). It should be noted that the neurogenesis hypothesis will be elucidated in a separate chapter, because of the importance for the thesis at hands.

2.1.3.1 Genetics

First of all, there are genetic theories, which are trying to define the occurrence as well as the symptomatology of MDD. Commonly used settings to investigate genetics are studies with twins (monozygotic or dizygotic) and adopted persons as well as explorations of family trees. These principles attempt to distinguish between genuine genetic effects and outcomes, which are additionally influenced by environmental factors named epigenetics (Belmaker & Agam, 2008; Sullivan, Neale, & Kendler, 2000). A meta-analysis of twin and adoption investigations by Sullivan et al. (2000) showed that the heritability of MDD is in the range of 31-42%. Even other studies indicated that there are hereditary genetic factors. They ascertained a higher occurrence of mental illness in monozygotic twins than dizygotic ones and noted that the resemblance between adopted individuals and their biological relatives exceed the similarity to their adopter in view of depression (Kendler, Gatz, Gardner, & Pedersen, 2006; Uher, 2009). This suggests that along with influential environmental factors, genetic variants seem to play a key role in the emergence of MDD.

However, apparently, not only a single gene is enrolled in the emergence of a so-called common or multifactorial disease like depression. It is more probable that different genes with a comparatively little influence sum up to a bigger effect, which can cause a clinically relevant outcome. In consequence, influences of various combinations of genes, which interact among themselves as well as with environmental factors are assumed (Manolio, Brooks, & Collins, 2008; Manolio & Collins, 2007). A lot of studies tried to identify underlying candidate genes (e.g., catechol-O-methyltransferase (COMP)) or polymorphic variants (e.g., serotonin-transporter-linked polymorphic region (*5-HTTLPR*)) in people suffering from MDD (for an overview see Ebmeier et al. (2006) or Kupfer et al. (2012)).

The establishment of genome-wide association studies (GWAS) appears to be a chance to promote the identification of relevant single-nucleotide polymorphisms (SNPs) for multifactorial disorders like MDD (MacArthur et al., 2017). “Genome-wide association studies […] assay at minimum hundreds of thousands of single-nucleotide polymorphisms […] to identify associations with complex clinical conditions and phenotypic traits.” (Welter et al., 2014). Based on that method, researchers could identify different genome-wide significant loci, for example, a SNP in the fragile

histidine triad (FHIT) gene, which could be assigned to the depressive symptomatology (Direk et al., 2017; Ikeda et al., 2016; Mekli et al., 2018). Additionally, SNPs of the brain-derived neurotrophic factor (BDNF) gene, e.g., the methionine (Met) allele of the functional valine/methionine (Val/Met) polymorphism rs6265, were associated with MDD and antidepressant treatment response (Kupfer et al., 2012; Licinio, Dong, & Wong, 2009). However, there are also negative results meaning that studies could not find any genome-wide significant loci in their analysis (Ripke et al., 2013). As a consequence, there is presently an inconsistent data situation and the direct link from genetics as well as epigenetics to the clinical picture of depression remains unclear.

2.1.3.2 Neurotransmission

With regard to pathogenesis, there are theories concerning the disturbance of neurotransmission. The most investigated one is the monoamine hypothesis (Schildkraut, 1965). The basis are monoamines like norepinephrine (NE) and serotonin (5-hydroxytryptamine, 5-HT), which play a crucial role in the central nervous system and are also allocated in neurons in the brain. They act as neurotransmitters and modulate various functions in an individual (Belmaker & Agam, 2008; Jesulola, Micalos, & Baguley, 2018).

NE is involved in processes like learning and memory or the regulation of behavior in general as well as attention (Jesulola et al., 2018; Roozendaal & Hermans, 2017). 5-HT matters in respect of modulation of mood and is enrolled in the control of sleep, appetite and sexual behavior. Most of these functions can be associated with depressive symptomatology. For example, there were diverse alterations observed representing a dysregulation of the serotonergic system like an increase in negative emotional states or aggressive behavior (Jesulola et al., 2018; Williams et al., 2003).

Consequently, the monoamine hypothesis of depression assumes that a deficiency in cerebral norepinephrine and/or serotonin neurotransmission could be one possible root cause for the appearance of the disease. Thereby different modalities are conceivable: the cerebral levels of neurotransmitters are reduced because of a decreased synthesis or an increased degradation, the protein transporters are malfunctioning or the neurotransmitter receptors are disadvantageously (Belmaker & Agam, 2008; Ferrari & Villa, 2017; Jesulola et al., 2018).

The general principle of neurotransmission as well as possible alterations in MDD are schematically illustrated in figure 1. The pathway for 5-HT is shown on the

left side, while the one of NE is right-sided. Immediately after the synthesis both 5-HT and NE are stored in vesicles in the presynaptic neuron. If a neuron is depolarized, the neurotransmitters are released in the synaptic cleft, where they influence the presynaptic as well as the postsynaptic cells via respective receptor molecules. The end of the synaptic action potential is controlled via neurotransmitter re-uptake in the neuron through 5-HT transporters (SERT) and NE transporters (NET), respectively. Additionally, there is a checkup via feedback for the regulation of the neurotransmitters' release. This control is mediated through auto-receptors at the presynaptic neuron: serotonin-1A (5-HT_{1A}) receptor and serotonin-1B (5-HT_{1B}) receptor, for instance, for serotonin and α2-noradrenergic ones for norepinephrine. Indirectly, the monoamine oxidase A (MAO-A), the major monoamine degrading enzyme in the brain, is also involved in the regulation of the presynaptic vesicular monoamine concentration. At the postsynaptic neuron 5-HT as well as NE bind to guanine nucleotide triphosphate-binding protein (G-protein)-coupled receptors: phosphatidylinositol (PI)-coupled and cyclic AMP (cAMP)-coupled monoamine receptors. In the former case, phospholipase C (PLC) is activated and restores inositol triphosphate (IP_3) and diacylglycerol (DAG), which then activate protein kinase C (PKC). In the other case, adenylate cyclase (AC) is activated, then cAMP is generated, thus activating protein kinase A (PKA). The two protein kinases A and C then influence the cAMP response element-binding protein (CREB). As shown in figure 1, there are few possible alterations in patients suffering from MDD: MAO-A ligand binding can be increased, polymorphisms of SERT can be observed as well as a reduction in cAMP, Inositol and CREB could be found in postmortem brains of depressed patients, for instance (Belmaker & Agam, 2008).

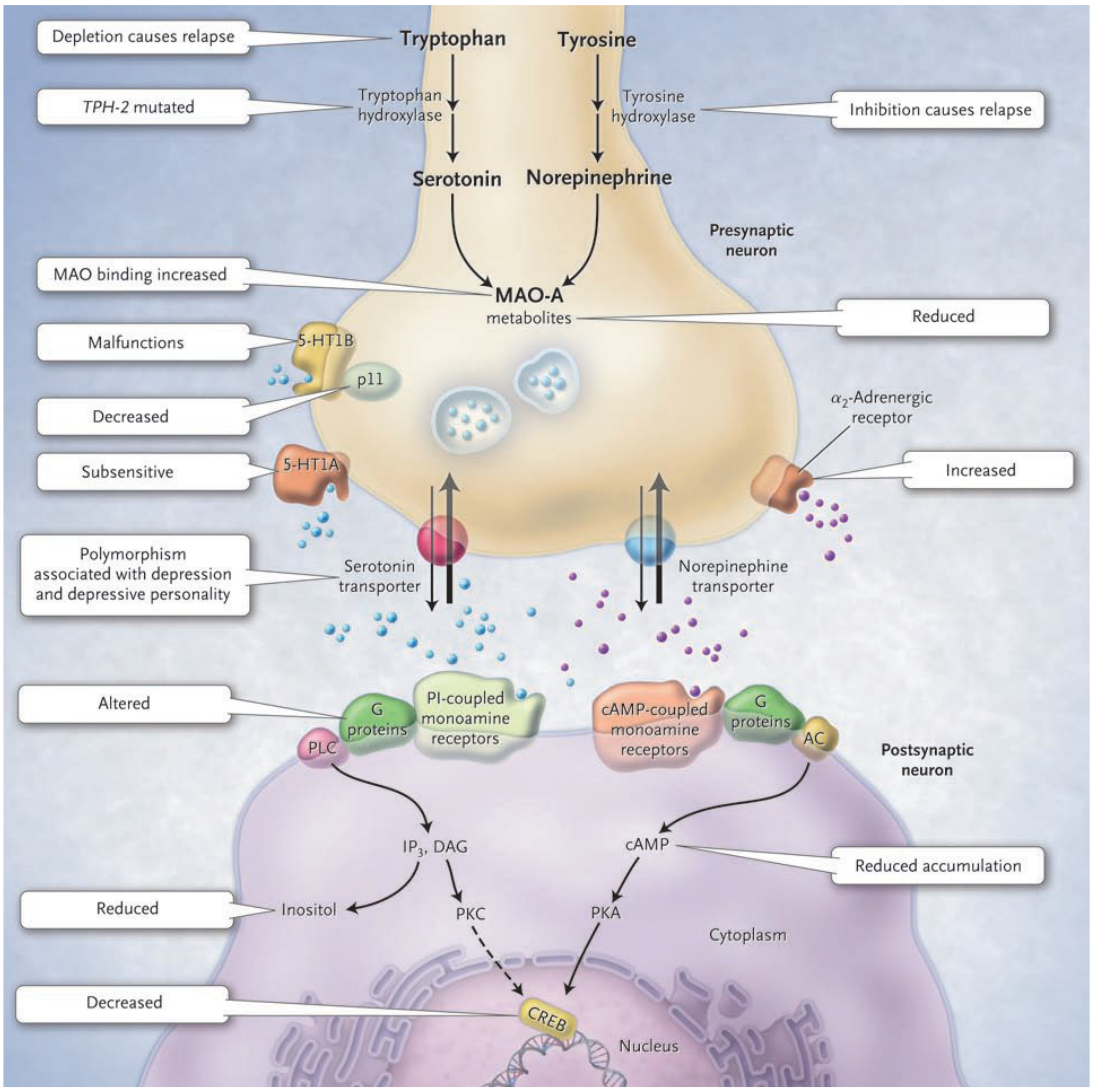

Figure 1: General principle of the serotonin and norepinephrine neurotransmission. In addition, possible alterations in patients with MDD are illustrated. Figure from Belmaker R.H. (Belmaker & Agam, 2008)

In addition to 5-HT and NE respectively, also the monoamine dopamine (DA) apparently has an impact on the manifestation of depression (Belmaker & Agam, 2008; Ferrari & Villa, 2017; Jesulola et al., 2018). DA is involved in the regulation of diverse functions such as motor behavior, cognition (e.g., attention or motivation) and emotional processing. The dysregulation of these tasks could be linked to the symptoms like difficulty in concentration or the lack of motivation observed in patients suffering from depression. (Grace, 2016; Jesulola et al., 2018; Schultz, 2007).

From today's view, the monoamine hypothesis of depression cannot by itself explain the whole complexity of MDD since not every patient responds to antidepressants, which mostly are modulating monoaminergic neurotransmission (Belmaker & Agam, 2008; Ferrari & Villa, 2017). It is more probable that the biological

mechanisms underlying the disease are not merely associated with the monoamines rather than being linked with additional factors such as genetic principals mentioned above.

2.1.3.3 Neuroendocrinology

Other theories regarding the presence of depression refer to neuroendocrine systems. In the context of MDD, alterations in the hypothalamic-pituitary-thyroid axis as well as the hypothalamic-pituitary-adrenal (HPA) axis could be observed. Hereinafter, the HPA axis is explained in more detail, because this system mainly adjusts the response to stress, which seems to be inappropriate in patients suffering from MDD (Butcher et al., 2009).

According to Ferrari and Villa (2017) stress " […] is considered as an event or experience that threatens the ability of an individual to adapt and cope." As mentioned before, such situations like the death of a closely related person have a substantial impact on the occurrence of depression (cf. 2.1.1). As illustrated in figure 2, the hypothalamus is activated (e.g., by noradrenergic pathways of the cortex) in response to stress. Thus, the corticotropin-releasing hormone (CRH) is secreted, which subsequently stimulates the release of corticotropin (adrenocorticotropic hormone, ACTH) through the anterior pituitary. Thence ACTH reaches the adrenal cortex by utilizing the bloodstream and triggers the releasing of cortisol. In healthy persons, cortisol inhibits further secretion of ACTH from the pituitary as well as CRH from the hypothalamus by negative feedback control. In contrast to that normal regulation, alterations could be found in patients with MDD (cf. figure 2). This implies that although cortisol is sufficiently generated and available, it cannot inhibits further production of CRH and ACTH, because the feedback system is malfunctioning (Butcher et al., 2009; Yehuda, 2002). As a consequence, patients with depression may exhibit increased plasma cortisol levels as well as enhanced CRH levels in the cerebrospinal fluid. Additionally, the anterior pituitary and the adrenal cortex are enlarged. It should be noted, that people with no risk factors regarding stress or evident malfunctioning HPA axis can also develop a MDD (Belmaker & Agam, 2008). This indicates that the depressive symptomatology cannot be explained by this hypothesis exclusively.

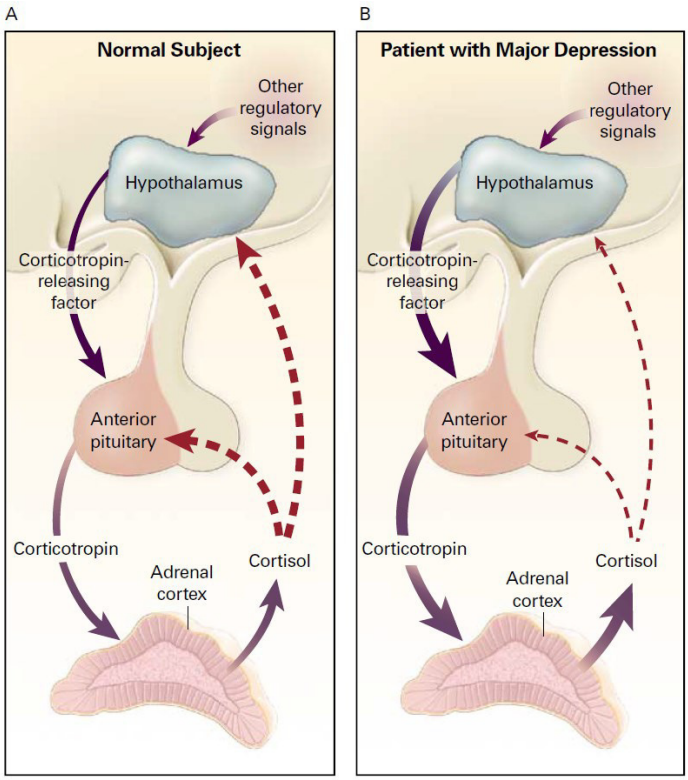

Figure 2: Stress response on the basis of the hypothalamic-pituitary-adrenal axis. (A) Illustration of the normal feedback and control system in healthy people. (B) Visualization of the altered pathway in patients with MDD. The thicker the single arrows, the larger the extent of the corresponding physiological reaction. Figure from Yehuda R. (Yehuda, 2002)

In summary, it can be stated that based on the current data situation no single theory can explain the pathogenesis of depression as a whole. For this reason, it seems that various alterations are influencing each other and collectively forming a biological basis for the comprehension of this disease as well as for most helpful therapies.

2.1.4 Therapies

As research regarding the underlying mechanisms of MDD progresses also caregiving further develops. Nowadays, there are various treatment options available like pharmacotherapy, non-medicinal biological therapies (e.g., sleep deprivation, transcranial magnetic stimulation and electroconvulsive therapy) as well as different forms of psychotherapy (e.g., cognitive behavioral therapy). Both monotherapies and treatment-combinations are common (Butcher et al., 2009; Kasper et al., 2012; Kupfer et al., 2012). The most frequently prescribed treatment option, namely pharmacotherapy, is discussed in more detail below. It should be noted, that a

discrete chapter will be devoted to electroconvulsive therapy, because of the importance for the thesis at hands.

According to Bauer et al. (2007), an acute treatment with an antidepressant (AD) should be applied right after the assessment of the patients' disease. There are two options of progress: the patient responds to the medication or not. In the first case, illustrated in figure 3, the patient shall carry on with the intake till total remission. Afterward, a continuation therapy for four to six months is indicated and if there is no relapse, the medication can be tapered off. Once there is a relapse or the depression is recurrent, the intake can be continued for months or years (maintenance treatment), also as a prophylactic therapy (Bauer et al., 2007; Kasper et al., 2017; Kasper et al., 2012)

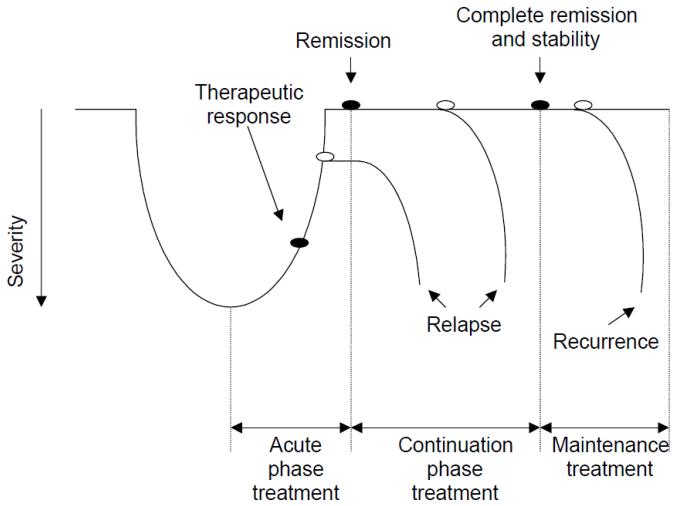

Figure 3: Antidepressant treatment in the course of depression. Adapted figure from Bauer M. (Bauer et al., 2007)

In the other case (cf. figure 4), where the patient shows only a partial reaction or no response to the treatment, the dosage of the same antidepressant should be increased. There are three possibilities if there is still no satisfying response: either combining two ADs of different pharmacodynamics, switching to another AD with the same or different pharmacodynamics or using an augmentation strategy. At any point in time, psychotherapy as well as electroconvulsive therapy should be considered (Bauer et al., 2007; Kasper et al., 2017; Kasper et al., 2012).

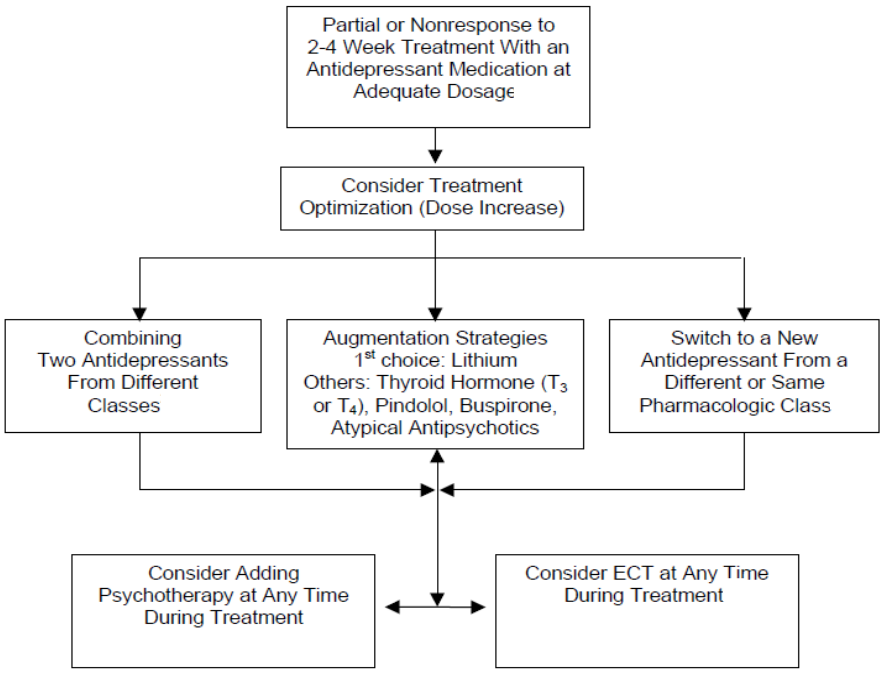

Figure 4: Process diagram relating to partial- and non-responders suffering from depression. Illustrated are the treatment options, if patients show no satisfying response to an initial antidepressant therapy. Adapted Figure, original from Bauer M. (Bauer et al., 2007)

Nowadays, various classes of ADs are available. Depending on the adverse drug effects, the personal tolerability, previous experiences and the severity of the depression as well as the expert knowledge of the physician an AD should be selected. Effective ADs for the treatment of depression are for example selective serotonin reuptake inhibitors, tricyclic antidepressants, MAO inhibitors or norepinephrine-dopamine reuptake inhibitors (Kasper et al., 2012; Kupfer et al., 2012).

A widespread problem in pharmacotherapy is that a lot of people do not satisfactorily respond to ADs. If these patients are not showing a sufficient improvement of the depressive symptomatology after two different treatment in adequate dosage and length, the disease can be classified as treatment-resistant depression (TRD). Based on that, different publications reported that approximately one out of three patients is diagnosed with TRD (Nemeroff, 2007; Rush, Trivedi, & Fava, 2003; Tendolkar et al., 2013). For these patients, alternative strategies like electroconvulsive therapy seem to be a chance to revert to a normal way of life.

2.2 Electroconvulsive Therapy

It was noticed in early observations that the spontaneous appearance of an epileptic seizure in patients suffering from schizophrenia leads to an improvement of the psychotic symptomatology. As a conclusion, seizures were thought to have a positive effect on mental illness and may even lead to total remission (Faedda et al., 2010). In the 1930s researchers induced seizures, initially only in animals, by either the application of chemical substances (e.g., camphor) or electricity (Bini, 1938; von Meduna, 1934). Then, the first electroconvulsive therapy (ECT) was successfully administered to a patient by Cerletti and Bini (1938 qtd. in Henkel and Grözinger (2013)). Overall, the principle of ECT is that "[…] a generalized seizure is provoked by electrical stimulation of the brain, is performed under short intravenous anesthesia and muscle relaxation." (Frey, Schreinzer, Heiden, & Kasper, 2001).

In the last decades a lot of research regarding efficiency, side effects as well as the underlying mechanisms of the treatment has been done. Meta-analyses in major depression showed that ECT is significantly more effective than sham ECT and exceeds the antidepressant effects of pharmacological therapies (Kho et al., 2003; UK ECT Review Group, 2003). Especially in terms of challenging courses of depression (e.g. high suicidal risk or treatment resistance), ECT represents the first-line treatment and shows response rates between 40% and 70% in patients diagnosed with treatment-resistant depression (TRD) and 75% up to 95% for those suffering from major depressive disorder (MDD) (Kasper et al., 2017). According to statistic calculations made by Henkel and Grözinger (2013), approximately two to three million ECTs are carried out per year.

The implementation of ECT, the treatment duration, contraindications and side effects as well as potential mechanisms of action are described in more detail in the following sections. Since ECT is a relative unspecific treatment option and effective in various psychiatric diseases such as mania or schizophrenia, it should be noted that only parameters relating to depression are presented (Frey, Schreinzer, et al., 2001; Kayser, Walter, & Schläpfer, 2010).

2.2.1 Implementation

Before starting ECT, the patient's course of depression and medication history should be assessed carefully by a physician. Even other clinical parameters like internistic and neurological status, laboratory tests as well as electrocardiogram (ECG) should not be neglected when assessing the benefit/risk ratio of ECT (Eitan & Lerer, 2006; Frey, Schreinzer, et al., 2001). Mostly inpatients are treated, but also the treatment of

outpatients is conceivable especially when it comes to continuation as well as maintenance ECT (Bauer et al., 2013). National and international guidelines concerning ECT are available (e.g., by the American Psychiatric Association, up-to-date version from 2001) and should be taken into account in conjunction with common research results to warrant both safety and effectiveness of the treatment.

2.2.1.1 Preparation

Prior to ECT, to guarantee the effectiveness and safety of anesthesia and stimulus administration, patients are asked not to eat nor smoke for at least six hours. Also dental prostheses should be removed. Additionally, skin cream or hairspray should not be used to ensure the attachment of the electrodes (Eitan & Lerer, 2006; Frey, Schreinzer, et al., 2001).

Through the whole procedure, vital functions are registered to ensure patients' safety. This includes an ECG, blood pressure measurements as well as transcutaneous oxygen saturation. Moreover, an electroencephalogram (EEG) is deduced by placing electrodes on the scalp: left and right frontal plus at the left and right mastoid as reference. The electromyogram (EMG) is recorded by an electrode on one forearm or lower leg. Both EEG and EMG are used to monitor the magnitude and duration of the later provoked generalized seizure in the brain and muscles, respectively. The next step is the intravenous administration of short anesthesia followed by respiration assistance with an oxygen mask. While the patient is anesthetized, a blood pressure cuff proximal to the EMG electrode (upper arm or knee) is inflated. This guarantees that the subsequent intravenously given muscle relaxant does not affect the muscles there and that the activity can be measured by EMG. Furthermore, a bite block is inserted in the patient's mouth to protect dentition during the seizure (Eitan & Lerer, 2006; Frey, Schreinzer, et al., 2001).

2.2.1.2 Electrode placement

The generalized seizure is triggered by current, which is delivered by two electrodes. With time different options regarding positioning have been developed. The most commonly used and investigated methods are shown in figure 3: unilateral (UL) and bilateral (BL, also named bifrontotemporal or bitemporal) electrode placement (American Psychiatric Association, 2001; Frey, Schreinzer, et al., 2001).

Regarding UL ECT, both electrodes are placed over one hemisphere. Currently, the positioning over the non-dominant hemisphere is used, which is in the majority of

the cases the right side. Almost all right-handed persons' non-dominant hemisphere is on the right side and this was also observed in 70-80% of left-handed people (American Psychiatric Association, 2001; Frey, Schreinzer, et al., 2001). According to Frey, Schreinzer, et al. (2001) in usual routine the electrodes are always attached on the right side (RUL). For the electrode placement the method by d'Elia and Raotma (1975) is recommended by the American Psychiatric Association (2001) and in clinical research often used (Joshi et al., 2016; Nickl-Jockschat et al., 2016; Nordanskog et al., 2010; Pirnia et al., 2016). As illustrated in figure 5, one electrode is placed on the vertex, about two to three centimeters lateral. The exact position of the vertex is determined by the midpoint between left and right tragus as well as the midpoint between inion and nasion. The other electrode is positioned on the temple on the right side halfway between the tragus and the external canthus and approximately two to three centimeters above (American Psychiatric Association, 2001; d'Elia & Raotma, 1975). In addition, d'Elia and Raotma (1975) advised that the space between both electrodes should not be less than 12-13 centimeters. This should be verified carefully to ensure that an adequate area is stimulated.

In the case of bilateral treatment, both electrodes are located on each side of the head, either similarly halfway between the tragus and the external canthus. Additionally, the electrodes should be placed approximately two to three centimeters above that midpoint as shown in figure 5 (American Psychiatric Association, 2001).

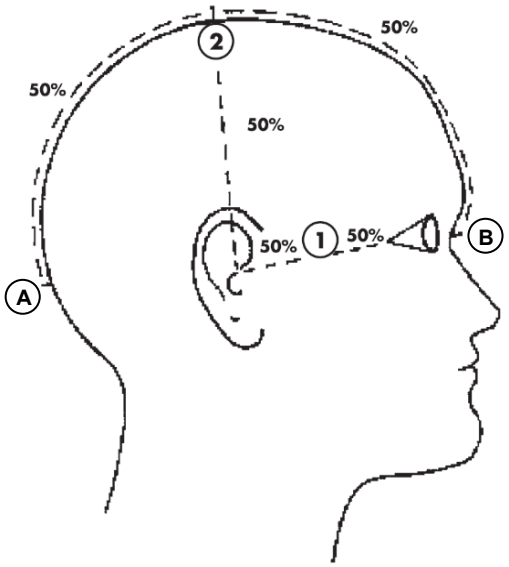

Figure 5: Electrode placement for electroconvulsive therapy. (1) Illustration of electrode location for bilateral stimulation. Both electrodes attached at the same location on the right and left side of the head, respectively (2) Visualization of the positioning of one electrode for right unilateral stimulation. The second electrode is placed at position 1 at the right side of the head. (A) Inion (B) Nasion. Adapted figure, original from the American Psychiatric Association (American Psychiatric Association, 2001)

Nowadays, UL and in particular RUL electrode placement is the preferred method (Frey, Schreinzer, et al., 2001; Loh, Nickl-Jockschat, Sheldrick, & Grozinger, 2013). Since the dominant hemisphere is not directly stimulated, less cognitive side effects are expected compared to the BL method (Kolshus, Jelovac, & McLoughlin, 2017; Sackeim et al., 2000; Semkovska, Keane, Babalola, & McLoughlin, 2011; Semkovska & McLoughlin, 2010; UK ECT Review Group, 2003). Concerning efficiency, RUL electrode placement seems to be less potent to improve the depressive symptomatology compared to BL stimulation (UK ECT Review Group, 2003). However, studies by Sackeim et al. (2000) as well as Kolshus et al. (2017) showed that the effectiveness of RUL ECT depends on the stimulus dosage with higher ones being more effective and comparable to BL treatment, respectively.

In conventional practice, BL ECT is considered either if the patient does not respond to four to five adequate applications of UL treatment or if a patient has already responded satisfactorily to BL ECT in the past (Frey, Schreinzer, et al., 2001). In any case, the physician should select the most suitable alternative for the patient in respect of symptom severity and acuteness. For instance, a person with a severe form of MDD might be stimulated with BL ECT from the session onwards, to ensure a quick symptom improvement and prevent suicidal actions, whereas milder forms should at first be treated unilaterally (Kellner et al., 2010; Zilles, Wolff-Menzler, & Wiltfang, 2015).

2.2.1.3 Stimulation

For the electrical stimulation, a special ECT device is necessary. Based on previous publications devices of two different corporations are in use: Thymatron® devices (SOMATICS, LLC, Florida, USA) and MECTA systems (MECTA Corp., Oregon, USA) (Frey, Schreinzer, et al., 2001; Jorgensen et al., 2016; Joshi et al., 2016; Nordanskog et al., 2014; Pirnia et al., 2016; Redlich et al., 2016; Tendolkar et al., 2013). The up-to-date version of the Thymatron® device, namely Thymatron® System IV, is commonly used in clinical practice especially in Europe and exemplarily shown in figure 6 (Frey, Schreinzer, et al., 2001; SOMATICS LLC, Retrieved 21.03.2018).

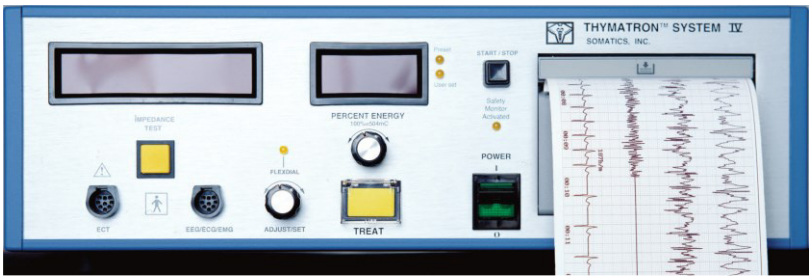

Figure 6: Thymatron® System IV. The device records parameters like EEG as well as EMG and delivers the energy for the electrical stimulation through electrodes. Figure by SOMATICS, LLC (SOMATICS LLC, Retrieved 21.03.2018)

Both systems record parameters like EEG and EMG for the assessment of the seizure in terms of duration and quality. In addition, the device delivers the energy needed to induce the seizure in the form of bipolar brief pulses with a recommended pulse width (PW) of half a millisecond, which corresponds to the neuronal refractory period (Frey, Schreinzer, et al., 2001). The current (I) chosen for administration may vary in a range of 500 to 900 milliamperes and pulse frequency (F) between 20 and 120 hertz. Additionally, the sequence of the short pulses (train duration, D) ranges from half a second to eight seconds. The finally applied stimulus dosage (total delivered charge, Q) is quantified in millicoulomb and characterized by the before mentioned variables, which are illustrated in figure 7 (American Psychiatric Association, 2001). By adjusting the total delivered charge with the formula $Q = \frac{I}{1000} \times PW \times 2F \times D$ the individual stimulus dosage can be determined (Eitan & Lerer, 2006). It is recommended to use constant current and to regulate train duration as well pulse frequency for the individual modulation of the stimulus dosage (American Psychiatric Association, 2001). Further, resistance is another influencing factor. This indicates that resistance of tissue between both stimulation electrodes should be measured before every ECT (Frey, Schreinzer, et al., 2001).

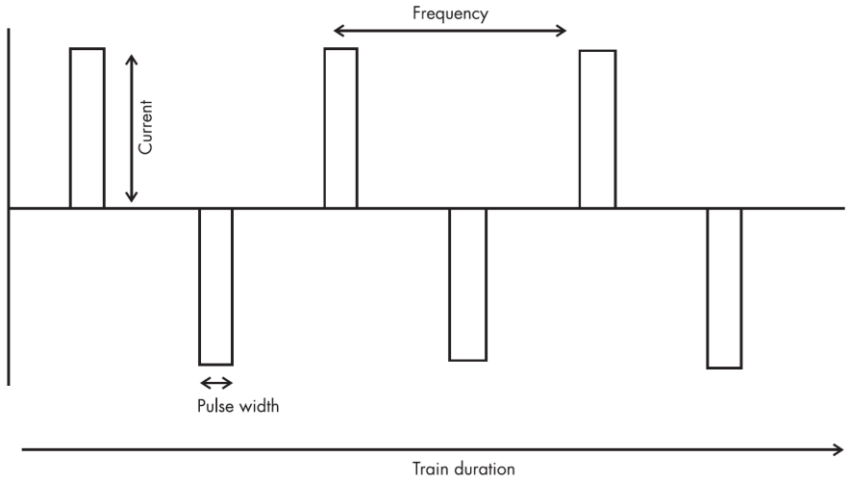

Figure 7: Illustration of bipolar brief pulse stimulation characteristics. Shown is the train duration with the factors current, pulse width and frequency of pulses. Figure from the American Psychiatric Association (American Psychiatric Association, 2001)

There are different practices in respect of stimulus dosage used during the first and the following ECT sessions. One option is the determination of the individual seizure threshold by titration (Petrides et al., 2009). “Seizure threshold was defined as the lowest stimulation level required to elicit an adequate seizure, defined as at least 25 seconds of EEG duration and at least 20 seconds of motor duration.” (Petrides et al., 2009). This procedure appears to be important, because it was shown that the threshold can differ widely between patients with influencing factors including sex and age as well as electrode placement (Shapira, Lidsky, Gorfine, & Lerer, 1996). Concerning stimulus titration, the patient should be initially stimulated with five or ten percent of the maximum charge. If no seizure of sufficient length and quality can be detected, an increased charge level (mostly doubled) is administered until a generalized seizure is observed. However, it is suggested to repeatedly stimulate only three times during one anesthesia (Frey, Schreinzer, et al., 2001). Once the seizure threshold is defined the charge applied during the following ECT sessions can be determined. The stimulation should be continued with a charge of at least 150% above or two and a half times the threshold when using a UL treatment (American Psychiatric Association, 2001; McCall, Reboussin, Weiner, & Sackeim, 2000; Sackeim et al., 2000). For BL ECT it is suggested to stimulate shortly above the seizure threshold in the subsequent sessions meaning only 50-150% or one and a half to two and a half times threshold, respectively (American Psychiatric Association, 2001). For example, Petrides et al. (2009) used a stimulus dosage of 50% higher than seizure threshold for the following ECTs. Since it was already shown by Sackeim et al. (2000) and

McCall et al. (2000) that antidepressant efficacy of ECT is affected by stimulus dosage relative to seizure threshold and not by absolute dosages, this method prevailed to adjust the dosage individually. On the other hand, other authors rejected this elaborated method for possibly increasing the risk of cardiovascular side effects because of the before mentioned repeated stimulations below seizure threshold (Petrides & Fink, 1996).

Another method concerning stimulus dosage is based on the patient's age. The underlying assumption is that the threshold for a generalized seizure depends on age, while it is lower in children compared to older people (Petrides et al., 2009; Petrides & Fink, 1996; Shapira et al., 1996). Overall, the general principle of this method is that the stimulus dosage is computed on the basis of the patient's age (Loh et al., 2013; Petrides et al., 2009; Petrides & Fink, 1996). This method was critically assessed as it is less customized for each patient and frequently led to higher stimulus dosages at the beginning of the ECT course than actually necessary (Tiller & Ingram, 2006).

It was shown that during the course of ECT seizure threshold increases and seizure duration decreases (Frey, Heiden, et al., 2001; Sackeim, 1999; Shapira et al., 1996). Additionally, there are various parameters that were shown to provide information about the quality of the provoked seizure. Five commonly estimated factors are: the duration of the seizure assessed by EEG and EMG activity, central inhibition (concordance of motor and EEG activity, postictal suppression), the amplitude of the seizure evaluated on the basis of the EEG, synchronicity (ictal coherence) and autonomic activation determined by the peak heart rate (Aksay et al., 2014; Bumb et al., 2015; Hoyer, Kranaster, Janke, & Sartorius, 2014; Kranaster, Hoyer, Janke, & Sartorius, 2013). As a result, to promote the antidepressant outcome, stimulus dosage as well as electrode placement must continuously be adjusted based on the quality parameters of the generalized seizure and the symptomatology.

2.2.1.4 Recovery phase

The time between the start of the anesthesia and waking up after the treatment is usually in a range of ten to twenty minutes (Frey, Schreinzer, et al., 2001). As soon as the seizure is terminated the patient should be strictly observed until vital functions are stable, in particular regarding respiration and cardiovascular function. Before discharge, a physician or nurse should check the patient's orientation and mentioned side effects like headache, nausea or cognitive restrictions in order to intervene as necessary. Since also outpatients are treated it is recommended that a caregiver

accompanies the patient after the recovery period in the establishment (American Psychiatric Association, 2001).

2.2.2 Treatment duration

In respect of ECT duration, it should be distinguished between acute and continuation as well as maintenance therapy. Continuation treatment refers to every therapy that is conducted within a time frame of six months after onset of remission. Whereas maintenance therapy relates to a treatment carried out for more than six months (American Psychiatric Association, 1990, 2001). The amount of stimulus administrations should be determined by individual assessment of the disease progression including the symptom degree as well as the occurrence and severity of undesirable side effects (American Psychiatric Association, 2001; Frey, Schreinzer, et al., 2001). Since the thesis at hands solely focuses on acute treatment, only the latter will be discussed in more detail below.

In the acute treatment phase of depression, ECT is usually carried out with a frequency of two to three times per week, independently of electrode placement. Typically, six to twelve treatments in total are administered in a period of three to four weeks. It is recommended to terminate therapy as soon as possible, especially if no further improvement of symptomatology can be observed after ~two consecutive ECT sessions or if total remission has been achieved. As a consequence, the individual evaluation of depressive symptoms and side effects between each session is of significant importance (American Psychiatric Association, 2001; Frey, Schreinzer, et al., 2001). As mentioned before, high response rates following ECT in patients suffering from TRD and MDD are observable ranging from 40% to 70% and 75% to 95%, respectively (Kasper et al., 2017). It is generally accepted that ECT is the most effective treatment option for depression (UK ECT Review Group, 2003). However, the antidepressant effects of ECT were shown to be short-term and a high risk of relapse is expected, especially in the first six months after an acute course of ECT (Jelovac, Kolshus, & McLoughlin, 2013; Sackeim et al., 2001). Jelovac et al. (2013) reported that approximately 40% of the patients are anticipated to relapse after a six months period, whereas after one year a rate of 50% can be assumed. Results from a placebo-controlled study by Sackeim et al. (2001) even exceeded these numbers and showed relapse rates of 84% six months after successful ECT. Due to the undisputed high relapse rates continuation as well as maintenance treatment should be considered.

2.2.3 Contraindications and side effects

As mentioned before, ECT is a highly effective treatment option especially regarding severe acute states of depression (MDD) as well as treatment-resistant processes (TRD) (Kasper et al., 2017; Kho et al., 2003; UK ECT Review Group, 2003). Still, there are some aspects in terms of contraindications as well as side effects that need to be considered before administering ECT.

The mortality risk of ECT corresponds to that for short anesthesia (Kasper et al., 2017). A recent analysis by Torring, Sanghani, Petrides, Kellner, and Ostergaard (2017) reported mortality of 2.1 per 100,000 treatments. Although it is challenging to deduce a causal relationship between ECT and cases of death, because of various individual influencing factors, it was concluded that ECT is a safe treatment option.

Generally, as with every treatment option, the aim of the physician should be to find the ideal balance between benefits and possible side effects to optimize the antidepressant outcome of ECT for every patient individually.

2.2.3.1 Contraindications

“There are no “absolute” medical contraindications to ECT.” the American Psychiatric Association (2001) stated. However, some medical conditions exist, which should be evaluated with care before the first ECT session. These conditions include cardiovascular states (e.g., myocardial infarction, aneurysms or vascular abnormalities), elevated intracranial pressure or space-occupying cerebral lesions, recent cerebral infarctions, pulmonary states (e.g., pneumonia) as well as an increased anesthetic risk (American Psychiatric Association, 2001). Besides, pacemakers, pregnancy or advanced age are no contraindications (American Psychiatric Association, 2001; Frey, Schreinzer, et al., 2001; Kayser et al., 2010). Depending on the occurrence and degree of the before mentioned conditions as well as correlated risks a physician should decide individually whether to conduct ECT or not.

2.2.3.2 Side effects

ECT may have negative implications on different domains, which can be roughly categorized as somatic or cognitive (American Psychiatric Association, 2001).

Frequent somatic side effects appearing during a course of ECT are headache, nausea and muscle soreness. These side effects can be assessed by the physician and treated symptomatically (American Psychiatric Association, 2001; Frey,

Schreinzer, et al., 2001; Kayser et al., 2010). Furthermore, medical morbidity thirty days after the administration of ECT mostly involves falls (5.5 per 10,000 ECTs) and pneumonia (3.8 per 10,000 ECTs), and was in sum relatively rare (16.8 per 10,000 treatments) (Blumberger et al., 2017). Moreover, somatic side effects include short-term heart rate, blood pressure and intracranial pressure increases (Bauer et al., 2013; Zilles et al., 2015).

Another side effect concerning both the somatic and cognitive domain is the so-called postictal delirium. Typically, the patient shows motor agitation and a lack of orientation as well as poor reactions to instructions. Furthermore, amnesia is common for that period. The delirium can occur only at one or several ECT sessions or a patient can develop it through the whole course of treatments. It is recommended to handle the postictal delirium based on severity and frequency of appearance. When occurring occasionally, it can be managed by the assistance of physicians or caregivers. Pharmacological interventions should be considered if it arises more often and severely, also as prevention before each ECT session (American Psychiatric Association, 2001).

The most extensively investigated side effect and typically the restraining factor for the application of ECT is cognitive impairment (American Psychiatric Association, 2001; Ebmeier et al., 2006; Frey, Schreinzer, et al., 2001; Kayser et al., 2010; Kolshus et al., 2017; Sackeim et al., 2000; Semkovska & McLoughlin, 2010). Cognitive deficits involve both anterograde amnesia, which means that new information cannot be kept in mind, and retrograde amnesia, which is a lack in remembering things of the past (Frey, Schreinzer, et al., 2001; Sackeim et al., 2007). There are different aspects of cognitive side effects, which are triggered by ECT. First, the time period matters in respect of the nature and degree of the cognitive impairment. As mentioned above, the postictal delirium is accompanied with disturbances of memory and orientation. This period is usually short-term (five to forty-five minutes until recovery) and the anterograde disruptions of cognition decline likewise. Based on that it can be assumed that these impairments, for example in orientation, are temporary with the strongest extent directly after the treatment (American Psychiatric Association, 2001). In addition, Semkovska and McLoughlin (2010) showed that deficits in cognition (e.g., in areas of episodic memory or executive functioning) were significantly increased after the treatment, but mostly confined to three successive days and no longer detectable after a 15 days period. Another critical factor is the used method, which includes a variety of influencing parameters like electrode placement, for instance. As previously stated, UL electrode placement over the non-dominant hemisphere is associated with less cognitive side effects than BL stimulus administration (American

Psychiatric Association, 2001; Sackeim et al., 2000; Semkovska et al., 2011; Semkovska & McLoughlin, 2010; UK ECT Review Group, 2003). Kolshus et al. (2017) outlined that distinct areas of cognitive functioning like orientation as well as retrograde autobiographical memory are less affected with UL treatment. However, another study showed that these differences are only detectable in the first three days after completing a series of ECT (Semkovska et al., 2011). Other influencing parameters include but are not limited to the frequency of ECTs - with lower rates associated with less cognitive side effects - or the anesthetic medication, which should be minimized to prevent cognitive side effects (American Psychiatric Association, 2001; UK ECT Review Group, 2003). Additionally, the extent of cognitive impairment is highly individual where advanced age, lowered intellect as well as female sex appear to be predictors for a worse outcome (American Psychiatric Association, 2001; Sackeim et al., 2007).

Hence, side effects should be evaluated at any time during a course of ECT. If necessary considering the occurrence of severe somatic and/or cognitive side effects, the implementation methods should be adjusted, for example switching from BL electrode placement to UL or the treatment series should be interrupted.

2.2.4 Biological mechanisms

In line with the various theories regarding the pathophysiology of MDD, hypotheses of the underlying mechanisms of ECT's induced antidepressant effects are heterogeneous. Different theories have been proposed that attempt to link impaired biological functions observed in people suffering from depression with the operating principles of ECT. However, until now, the exact mechanism of action of this treatment option has yet to be decrypted. Hereafter, commonly investigated approaches, which can be associated with the previously discussed biological mechanisms of depression (cf. 2.1.3), are described in more detail. These encompass genetic models as well as neurobiochemical concepts regarding neurotransmission and neurohormonal regulation (Frey, Schreinzer, et al., 2001; Pinna et al., 2016; Singh & Kar, 2017). Furthermore, the theory concerning neurogenesis belongs to a separate chapter due to the special importance for this thesis.

2.2.4.1 Genetics

Genetics appear to play a major role in the underlying mechanisms of ECT's antidepressant effects. Due to the given circumstance that some persons do respond to the treatment while others do not, a possible explanation for that variation is based on genetic variations (Pinna et al., 2016). For instance, Huuhka et al. (2008) showed that the genotype of dopamine 2 receptor gene (*DRD2*) polymorphism C957T (rs6277) and *COMT* polymorphism Val158Met (rs4680) affects the response to ECT. In 118 MDD patients those exhibiting a low DA activity, caused by a specific combination of the before mentioned gene polymorphisms, show better response rates than patients with other genotypes and corresponding high DA activity. Furthermore, another study including 119 TRD patients showed that the interaction of the serotonin transporter (*5-HTTLPR*) and norepinephrine transporter (NET182C) polymorphisms are associated with the outcome of ECT, while both polymorphisms taken individually could not predict treatment response. Patients with a specific allele combination of both polymorphisms and resulting low NE and 5-HT concentrations showed a worse response to ECT (Kautto et al., 2015).

Based on the given examples it is conceivable that polymorphisms of specific genes or their interaction are involved in ECT-induced antidepressant effects. If so, genes encoding for major players of neurotransmission may represent promising variables for predicting the outcome of ECT. Conversely, it is questionable to what extent ECT is able to influence that mechanisms.

2.2.4.2 Neurotransmission

Since neurotransmission can be altered in various ways and it was shown that these changes are related to the development and manifestation of depression (cf. 2.1.3), theories of ECT's mode of action consider this biological regulating and modulating system. In this context, neurotransmitters like 5-HT, DA and NE as well as their receptors and postsynaptic signal pathways were brought into special focus (Baldinger et al., 2014; Eitan & Lerer, 2006).

First of all, the 5-HT neurotransmission system and its modulation through a course of ECT could be a possibility for the operating principle of that treatment. It was shown that patients suffering from depression exhibit subsensitive 5-HT_{1A} receptors as well as malfunctioning 5-HT_{1B} receptors, for instance (Belmaker & Agam, 2008). A positron-emission tomography (PET) study by Saijo et al. (2010) investigated the 5-HT_{1A} receptor binding in nine patients with MDD, who were treated with six to seven ECT sessions. They found no significant changes in receptor binding by

comparing data from baseline (before ECT) and after the treatment course, although all patients recuperated from depression. In contrast, another study found changes in 5-HT_{1A} receptor binding potential in specific brain regions of 12 patients suffering from TRD, who were treated with a mean of ten ECT sessions. It was shown that especially in brain regions related to mood a reduction in 5-HT_{1A} receptor binding occurred after ECT. The most powerful decreases were observed in the subgenual part of the anterior cingulate, the orbitofrontal cortex, the amygdala, the hippocampus as well as the insula. Based on that, it was suggested that ECT has an effect on serotonergic neurotransmission and especially on the 5-HT_{1A} receptor binding (Lanzenberger et al., 2013). Furthermore, Yatham et al. (2010) investigated the 5-HT_{2A} receptor by examining 15 subjects suffering from TRD, who underwent a course of ECT and two PET scans (baseline and after treatment). They showed an extended reduction in 5-HT_{2A} receptors in all cortical areas and concluded that this might be a result of one mechanism of action of the treatment with ECT. However, the decline in depressive symptomatology did not correlate with that reduction.

Another potential target for the antidepressant effect of ECT regarding neurotransmission is the DA system; however, the data situation on this topic is inconsistent (Belmaker & Agam, 2008; Ferrari & Villa, 2017; Jesulola et al., 2018). One study by Nikisch and Mathe (2008) measured homovanillic acid, the degradation product of DA, after ECT. They found a significant heightening of that substance in the cerebral spinal fluid in six patients, who underwent eight ECT treatment sessions. Conversely, another study measured homovanillic acid plasma levels in 18 TRD patients after a course of ECT and found decreased levels of that substance (Okamoto et al., 2008). Moreover, the *DRD2* and the before mentioned combinations of gene polymorphisms seems to play a role in ECT's mechanisms of action (Huuhka et al., 2008). In addition, Dannlowski et al. (2013) showed that dopamine D3 receptor gene (*DRD3*) variants might be linked to the response and remission after ECT. They examined 104 patients with TRD and pointed out that particular polymorphisms of *DRD3* variants, which were related to a better treatment outcome were also correlated with increased striatal responsiveness to happy facial expressions assessed by magnetic resonance imaging (MRI).

In summary, both the 5-HT and the DA neurotransmission systems seem to be involved in the underlying mechanisms of ECT. Furthermore, additional neurotransmitters like NE, glutamate and γ-aminobutyric acid (GABA) should be considered. Above all, the modulation of various factors rather than single ones is assumed to be involved in the antidepressant effect of ECT. Further investigations in humans, especially with non-invasive neuroimaging techniques, may be able to

facilitate the decoding of the ECT's mechanism of action (Baldinger et al., 2014; Singh & Kar, 2017).

2.2.4.3 Neuroendocrinology

As stated before, one possible explanation for the development of depression refers to the neuroendocrine system. In brief, it was shown that this biological system is malfunctioning in people suffering from depression. Especially alterations of the HPA axis, which is involved in stress response operating on the basis of feedback control, are evident. As a consequence, patients with MDD may have increased cortisol or CRH levels, for instance, compared to healthy persons (Belmaker & Agam, 2008; Butcher et al., 2009; Yehuda, 2002). This theory is in accordance with one suggestion regarding ECT's working mechanism. It was shown that levels of cortisol as well as CRH decrease in patients suffering from depression after an acute course of ECT (Burgese & Bassitt, 2015; Nikisch & Mathe, 2008; Ozsoy et al., 2008; Yuuki et al., 2005). In this context, Burgese and Bassitt (2015) demonstrated that initially increased cortisol blood levels declined during ECT and were comparable to levels of healthy controls after the completion of ~12 ECT sessions. They concluded that ECT restores the physiological function of the HPA axis. In contrast, Markianos, Hatzimanolis, and Lykouras (2002) found no changes in prior elevated plasma cortisol levels of depressed patients in comparison to healthy controls after finishing a course of eight to thirteen ECT sessions.

Furthermore, Fink and Ottosson (1980) suggested that substances released by the hypothalamus as a result to the electrical stimulation, lead to a normalization of mood (e.g., suicidal thoughts) and vegetative functions (e.g., sleep, appetite) in patients with depression. Consequently, these hypothalamic substances were thought to be involved in the antidepressant effect of ECT. This suggestion is in line with observable increases in hypothalamic hormones like prolactin, ACTH, vasopressin, neuropeptide Y and cortisol right after an ECT session. It was annotated that this promoted release is short-term, which seems to indicate the need for repeated treatments (Bolwig, 2011; Fink & Ottosson, 1980; Fosse & Read, 2013; Haskett, 2014; Singh & Kar, 2017).

It can be concluded that the data regarding neuroendocrine underpinning of ECT are heterogeneous. In addition, it remains unclear whether possible hormonal changes (e.g., in cortisol levels) are primarily responsible for the antidepressant effect of ECT or if these shifts are provoked by other brain changes during the seizure (Bolwig, 2011; Burgese & Bassitt, 2015; Haskett, 2014; Singh & Kar, 2017).

As a conclusion, so far the available data could not entirely explain the mechanisms of action of ECT. Certainly, ECT triggers diverse biological modifications at all levels mentioned above and these alterations taken together form the basis for the high-ranking response rates. Further investigations aiming at understanding the neurobiological mechanisms are warranted to minimize side effects and optimize safety as well as antidepressant outcome in depression.

2.3 Adult neurogenesis

There are various theories regarding the biological mechanisms underlying depression and the mechanism of action of ECT. Aside from the previously discussed impact of genetics, neurotransmission and the neuroendocrine systems (cf. 2.1.3 and 2.2.4), neurogenesis is a potential target when it comes to the pathophysiology of depression and the antidepressant effect of ECT (Eitan & Lerer, 2006; Ferrari & Villa, 2017; Kaneko & Sawamoto, 2009; Singh & Kar, 2017). In general, "[n]eurogenesis is the process of producing new neurons from neural stem cells […]." (Apple, Fonseca, & Kokovay, 2017). This process, besides others like synaptogenesis, dendrogenesis, angiogenesis and gliogenesis, is involved in neuroplasticity (Singh & Kar, 2017).

Early investigations in rats showed that neurogenesis is not restricted to embryonic development, but even occurs in the adult brain (Altman, 1969; Kaplan & Hinds, 1977). In general, there are two brain structures in mammalians, which mediate the growth of new neurons: the subventricular zone and the subgranular zone (SGZ) in the dentate gyrus of the hippocampus (Drew & Hen, 2007; Kaneko & Sawamoto, 2009). Besides, Eriksson et al. (1998) demonstrated adult neurogenesis in humans. Five cancer patients were given a thymidine analog infusion labeling dividing cells by integrating this substance in the DNA. The postmortem hippocampal tissue from these patients was subsequently examined by using immunohistochemical techniques. They found newly generated cells, which are morphologically and phenotypically similar to the characteristics of neurons and concluded that neurogenesis occurs in the SGZ in the dentate gyrus throughout life. Moreover, alterations in these hippocampal processes were associated with neurodegenerative disorders as well as psychiatric diseases like MDD (Apple et al., 2017; Drew & Hen, 2007; Kaneko & Sawamoto, 2009).

The hippocampus is involved in various processes, namely the declarative and contextual memory, for instance, and is prone to stress and especially stress hormones. These memory functions and physiological processes, among others, were shown to be altered in patients suffering from depression (McEwen & Magarinos,

2001). Therefore, the following part of this thesis will focus on hippocampal neurogenesis.

Since the majority of studies investigated neurogenesis in rodents, the general structures and processes involved in hippocampal neuronal growth are shown in this model. However, it is assumed that neurogenesis pathways including proliferation and migration are similar in humans due to the strong conservation of mechanisms in higher mammalians (Apple et al., 2017). Apart from pathways from subcortical regions (e.g., raphe nucleus and locus coeruleus), the hippocampus gets input from the entorhinal cortex via the perforant path (cf. figure 8). Cells of the entorhinal cortex form synapses with granule cells in the molecular layer (ML) in the dentate gyrus. The cell bodies of the granule cells are located in the granule cell layer (GCL) and the axons (mossy fibers) are connected with pyramidal cells in the CA3 region of the hippocampus (Kaneko & Sawamoto, 2009).

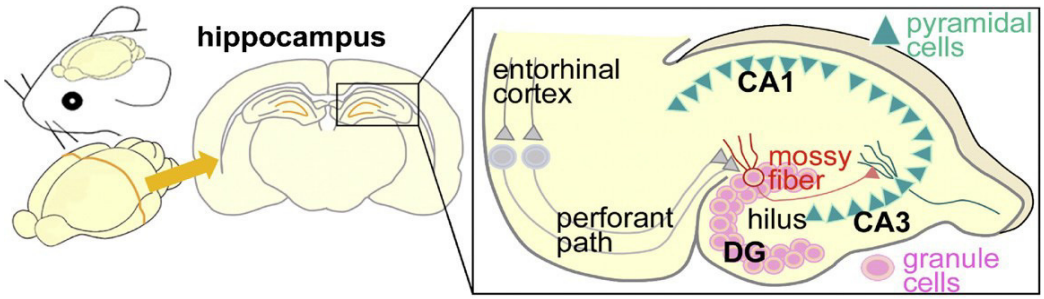

Figure 8: Neuronal composition and circuit of the dentate gyrus in the hippocampus of the adult rodent brain. DG-dentate gyrus. Figure from Kaneko N. (Kaneko & Sawamoto, 2009)

As illustrated in figure 9, neural stem and progenitor cells are located in the SGZ of the dentate gyrus. This thin region is situated between the GCL and the dentate hilus. A neural stem cell proliferates and gives rise to three levels of transiently amplifying progenitor cells. These stages differ in the degree of proliferative potential as well as neural differentiation level. Subsequently, immature granule cells are generated, which migrate into the GCL and differentiate into mature granule cells. They develop dendrites to the ML, form mossy fibers to the CA3 region of the hippocampus and get integrated into the neural circuit of the hippocampus (Kaneko & Sawamoto, 2009; Kempermann, Jessberger, Steiner, & Kronenberg, 2004). Furthermore, there are polypeptide growth factors, namely neurotrophins, which shape the processes of neurogenesis. They are involved in proliferation, differentiation as well as the survival and death of neuronal cells. The degree of influence hinges on more or less levels of

these neurotrophins, for instance (Chao, Rajagopal, & Lee, 2006). Especially the brain-derived neurotrophic factor (BDNF) appears to play a crucial role, when it comes to neurodegenerative disorders or psychiatric disorders like MDD and the antidepressant effects of treatments such as ECT (Chao et al., 2006; Rocha et al., 2016).

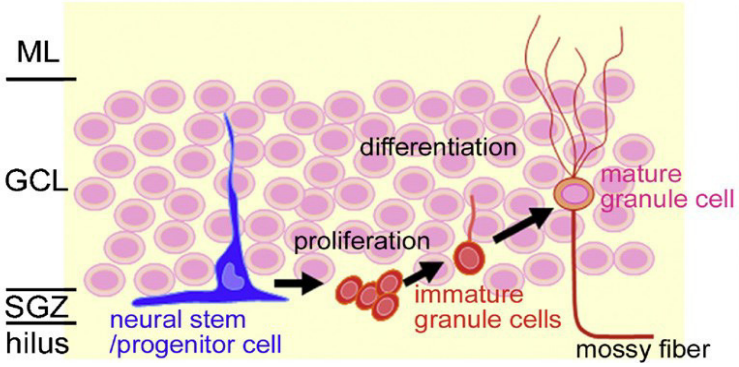

Figure 9: Neurogenesis in the dentate gyrus of the hippocampus of the adult rodent brain. GCL-granule cell layer, ML-molecular layer, SGZ-subgranular zone. Figure from Kaneko N. (Kaneko & Sawamoto, 2009)

Cell turnover dynamics in the human hippocampus were investigated by measuring the concentration of ^{14}C (elevated by nuclear bomb tests 1955-1963) in genomic DNA in postmortem brain tissue. It was shown that about one-third of all hippocampal neurons, the vast majority of dentate gyrus neurons, are regenerating. Basically, approximately 700 new neurons are added every day in each hippocampus and particularly 0.004% of the neurons in the dentate gyrus are replaced daily. In sum, this results in a turnover rate of 1.75% of neurons per year in the before mentioned regenerating subpopulation of hippocampal neurons. Additionally, it was demonstrated that neurogenesis decreases moderately during the lifespan, namely around fourfold. Based on these findings, the authors suggested that the hippocampal neurogenesis in adult humans may be involved in human brain functions like cognitive adaptability (Spalding et al., 2013). This is in accordance with results from another study analyzing postmortem tissues of 54 persons aged between 0 and 100 years. Here it was equally demonstrated that hippocampal neurogenesis declines with increasing age (Knoth et al., 2010).

Neurogenesis is influenced by various factors: stress, a less enriched environment, sparsely learning, aging and depression decrease the processes of neurogenesis (Bergmann, Spalding, & Frisen, 2015; Eitan & Lerer, 2006). On the other hand, factors like a more enriched environment, learning, physical activity,

neurotrophic factors (e.g., BDNF) and antidepressant treatments seem to enhance adult neurogenesis (Bambico & Belzung, 2013; Bergmann et al., 2015). Neuroimaging techniques like magnetic resonance imaging (MRI) showed that these parameters have an impact on the hippocampal volume (for an overview see Ho, Hooker, Sahay, Holt, and Roffman (2013)). Therefore, it was concluded that alterations in hippocampal neurogenesis are mirrored in varying hippocampal volume (Bergmann et al., 2015).

Hereinafter, neurogenesis in the context of major depression is described in more detail. Finally, neurogenesis as a factor underlying ECT's antidepressant effect is further discussed.

2.3.1 Neurogenesis and MDD

The hippocampus is involved in various cognitive processes including the declarative, spatial and contextual memory (McEwen & Magarinos, 2001). As cognitive alterations were often shown to co-occur during a depressive episode, the hippocampus and neurogenesis in this brain structure are thought to be involved in the development of depression (Belmaker & Agam, 2008; Butcher et al., 2009). This theory is supported by various neuroimaging studies. Bremner et al. (2000), for instance, investigated the hippocampal volume of 16 patients with MDD and 16 matched healthy controls using MRI. They found a 19% smaller left hippocampal volume in the depressed group compared to the control population. Other brain regions (e.g., frontal or temporal lobe) revealed no volume differences between both groups, which underlines the importance of the hippocampus in the context of depression. Another MRI study examined 43 patients with MDD and 32 control persons. Patients suffering from depression exhibited a significantly smaller bilateral hippocampal volume in comparison to healthy persons (Joshi et al., 2016). These examples are in accordance with other studies demonstrating either unilateral or bilateral declined hippocampal volumes in patients with MDD (Dukart et al., 2014; Redlich et al., 2016; Wolf et al., 2016). In contrast, some MRI studies could not find differences in hippocampal volumes between depressed patients and healthy subjects (Abbott et al., 2014; Posener et al., 2003; Rusch, Abercrombie, Oakes, Schaefer, & Davidson, 2001; van Eijndhoven et al., 2016). A meta-analysis by Videbech and Ravnkilde (2004) clarified these inconsistencies: they included 12 studies with a total of 351 depressed patients and 279 healthy controls and found an average volume reduction of eight percent in the left as well as ten percent in the right hippocampus. These outcomes were replicated by other meta-analyses showing smaller hippocampal

volumes in depressed people compared to healthy controls (Arnone, McIntosh, Ebmeier, Munafo, & Anderson, 2012; Campbell, Marriott, Nahmias, & MacQueen, 2004; Kempton et al., 2011; Koolschijn, van Haren, Lensvelt-Mulders, Hulshoff Pol, & Kahn, 2009). Overall, these investigations indicate an essential role of the hippocampus in the emergence of depression, although no conclusions regarding the reasons for hippocampal shrinkage can be drawn on that basis.

One proposed mechanism causing the altered hippocampal neurogenesis in MDD is stress and especially elevated levels of glucocorticoids (Dranovsky & Hen, 2006; Drew & Hen, 2007; Pittenger & Duman, 2008). It was shown that neuroendocrine responses to stressors are altered in individuals suffering from depression (cf. 2.1.3) and that chronic or severe stress disturbs memory processes related to the hippocampus in animal models. Consequently, a link between stress, neurogenesis and the emergence of depression is assumed (Pittenger & Duman, 2008). The impact of stressors on hippocampal neurogenesis has mostly been investigated in rodents. For this purpose, animals are exposed to different levels of stress, acute or chronic. Subsequently, occurring depressive-like behaviors (e.g., anhedonia, changes in the sleep-wake cycle or decreased grooming) are recorded using various behavioral tests (e.g., forced swim test) (Dranovsky & Hen, 2006; Drew & Hen, 2007). Further steps include measurements of stress hormones as well as analyses of postmortem brain tissue. Based on these experimental procedures it was shown that neurogenesis in the dentate gyrus of the hippocampus is decreased in animal models of acute and chronic stress, as shown in figure 10 (Dranovsky & Hen, 2006; Drew & Hen, 2007; Duman & Monteggia, 2006; Eitan & Lerer, 2006). It seems that all stages of neurogenesis can be affected including proliferation processes as well as the survival of new neurons, for instance (Bambico & Belzung, 2013). The above mentioned depressive-like behaviors as well as the reduced hippocampal neurogenesis can be restored by antidepressant treatment (cf. figure 10). This additional factor contributes to the theory that neurogenesis is involved in the development of depression (Dranovsky & Hen, 2006; Drew & Hen, 2007; Duman & Monteggia, 2006; Eitan & Lerer, 2006; Warner-Schmidt & Duman, 2006).

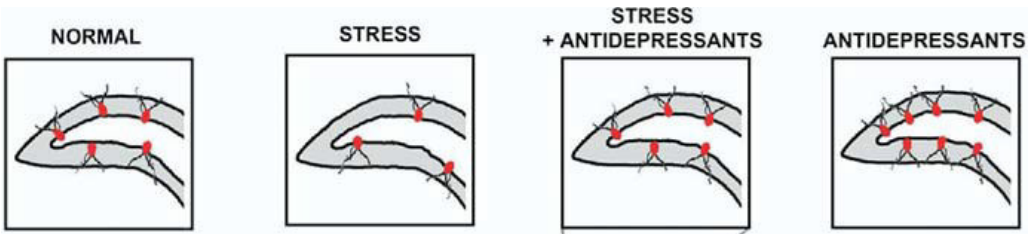

Figure 10: Neurogenesis in the dentate gyrus of the hippocampus in mouse. The red dots represent the cell bodies of young neurons in the subgranule layer and their dendrites passing through the granule cell layer. Illustrated is the normal neurogenesis, its downregulation as a consequence of stress as well as the normalization of that process by antidepressants. Additionally, increased neurogenesis due to antidepressants without any stressors is visualized. Adapted figure, original from Dranovsky A. (Dranovsky & Hen, 2006)

As shortly mentioned before, BDNF seems to be an important player of neurogenesis and consequently in the pathophysiology of depression (Chao et al., 2006; Rocha et al., 2016). Firstly, it was shown that brain BDNF and peripheral serum BDNF levels are correlated and undergo similar changes during lifetime in rodents (Karege, Schwald, & Cisse, 2002). Based on these findings, it is generally accepted to measure BDNF non-invasively in the periphery in order to mirror levels of that neurotrophin in the brain. As a result, BDNF concentrations were quantified in several studies in humans (Bambico & Belzung, 2013; Duman & Monteggia, 2006; Sen, Duman, & Sanacora, 2008). For example, Karege, Perret, et al. (2002) compared serum BDNF levels of 30 depressed patients and 30 healthy subjects. They showed significantly lower BDNF concentrations in patients suffering from depression. In addition, the lowered serum BDNF levels were negatively correlated with the MADRS scores. Based on that, the authors concluded that decreased serum BDNF concentrations are a characteristic of MDD. Moreover, a meta-analysis by Sen et al. (2008) evaluated 11 studies with a total of 366 patients with depression and 382 controls showing that serum BDNF levels were decreased in depressed individuals compared to controls. Additionally, the declined levels were significantly heightened after antidepressant treatment. In sum, BDNF, among other neurotrophins, mirrors processes of neurogenesis. Simply, if this factor is decreased neurogenesis is similarly decreased in individuals suffering from depression and antidepressant treatment have the potential to normalize BDNF levels.

Based on the previously mentioned findings it is conceivable that there is a causal link between altered hippocampal neurogenesis and the development of depression. Although data concerning cellular alterations in humans are scarce, the neuroimaging

outcomes (hippocampal shrinkage) and BDNF measurements as well as the cellular findings in animal models indicate an involvement of that process. However, it remains to be shown whether the declined neurogenesis is the cause for depression or rather its consequence.

2.3.2 Neurogenesis and ECT

As it was shown that hippocampal shrinkage as well as decreased BDNF levels were related to depression, the modulation of adult neurogenesis through ECT was addressed in several investigations (Bolwig, 2011; Bouckaert et al., 2014; Singh & Kar, 2017).

Preclinical studies investigated the effects of electroconvulsive shocks (ECS) on neurogenesis in rodents. Madsen et al. (2000) administered ECS either once or in a series of ten treatments to rats and compared postmortem the hippocampal tissue with sham-treated animals (identical handling, but no current administration). They found a significant increase in cell proliferation within the dentate gyrus with the highest rate being threefold compared to the sham-treated group. Additionally, the cell number of newly generated cells was positively correlated with the number of ECS. It is noteworthy that these newly generated cells could be observed for at least three months. The findings are in accordance with other studies examining rodents that similarly demonstrated elevated hippocampal neurogenesis following the administration of ECS (Ito et al., 2010; Nakamura et al., 2013; Scott, Wojtowicz, & Burnham, 2000; Weber et al., 2013). Comparable results were obtained when investigating ECS-induced effects on hippocampal neurogenesis in non-human primates. Perera et al. (2007) showed a tenfold increase in the number of proliferating cells in the dentate gyrus in bonnet monkeys that were treated with 12 ECS. The ECS group was compared to sham-treated animals (anesthesia and muscle relaxation without ECS administration) and animals without any treatment. The elevated cell numbers were observable right after the intervention as well as four weeks afterward. Based on these preclinical findings it was assumed that electroconvulsive shocks might generally stimulate neurogenesis and that this may also apply to ECT in humans (Bolwig, 2011; Madsen et al., 2000).

Other preclinical studies focused on BDNF levels. Altar, Whitehead, Chen, Wortwein, and Madsen (2003) demonstrated BDNF level increases in the hippocampus of approximately 132% in rats after ECS. The BDNF levels increased successively and remained elevated for at least three days after the last ECS. Similar results were shown in the investigations of Li, Suemaru, Cui, and Araki (2007), where

ECS were administered daily for a 14-day period to rodents. They detected markedly increased BDNF levels in the hippocampus that remained heightened after a minimum of seven days. In contrast, Angelucci, Aloe, Jimenez-Vasquez, and Mathe (2003) found no changes in BDNF concentrations in the hippocampus of rats following ECS. However, a meta-analysis of 23 studies pointed out a general increase in brain BDNF levels related to ECS in preclinical studies with rats. These effects were higher when administering several ECS compared to single applications. Additionally, the largest effect size was obtained when considering BDNF concentrations in the dentate gyrus, a crucial region for adult neurogenesis (Polyakova et al., 2015).

Within the context of these findings, it was suggested that BDNF concentrations would also be increased in humans after a course of ECT and that these effects would mirror a promoted neurogenesis. Hu et al. (2010), for instance, measured serum BDNF concentrations of 28 patients with MDD and 28 healthy controls. Blood samples from patients were taken before and after two weeks each with three ECT sessions. In MDD patients serum BDNF levels were lower than in control subjects at baseline (before ECT). After ECT BDNF concentrations increased significantly and were comparable to those of healthy controls. Additionally, the heightened serum BDNF concentrations were negatively correlated with HAM-D scores that were significantly decreased after ECT. The authors concluded that the effect of ECT on BDNF levels is directly related to the improvement of depressive symptomatology. Similar results were obtained by Marano et al. (2007), who showed a significant increase in plasma BDNF levels and accompanying HAM-D score decline in patients undergoing an average of seven ECT sessions. Conversely, while other studies could replicate the elevation of serum BDNF concentrations after ECT, they did not find the correlation with depressive symptoms (Bilgen et al., 2014; Bocchio-Chiavetto et al., 2006). In addition, there are studies that could not detect any changes in BDNF levels (Bouckaert, Dols, et al., 2016; Fernandes et al., 2009). For example, Bouckaert, Dols, et al. (2016) measured serum BDNF concentrations in 88 depressed patients before, during and after a course of ECT with an average of 12 sessions. There were no changes of serum BDNF concentrations at any time point, although a significant decline in MADRS scores was observed after ECT. Several meta-analyses were published to homogenize the data on this topic (Brunoni, Baeken, Machado-Vieira, Gattaz, & Vanderhasselt, 2014; Polyakova et al., 2015; Rocha et al., 2016). Common to all is the finding that blood BDNF concentrations are increased after a course ECT. Additionally, Polyakova et al. (2015) calculated the influence of the number of ECT sessions. In accordance with preclinical findings, the number of ECT sessions was positively correlated with the increase in BDNF concentrations. Nevertheless, neither

Brunoni et al. (2014) nor Polyakova et al. (2015) found a correlation between the elevated blood BDNF concentrations and symptom improvement. However, this might be in consequence of the high heterogeneity of the studies included.

Using MRI, MDD patients were shown to exhibit decreased hippocampal volumes compared to healthy controls (Arnone et al., 2012; Campbell et al., 2004; Kempton et al., 2011; Koolschijn et al., 2009; Videbech & Ravnkilde, 2004). Preclinical findings point towards the fact that declined neurogenesis might be a causal mechanism and that antidepressant treatments might counteract this effect (cf. 2.3.1). Consequently, the relationship between ECT's antidepressant effect and hippocampal volume was further investigated by several authors. Joshi et al. (2016) measured hippocampal volumes of 43 patients with MDD, which underwent a mean of 11 ECT sessions. They showed that the volume of both left and right hippocampus increased significantly after the completion of ECT and that this enhancement was correlated with the significant improvement in depressive symptomatology assessed by the HAM-D. This is in line with another study demonstrating a correlation of hippocampal volume increase and treatment efficacy (Dukart et al., 2014). Although various other investigations could replicate the increase of hippocampal volumes in depressed patients after ECT using structural MRI, they failed to associate these volume gains with the antidepressant outcome of ECT (Abbott et al., 2014; Bouckaert, De Winter, et al., 2016; Jorgensen et al., 2016; Nordanskog et al., 2014; Sartorius et al., 2016; Tendolkar et al., 2013). It is noteworthy that the observed hippocampal volume increases after ECT were not persistent but annulled after approximately six months (Bouckaert, Dols, et al., 2016; Nordanskog et al., 2014). A meta-analysis by Wilkinson, Sanacora, and Bloch (2017) evaluated these divergent results by calculating hippocampal volume changes on the basis of nine studies. They figured out significant bilateral hippocampal volume increases in 174 MDD patients after ECT. The latter was not correlated with the improvement in depressive symptomatology. The results are in line with another recent meta-analysis (Takamiya et al., 2018). In addition, Takamiya et al. (2018) demonstrated that age and the percentage of responders and remitters were negatively correlated with left hippocampal volume increases.

In sum, there is evidence for the involvement of neurogenesis in the mechanisms of action of ECT. As it was shown that altered BDNF concentrations as well as hippocampal volumes could be normalized after ECT, the processes of neurogenesis appear to be a potential target to explain the antidepressant effects of this treatment option. As described above, data covering this topic and more specifically the link

between BDNF concentrations and hippocampal volumes, respectively, and the improvement of depressive symptoms are heterogeneous. These inconsistencies might be related to methodological issues, for instance, differing ECT procedures (e.g., electrode placement, number of administered treatments), distinct measurement methods (e.g., time of blood sampling) or the characteristics of the examined patients (e.g., age). Eventually, these experimental settings should be standardized to enable a more precise insight into the mechanism of action of ECT.

2.4 Aim of the thesis

As demonstrated in the last chapters, the mechanisms underlying the development of depression and the antidepressant effect of ECT are still not fully understood. Adult neurogenesis, its downregulation associated with the disease as well as the normalization through ECT appear to be a plausible mechanism to explain ECT's effects. Especially the hippocampal volume alterations in depressed patients described in the literature represent a promising research target when it comes to investigating neurobiological effects of ECT.

One difficulty in determining the real effect size of ECT on hippocampal volume is the small sample size of each publication, particularly in those performed in humans. Therefore, ideally, future studies should be carried out with more patients. However, due to limiting resources, the alternative is to merge the available data on the topic by means of a meta-analysis to ascertain ECT's effects, which are possibly underestimated or hidden by the small number of examined patients in each study. Hence, the aim of this thesis is to calculate the real effect size of ECT on hippocampal volume by combining outcomes from multiple MRI studies with patients suffering from depression. The hypotheses resulting from the previously described theoretical background are presented below.

Hypothesis 1

The hippocampal volume of patients with MDD increases (bilaterally) after a course of ECT.

Hypothesis 2

Hippocampal volume increases are negatively correlated with the degree of depressive symptoms assessed by psychometrical scales.

3 MATERIAL AND METHODS

3.1 Study selection

The medical database PubMed was searched for publications containing the keywords “ECT” or “electroconvulsive therapy” and “structural MRI” or “gray matter volume”. Based on this, 57 studies were identified. Following a first exploration, only 20 studies serve our purpose. From these remaining studies, data were extracted according to predefined criteria as listed below. In order to complete missing information, authors were contacted via email twice.

3.1.1 Inclusion criteria

First of all and most importantly, studies should provide absolute volumetric data and standard deviations for the hippocampus at two time points, namely before and after ECT. Furthermore, scores of depression severity should be evaluated on the basis of psychometrical scales and recorded pre and post ECT. Since the studies used different psychometrical scales to assess depressive symptoms, a selection was made based on a previous investigation assessing the comparability of psychometric scales in this context. Leucht, Fennema, Engel, Kaspers-Janssen, and Szegedi (2018) explored the relationship between HAM-D (17 items) and MADRS scores. They combined 31 antidepressant studies with a total of 4388 MDD patients, whose depression severity was assessed at baseline and seven, fourteen as well as twenty-eight days after the beginning of antidepressant treatment. Based on the calculations they demonstrated significant correlation of the HAM-D (17 items) and MADRS based on total scores ($p < 0.0001$). Additionally, a percentage improvement was approximately equal in both scales. For instance, a reduction of 50% of the HAM-D score was equivalent to 48% reduction of the MADRS score. Consequently, studies using HAM-D (17 items) and MADRS were considered to be comparable and included in the present analysis. Furthermore, Heo, Murphy, and Meyers (2007) proposed to prorate HAMD-21 or HAMD-24 scores into the 17-item scale by applying the following formula: $\frac{17 \times HAM-D_{21\ OR\ 24}}{21\ OR\ 24}$. Based on this evidence, we included studies using the longer HAM-D versions. Apart from that, studies should ideally provide demographic variables such as number of included patients, clinical factors like diagnosis based on the ICD or the Diagnostic and Statistical Manual of Mental Disorders (DSM), current medication as well as methodological parameters concerning ECT administration and MRI measurements, respectively.

3.1.2 Exclusion criteria

Studies were excluded if provided MR data were not sufficient, even after contacting the authors, more specifically when no absolute regional volume values were available. In addition, investigations were excluded if they involved patients with other psychiatric diseases (e.g., anxiety disorder or schizophrenia) neurologic (e.g., Alzheimer's disease) as well as somatic disorders. Moreover, if studies examined overlapping samples, the publication describing the data in more detail was included.

Finally, 11 studies could be integrated into the statistical analysis (Abbott et al., 2014; Bouckaert, Dols, et al., 2016; Dukart et al., 2014; Jorgensen et al., 2016; Nordanskog et al., 2010; Oltedal et al., 2015; Ota et al., 2015; Redlich et al., 2016; Sartorius et al., 2016; Tendolkar et al., 2013; Wade et al., 2016).

3.2 Data extraction

All data were extracted from each single investigation either on the basis of the publication or the additional information sent by the authors. The information extracted was: magnetic field strength, type of MR scanner, number and time point of MR scans, total number of patients, ratio of men and women, mean (±standard deviation (SD)) age, diagnosis (major depressive disorder or bipolar disorder), mean (±SD) depression severity assessed by psychometrical scales (before and after ECT), current medication, electrode placement, ECT device, mean (±SD) number and frequency of ECT sessions, measurement outcome, absolute volumetric data (±SD) of both time points (pre and post treatment) of the hippocampus (if available bilaterally).

3.3 Data analysis

The statistical analysis followed an approach described earlier in Gryglewski, Lanzenberger, Kranz, and Cumming (2014). In general, data analyses were executed using the software package R 3.0.1. Meta-analysis calculations were performed in the metaphor package, version 1.9-1.

3.3.1 Individual study effect sizes

All included MRI studies used a region of interest (ROI) approach with two different outcomes: gray matter volume (GMV) or total volume. These different outcomes

regarding hippocampal volume require the computation of the standardized effect sizes, which subsequently can be combined in the meta-analysis (Gryglewski et al., 2014). For every single publication, the standardized change score was calculated by using the following formula: $\frac{M_{post}-M_{pre}}{SD_D}$ with M representing the mean of the pre or post MRI measurement, respectively, and SD_D indicating the standard deviations of the pre-post difference scores (Morris & DeShon, 2002). The standardized change score defines the difference in means of two time points (pre and post treatment) in units of the SD of change and was complemented with 95% confidence intervals (CI) (Gryglewski et al., 2014). Furthermore, the effect sizes of the individual studies were calculated separately for the left, right and total hippocampus. If studies provided only lateralized data, a fixed-effects model meta-analysis was conducted to obtain the average bilateral effect.

Besides varying MRI outcomes, the included studies also applied different psychometrical scales (HAM-D with 17, 21 or 24 items or MADRS) to assess depressive symptoms. Therefore, the computation of individual effect sizes was necessary (Gryglewski et al., 2014). Since the single studies reported solely pre (±SD) and post (±SD) treatment rating scores rather than change scores (±SD), the standardized mean change (raw score standardization) was chosen as outcome measure. Consequently, the equation $\frac{M_{post}-M_{pre}}{SD_{pre}}$ was used for calculations: M constitutes the mean of the pre or post treatment rating score, respectively, and SD_{pre} the standard deviations before ECT (Morris & DeShon, 2002). Furthermore, all estimates were supplemented with 95% CI. Finally, the standardized mean change reveals the difference in means of the depression rating scores before and after ECT in units of the SD before treatment (Gryglewski et al., 2014).

3.3.2 Summary effect sizes

Similar to the individual study effect estimates, the summary effect sizes were calculated separately for the left, right and total hippocampal volume. In a random-effects model the single study effect sizes were weighted reciprocally proportional to the amount of sampling variance (v_i) as well as the between-study variance (τ). The restricted maximum likelihood estimation was utilized to calculate the between-study variance τ. This includes the computation of the summary effect size and τ^2 from the same data. Moreover, Higgins' I^2 was computed. This value delineates an intuitive measure of variation of the study estimates, which is determined by the between-study heterogeneity. Additionally, 95% confidence intervals for the summary effect

sizes (standardized change scores) were calculated. The leave-one-out approach was used for sensitivity analyses. Furthermore, a test for funnel plot asymmetry was applied to ascertain the publication bias (Gryglewski et al., 2014).

The calculation of the summary effect size for the depressive symptomatology followed the approach described above. However, the only exception is that the summary effect size was expressed as standardized mean change (raw score standardization) instead of standardized change score. Here again, the summary effect size was complemented with 95% CI and Higgins' I^2 was calculated (Gryglewski et al., 2014). The leave-one-out approach was not applied, because the effect of ECT on depressive symptoms was consistent throughout all included studies.

3.3.3 Meta-regression analysis

A number of meta-regression analyses were performed to assess the correlation between hippocampal volume changes and different demographical, clinical and methodological moderators (Gryglewski et al., 2014). These parameters were: age, the percentage of women, depressive symptoms, number of ECT sessions, electrode placement (RUL or BL), the magnetic field strength of the MRI scanner (one and a half or three tesla) and measurement outcome (GMV or total volume).

4 RESULTS

Data from 11 studies were included in the present meta-analysis containing a total of 235 patients suffering from depression (cf. table 1).

4.1 Hypothesis 1: Hippocampal volume changes

The primary outcome of the present meta-analysis is the effect size of ECT on hippocampal volume by comparing pre and post treatment MRI measurements of depressed patients. Hereinafter, total hippocampal volume changes are presented. Additionally, left and right volume changes of the hippocampus are shown separately.

The total hippocampal volume change was calculated on the basis of all 11 included studies with a total of 235 patients (cf. figure 11). The heterogeneity between the studies was considerable (I^2 = 64.03%). All studies revealed positive effect sizes to a greater or lesser extent on the entire hippocampal volume induced by ECT. The summary effect estimate (0.86, 95% CI: [0.59, 1.13]; $p < 0.0001$) indicates a strong positive effect of ECT on the total hippocampal volume. The leave-one-out sensitivity approach excluded considerable influences of individual studies. In addition, the test for funnel plot asymmetry pointed to an estimated number of four missing investigations. Following the calculation with four theoretical studies, the summary effect size decreased to 0.63 (95% CI: [0.29, 0.96]; $p = 0.0003$; $n = 15$) and the between-study heterogeneity was raised to I^2 = 79.90%.

Table 1: *Characteristics of studies included in the meta-analysis. BD-Bipolar disorder, BL-Bilateral, GMV-Gray matter volume, MADRS-Montgomery-Åsberg Depression Rating Scale, MDD-Major depressive disorder, N-Number of patients, n.a.-Not available, RUL-Right unilateral, SD-Standard deviation, V-Volume.*

Study	N	Sex	Age	Diagnosis	Depression rating scale	Symptom reduction	Electrode placement	ECT sessions	Magnetic field strength	Measurement outcome
		N (%) women	*Mean (±SD)*			*Mean %*		*Mean (±SD)*	*tesla*	
Abbott (2014)	19	13 (68)	65.3 (8.0)	MDD	HAM-D	74.2	RUL/BL	11.0 (2.7)	3	Total V
Bouckaert (2016)	66	44 (67)	72.6 (8.5)	MDD	MADRS	65.5	RUL/BL	12.0 (5.6)	3	GMV
Dukart (2014)	10	6 (60)	53.9 (10.7)	MDD/BD	HAM-D	64.2	RUL	n.a.	1.5	GMV
Jorgensen (2016)	17	12 (71)	52.3 (11.5)	MDD/BD	HAM-D	52.9	RUL/BL	15.3 (5.6)	3	Total V
Nordanskog (2010)	12	10 (83)	40.0 (16.0)	MDD/BD	MADRS	65.8	RUL/BL	10.0 (n.a.)	3	Total V
Oltedal (2015)	6	5 (83)	48.3 (11.7)	MDD	MADRS	51.6	RUL	11.8 (4.7)	3	GMV
Ota (2015)	15	6 (40)	52.1 (14.4)	MDD	HAM-D	56.85	BL	9.0 (2.3)	1.5	Total V
Redlich (2016)	23	14 (61)	45.7 (9.8)	MDD	HAM-D	49.6	RUL/BL	14.0 (3.8)	3	GMV
Sartorius (2016)	18	9 (50)	52.0 (14)	MDD	HAM-D	66.7	RUL/BL	11.3 (4.8)	3	GMV
Tendolkar (2013)	15	8 (53)	52.8 (7.6)	MDD	HAM-D	40.9	RUL/BL	Median 18.0	1.5	Total V
Wade (2016)	34	16 (47)	41.7 (13.9)	MDD/BD	HAM-D	48.8	RUL/BL	10.4 (3.79)	3	Total V

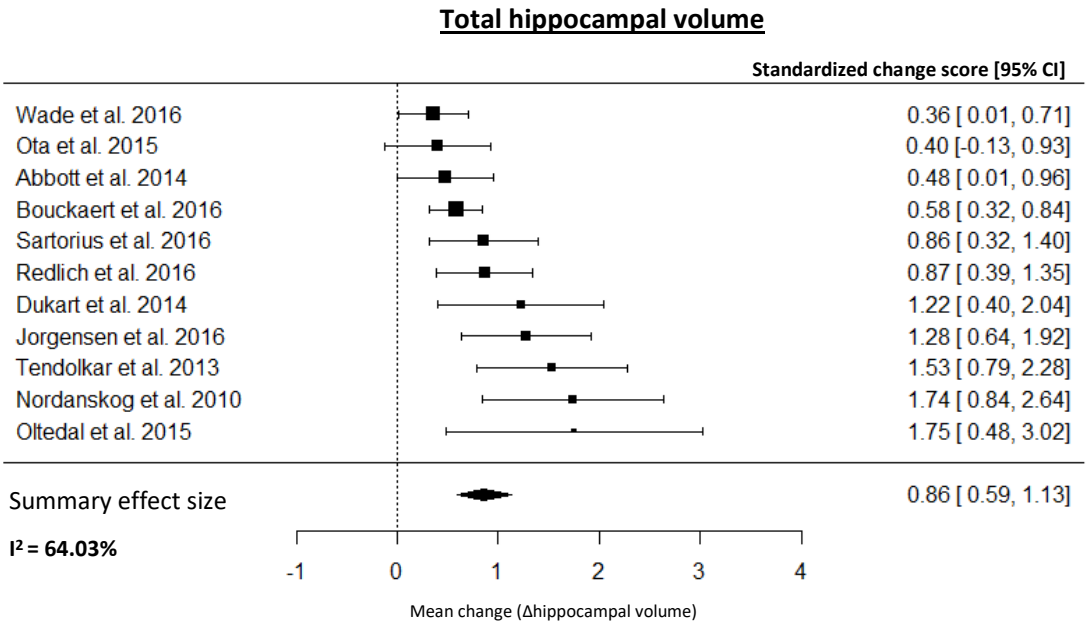

Figure 11: Forest plot of total hippocampal volume changes. Presented are the effect estimates of every publication and the summary effect size. Additionally, the between-study heterogeneity I^2 is indicated. CI-Confidence interval.

Nine studies containing 212 patients were included in the calculation of left hippocampal volume changes (cf. figure 12). All investigations revealed positive effect estimates. Overall, this very heterogeneous sample of studies (I^2 = 74.67%) showed a summary effect size of 0.71 (95% CI: [0.38, 1.03]; p < 0.0001) pointing out a powerful positive effect of ECT on left hippocampal volume. The result was not susceptible to the leave-one-out sensitivity analysis. The test for funnel plot asymmetry indicated two missing studies. Based on a random-effects model with two theoretical investigations the summary effect size was decreased to 0.55 (95% CI: [0.16, 0.93]; p = 0.0055; n = 11), whereas the between-study heterogeneity increased (I^2 = 83.60%).

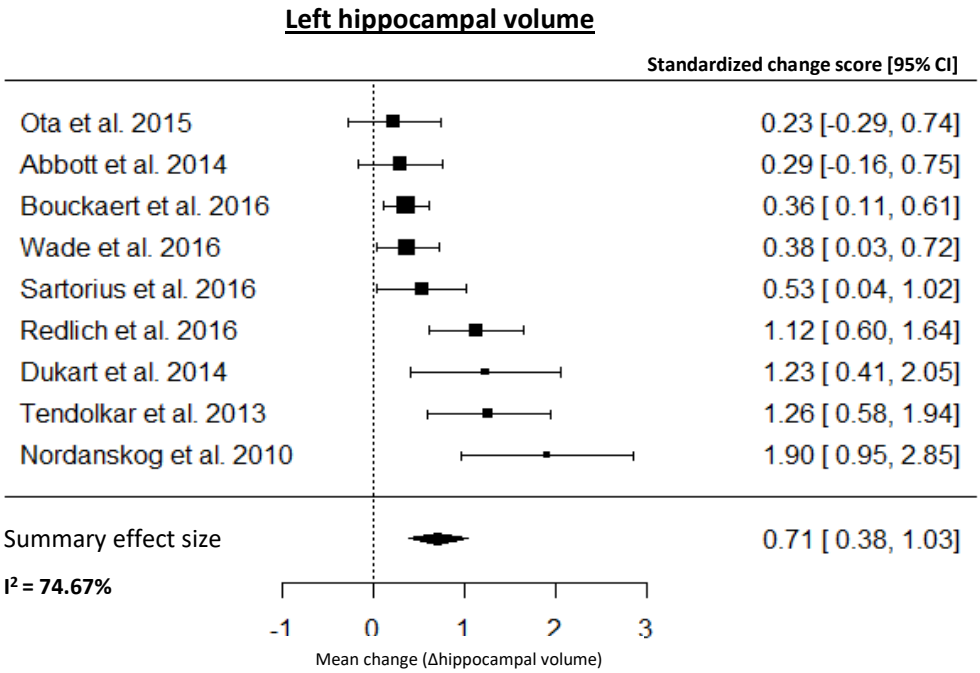

Figure 12: Forest plot of left hippocampal volume changes. Illustrated are the effect estimates of single publications and the summary effect size. In addition, the between-study heterogeneity I^2 is shown. CI-Confidence interval.

Calculations for the right hippocampus were carried out by using the same nine studies as for the left hippocampus including equally 212 patients (cf. figure 13). The studies showed substantial heterogeneity with an estimate of I^2 = 68.01%. As all individual study effect sizes were positive, the overall effect size (0.84; 95% CI: [0.54, 1.14]; $p < 0.0001$) indicates a strong positive effect of ECT on the right hippocampal volume. The result was resilient to the leave-one-out sensitivity approach. There were four missing studies assessed by the test for funnel plot asymmetry. Calculating the random-effects model with four theoretical studies, the between-study heterogeneity was increased (I^2 = 84.30%) and the summary effect size was decreased (0.55, 95% CI: [0.16, 0.93]; $p < 0.0055$; n = 13).

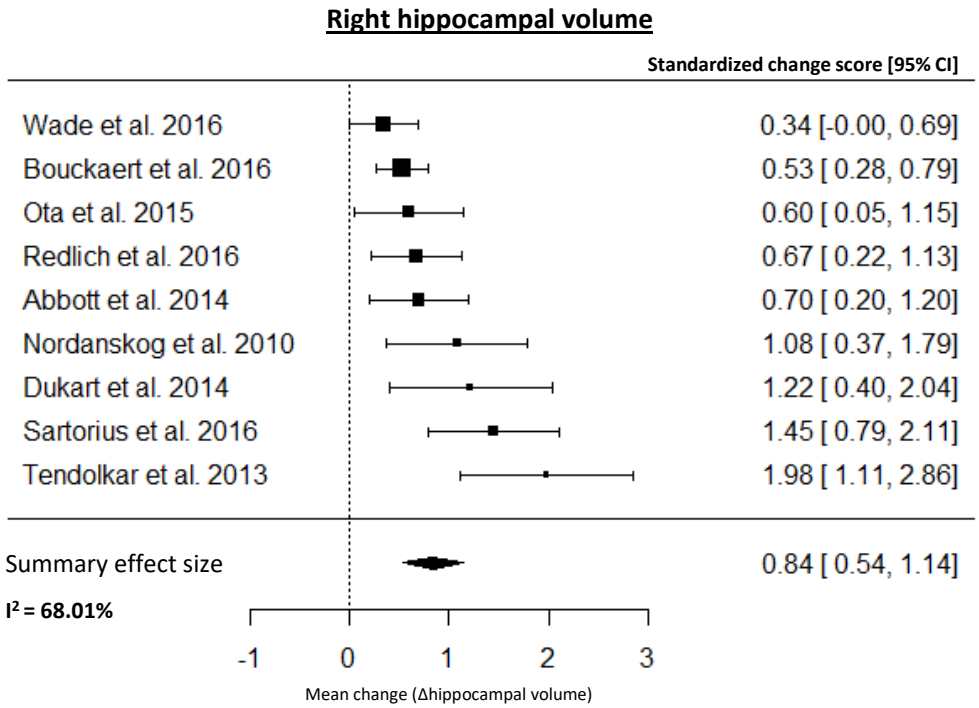

Figure 13: Forest plot of right hippocampal volume changes. Shown are the effect estimates of every publication and the summary effect size. In addition, the between-study heterogeneity I^2 is indicated. CI-Confidence interval.

4.2 Hypothesis 2: Correlation hippocampal volume – depressive symptoms

First of all, a meta-analysis regarding ECT's effects on the depressive symptomatology was conducted. All 11 studies including a total of 235 patients were used for the calculation (cf. figure 14) where the correlation between pre and post treatment rating scores was assumed to be zero (conservative assumption). The summary effect size (2.38, 95% CI: [1.93, 2.82]; $p < 0.0001$) mirrors a powerful positive effect of ECT on the depressive outcome meaning that the symptoms significantly improved after the treatment. The sample of investigations showed a substantial between-study heterogeneity ($I^2 = 52.61$). Alternatively, the correlation between the rating scores before and after ECT was set to one. This modification results in a minimally different summary effect size (2.42, 95% CI: [1.95, 2.89]; $p < 0.0001$) and a higher heterogeneity of $I^2 = 77.59\%$ due to lower within-study error estimates.

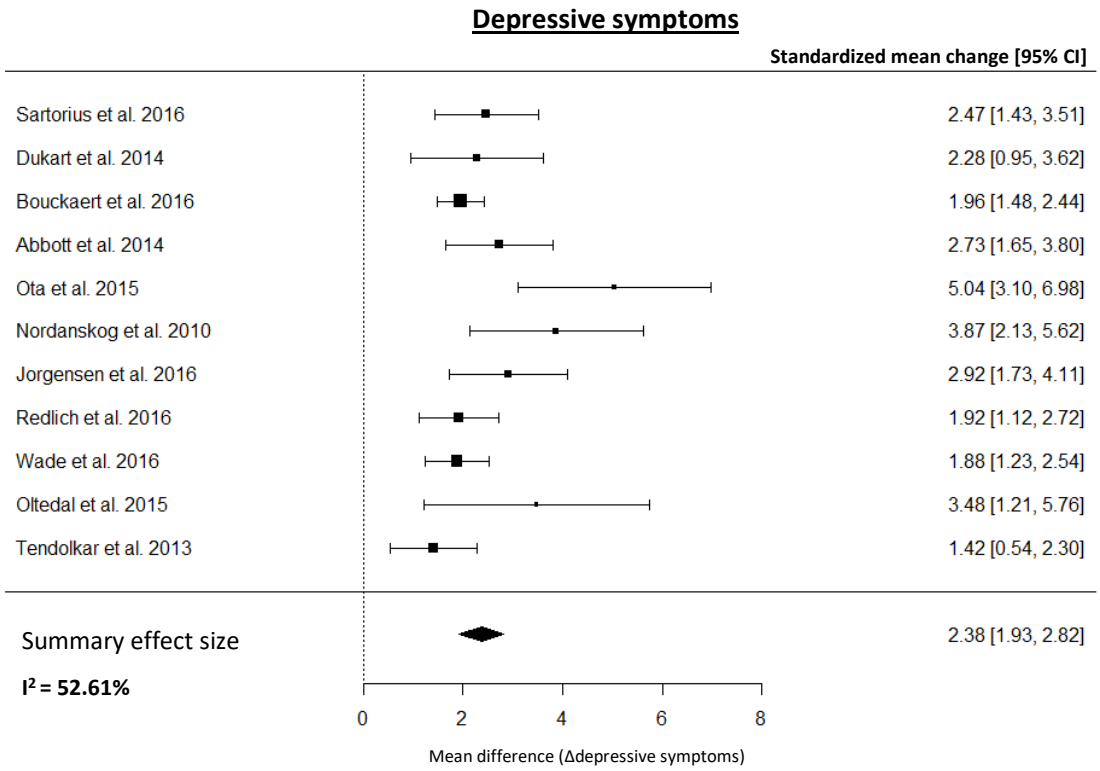

Figure 14: Forest plot of changes in depressive symptoms. Shown are the effect estimates of single publications and the summary effect size. Additionally, between-study heterogeneity I^2 is presented. CI-Confidence interval.

The meta-regression model regarding the relationship between the decreased depressive symptoms and the increased hippocampal volume showed no correlation between these factors ($p > 0.1$)

4.3 Correlation hippocampal volume – moderators

Furthermore, a meta-regression analysis referring to demographical and methodological parameters was carried out. Similarly to the findings concerning the depressive symptomatology no correlation between hippocampal volume change and age, electrode placement (RUL or BL), magnetic field strength of the MRI scanner (one and a half or three tesla) or measurement outcome (GMV or total volume), respectively, was detected ($p > 0.1$, $n = 11$). The number of ECT sessions ($p = 0.0582$, $n = 9$) and the percentage of women ($p = 0.0531$, $n = 11$) showed a trend towards a relationship with the alteration in hippocampal volume.

5 DISCUSSION

To the best of our knowledge, the present meta-analysis uses the largest sample size to calculate the real effect size of ECT on hippocampal volume by combining data from 11 MRI studies with a total of 235 patients suffering from major depression. As shown in the results section of this thesis, significant bilateral hippocampal volume increases were detectable after a course of ECT. Additionally, depressive symptoms decreased as expected following treatment. However, hippocampal volume alterations and changes in depressive symptomatology were not correlated. Moreover, other parameters such as age, the percentage of women, number of ECT sessions, electrode placement, the magnetic field strength of the MRI scanner and measurement outcome were not associated with hippocampal volume increases. Hereinafter, the findings regarding hippocampal volume, depressive symptoms and their relationship are discussed in the context of the theoretical background.

5.1 Hypothesis 1: Hippocampal volume changes

In the first hypothesis it was postulated that hippocampal volume would increase bilaterally after a course of ECT. On the basis of the present meta-analysis, this theory could be substantiated as it was shown that bilateral hippocampal volume increases significantly.

In rodents and humans, neurogenesis occurs during the entire lifespan, particularly in the dentate gyrus of the hippocampus (Altman, 1969; Eriksson et al., 1998; Kaplan & Hinds, 1977; Spalding et al., 2013). These processes seem to be disturbed in patients suffering from depression (Bambico & Belzung, 2013; Bergmann et al., 2015; Eitan & Lerer, 2006). Furthermore, alterations in adult neurogenesis are mirrored in varying hippocampal volume measured by means of MRI (Bergmann et al., 2015; Ho et al., 2013). In general, it was shown that patients suffering from depression exhibit decreased bilateral hippocampal volumes in comparison to healthy controls (Arnone et al., 2012; Campbell et al., 2004; Kempton et al., 2011; Koolschijn et al., 2009; Videbech & Ravnkilde, 2004). This shrinkage normalizes after a course of ECT and was linked to increased neurogenesis, since antidepressant treatment appears to promote these processes of neuroplasticity mirrored for instance in elevated BDNF levels and/or increased hippocampal volumes (Abbott et al., 2014; Dranovsky & Hen, 2006; Dukart et al., 2014; Hu et al., 2010; Joshi et al., 2016; Marano et al., 2007; Nordanskog et al., 2014; Sartorius et al., 2016; Tendolkar et al., 2013). Moreover, various preclinical investigations in rodents and non-human primates have

demonstrated increased hippocampal neurogenesis following the administration of ECS (Ito et al., 2010; Madsen et al., 2000; Nakamura et al., 2013; Perera et al., 2007; Scott et al., 2000; Weber et al., 2013). Based on the previously discussed findings in preclinical and neuroimaging studies (cf. 2.3.1 and 2.3.2), it can be assumed that the increase in hippocampal volume after a course of ECT, as shown by the present meta-analysis, may be linked to increased neurogenesis in this brain region.

Since neurogenesis is only one mechanism of neuroplasticity, also others may be responsible for the volume alterations observed in the hippocampus in depressed patients as well as for ECT's high antidepressant effect. "Neuroplasticity refers to the brain's ability to reorganize itself." (Bouckaert et al., 2014). Beside neurogenesis, this reorganization encompasses processes like synaptogenesis, dendrogenesis, angiogenesis and gliogenesis, which seems to be involved in ECT's mechanism of action and are mostly investigated in preclinical studies (Bouckaert et al., 2014; Singh & Kar, 2017). For instance, Chen, Madsen, Wegener, and Nyengaard (2009) demonstrated ECT-related effects on synaptogenesis in the hippocampus. Eleven rats were treated with ECS on a ten day period daily. Subsequently, the number of synapses in the postmortem hippocampal tissue of these animals was compared to a sham-treated group of nine rats (same handling without electrical stimulation). They found that the number of synapses (total number and number of spine synapses) and synapse height was significantly increased in the group treated with ECS. In summary, they hypothesized that ECS induces synaptogenesis and remodels synapses in the hippocampus of rats. This is in accordance with another study suggesting that ECS administration encourages the formation of new spines and therefore new synapses, which leads to new connections within the hippocampal circuitry (Zhao, Warner-Schmidt, Duman, & Gage, 2012). Other investigations consider angiogenesis in the hippocampus. Hellsten et al. (2005), for instance, compared postmortem hippocampal tissue of six rats treated with ten ECS with six other animals receiving only a sham treatment (same handling, no current administration). They found a ~30% increase in the total number of endothelial cells and a ~16% increase in vessel length in the ECS treated group. Based on their findings they proposed that decreased vascularization may be one possible parameter inducing hippocampal shrinkage in patients with MDD and that ECT may counteract these processes by stimulating hippocampal angiogenesis. Overall, these results are in line with other studies examining rats following the administration of ECS, which similarly revealed increased angiogenesis in the hippocampus (Hellsten, Wennstrom, Bengzon, Mohapel, & Tingstrom, 2004; Newton, Girgenti, Collier, & Duman, 2006). Furthermore, Hellsten et al. (2004) suggested that endothelial cell

proliferation (angiogenesis) and neural proliferation (neurogenesis) are simultaneously regulated and that both processes support each other. In consequence, this may contribute to structural changes within the hippocampus. Due to the specific difficulty of investigating the processes of neuroplasticity in humans separately, it is still unresolved how they are exactly modulated via ECT in depressed patients.

Another possibility to explain the increase in hippocampal volume is an unspecific effect, the so-called brain edema. “Brain edema is best defined as an increase in brain volume that is due to an increase in its water content.” (Fishman, 1975). Szabo et al. (2007) investigated this alternative explanation by exploring water molecule mobility in the brain via diffusion-weighted imaging (DWI) in MDD. A total of ten patients was examined: two after one ECT session and eight after at least seven ECT administrations. They showed that there was no evident signal change on DWI directly after ECT administrations (< 15 hours), which indicates the absence of brain edema. Moreover, Kunigiri, Jayakumar, Janakiramaiah, and Gangadhar (2007) investigated MRI T_2 relaxation time as a measure of brain edema in 15 patients with MDD two hours after their second ECT session. They demonstrated no change in T_2 relaxation time in five regions of interest including the hippocampus and suggested that ECT did not cause brain edema. This is consistent with two other studies exhibiting no evidence of brain edema in patients with depression after a course of ECT (Jorgensen et al., 2016; Nordanskog et al., 2010). In total, these findings may rule out unspecific ECT-related effects like brain edema provoking the increase of hippocampal volume and support the assumption of increased neurogenesis.

The present results are in line with a wide range of single studies reporting hippocampal volume increase after the administration of ECT in patients with depression (Bouckaert, Dols, et al., 2016; Cano et al., 2017; Jorgensen et al., 2016; Joshi et al., 2016; Nordanskog et al., 2010; Nordanskog et al., 2014; Ota et al., 2015; Redlich et al., 2016; Sartorius et al., 2016; Tendolkar et al., 2013). Additionally, two other recent meta-analyses examining hippocampal volume changes in depressed patients after a course of ECT (Takamiya et al., 2018; Wilkinson et al., 2017). Both studies reported, comparable to our outcomes, an increased volume in both the left and right hippocampus. Furthermore, Wilkinson et al. (2017) demonstrated an increase in total hippocampal volume, which was similarly shown in our results.

One difference between both recent meta-analyses and our calculations is the number of included studies and consequently the sample size of patients. We analyzed 11 studies with a total of 235 patients suffering from depression, whereas Wilkinson et al. (2017) included only nine studies containing 174 patients with MDD

and Takamiya et al. (2018) examined solely eight studies with a total of 193 depressed patients. Moreover, both other meta-analyses computed the standardized mean difference (SMD) to demonstrate the effect of ECT on hippocampal volume. Generally, the SMD is calculated using pooled standard deviations (Faraone, 2008). Based on this it can be assumed that our analysis method (standardized change score) is more accurate since the standard deviations of the pre-post difference scores were applied. Overall, the thesis at hands reflects the real effect size of ECT on hippocampal volume more precisely in comparison to the other calculations.

In sum, the present meta-analysis demonstrated a strong positive effect of ECT on the bilateral hippocampal volume in patients with depression. Based on previous preclinical examinations it is conceivable that ECT enhances neurogenesis, which is mirrored in the increased hippocampal volume observed in our calculations. However, the reported findings should be interpreted carefully, as a publication bias is conceivable. Moreover, neuroimaging outcomes cannot directly be linked to biological mechanisms. Still, neuroplasticity and especially adult neurogenesis appear to be a plausible target to explain ECT's antidepressant effects.

5.2 Hypothesis 2: Correlation hippocampal volume – depressive symptoms

In the second hypothesis of this thesis it was postulated that hippocampal volume increases are negatively correlated with the degree of depressive symptoms assessed by psychometrical scales. As presented in the results section we could not detect this correlation and therefore have to reject this theory.

Our findings are in line with various previous studies, which similarly could not identify a relationship between increased hippocampal volume and decreased depressive symptomatology (Abbott et al., 2014; Bouckaert, De Winter, et al., 2016; Bouckaert, Dols, et al., 2016; Jorgensen et al., 2016; Nordanskog et al., 2014; Sartorius et al., 2016; Tendolkar et al., 2013). Moreover, both recent meta-analyses on this topic ascertained our results (Takamiya et al., 2018; Wilkinson et al., 2017). In contrast, two other investigations demonstrated a correlation between these factors (Dukart et al., 2014; Joshi et al., 2016). The absence of a correlation may be due to the relatively small number of studies included in our calculations as well as the equally small sample size of patients in the single investigations. In addition, the included studies used different psychometrical scales to evaluate depressive symptoms. Although the scales were shown to be comparable (c.f. 3.1.1) the

administration of different assessment methods may influence our outcomes. As a consequence, it is conceivable that a possible correlation between volume changes and depressive symptomatology is hidden or underestimated by the small number of examined patients and the application of different psychometrical scales, respectively.

Another possible reason for the lack of a correlation is that beside hippocampal volume other outcomes regarding neuroplasticity may be responsible for the improvement in depressive symptomatology. For instance, Abbott et al. (2014) examined 19 patients with MDD undergoing a mean of 11 ECT sessions and MRI measurements before and after the treatment. They demonstrated that the reduction in depressive symptoms was correlated with increased right hippocampal functional connectivity. Even though they additionally showed increases in right hippocampal volumes, these structural changes were not correlated with the improvement in depressive symptoms. They proposed that complementary but different processes of neuroplasticity contribute to the increases in volume and connectivity: neurogenesis and gliogenesis for volume alterations and synaptogenesis for connectivity changes. In sum, it is conceivable that other parameters like alterations in hippocampal connectivity along with hippocampal volume changes contribute to the antidepressant effects of ECT. The extent and the relationship between different processes of neuroplasticity as well as their correlation with alterations in depressive symptomatology should be addressed in future studies by combining measurements of several outcomes (e.g., hippocampal volume and connectivity).

5.3 Correlation hippocampal volume – moderators

On the basis of the present meta-analysis it was demonstrated that moderators like age, the percentage of women, number of ECT sessions, electrode placement, the magnetic field strength of the MRI scanner as well as measurement outcome did not correlate with changes in hippocampal volume. Nevertheless, the percentage of women and the number of ECT sessions showed a trend towards a relationship. The latter one is in line with preclinical findings in rats demonstrating that the number of newly generated cells was positively correlated with the number of ECS administrations (Madsen et al., 2000). Further studies containing large sample sizes are needed to verify this finding in humans.

On the one hand, the relatively small sample of included studies in our calculations and the equally small sample size of patients with MDD in the individual investigations may be the reason for the lack of a significant correlation. On the other

hand, the high between-study heterogeneity may mask a possible correlation between hippocampal volume change and the parameters mentioned above.

5.4 Limitations

Even though the present meta-analysis revealed a substantial positive effect of ECT on hippocampal volume and depressive symptoms, there are some limitations, which should be considered. First, the number of investigations included in the calculations was relatively small. Two reasons are the poor data situation on that topic generally and that approximately half of the 20 initially found studies had to be excluded due to missing data. As a consequence, this may have biased our results. Another factor, which should be taken into account, is the strong between-study heterogeneity observed in our analyses. This inhomogeneity indicates that the single studies used very different methodological approaches in respect of ECT procedures (electrode placement, number of ECT sessions, frequency of ECT administration), MRI measurements (magnetic field strength, time between the last ECT session and the last MRI scan, time between pre and post treatment MRI scan), volume analyses (manual or automatic segmentation of the hippocampus) and the assessment of depressive symptoms (HAM-D with 17, 21 or 24 items or MADRS). Additionally, the patients included in the single publications showed different characteristics concerning age, sex, psychiatric diagnosis (MDD or BD) and medication status (additional medication or not). Consequently, it is challenging to draw a general conclusion about ECT induced effects. Still, the presented results point towards a strong positive effect of ECT on hippocampal volume despite this heterogeneity. Furthermore, we performed the meta-analysis by using the overall estimates reported in the included studies instead of single datasets from every patient. This and the high between-study heterogeneity may be the cause that we did not detect a correlation between the hippocampal volume increase and decreased depressive symptoms or other demographical or methodological parameters (age, percentage of women, number of ECT sessions, electrode placement, magnetic field strength of the MRI scanner, measurement outcome), respectively. In addition, a publication bias can be assumed since the test for funnel plot asymmetry indicated missing studies in the calculations of the summary effect sizes for the left, right and total hippocampal volume, respectively. Nevertheless, the strong positive effect of ECT on hippocampal volume persisted when performing the computation with the estimated number of missing studies. Moreover, we calculated the effect size regarding depressive symptoms by using the standardized mean change (raw score standardization) with

the standard deviations before treatment. This may affect our results as calculations with the standard deviations of the pre-post changes are thought to be more precise. Due to the lack of information provided by the included studies, we were not able to perform the meta-analysis with these estimates. Finally, it is questionable, if the volume changes are specific to the hippocampus. For instance, some investigations demonstrated volume increases in the amygdala after ECT administration (Jorgensen et al., 2016; Joshi et al., 2016; Tendolkar et al., 2013). However, since studies regarding volume measurements of other brain regions in patients with MDD after a course of ECT are scarce, no definite conclusion can be drawn here. Based on the currently available data on this topic, the hippocampus appears to be the most potential target to explain at least one mechanism of action of ECT in the context of depression.

6 CONCLUSION AND FUTURE PERSPECTIVES

The aim of the present thesis was to calculate the real effect size of ECT on hippocampal volume in patients suffering from depression by combining the outcomes of multiple MRI studies. The result of the meta-analysis points towards a strong positive effect of ECT on bilateral hippocampal volume. One possible mechanism behind the volumetric expansion of this brain region is a change in neuroplasticity processes, more specifically in adult neurogenesis. This assumption is supported by various preclinical and clinical investigations, which demonstrated decreased neurogenesis in animal models of depression and patients with MDD as well as increased neurogenesis after the administration of ECS and ECT, respectively (cf. 2.3.1 and 2.3.2). Although the depressive symptoms declined significantly following a course of ECT, the meta-regression analysis showed no correlation with alterations in hippocampal volume. Additionally, neither age, sex, the number of ECT sessions, electrode placement, the magnetic field strength of the MRI scanner nor the measurement outcome was associated with hippocampal volume alterations. However, the lack of a correlation between these parameters may be underestimated or hidden due to the relatively small number of included studies and patients, respectively.

An option to manage the underestimation of ECT's effects in future studies is to carry out investigations with a larger sample size of depressed patients. Due to limiting resources, the alternative is to perform meta-analyses by combining results of multiple published investigations like in the thesis at hands. However, future analyses should preferably be based on the original datasets from each patient included instead of the already summarized estimates from the single publications. Moreover, one possibility to overcome the high heterogeneity in investigations relating to ECT is to standardize procedures regarding the assessment of the disease (application of one psychometrical scale), the measurement and evaluation of brain volume (MRI protocols and data processing techniques) and the administration of ECT (ECT procedures). Since it can be assumed that different disorders are caused by various biological, psychosocial or cognitive-behavioral components, future studies should examine only one psychiatric disease instead of mixing patients with diverse diagnoses (e.g., MDD and BD). In sum, this may lead to a more precise insight into the underlying neurobiological underpinnings of major depression and the mechanism of action of ECT.

Nowadays, psychiatric disorders like MDD and especially the treatment with ECT are still massively stigmatized. Hence, the present thesis may contribute to a

better understanding of ECT's induced effects and consequently to a wider acceptance of that treatment option in general.

A LIST OF LITERATURE

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