Chapter 7

Summary and general discussion

1. Summary of main findings

The aim of this thesis was to contribute to the improvement of the treatment of major depressive disorder (MDD) by studying the efficacy of neuromodulation. We focused specifically on patients with treatment resistant depression and used a particular novel neuromodulation device to treat MDD: transcranial Pulsed Electromagnetic Fields (tPEMF).

1.1. 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, different neuromodulation techniques (rTMS, tDCS, and tPEMF) were discussed in a systematic review of the literature. Their effects were explored on four different subtypes of functional somatic symptoms (FSS): a group of sensory and pain related symptoms (Complex Regional Pain Syndrome type I (CRPS I) and fibromyalgia) and a group of movement related symptoms (paresis and movement disorders).

The use of neuromodulation in FSS was most thoroughly studied by means of placebo controlled RCTs in fibromyalgia, a pain related symptom. It appeared that especially applying tDCS reduced pain intensity in fibromyalgia. In contrast, in CRPS I the number of studies was very limited and both the placebo effect and the treatment

effect of rTMS have been considerable in the described studies. For movement related symptoms, the number of clinical studies was evenly low: one placebo-controlled study in patients with paresis has suggested that rTMS below motor threshold could be a therapeutic option (Broersma et al. 2015). No RCTs have been conducted for movement disorders (chapter 2). Clearly, larger studies with better methodological standards are needed in order to fully establish (or refute) possible positive effects of neuromodulation in FSS.

In chapter 3, possible mechanisms of action that might contribute to the antidepressive effects of tPEMF and similar global neuromodulation devices were explored in a review of the literature. One study has shown that a tPEMF-like device can influence brain glucose metabolism (Volkow et al. 2010). Furthermore, an effect of tPEMF on functional connectivity between certain brain areas has been shown, which led to the speculation that antidepressive effects of tPEMF stimulation partly involve a synchronization of cortical firing of neuronal networks. Other preliminary evidence would suggest that tPEMF might influence neuronal growth. Some studies have shown that the antidepressive properties of tPEMF may be partly attributed to its effects on low-grade inflammatory processes. The evidence for an effect of tPEMF on the biological clock was also considered. Although some studies have shown that weak magnetic fields can entrain circadian rhythms in fruit flies, it is implausible that this could explain an antidepressive effect of tPEMF.

1.2. Part two: quantifying treatment resistance in depression

Part two focused specifically on quantification of treatment resistant depression. In chapter 4 the predictive properties of the Maudsley Staging Method (MSM) for the course and outcome of depression were examined using a large and well phenotyped naturalistic cohort of depressed patients (Netherlands Study of Depression and Anxiety (NESDA)). The intensity and duration of depressive symptoms during a 2-year period was determined in 634 subjects suffering from MDD. Results showed that a higher score on the MSM predicted the duration of the current depressive episode. Furthermore, the score on the MSM was associated with being in a depressive episode for 50% of the follow-up time. This prediction appeared independent of treatment provided at baseline or during follow-up. The MSM is thus a reliable and valid tool to predict poor outcome in depressed patients irrespective of treatment, in a wide range of patients with MDD (Fekadu, Wooderson et al. 2009a; Fekadu, Wooderson et al. 2009b; van Belkum et al. 2018).

1.3. Part three: a novel treatment for MDD?

The goal of part three of this thesis was to replicate the first study of the antidepressive

effects of tPEMF (Martiny, Lunde, Bech 2010). Moreover, we aimed to investigate long-term effects and to evaluate the effect of tPEMF on the brain. In chapter 5 and 6 the results were presented of the Dutch tPEMF trial, a double blind multicenter RCT comparing active tPEMF treatment versus sham treatment in 55 depressed patients with TRD. Patients were recruited and treated at major mental health care institutions in the northern part of The Netherlands. Eligible patients were randomly assigned to either active tPEMF or sham stimulation. Differences in HAMD-17 scores were determined based on pre- and post-treatment measures and differences in IDS-SR scores were determined based on weekly measures. Follow-up was fifteen weeks. Functional MR-scans were made pre- and post-treatment. During scanning participants performed two tasks to investigate two different processes. To study emotional cognitive processing we used the Wall-of-Faces (WoF) task (Simmons et al. 2006). To study reward processing we used a Monetary Incentive Delay (MID) task (Pizzagalli et al. 2009).

In chapter 5 the clinical results of the tPEMF trial were presented. Mean severity on baseline was a HAMD-17-score of 22 points for both conditions. In general, participants did improve over time, but there was no difference between intervention and control condition: participants in both conditions improved five points on the HAMD-17 after five weeks. This improvement lasted at least fifteen weeks. Also on secondary measures like the IDS-SR no differences between both groups as a result of treatment existed.

In chapter 6 results from the functional MR-scans were presented, comparing activation patterns pre- and post-treatment. For the WoF-task there were no significant differences over time for any of the contrasts. For the MID-task differences between the two treatment groups in differences over time were found during the consumption phase of reward processing in the left inferior frontal gyrus (IFG) and in a cluster comprising the right lingual gyrus and the posterior part of the middle temporal gyrus. In both clusters a larger decrease was observed in activation for the active condition compared to the sham condition. These findings suggest that there is an effect of tPEMF on the brain in absence of a clinical antidepressive effect.

2. General discussion

MDD is a highly prevalent disorder (Kruijshaar et al. 2005) and treatment overall is only moderately effective (Cipriani et al. 2018; Cuijpers et al. 2013). Given the personal (Ferrari et al. 2013) and societal (Greden 2001; Ivanova et al. 2010) costs of MDD, it is paramount to improve treatment efficacy for MDD. Different general strategies to do so exist: adhering to existing treatments more rigorously (see introduction), focusing treatments on individual patient characteristics, and developing novel treatment options. First, considerations regarding developing novel treatments for depression will be discussed, followed by approaches to personalize treatment of depression. Last, some general factors of the treatment of depression will be discussed, by highlighting elements that might have played a role in the placebo effect of the tPEMF trial.

2.1. Neurobiological effects to guide treatment

In developing novel treatments for MDD, it is especially important for stimulation-based treatments to employ biological markers besides clinical markers to study efficacy (Brunoni and Fregni 2011). Indeed, a neurobiological approach to study treatments of MDD could lead to treatments tailored to the individuals' biotypes (Drysdale et al. 2017). A particular example of this is a hallmark study that has identified neurophysiological biotypes based on connectivity analysis, which were used to predict responsiveness to rTMS (Drysdale et al. 2017). In this study, four homogeneous patterns of abnormal functional connectivity have been found in 220 patients with depression compared to healthy controls (n=378). This has led to a common neuroanatomical core underlying all four biotypes. Furthermore, each of these four has been associated with a specific abnormal functional connectivity pattern. Subsequently, high-frequency rTMS of the dorsomedial prefrontal cortex in 124 participants has shown that treatment response varied according to subtype membership and that subtype membership predicted treatment response better than clinical symptoms alone (Drysdale et al. 2017). This study has shown that functional connectivity could be a successful biomarker to guide treatment, although replication studies are needed to further develop this strategy. It also serves as an example to study novel treatments for psychiatric disorders not only in light of their clinical effects, but also with regard to their neurobiological effects. Indeed, psychiatric disorders are increasingly conceptualized as brain disorders, especially disorders of brain circuitry, which should be studied using the tools of clinical neuroscience against the framework of specific research domain criteria (RDoCs) (Insel et al. 2010).

Studying the neurobiological effects of stimulation-based treatments for MDD seems particularly important in the case of global neuromodulation devices, in which

mechanistic effects are present but a general antidepressive effect is still uncertain (van Belkum et al. 2016). Studying these effects could guide treatments tailored to individuals' biotypes, similar to how tDCS could be particularly effective for 'cognitive disturbance' in MDD (D'Urso et al. 2017). Two examples will be discussed here, based on work presented in this thesis and some recent studies, of how global stimulation could have an effect on specific characteristics of MDD and thus contribute to the treatment for some MDD patients.

2.1.1. Using deficiencies of reward/motivational systems to guide treatment

There is evidence that tPEMF-like stimulation has an effect on the growth of especially dopaminergic neuronal cells (van Belkum et al. 2016) (see chapter 3), which have an important role in reward processing (Dunlop and Nemeroff 2007). Patients with MDD have a deficiency of the reward/motivational systems in the brain (Dunlop and Nemeroff 2007) and treatment of MDD has an effect on the reward system. A recent study has shown a normalization of brain activation in the striatum during reward processing, after successful pharmacological treatment (Stoy et al. 2012). In this study unmedicated MDD patients who were subsequently treated for six weeks with escitalopram were compared to healthy controls. A MID-task was used to study neural responses. This study has found that a pretreatment hypo-activity in the ventral striatum diminished after successful treatment with escitalopram (Stoy et al. 2012). Another study has found an increase of activation in the dorsal striatum after a psychotherapeutic intervention (Dichter et al. 2009). Thus, multiple treatment modalities of depression have shown to have an effect on reward processing in depressed patients.

Neuromodulation has shown to have an effect on reward processing after stimulation healthy participants. For example, in one study healthy participants were stimulated using a single TMS pulse to either inferior parietal lobe (IPL) or supplemental motor area (SMA) whilst participants performed the MID-task. These TMS pulses produced significant reaction time slowing of participants during the task, which was greater when targeting the IPL compared to the SMA, suggesting that targeting these regions could modulate reward circuit deficits (Stanford et al. 2013). Another study has investigated the effect of rTMS of the left and right DLPFC on prefrontal dopamine using Positron-Emission Tomography (PET) (Cho et al. 2012). It has shown extrastriatal dopamine modulation after left DLPFC rTMS-stimulation in healthy subjects, in particular a specific reduction in binding potential in the ipsilateral subgenual anterior cingulate cortex (ACC), pregenual ACC and medial orbitofrontal gyrus (Cho et al. 2012).

As presented in chapter 6, tPEMF decreases activation during reward processing in the left inferior frontal gyrus (IFG). Although speculative, it provides tentative indications of a possible effect of tPEMF on specific symptoms related to reward processing, for example anhedonia, more than on depressive symptoms in general. If this holds true, tPEMF could be useful as a treatment in an 'anhedonia type' of depression. So far, clinical and behavioral data have not yet supported this claim.

2.1.2. Using brain-derived neurotrophic factor (BDNF) to monitor treatment

Evidence suggests that global neuromodulation has a positive effect on brain-derived neurotrophic factor (BDNF). BDNF is a growth factor involved in the survival and growth of neurons. A recent study has shown an increase of BDNF after LFMS (Xiao et al. 2018). In this study, patients with MDD had been stimulated with LFMS, either using rhythmic alpha stimulation (RAS; using a stimulation frequency of 8 ~ 12 Hz) or rhythmic delta stimulation (RDS; using a stimulation frequency of 0.5 Hz). The latter stimulation-frequency is similar to the frequency used by Rohan et al. (Fava et al. 2018; Rohan et al. 2004; Rohan et al. 2013). A total of 22 patients were randomized to receive RAS (n=11) or RDS (n=11). Participant's response- and remission-rates were lower in the RAS condition, although this difference lacked statistical significance. BDNF-levels had increased significantly over time after treatment with RAS and RDS, although it fluctuated more in the RDS condition. This study has thus suggested that LFMS was a successful treatment of MDD, reflected by both clinical and neurobiological markers (Xiao et al. 2018).

Levels of BDNF in blood have found to be decreased in depressed patients compared to healthy controls (Brunoni, Lopes, Fregni 2008; Molendijk et al. 2014; Player et al. 2013; Sen, Duman, Sanacora 2008) to increase following antidepressant drug treatment (Brunoni, Lopes, Fregni 2008; Molendijk et al. 2014). A meta-analysis of longitudinal studies in MDD has recently shown that BDNF levels increase particular in remitters and responders to treatment, but remain unchanged in non-responders, thus showing that BDNF levels may be a useful biomarker for prediction of treatment outcome of MDD (Polyakova et al. 2015). If indeed BDNF levels are a marker of TRD, one could adjust treatment if the increase of BDNF levels during treatment fall below a certain mark. Global neuromodulation devices could then be employed to increase the levels of BDNF, and thus deliver an antidepressive effect (Xiao et al. 2018). However, it is unclear if monitoring BDNF in blood during treatment has added value, as quantifying TRD can be done less invasively as well, for example by employing the MSM (Fekadu, Wooderson et al. 2009a; Fekadu, Wooderson et al. 2009b; van Belkum et al. 2016). So, monitoring BDNF to guide treatment might not be the most suitable approach.

2.2. Personalizing MDD

In this thesis, some emphasis has been put on employing biological markers besides clinical markers to study efficacy of tPEMF as a potentially novel treatment for MDD. However, MDD is a heterogeneous disorder in terms of individual symptomatology, other clinical characteristics, and underlying pathophysiology (Fried 2015; Hasler 2010; Kendler, Gardner, Prescott 1999; Lux and Kendler 2010), suggesting that a 'one size fits all' approach of treating MDD may not be the optimal approach. Indeed, it has been suggested that future research of novel treatments for depression should focus on specific symptoms or symptom clusters (e.g. depressed mood) and not on total scores of a heterogeneous set of symptoms (Fried 2015; Fried et al. 2017). Besides a symptom-tailored approach, also another option has been put forward.

One such approach is through clinical staging, in which disease characteristics are identified "that are clinically detectable, reflect severity in terms of risk of death or residual impairment, and possess clinical significance for prognosis and choice of therapeutic modality" (Gonnella, Hornbrook, Louis 1984). Using a clinical staging model, treatment of MDD can be adjusted based upon chances of success related to specific stages of depression. To do so, valid staging models are needed. Staging models could fit multiple purposes, for example staging illness progression (Hetrick et al. 2008), predicting its course, or quantifying treatment resistance (Ruhe et al. 2012). A staging method based on illness progression, dividing the course of MDD based on severity, duration and number of episodes, has shown to have construct validity across stages and predictive validity for the course of depression for preclinical stages, with no clear predictive validity for the clinical stages (Verduijn et al. 2015). Thus some preliminary evidence suggests that staging disease progression is feasible although models may still need to be improved (Verduijn et al. 2015).

For the staging of treatment resistance different models have been proposed (Ruhe et al. 2012). Of these, the Maudsley Staging Method (MSM) seems most promising, as it has been most extensively empirically tested (Ruhe et al. 2012). There is also a modification of the MSM (the Dutch Measure for quantification of TRD (DM-TRD)), which includes profilers like functional impairment, comorbid anxiety and personality disorders, and psychosocial stressors (Peeters et al. 2016). It has been shown that the DM-TRD is able to predict severity of future depressive symptomatology and remission equally well compared to the MSM and that including some profilers could have added value (Peeters et al. 2016). Nevertheless, more research on the DM-TRD is needed. As presented in chapter 3, the MSM could already be of help in further advancing treatment of MDD by identification of patients who are at risk of developing TRD and by determining the severity of TRD. This makes it possible to

investigate if subjects with different levels of therapy resistance will respond differently to specific treatments (van Belkum et al. 2018). However, further research is necessary to determine if this is a fruitful approach.

Focusing treatment on less heterogeneous clusters of clinical symptoms is another approach to focus treatment of MDD. Indeed, targeting pharmacological or psychotherapeutic treatments at particular clinical symptom clusters of depression seems to have some benefit over treating MDD as a whole. A post-hoc analysis of 18 previous RCTs of selective serotonin reuptake Inhibitors (SSRIs) has shown that the effect size of these antidepressants on the HAMD-17 item 'Depressed mood' was higher compared the effect size of the sum-score of the HAMD-17 (Hieronymus et al. 2016), suggesting that antidepressants like SSRIs have a bigger effect on specific symptom domains (in particular depressed mood) than on MDD as a whole. Likewise, based on two multisite clinical trials of pharmacological treatment of depression (STAR*D (see introduction) and CO-MED (a single blind RCT comparing the efficacy of medication combinations)), it has been shown that antidepressants have a higher effect size for core emotional and sleep symptoms compared to atypical symptoms (Chekroud et al. 2017). Furthermore, a network analysis of depressive symptoms has shown that the combination of psychotherapy and pharmacotherapy has an antidepressive effect on some particular depressive symptoms in this network (e.g. feeling entrapped and emotional lability) and this combination outperforms psychotherapy on its own (Bekhuis et al. 2018). However, a recent study identifying four distinctive factors of symptoms based on various scales of depression severity (the HAMD-17, the Beck Depression Inventory (BDI), and the Montgomery Åsberg Depression Rating Scale (MADRS)) has questioned the durability of the treatment effect of different sorts of treatment (pharmacological and psychotherapeutic). This study has shown that depression severity as measured with the factors 'Despair' and 'Mood and Interest' decreased quicker in response to antidepressants (escitalopram and duloxetine) compared to Cognitive Behavioural Therapy (CBT), although after three months no difference remained between receiving antidepressants and CBT (Dunlop et al. 2018).

The effects on symptom clusters of novel treatment approaches like various neuromodulation techniques for depression have also been explored. In order to get a broader grasp of the effects of neuromodulation on a specific cluster, the effects of neuromodulation on FSS were studied in chapter 2. FSS are associated and often comorbid with MDD (Lieb, Meinlschmidt, Araya 2007), thus possibly lending itself for a broader investigation of this specific effects of neuromodulation. However, only a small number of studies of low quality have investigated the effects of neuromodulation in FSS (chapter 2), thus limiting the conclusions that could be drawn. Further, there is

limited evidence for an effect of neuromodulation specifically on somatic symptoms in depression. TDCS seems to have a general effect on "Cognitive disturbance" and "Retardation" symptoms of depression, while it has only a small effect on "Anxiety/ Somatic Symptoms" (D'Urso et al. 2017). Accordingly, rTMS has an effect on specific cognitive-affective symptoms in depression, but has no effect on somatic symptoms (Rostami et al. 2017).

Taken together, the effect of treatment of MDD can be studied based on clustering of clinical symptoms. As shown, antidepressant medication or psychotherapy aimed at particular symptom clusters have benefit over treating MDD as a whole. In treatment with neuromodulation, there may be some therapeutic benefit in clustering of MDD symptoms.

2.3. Placebo effects

Pharmacological treatment of MDD is prone to placebo effects (Furukawa et al. 2016). The same is true for antidepressive treatment using rTMS (Razza et al. 2018). In the first study of tPEMF in depression, placebo effects concerned 50% of the total effects: participants improved 5 points on the HAMD-17 in the sham and 10 points in the active group (Martiny, Lunde, Bech 2010). In our tPEMF trial this was 100%: participants in both groups improved five points on the HAMD-17 after five weeks (chapter 5). A mean overall improvement of five points on the HAMD-17 is of (minimal) clinical significance (Furukawa et al. 2007). This improvement in the tPEMF trial was not likely a result of natural course, as median duration of illness was 23 (active group) and 33 (sham group) months (chapter 5), suggesting a likely placebo effect. Similar to discussions in psychotherapy (Mulder, Murray, Rucklidge 2017), non-specific factors will be discussed here that might have contributed to this placebo effect.

2.3.1. Activation

Activation of participants, especially Behavioral Activation (BA), might have contributed to the placebo effect in the tPEMF trial. In the treatment of MDD, general interventions include activation and BA as part of a Cognitive Behavioral Therapy (National Institute for Health and Clinical Excellence 2009; Spijker et al. 2013). In BA patients with depression are encouraged to expose themselves to environmental positive reinforcements, an effective technique to treat depression (Ekers et al. 2014). There is some anecdotal evidence that possibly suggests that participants of the tPEMF trial improved as a result of BA. For example, one female participant told the members of the research team that due to the strict schedule of the treatment sessions (sessions took place every weekday for 30 minutes during office-hours, on

the same time every day, with minimal deviations), she felt motivated to do her daily chores before visiting the hospital, instead of procrastinating as she was used to. As a result, after a couple of weeks she found time to enjoy here old hobbies again, as all her daily chores were finished by the time she went home after a session. Indeed, her depressive symptoms improved, hinting at a possible role for BA as one of the factors of the placebo effect in the trial.

2.3.2. Treatment expectations

Placebo effects can be partly explained by the expectations participants have of a particular experimental treatment. In a recent study on the effects of open-label citalopram versus citalopram administrated in an RCT with placebo condition, a difference in efficacy of six points on the HAMD-17 scale was found in favor of open label treatment. The difference was partly mediated by treatment expectancy (Rutherford et al. 2017), making treatment expectancy an important driver of the placebo effect (Rutherford et al. 2017; Wager et al. 2004).

In the tPEMF trial, participants' expectations were scored prior to the start of the treatment. Mean treatment expectancy was six on a scale of one to ten (one meaning low expectations and ten meaning high expectations), with no clear differences between both treatment groups. There was also no association between participants' expectations prior to treatment and treatment outcome (unpublished). Interestingly, a numerical difference in the number of participants that guessed their condition as 'active' between participants from the active condition and the sham condition was found (chapter 5). In the active condition, 48% guessed their condition as 'active'; in the sham condition 64% guessed their treatment condition as 'active'. The difference in expectancy between the two treatment conditions was not statistically significant and had no effect on outcome (chapter 5). Thus, the degree of treatment expectancy could be an important driver of the placebo effect. However, we found no clear indication of the effects of treatment expectancy in the tPEMF-trial.

2.3.3. Common factors

When delivering pharmacological treatment of MDD, it is not only important which particular agent is delivered (active or passive pharmacological agent), but it is also important by whom it is delivered (McKay, Imel, Wampold 2006). The same seems true for psychotherapeutic treatment of MDD (Mulder, Murray, Rucklidge 2017). Beneficial factors shared across psychotherapies are referred to as 'common factors' (e.g., positive working alliance and expectation), as opposed to specific treatment factors (e.g., cognitive restructuring in depression or exposure in anxiety disorders) (Mulder, Murray, Rucklidge 2017; Wampold 2015). Various common factors can be

responsible for treatment success: alliance, empathy, expectations, cultural adaptation of evidence-based treatments, and therapist effects (Wampold 2015). Some of these common factors might have also contributed to the placebo effects of the tPEMF trial. These will be discussed here.

First, the setting of the tPEMF trial will be discussed, as this illustrates which beneficial processes might have emerged during the daily stimulation of individual participants. The presence of a team member was required during every treatment session. This member was responsible for starting and stopping the device and accompanied the participants during the sessions. Members of the research team of the tPEMF trial were students, not trained psychotherapists, and the trial did not have any psychotherapeutic objectives. Nevertheless, they were eager to help in a scientific study and eager to engage with 'real patients', instead of doing training sessions with actors, as was common during their studies. Members were polite and forthcoming, with a genuine interest in the participant. There was much consistency in the presence of the members of the research team; a participant met two or three members at most. Thus, given the daily contact between a specific member and a participant, a particular relationship could have emerged that can best be described in the psychotherapeutic discourse.

Out of this particular relationship some factors can be distilled that could have contributed to the antidepressive effect. Here, the focus will be on the factors 'empathy', 'a real relationship', and 'alliance'. Most members of the research team were genuinely interested in the participant and acted empathetically to participants. Empathy seems critical in forming what is called 'a real relationship' (Wampold 2015), which can be defined as "the personal relationship between therapist and patient marked by the extent to which each is genuine with the other and perceives/experiences the other in ways that befit the other" (Gelso 2014). Probably a 'therapeutic relationship', characterized by trust, warmth, understanding, acceptance, kindness, and human wisdom (Lambert 2005), emerged between the member and the participant. Finally, the possibility cannot be discarded that what is called 'an alliance' was formed, consisting of a bond, agreement about the goals of the treatment, and the agreement about the tasks of the treatment (Wampold 2015).

Some of the common factors discussed above are identified to be quite therapeutic in psychotherapy. 'Alliance' early in a therapy correlated strongly with final outcome of the therapy (Cohen's d of 0.57; n=200 studies) (Horvath et al. 2011; Wampold 2015). A relatively large effect (Cohen's d 0.63; n=59 studies) has been attributed to the effect of empathy (Elliott et al. 2011). Furthermore, there is evidence that forming a 'real relationship' is related to a positive outcome in psychotherapy (Wampold 2015). The

common factor ‘expectation’ has been thoroughly discussed (see above) and seems to have a relatively small effect (Cohen’s d=0.24, n=46 studies) (Wampold 2015). Thus, although the tPEMF trial did not have any psychotherapeutic objectives, the possibility cannot be excluded that factors as alliance, empathy, the forming of a ‘real relationship’, and expectations contributed to the overall improvement of patients who participated in the trial.

3. Methodological considerations

In this part, methodological considerations regarding the different approaches to global neuromodulation will be discussed. Each study presented in this thesis also had some inherent strengths and was liable to particular limitations. These were addressed in each individual chapter.

As became apparent, three different approaches to global neuromodulation exist, using Low Field Magnetic Stimulation (LFMS), synchronized TMS (sTMS), and transcranial Pulsed Electromagnetic Fields (tPEMF). The antidepressive effects of LFMS were promising in the first pilot studies (Rohan et al. 2004; Rohan et al. 2013), but were not replicated in a larger study by the same research group (Fava et al. 2018). The same holds true for sTMS (Jin and Phillips 2014; Leuchter et al. 2015). The antidepressive effect of tPEMF was also quite promising initially (Martiny, Lunde, Bech 2010). However, our independent replication using a similar study design and power calculation was not able to replicate the antidepressive effect of tPEMF (chapter 5). It should therefore be concluded that, at this point, the antidepressive effects of global neuromodulation devices have been inconsistent. One explanation for this could be the well-known phenomenon of "regression towards the mean". This statistical phenomenon states that if a variable is unusually small or large the first time it is measured, it will be closer to the mean the next time it is measured (Barnett, van der Pols, Dobson 2005). This accounts for differences on subject, but also on group level. It could partially explain why there is a discrepancy between the first and second study of each global neuromodulation technique (LFMS, sTMS, and tPEMF). However, in the case of tPEMF, in our trial no antidepressive effect was found at all, which cannot be adequately explained by this phenomenon of regression towards the mean. Thus more research is needed with bigger sample sizes and possibly using meta-analyses to fully investigate the antidepressive effects of global neuromodulation devices.

Study design characteristics might be another explanation of the mixed results of the antidepressive effects of global neuromodulation devices. For example, small sample sizes may lead to underpowered studies and insufficient blinding might bias results. In chapter 2, a tool to structurally assess the risk of bias of clinical studies was used, to get an indication of the quality of the studies. In this particular chapter we showed that this risk was mostly 'unclear' for the analyzed studies (chapter 2). Studies investigating the effects of neuromodulation devices moreover are prone to particular design issues (Brunoni and Fregni 2011). As a solution to this problem the following has been recommended: (i) estimating the sample size a priori; (ii) measuring the degree of refractoriness of the subjects; (iii) specifying the primary hypothesis and

statistical tests; (iv) controlling predictor variables through stratification randomization methods or using strict eligibility criteria; (v) adjusting the study design to the target population; (vi) using adaptive designs (e.g. by testing either different stimulation 'doses' or stimulation sites in the scalp, dropping weaker treatments during the study); and (vii) exploring non-invasive brain stimulation efficacy employing biological markers (Brunoni and Fregni 2011). Interestingly, Rohan et al. and Fava et al. adhered to one of these recommendations (specifying the primary hypothesis and statistical tests) (Fava et al. 2018; Rohan et al. 2013), Leuchter et al. adhered to two (numbers iii and iv) (Leuchter et al. 2015), and Martiny et al. adhered to four (numbers i, ii, iii, and iv) (Martiny, Lunde, Bech 2010). In the tPEMF trial, we adhered to five of these seven recommendations (numbers i, ii, iii, iv, and vii) (chapter 5). This would suggest that most studies investigating the antidepressive effects of global neuromodulation devices could have been potentially biased, limiting the validity of findings of each individual study.

A particular strength of our tPEMF trial was indeed that it adhered to the majority of the recommendations of Brunoni et al. (Brunoni and Fregni 2011), also including different biological markers to study efficacy (recommendation vii). Although the absence of an antidepressive effect of tPEMF was found (chapter 5), the inclusion of biological markers to explore efficacy of tPEMF led to the nuance that brain activation during reward processing differed as a result of tPEMF stimulation, thus suggesting that there were biological effects and that changes on the neural level might be more sensitive to change due to tPEMF stimulation (chapter 6).

4. Future perspectives

In general, non-invasive neuromodulation has an important advantage over other biological treatments for depression, for example pharmacological treatment: it specifically and directly targets the cortex of the brain, which is relevant in MDD patients. As a result, local adverse events are sparse and systemic adverse events are lacking (Rossi et al. 2009). Nevertheless, more research is needed before neuromodulation can be applied in clinical practice. This is especially true, as is apparent from this thesis, for global neuromodulation devices. Clinical antidepressive effects of these devices are not yet substantial, but there is some evidence for a neurobiological effect. However, the neurobiological efficacy cannot yet be aligned to an underlying pathology of MDD, as this is still a heterogeneous disorder. Thus, there is still an important gap between the mechanistic evidence of tPEMF and the clinical effects.

Resting state fMRI data, which were collected in the tPEMF trial as part of the total procedure, could be used to replicate the biotypes of Drysdale et al. (Drysdale et al. 2017) to see if certain biotypes of depression could predict treatment outcome of tPEMF. However, sample size would be problematic given the current sample (n=55) of the tPEMF trial, possibly impeding such investigation. Thus, a new and larger (multicenter) trial investigating the effects of tPEMF on different symptom clusters of MDD and their neurobiological underpinnings can be considered, in line with studies on rTMS and apathy (Padala et al. 2018; Prikryl et al. 2013).

The antidepressive effects of tPEMF are as yet unsubstantial according to our findings. This suggests that additional RCTs investigating the effects of tPEMF are necessary, probably entailing a phase III study, confirmatory in nature and thus testing the effectiveness in a larger number of patients. Pending such a study, tPEMF should not be used in daily practice. However, one could also consider adjusting the stimulation method of tPEMF. For example, a recent study has shown that some type of global stimulation can be used to focally stimulate neurons without recruiting overlying cortical neurons in the mouse brain. This was a result of temporal interference (Grossman et al. 2017). When waves, for example electromagnetic waves, oscillate at slightly different frequencies, a pattern of interference is created where these waves overlap, thus forming a resultant wave that has greater, lower, or similar amplitude. In temporal interference, an envelope wave having its own frequency can be made. Due to temporal interference it is possible to stimulate the (mouse) brain using electromagnetic fields of different frequencies that are unable to stimulate the brain individually (Grossman et al. 2017). It is also possible to stimulate deep neuronal structures that cannot otherwise be stimulated directly due to non-invasive brain

stimulation (Grossman et al. 2017). Thus, by employing this concept of interference, global stimulation can result in a distinct focal stimulation.

There is substantial difference between the mouse and human brain, but physically there are no obstacles to apply the same technique in the human brain (Grossman et al. 2017). Given the flexibility of adjusting the frequencies of global neuromodulation devices (Xiao et al. 2018), one might try to develop similar interference patterns, in order to stimulate globally but act locally. Then, one can treat the brain areas related to the disorder.

5. Concluding remarks

In this thesis, optimizing treatment of MDD was investigated by exploring the effects of a particular novel neuromodulation device for MDD: tPEMF. In the discussion of this thesis the relevance was emphasized of employing biological markers besides clinical markers to study efficacy and underlying mechanisms of novel neuromodulation treatments for MDD. Indeed, more research is clearly needed for a comprehensive evaluation of neuromodulation's potential. Depression is a heterogeneous concept and global neuromodulation devices show inconsistent results. On the other hand, further exploration of different stimulation modalities and parameters may hold promise for a clinically relevant contribution. The prospects of advances in psychiatric research raise hopes: ultimately, electromagnetic energy might bring light in the darkness of depression.