Chapter 1

General introduction
1. Depression

1.1. Symptomatology and epidemiology

Major depressive disorder (MDD) is a mood disorder characterized by episodes of pathological low mood and/or loss of interest during at least a consecutive two-week period. Patients also experience other symptoms like change in weight, sleeping problems, psychomotor changes, fatigue or loss of energy, feelings of worthlessness or excessive feelings of guilt, difficulty concentrating or indecisiveness, and suicidal thoughts. These symptoms cause clinically significant distress in social, occupational, or other important areas of functioning. Furthermore, anxiety symptoms, psychotic features, or catatonia can accompany MDD (American Psychiatric Association 2013).

MDD is a prevalent disorder. The lifetime prevalence, i.e. the proportion of people ever having experienced at least one episode of MDD during lifetime, is estimated to be 30% in men and 40% in women, and mean episode duration is around 24 weeks (Kruijshaar et al. 2005). MDD has a significant impact on patients and their quality of life. This is reflected by the amount of healthy years of life lost, captured by the concept of ‘disability adjusted life years’ (DALYs), summing ‘the ‘Years of Life Lost’ (YLL) due to premature mortality in the population and the ‘Years Lost due to Disability’ (YLD) for people living with the health condition or its consequences” (WHO 2018). Globally, MDD is one of the leading causes of disease burden according to the WHO.
Global Burden of Disease study. It accounts for 3% of 2.5 billion DALYs and 8% of all YLDs, ranking second as cause of all YLDs (Ferrari et al. 2013). Furthermore, MDD is responsible for large societal costs (Greden 2001; Ivanova et al. 2010). This makes MDD a severe mental disorder with significant impact on personal and societal functioning.

1.2. Treatment

1.2.1. Treatment challenges

Choosing an appropriate treatment for MDD depends, among other things, on the severity of illness, accompanying symptoms, treatment history, and the preferences of the patient. General interventions include psycho-education, active monitoring, optimizing the structure of the day, activation, and optimizing sleep hygiene. If a depressive episode is more severe, a treatment regime of psychotherapy, antidepressant medication, or a combination of these two is recommended (National Institute for Health and Clinical Excellence 2009; Spijker et al. 2013). Examples of psychotherapy include Cognitive Behavioral Therapy (including Behavioral Activation), Interpersonal Therapy (IPT), and short-term psychodynamic psychotherapy. Examples of antidepressant medication include selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), lithium augmentation and MAO inhibitors (MAOIs) (Spijker and Nolen 2010). In general, treatment of depression has moderate efficacy (Cipriani et al. 2009; Cuijpers et al. 2018; Cuijpers, Berking et al. 2013; Cuijpers, Sijbrandij et al. 2013; de Maat et al. 2007). Treatment appears not to be effective for a subset of patients, who are described as having Treatment Resistant Depression (TRD).

TRD is often categorically defined as non-response to ≥2 adequate trials with antidepressants (Berlim and Turecki 2007a; Berlim and Turecki 2007b; Ruhe et al. 2012; Souery et al. 1999; Souery, Papakostas, Trivedi 2006). Given the results of the largest treatment study to date, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, it is questionable if TRD has to be represented as a dichotomy. The STAR*D study encompasses a protocol in which a series of randomized controlled treatment trials (RCT) is provided to a large group (N=3671) of depressed outpatients, such that they received one to four successive acute treatment steps. This study has shown that 49% of participants showed a response (≥50% improvement on the Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR16)), and 37% remission (≤5 on the QIDS-SR16) after the first antidepressant. Remission-rates however gradually declined with each sequential step thereafter. After four treatment trials 33% of patients had not achieved remission.
(Rush et al. 2006). Therefore, treatment resistance spans a spectrum, running from quick remission to severe treatment resistance with no treatment response to ECT and other third-line treatment regimens (Berlim and Turecki 2007b; Ruhe et al. 2012; van Belkum et al. 2018).

1.2.2. Treatment perspectives

The STAR*D study gives some focus on how we could study TRD. However, if the outcome of that study is taken at face value, it also shows that a substantial number of patients have not or only partial benefitted from pharmacological treatment of MDD, given that one-third of MDD patients will not achieve remission (Rush et al. 2006). Given the personal and societal costs of MDD, it is paramount to improve treatment efficacy for MDD.

There are different general strategies to improve treatment efficacy for MDD: adhering to existing treatments, focusing treatments, and developing novel treatments. One approach of adhering to existing treatments is by ways of ‘measurement based care’, i.e. “the routine measurement of symptoms and side effects at each treatment visit and the use of a treatment manual describing when and how to modify medication doses based on these measures” (Trivedi et al. 2006). In an RCT with assessors blind to protocol and treatment group it has been shown in an outpatient group of participants suffering from non-psychotic MDD (N=120) that measurement based care yields better outcome (response 87%; remission 74%) compared to standard treatment, in which participants were treated by their psychiatrists according to their clinical needs (response 63%; remission 29%) (Guo et al. 2015).

A second strategy to improve treatment efficacy for MDD is to further develop personalized treatments. At present, treatment of MDD follows a general protocol, not systematically accounting for patients’ unique clinical characteristics or biological markers (Spijker and Nolen 2010). This ‘one size fits all’-approach can be partly held responsible for the difficulties in successfully treating MDD, especially given the heterogeneous nature of this disorder (Fried 2015; Hasler 2010; Kendler, Gardner, Prescott 1999; Lux and Kendler 2010). Researchers believe that treatment of MDD can be improved if patients were matched to their optimal treatments, which is the aim of precision psychiatry (Williams 2016).

A last strategy to improve treatment efficacy for MDD is to develop novel treatment options. For example, there is a rise in the use of psychoactive drugs for depression, like ketamine, a noncompetitive N-methyl-d-aspartate (NMDA) receptor antagonist working on the glutamatergic system (Ionescu and Papakostas 2016), or psilocybin, a plant alkaloid that after metabolization acts as an agonist on the serotonin receptor.
Neuromodulation and Depression

(Carhart-Harris et al. 2016). Another example of a novel approach to treat MDD is treatment by means of neuromodulation, which directly relates to the subject of this thesis.
2. Neuromodulation

Neuromodulation concerns electrical or electromagnetic modification of the central nervous system, intended to change behavior or modify brain processing. Historically, it appears that the use of electricity to modify physiological processes was first described at 15 A.D., when a man suffering from gout stepped on an electric fish and experienced an electric shock, alleviating his pain. Consequently, his treating physician started using these electric fish to treat pain, not only for gout but also chronic headaches (Kellaway 1946). The first recorded use of electricity to stimulate the human brain directly was in the 19th century, when a patient with a purulent ulcer of the scalp underwent surgery, leaving the cortex exposed; electric stimulation of the cortex led to contraction of a muscle (Gildenberg 2005). Over the 20th century, invasive and noninvasive neuromodulation was used for multiple neurological and psychiatric disorders (Gildenberg 2005).

Currently, multiple forms of neuromodulation exist that can be categorized into two broad categories: invasive and non-invasive neuromodulation. In invasive neuromodulation, electrodes are implanted in discrete brain targets (Deep Brain Stimulation (DBS)) or in the vagus nerve (cranial nerve X) in the neck (Vagus Nerve Stimulation (VNS)). Invasive neuromodulation for MDD is mostly used as a last resort option (Aaronson et al. 2017; Graat, Figee, Denys 2017; Rush et al. 2005). In non-invasive neuromodulation, a procedure to implant electrodes is not needed. This category is more widespread and can be subdivided in smaller categories. Also, two generations can be recognized, subdivided by a different mechanism of action.

2.1. First generation

The first generation of non-invasive neuromodulation relies on the induction of seizures as a treatment for psychiatric diseases. Although first camphor was used to induce seizures (Fink and Taylor 2007), soon this was replaced with the use of electroconvulsive therapy (ECT) (Bini 1995; Hoy and Fitzgerald 2010). In recent years, magnetic seizure therapy (MST) has been introduced as a novel form to induce seizures (Lisanby 2002).

2.1.1. Electroconvulsive Therapy (ECT)

In ECT, a seizure is induced by applying an electrical stimulus through the scalp to the brain, under general anesthesia and muscle relaxation in a well-controlled clinical setting (Allan and Ebmeier 2011). ECT is indicated for severe psychiatric disorders, especially (unipolar and bipolar) TRD (Allan and Ebmeier 2011; Fink and Taylor 2007). It may be particularly useful for psychotic depression (Fink and Taylor
As such, ECT is highly effective with reported response rates of 60% (Hoy and Fitzgerald 2010). However, memory impairments are an important potential side effect of ECT: a minority of patients develops retrograde amnesia, particularly for autobiographical memory (Allan and Ebmeier 2011).

### 2.1.2. Magnetic Seizure Therapy (MST)

Magnetic Seizure Therapy (MST) is the induction of a seizure for therapeutic purposes using repetitive Transcranial Magnetic Stimulation (rTMS; see below). MST is administered under general anesthesia, conform ECT (Lisanby 2002). However, MST does not involve an electrical current passing through deep brain structures. Without affecting hippocampal structures, MST has less cognitive side effects compared to ECT (Allan and Ebmeier 2011). In depression MST appears to have a slightly lower efficacy compared to ECT (Fitzgerald et al. 2018; Hoy and Fitzgerald 2010).

### 2.2. Second generation

In the second generation of non-invasive neuromodulation, neural activity is influenced based on different electromagnetic principles. Two major types can be distinguished: locally and globally applied neuromodulation.

#### 2.2.1. Local neuromodulation

Local neuromodulation relies on modulation of local brain regions. Multiple types exist, differing mostly in the acute effects of the different techniques (Yavari et al. 2018). For repetitive Transcranial Magnetic Stimulation (rTMS) depolarization of neurons in the cerebral cortex is achieved. On the other hand, during transcranial Direct Current Stimulation (tDCS) only polarization of the brain is achieved (Yavari et al. 2018).

*Repetitive Transcranial Magnetic Stimulation (rTMS)*

With Transcranial Magnetic Stimulation (TMS) a non-invasive focused magnetic field is used to stimulate nerve cells in the cortical areas of the brain. It is based on the principle of electromagnetic induction: the production of electric voltage across a conductor due to the dynamic interaction with a magnetic field. A large, rapidly changing electrical current that is passed through a coil produces a TMS pulse: a fluctuating magnetic field that is able to induce a small current in the brain (Hallett 2007). In repetitive Transcranial Magnetic Stimulation (rTMS) a series of pulses (up to 100 Hz) can be applied. These pulses alter brain functioning and the duration of the effect exceeds the duration of the stimulation (Fitzgerald, Fountain, Daskalakis...
The clinical effects of rTMS are prominent in MDD: in a meta-analysis of 40 RCTs high frequency rTMS aimed at the left dorsolateral prefrontal cortex (DLPFC) has shown superiority to sham for response and remission rates (Brunoni et al. 2017) and high-frequency rTMS is recommended as treatment for depression (Perera et al. 2016).

One of the rationales in applying high-frequency rTMS in depression at the left DLPFC comes from the observation that MDD patients demonstrate prefrontal lobe hypometabolism observed with functional Single-Photon Emission Computed Tomography (SPECT) and Positron-Emission Tomography (PET) (George, Ketter, Post 1994). High-frequency rTMS applied to this region was hypothesized to increase activity. Indeed, most studies have demonstrated a clinical benefit after stimulation of 10 Hz on the left DLPFC in depressed patients (Lefaucheur et al. 2014). However, in most clinical rTMS studies blinding integrity has not been reported (Broadbent et al. 2011; Brunoni et al. 2009; Razza et al. 2018), introducing a large potential bias with regard to placebo effect.

**Transcranial Direct Current Stimulation (tDCS)**

In transcranial Direct Current Stimulation (tDCS) a continuous low-amplitude electrical current is applied to a specific cortical region of the brain by placing anodal and cathodal electrodes to the scalp. As a result of a relative hyperpolarization under the anodal electrode and a relative depolarization under the cathodal electrode a polarity-dependent shift (polarization) of resting membrane potential is achieved, without depolarization of the neuronal membrane (Brunoni et al. 2012; Hoy and Fitzgerald 2010). In MDD, response and remission rates are similar to rTMS (Brunoni et al. 2016), although the quality of the studies of tDCS is less (Lefaucheur et al. 2017).

### 2.2.2. Global neurostimulation

Global modulation of the brain refers to weak electromagnetic stimulation at multiple scalp sites simultaneously or with a more or less homogeneous magnetic field (Rohan et al. 2004; Rohan et al. 2013; van Belkum et al. 2016). These techniques have recently been developed and no clear consensus yet exists regarding which techniques can be called global modulation. Here, three different approaches are presented, Low Field Magnetic Stimulation (LFMS), synchronized TMS (sTMS), and transcranial Pulsed Electromagnetic Fields (tPEMF).

**Low Field Magnetic Stimulation (LFMS)**

Low Field Magnetic Stimulation (LFMS) is a technique in which the time-varying
gradient magnetic fields of an Echo-Planar Magnetic Resonance Spectroscopy (EP-MRSI) scan is used. A chance finding of mood improvement after scanning with this particular MR-protocol has led to a single blind RCT in which 40 participants suffering from bipolar disorder currently in a depressive episode and fourteen healthy controls underwent a single stimulation-session lasting 15 minutes. This study has shown a significant improvement in mood for participants with a bipolar depressive disorder receiving active treatment (n=30) (Rohan et al. 2004). The same technique has shown a positive antidepressive effect on depressive-like behavior in rats (Carlezon et al. 2005). The effect was replicated in mice (Aksoz et al. 2008; Rokni-Yazdi et al. 2007). Furthermore, in a double blind RCT it was shown that LFMS had an immediate positive effect on unipolar and bipolar depression severity, 10-15 minutes after completion of a single intervention (Rohan et al. 2013). Subjects who underwent the active condition (n=34) experienced a greater improvement compared to sham (n=29). No statistical difference was found when individual diagnostic subgroups (unipolar or bipolar depression) were analyzed separately (Rohan et al. 2013), suggesting that the antidepressive effect was small. Moreover, this study used HAMD-17 as a severity measure for measuring short-term change (over minutes to hours), while this particular rating-scale is intended for measuring longer-term change (over days) (Hamilton 1960). In a third clinical study of this technique, no clear difference between active and sham LFMS was found (Fava et al. 2018). In this double blind RCT 84 participants suffering from TRD were included. Participants underwent active (n=26) or sham (n=29) LFMS for 20 minutes for four days or sham treatment for two days followed by LFMS for two days (n=29). Although the study aimed to demonstrate superior outcome for active LFMS over sham on the 6-item Hamilton Rating Scale for Depression (HAMD-6) within 48 hours, they have failed to show this: improvement in both conditions was similar (Fava et al. 2018). The antidepressant effect of LFMS has thus been investigated in rodent models and in humans. Although the first pilot studies were quite promising, later studies have shown no clear antidepressant effect. This suggests that the antidepressant effect of LFMS is minimal at best.

Synchronized Transcranial Magnetic Stimulation (sTMS)

Synchronized Transcranial Magnetic Stimulation (sTMS) is a technique that aims to stimulate at one’s individual alpha frequency band using a low magnetic field strength sinusoidal waveform transcranial magnetic stimulation device (Jin and Phillips 2014; Leuchter et al. 2013; Leuchter et al. 2015). A pilot study (a double blind RCT with three arms) to the effects of sTMS in 52 depressed participants has shown a statistically significant decrease in HAMD-17 scores in participants receiving active stimulation compared to sham (Jin and Phillips 2014), suggesting that sTMS could be an efficacious treatment for MDD. However, a larger double blind RCT of this technique has shown
a less clear outcome. In this study, 202 participants with MDD were stimulated with sTMS for five times a week during six weeks, which were analyzed in an Intention to Treat (ITT) analysis. Due to dropout and technical difficulties, 120 participants were analyzed in a Per Protocol (PP) analysis. No significant difference between active and sham was found in the ITT analysis. In the PP analysis, HAMD-17 scores improved 41% for active and 32% for sham, a statistically significant difference. Response and remission rates did not significantly differ (Leuchter et al. 2015). This suggests that the antidepressive effects of sTMS are less evident than the first pilot study would suggest.

Transcranial Pulsed Electromagnetic Fields (tPEMF)

In transcranial Pulsed Electromagnetic Fields (tPEMF) a head device with multiple small coils is used to generate continuous trains of low-voltage alternating currents. In psychiatry, this type of neuromodulation was first described in 2010, when a Danish research group published their findings of the antidepressive effects of tPEMF in TRD (Martiny, Lunde, Bech 2010). This stimulation method was adapted from earlier studies in orthopedics in which Pulsed Electromagnetic Fields (PEMF) has been used for the treatment of osteoarthritis and acute fractures (Hannemann et al. 2014; McCarthy, Callaghan, Oldham 2006; Ryang We et al. 2013). A method comparable to PEMF has been used for the treatment of pain, which has been investigated in snails (Thomas et al. 1997), rodents (Del Seppia et al. 2007), and humans (Kortekaas et al. 2013; Shupak, Prato, Thomas 2004).

Martiny et al. (Martiny, Lunde, Bech 2010) were the first to apply PEMF transcranially (hence tPEMF) in human participants suffering from unipolar TRD. They have investigated the efficacy in a double blind RCT using 50 participants, equally divided in an active and a sham condition. After five consecutive weeks of stimulation, depression severity (measured with the HAMD-17) decreased significantly more in the active stimulation group (difference in HAMD-17: 48%) compared to sham stimulation (difference in HAMD-17: 24%) (Martiny, Lunde, Bech 2010). Similar improvements have been found on secondary outcome measures, like the HAMD-6 and the Melancholia Scale (MES) (Martiny, Lunde, Bech 2010). In a subsequent dose effect study, it has been found that eight weeks of tPEMF stimulation augmented to antidepressant medication in 65 participants with TRD reduced HAMD-17 scores with 74% and 68% (13 and 14 points) if treated respectively with one vs. two daily tPEMF doses (Straaso et al. 2014). No sham treatment was given. No statistically significant difference was found between the two groups, suggesting that both dosing regimens worked equally well (Straaso et al. 2014).
**Concluding remark**

Global neuromodulation devices seem to have practical advantages over most local neurostimulation devices like rTMS for the treatment of MDD, because of the ability to use global neuromodulation devices in a domestic environment, thus reducing the need of patients to come to a hospital or mental health institution and increasing the applicability of neuromodulation techniques. However, so far both LFMS and sTMS have not convincingly shown to be efficacious for the treatment of MDD. Treatment using tPEMF has shown some first favorable results, but more research is needed to further investigate the antidepressive effects of tPEMF.
3. Aim and outline of this thesis

This thesis aims to contribute to the improvement of the treatment of major depressive disorder (MDD) by using neuromodulation. It will focus specifically on patients with treatment resistant depression and the use of a particular novel neuromodulation device to treat MDD: transcranial Pulsed Electromagnetic Fields (tPEMF). In the first part of this thesis (chapter 2 and 3) the effects of tPEMF and related neuromodulation devices will be described. Part two (chapter 4) will focus specifically on quantification of treatment resistant depression. The goal of part three of this thesis (chapter 5 and 6) is to replicate the first study of the antidepressive effects of tPEMF (Martiny, Lunde, Bech 2010). Moreover, in this part the long-term effects will be investigated and the effect of tPEMF on the brain will be evaluated.

3.1. Part one: effects of tPEMF and related neuromodulation devices

In the first part of this thesis the effects of tPEMF and related neuromodulation devices are described. First in chapter 2 a broader theme will be discussed, focusing on the effects of neuromodulation on Functional Somatic Symptoms (FSS), by reviewing the effects of various neuromodulation techniques (rTMS, tDCS, and tPEMF) on four different FSS subtypes. Functional Somatic Symptoms (FSS) concern a group of symptoms that affect motor or sensory functioning and cannot be adequately explained by any known physical pathology (American Psychiatric Association 2013). There is an association between FSS and MDD (Lieb, Meinlschmidt, Araya 2007), not in the least because some symptoms of MDD encompass multiple somatic symptoms, like change in weight, problems sleeping, psychomotor changes, and fatigue or loss of energy, making FSS and MDD comorbid (American Psychiatric Association 2013). By studying the effects of neuromodulation on FSS, the effect of neuromodulation devices on somatic symptoms of MDD could possibly be clarified further.

In chapter 3, possible mechanisms that might contribute to the antidepressant effects of tPEMF are explored in a review of the literature. First, an acute effect of tPEMF on local brain activity and glucose metabolism will be discussed. These findings are in line with current ideas that connectivity between different cortical regions is disrupted in depression, and that antidepressive treatment should be targeted at restoring the communication between neuronal networks. Moreover, other preliminary evidence would suggest that tPEMF might influence neuronal growth. Some studies have also shown that the antidepressive properties of tPEMF may be partly attributed to its effects on low-grade inflammatory processes. Lastly, the possibility of an antidepressive effect through the biological clock will be discussed.
3.2. Part two: quantifying treatment resistance in depression

Part two focuses specifically on treatment resistant depression. Chapter 4 describes a way to quantify TRD by means of the Maudsley Staging Method (MSM) by applying it to a large number of subjects who participate in the Netherlands Study of Depression and Anxiety (NESDA). The question will be addressed whether the MSM can be used in general psychiatric practices to predict the course and treatment outcome of MDD, in addition to its earlier use in tertiary population. In the long term, this could help in offering specific or more intensified treatment regimens in an earlier phase of treatment compared to current practice, and could thus lead to a more focused and precise use of neuromodulation devices.

3.3. Part three: a novel treatment for MDD?

Part three of this thesis consists of a randomized placebo-controlled double blind clinical trial to study the efficacy of tPEMF as a potential novel treatment for MDD. The design was a replication of the earlier, positive study of Martiny et al. (Martiny, Lunde, Bech 2010). We studied both the short-term and follow-up outcome, and also evaluated the effects of tPEMF on brain activation during two different processes using functional magnetic resonance imaging (fMRI).

Chapter 5 and 6 are based on this RCT in patients with TRD, who were treated with tPEMF for five weeks in a row, five times a week. These chapters focus on the short- and long-term effects of tPEMF on TRD (chapter 5) and on the effect of tPEMF on brain activation (chapter 6).
Part 1

Effects of tPEMF and related neuromodulation devices