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Neuromodulation and Depression

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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 (MAOi's) (Spijker and Nolen 2010). In general, treatment of depression has moderate efficacy (Cipriani et al. 2009; Cipriani 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-SR_{16})), and 37% remission (≤5 on the QIDS-SR_{16}) 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

(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

2007). 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

2006). 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 of 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

Chapter 2

Non-invasive neuromodulation as a new therapeutic strategy in the management of functional somatic symptoms

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Submitted.

Objective

A large proportion of medical symptoms remain unexplained and medical management of these symptoms is often inadequate. These unexplained symptoms include functional neurological motor symptoms, fibromyalgia and complex regional pain syndrome. Due to the absence of an aetiological framework there are currently no curing and disorder-specific treatments. Here we review the evidence on an upcoming therapeutic option, non-invasive neuromodulation, as a method of treatment for functional somatic symptoms.

Methods

A systematic search of the literature was performed: two independent readers screened the abstracts identified with specific search strings in the four databases. The resulting hits were screened on the inclusion criteria and after full text reading the Risk of Bias was applied to all included studies.

Results

Neuromodulation as a treatment option for functional somatic symptoms is under investigation in multiple medical disciplines. While in some symptom categories such as fibromyalgia and paresis placebo-controlled randomized controlled trials are available, case-studies or small groups are reported in other such as functional neurological symptom disorder. First results are promising but further research is warranted as is standardisation of treatment protocols.

Conclusions

The literature indicates that various forms of neuromodulation yield positive therapeutic results with very infrequent side effects. The involvement and relevance of a placebo effect is discussed.

1. Introduction

Currently there is no established etiological framework for Functional Somatic Symptoms (FSS). As a consequence, these symptoms constitute a significant clinical challenge in terms of therapeutic management. Non-invasive neuromodulation inspire new hope of finding an effective treatment for FSS in addition to behavioral therapies. The current review aims to provide an overview of the first studies on neuromodulation methods in FSS.

FSS concern a group of symptoms that affect motor or sensory functioning and cannot be adequately explained by any known physical pathology (DSM-5) (American Psychiatric Association 2013). This classification refers to a heterogeneous group (Barsky and Borus 1999; Fink and Schroder 2010) and includes sensory related phenomena such as chronic pain and tinnitus, motor related phenomena such as conversion paresis and more elaborate syndromes such as irritable bowel syndrome, fibromyalgia and complex regional pain syndrome type I (CRPS-1). Functional symptoms have to be distinguished from intentionally simulated symptoms in which the patient is in search of financial gain (malingering) or psychological support (factitious disorder). The prevalence of functional symptoms is high and reports vary between 22 – 50% of patients that present FSS in primary care, depending on the methodology used (e.g. inclusion criteria) and the clinical setting that reports the numbers (Escobar et al. 1998; Mergl et al. 2007; Nimnuan, Hotopf, Wessely 2001;

Olde Hartman et al. 2009; Roca et al. 2009).

Previously FSS were labeled as 'non-organic', 'psychogenic' or 'hysteric' referring to the assumed role of psychological factors in the etiology of these symptoms (Lipowski 1988) Whereas in former editions of the DSM the presence of a psychological conflict was mandatory for the diagnosis of FSS, the current diagnostic criteria no longer require this. This change in terminology is important as it reflects a shift in theory and clinical criteria for the diagnosis of FSS from the DSM-IV-TR to the DSM-5 (American Psychiatric Association 2013). Cognitive theories on FSS stress that symptoms are not intentionally produced but are the result of wrongfully activating cognitive schemata while inhibiting the relevant ones (Brown 2004). The physical symptom that is the result of this process is perceived by the patient but the underlying erroneous executive management of schemata is not within the patient's control.

In search of the etiological mechanisms of FSS neuroimaging methods increase understanding of brain mechanisms involved. Several studies report abnormal functional brain activity in patients with FSS compared to patients with a known pathology or healthy controls (Picarelli et al. 2010; van Beilen et al. 2011). The use of neuromodulation techniques that have the potential to bring about changes in cortical excitability and plasticity (Bilek et al. 2013; Hsieh et al. 2015) could be a promising treatment by influencing brain activity (Pollak et al. 2014). A new method of treatment is welcome, since current clinical therapeutic options are often insufficient. In addition, treatments commonly used such as Cognitive Behavioral Therapy (Kroenke 2007), physical therapy (Moene et al. 2002), and hypnosis (Zonneveld et al. 2012) require motivation for a behavioral approach of somatic symptoms. It can be difficult to motivate patients for a behavioral intervention when underlying mechanisms of the symptoms remain unexplained.

1.1. Cerebral involvement in Functional Somatic Symptoms

Neuromodulation as a treatment in FSS disorders implicates the existence of abnormal cerebral functioning in patients. Indeed, for a wide range of functional symptoms neuroimaging research has confirmed abnormal brain function (Aybek et al. 2014; Cagnie et al. 2014; Cojan et al. 2009; de Lange, Roelofs, Toni 2007; Di Pietro et al. 2013; Halligan et al. 2000; Jorge and Amaro 2012; Labate et al. 2012; Linnman, Becerra, Borsook 2013; Marshall et al. 1997; Nicholson et al. 2014; Pollak et al. 2014; Voon et al. 2010; Voon et al. 2011). This does not imply that abnormal brain function is the cause of the symptoms; it might just as well be the result of them. The mechanisms of the persistence of FSS are circular, and abnormal brain activation is taking part in that circle. Typically multi-causality is assumed and

the symptoms originate, perpetuate and sometimes vanish and point at a complex interaction between somatic, behavioral, medical, societal and cultural factors.

The current review aims to provide an overview of the first literature currently available on neuromodulation methods in a variety of FSS. FSS include a heterogeneous group of symptoms and hence differences in related brain function is assumed. In this review the focus is on those symptoms in which some evidence is reported for abnormal neuroimaging results or the symptoms are of a neurological behavioral nature. These syndromes include sensory related phenomena such as fibromyalgia and CRPS-1 and motor related phenomena such as conversion paresis. Before providing an overview of the available literature on non-invasive neuromodulation in FSS, we briefly describe the current neuromodulation techniques.

1.2. Subtypes of non-invasive neuromodulation

1.2.1. (Repetitive) Transcranial Magnetic Stimulation (TMS and rTMS)

Transcranial Magnetic Stimulation is a non-invasive technique used to stimulate nerve cells in the superficial areas of the brain. It is based on the principle of electromagnetic induction. A TMS pulse is produced by generating a large, rapidly changing electrical current that is passed through a coil. This pulse generates a fluctuating magnetic field, which induces a small current in the brain. For example, the hand muscles of a patient with functional paresis can be activated with the use of TMS. In repetitive Transcranial Magnetic Stimulation (rTMS) 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. A pulse delivered at a frequency below 1 Hz inhibits cortical excitability and above 5 Hz increases the cortical excitability (Fitzgerald, Fountain, Daskalakis 2006).

1.2.2. Pulsed electromagnetic fields (PEMF)

PEMF is an intervention in which physical principles similar to TMS are applied. However, in PEMF the field strength is much weaker (< 10 mT). The stimulation fits the physiological signals better than the pulses used by TMS. The frequency content of the signals is generally in the extremely low frequency band (ELF - 3 Hz to 3 kHz) and even 0.1 Hz. PEMF can effectively induce acute (minutes) and sustained (days) changes in cell cultures (Atalay et al. 2013), whole animals (Elmusharaf et al. 2007; Martin, Koren, Persinger 2004), and humans (Kortekaas et al. 2013; Persinger, Hoang, Baker-Price 2009).

1.2.3. Transcranial Direct Current Stimulation (tDCS)

In tDCS a non-invasive direct current is applied to the head. In the simplest form, two sponge electrodes are attached to the head and a small (1-2 mA) electrical current is applied. The positive or anodal electrode is thought to stimulate the underlying brain area while the negative or cathodal electrode is thought to have an inhibitory effect (Stagg and Nitsche 2011). tDCS can modulate neurotransmitter release, leading to changed neuronal activity, cerebral blood flow, oscillatory brain activity and functional connectivity in the brain (Hansen 2012).

2. Methods

2.1. Search protocol

The database search was updated last in April 2017. Databases searched: PubMed, PsycINFO, Cochrane and Embase.

2.2. Search terms

For each category of disorders, symptoms or syndromes a specific search string was used, see supplemental digital content for details.

2.3. Inclusion criteria studies

All abstracts were screened and selected by two independent observers (EK; SvB). After the initial selection based on the abstract, the full text of the articles was screened and the Risk of Bias was applied to all included articles to get an indication of the quality of the studies included. Of the papers identified by the search string further selection was based on the following criteria:

- General information: year, first author, disorder, N.
- Methodology: type of neuromodulation, location of stimulation, duration of stimulation, intensity of stimulation, RCT, placebo device, type of control group/ treatment.
- Clinical outcome measures: symptom reduction, other outcome measurements, and additional effects neuromodulation.

2.4. Functional symptom categories

The focus in this review is on symptoms that generally warrant a referral to the neurologist. Subtypes of Functional Somatic Syndrome Disorders and other MU Symptoms included are:

1. Sensory and specifically pain related:

- Complex Regional Pain Syndrome (CRPS I)
- Fibromyalgia

2. Movement related:

- Paresis (reduced movement)
- Movement disorders (excessive movement, such as tremor)

3. Results

For an overview of the quality of the randomized controlled trials (RCTs), see Figures 2.1 and 2.2. The risk of bias shows that most of the information reported in this review comes from studies with a low or unclear risk of bias. See table 2.1 for an overview of the methodology used and results presented in the included papers.

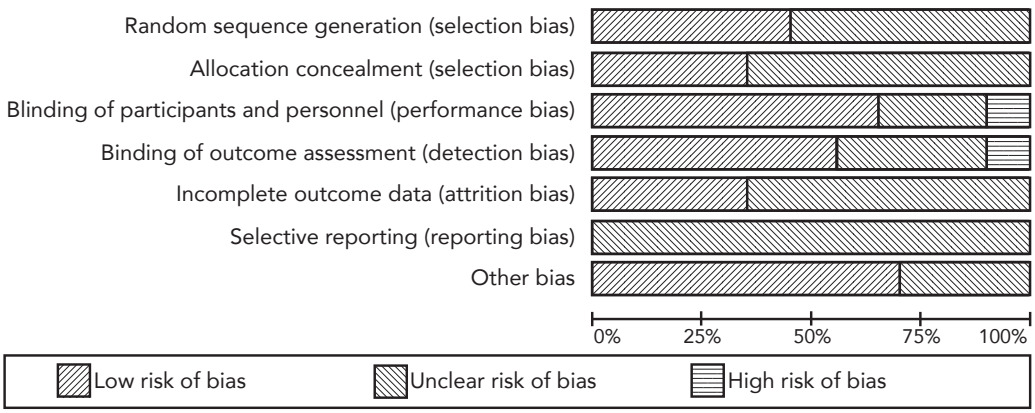

Figure 2.1: Risk of Bias of all investigated RCTs.

3.1. Complex Regional Pain Syndrome type I

CRPS-I is a chronic condition characterized by severe pain, sensory abnormalities (e.g. hyperalgesia and allodynia), vasomotor instability (e.g. temperature and skin colour changes), sudomotor abnormalities (e.g. oedema or sweating), motor changes (decreased range of motion or motor dysfunction) and trophic changes (e.g. hair, nail and skin) (Harden et al. 2007). Symptoms frequently emerge following traumatic injury, or a clinical condition such as a heart attack, stroke, cancer, infection, spinal cord injury, arthritis, or polymyalgia. Symptoms can arise in the absence of a triggering injury or illness as well. A striking feature is that the symptoms are disproportional to the severity of the trauma. The International Association for the Study of Pain distinguishes between two types of CRPS (1986). In CRPS-I no evident nerve injury is present, whereas in CRPS-II the cause can be ascribed to a definable major nerve injury, like a lesion or a tumor.

The pathophysiology of CRPS-I is yet to be defined, but appears to be associated with dysregulation of the central nervous system and autonomic nervous system . The available literature describes the various potential mechanisms for CRPS symptoms such as trauma-related cytokine release, exaggerated neurogenic inflammation, sympathetically maintained pain and cortical reorganization (Birklein 2005).

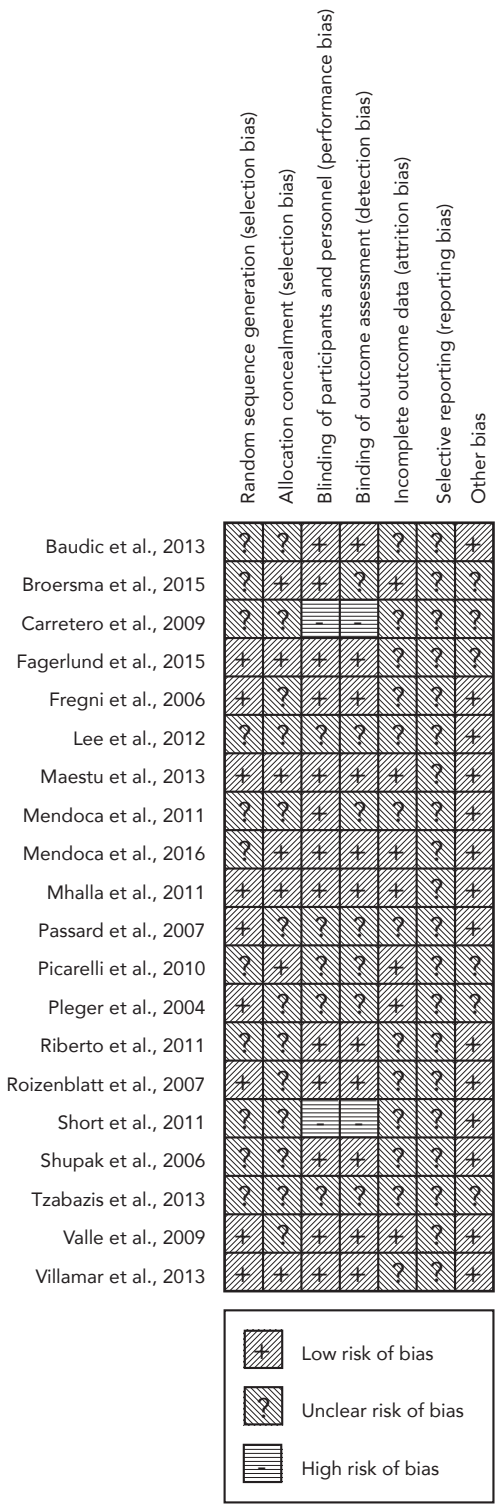

Figure 2.2: Risk of Bias per RCT.

3.1.1. Neuroimaging

Studies that focus on brain imaging indicate that patients with CRPS-I exhibit alterations in the parietal lobes, mid-insula, mid-cingulate gyrus, superior medial frontal gyrus and the primary somatosensory cortex (S1) (Linnman, Becerra, Borsook 2013). A systematic review of the latter area revealed a smaller S1 representation of the affected hand in patients compared to controls (Di Pietro et al. 2013). There is evidence that sensory and motor hyper excitability correspond to regions in the brain involved with the central nervous system of patients with well-localized CRPS-I (Eisenberg et al. 2005). The presence of abnormal brain activity may suggest that cortically directed treatments could have a positive effect on pain perception in CRPS-I patients.

3.1.2. Neuromodulation

Neuromodulation may be effective in altering pain perception in CRPS-I according to two RCTs applying neuromodulation to the motor cortex. A randomized controlled trial (RCT) on single-session rTMS as an add-on therapy to regular treatment applied to the motor cortex found a decrease in pain intensity in 7 out of 10 patients with CRPS-I whereas placebo treatment did not (Pleger et al. 2004). Another RCT with repetitive sessions of high-frequency TMS stimulation of the motor cortex found a decrease in pain intensity in 51% of 23 patients with CRPS-I, whereas pain intensity decreased in 25% of patients in the placebo condition (Picarelli et al. 2010). At the 10th session

58% (n=7) of patients had achieved a reduction in VAS-score of more than 40% whereas only 25% (n=2) in the sham group showed a similar improvement. Adverse effects reported such as headache, neck pain and dizziness were also reported in the sham groups. The number of studies is however very limited, and both the placebo effect and the treatment effect were considerable.

3.2. Fibromyalgia syndrome

Fibromyalgia syndrome (FMS) is characterized by widespread musculoskeletal pain with diffuse tenderness at multiple tender points (Wolfe et al. 2010). Other symptoms of FMS are distress, fatigue, unrefreshing sleep, and cognitive and somatic problems (Fitzcharles et al. 2013). It is estimated that point-prevalence is around 2-8%, depending on the diagnostic criteria (Clauw 2014). The pathophysiology of FMS is still unclear. Although widespread pain is felt peripheral, there is no evidence for peripheral tissue pathology, structural abnormalities, or otherwise chronic stimulation of pain afferents (Meeus and Nijs 2007). It has been thought that physical or emotional stressors, such as emotional or physical trauma, can trigger symptoms (Schmidt-Wilcke and Clauw 2011), especially when there is a genetic vulnerability (Fitzcharles et al. 2013). However, there is evidence for pain-related pathophysiological changes in the central nervous system (Schmidt-Wilcke and Clauw 2011).

3.2.1. Neuroimaging

Neuroimaging findings in FMS are plentiful and include grey matter atrophy mainly in the anterior cingulate cortex (ACC), prefrontal cortex (PFC) and insula, altered functional connectivity, and an increased activation of the pain matrix (thalamus, insula, ACC, S1 and PFC) (Cagnie et al. 2014; Jorge and Amaro 2012). It is hypothesized that this increased activation amplifies nociceptive signals, which in turn explains exaggerated pain in the presence of minimal and undetectable tissue damage as seen in FMS (Meeus and Nijs 2007).

3.2.2. Neuromodulation

Twenty-seven eligible studies were identified for FMS. Eight sham controlled FMS studies applied rTMS to various brain areas (M1, DLPFC, dACC). Six studies reported pain scores as measured by numeric rating scale (NRS) or visual analogue scale (VAS), one study reported effect of rTMS on cognition, and one study described the effects on quality of life and pain. Most studies showed an improvement of pain scores over time; however, in three of the six studies there was no statistically significant difference between active and sham (Carretero et al. 2009; Lee et al. 2012; Tzabazis et al. 2013).

Others did show a significant greater improvement over time in the active condition: NRS 62 to 50 (Mhalla et al. 2011), NRS 66 to 50 (Passard et al. 2007), and NRS 67 to 40 (Short et al. 2011). With regard to cognition no improvement was seen (Baudic et al. 2013). When rTMS was applied to study the effects on Quality of Life (QoL) and pain, it became clear that it has effect on QoL but not on pain (Boyer et al. 2014). Two meta-analyses dedicated to the effect of rTMS for FMS found that there is no evidence for a clinically significant effect of rTMS (Saltychev and Laimi 2017) and that rTMS is not superior to sham (Knijnik et al. 2016). So, rTMS does not seem to be effective for treatment of FMS.

Seven randomized sham controlled studies used tDCS as an experimental treatment for FMS patients (Fagerlund, Hansen, Aslaksen 2015; Fregni et al. 2006; Mendonca et al. 2011; Mendonca et al. 2016; Riberto et al. 2011; Valle et al. 2009; Villamar et al. 2013). One study reported the add-on effects on aerobic exercise of tDCS compared to sham (Mendonca et al. 2016). One study used a crossover design (Villamar et al. 2013), the others a parallel design. All had the left primary motor cortex (M1) as stimulation site; two targeted in addition the left Dorsal Lateral Prefrontal cortex (DLPFC) (Fregni et al. 2006; Valle et al. 2009) and one the frontal pole (FP) (Mendonca et al. 2011). All studies reported anodal effects over the stimulation site; two reported additional cathodal stimulation (Mendonca et al. 2011; Villamar et al. 2013).

With regard to anodal stimulation over the left M1, no significant improvement was seen in three studies (Mendonca et al. 2011; Mendonca et al. 2016; Riberto et al. 2011). The most recent of these three studies investigated tDCS as an add-on therapy in combination with aerobic exercise (Mendonca et al. 2016). They showed an improvement of 29 points on the NRS when tDCS was combined with aerobic exercise. Subjects treated with only tDCS improved least compared to exercise and sham or to exercise and active tDCS (Mendonca et al. 2016). Significant greater improvement of pain scores over time in the active condition was seen in the other four studies: VAS difference 40 (Fregni et al. 2006), VAS difference 20 (Valle et al. 2009), VAS difference 14 (Villamar et al. 2013), and NRS difference 7 (Fagerlund, Hansen, Aslaksen 2015). Active anodal stimulation over the left M1 did result in higher improvement of sleep efficiency compared to sham (Roizenblatt et al. 2007), in the same study population as described in an earlier study (Fregni et al. 2006). Three studies had additional anodal stimulation sites. The effects of left DLPFC-stimulation are mixed. One study did find significant more improvement of about 20 on the VAS after DLPFC-stimulation (Valle et al. 2009); the other did not find a significant improvement of pain (Fregni et al. 2006). One study reported the effect of frontal pole stimulation; they showed a significant improvement of about 50 on the VAS (Mendonca et al. 2011). Cathodal stimulation over the left M1 showed no

improvement in one study (Mendonca et al. 2011) versus a VAS difference of 14 in another study (Villamar et al. 2013). Cathodal tDCS-stimulation over the frontal pole, however, did result in an improvement of 20 on the VAS (Mendonca et al. 2011). One meta-analysis dedicated to the effect of tDCS for FMS found that anodal tDCS over the left M1 might relieve pain in FMS. No effect for cathodal stimulation over the left M1 or anodal stimulation over the DLPFC was found (Zhu et al. 2017). Thus, with regard to tDCS for FMS we can conclude that there is some positive effect on pain when anodal stimulation is applied to the left M1.

Two sham controlled studies tested efficacy of transcranial applied PEMF against FMS in an RCT. A single session of 30 minutes significantly improved pain compared to sham (Shupak et al. 2006). Another study reported an increase in pain thresholds when tested with an algometer over tender points, after 8 weeks of 1 day per week active PEMF-stimulation compared to a decrease in the sham condition (Maestu et al. 2013).

In short, based on the previous meta-analyses and on the individual studies, it seems that rTMS is not as effective in reducing reported pain intensity in fibromyalgia. There is some more evidence for an effect of tDCS on pain intensity in FMS. Also PEMF does appear to have a small positive effect.

3.3. Functional Neurological Symptom Disorder - Movement Disorder

Functional Neurological Symptom Disorder (FNSD) with abnormal movement as the core symptom (Movement disorders; FNSD-MD), also referred to as psychogenic movement disorder (PMD), describes a subclass of disorders with positive motor symptoms that cannot be attributed to anatomical or neurochemical disturbances (F44.4 (American Psychiatric Association 2013)). The symptoms often resemble organic diseases like Parkinson's disease, or symptoms such as tics, tremor, dystonia, myocloni, spasms and gait disorders (Jankovic, Vuong, Thomas 2006). The most frequently encountered symptoms are tremor and dystonia (Gupta and Lang 2009; Hallett, Weiner, Kompoliti 2012; Jankovic, Vuong, Thomas 2006). Other descriptions of the same condition are 'conversion tremor', 'non-organic movement disorders', 'functional movement disorder' and 'functional motor disorder'. In present days, the diagnosis is based on positive neurological criteria (e.g. abrupt onset or distractibility) (Stone and Carson 2011) and neurophysiological measurements (e.g. EEG, fMRI) are used to rule out organic causes. Current treatment options include psychotherapy, placebo therapy, pharmacotherapy (antidepressants) and physical therapy (Gupta and Lang 2009; Nowak and Fink 2009; Peckham and Hallett 2009).

3.3.1. Neuroimaging

Neuroimaging studies in patients with FNSD- tremor and FNSD-myoclonus dystonia reveal abnormal activity in various brain regions. In FNSD-tremor, studies report decreased activation in the right temporoparietal junction (TPJ) and the left supplementary motor area (SMA). Increased activation is reported in the right amygdala, the left anterior insula and bilateral posterior cingulate. In addition, lower connectivity between TPJ and sensorimotor regions and between the left SMA and bilateral dorsolateral prefrontal regions is reported (Voon et al. 2010; Voon et al. 2011).

3.3.2. Neuromodulation

Four eligible studies in which rTMS was used were identified for FNSD (Chastan and Parain 2010; Dafotakis et al. 2011; Garcin et al. 2013; Shah et al. 2015). FNSD-MD (tremor, myoclonia, dystonia, parkinsonism or stereotypies) were reduced in more than 70% of patients, with a total remission rate of symptoms ranging from 36% (Dafotakis et al. 2011) to 79% (Chastan and Parain 2010). One study on patients with various FNSD-MD reported improved physical but decreased psychological Quality of Life, after premotor cortex rTMS (Shah et al. 2015). This study included 6 patients with a longer illness duration (3-16 years) and stimulation intensity was below motor threshold. Overall, adverse effects reported were headaches and temporary worsening of symptoms (Shah et al. 2015), and one patient developed a presyncope with a feeling of faintness immediately after treatment (Dafotakis et al. 2011). No adverse effects were persistent.

In conclusion, a positive effect of neuromodulation above motor threshold is reported in patients with FNSD. This finding is highly relevant in clinical perspective as no other intervention is associated with recovery rates this high. However, RCTs have yet to be conducted.

3.4. Functional Neurological Symptom Disorder – Paresis

Paresis is a common form of FNSD. It is characterized by a loss of voluntary muscle strength and movement. Patients appear to no longer automatize muscle function, as part of an attentional deficit (Stins et al. 2015). FNSD paresis is diagnosed by a neurologist based on intact neurophysiological measures and positive diagnostic neurological signs such as the Hoover's sign (Shahar et al. 2012).

3.4.1. Neuroimaging

Abnormal brain functioning in FNSD paresis is better studied than other functional neurological symptoms (Voon 2014), as patients with paresis are well suited candidates for neuroimaging research due to the absence of motion artifacts. Abnormal brain functioning appears to be present in FSND paresis. The first theory about the underlying mechanisms involved is described as active inhibition of intact motor function, with associated over-activation of the anterior cingulated gyrus (Halligan et al. 2000; Marshall et al. 1997). After this, the idea of increased self-monitoring of symptoms was related to abnormal activity in the temporal cortex (de Lange, Roelofs, Toni 2007). Recently, involvement of parietal regions such as the precuneus and the supramarginal gyrus is discussed (Cojan et al. 2009; van Beilen et al. 2011). These regions play a role in the early stages of motor initiation, such as the cognitive planning of intentional movement. Parietal regions are also associated with psychological functions such as level of consciousness, episodic memory, self-agency and self-reflection (van Beilen et al. 2011). Finally, anatomical abnormalities in the premotor cortex and the SMA are also reported (Aybek et al. 2014; Nicholson et al. 2014). In conclusion, FS paresis is related to varying abnormal brain activity, depending on the methodology, control groups and task used in the MRI scanner.

3.4.2. Neuromodulation

Three rTMS studies on the symptoms of conversion paralysis were identified. In the first study, four patients were treated with rTMS for the duration of 5 - 12 weeks, applied to the contralateral motor cortex in combination with therapies other than psychotherapy such as sports therapy or relaxation exercises (Schonfeldt-Lecuona et al. 2006). In three out of four patients the motor functions improved markedly. The patient that did not improve was later diagnosed as malingering. In the first two weeks stimulation above motor threshold was used, i.e. the patient could actually see and feel the paralyzed limb move. Second, in seventy patients, rTMS was applied to the contralateral motor cortex of the affected limb at a maximal intensity of 2.5 Tesla. In 89% the rTMS treatment appeared to improve motor symptoms, more improvement was observed in patients with recently acquired symptoms (Chastan and Parain 2010). Third, in 12 patients rTMS was applied to the motor cortex in a placebo-controlled cross-over design. This study showed that active rTMS increased muscle strength while placebo rTMS did not (Broersma et al. 2015). Interestingly, an effect of rTMS was found when applied below the motor threshold. Patients did not see or feel their thumb move during treatment. No adverse effects were reported for any of the studies. A first placebo-controlled study confirms that neuromodulation in paresis below motor threshold is a promising therapeutic option.

Table 2.1: Overview of the methodology used and results presented in the included papers.

Author	Method	Duration	Stimulation site	n	Outcome scores	Result
			CRPS-I			
Pleger et al., 2004	rTMS: 10 Hz	Single session	Contralateral M1	10	VAS	Significant reduction in VAS score: in 7 of 10 patients. Biggest reduction after 45 minutes (contrary to what they report at 15).
Picarelli et al., 2010	rTMS: 10 Hz	10 daily sessions	Bilateral M1	23	VAS, MPQ, SF-36, HDRS	Significant reduction in VAS scores: 50.9% (4.65) in treatment group vs 24.7% (2.18) in sham group.
			Fibromyalgia			
Fregni et al., 2006	tDCS	5 days	M1 Left, DLPFC Left	32	Visual numeric scale pain (1-10)	Small difference but statistically significant difference of 4 points improved in tDCS group vs 3 points in the sham group.
Passard et al, 2007	rTMS: 10 Hz	2 weeks; 5 days per week	M1 Left	30	Numeric rating scale pain (1-10)	Significant improvement in pain in rTMS group: 1.8 points improvement vs 0.1 in sham group.
Carretero et al., 2009	rTMS: 10 Hz	4 weeks; 5 days per week	Right DLPFC	26	Likert scale pain (0-10)	No significant improvement.
Valle et al., 2009	tDCS	10 sessions, 2 weeks of 5 days	M1 Left, DLPFC Left	41	Visual analogue scale pain (1-10)	Significant improvement M1 and DLPFC tDCS group compared to sham (2 vs 0.5 points).
Mhalla et al, 2011	rTMS: 10 Hz	14 sessions; over 21 weeks	M1 Left	40	Numeric rating scale pain (1-10)	Significant improvement in pain in rTMS group: 1 point vs 0.5 in sham group.
Mendonca et al., 2011	tDCS	Single session	M1 Left; supraorbital	30	Visual numeric scale pain (1-10)	Significant improvement supraorbital stimulation (2-5 points), no significant improvement in M1 stimulation.
Riberto et al., 2011	tDCS	Daily for 10 weeks	M1 Left	23	Visual numeric scale pain (1-10)	No significant improvement.
Short et al., 2011	rTMS: 10 Hz	2 weeks; 5 days per week	DLPFC Left	20	Numeric rating scale pain (1-10)	Significant improvement in pain, 1.6 in rTMS group vs 0.3 in sham group.

Author	Method	Duration	Stimulation site	n	Outcome scores	Result
Baudic et al., 2013	rTMS: 10 Hz	14 sessions; over 21 weeks	M1 Left	38	Cognitive test	No significant improvement in cognition.
Lee et al., 2013	rTMS: 10 Hz	2 weeks; 5 days per week	Right DLPFC	22	VAS pain	No significant improvement.
Tzabazis et al., 2013	rTMS: 10 Hz	4 weeks; 5 days per week	dACC	16	Numeric rating scale pain (1-10)	No significant improvement.
Villamar et al., 2013	tDCS	Single session	M1 Left	18	Visual numeric scale pain (1-10)	Significant improvement after 30 minutes: 1.38 - 1.41 points improvement in active vs 0.69 in sham group.
Boyer et al., 2014	rTMS: High freq	10 weeks; 14 sessions	M1 Left	38	QOL; FIQ	Significant improvement on QoL in rTMS group (10 points) vs sham (2 points worsening), no effect on pain.
Fagerlund et al., 2015	tDCS	5 days	M1 Left	48	Numeric rating scale pain (1-10)	Small significant improvement in pain intensity in tDCS group 0.66 points improved vs. 0.09 in sham.
Mendonca et al., 2016	tDCS	4 weeks; 3 days a week	M1 Left	45	Visual numeric scale pain (1-10)	No significant improvement tDCS only, combination with aerobic exercises superior.
					Paresis	
Schönfeldt-Lecuona et al., 2006	rTMS: 15 Hz	5-12 weeks	M1 contralateral	4	?	Improved motor function in 3 out of 4 patients. The latter one diagnosed as malingerer.
Chastan & Parain, 2010	rTMS 0.2-0.25 Hz	30 stimuli	M1 contralateral	70	?	Effective in 89% of patients, total recovery in 43 patients immediately after stimulation, 2 after a few days.
Broersma et al., 2015	rTMS: 15 Hz	10 days	M1 contralateral	12	Dynamometer to assess hand strength	Significant increase in hand strength in treatment group. Increase of at least 20% in 8 patients.

Author	Method	Duration	Stimulation site	n	Outcome scores	Result
			Movement/tremor			
Dafotakis et al.,	rTMS: 0.2 Hz	30 pulses	Contralateral M1 of hand area	11	?	Symptom relief transient in 7 patients, 4 patients lasting relief.
Chastan et al., 2012	rTMS: 0.2 Hz	30 pulses	Contralateral M1	19	?	Total recovery in 15 patients, no effect in 1. Symptoms recurred in 4 patients.
Garcin et al., 2013	rTMS: 0.25 Hz	?	Contralateral M1	24	Severity score by 2 physicians; Self-report after 1 year	6 absolute resolution of symptoms, 12 patients who improved >50% still improved at last follow-up. 2 felt worse. 10 relapsed, 4 returned to work.
Shah et al., 2015	rTMS: 0.33 Hz	5 days, 50 pulses	Dominant M1, Premotor	6	CGI patietrated global impression of change; WHO-QOL-BREF	Significant improvement in physical domain forpremotor cortex rTMS (20.9 points on WHO-QOL-BREF).

4. Discussion & conclusion

First results of non-invasive neuromodulation are promising in terms of symptom relief and larger studies with better methodological standards should be the next step. Underlying brain mechanisms are not yet investigated. In general, neuromodulation has the potential to bring about changes in cortical excitability and plasticity (Bilek et al. 2013; Hsieh et al. 2015). It is a promising treatment option to target the functional activation differences present in patients with FSS (Pollak et al. 2014).

The use of neuromodulation in FSS is most thoroughly studied in fibromyalgia by means of placebo RCTs. Non-invasive neuromodulation (rTMS, tDCS and PEMF) significantly reduced pain levels in eleven out of eighteen fibromyalgia studies. tDCS and PEMF provide the most positive results, although for the latter the number of studies are still limited. In addition, two studies performed on CRPS-I were also placebo-controlled and report that rTMS is able to alter pain perception.

In FNSD with paresis first results suggest that rTMS may be able to increase muscle strength compared to placebo, even when the stimulation applied is below motor threshold. Stimulation above threshold elicits movement of the affected limb and this approach shows promising results in terms of recovery rates. In FNSD movement disorders symptoms were reduced in the majority of patients and total remission ranged from 36 – 79%. Case-studies on symptoms such as headaches or aphonia suggest neuromodulation is a promising therapeutic tool in FNSD. A RCT in FNSD with sufficient power and follow-up measurements is currently not available.

4.1. Clinical advantage of neuromodulation

In clinical settings the focus is nowadays on cognitive and behavioral changes that the patient is required to make. The advantage of neuromodulation is the addition of a somatic approach on the symptoms without decreasing the behavioral and psychological responsibility of patients in the management of their symptoms.

A complication in clinical practice is that the somatic nature of neuromodulation might not conform to the current referral protocol of medical professionals. In recent years, the therapeutic approach has been to guide patients away from a somatic interpretation of symptoms and to stop them seeking medical assessment. From this perspective, concerns might be raised of further medicalization, increased healthcare consumption and diminished motivation for behavioral interventions after referral to neuromodulation therapy. The presence of abnormal brain function does not diminish the importance of behavioral management of symptoms however. Neuroimaging results can educate patients about the interaction between body and behavior with

the brain as the mediating entity. Brain function is a close correlate of both behavior and bodily sensations and should be explained to patients as part of a behavioral-cerebral-somatic circular process. Neuromodulation can easily be combined with existing behavioral and somatic interventions.

4.2. Adverse effects or side-effects

No major adverse events or negative side-effects are reported in the literature. Neuromodulation appears to be a safe method in FS symptoms. Minor non-persistent side-effects were reported. Although these were transient, one patient discontinued the trial (Dafotakis et al. 2011). Patients with CRPS-I reported headache, neck pain and dizziness, but so did the participants in the placebo group.

A potential negative side effect could relate to neuromodulation being an extensive somatic treatment involving multiple contacts. This might result in aggravation of symptoms in reaction to a medical public, and decreased employment of self-management and behavioral coping strategies, or even to a lack of symptom improvement to secure sustained medical attention.

Unexpected additional positive effects are also reported. In functional neurological paresis rTMS on the hand area of the motor cortex did also improve motor function of the leg. In fibromyalgia, improved quality of life in absence of improvement of pain and improvement of sleep was reported after neuromodulation, and in another two patients headaches and migraine improved.

4.3. Limitations

It is a well-known phenomenon that studies with a new method tend to report larger effect sizes than later studies do. This is partly due to the smaller sample size seen in pilot studies. A publication bias may play a role since positive studies are more readily published than negative studies. It should also be noted that behavioral adverse events or changes in medical consumption were not taken into consideration in most studies, control conditions are usually explained symptom categories while care as usual will be an interesting comparison. Follow-up studies are scarce and behavioral outcome measures are not included.

4.4. Conclusion

Non-invasive brain modulation appears to be a treatment option worth exploring for a wide range of functional somatic symptoms including pain and various neurological symptoms. Few adverse events are reported. Consensus on the optimal stimulus

parameters (e.g. intensity, duration or stimulation site) or neuromodulation techniques is absent. Further research on behavioral side-effects and the duration of the effect is needed in comparison to care as usual. The use of neuromodulation may be most valuable as a clinical tool when it is used in combination with behavioral interventions.

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6. Disclosure

Conflicts of interest: None.

Supplemental - search terms

Pubmed

CRPS

("complex regional pain syndrome" OR (CRPS AND pain) OR dystroph*) AND (picotesla OR nanotesla OR micro tesla OR magnetic field* OR "pulsed magnetic field" OR "pulsed electromagnetic field" OR "extremely low frequency magnetic field" OR "extremely low frequency electromagnetic field" OR "pulsed magnetic fields" OR "pulsed electromagnetic fields" OR "extremely low frequency magnetic fields" OR "extremely low frequency electromagnetic fields" OR tDCS OR "transcranial direct current" OR "transcranial electric stimulation" OR "transcranial electrical stimulation" OR tSOS OR tACS OR TBS OR "theta burst stimulation" OR TMS OR sTMS OR rTMS OR "transcranial magneti*")

Fibromyalgia

("fibromyalgia") AND (picotesla OR nanotesla OR micro tesla OR magnetic field* OR "pulsed magnetic field" OR "pulsed electromagnetic field" OR "extremely low frequency magnetic field" OR "extremely low frequency electromagnetic field" OR "pulsed magnetic fields" OR "pulsed electromagnetic fields" OR "extremely low frequency magnetic fields" OR "extremely low frequency electromagnetic fields" OR tdcs OR "transcranial direct current" OR "transcranial electric stimulation" OR "transcranial electrical stimulation" OR tsos OR tacs OR TBS OR "theta burst stimulation" OR TMS OR stms OR rtms OR "transcranial magneti*") NOT ("Reflex Sympathetic Dystrophy"(Mesh) OR "Complex Regional Pain Syndromes"(Mesh))

FNSD movement

(("tremor" OR "psychogenic movement disorder") AND (Conversion OR nonorganic OR non- organic OR psychogenic OR unexplained)) AND (picotesla OR nanotesla OR micro tesla OR magnetic field* OR "pulsed magnetic field" OR "pulsed electromagnetic field" OR "extremely low frequency magnetic field" OR "extremely low frequency electromagnetic field" OR "pulsed magnetic fields" OR "pulsed electromagnetic fields" OR "extremely low frequency magnetic fields" OR "extremely low frequency electromagnetic fields" OR tdcs OR "transcranial direct current" OR "transcranial electric stimulation" OR "transcranial electrical stimulation" OR tsos OR tacs OR TBS OR "theta burst stimulation" OR TMS OR stms OR rtms OR "transcranial magneti*")

FNSD paresis

(conversion disorder OR functional paralysis OR functional paresis OR psychosomatic hemiparesis OR psychogenic hemiparesis OR psychosomatic paresis OR psychosomatic paralysis OR psychogenic paresis OR psychogenic paralysis OR psychogenic hemiparesis OR psychogenic hemiparalysis) AND (picotesla OR nanotesla OR micro tesla OR magnetic field* OR "pulsed magnetic field" OR "pulsed electromagnetic field" OR "extremely low frequency magnetic field" OR "extremely low frequency electromagnetic field" OR "pulsed magnetic fields" OR "pulsed electromagnetic fields" OR "extremely low frequency magnetic fields" OR "extremely low frequency electromagnetic fields" OR tDCS OR "transcranial direct current" OR "transcranial electric stimulation" OR "transcranial electrical stimulation" OR tSOS OR tACS OR TBS OR "theta burst stimulation" OR TMS OR sTMS OR rTMS OR "transcranial magneti*")

Cochrane

CRPS

(complex regional pain syndrome OR (CRPS AND pain) OR dystroph*) AND (picotesla OR nanotesla OR micro tesla OR magnetic field* OR pulsed magnetic field OR pulsed electromagnetic field OR extremely low frequency magnetic field OR extremely low frequency electromagnetic field OR pulsed magnetic fields OR pulsed electromagnetic fields OR extremely low frequency magnetic fields OR extremely low frequency electromagnetic fields OR tDCS OR transcranial direct current OR transcranial electric stimulation OR transcranial electrical stimulation OR tSOS OR tACS OR TBS OR theta burst stimulation OR TMS OR sTMS OR rTMS OR transcranial magneti*)

Fibromyalgia

(fibromyalgia) AND (picotesla OR nanotesla OR micro tesla OR magnetic field* OR pulsed magnetic field OR pulsed electromagnetic field OR extremely low frequency magnetic field OR extremely low frequency electromagnetic field OR pulsed magnetic fields OR pulsed electromagnetic fields OR extremely low frequency magnetic fields OR extremely low frequency electromagnetic fields OR tdcs OR transcranial direct current OR transcranial electric stimulation OR transcranial electrical stimulation OR tsos OR tacs OR TBS OR theta burst stimulation OR TMS OR stms OR rtms OR transcranial magneti*) NOT (Reflex Sympathetic Dystrophy OR Complex Regional Pain Syndromes)

FNSD paresis

(conversion disorder OR functional paralysis OR functional paresis OR psychosomatic hemiparesis OR psychogenic hemiparesis OR psychosomatic paresis OR psychosomatic paralysis OR psychogenic paresis OR psychogenic paralysis OR psychogenic hemiparesis OR psychogenic hemiparalysis) AND (picotesla OR nanotesla OR micro tesla OR magnetic field* OR pulsed magnetic field OR pulsed electromagnetic field OR extremely low frequency magnetic field OR extremely low frequency electromagnetic field OR pulsed magnetic fields OR pulsed electromagnetic fields OR extremely low frequency magnetic fields OR extremely low frequency electromagnetic fields OR tDCS OR transcranial direct current OR transcranial electric stimulation OR transcranial electrical stimulation OR tSOS OR tACS OR TBS OR theta burst stimulation OR TMS OR sTMS OR rTMS OR transcranial magneti*)

FNSD movement

((tremor OR psychogenic movement disorder) AND (Conversion OR nonorganic OR non-organic OR psychogenic OR unexplained)) AND (picotesla OR nanotesla OR micro tesla OR magnetic field* OR pulsed magnetic field OR pulsed electromagnetic field OR extremely low frequency magnetic field OR extremely low frequency electromagnetic field OR pulsed magnetic fields OR pulsed electromagnetic fields OR extremely low frequency magnetic fields OR extremely low frequency electromagnetic fields OR tdcs OR transcranial direct current OR transcranial electric stimulation OR transcranial electrical stimulation OR tsos OR tacs OR TBS OR theta burst stimulation OR TMS OR stms OR rtms OR transcranial magneti*)

Embase

CRPS

('complex regional pain syndrome' OR (CRPS AND pain) OR dystroph*) AND (picotesla OR nanotesla OR micro tesla OR magnetic field* OR 'pulsed magnetic field' OR 'pulsed electromagnetic field' OR 'extremely low frequency magnetic field' OR 'extremely low frequency electromagnetic field' OR 'pulsed magnetic fields' OR 'pulsed electromagnetic fields' OR 'extremely low frequency magnetic fields' OR 'extremely low frequency electromagnetic fields' OR tDCS OR 'transcranial direct current' OR 'transcranial electric stimulation' OR 'transcranial electrical stimulation' OR tSOS OR tACS OR TBS OR 'theta burst stimulation' OR TMS OR sTMS OR rTMS OR 'transcranial magneti*')

Fibromyalgia

(fibromyalgia) AND (picotesla OR nanotesla OR micro tesla OR magnetic field* OR 'pulsed magnetic field' OR 'pulsed electromagnetic field' OR 'extremely low frequency magnetic field' OR 'extremely low frequency electromagnetic field' OR 'pulsed magnetic fields' OR 'pulsed electromagnetic fields' OR 'extremely low frequency magnetic fields' OR 'extremely low frequency electromagnetic fields' OR tdcs OR 'transcranial direct current' OR 'transcranial electric stimulation' OR 'transcranial electrical stimulation' OR tsos OR tacs OR TBS OR 'theta burst stimulation' OR TMS OR stms OR rtms OR 'transcranial magneti*')

FNSD movement

(('tremor' OR 'psychogenic movement disorder') AND (Conversion OR nonorganic OR non- organic OR psychogenic OR unexplained)) AND (picotesla OR nanotesla OR micro tesla OR magnetic field* OR 'pulsed magnetic field' OR 'pulsed electromagnetic field' OR 'extremely low frequency magnetic field' OR 'extremely low frequency electromagnetic field' OR 'pulsed magnetic fields' OR 'pulsed electromagnetic fields' OR 'extremely low frequency magnetic fields' OR 'extremely low frequency electromagnetic fields' OR tdcs OR 'transcranial direct current' OR 'transcranial electric stimulation' OR 'transcranial electrical stimulation' OR tsos OR tacs OR TBS OR 'theta burst stimulation' OR TMS OR stms OR rtms OR 'transcranial magneti*')

FNSD paresis

('conversion disorder' OR 'functional paralysis' OR 'functional paresis' OR 'psychosomatic hemiparesis' OR 'psychogenic hemiparesis' OR 'psychosomatic paresis' OR 'psychosomatic paralysis' OR 'psychogenic paresis' OR 'psychogenic paralysis' OR 'psychogenic hemiparesis' OR 'psychogenic hemiparalysis') AND (picotesla OR nanotesla OR micro tesla OR magnetic field* OR 'pulsed magnetic field' OR 'pulsed electromagnetic field' OR 'extremely low frequency magnetic field' OR 'extremely low frequency electromagnetic field' OR 'pulsed magnetic fields' OR 'pulsed electromagnetic fields' OR 'extremely low frequency magnetic fields' OR 'extremely low frequency electromagnetic fields' OR tDCS OR 'transcranial direct current' OR 'transcranial electric stimulation' OR 'transcranial electrical stimulation' OR tSOS OR tACS OR TBS OR 'theta burst stimulation' OR TMS OR sTMS OR rTMS OR 'transcranial magneti*')

Chapter 3

Treatment of depression with low strength transcranial pulsed electromagnetic fields: a mechanistic point of view

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Background
Mood disorders constitute a high burden for both patients and society. Notwithstanding the large arsenal of available treatment options, a considerable group of patients does not remit on current antidepressive treatment. There is an urgent need to develop alternative treatment strategies. Recently, low strength transcranial pulsed electromagnetic field (tPEMF) stimulation has been purported as a promising strategy for such treatment resistant depression (TRD). The mode of action of this new technique is however largely unknown.

Methods
We searched PubMed for literature reports on the effects of tPEMF and for information regarding its working mechanism and biological substrate.

Results
Most studies more or less connect with the major hypotheses of depression and concern the effects of tPEMF on brain metabolism, neuronal connectivity, brain plasticity and the immune system. Relatively few studies paid attention to the possible chronobiologic effects of electromagnetic fields.

Limitations
We reviewed the literature of a new and still developing field. Some of the reports involved translational studies, which inevitably limits the reach of the conclusions.

Conclusion
Weak magnetic fields influence divergent neurobiological processes. The antidepressive effect of tPEMF may be specifically attributable to its effects on local brain activity and connectivity.

1. Introduction

Major depressive disorder (MDD) is a severe mental disorder with an estimated lifetime prevalence of 30% in men and 40% in women (Kruijshaar et al. 2005). According to the WHO Global Burden of Disease study, MDD was the leading cause of disease burden in 2010, making it a global health priority (Ferrari et al. 2013). Treatment of MDD mostly relies on a combination of psychotherapy and pharmacotherapy. However, the currently available treatment strategies have only limited efficacy (Rush et al. 2006). Overall, 30% of patients have Treatment Resistant Depression (TRD), defined as "an episode of MDD" which has not improved after at least two adequate trials of different classes of antidepressants" (Ruhe et al. 2012). To improve efficacy new treatment options for depression are under investigation.

In the last decade, several novel approaches have been proposed to treat MDD and TRD. Of particular interest are non-invasive brain-stimulation (NIBS) techniques to alter the function of specific neural structures in a less invasive manner (Holtzheimer and Mayberg 2012). A well-known and highly effective form of NIBS, electroconvulsive therapy (ECT), has been practiced for over 75 years (Bolwig 2011; Pagnin et al. 2004; UK ECT Review Group 2003). Recently, several new NIBS techniques have emerged, with Transcranial Magnetic Stimulation (TMS) as one of the most promising options (Edelmuth et al. 2010). TMS involves the positioning of an electric coil over the scalp and running trains of high-energy current pulses through this coil.

The ensuing powerful magnetic fields of around 1-3 tesla induce an electric current in the underlying brain tissue (Barker, Jalinous, Freeston 1985).

The antidepressive effects of TMS are well established. A meta-analysis of 32 studies reported a moderate effect of active TMS treatment on depression severity, as measured for instance by the 17 item Hamilton Depression Rating Scale (HAMD-17). The overall conclusion was that TMS is an effective treatment of depression (Allan, Herrmann, Ebmeier 2011). A more recent systematic review investigating 63 studies concluded that rTMS stimulation has a statistically significant antidepressive effect, but due to the rather large placebo response its clinical relevance is still a matter of debate (Lepping et al. 2014). Moreover, there is still controversy about the exact location of the coil and the dosing strategy including the frequency and intensity of the electromagnetic stimulation (George, Taylor, Short 2013).

Transcranial Direct Current Stimulation (tDCS) is another NIBS technique. In tDCS the brain is polarized by administering a direct, weak electric current into the brain, by placing electrodes directly onto the scalp (Priori 2003). In contrast to TMS, tDCS does not result in a depolarization of the neuronal membrane (Brunoni et al. 2012; Nitsche et al. 2008). Focal stimulation of the left dorsolateral prefrontal cortex (DLPFC) in patients with depressive disorder however does have a similar effect size as the effect size reported in rTMS, as a recent meta-analyses of individual patient data from 6 RCTs and 289 patients showed (Brunoni et al. 2016).

1.1. Antidepressant effect of tPEMF

There is also growing interest for the divergent clinical effects of weaker magnetic fields (<0.1 T) in the low frequency range, as induced by pulsed (i.e.: non-static) electromagnetic fields (PEMF), which can be applied transcranially as well (tPEMF). In case of the latter, a Helmholtz coil (two solenoid electromagnets) or similar can be used, which can be placed over patients heads (Rohan et al. 2013). A cap with multiple smaller coils is also used (Kortekaas et al. 2013; Martiny, Lunde, Bech 2010). A notable difference between tPEMF and tDCS or rTMS is that in the former no focal stimulation is applied, but in contrast the whole cortex is being stimulated

Effects of PEMF have been established in the field of orthopedic surgery. Several high quality studies have shown efficacy of PEMF on symptoms of knee osteoarthritis (Ryang We et al. 2013). PEMF also shortened time to radiological and clinical union in the conservative treatment of acute fractures (Hannemann et al. 2014). It has been proposed that the effect of PEMF on bone growth is related to stimulation of osteoblasts and growth factors (Chalidis et al. 2011).

Effects of PEMF stimulation have also been studied in the field of neuroscience, both pre-clinically and clinically. An early study showed that specific magnetic fields (0,1 mT; CNP-pulse) have analgesic effects in land snails that were placed on a warm (40°C) surface (Thomas et al. 1997). Moreover, a single 15 minutes stimulation by this particular low frequency pulsed magnetic wave had a significant analgesic effect in terms of the time needed to avoid this particular stimulus, as opposed to other waveforms and a control group (Thomas et al. 1997). The analgesic effects of PEMF have been reproduced in other land snails, as well as in mice and rats (for review, see (Del Seppia et al. 2007)). In humans tPEMF reportedly increase pain thresholds in healthy subjects (both: 0,1 mT; CNP-pulse) (Kortekaas et al. 2013; Shupak, Prato, Thomas 2004). Furthermore, tPEMF stimulation has analgesic effects in patients with musculoskeletal pain or fibromyalgia ((Shupak et al. 2006; Thomas et al. 2007): < 1000 Hz; 0,4 mT; CNP-pulse; (Maestu et al. 2013): 8 Hz; 43nT) (Maestu et al. 2013; Shupak et al. 2006; Thomas et al. 2007)

The alleged antidepressive effects of tPEMF stimulation have also been investigated in both pre-clinical and clinical studies. For instance, low-energy variable electromagnetic fields (1000 Hz; 0,75 V/m) showed a positive effect on depressive-like behavior in rats (Carlezon et al. 2005). Interestingly, electromagnetic field stimulation appeared to be superior to treatment with the antidepressant fluoxetine in the forced swim test and an open field test, both of which are established rodent models for depression (Carlezon et al. 2005). The pulsating magnetic field was produced by a table top device. The effect was replicated in mice (1000 Hz), using an MR-like device (Rokni-Yazdi et al. 2007; Aksoz et al. 2008). Finally, the antidepressive-like effect of magnetic fields in rodents appeared to be dependent of the non-static magnetic field strength (Carlezon et al. 2005; Rokni-Yazdi et al. 2007; Aksoz et al. 2008).

In humans it was reported that the acquisition of a magnetic resonance spectrum from the brain had a mood-elevating effect in 30 depressed bipolar patients (1000 Hz; 0,7 V/m) (Rohan et al. 2004). This was investigated in a sham controlled, single blind study in healthy subjects and in subjects suffering from a bipolar depression, which explored an earlier chance finding of mood improvement after scanning with this particular MR-protocol. The quick mood-elevating effect appeared to depend on the magnetic gradients used by the MR-scanner, which are similar to those with tPEMF stimulation (Rohan et al. 2004). A double blind Randomized Controlled Trial (RCT) in patients with MDD showed efficacy of tPEMF in treatment resistant depression, using a head device with coils and continuous trains of alternating currents (<333 Hz; 1,9mT; 0,22 V/m) (Martiny, Lunde, Bech 2010). After stimulating 50 patients with TRD for five weeks in a row, Hamilton Depression Rating Scale-17 (HAMD-17) scores improved significantly, both statistically and clinically in the treatment group

as opposed to placebo (Martiny, Lunde, Bech 2010). Another randomized, double blind, sham controlled treatment trial showed that a portable electromagnetic device producing quickly oscillating electromagnetic fields (< 1000 Hz; < 2 mT; 0,72 V/m) had an immediate positive effect on depression severity, 10-15 minutes after completion of a single intervention, in 63 patients with a unipolar or bipolar depression (Rohan et al. 2013). Subjects who underwent the active condition experienced a rapid improvement of 8.13 points on the HAMD-17 and 1.66 points on a 10-point Visual Analog Scale (VAS). The control group, receiving a sham treatment, improved only 5.02 points on the HAMD-17 and 0.60 points on the VAS, a statistically significant difference. Longer-term effects were not studied (Rohan et al. 2013). In a dose-remission study, it was found that augmentation with tPEMF stimulation (50 Hz; 0,4 V/m) in 65 patients with TRD during 8 weeks reduced HAMD-17 scores with 74% and 68% (13 and 14 points) if treated with one vs. two daily tPEMF doses, respectively (Straaso et al. 2014). No sham treatment was given. However, no statistically significant difference was found between the two groups and the conclusion was that both dosing regimens worked equally well (Straaso et al. 2014).

Side effects of tPEMF-treatment in depression appear to be few and mild. For example, in the study of Martiny, no significant differences were seen between side effects in the active versus the sham group (Martiny, Lunde, Bech 2010). Moreover, Rohan reported that no side effects or adverse events were noted one week after treatment (Rohan et al. 2013).

Although the numbers of studies are still limited, findings on the analgesic and antidepressive effects of tPEMF are promising. However, the mechanisms by which electromagnetic fields can produce an antidepressive effect are far from understood. In this paper we will give an overview of putative mechanisms underlying the antidepressive effects of tPEMF.

2. Methods

We searched PubMed with the following search term as a description of tPEMF: ("picotesla" OR "nanotesla" OR "micro tesla" OR "milli tesla" OR "magnetic field*" OR "pulsed magnetic field" OR "pulsed electromagnetic field" OR "extremely low frequency magnetic field" OR "extremely low frequency electromagnetic field" OR "pulsed magnetic fields" OR "pulsed electromagnetic fields" OR "extremely low frequency magnetic fields" OR "extremely low frequency electromagnetic fields"). We combined the term with supposed working mechanisms of tPEMF, which were formulated earlier (Kortekaas et al. 2013). We focused specifically on the effects of tPEMF in mood disorders. We reviewed titles and abstracts looking for potential working mechanisms of tPEMF and read the articles completely if deemed eligible. We further reviewed references of these articles to find additional literature.

3. Results

3.1. Electrophysiological effects

Neuroimaging studies in MDD have consistently shown decreased activity in the dorsolateral prefrontal cortex (DLPFC), an area involved in executive functioning (Drevets 2001; Lepping et al. 2014; Pascual-Leone et al. 1996; Videbech 2000). These observations are in line with [18F]-fluorodeoxyglucose (FDG) PET-studies showing lower prefrontal glucose metabolism in MDD (Hosokawa, Momose, Kasai 2009; Videbech 2000). Following treatment with the SSRI paroxetine increases of glucose metabolism were observed in cortical brain areas previously implicated in MDD, including parts of the prefrontal, the parietal, and the dorsal anterior cingulate cortex (Kennedy et al. 2001).

Importantly, in both pre-clinical and clinical studies repetitive TMS (rTMS) also appears capable of increasing glucose metabolism in these areas. For instance, increased FDG uptake was seen in rats after rTMS-stimulation for 1 Hz and 50 Hz, as compared to sham-stimulation (Parthoens et al. 2014). Changes in FDG uptake were also observed in healthy volunteers stimulated with active or sham rTMS (Cho et al. 2012; Kimbrell et al. 2002). Moreover, rTMS aimed at the DLPFC of patients suffering from MDD has been shown to both increase cortical excitability and relieve depressive symptoms (Lepping et al. 2014; Pascual-Leone et al. 1996).

The electrophysiology involved in the increased cortical excitability is relatively well understood. Yet, it is important to make a distinction between the effects of acute and repeated stimulation. Clearly, transcranial magnetic stimulation can promote action potentials in neurons, as witnessed by the capacity of TMS to induce motor responses (Barker, Jalinous, Freeston 1985; Pell, Roth, Zangen 2011; Siebner et al. 2009). However, repetitive stimulation at higher frequencies (>1 Hz) might trigger more complex mechanisms leading to a sustained increased excitability of the cortical area involved. This adaptive process likely involves long-lasting changes of synaptic activity through neurophysiological mechanisms reminiscent of long term potentiation (LTP) and long term depression (LTD) (Pell, Roth, Zangen 2011).

The subject of this review is tPEMF stimulation, a much lower electromagnetic field strength variant of rTMS. Brain stimulation with tPEMF is a relatively new technique and as a consequence only limited information is available regarding its mode of action. However, given the fact that both rTMS and tPEMF use fluctuating magnetic fields to induce small currents in the brain (Faraday's law) their effects on action potentials and synaptic plasticity might bare some resemblance. Yet, compared to rTMS, the effects of tPEMF are likely to be more subtle making it questionable

whether tPEMF can actually induce action potentials (Rahbek, Tritsaris, Dissing 2005). A more likely explanation would be that merely energy barriers are lowered at the lower electromagnetic field strength of tPEMF thus facilitating the generation of action potentials. Based on data from mice (Prato et al. 2011) the penetration depth at which this occurs is expected to be 2-3 cm from the coil into the underlying brain tissue (Kortekaas et al. 2013), which is comparable with the penetration depths reported for TMS (Silva, Basser, Miranda 2008).

Notably, tPEMF has been reported to influence brain glucose metabolism, thus affecting local brain activity (Volkow et al. 2010). In this study, the electromagnetic field stimulation was applied through the EPI-gradient of a MR-scanner to 15 healthy controls in a sham-controlled manner. Glucose metabolism was assessed by an FDG PET-scan directly afterwards. Interestingly, brain glucose metabolism during the active EPI-gradient decreased in inferior occipital, inferior frontal, superior parietal and posterior insular cortices (Volkow et al. 2010).

3.2. Effects on oscillatory states

Electroencephalographic studies indicate that focally applied rTMS in depressed patients has effects in the brain beyond the stimulated area (Leuchter et al. 2013). This is in agreement with growing evidence that an extensive network of brain regions is affected in MDD (Fingelkurts et al. 2006). Given the clear changes in EEG alpha band connections between brain areas, MDD is increasingly regarded as a disorder that affects connectivity between cortical regions (Fingelkurts et al. 2006; Leuchter et al. 2013).

This disrupted connectivity has been associated with desynchronization of neuronal firing (Anastassiou et al. 2011; Fingelkurts et al. 2006). Arguably, weak electromagnetic fields might influence the underlying disorganization in oscillatory states of neurons. This is supported by studies showing that low strength pulsed magnetic fields are indeed capable of affecting EEG activity (Cook et al. 2005; Cook et al. 2009). For example, in a crossover randomized controlled design with 20 healthy volunteers, tPEMF stimulation (<500 Hz; 0,2 mT; CNP-pulse) resulted in decreased alpha wave activity in rest over the occipital and parietal region during magnetic fields exposure, as compared to sham exposure, when first exposed to active stimulation (Cook et al. 2005). This effect did not persist during the post-exposure period (Cook et al. 2005). In another crossover single blind randomized controlled study with 32 healthy volunteers, similar effects of magnetic fields exposure (<500 Hz; 0,2 mT; CNP-pulse) on alpha activity were found (Cook et al. 2009). Moreover, tPEMF stimulation in healthy volunteers has been reported to directly influence functional connectivity

between Broca's and Wernicke's areas as measured with NIRS (Near Infrared Spectroscopy) and EEG (Curcic-Blake 2014). It can be speculated that antidepressive effects of tPEMF stimulation partly involve a synchronization of cortical firing in whole networks of affected brain regions.

3.3. Effects on neuronal growth

Biomarker studies have shown that levels of brain-derived neurotrophic factor (BDNF) in blood are decreased in depressed patients compared to healthy controls (Brunoni, Lopes, Fregni 2008; Molendijk et al. 2014; Player et al. 2013; Sen, Duman, Sanacora 2008). The peptide BDNF is a growth factor involved in the survival and growth of neurons. The significant decrease of BDNF levels in depressed patients is one of the pillars under the neurogenesis/neuroplasticity hypothesis of MDD (Gould 1999; Kempermann and Kronenberg 2003; Molendijk et al. 2014; Sapolsky 2004). Another argument in favor of the neurogenesis/neuroplasticity hypothesis is the increase of BDNF levels in blood from patients with MDD following antidepressant drug treatment (Brunoni, Lopes, Fregni 2008; Molendijk et al. 2014). Changes in BDNF-levels following rTMS-treatment are less pronounced, as levels can increase (Dall'Agnol et al. 2014; Zhang et al. 2007), decrease (Schaller et al. 2014), or not change at all (Lang et al. 2008). A recent systematic review and meta-analysis showed no change of BDNF-levels after rTMS-stimulation (Brunoni et al. 2015).

The effect of tPEMF on BDNF-levels in humans has not yet been assessed. There is, however, circumstantial evidence that PEMF stimulation influences neuronal growth. An in vitro study in a murine MN9D dopaminergic cell line showed that PEMF signals (27,12 MHz; 5 uT; 13 V/m) increased neurite length and cell body size in three days' time, as opposed to a control and a null condition (Lekhraj et al. 2014). Furthermore, mRNA expression of BDNF was reported to increase in neonatal rat dorsal root ganglion neurons after exposure to PEMF (50 Hz; 1 mT) (Li et al. 2014). Accordingly, tPEMF might also influence neuronal growth in living beings. Clearly studies in animals and patients are warranted to verify and support such assumption.

3.4. Immunological effects

The immune hypothesis of MDD postulates that inflammatory processes are involved in the onset of depression (Maes 1995). It has been proposed that pro-inflammatory cytokines such as IL-1β and TNF-α trigger HPA-axis hyperactivity (Leonard 2001), eventually leading to reduced synthesis of serotonin as well as the formation of neurotoxic kynurenines and isoquinolines and also a decrease of neurogenesis (Dantzer et al. 2008; Jentsch et al. 2015; Maes et al. 2011). The immune hypothesis is supported by two meta-analyses showing a positive association between depression

and increased levels of pro-inflammatory markers (Dowlati et al. 2010; Howren, Lamkin, Suls 2009). Inflammatory dysregulation in depression is also supported by an intervention study with the pro-inflammatory drug interferon-α (Friebe et al. 2010) and by several randomized clinical trials with nonsteroidal anti-inflammatory drugs and cytokine inhibitors (Kohler et al. 2014).

Cytokines are small signaling proteins that can be divided in a pro-inflammatory (TH1) and an anti-inflammatory group (TH2 and TH3). Increased levels of pro-inflammatory cytokines are indeed a hallmark of an inflammatory response in depression (Anisman et al. 2002; Licinio and Wong 1999; Miller, Maletic, Raison 2009) but results for anti-inflammatory TH2 cytokines were far less consistent. However, because cytokines influence each other's release, the balance between pro-inflammatory cytokines (TH1) and anti-inflammatory cytokines (TH2 and TH3) might be particularly important (Kim et al. 2007).

PEMF stimulation might have anti-inflammatory effects and influence cytokine levels (Pesce et al. 2013). Most of the evidence comes from studies in the fields of orthopedics and general surgery. For example, a recent study showed a significant decrease in human fibroblast-like cell cultures of the production of cytokines IL-1β and TNF-α on 14 and 21 days after PEMF stimulation on days 7, 8 and 9 (50 Hz; 2,25 mT) versus a control condition (Gomez-Ochoa et al. 2011). A study, aimed at the progression of osteoarthritis in a rabbit model, showed a clear decrease of serum TNF-α levels following 10 days of 30 min PEMF-stimulation (75 Hz), as compared with a control group (Guo et al. 2011). Additional evidence comes from a study in rats showing that PEMF stimulation 1 h per day for 9 days (7,5 Hz; 66 μT; 0,48 V/m) reduced levels of the cytokines IL-1β, IL-6 and TNF-α, as measured in these 9 days (Chang et al. 2004).

In humans PEMF stimulation specifically decreases IL-1β levels in wound exudate (Rohde et al. 2010). This was shown in a double blind, placebo-controlled, randomized study applying PEMF-stimulation for 20 minutes every 4 hours for the first 3 days, then once every 8 hours for the next 3 days, then twice daily (27,12 MHz; 5 uT; 3,2 V/m) directly after breast reduction surgery. Six hours after surgery, IL-1β in wound exudate was significantly reduced in the active treatment group compared to placebo. This difference sustained up to 24-hours postoperatively, after which no more measurements were done. No significant effect was found on TNF-α (Rohde et al. 2010). This effect of PEMF stimulation on IL-1β is particularly interesting in view of a head injury study in rats showing significant decreases of IL-1β levels in liquor following PEMF-treatment (Rasouli et al. 2012). Rats were injured under two different conditions. Firstly, they were given head injury and exposed to PEMF-treatment in

a constant regimen of 5 minute stimulation in every 20 minutes for 6 hours (27,12 MHz; 40 V/m). Secondly, they were exposed to penetrating brain surgery and then stimulated with PEMF. In a control experiment, without PEMF-stimulation, both conditions gave rise to an increase of IL-1β levels in liquor six hours after the injury. However, there was a significant decrease of IL-1β levels in the PEMF stimulated group compared to control (Rasouli et al. 2012). The latter study is important because it indicates that tPEMF stimulation can indeed alter CSF-levels of IL-1β, at least in rats and at a high frequency.

Summarizing, there is evidence for a low-grade inflammatory process in the pathophysiology of depression. This process could be important in both the onset of depression (Friebe et al. 2010) and its treatment with adjuvant anti-inflammatory drugs (Kohler et al. 2014). PEMF stimulation might also target inflammatory processes as witnessed by its capability to decrease cytokine levels in vitro and in vivo (Chang et al. 2004; Gomez-Ochoa et al. 2011; Guo et al. 2011; Rasouli et al. 2012). There are no literature data available on the effects of tPEMF stimulation on cytokine CSF and serum levels in humans. Yet, the circumstantial evidence collected thus far suggests that the antidepressive properties of PEMF may be partly attributed to its effects on low-grade inflammatory processes in depression, possibly through restoration of the balance between pro- and anti-inflammatory cytokines.

3.5. Chronobiologic effects of tPEMF

A well-entrained biological clock is essential for mental well-being in both humans and animals (Barnard and Nolan 2008; Bunney and Bunney 2000; McClung 2007; McClung 2011). Mood may particularly vary with changes and disruptions of the biological clock (Monteleone and Maj 2008; Barnard and Nolan 2008; Hasler 2010; Boivin et al. 1997; McClung 2007). Furthermore, it is clear that restoring biological rhythms has a beneficial effect on depressive symptoms. For example, the efficacy of light therapy for both Seasonal Affective Disorder (SAD) and non-seasonal depression might suggest that restoring circadian rhythms is relevant for the treatment of mood disorders (Benedetti et al. 2007; Rosenthal et al. 1984; Terman 2007). Because some evidence exists that electromagnetic fields can influence circadian rhythms we have explored the possibility that the antidepressive effects of tPEMF are somehow connected with the biological clock.

Firstly, there is circumstantial evidence that weak alternating electromagnetic fields may shorten circadian rhythms in healthy controls (Wever 1970; Wever 1973). This was investigated in a set of two experiments. In the first experiment the circadian rhythms of 82 human subjects were studied in an underground bunker, shielded

from all environmental influences. The isolation unit contained two separate sections with one shielded from external electromagnetic fields but the other not. It was shown that shielding from external electromagnetic fields significantly lengthened circadian periods (Wever 1970; Wever 1973). In a second experiment, alternating weak electromagnetic fields (10 Hz) were generated in the shielded section only. This intervention shortened the circadian periods significantly with 1,3 hour (Wever 1970; Wever 1973).

Secondly, there is evidence that the biological clock protein cryptochrome is sensitive to weak magnetic fields. The protein cryptochrome inhibits the transcriptional-translational feedback loop that controls circadian rhythms (Reppert and Weaver 2001; Reppert and Weaver 2002), and is thus an intrinsic molecular regulator of the biological clock (Chaves et al. 2011; Emery et al. 1998; Griffin, Staknis, Weitz 1999; Thresher et al. 1998; van der Horst et al. 1999; Vitaterna et al. 1999). Cryptochrome proteins are sensitive to weak magnetic fields by their ability to form radical pairs from molecules with a single unpaired electron (Maeda et al. 2012; Solov'yov et al. 2012). This was shown by measuring the amount of radicals produced in cryptochrome protein samples from the plant Arabidopsis Thaliana when exposed to pulsed magnetic fields (non-static; 29 mT). It was also shown that cryptochrome responds to Earth-strength magnetic fields of approximately 50 μT at physiological temperatures (Maeda et al. 2012).

Moreover, it has been shown that weak magnetic fields can entrain circadian rhythms in Drosophila fruit flies (Yoshii, Ahmad, Helfrich-Forster 2009). In this experiment free-running periods of locomotor activity were recorded before and during exposure to static magnetic fields of different field strengths. Period changes in the locomotor activity appeared to significantly depend on the strength of the magnetic field (mostly 0,3 mT) and appeared also to be cryptochrome-dependent (Yoshii, Ahmad, Helfrich-Forster 2009). In humans sensitivity to weak magnetic fields has not yet been investigated. However, a trans-genetic approach showed that human cryptochrome is sensitive to static magnetic fields (Foley, Gegear, Reppert 2011). To this end the human hCRY2-gene was expressed in CRY-deficient Drosophila fruit flies. In a T-maze two-coil system, starved flies were conditioned to associate the presence of static 0.01 mT – 0.5 mT magnetic fields with a food source. Knockout flies did not respond to the magnetic fields (Foley, Gegear, Reppert 2011). These experiments suggest that the human cryptochrome has the capability to respond to magnetic fields.

We were unable to find studies investigating the effects of non-static or pulsed electromagnetic fields either on the protein cryptochrome or on the phase of circadian rhythms in humans. Thus the idea that electromagnetic fields can entrain

circadian rhythms in humans remains purely hypothetical. Even when supported by future studies in humans it is not very plausible that entraining the biological clock is responsible for the antidepressive effect of PEMF. The argument that the antidepressive effect of light therapy in SAD would involve the biological clock is also not very convincing, as witnessed by a recent longitudinal study of gene expression in winter depression which reported statistically significant associations of light therapy with divergent neuronal and immunological processes but not with 350 investigated circadian genes (Bosker et al. 2015). The latter is more in line with the photon-count hypothesis, which states that a short photoperiod in winter deprives susceptible patients from the absorption of sufficient light energy needed for normal physiological and psychological functioning, thus circumventing any involvement of the biological clock (Lee et al. 1997; Terman 2007).

4. Concluding remarks

There are clear indications that weak magnetic fields have an antidepressive effect. The effects of such weak magnetic fields on the depressed brain may be divergent. Accordingly, we have explored various mechanisms that might contribute to the antidepressive effects of tPEMF. Perhaps not completely unexpected the most solid evidence was found for mechanisms that fit well in the major hypotheses of MDD. The most consistent finding, however, was an acute effect of tPEMF on local brain activity and glucose metabolism. This is also 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. We also found support with respect to the neurogenesis/neuroplasticity and immune hypotheses as witnessed by the beneficial effects of tPEMF on neuronal growth and pro-inflammatory cytokines. An alternative explanation involving the biological clock was considered to be rather implausible. When comparing tPEMF with tDCS, it seems plausible that both techniques involve subthreshold modulation of the neuronal membrane resting potential. However, while the effect of tDCS is highly focalized (Nitsche et al. 2009), the reach of tPEMF stimulation is broader and arguably more diffuse, involving the whole cortex and even brain areas beyond that.

Summarizing, novel therapies for MDD and TRD are highly needed. The evidence collected thus far indicates that a well-timed intervention with tPEMF has an antidepressive effect, possibly involving a restoration of the disrupted brain connectivity in MDD. Several studies are currently directed at investigating the efficacy of this new technique and further exploring its working mechanism. For the latter biomarker measurements are likely to prove indispensable. However, future experiments must also be directed at optimizing the stimulation conditions.

5. Limitations

A number of limitations should be taken into account when interpreting the findings of the review. Firstly, we reviewed the literature of a new and developing field with a small number of studies. In some cases only preclinical data were available and their translation to the human condition inevitably limits the reach of the conclusions. Secondly, the information regarding the optimal conditions for pulsed electromagnetic field stimulation is still far from complete. For example, do different frequencies have a similar effect on brain tissue? We tried to report all the elementary parameters such as frequency, strength of the used electromagnetic field and the induced electric field, but encountered several problems. Some of the papers did not report all of these parameters, and there was also a general lack of uniformity especially with the strength of the induced electric field which could vary in magnitude from 0,4 V/m (Straaso et al. 2014) to 40 V/m (Rasouli et al. 2012). Fortunately, the studies explicitly describing the antidepressive effects of tPEMF stimulation did use similar parameters.

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7. Financial Disclosures

RK is cofounder and co-owner of microTMS B.V., a company that develops and sells magnetic stimulators. RK is owner of Magnolia Therapeutics, a company that offers magnetic stimulation and counseling directly to the public.

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Part 2

Quantifying treatment resistance in depression

Chapter 4

Validity of the Maudsley Staging Method in predicting treatment resistant depression outcome using the Netherlands Study of Depression and Anxiety

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Objective
We investigated if the degree of treatment resistance of depression, as measured by the Maudsley Staging Method (MSM), is predictive of a worse depression outcome by using a large naturalistic cohort of depressed patients.

Methods
643 subjects from the general population, primary care, and secondary care who suffered from current depressive disorder were included from the Netherlands Study of Depression and Anxiety (NESDA) baseline assessment. The diagnostic criteria was Major Depressive Disorder (MDD) in the last month, based on the Composite Interview Diagnostic Instrument (CIDI), or a CIDI diagnosis of MDD in the past 6 months with an Inventory of Depressive Symptomatology Self- Report score >24 at baseline. In these subjects, composite scores of the MSM, based on duration, severity, and treatment history of current episode, were determined retrospectively. We then determined if the MSM score prospectively predicted the 2-year course of depression after baseline. The primary outcomes were percentage of follow-up time spent in a depressive episode and being "mostly depressed" (≥50% of the follow-up) between baseline and 2-year follow-up.

Results
The MSM predicted "percentage of follow-up time with depression" (P<.001) and was associated with being "mostly depressed"; (OR=1.40; 95% CI, 1.23 – 1.60; P<.001). These effects were not modified by having received treatment.

Conclusion
The current study shows that the MSM is a promising tool to predict worse depression outcomes in depressed patients. In this study that adds to previous work, we show the applicability of MSM in a wider range of primary and secondary care patients with depression.

1. Introduction

Treatment of major depressive disorder (MDD) mainly consists of different forms and combinations of psychotherapy and antidepressant medication. Overall, it has moderate efficacy (Cipriani et al. 2009; Cuijpers, Berking et al. 2013; Cuijpers, Sijbrandij et al. 2013; de Maat et al. 2007). However, treatment appears not to be effective for a particular group of patients, who are then categorized as suffering from Treatment Resistant Depression (TRD). In the largest treatment study to date, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D), 49% of patients 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 (Rush et al. 2006). Remission-rates gradually declined with each sequential step thereafter. Moreover, in this study, even after 4 treatment trials 33% of patients had not achieved remission (Rush et al. 2006). Treatment resistance is the main cause for the large societal costs of depression (Greden 2001; Ivanova et al. 2010). Timely identification of patients with treatment resistance would provide the opportunity of an earlier start of intensified treatment regimes to address MDD-symptoms more aggressively with potentially better health-care outcomes.

Unfortunately, research on TRD is hampered by the lack of consensus on its definition. It is often categorically defined as non-response to ≥2 adequate antidepressants trials

(Berlim and Turecki 2007a; Berlim and Turecki 2007b; Ruhe et al. 2012; Souery et al. 1999; Souery, Papakostas, Trivedi 2006). However, over 10 other definitions of TRD have been proposed, differing mostly on the number of pharmacological treatment steps patients have had (Berlim and Turecki 2007a; Berlim and Turecki 2007b; Malhi et al. 2005). Furthermore, although TRD is mostly represented as a dichotomy, this does not seem to represent clinical reality, as was shown in the STAR*D and other antidepressant switch-trials (Ruhe et al. 2006; Rush et al. 2006). TRD might therefore better be considered as a dimensional construct (Berlim and Turecki 2007a; Ruhe et al. 2012). Treatment resistance, then, is scored on a spectrum, running from quick remission (sometimes even without treatment) to the other extreme: severe treatment resistance when no treatment response occurs after ECT and other third-line treatment regimens.

Over the last decade, progress has been made in methods to quantify TRD and use this quantification to predict the course and outcome of depression (Ruhe et al. 2012). However, these methods have been validated to a limited extent only. Of these methods, the Maudsley Staging Method (MSM) appeared to be one of the most promising (Fekadu, Wooderson et al. 2009b; Ruhe et al. 2012). The MSM was created to represent the broad theoretical basis of treatment resistance and is aimed at predicting outcome of depression. In developing the MSM, incorporation of severity and duration in predicting worse depression outcome showed added value, as these are strong and consistent predictors of the prognosis of MDD (Spijker et al. 2002; Spijker et al. 2004; Vuorilehto, Melartin, Isometsa 2009). Both the MSM as a whole as well as its different components were shown to independently predict both failure to achieve remission (Fekadu, Wooderson et al. 2009b) and persistence of the depressive episode (Fekadu, Wooderson et al. 2009a).

However, the MSM has only been investigated using a relatively small sample (n=88) of patients who were treated in tertiary care (Fekadu, Wooderson et al. 2009a; Fekadu, Wooderson et al. 2009b). Generalizability to the much larger community-based population of depressed patients and those attending primary and secondary care is required to maximize the utility of the tool for predicting remission, episode persistence and/or future treatment resistance. Therefore, the aim of this study was to further validate the predictive value of the MSM. We examined if the degree of treatment resistance over its full spectrum, as measured by the MSM, is predictive for a chronic course of illness using the large naturalistic cohort of the Netherlands Study of Depression and Anxiety (NESDA) (Penninx et al. 2008). We expected the MSM to be predictive of the longitudinal course of illness during 2 years of follow-up.

2. Methods

2.1. Setting

The Netherlands Study of Depression and Anxiety (NESDA) is a multi-site, naturalistic cohort study with data from 2329 patients with MDD and/or anxiety, sampled from the general population (by interviewing household members of private households or children of parents who were treated for depressive disorder), primary care (i.e. general practitioner), and secondary care (i.e. specialized mental health institutions), and 652 controls, aged 18 through 65 (Penninx et al. 2008). After approval from the Medical Ethics Review Committee of the VUmc, written informed consent of every subject was obtained.

2.2. Sample

Inclusion criteria for our study were: (i) a diagnosis of MDD in the last month (based on the Composite Interview Diagnostic Instrument (CIDI, lifetime version 2.1) (Wittchen 1994) or a CIDI diagnosis of MDD in the past 6 months with an IDS-SR score >24 (the clinical cutoff value for moderately severe depression (Rush A.J. et al. 2008; Rush et al. 1996)) at baseline, (ii) availability of all data needed to calculate the MSM score and (iii) availability of sufficient data to determine outcome during 2 years follow-up. To cover the full spectrum of treatment resistance, from null to a more severe form, we also included depressed subjects from primary or secondary care who had not yet received treatment, as well as subjects from the general population who despite having depressive symptoms had not yet sought treatment.

2.3. Determinants: MSM

The MSM is composed of three items: (i) duration; which is scored 1 to 3, (ii) severity; which is scored 1-5 and (iii) treatment failures. Treatment failures are scored 0 to 5 with regard to antidepressants used in the current episode, 0 or 1 with regard to augmentation used in the current episode, and 0 or 1 with regard to ECT used in the current episode (Fekadu, Wooderson et al. 2009b). (See Supplemental Methods, eTable 1 for a reprint of the MSM published by Fekadu et al. (Fekadu, Wooderson et al. 2009b)) We used different variables from the NESDA database to obtain the three item-scores to determine the degree of treatment resistance. (i) Duration of the current episode at baseline was established using the retrospective Life-Chart Interview (LCI) (Lyketsos et al. 1994). The LCI relies on self-generated and affectively laden landmarks as anchors for participants to refresh memory. After determining these anchors, presence and severity of depressive symptoms was assessed during each quarter of the past four years prior to baseline. (ii) Severity of depression was

assessed according to DSM-IV, as determined by the CIDI. (iii) Treatment history was scored based on the amount of subsequently used antidepressants and augmentation strategies during the index-episode, at and prior to baseline. A specific drug was scored as being used if the frequency of use was on a daily basis, if the dosage was at least the Daily Defined Dose and if it was used for at least 4 weeks (1 month) (WHO Collaborating Centre for Drug Statistics Methodology 2016). (See also Supplementary Methods.) The subscores of these three items (duration, severity, and total score of treatment failures) are added together to obtain a total score.

2.4. Outcome: Course trajectory of depression in NESDA

In the present paper, following Fekadu et al. (Fekadu, Wooderson et al. 2009a), we focused on the intensity and duration of depressive symptoms during 2-year follow-up in subjects with a depressive disorder (index episode) at baseline. In order to predict the course of the depressive episode after baseline, the primary outcome was persistence of the depressive episode based on LCI- data between baseline and 2-year follow-up. We made two different variables: (i) the variable 'percentage of follow-up time with depression' was expressed as the ratio between months spent in a depressive episode since baseline until remission, divided by total follow-up time (24 months). In line with the prevailing method in the NESDA-database (Penninx et al. 2011), remission was defined as experiencing a period of three consecutive months without symptoms, or with symptoms but without burden or interference with life (as indicated by the participant). The month of remission was defined as the first month after this three-month period. (ii) Analogous to the previous validation study (Fekadu, Wooderson et al. 2009a), we defined the categorical variable 'persistent depression' as being persistently depressed for ≥50% of the time of our follow-up period of two years.

For our secondary outcome we used course trajectories as described in NESDA by Rhebergen et al. (Rhebergen et al. 2012). Rhebergen used latent class growth analysis (LCGA), a statistical data-driven technique to describe patterns inherently present in data, in this case representing depression course trajectories. In brief, with input of LCI-data from NESDA Wave 3 which covers the entire 2-year follow-up period, five course trajectories were identified: (i) a quick remission course, (ii) a decline course with moderate severity, (iii) a decline course with high severity, (iv) a chronic course with moderate severity and (v) a chronic course with high severity (Rhebergen et al. 2012).

2.5. Statistical analysis

Analyses were performed with IBM-SPSS, version 20 (IBM, Chicago IL, USA).

Analyses for primary outcomes were performed using linear regression analysis and logistic regression analysis for 'percentage time depressed' and 'persistent depression', respectively. For our secondary outcome we used multinomial logistic regression to calculate maximum likelihood estimates of odds ratios (ORs) and 95% confidence intervals (CIs) for course trajectories. The 'quick remission' trajectory served as a reference group.

In order to examine the effect of treatment received during the study, which was not offered to all participants in this naturalistic study, we looked for effect-modification by dichotomizing the group on having received pharmacological treatment after baseline (including treatment started on baseline itself) or not. We performed stratified analyses on primary outcomes and modeled interaction terms in the regression analyses with total MSM score to estimate significance of effect-modification if present.

We analyzed the effect of both the total MSM score as well as its components independently. P-values of $p < 0.05$ were considered significant.

3. Results

3.1. Descriptive

Out of the total sample of 2981 NESDA participants, exclusion of controls (n = 652) and patients not meeting the inclusion-criteria of having an ongoing episode of depression at baseline resulted in a raw sample of 965 depressed persons. Due to missing data amongst variables required for MSM-scores, our second inclusion criterion narrowed this sample down to 829. Regarding gender distribution, age, and education, this sample was comparable to the raw sample. The third inclusion criterion, regarding the availability of follow-up data, resulted in 643 respondents up for analysis. Regarding gender distribution, age, and education, this sample was comparable to the raw sample. Moreover, MSM-scores were comparable as well: in the sample of 829 subjects, mean score was 4.92 (SD: 1.20), while in the final sample (n=643), this was 4.93 (SD: 1.22). See Supplemental Results, eFigure 4.1 for flow-chart of patient disposition.

Of our sample, mean age was 41 years (SD: 12.2), 428 (67%) were female and 304 (47%) had a first depressive episode (Table 4.1). A total of 560 (87%) subjects suffered from depression for less than or equal to 12 months prior to baseline. Further, 51 (8%)

Table 4.1: Demographics and characteristics with distribution over categories of final sample (n = 643).

Variable	n (%)	Mean (SD)	Median (IQR)
Age, y		41±12.2	
Female gender	428 (67%)		
Sample origin			
General population	43 (7%)		
Primary Care	228 (36%)		
Secondary Care	372 (58%)		
Education			
Basic	64 (10%)		
Intermediate	414 (65%)		
High	165 (26%)		
Depression type			
MDD first episode	304 (47%)		
MDD recurrent episode	339 (53%)		

Variable	n (%)	Mean (SD)	Median (IQR)
Duration of episode (scoring 1-3)			
Acute (≤12 mo)	560 (87%)	1.21±0.57	1 (2)
Sub-acute (13 – 24 mo)	32 (5%)		
Chronic (> 24 mo)	51 (8%)		
Symptom severity (at baseline) (scoring 1-5)			
Subsyndromal[a]		3.15±0.81	3 (2)
Mild	168 (26%)		
Moderate	210 (33%)		
Severe without psychosis	265 (41%)		
Severe with psychosis[a]			
Antidepressants used in current episode (scoring 0-5)			
None[b]	310 (48%)	0.57±0.60	1 (3)
Level 1: 1 – 2	302 (47%)		
Level 2: 3 – 4	28 (4%)		
Level 3: 5 – 6	3 (0%)		
Level 4: 7 – 10			
Level 5: > 10			
Augmentation used in current episode (0-1)			
Not used	622 (97%)	0.03±0.18	0 (1)
Used	21 (3%)		
ECT[a] used in current episode (0-1)			
Not used			
Used			
MSM-total		4.93±1.22	5 (6)

[a] This information is not available in the Netherlands Study of Depression and Anxiety database-database;

[b] This item is not scored in the original MSM.

Abbreviations: ECT = electroconvulsive therapy, IQR = interquartile range, MDD = major depressive disorder, MSM = Maudsley Staging Method.

already had a chronic depressive episode at baseline, i.e., had been depressed for >24 months. Of the subjects 265 (41%) had a severe depression and 310 (48%) had not used antidepressants at baseline. The median number of AD-drugs used at baseline

was 1. Twenty-one patients (3%) had used augmentation medication at baseline. The mean MSM-score was 4.9 (SD: 1.2).

3.2. Prediction of course of illness during follow-up

Regarding our primary outcomes, the MSM significantly predicted 'percentage time depressed' ($p<.001$) and was significantly associated with 'persistent depression' (≥50% of the follow-up) (OR=1.40 (95% CI 1.23 – 1.60); $p<.001$) (Table 4.2). Participants in this group were on average depressed for 89% of the follow-up period. Correction for age and sex did not substantially affect these outcomes (available on request).

We examined how individual model components predicted 'percentage time depressed' and depression during follow-up. Except augmentation, individual model components in both models univariately predicted a chronic depression during follow-up. In the multivariate model, duration and severity in both models predicted a chronic depression during follow-up. Prediction of the secondary outcome course trajectory showed that each point increase on the MSM significantly predicted a worse course of depression over the following two years (Table 4.3). Correction for age and sex did not substantially affect these outcomes.

3.3 Sensitivity analyses

When we stratified the predictions for those who received pharmacological treatment or not, this showed slightly lower estimates in the 'received treatment' group, indicating some modification of effect. However, for the prediction of '% time depressed', stratification resulted in absence of significance ($p = .059$) for those who did receive treatment. The MSM was significantly associated with 'persistent depression' (≥50% of the follow-up) in both subgroups that received treatment or those who did not. The interaction MSM*treatment was not significant for any of these outcomes (see supplemental; eTable 4.2).

The stratified analysis of our secondary outcome revealed an absence of significance for patients who received pharmacological treatment for the course trajectories 'decline course, moderate severity' and 'chronic course, high severity'. Moreover, patients who had not received pharmacological treatment showed an absence of significance for the course trajectories 'decline course, high severity' and 'chronic course, moderate severity' (eTable 4.3). The MSM-score by treatment interaction showed no significant results for either course trajectory (eTable 4.4).

Table 4.2: Prediction of Time being depressed ('% time depressed'; linear regression model)[a] and Persistent depression (logistic regression model)[b].

% Time depressed	B	95% CI	p-value
Univariate models of individual items			
Duration	0.076	0.027 – 0.126	.002
Severity	0.061	0.025 – 0.096	.001
Antidepressants	0.055	0.007 – 0.103	.026
Augmentation	0.096	-0.069 – 0.262	.254
Multivariate model of individual items[c]			
Duration	0.079	0.030 – 0.128	.002
Severity	0.058	0.022 – 0.094	.002
Antidepressants	0.037	-0.011 – 0.086	.130
Augmentation	0.064	-0.100 – 0.229	.442
Final model[d]			
MSM-score	0.057	0.034 – 0.081	< .001
Persistent depression	**OR**	**95% CI**	**p-value**
Univariate models of individual items			
Duration	1.90	1.41 – 2.57	< .001
Severity	1.31	1.08 – 1.59	.007
Antidepressants	1.36	1.05 – 1.77	.020
Augmentation	1.90	0.78 – 4.64	.161
Multivariate model of individual items[e]			
Duration	1.94	1.43 – 2.62	< .001
Severity	1.30	1.07 – 1.60	.010
Antidepressants	1.25	0.95 – 1.65	.105
Augmentation	1.62	0.65 – 4.05	.303
Final model[f]			
MSM-score	1.40	1.23 – 1.60	< .001

[a] Linear regression model: to test for the variable 'percentage time depressed' as independent variable.

[b] Binary logistic regression model: MSM score as a dependent variable and the variable 'persistent depression' as independent variable. Both models left uncorrected.

[c] Akaike information criterion (AIC): -590,79; [d] AIC: -595,93; [e] AIC: 865,85; [f] AIC: 866,95.

Abbreviations: MSM = Maudsley Staging Method, OR = odds ratio.

4. Discussion

In the present study we aimed to assess whether the MSM predicts the two-year course of MDD in a population-based cohort of depressed subjects. Our study shows that higher MSM-scores adequately predict worse depression outcomes in a large and clinically heterogeneous sample of MDD patients recruited in the general population, primary care, and secondary care who were followed up over a two-year period. Furthermore, this prediction appeared independent of treatment provided at baseline or during follow-up. This suggests that, in addition to the tertiary population studied by Fedaku et al. (Fekadu, Wooderson et al. 2009a; Fekadu, Wooderson et al. 2009b), the MSM can also be used in general psychiatric practices and that the MSM can be used for both prediction of treatment outcome and course of MDD.

Table 4.3: Prediction of different course trajectories[a]

Course trajectory	N	OR	95% CI	p-value
Quick remission course	265 (41%)		Reference	
Decline course, moderate severity	165 (26%)	1.30	1.10 – 1.53	.002
Decline course, high severity	69 (11%)	1.56	1.25 – 1.95	< .001
Chronic course, moderate severity	93 (15%)	1.50	1.22 – 1.83	< .001
Chronic course, high severity	51 (8%)	1.46	1.13 – 1.88	.004

[a] Final model: $\chi 24 = 28{,}625$, $P < .001$. Multinomial logistic regression model for showing maximum likelihood estimates of odds ratios (OR) and 95% confidence intervals (95% CI) for all courses of depressive symptoms in relation to Maudsley Staging Method scores. Quick remission was taken as reference. Model left uncorrected.

When comparing our sample to Fekadu's, the current sample has a lower overall MSM-score (4.9 (SD: 1.2) vs 10.7 (SD: 2.3)) (Fekadu, Wooderson et al. 2009b). Indeed, the current sample is more heterogeneous and less often chronically ill, although, in terms of dispersion, our samples appear to have similar variance. In our sample 8% had a chronic course at baseline, compared to 61% in the sample of Fedaku (Fekadu, Wooderson et al. 2009a; Fekadu, Wooderson et al. 2009b), whereas mild depression was present in 26% versus 10% respectively. Also, our sample has a greater variety of severity of depression and overall a less extensive treatment history. In the Fedaku sample 13% had been using only 1 or 2 antidepressants and most subjects had been using more medications (Fekadu, Wooderson et al. 2009b). In our sample, 47% had been using only 1 or 2 antidepressants. To cover the full spectrum of treatment resistance we also included patients from primary or secondary care who had not been using any antidepressant medication for the current episode at baseline but who did receive treatment during follow-up. By showing no significant interaction

(MSM*received treatment) we show that the MSM can both predict course of illness and chances of unfavorable outcome irrespective of treatment during follow-up.

Despite the sample differences between these studies, the MSM performed equally well with regard to predictive validity. First, we found a positive linear correlation between the MSM-score and time subjects remained depressed, suggesting that subjects who have a higher MSM-score will remain depressed for a longer time. Second, we found that a one-point increase on the MSM was associated with 1.4-fold increased odds of being depressed for most of the follow-up time. This is comparable to the OR of 1.5 reported in tertiary care (Fekadu, Wooderson et al. 2009a). Given this remarkable similarity, this suggests that the MSM is applicable in the full spectrum of persons with depression ranging from the population to tertiary care levels and that it can be validly used for predicting untoward depression outcomes across those different groups.

The individual components of the MSM showed predictive validity. In multivariate analyses, duration and severity contributed significantly to the final models, either linear or logistic, while treatment history did not any longer. This could be explained by the fact that severity at baseline correlates with the initiation of pharmacological treatment (i.e. antidepressant use; this correlation was 0.17 ($p<.001$) in our sample).

The difference between how well both models –the multivariate model containing the individual items and the final model containing only the total score– fitted the data was however small. As an indication of the optimal fit of these models, we computed the Akaike Information Criterion, indicating explained variance penalized for the number of explanatory variables (smaller is better). The multivariate model fitted slightly less well (AIC: -590.79) than the model with only the MSM-score (AIC: -595.93), when tested in a linear regression. When tested in a logistic regression, the reverse was true (AIC: 865.85 for the multivariate model versus AIC: 866.95 for the MSM-score only). We therefore propose to retain treatment history in the model. Previous models of quantifying TRD, like the Thase and Rush Staging Method (TRSM) (Thase and Rush 1997) or a variation thereof, the Massachusetts General Hospital staging method (MGH-S) (Fava 2003) only used the number of classes of antidepressants (TRSM) or the number of failed trials (MGH-S) to which the patient has not responded. We however show that prediction of outcome is improved when clinical variables are included apart from failed treatments.

With regard to our secondary analyses, the MSM significantly predicted chronic course trajectories (Rhebergen et al. 2012). These two-year course trajectories, modeled with accurate information of symptom levels on a per month basis, better

represent the course of illness than merely the percentage of time being depressed or a dichotomous distinction between more or less than 50% of time spent in depression. As such these results confirm the validity of the MSM to predict treatment resistant depression even further.

A limitation of our study is that NESDA is a naturalistic cohort-study, describing the course of depression irrespective of treatment. This potentially limits the scope of our conclusions on treatment resistance. Investigations of treatment-effects in naturalistic cohorts like NESDA may be hampered by several factors. This include confounding by indication as a result of physician preferences and current treatment algorithms (Spijker and Nolen 2010), meaning that there are reasons for participants to receive different pharmacological treatments based on their clinical presentation (e.g. higher disease severity), and that these reasons then are found to be associated with treatment resistance or other outcomes. Secondly, power may be insufficient to address all possible treatment strategies. However, most investigations of other tools to predict TRD show that prediction of treatment outcome is possible irrespective of the precise description of the treatment provided (Fava 2003; Fekadu, Wooderson et al. 2009a; Fekadu, Wooderson et al. 2009b; Thase and Rush 1997). Furthermore, we found little evidence of effect-modification by pharmacological treatment in our study, so the predictive value of the MSM seemed independent of receiving pharmacological treatment.

In line with this, another limitation of the NESDA-cohort is the limited availability of exact (pharmacological) treatment data. Although we know the minimal and maximum dose prescribed per antidepressant received and operationalized adequate dosages, we cannot infer the exact time-periods of 'adequate treatment' (i.e. at minimal effective dose for at least 4 weeks) nor compliance to the prescribed treatments. As a result, the number of adequate trials of antidepressants at baseline or the adequacy of received treatment after baseline might have been overestimated.

We used the number of symptoms recorded according to the CIDI to determine severity. Instead one might expect a more direct score from e.g. the IDS-SR. Here, we followed the initial method proposed by Fekadu et al. (Fekadu, Wooderson et al. 2009b), which might also better reflect daily clinical practice. This method was chosen to increase the applicability of the MSM for clinical practice. To assess whether our method of scoring severity affected our outcomes, we repeated the main analysis with the IDS-score as a severity measure (see eTable 5 in Supplementary Results), which did not substantially affect outcomes. An additional analysis in which we left severity out of the MSM and tested a three-way interaction MSM*severity*received treatment, resulted in a non-significant finding, both for severity as scored by CIDI-

criteria (p = 0.215) and for severity as scored by the IDS (p = 0.670). So, our results are not affected by an interaction with severity.

Future studies are needed to establish whether specific treatments are especially effective in certain ranges of the MSM and whether such ranges are sensitive and specific for individual patients. This will be the next step to fully validate the MSM as a profiling tool to guide treatment. Whether additional variables may be helpful to improve this prediction (Ruhe et al. 2012) is another issue under debate (Peeters et al. 2016). The MSM might then be helpful for the apparent clinical need to better predict the course of depression. The MSM might enable clinicians to accurately identify patients who are at risk of developing TRD. An accurate identification could help in offering specific (or more intensified) treatment regimens in an earlier phase than we currently do. Whether this treatment should be another antidepressant, (the addition of) psychotherapy or other forms of treatment such as neurostimulation remains to be elucidated, but an accurate identification in an earlier phase might provide an important approach to achieve quicker remission of depression. Vice versa, this might also help clinicians to identify patients who have a low risk of an unfavorable course of illness. It should be noted that further study is needed to determine whether patients with lower MSM scores may actually benefit from minimal or only supportive treatment. Until then, it would be advisable to use the MSM in randomized controlled trials to quantify and potentially stratify subjects according to their level of treatment resistance (de Kwaasteniet et al. 2015), making it possible to investigate if subjects with different levels of therapy resistance will respond differently to specific treatments.

4.1. Conclusion

The current study has attempted to validate the predictive value of the MSM as a tool to quantify TRD. With consideration of the sample related limitations, we conclude that the MSM is a reliable and valid tool to predict poor outcome in depressed patients irrespective of treatment. As an addition to previous work, we show its applicability in a wider range of primary and secondary care patients with MDD, with varying and degrees of prior treatment non-response, which is relevant for the description of studied samples in trials investigating TRD. Future aims should be directed to enable the use of MSM-scores as a clinically applicable tool to guide clinical treatment selection.

5. Funding and Disclosure

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The sponsor had no role in the design, analysis, interpretation, or publication of this study.

The authors of this paper do not have any conflict of interest.

6. Additional information

The original data set for the Netherlands Study of Depression and Anxiety (NESDA) is available from http://www.nesda.nl.

Supplementary Methods

Determining MSM-scores in NESDA

Duration of current episode before baseline assessment

Duration of 1 year of less was considered acute, between 1 and 2 years was considered sub-acute, and a duration of more than 2 years chronic. For determining duration of episode, the Life chart interview (LCI) at baseline was used. The LCI asked respondents the amount of months in the year before the baseline assessment that were spent with symptoms and the highest perceived burden during these months. Due to difficulties in NESDA to determine the precise length of the depressive episode, episode duration was considered longer than the examined retrospective year if the patient had spent at least 10 months with symptoms and a burden greater than 'not troubled at all' (e.g. not meeting this criterion meant episode duration was considered 'acute').

Severity

Severity of depression was assessed according to the DSM-IV classification in three categories: (i) mild, (ii) moderate, and (iii) severe. We followed the categorization used by the CIDI [WHO 1998; Wittchen 1994]. Due to exclusion criteria of the NESDA-cohort and lack of information on psychotic symptoms, we could not score for these. Subthreshold depression was not included in the cohorts used for course descriptions and could therefore not be included in the analysis.

Antidepressants

To assess current treatment failures we made use of treatment counts in NESDA. Respondents were asked to bring their medicine boxes so an inventory of names, dosage and daily amount could be made, with a specification of medication adherence per drug taken (daily, frequent (>50%), infrequent (<50%), sporadic). Medication use was counted if frequency of use was on a daily basis, if dosage was at least the Daily Defined Dose (DDD) and if it was used for at least 4 weeks (1 month). The DDD is the average daily maintenance dose for use in adults. For the treatment of MDD this is the appropriate dosage for treatment of a moderate to severe depressive episode [WHO 2012]. The MSM specifies the use of the Maudsley Prescribing Guidelines for determining correct daily dose and sets a minimum of at least 6 weeks for adequate use [Fekadu 2009a]. Because no start and stop dates of prescribed drugs were available in NESDA, and uncertainty on when the depressive episode started exactly, medication listed in NESDA is not linked to specific episodes. An extra null category was added to include participants without any previous antidepressant use, for which a score of

0 was appointed.

Augmentation

The use of augmentation was determined for current medication use and for the whole three-year retrospective period. Medication regarded as augmentation were the following: lithium, anticonvulsants (valproic acid, carbamazepine and lamotrigine), triiodothyronine (T3, synthetic thyroid hormone), pindolol and buspirone. For counting augmentation, the same conditions for frequency, dose and duration applied. Scoring was equal to the proposed scoring in both models.

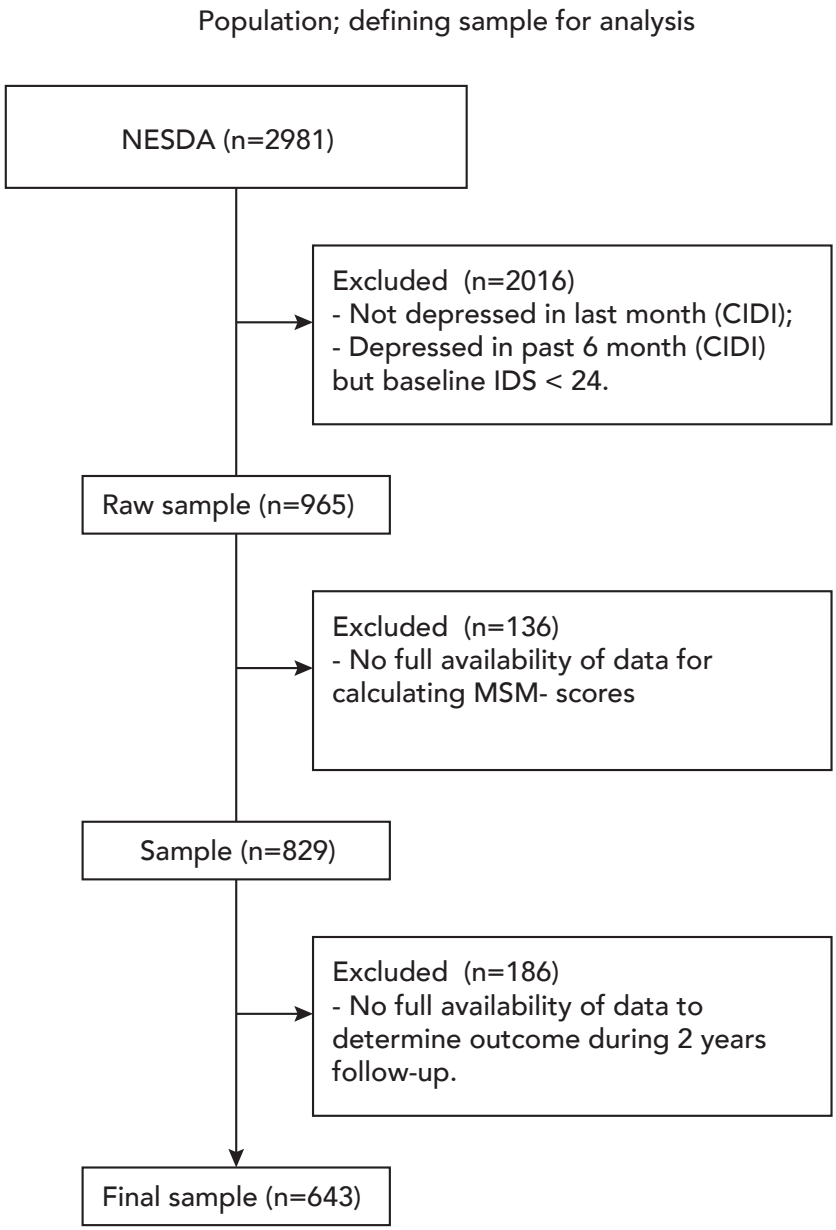
ECT

Scores of treatment with electroconvulsive therapy (ECT) could not be determined due to the fact that this was not recorded in the NESDA-database.

eTable 4.1: Original MSM-scoring, reprinted with permission (Fekadu 2009, A Multidimensional Tool to Quantify Treatment Resistance in Depression: The Maudsley Staging Method, J. Clin. Psychiatry).

Parameter/Dimension	Parameter Specification	Score
Duration	Acute (≤ 12 months)	1
	Sub-acute (13-24 months)	2
	Chronic (> 24 months)	3
Symptom severity (at baseline)	Subsyndromal	1
	Syndromal	
	Mild	2
	Moderate	3
	Severe without psychosis	4
	Severe with psychosis	5
Treatment failures		
Antidepressants	Level 1: 1-2 medications	1
	Level 2: 3-4 medications	2
	Level 3: 5-6 medications	3
	Level 4: 7-10 medications	4
	Level 5: >10 medications	5
Augmentation	Not used	0
	Used	1
Electroconvulsive therapy	Not used	0
	Used	1
Total		(15)

Supplementary Results



eFigure 4.1: Flow-chart of patient disposition.

eTable 4.2: Prediction of Time being depressed ('% time depressed'; linear regression model)[a] and Persistent depression (logistic regression model)[b].

% Time depressed	B	95% CI	p-value
MSM stratified by treatment[c]			
MSM –no treatment	0.069	0.024 – 0.125	.003
MSM –treatment	0.031	-0.001 – 0.064	.059
Persistent depression	**OR**	**95% CI**	**p-value**
MSM stratified by treatment[d]			
MSM –no treatment	1.47	1.11 – 1.94	.007
MSM –treatment	1.27	1.06 – 1.52	.020

[a] Linear regression model: to test for the variable 'percentage time depressed' as independent variable.

[b] Binary logistic regression model: MSM score as a dependent variable and the variable 'persistently depressed' as independent variable.

[c] Interaction MSM*'received treatment' (after baseline): p = .191;

[d] Interaction MSM*'received treatment' (after baseline): p = .381.

eTable 4.3: Prediction of different course trajectories stratified by treatment.

	No treatment[a]			Received treatment[b]		
Course trajectory	OR	95% CI	p-value	OR	95% CI	p-value
Quick remission course		Reference			Reference	
Decline course, moderate severity	1.44	1.04 – 2.00	0.026	1.18	0.94 – 1.49	.155
Decline course, high severity	1.50	0.89 – 2.52	0.128	1.37	1.02 – 1.83	.035
Chronic course, moderate severity	1.47	0.96 – 2.26	0.080	1.37	1.05 – 1.79	.022
Chronic course, high severity	1.74	0.90 – 3.35	0.098	1.13	0.82 – 1.55	.464

[a] Final model: chi-square (df): 8.616 (4), p < .071; [b] Final model: chi-square (df): 7.676 (4), p < .104.

eTable 4.4: Prediction of different course trajectories, including the interaction term with received treatment.

Course trajectory	OR	95% CI	p-value
Quick remission course		Reference	
Decline course, moderate severity			
MSM-score	1.44	1.04 – 2.00	.026
Interaction MSM*'received treatment'	0.82	0.55 – 1.22	.325
Decline course, high severity			
MSM-score	1.50	0.89 – 2.52	.128
Interaction MSM*'received treatment'	0.91	0.50 – 1.66	.764
Chronic course, moderate severity			
MSM-score	1.47	0.96 – 2.26	.080
Interaction MSM*'received treatment'	0.93	0.56 – 1.54	.780
Chronic course, high severity			
MSM-score	1.74	0.90 – 3.35	.098
Interaction MSM*'received treatment'	0.65	0.31 – 1.34	.242

Final model: chi-square (df): 38.546 (12), $p < .001$

eTable 4.5: Prediction of Time being depressed ('% time depressed'; linear regression model)[a] and Persistent depression (logistic regression model)[b], using IDS-SR as severity measure, instead of CIDI-methodology (complementary to Table 2).

% Time depressed	B	95% CI	p-value
Univariate models of individual items			
Duration	0.076	0.027 – 0.126	.002
Severity	0.091	0.052 – 0.130	< .001
Antidepressants	0.055	0.007 – 0.103	.026
Augmentation	0.096	-0.069 – 0.262	.254
Multivariate model of individual items			
Duration	0.060	0.011– 0.109	.017
Severity	0.077	0.037 – 0.117	< .001
Antidepressants	0.029	-0.020 – 0.078	.251
Augmentation	0.062	-0.102 – 0.226	.457
Final model			
MSM-score	0.058	0.036 – 0.080	< .001
Persistent depression	**OR**	**95% CI**	**p-value**
Univariate models of individual items			
Duration	1.90	1.41 – 2.57	< .001
Severity	1.66	1.31 – 2.08	< .001
Antidepressants	1.36	1.05 – 1.77	.020
Augmentation	1.90	0.78 – 4.64	.161
Multivariate model of individual items			
Duration	1.77	1.30 – 2.40	< .001
Severity	1.49	1.18 – 1.89	.001
Antidepressants	1.19	0.90 – 1.57	.215
Augmentation	1.61	0.64 – 4.05	.307
Final model			
MSM-score	1.45	1.27 – 1.65	< .001

[a] Linear regression model: to test for the variable 'percentage time depressed' as independent variable.

[b] Binary logistic regression model: MSM score as a dependent variable and the variable 'persistent depression' as independent variable. Both models left uncorrected.

Part 3

A novel treatment for MDD?

Chapter 5

No antidepressive effects of transcranial pulsed electromagnetic fields for treatment resistant depression – a replication randomized controlled trial

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Submitted.

Background
Noninvasive neurostimulation with transcranial Pulsed Electromagnetic Fields (tPEMF) is a promising method for the treatment of treatment resistant depression (TRD). An earlier RCT has shown substantial improvement of depressive symptoms in patients with TRD but this has not been replicated yet. Furthermore, there is no information on long-term antidepressive effects. The aim of this study was to investigate the short- and long-term efficacy of tPEMF in participants with TRD.

Methods
Eligible participants with TRD in this sham-controlled double-blind multicenter trial were randomly assigned to five weeks either daily active or sham tPEMF. Severity of depression and anxiety was assessed pre- and directly post-treatment and five and fifteen weeks post-treatment. Primary outcome was change on the 17-item Hamilton depression rating scale directly post-treatment. Secondary outcome was change on the Hamilton-17 during follow-up and change on the Inventory of Depressive Symptomatology Self-Report and the Beck Anxiety Index.

Results
Of the 55 included participants, 50 completed the treatment protocol. Depressive symptoms improved over time, independent of treatment type. The improvement continued after until the last follow-up measure. There was no difference in outcome between the active and the sham group on change in depression post-treatment or on any secondary measure.

Conclusion
Treatment with active tPEMF was not superior to sham in patients with TRD. This is in contrast to a previous study using a similar design and power calculation that reported improvement of depression after treatment with tPEMF compared to sham.

The trial was registered at the Dutch Trial Register (http://www.trialregister.nl), NTR3702.

1. Introduction

Treatment of depression is often challenging; up to one third of patients suffering from a severe major depressive disorder (MDD) do not respond to four consecutively prescribed antidepressants (Rush et al. 2006) and are suffering from Treatment Resistant Depression (TRD). TRD is the main cause for the large societal costs of depression (Greden 2001; Ivanova et al. 2010), making it paramount to improve treatment efficacy of MDD. To do so, new treatment possibilities are being investigated, of which non-invasive neurostimulation is of growing interest (Holtzheimer and Mayberg 2012).

Non-invasive neuromodulation for depression can be categorized into two broad categories: local or global modulation. Local modulation relies on modulation of local brain regions, for example using repetitive Transcranial Magnetic Stimulation (rTMS) (Allan, Herrmann, Ebmeier 2011). In rTMS, modulation of local brain regions is achieved by depolarization of the neuronal membrane by inducing electric currents in the brain (Barker, Jalinous, Freeston 1985), rTMS has become an established treatment for TRD and has been included in the NICE-guidelines (https://www.nice.org.uk/guidance/ipg542).

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). An important development

in this field of research was the study conducted by Martiny et al. (Martiny, Lunde, Bech 2010). This research group adapted a magnetic stimulation method mostly used in orthopedics dubbed 'Pulsed Electro-Magnetic Fields' (PEMF) (Hannemann et al. 2014; Ryang We et al. 2013). Martiny et al. have applied this treatment transcranially (tPEMF) in patients with TRD and investigated the efficacy in a Randomized Controlled Trial (RCT). After five consecutive weeks of daily stimulation, depression severity (measured with the Hamilton Depression Rating Scale-17 (HAMD-17)) decreased significantly more in the active stimulation group compared to sham stimulation (Martiny, Lunde, Bech 2010).

Other RCTs have also shown a positive effect of global neuromodulation using pulsed electromagnetic fields, although different parameters with regard to pulse frequency, field strength and amount of coils were used (Leuchter et al. 2015; Rohan et al. 2013). For example, in one RCT the effect of a portable electromagnetic device producing rapidly oscillating electromagnetic fields was investigated. An immediate positive effect on depression severity in patients with a unipolar or bipolar depression was found after a single treatment-stimulus (Rohan et al. 2013). Another study has used a device with three rotating magnets (synchronized TMS or sTMS) and also showed some antidepressive effects (Leuchter et al. 2015).

Global stimulation adds an interesting branch to the expanding antidepressive neuromodulation tree, but only a few RCTs investigating global stimulation with weak electromagnetic fields have been reported, all differing in their stimulation parameters. Up until now only one RCT has investigated the specific effects of tPEMF on depression (Martiny, Lunde, Bech 2010) with no information on the long-term duration of the antidepressive effect.

Using a lightweight neurostimulator, that previously was found to be effective against experimental pain in healthy subjects (Kortekaas et al. 2013), we aimed to replicate the study of Martiny et al. (Martiny, Lunde, Bech 2010) of antidepressive effects in TRD. Moreover, we aimed to investigate long-term effects, and to evaluate the effect of tPEMF on the brain (reported separately).

2. Methods and materials

2.1. Study design

We included 55 depressed participants in a double blind, randomized controlled multicenter trial comparing active tPEMF treatment versus sham treatment in a 1:1 ratio, in three mental health institutions in the north of The Netherlands (Department of Psychiatry of the University Medical Center Groningen (UMCG), the mental healthcare provider GGZ Drenthe, and the Department of Psychiatry of the general hospital in Sneek). This study was approved by the Medical Ethical Committee of the UMCG, and at the study coordination center of each participating site. Written informed consent was obtained from each participant. The study was conducted according to the Declaration of Helsinki. The trial was registered at the Dutch Trial Register (http://www.trialregister.nl), part of the Dutch Cochrane Centre, under number NTR3702.

2.2. Study population

We recruited patients at major mental health care institutions (regular and academic mental health care institutions) in the northern part of the Netherlands and via media coverage. We included patients who met DSM-IV criteria for MDD and who were at the time in a first or recurrent depressive episode, assessed by the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al. 1998). Inclusion criteria were presence of at least a moderately severe depression (>17 on HAMD-17), non-responsiveness to one or more antidepressants, given for at least four weeks and in an adequate dose (i.e. the defined daily dose (DDD) (WHO Collaborating Centre for Drug Statistics Methodology 2016)) during the current episode, age between 18 and 80 years, and having a good understanding of the Dutch language (including writing skills). We included both in- and outpatients.

Exclusion criteria were presence of MDD with psychotic features, other major psychiatric disorders such as a primary psychotic disorder or an antisocial or borderline personality disorder, a neurological disorder such as dementia or epilepsy, visual or hearing problems that could not be corrected, suicidal thoughts (>2 on HAMD-17 for suicidal ideation) or a history of a serious suicide attempt, recent (past three months) alcohol or drug abuse or dependence, pregnancy, lactation, inability to comply with treatments and/or assessments, recent change (last four weeks) in antidepressant medication or requirement to change antidepressant medication during the course of the study, use of benzodiazepine(s) more than 2 mg lorazepam or equivalent per day within the last four weeks or during the course of the study, use of medication indicated for a somatic disease that may have affected mood within the last four

weeks, excessive use of coffee (>10 units per day) or alcohol (>5 units per day), or recent use (within four weeks) of cannabis or any other non-prescribed psychotropic drugs or unwillingness to abstain from these substances during the study. The use of antipsychotics and lithium was allowed. Because of the use of additional magnetic resonance imaging (MRI) (results will be reported elsewhere), there were additional exclusion criteria related to MRI incompatibility, for example the presence of metal implants in the body.

2.3. Treatment protocol

Eligible participants were randomly assigned to either five weeks active tPEMF stimulation or five weeks of sham stimulation. One of the authors (SvB) enrolled participants. Stimulation was administered by trained members of the research team who were present during the whole session, under medical supervision of one of the authors (SvB). Two identical tPEMF-stimulators were used for treatment at the different treatment sites and were moved if necessary. During a session, participants were seated next to the PEMF-stimulator in a quiet room while wearing the treatment cap. There were no restrictions for participants during these sessions and talking was allowed on their own initiative. Sessions took place every weekday for 30 minutes during office-hours, on the same time every day, with minimal deviations.

Properties of the magnetic stimulator have previously been published in detail (Kortekaas et al. 2013). A laptop computer (Dell Latitude D610, Round Rock, Texas,

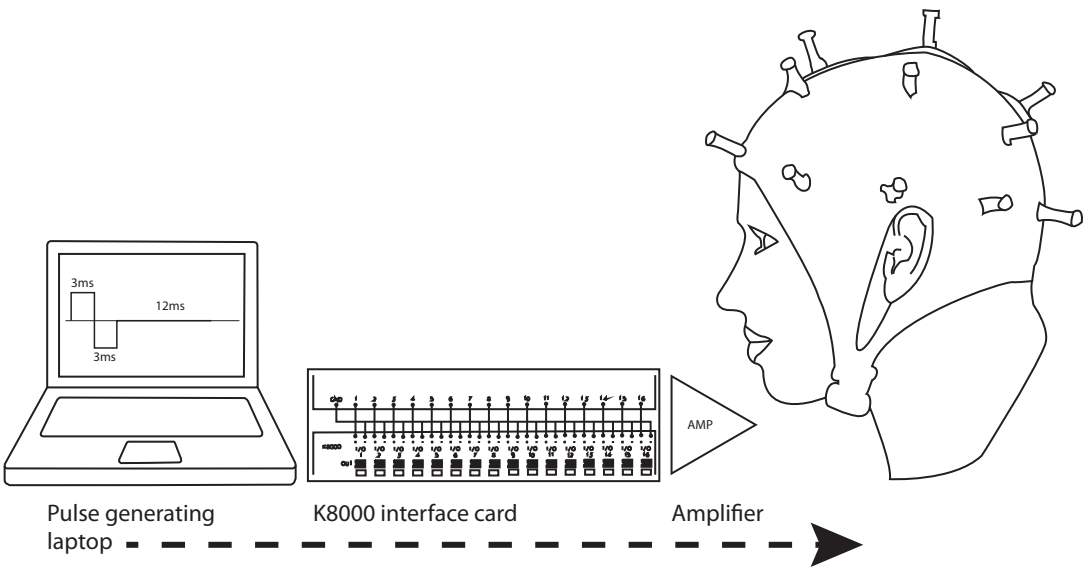

Figure 5.1: Schematic overview of the hardware. The interface card translates digital values into values. The amplifier in turn increases power.

USA) and interface card (K8000, Velleman, Gavere, Belgium) were used as a waveform generator (see figure 1). The computer ran Xubuntu Linux (www.xubuntu.org). A low voltage DC coupled amplifier with a medical power supply and an isolation unit as additional safety features was used to increase the output power. For the active condition, alternating bipolar square pulses of 7 V were used as input, equal to the bipolar pulses used in the stimulation set of Martiny et al. (Martiny, Lunde, Bech 2010). The stimulation pattern consisted of 3 ms north and 3 ms south and 12 ms pause, thus lasting 18 ms in total. For the sham condition no pulse was generated; only a signal filled with zeroes. The stimulator did not produce sound, heat, nor skin sensations. It was thus impossible for participants and the research team to distinguish between the active and sham condition.

The electromagnets of the cap consisted of 25 mm long, 9 mm thick reed relays (Reed Relay 275–232, Radio Shack, Fort Worth, TX, USA) of which the reed switch was replaced by a steel bolt, transforming them into iron core electromagnets. Nineteen of these electromagnets were radially attached to a regular EEG cap with a chinstrap (SU-60 and KR, MedCaT, Erica, The Netherlands) using non-metallic nuts on the inside of the cap. Electromagnets were positioned according to the international 10/20 system for EEG electrodes.

2.4. Stratification, randomization and blinding

Participants were stratified by duration of the depressive episode (less or more than one year) and depression severity (HAMD-17 baseline score between 18 and 25 or 25 and higher), resulting in four strata. We did not adopt a minimization procedure (Pocock and Simon 1975). One of the authors (SvB) assigned each participant a unique subject code, composed of two parts: the first indicating the number of the stratum (1 – 4) and the second indicating the sequence of enrollment. Thus, the first subject in stratum 1 received the number 'stratum 1 participant 1', or, in abbreviated form: s1p1. These unique codes corresponded to the names of different data files on the pulse generating PC. Each data file contained a description of one of the two treatment waves that were offered: an active wave or a sham 'wave'. These data files were a direct copy of either the active master file or the sham master file and were automatically and randomly created in the preparation phase of the study by a computerized random number generator under responsibility of one of the authors (RK). Due to the sequential numbering of the data files, which were identical in appearance and were contained in an inaccessible folder on the pulse generating PCs, allocation to the treatment was adequately concealed. In order to administrate treatment, members of the research team had to enter the unique subject code. The participant, researchers and health-care personnel were all blind for the treatment condition. To assess adequate blinding,

participants were asked to guess which treatment they received. The code was broken after the last participant had completed the last measurement.

2.5. Study Outcome and psychometrics

The primary outcome was change in depression severity measured by the HAMD-17 (Hamilton 1960) immediately post-treatment. Secondary outcome measures consisted of changes in depression severity as assessed at five and fifteen week follow-up with the HAMD-17. Furthermore, we calculated response (50% improvement of HAMD-17) and remission (HAMD-17 < 8) rates, assessed weekly changes in depression severity during treatment and at five and fifteen week follow-up with the self-rated Inventory of Depressive Symptomatology Self-Report (IDS-SR) (Rush et al. 1986; Rush et al. 1996), and assessed changes of anxiety symptoms as measured with the Beck Anxiety Index (BAI) (Beck et al. 1988). At baseline, an expectancy scale with regard to the effect of treatment was administered, ranging from one to ten, one meaning low expectations and ten meaning high expectations. The degree of treatment resistance was quantified using the Maudsley Staging Method (MSM), a sum score based on duration and severity of illness and treatment history of the current episode (Fekadu, Wooderson et al. 2009b). A higher score is associated with a worse depression outcome (Fekadu, Wooderson et al. 2009a; Fekadu, Wooderson et al. 2009b; van Belkum et al. 2018).

2.6. Statistical analyses

Sample size calculation was based on change in HAMD-17 scores between baseline (week -1) and directly post-treatment (week 5) as reported in a previous publication (Martiny, Lunde, Bech 2010). Assuming a two-sided alpha level 0.05, and a beta of 0.8, we calculated n=25 per group. Participants that dropped out were replaced so that the total sample at follow-up consisted of 50 participants. Therefore, the total number of participants that started the study proportionally increased. Data were analyzed using the intent-to-treat (ITT) principle so that all randomized participants were included in the analyses.

Analyses were performed with IBM SPSS version 24.0 software (IBM, Chicago IL, USA). Baseline characteristics in each group were compared with Chi-square test, independent t-test or the Mann-Whitney U test where appropriate.

To test for the effect of treatment on the main outcome measure, a linear mixed model with a random intercept was applied with post-treatment HAMD-17 score as dependent variable and treatment group, time (baseline, week 5), the interaction between time and treatment group, and baseline HAMD-17-score as covariates.

Secondarily, we added the remaining time points (week 10 and week 20) as covariates. Subsequently we corrected for duration, type of episode (single or recurrent), number of episodes, treatment expectancy, and treatment guess by adding these variable as covariate to the model. Post-hoc we applied a linear mixed model in the four different strata, equal to the analysis of the main outcome. To test for the effect of treatment on the secondary outcome measures, we applied two different linear mixed models with a random intercept with 1) post-treatment IDS or 2) post-treatment BAI scores as dependent variable, and treatment group, time, and the interaction between time and treatment group as covariates for both dependent variables. The level of statistical significance was set at $\alpha < 0.05$.

3. Results

3.1. Sample description

Between May 2013 and October 2016 we included 55 participants, 27 female (49%). The trial ended after the aimed sample-size was reached. Participants were randomized to either the active treatment group (n = 29) or to sham treatment (n = 26). After randomization and before starting the first treatment session, two participants (both randomized for the active treatment) refused further participation. Three participants dropped out during the study: one (in the active treatment group) dropped out less than a week after starting the treatment sessions due to admittance to a closed ward because of severe suicidal ideations. Retrospectively, it became clear that these suicidal ideations were already present on baseline but had not been reported by this participant. Two other participants (one active, one sham) discontinued intervention due to absence of subjective treatment effect. Two participants did not attend the appointment at the 20-week follow-up measurement. In total, 50 participants completed all treatment sessions, 25 in each group. Data from all 55 participants were analyzed. See supplemental for the CONSORT flow diagram.

Table 5.1: Sociodemographic and clinical parameters.

Variable	Active (n = 29)	Sham (n = 26)	p-value
Age (years) (mean (SD))	49 (13)	45 (12)	.309[a]
Female gender	15 (52%)	12 (46%)	.680[b]
Marital status			.422[b]
Single	10 (34%)	9 (35%)	
Married	15 (52%)	16 (62%)	
Divorced	4 (14%)	1 (4%)	
Educational background			.460[b]
Primary	2 (7%)	0 (0%)	
Lower secondary	9 (31%)	11 (42%)	
Upper secondary	13 (45%)	12 (46%)	
University	5 (17%)	3 (12%)	
Presence of somatic complaints	18 (62%)	21 (81%)	.127[b]
MDD-type			.324[b]
MDD first episode	14 (48%)	16 (62%)	
MDD recurrent episode	15 (52%)	10 (38%)	

Variable	Active (n = 29)	Sham (n = 26)	p-value
Number of episodes (median (IQR))	2 (1 - 2.5)	1 (1 - 3)	.746[c]
Duration of current episode (months) (median (IQR))	23 (16 - 66)	33 (12 - 107)	.468[c]
Presence of comorbidity	14 (48%)	11 (42%)	.657[b]
Anxiety Disorders[d]	9 (31%)	6 (23%)	.508[b]
Personality Disorders[e]	5 (17%)	5 (19%)	.849[b]
Miscellaneous[f]	2 (7%)	0 (0%)	.173[b]
MSM-score (mean (SD))	7.8 (1.60)	8.3 (2.29)	.402[a]
Treatment expectancy (scoring 1-10) (mean (SD))	5.8 (2.3)	6.4 (2.1)	.373[a]
Correct guess to treatment allocation	12 (48%)	9 (36%)	.254[b]
Stratum			.986[b]
S1	5 (17%)	5 (19%)	
S2	20 (69%)	18 (69%)	
S3	1 (3%)	1 (4%)	
S4	3 (10%)	2 (8%)	

[a] 2-tailed t-test.

[b] Chi-square.

[c] Mann-Whitney U.

[d] General Anxiety Disorder, Panic Disorder, Social Phobia, Obsessive Compulsive Disorder, Post-traumatic stress disorder, and Not Otherwise Specified.

[e] Avoidant Personality Disorder, Obsessive–compulsive personality disorder, and Not Otherwise Specified.

[f] Asperger's disorder, Attention deficit hyperactivity disorder.

Abbreviations: MDD = major depressive disorder, IQR = interquartile range, MSM = Maudsley Staging Method.

Table 5.1 shows that the treatment groups were similar in socio-demographic data and clinical measurements (recurrence and number of episodes, duration of present episode, presence of comorbidity and the MSM-score). On the expectancy scale, mean treatment expectancy was 5.8 (SD 2.3) for participants in the active group and 6.3 (SD 2.1) for participants in the sham group. In the active group, twelve participants (48%) guessed their condition as 'active'; in the sham group sixteen participants (64%) guessed their treatment condition as 'active', indicating adequate concealment of the treatment condition. These differences between the two treatment conditions were not statistically significant.

eTable 5.1 shows the treatment history of the current episode. Most participants had used an SSRI and an SNRI, with no significant differences between both treatment groups. More participants in the sham condition had received ECT, but numbers

Table 5.2: Change in HAMD-17 scores over time, overall and per stratum.

	Overall[a]	
	Active	Sham
	Mean (SD)	Mean (SD)
HAMD week 0	22 (3.2)	22 (2.5)
HAMD week 5	16 (5.4)	17 (5.4)
HAMD week 10	15 (6.1)	14 (6.6)
HAMD week 20	15 (6.6)	13 (6.2)

	Stratum 1[b]		Stratum 2[c]	
	Active	Sham	Active	Sham
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
HAMD week 0	21 (3.0)	20 (2.1)	21 (2.3)	22 (2.1)
HAMD week 5	13 (3.7)	13 (5.0)	16 (4.4)	17 (4.7)
HAMD week 10	9 (8.2)	13 (7.6)	15 (4.6)	14 (7.0)
HAMD week 20	14 (10.0)	9 (4.0)	14 (6.0)	13 (5.0)

	Stratum 3		Stratum 4[e]	
	Active	Sham	Active	Sham
	Score[d]	Score[d]	Mean (SD)	Mean (SD)
HAMD week 0	28	26	27 (2.6)	26 (0.0)
HAMD week 5	24	30	17 (10.4)	17 (0.0)
HAMD week 10	25	18	20 (3.6)	13 (2.8)
HAMD week 20	21	23	20 (2.5)	19 (1.4)

[a] time*group interaction: F(3;66) 0.933; p = .338.

[b] time*group interaction: F(3;22) 1.069; p = .383.

[c] time*group interaction: F(3;99) 0.612; p = .609.

[d] n = 1.

[e] time*group interaction: F(3;13) 0.535; p = .667.

Abbreviations: HAMD = Hamilton-17.

were low and this difference was statistically not significant. Almost all had received a psychotherapeutic intervention, with no differences between groups. With regard to comorbidity it is clear that the most prevalent comorbid disorders were anxiety disorders. Five participants in both groups had comorbid personality disorders (DSM IV cluster C or not otherwise specified).

3.2. Effects of treatment

Mean severity at baseline was a HAMD-17-score of 22 for both groups (table 5.2). In general, participants did improve significantly over time (F 14.768; $p < .001$) (figure 5.2), but showed no difference between intervention and control group; the interaction time*group was not significant (F 0.933; $p = .338$). Correction for duration, type of episode (single or recurrent), number of episodes, treatment expectancy, and treatment guess did not affect these outcomes (eTable 5.2). The number of participants who responded (50% improvement of HAMD-17) was similar for those receiving active (3 (10%)) and sham (2 (8%)) treatment. Remission numbers were similar as well (active: 1 (3%) and sham: 1 (4%)).

In addition, there was a difference in stratum 3 between active and sham treatment of 8 points where the tPEMF participants improved and the sham participants worsened

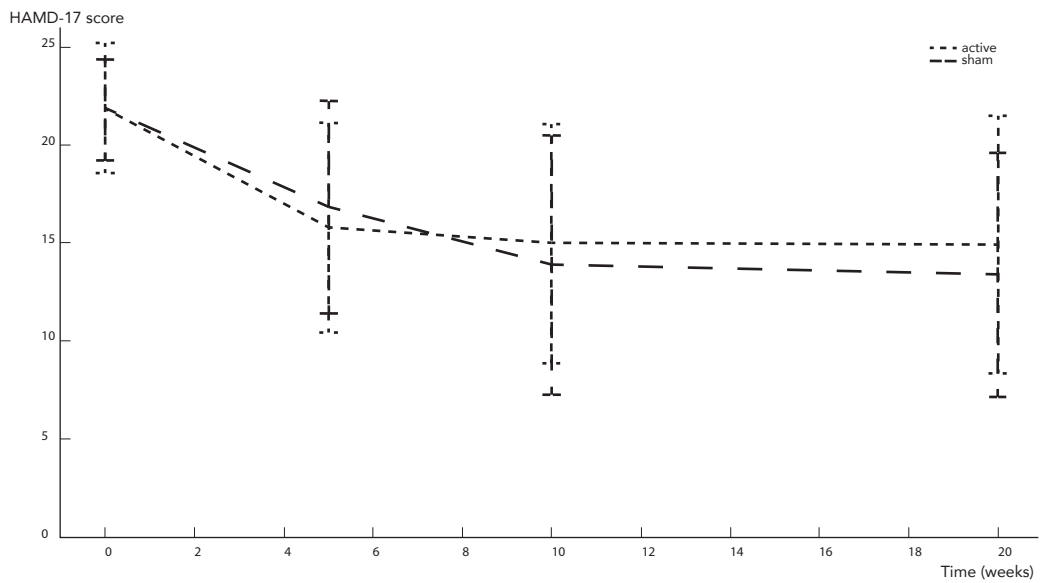

Figure 5.2: Decrease of Hamilton-17 scores over time for both groups.

Table 5.3: Change in IDS-scores over time.

	Active	Sham
	Mean (SD)	Mean (SD)
IDS week 0	44 (9.8)	45 (8.9)
IDS week 1	41 (9.7)	41 (11.2)
IDS week 2	41 (10.4)	38 (11.1)
IDS week 3	40 (10.5)	38 (12.8)
IDS week 4	37 (11.4)	36 (13.4)
IDS week 5	38 (13.3)	38 (12.4)
IDS week 10	34 (13.3)	35 (13.2)
IDS week 20	38 (14.9)	33 (15.1)

time*group interaction: F(7;340) 0.683; p = .687.

Abbreviations: IDS = Inventory of Depressive Symptomatology Self-Report.

on the HAMD-17. However, there were only two participants in this stratum (table 5.2). In the other strata the difference between active and sham treatment was minimal and non-significant. Also, no clear differences were observed between participants who used antidepressants at baseline versus participants who did not use antidepressant medication at baseline (eTable 5.3).

3.3. Secondary outcome measures

With regard to our secondary outcome measures, we found improvement of IDS-SR scores over time (F 10.002; p < .001), but no difference between the two treatment conditions directly post-treatment, and no interaction of time by group (F 0.683; p = .687) (table 5.3). The interaction time*group for the difference in BAI-score of participants was not statistical significant (F: 2.363; p = .055) (table 5.4).

3.4. Reported adverse effects

eTable 5.4 shows reported adverse effects of treatment. A total of 22 participants (40%) reported adverse events with no differences between both groups. Experience of headaches was mostly mentioned. Of those who dropped out of the study, two participants experienced headaches. They were equally distributed over both treatment conditions. None of the adverse events were cause of concern for the participant or reasons to seek medical attention.

Table 5.4: Decrease of BAI-scores over time.

	Active	Sham
	Mean (SD)	Mean (SD)
BAI week 0	22 (10.3)	28 (12.4)
BAI week 2	20 (10.6)	21 (11.4)
BAI week 5	16 (9.7)	23 (11.8)
BAI week 10	14 (9.7)	19 (11.7)
BAI week 20	18 (9.5)	18 (10.9)

time*group interaction: F(4;192) 2.362; p = .055

Abbreviations: BAI = Beck Anxiety Index.

4. Discussion

In this study we aimed to replicate the study of Martiny and colleagues (Martiny, Lunde, Bech 2010) that has shown promising results of tPEMF for patients with TRD. Using a similar design and power calculation we observed an improvement of depression severity over time that continued for fifteen weeks after the last stimulation. However, we found no differences in improvement between the active treatment group and the sham group and were not able to replicate the earlier findings (Martiny, Lunde, Bech 2010).

Several clinical variables related to treatment resistance might have influenced our results. The degree of treatment resistance in our sample was measured with the Maudsley Staging Method (MSM) (Fekadu, Wooderson et al. 2009b). Participants in our sample suffered from moderate treatment resistance (MSM-score: 8), with higher scores indicating a worse depression outcome (Fekadu, Wooderson et al. 2009a; Fekadu, Wooderson et al. 2009b; van Belkum et al. 2018). To explore whether different levels of treatment resistance may have played a role, we stratified our treatment group into four different strata, based on severity and duration of illness, which are known TRD determinants. Sub-analyses of the strata again revealed no differences in improvement of HAMD-17 between treatment conditions. Adding duration and number of antidepressants used as covariates to our analyses also did not substantially affect outcome. Furthermore, on these clinical parameters no clear difference exists between our sample and the previous sample of Martiny (Martiny, Lunde, Bech 2010). Thus, our negative findings are not likely to be due to the distribution of clinical factors that contribute to treatment resistance.

There is one aspect of this study that differs from the original study by Martiny et al. (Martiny, Lunde, Bech 2010) and that might explain the differences in findings, which is difference between the stimulation caps used in both studies. In the current study, we applied 7 V over a cap with 19 small iron core coils positioned according to the international 10/20 system (Myslobodsky et al. 1990). The induced magnetic flux density of this cap is inhomogeneous with a relative stronger magnetic field directly under the coils and a weaker field between coils. In contrast, Martiny et al. used a set of seven air coils, placed on the anterior and posterior temporal regions, the upper parietal regions, and the center of the lower occipital region (Martiny, Lunde, Bech 2010). The relevance of the difference between these treatment-caps is unclear, as the stimulation parameters are the same and inhomogeneous electromagnetic fields have a biological effect (Grossman et al. 2017). However, the difference between the treatment-caps with regard to the precise localization of the coils and the supposed aim could still be of importance. In our set-up, one of the areas covered by the

electromagnets was the frontal lobe, an area often targeted with neurostimulation in treating depression (Brunoni et al. 2016; Lepping et al. 2014). This could be considered to be an advantage of our treatment-cap over the cap of Martiny et al. (Martiny, Lunde, Bech 2010) but the results clearly did not show this. Based on our rough estimation, it could also have been possible that Martiny et al. did in fact influence the local field potentials in the anterior cingulate cortex (ACC), instead of a more global stimulation (Martiny, Lunde, Bech 2010). The ACC also plays an important role in affect in general and depression in particular (Groenewold et al. 2013; Warren, Pringle, Harmer 2015), but non-invasive neurostimulation of the ACC is often difficult due to the depth of this area, even more so when low strength magnetic fields are used. The significance of this difference between caps is thus still unclear and it is questionable if this difference could explain the dissimilarity in findings between our two studies.

In finding an explanation for the difference in findings between these two studies, there is a possibility that the effect-size of tPEMF treatment is much lower than initially thought and therefore our study may have lacked power. However, we calculated our sample size based on the effect-sizes of the previous study (Martiny, Lunde, Bech 2010) and in line with pilot studies of rTMS and tDCS (Lefaucheur et al. 2014; Lefaucheur et al. 2017). Furthermore, the effect-sizes we found were negligible, which would limit the clinical relevance of this stimulation method if replicated in larger samples.

A clear effect in our study was that the average person improved over the course of the study and that this effect lasted for at least fifteen weeks after the last treatment. Placebo effects can be of considerable magnitude in the treatment of depression. For example, effect-sizes for treatment with citalopram are higher when MDD-patients are being treated in an open label study compared to an RCT, even if the same treatment regimen is used (Rutherford et al. 2017). Martiny et al. have reported that their active stimulator did emit a faint humming sound (Martiny, Lunde, Bech 2010). Participants could thus have been partially aware of the treatment condition they were in. However, no clear evidence was found in the study of Martiny et al. that participants did actually hear the faint humming noise, as reflected by the amount of people that correctly guessed their treatment condition which was no better than chance in both groups (Martiny, Lunde, Bech 2010). This also was similar to our study, in which participants were not able to guess in what condition they were.

In line with the finding of Martiny et al., other studies with different stimulation parameters have also reported on global neuromodulation techniques (Leuchter et al. 2015; Rohan et al. 2013; Straaso et al. 2014). For example, a dose-remission study without a sham condition has found that augmentation with tPEMF stimulation in patients with TRD during eight weeks reduced HAMD-17 scores with 74% and 68%

(13 and 14 points) if treated with one vs. two daily tPEMF doses (Straaso et al. 2014). Another study, a double blind sham controlled RCT, applying Low Field Magnetic Stimulation (LFMS) to stimulate the whole cortex with oscillating electromagnetic fields in 63 depressed participants, has found that this had an immediate positive effect on depression severity (Rohan et al. 2013) . Another device with three rotating magnets has shown antidepressive effects in a double blind sham controlled RCT in 202 depressed participants (Leuchter et al. 2015). These studies point in the direction of an antidepressive effect of global neuromodulation devices, in support of the study by Martiny et al. (Martiny, Lunde, Bech 2010). However, the later studies all had methodological caveats: they either lacked a sham condition (Straaso et al. 2014) used a rating-scale not validated for measuring short-term change (Rohan et al. 2013), or found no difference on the primary outcome despite reporting some antidepressive effect (Leuchter et al. 2015).

To summarize, although there were minor differences in sample and set-up between the studies, we were not able to replicate the promising findings of an earlier tPEMF study using a similar design. For the time being the conclusion must therefore be that transcranial pulsed electromagnetic fields do not have consistent antidepressive effects. Alternatively, moderator variables that either enhance or preclude such effects may be at work and need to be identified. More studies will be needed for a more definite answer to the question whether tPEMF can be of clinical value in the treatment of TRD. In addition, studies into putative neurobiological mechanisms are needed to clarify biological plausibility for clinical effects to occur.

5. Acknowledgements

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6. Funding and Disclosure

RK is owner of Magnolia Therapeutics, a company that develops and sells magnetic stimulators and that offers magnetic stimulation and counseling directly to the public.

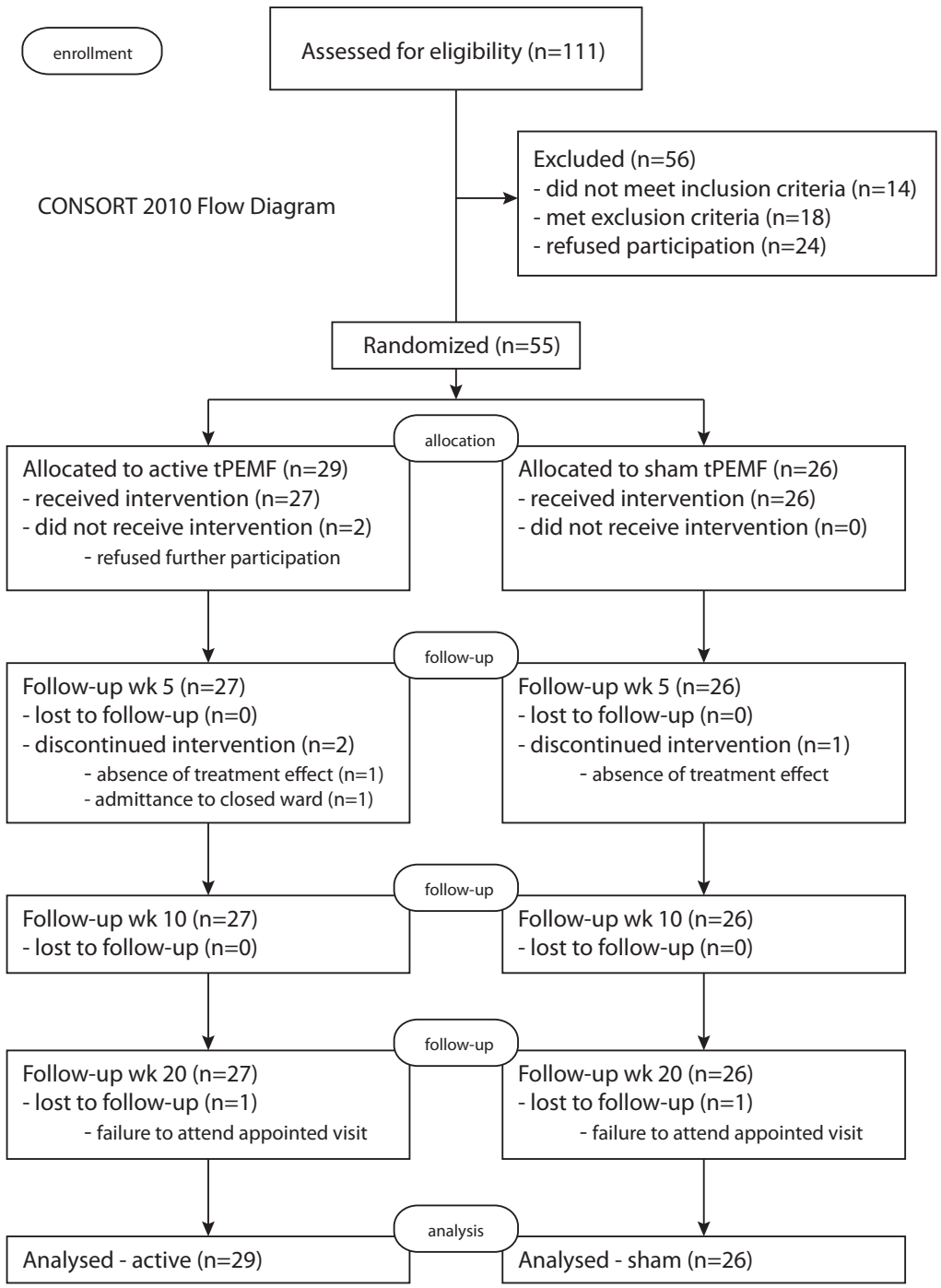
No conflicts of interests for SvB; MdB; EO; FW; RH; HK; AA; RS.

Supplementary Methods

Changes in protocol

The trial started out as a single center trial. Due to a low recruitment rate, we changed the study to a multicenter trial. Furthermore we changed our eligibility criteria. In the first protocol, inclusion criteria stated that participants should not have responded to two or more antidepressants. We changed this to not having responded to one or more antidepressant, as this was more in line with the method of Martiny et al. (2010). Furthermore, in the first protocol, mood stabilizers and antipsychotics were not allowed in the last four weeks before or during the course of the study. We changed this to the allowance of these medications during the whole period. Blinding was not affected by these changes and the Medical Ethical Committee of the UMCG approved all changes.

Supplementary Results



eFigure 5.1: Flow-chart of patient disposition.

eTable 5.1: Treatment history of current episode.

Treatment-history current episode	Active	Sham	p-value
Number of antidepressant used (median (IQR))	2 (1 - 3)	2 (1 - 4)	.390[a]
Antidepressant used in current episode			
TCA (%)	12 (41%)	10 (38%)	
SSRI (%)	20 (69%)	21 (81%)	
SNRI (%)	15 (52%)	15 (58%)	
MAOI (%)	1 (3%)	3 (12%)	
MAOA (%)	1 (3%)	1 (4%)	
Misc (%) (Agomelatine, Bupropion, Mirtazapine, Trazodon)	7 (24%)	12 (46%)	
Other psychopharmacology used in current episode			
Benzodiazepines (%)	5 (17%)	8 (31%)	
Antipsychotics (%)	6 (21%)	4 (15%)	
Lithium (%)	5 (17%)	5 (19%)	
Antiepileptics (%)	3 (10%)	3 (12%)	
Psychotherapeutic treatment in current episode			.926[b]
None (%)	1 (3%)	1 (4%)	
Supportive (%)	12 (41%)	13 (50%)	
1 protocolized (%)	13 (45%)	10 (38%)	
2+ protocolized (%)	3 (10%)	2 (8%)	
ECT (% yes)	0 (0%)	3 (12%)	.060[b]
Intensified treatment of current episode			.270[b]
None (%)	18 (62%)	18 (69%)	
Day-care <12 weeks or < 3days/week	0 (0%)	0 (0%)	
Day-care >12 weeks or > 3days/week	8 (28%)	3 (12%)	
Clinical admission	3 (10%)	5 (19%)	

[a] Mann-Whitney U

[b] Chi-square

eTable 5.2: Correction for duration of episode, DSM-code, number of episodes, treatment expectancy, and treatment guess did not substantially affect the primary outcome, both univariate and multivariate.

UNIVARIATE	Numerator df	Denominator df	F	p-value
Duration	1	48.356	0.795	.377
time*group[a]	1	48.356	0.795	.377
Number of episodes	1	36.371	0.052	.820
time*group[b]	3	14.852	0.937	.424
Single or recurrent episode	1	49.704	4.330	.070
time*group[c]	3	148.513	0.929	.428
Treatment guess	1	50.961	2.183	.146
time*group[d]	3	14.865	0.935	.425
Treatment expectancy	1	48.027	0.439	.511
time*group[e]	3	14.550	1.107	.348
MULTIVARIATE[f]	Numerator df	Denominator df	F	p-value
Time	3	143.975	26.213	< .001
Baseline HAMD-score	1	33.200	39.622	< .001
Duration	1	42.674	0.432	.515
Number of episodes	1	32.835	2.538	.121
Single or recurrent episode	1	46.554	4.782	.034
Treatment guess	1	42.250	1.151	.289
Treatment expectancy	1	43.099	0.182	.672
Group	1	41.735	0.798	.377
time*group	3	145.199	1.098	.352

[a] Adjusted for duration.

[b] Adjusted for number of episodes.

[c] Adjusted for single or recurrent episode.

[d] Adjusted for treatment guess.

[e] Adjusted for treatment expectancy.

[f] Dependent Variable: Hamilton-score.

Abbreviations: df = degrees of freedom.

eTable 5.3: Change in HAMD-17 scores divided based on use of antidepressant.

	No AD use on baseline[a]		AD use on baseline[b]	
	Active	Sham	Active	Sham
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
HAMD week 0	22 (2.9)	22 (2.9)	22 (3.5)	22 (2.4)
HAMD week 5	14 (4.9)	16 (4.5)	17 (5.5)	17 (5.9)
HAMD week 10	15 (5.7)	12 (5.5)	15 (6.6)	15 (7.1)
HAMD week 20	13 (6.1)	13 (8.4)	17 (6.5)	13 (4.8)

[a] time*group interaction: F(3;55) 1.895; p = .141.

[b] time*group interaction: F(3;88) 1.049; p = .375.

Abbreviations: AD = antidepressant, HAMD = Hamilton-17.

eTable 5.4: Adverse events present across both treatment groups.

Study related adverse events	Active	Sham	p-value
Adverse Events present	10 (34%)	12 (46%)	.378
Adverse Events present in dropouts	1 (3%)	1 (4%)	.171
Presence of headache	8 (28%)	9 (35%)	.573
Presence of sleep disturbances	5 (17%)	2 (8%)	.289
Presence of concentration disturbances	1 (3%)	0 (0%)	.339
Presence of tingling sensations	2 (7%)	1 (4%)	.619
Presence of tension	1 (3%)	1 (4%)	.937
Presence of fatigue	1 (3%)	0 (0%)	.339
Presence of nausea	1 (3%)	1 (4%)	.937

Chapter 6

Change in brain activation after transcranial pulsed electromagnetic fields in treatment resistant depression

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Submitted.

Background
Preliminary evidence suggests an antidepressive effects of transcranial pulsed electromagnetic fields (tPEMF). However, the precise mechanism of action in the brain is still unknown. The aim of this study was to investigate the influence of tPEMF on brain activation in patients with treatment-resistant depression (TRD) by studying two processes that might be of particular interest in relation to the symptoms of depression: emotional processing and reward processing.

Methods
Eligible participants (n=50) with TRD in this sham-controlled double-blind multicenter trial (registered at the Dutch Trial Register (http://www.trialregister.nl), NTR3702) were randomly assigned to five weeks daily active or sham tPEMF. Pre- and post-treatment functional MR-scans were made during which participants performed a social-emotional task and a reward task.

Results
Participants in the active treatment group showed a stronger decrease in activation post-treatment compared to sham during reward-outcome processing in the left inferior frontal gyrus and in a cluster comprising the right lingual gyrus and the posterior part of the middle temporal gyrus. No effect of tPEMF was found on activation during the social-emotional task. Neurostimulation with tPEMF did also not affect behavioral performance for both tasks.

Conclusions
We found a decrease in reward-related activation as a result of tPEMF-stimulation, while no effect of tPEMF on social-emotional processing was found. The treatment-related reduction in activation of regulatory regions may reflect normalization and may have implications for anhedonia. These findings suggest that there is an effect of tPEMF on brain activation of relevant circuits, albeit in the absence of a clinical antidepressive effect.

1. Introduction

Non-invasive brain stimulation is a promising new treatment approach for Major Depressive Disorder (MDD). Repetitive Transcranial Magnetic Stimulation (rTMS) (Allan, Herrmann, Ebmeier 2011; Lepping et al. 2014), a stimulation technique aimed at activation of local brain regions through depolarization of the neuronal membrane, has shown consistent antidepressive effects (Perera et al. 2016). Global stimulation with weak electromagnetic fields may also have beneficial effects, with simultaneous stimulation at multiple scalp sites and without depolarization (Leuchter et al. 2013; van Belkum et al. 2016). This technique uses smaller devices and without the use of a localization paradigm. An example is stimulation with transcranial Pulsed Electromagnetic Fields (tPEMF) (Martiny, Lunde, Bech 2010), which at this point has yielded mixed results. One RCT has shown a positive effect of tPEMF on depression severity in MDD patients (Martiny, Lunde, Bech 2010). In a recent replication study using a similar setup, we found no antidepressive effect (van Belkum et al. 2018). There is thus some preliminary evidence of antidepressive effects of tPEMF, although the precise mechanism of action on the brain is still unclear (van Belkum et al. 2016). Therefore, as an integral part of this latter RCT we evaluated the effects of tPEMF on brain activation.

To investigate the influence of tPEMF on the brain of patients with treatment resistant depression (TRD), two processes might be of particular interest: emotional processing

and reward processing. MDD has been associated with a change in emotional cognitive processing, in particular a biased interpretation of negative information (Harmer, Goodwin, Cowen 2009; Leppanen 2006; Roiser, Elliott, Sahakian 2012), which manifests in the perception and identification of facial emotions (Bourke, Douglas, Porter 2010; Gur et al. 1992) and during emotional attention-tasks (Roiser, Elliott, Sahakian 2012). One task combining this is the Wall of Faces (WoF), an emotional attention-task (Simmons et al. 2006). In healthy participants increased activation was found among others in the anterior cingulate cortex (ACC) and ventral medial prefrontal cortex (VMPFC) during emotional trials compared to control trials (Simmons et al. 2006). These particular areas have also been found to be more activated during emotional processing in depressed patients, although a larger network of also limbic areas seems to be involved (Groenewold et al. 2013; Rive et al. 2013). Stimulation with rTMS on the left dorsolateral PFC (DLPFC) has been found to indirectly decrease activation in the ACC and VMPFC (Fox et al. 2012). It could be hypothesized that as a result of tPEMF stimulation, changes could occur in activation in the areas involved in emotional processing.

Another important mechanism underlying core symptoms of MDD, with anhedonia in particular, is reward processing (Nusslock and Alloy 2017). The reward system is driven by a frontostriatal circuit comprising the ACC, the orbital PFC, the (ventral and dorsal) striatum, the ventral pallidum, and the midbrain dopamine neurons (Haber and Knutson 2010). During a monetary incentive delay (MID) task, it has been shown that patients with MDD show hyporesponsivity of the left caudate and hyperresponsivity of the bilateral middle frontal gyrus, the right ACC, and right orbital frontal lobe during reward anticipation, and hyporesponsivity of the left caudate during reward consumption (Zhang et al. 2013). In preclinical in vitro studies it has been shown that PEMF-signals influence rodent dopaminergic cells (Lekhraj et al. 2014). Therefore, it could be hypothesized that by targeting the dopamine system, tPEMF may influence reward processing.

The aim of this study was to investigate the influence of tPEMF on brain activation of patients with TRD. Therefore, patients performed an emotion attention-task and a reward-processing task during fMRI.

2. Methods

2.1. Study design

We included 55 depressed patients in a double blind, multicenter RCT comparing active tPEMF versus sham in a 1:1 ratio. Fifty completed the trial and were included in the current analyses. This study was approved by the Medical Ethical Committee of the University Medical Center Groningen (UMCG), and by the local research office of each participating site. Written informed consent was obtained from each participant. The study was conducted according to the Declaration of Helsinki. The trial was registered at the Dutch Trial Register (http://www.trialregister.nl) under number NTR3702.

2.2. Study population

We included patients who met DSM-IV criteria for MDD, currently in a depressive episode, assessed by the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al. 1998). Inclusion criteria were presence of at least a moderately severe depression (>17 on HAMD-17), non-responsiveness to one or more antidepressants given for at least four weeks in an adequate dose (i.e. the defined daily dose (DDD) (WHO Collaborating Centre for Drug Statistics Methodology 2016)) during the current episode, age between 18 and 80 years, and having a good understanding of spoken and written Dutch.

Patients were excluded if they were Magnetic Resonance Imaging (MRI) incompatible (having metal implants, claustrophobia, refusal to get informed of structural brain abnormalities, and suspected pregnancy). Additional exclusion criteria were presence of MDD with psychotic features, other major psychiatric disorders such as a primary psychotic disorder or an antisocial or borderline personality disorder, a neurological disorder such as dementia or epilepsy, visual or hearing problems that could not be corrected, suicidal thoughts (>2 on HAMD-17 for suicidal ideation) or a history of a serious suicide attempt, recent (past three months) alcohol or drug abuse or dependence, lactation, inability to comply with treatments and/or assessments, recent change (last four weeks) in antidepressant medication or requirement to change antidepressant medication during the course of the study, use of benzodiazepine(s) more than 2 mg lorazepam or equivalent per day within the last four weeks or during the course of the study, use of medication indicated for a somatic disease that may have affected mood within the last four weeks, excessive use of coffee (>10 units per day) or alcohol (>5 units per day), or recent use (within four weeks) of cannabis or any other non-prescribed psychotropic drugs or unwillingness to abstain from these substances during the study. The use of antipsychotics and lithium was allowed.

2.3. Treatment

Eligible patients were randomly assigned to either five weeks active tPEMF or five weeks sham stimulation. Sessions took place on weekdays for 30 minutes during office-hours. All involved were blinded for the treatment condition. Further details regarding randomization and treatment procedure are described elsewhere (van Belkum et al. 2018). Functional MR-scans were made at a maximum of five days pre-treatment and at the same day of the last treatment session. During the scans participants performed two tasks: the Wall-of-Faces (WoF) task (Simmons et al. 2006) and a Monetary Incentive Delay (MID) task (Pizzagalli et al. 2009).

2.4. WoF-Task

During the WoF-task, an array of 32 human faces was presented for 3 seconds followed by an additional reaction period of 1.5s. Participants had to indicate whether they saw more happy or angry facial expressions –an affective judgment– or whether they saw more male or female faces –a gender judgment-, used as a control condition. In half of the trials the majority of faces was clear (unambiguous trials), because the array was presented in a 26-6 or 6-26 ratio. In the other half of the trials the ratio of faces was presented in a 16-16 ratio and thus ambiguous. This resulted in two different ambiguous conditions (affect: angry = happy (16-16); gender: male = female (16-16)) and two unambiguous conditions (affect: angry ≠ happy (26-6 or 6-26); gender: male ≠ female (26-6 or 6-26)). In total there were eight epochs; four in which participants had to perform an affective judgment and four in which they had to perform a gender judgment. During one epoch the ambiguous (four per epoch) and the unambiguous trials (four per epoch) were presented in random order. The four conditions were thus presented sixteen times in total. Stimuli were presented in E-prime version 2.0 (Psychology Software Tools, Sharpsburg, PA). A short practice session was performed prior to scanning.

2.5. MID-Task

The Monetary Incentive Delay task was adapted from (Pizzagalli et al. 2009). This event-related task consisted of 20 reward trials (monetary gain), 20 neutral trials (no gain no loss), and twelve loss trials (monetary loss). The total reward obtained during scanning was added to the financial compensation for participation; the total amount was fixed so participants unknowingly always gained € 10,-. During a trial, participants saw a cue for 1.5 second for one of the potential outcomes: reward (+€), neutral (=€), or loss (-€), which was followed by a blue squared target presented for 0.5s. Participants were instructed to press a button in response to the cue as fast as possible to maximize their outcome. Feedback (1.5s) concerning the outcome was

given directly after the cue. The inter-stimulus-interval (ISI) varied between trials (ISI-1 between cue of the possible outcome and target: 3.5s–9.5s; ISI-2 between target and outcome: 2.5s–8.5s) to prevent expectancy effects, as did the duration of trial-separating fixation cross (3.0s–7.0s). Participants completed four blocks of thirteen trials comprising all conditions, interspersed with 10s resting periods. The pseudo-randomized order of trials and ISIs was determined with optimized experimental design to maximize efficiency (Dale 1999; Liu et al. 2001). Reward success rates were set at 80% to prevent habituation. Outcome for the neutral and loss trials was set at 100%, so that in the neutral trials participants never received a reward and that in the loss trials participants always lost money. Stimuli were presented in E-prime version 2.0 (Psychology Software Tools, Sharpsburg, PA). A short practice session was performed prior to scanning.

2.6. MRI acquisition parameters

All fMRI-images were acquired using a 3 Tesla Philips MRI scanner (Best, The Netherlands). Functional images were acquired using T2*-weighted echo planar images sequences. Sequence parameters: single shot EPI; 37 slices; 3.5 mm slice thickness; 0.0 mm gap; 224 x 129.5 x 224 mm (anterior-posterior, foot-head, right-left) field of view; 64×61 scan matrix; transverse slice orientation; repetition time 2000 ms; echo time 20 ms; flip angle 70°. In addition, a T1-weighted whole brain anatomical image was acquired (resolution 1×1×1 mm).

2.7. Statistical analyses of behavioral data

Analyses of behavioral data were performed using IBM SPSS version 24.0 software (IBM, Chicago IL, USA). For the WoF-task we calculated median scores (non-normally distributed) for the response times of the conditions affect ambiguous, affect unambiguous, gender ambiguous, and gender unambiguous. For the MID-task we calculated median scores for the response time to the target cue for the three conditions (reward, neutral, or loss). Outliers were calculated using the median absolute deviation (MAD) (Leys et al. 2013). We used a criterion of 3 + or – the MAD for the different conditions to remove outliers. Differences between the conditions were tested using Wilcoxon rank tests for the median scores. To test for the effect of treatment on behavioral outcome, a linear mixed model with a random intercept was applied with response time score per different condition as dependent variable and treatment group, time (baseline or week five), and the interaction between time and treatment group as covariates. The level of statistical significance was set at $\alpha<0.05$.

2.8. MRI data pre-processing

Analyses of MRI-data were performed using Statistical Parametric Mapping (SPM12, version number 6470; FIL Wellcome Department of Imaging Neuroscience, London, UK), implemented in MatLab (r2015a). First, PAR-files were converted to NIFTI format with an in-house script. Both anatomical and functional images were manually reoriented to the anterior commissure – posterior commissure plane. Further preprocessing consisted of realignment of functional images. Realignment-parameters were visually checked. For all realignment-parameters their first derivatives and the framewise displacement (Power et al. 2012; Siegel et al. 2014) were calculated to add as covariate in the first-level model later on. Participants were excluded for that particular task if there was progressive movement exceeding 3mm; in case a single volume would exceed 3mm, we assumed that scrubbing would compensate for this. Next, coregistration of the functional images to the anatomical image, and spatial normalization to the Montreal Neurological Institute (MNI) space, reslicing the images into a 3 x 3 x 3 mm voxel grid were performed. Coregistration and normalization were visually checked to see if manual correction was necessary, which was not the case. The data was spatially smoothed with an 8 mm full-width at half-maximum Gaussian Kernel.

2.9. First level models

For both tasks, a first-level GLM was set up per participant containing two time-sessions. Regressors for the different onset-times of the conditions were convolved with a canonical hemodynamic response function. Other regressors in the GLM were realignment-parameters, their first derivatives, and dummy variables for the volumes showing a framewise displacement of >0.9 (Power et al. 2012; Siegel et al. 2014).

2.10. Wall of faces Task

For the WoF-task five different regressors were defined: affective ambiguous and unambiguous, gender ambiguous and unambiguous, and instructions. We calculated the following contrasts on baseline: affect > gender, ambiguous affect > ambiguous gender, affect ambiguity > affect unambiguity. For the interaction over time, we calculated contrasts for: affect > gender (pre>post), ambiguous affect > gender (pre>post), and affect ambiguity > unambiguity (pre>post),

2.11. Monetary Incentive Delay Task

For the MID-task six regressors were defined: anticipation of reward, loss, and neutral and consummation of reward, loss, and neutral. We calculated contrasts (at baseline)

for: anticipation reward > neutral, anticipation loss > neutral, anticipation reward > loss, consumption reward > neutral, consumption loss > neutral, and consumption reward > loss. For the effects over time, we calculated contrasts for: anticipation reward > neutral (pre>post), anticipation loss > neutral (pre>post), anticipation reward > loss (pre>post), consumption reward > neutral (pre>post), consumption loss > neutral (pre>post), and consumption reward > loss (pre>post),

2.12. Second level

For second-level analyses, a two-sample t-test model was built. We determined task activation using the baseline scans and compared baseline activation between the treatment groups (sham versus active). For the effect over time we used the respective first level contrasts to compare the treatment groups. We performed whole brain correction. The threshold was set at $p<.05$ Family Wise Error (FWE)-corrected at cluster level, with an initial voxel-defining threshold of $p<.001$.

For visualization purposes we built a full factorial model containing scans for the two groups and two time moments (pre-treatment, post-treatment for sham and active treatment). We used the significant clusters of the effect over time as a mask to extract the first eigenvariate for each condition and time moment and these were used for plotting bar graphs. No statistics were applied on these values.

3. Results

3.1. Sample description

Of the 50 participants, 25 were randomized to the active resp. sham condition. For the WoF-task five participants were excluded due to excessive movement, so we retained 45 participants for analysis of the WoF-task, 23 in the active and 22 in the sham group. For the MID-task one participant was excluded due to excessive movement, retaining 49 participants for analysis: 25 in the active and 24 in the sham group. Table 6.1 shows that both treatment groups were comparable on socio-demographic data and clinical measurements.

Table 6.1: Sociodemographic and clinical parameters.

Variable	Active (n = 25)	Sham (n = 25)	p-value
Age (years) (mean (SD))	49 (14)	45 (12)	.331[a]
Female gender	14 (56%)	11 (44%)	.396[b]
Marital status			.768[b]
Single	10 (40%)	9 (36%)	
Married	13 (52%)	15 (60%)	
Divorced	2 (8%)	1 (4%)	
Educational background			.321[b]
Primary	2 (8%)	0 (0%)	
Lower secondary	6 (24%)	10 (40%)	
Upper secondary	12 (48%)	12 (48%)	
University	5 (20%)	3 (12%)	
Presence of somatic complaints	16 (64%)	20 (80%)	.208[b]
MDD-type			.395[b]
MDD first episode	12 (48%)	15 (60%)	
MDD recurrent episode	13 (52%)	10 (40%)	
Number of episodes (median (IQR))	1 (1 - 3)	1 (1 - 3)	.782[c]
Duration of current episode (months) (median (IQR))	23 (13 - 54)	29 (12 - 78)	.534[c]
Presence of comorbidity	14 (56%)	10 (40%)	.258[b]

[a] 2-tailed t-test.

[b] Chi-square.

[c] Mann-Whitney U.

Abbreviations: MDD = major depressive disorder, IQR = interquartile range.

3.2. Behavioral results - Wall of Faces Task

There was no significant effect of group, no significant effect of time, and no significant group*time interaction for the affect ambiguous compared to the affect unambiguous condition, for all conditions.

3.3. Behavioral results – Monetary Incentive Delay Task

There was no significant effect of group, no significant effect of time, and no significant group*time interaction for all conditions.

3.4. Functional Neuroimaging Results - Wall of Faces Task

The contrast affect > gender showed activation in the bilateral middle temporal gyrus (MTG, table 6.2). For the contrast ambiguous affect > gender activation was found in the left lingual gyrus, left precentral gyrus, bilateral MTG, and right inferior frontal gyrus (IFG). For the affect ambiguity > affect unambiguity a difference in activation was seen in the right lingual gyrus.

There were no significant differences at baseline between the two groups for any of the contrasts. Moreover, there were no significant differences between the groups in differences over time for any of the contrasts.

Table 6.2: Functional Neuroimaging Results. Whole brain correction for task activation for Wall of Faces Task-task.

Area	K	x	y	z	t-score	p-value[a]
Contrast affect vs. gender						
Middle temporal gyrus (right)	378	54	-34	-4	5.57	< .001
Middle temporal gyrus (left)	352	-60	-37	2	5.30	< .001
Contrast ambiguous affect vs. gender						
Lingual gyrus (left)	842	-21	-70	-13	5.97	< .001
Precentral gyrus (left)	306	-36	-13	65	5.22	< .001
Middle temporal gyrus (left)	231	-60	-40	2	4.91	< .001
Middle temporal gyrus (right)	162	54	-37	-4	4.90	.003
Inferior Frontal gyrus (right)	84	54	23	-4	4.42	.045
Contrast affect ambiguous vs. unambiguous						
Lingual gyrus (right)	369	15	-82	-7	4.92	< .001

[a] FWE corrected at cluster level.

3.5. Functional Neuroimaging Results - Monetary Incentive Delay Task

For the contrast anticipation reward > neutral we observed task activation in the left ACC. The contrast consumption reward > neutral at baseline showed more activation in the right supramarginal gyrus, right medial superior frontal gyrus extending to the ACC, bilateral insula, left inferior parietal gyrus, bilateral inferior frontal gyrus (IFG), the right middle cingulate gyrus, the left inferior temporal gyrus, and the right lingual gyrus. More activation was found for the contrast consumption loss > neutral at baseline in the right medial superior frontal gyrus, the right IFG, and the right inferior parietal gyrus. For the contrast consumption reward > loss at baseline there was more activation in the right postcentral gyrus and the right lingual gyrus.

More activation was found for the active treatment group compared to the sham group in the left cuneus and the left middle temporal gyrus at baseline for the contrast consumption reward > neutral (table 6.3). There were no differences between the groups on the other contrasts.

We found differences between the groups in differences over time for the contrast consumption reward > neutral in the left IFG and in a cluster comprising the right lingual gyrus and the posterior part of the middle temporal gyrus (see figures 6.1 and 6.2; table 6.3)). Both clusters showed a larger decrease of activation in the active treatment group compared to the sham group.

Table 6.3: Functional Neuroimaging Results. Whole brain correction for task activation for Monetary Incentive Delay-task.

Area	K	x	y	z	t-score	p-value[a]
Task activation; contrast anticipation reward > neutral						
Anterior cingulate gyrus (left)	155	-6	26	29	4.23	.005
Task activation; contrast ambiguous affect vs. gender						
Supramarginal gyrus (right)	571	48	-40	44	7.53	< .001
Superior frontal medial gyrus (right)	655	6	29	44	7.48	< .001
Insula (right)	166	33	23	-4	6.88	.002
Inferior parietal (left)	404	-54	-40	47	6.39	< .001
Inferior frontal (right)	695	48	8	20	6.09	< .001
Middle cingulate gyrus (right)	216	0	-22	32	5.90	.001
Inferior temporal gyrus (left)	176	-51	-52	-13	5.59	.002
Lingual gyrus (right)	233	15	-82	-7	5.51	< .001
Inferior frontal gyrus (left)	301	-39	5	29	5.25	< .001
Insula (left)	170	-39	17	-10	5.21	.002
Task activation; contrast consumption loss vs. neutral						
Superior frontal medial gyrus (right)	129	9	29	41	5.72	.010
Inferior frontal gyrus (right)	90	42	38	17	4.47	.036
Inferior parietal gyrus (right)	181	45	-43	47	4.35	.002
Task activation; contrast consumption reward vs. loss						
Postcentral gyrus (right)	117	48	-25	41	5.24	.013
Lingual gyrus (right)	87	12	-82	-7	5.10	.038
Baseline, sham < active; contrast consumption reward > neutral						
Cuneus (left)	1754	-15	-85	38	5.06	< .001
Middle Temporal gyrus (left)	198	-63	-25	2	4.22	.001
Group*time interaction, sham < active; contrast consumption reward > neutral						
Inferior frontal gyrus (left)	185	-48	26	11	4.61	.003
Lingual & Middle temporal gyrus (right)	136	33	-61	-1	4.46	.011

[a] FWE corrected at cluster level.

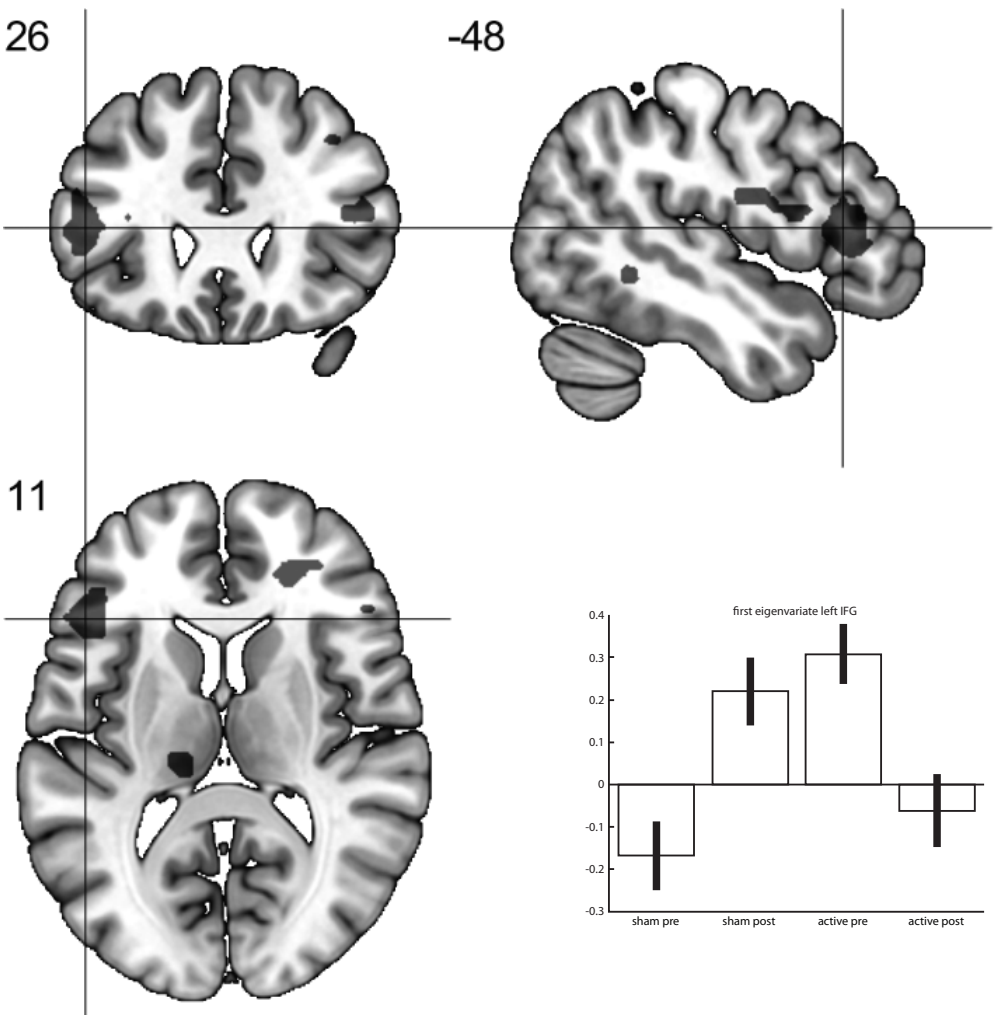

Figure 6.1: Larger decrease of activation in the active group compared to the sham group over time in the left Inferior Frontal Gyrus (IFG) for the contrast consumption reward > neutral. Neurological convention.

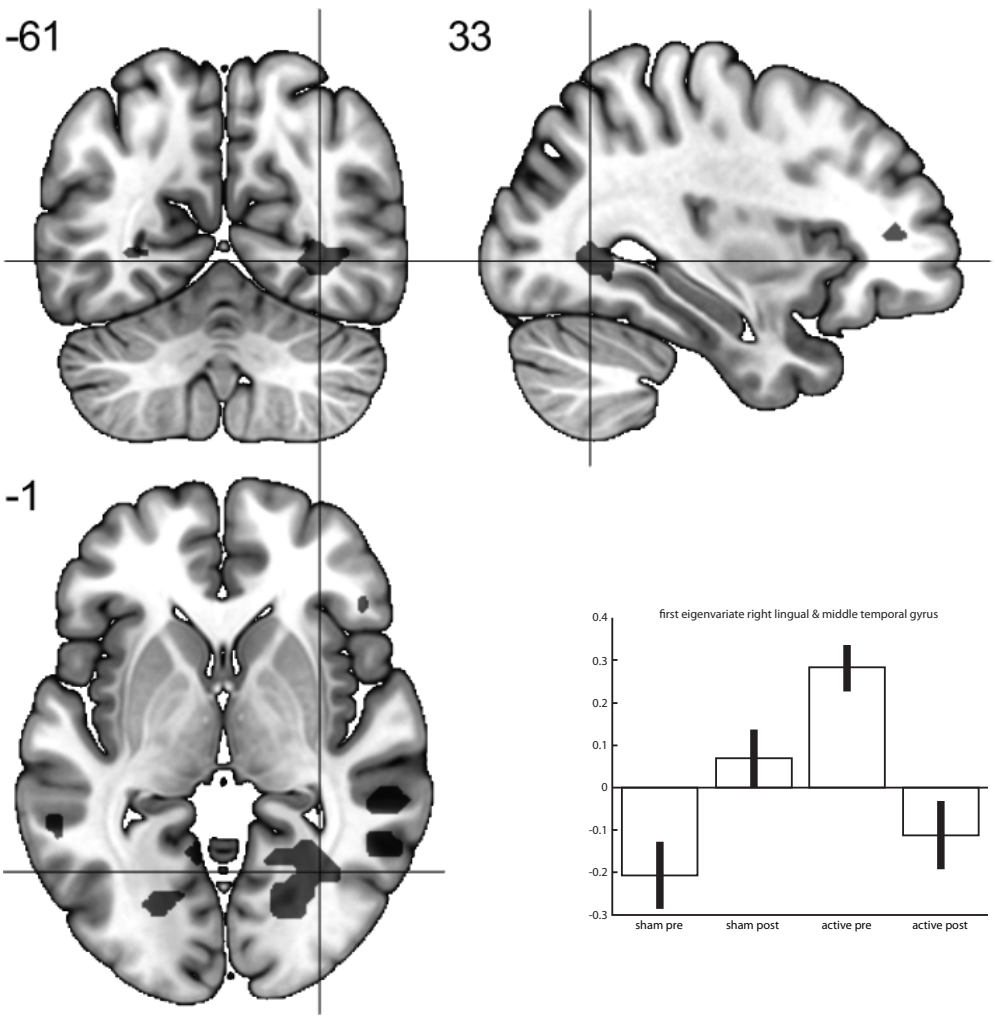

Figure 6.2: Larger decrease of activation in the active group compared to the sham group over time in a cluster comprising the right lingual gyrus and the posterior part of the middle temporal gyrus for the contrast consumption reward > neutral. Neurological convention.

4. Discussion

The aim of this study was to evaluate the effects of tPEMF on brain activation during emotion and reward processing. We showed that tPEMF stimulation decreased activation during reward-related 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 MDD-patients with a treatment resistant depression. We did not find an effect of tPEMF on emotion processing during the WoF-task. No behavioral effect or clinical effect (van Belkum et al. 2018) of tPEMF was found. These findings suggest that tPEMF may affect brain activation during reward processing in absence of a clinical antidepressive effect.

Studies investigating the effects of global stimulation devices with tPEMF or comparable stimulation methods on brain activation are sparse. However, there is some evidence that tPEMF-like stimulation has an effect on glucose metabolism in the left IFG in healthy controls (Volkow et al. 2010). In this previous study the effect of the whole brain electromagnetic gradients of echo planar imaging (EPI), a standard for functional MRI, on brain glucose was investigated in 15 healthy male subjects, using Positron-Emission Tomography (PET) 18FDG imaging. All subjects underwent one MR-PET-scan with EPI-gradients on, and one with EPI-gradient off (sham condition), the order of which was randomly assigned. When the EPI-gradient was turned on, a decrease in glucose metabolism in the left IFG was found in absence of an effect on mood-scores. This was also the case in clusters that included the inferior occipital, superior parietal and posterior insular cortices (Volkow et al. 2010). Our results are in line with this effect of global magnetic stimulation on the left IFG. A decrease in frontal activation during reward outcome has been reported before in healthy subjects in a test-retest design, albeit in a more ventral and medial region (Balodis et al. 2016). Thus, such a decrease in activation in a second measurement in a patient sample could perhaps be interpreted as "normalization", supporting a beneficial effect of tPEMF, whereas the lack of such a decrease may be associated with pathology.

Consistent with a putative effect of tPEMF on reward-related brain activation, there is some evidence that tPEMF-like stimulation may have an effect on the growth of dopaminergic cells (Lekhraj et al. 2014). On the other hand, the left IFG and the extended area described as ventrolateral prefrontal cortex (VLPFC), have both not been described as key areas of the reward network. Nevertheless, it could be suggested that they do play a role in associated regulatory processes (Yip et al. 2016). The left IFG is implicated in cognitive and emotional control, especially cognitive reappraisal (Ochsner and Gross 2005) and cognitive inhibition (Menon et al. 2001; Swick, Ashley, Turken 2011). Therefore, it could be speculated that during reward

consumption the IFG inhibits ventral striatal regions subserving the subjective feeling of reward. Our finding of reduced IFG activation after tPEMF stimulation might indicate a reduction of this inhibitory effect and thereby an increase of the rewarding feeling. This explanation however is speculative and needs further confirmation. Still, 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. In that case, tPEMF might also have an effect on symptoms in other disorders where impairments of reward processing play a role, like schizophrenia and addiction. Therefore, our finding of change in reward-related brain activation may also be relevant for future research to tPEMF as a novel treatment option for psychiatric symptoms in other disorders than MDD.

Apart from the effect on the left IFG, we found a group by time interaction indicating decreased activation during reward consumption in a cluster comprising the right lingual gyrus and the posterior part of the middle temporal gyrus. Interestingly, MDD has been associated with more activation in the cuneus and lingual gyrus during reward processing (Zhang et al. 2013). The observed decrease over time in the active treatment group might suggest normalization of brain activation patterns in the lingual gyrus as a result of tPEMF treatment. However, due to lack of a healthy control group this could not be tested. Surprisingly, we also observed higher activation on baseline in the active treatment group compared to the sham group in this cluster. This might also suggest that the effect is related to regression to the mean. Therefore, at this point it is difficult to draw definitive conclusions.

Apart from the effects on reward processing, we also studied the effects of tPEMF on emotion processing. For this we used the WoF-task, an emotional attention-task that probes neural circuitry underlying affective appraisal of multiple simultaneously presented faces (Simmons et al. 2006). This task was used earlier in healthy controls (Simmons et al. 2006), anxious individuals (Simmons, Matthews, Feinstein et al. 2008; Simmons, Matthews, Paulus et al. 2008) and patients with schizophrenia (Liemburg et al. 2017), but not yet in MDD. In healthy controls, Simmons and colleagues reported activation of the dorsal ACC, dorsolateral PFC, and the posterior parietal cortex during ambiguous trials in general (Simmons et al. 2006). During emotional ambiguous trials more activation was found in the right supramarginal gyrus, right superior temporal gyrus, and the ventromedial PFC (including the ventral ACC) compared with ambiguous gender trials (Simmons et al. 2006). We observed task activation during ambiguous affective trials compared to ambiguous gender trials in the left lingual gyrus, left precentral gyrus, bilateral MTG and the right IFG, and during ambiguous affective trials compared to unambiguous emotional trials more activation in the right lingual gyrus. Thus, even though there was little overlap between

the areas found by Simmons et al, we found involvement of areas known to subserve processing of faces and emotional expressions (Sabatinelli et al. 2011). The absence of overlap could be partly due to the difference in population and it might be that patients with MDD show a different pattern of activation during this task.

Brain areas involved in emotional processing, like the dorsal ACC and ventromedial PFC, as well as the amygdala and parahippocampal cortex (Groenewold et al. 2013) can be indirectly influenced after left DLPFC rTMS stimulation due to the high connectivity with superficial cortical areas (Fox et al. 2012; Padberg and George 2009). We did not find an effect of tPEMF on these brain areas or an effect of tPEMF on behavioral emotional processing data, suggesting that tPEMF with our settings has no impact on these deeper areas during emotional processing.

4.1. Limitations

The current study focused on the differences between tPEMF-stimulation and sham treatment in a randomized clinical trial. As we did not have a healthy control group it was not possible to draw firm conclusions regarding the level of task-related activation during the ambiguous emotional faces task. In addition, because tPEMF did not show clinical improvement (van Belkum et al. 2018), we could not relate our fMRI-findings to clinical outcome. On the other hand this implies that changes on the neural level could be more sensitive to change as we did find differences in brain activation related to tPEMF stimulation.

4.2. Conclusion

We evaluated the effects of tPEMF on brain activation by investigating different processes underlying hallmark symptoms of MDD: emotional and reward processing. We found a decrease in brain activation in the left IFG during reward-outcome processing as a result of tPEMF-stimulation, while no effect of tPEMF on emotional processing was found. These findings suggest that tPEMF may affect relevant brain activation (though in our study in the absence of a clinical antidepressive effect) and encourage further investigation with different parameters (e.g., regarding intensity, duration and location of stimulation).

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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.

Nederlandse samenvatting

1. Inleiding

Depressie is een stoornis die 30% van de mannen en 40% van vrouwen in hun leven kan treffen. De behandeling van depressie bestaat uit een combinatie van gesprekstherapie en/of antidepressieve medicatie. Voor een kleine groep patiënten is behandeling echter niet succesvol. Deze patiënten hebben een therapieresistente depressie (TRD). Er zijn meerdere manieren om de uitkomst van de behandeling van depressie te verbeteren. In dit proefschrift wordt stilgestaan bij het effect van neuromodulatie-technieken op depressie.

Neuromodulatie-technieken maken gebruik van elektrische stimulatie of een elektromagnetisch veld gericht op de hersenen. Op die manier is het mogelijk om hersenprocessen van buiten af te beïnvloeden, om zo stemming en gedrag positief te veranderen. Bepaalde neuromodulatie-technieken hebben al een bewezen antidepressief effect. Dit betreffen vooral technieken waarbij de hersenschors lokaal gestimuleerd wordt.

Dit proefschrift richt zich echter op het effect van globale neuromodulatie. Dit is een techniek waarbij de gehele hersenschors met een zwak elektromagnetisch veld wordt gestimuleerd. In het bijzonder staan we stil bij het antidepressieve effect van gepulste transcraniële elektromagnetische stimulatie (*transcranial Pulsed Electromagnetic Fields* (tPEMF)). Een studie in Denemarken heeft laten zien dat de depressie van

patiënten met een therapieresistente depressieve stoornis sterk opknapte na stimulatie met tPEMF (Martiny, Lunde, Beck 2010). In dit proefschrift proberen we meer te weten te komen over deze specifieke techniek.

2. Deel één: effecten van tPEMF en gerelateerde neuromodulatie-technieken

In deel één van dit proefschrift worden de klinische effecten van verschillende neuromodulatie-technieken beschreven op depressie en functionele somatische symptomen.

In hoofdstuk 2 wordt in een systematisch overzicht van de literatuur stilgestaan bij het effect van drie verschillende neuromodulatie-technieken (repetitieve Transcraniële Magnetische Stimulatie (rTMS), transcraniële *Direct Current Stimulation* (tDCS) en tPEMF) op vier verschillende subtypes van functionele somatische symptomen (FSS): klachten die wel aanwezig zijn maar waarvoor geen duidelijke somatische oorzaak is gevonden. In dit literatuuroverzicht is er voor gekozen om specifiek het effect van neuromodulatie op een groep sensorische en pijn gerelateerde symptomen (complex regionaal pijnsyndroom type I (CRPS I) en fibromyalgie) en een groep beweging gerelateerde symptomen (parese en bewegingsstoornissen)) te bestuderen.

Het gebruik van neuromodulatie bij FSS is het meest uitgebreid bestudeerd bij fibromyalgie, een pijn gerelateerd symptoom. Het effect van neuromodulatie bij fibromyalgie is onderzocht door middel van placebo-gecontroleerde gerandomiseerde klinische studies (*Randomized Clinical Trials*; RCT's). Het is gebleken dat met name stimulatie met tDCS de intensiteit van pijn bij fibromyalgie zou kunnen verminderen. Bij CRPS I zijn er studies gedaan naar het effect van rTMS op pijn, maar is het aantal studies zeer klein. Daarnaast is er bij veel van deze studies een aanzienlijk placebo-effect. Ook voor beweging gerelateerde symptomen is het aantal klinische studies laag. Er is één placebogecontroleerd onderzoek bij patiënten met parese. Dit onderzoek heeft laten zien dat rTMS een therapeutische optie zou kunnen zijn als op de juiste manier gestimuleerd wordt. Er zijn geen RCT's uitgevoerd naar neuromodulatie voor de bewegingsstoornissen die in dit hoofdstuk zijn onderzocht. (hoofdstuk 2). Alles bij elkaar genomen kan er geconcludeerd worden dat er meer en grotere studies met betere methodologische standaarden nodig zijn om mogelijke positieve effecten van neuromodulatie in FSS verder te onderzoeken.

Hoofdstuk 3 betreft een overzicht van de literatuur over mogelijke mechanismen die kunnen bijdragen aan de antidepressieve effecten van globale neuromodulatie-technieken, zoals tPEMF. Hier worden deze mechanismen kort samengevat.

Ten eerste zou het kunnen zijn dat globale neuromodulatie een effect heeft op het glucosemetabolisme van bepaalde gebieden van het brein. Dit zou kunnen betekenen dat globale neuromodulatie bepaalde gebieden van het depressieve brein meer of minder actief zou kunnen maken. Ten tweede zou globale neuromodulatie de functionele

verbinding tussen bepaalde hersengebieden kunnen beïnvloeden. Het resultaat zou kunnen zijn dat netwerken in het depressieve brein meer in overeenstemming met elkaar gaan communiceren. Ten derde zijn er aanwijzingen dat tPEMF de groei van zenuwcellen zou kunnen beïnvloeden. Het depressieve brein zou in dat geval beter nieuwere verbindingen aan kunnen gaan binnen bepaalde hersengebieden. Ten vierde hebben bepaalde onderzoeken laten zien dat de antidepressieve eigenschappen van tPEMF gedeeltelijk kunnen worden toegeschreven aan de remmende effecten op laaggradige ontstekingsprocessen. Deze laaggradige ontstekingsprocessen spelen mogelijk ook een rol in het ontstaan of voortduren van een depressieve stoornis. Het bewijs voor een effect van tPEMF op de biologische klok is ten vijfde ook beschouwd. Hoewel sommige studies hebben aangetoond dat zwakke magnetische velden circadiane ritmen (dag-nachtritmen) in fruitvliegen kunnen beïnvloeden, is het onwaarschijnlijk dat dit het antidepressieve effect van tPEMF zou kunnen verklaren.

3. Deel twee: kwantificeren van behandelingsresistentie bij depressie

Deel twee van dit proefschrift gaat specifiek over therapieresistente depressie (TRD). TRD komt in verschillende gradaties voor, afhankelijk van hoeveel behandelingen een patiënt heeft gehad. Er is niet één specifieke definitie voor therapieresistentie. Als een gevolg daarvan is TRD ook moeilijk te meten. Volgens een veel gebruikte definitie treft TRD wel één op de drie patiënten lijdende aan een depressie.

In hoofdstuk 4 wordt een scoringslijst bestudeerd die gebruikt kan worden om het beloop en de uitkomst van een depressie van een patiënt te voorspellen. Deze scoringslijst betreft de *Maudsley Staging Method* (MSM). In kleinere onderzoeken is al aangetoond dat de MSM het beloop en de uitkomst van een depressie voor een patiënt in zekere mate kan voorspellen. In ons onderzoek bestuderen we dit verder met behulp van een groot en goed beschreven naturalistisch cohort van depressieve patiënten (*Netherlands Study of Depression and Anxiety* (NESDA)). Hiervoor is de intensiteit en duur van depressieve symptomen gedurende een periode van 2 jaar bepaald bij 634 patiënten met een depressieve stoornis.

Een hogere score op de MSM was voorspellend voor een langere duur van de huidige depressieve episode. Dat betekent dus dat patiënten die een hogere mate van therapieresistentie volgens de MSM hadden, gemiddeld genomen langer voldeden aan de criteria van een depressieve stoornis. Bovendien is de score op de MSM geassocieerd met een depressieve episode gedurende 50% van de follow-up tijd. Dat betekent dus dat de patiënten die een hogere mate van therapieresistentie hadden, gedurende de twee jaar volgend op de eerste meting een groter deel van de tijd een depressie hadden. Deze voorspelling lijkt onafhankelijk te zijn van de behandeling die is gegeven tijdens de eerste meting of tijdens de vervolgperiode van twee jaar. De MSM is dus een betrouwbaar en geldig hulpmiddel om de uitkomst van een depressie te voorspellen ongeacht behandeling na afname van de MSM, bij een breed scala van patiënten met depressie.

4. Deel drie: een nieuwe behandeling voor depressie?

In deel drie van dit proefschrift wordt er specifiek ingegaan op het antidepressieve effect en het neurobiologische effect van tPEMF. Ten eerste wordt er getracht de resultaten van de eerste studie van de antidepressieve effecten van tPEMF te repliceren. Verder zijn de lange termijn antidepressieve effecten van tPEMF onderzocht. Tenslotte is het effect van tPEMF op het brein bestudeerd.

In hoofdstuk 5 en 6 zijn de resultaten gepresenteerd van de Nederlandse tPEMF-studie, een dubbelblinde multicenter RCT. In deze studie werd actieve tPEMF-behandeling vergeleken met schijnbehandeling in 55 depressieve patiënten met TRD. Patiënten zijn gerekruteerd en behandeld in een aantal grote geestelijke gezondheidszorg (GGZ) instellingen in het noorden van Nederland. Patiënten die in aanmerking kwamen om mee te doen met de studie zijn willekeurig toegewezen aan actieve tPEMF-stimulatie of aan schijnstimulatie. Aan de hand van verschillende vragenlijsten werd het effect van beide soorten stimulatie gemeten. Zo werd de ernst van de depressie aan de hand van de '*17-item Hamilton depression rating*' (HAMD-17) gemeten direct voorafgaand aan en direct na de stimulatie-sessies en op verschillende momenten na de sessies. De ernst van de depressie werd wekelijks gemeten tijdens met een andere vragenlijst voor de ernst van een depressie: de '*Inventory of Depressive Symptomatology Self-Report*' (IDS-SR). Deelnemers werden tot vijftien weken na de laatste stimulatie-sessie gevolgd.

Bij alle deelnemers is er een functionele magnetische resonantiescan (fMRI) gemaakt voor en direct na de behandeling. Tijdens het scannen hebben deelnemers twee taken uitgevoerd om twee verschillende hersenprocessen te onderzoeken. Om de emotionele cognitieve verwerking in het brein te bestuderen, is de '*Wall-of-Faces'* (WoF) taak (Simmons et al. 2006) gebruikt. Om de verwerking van beloning in het brein te bestuderen, is een '*Monetary Incentive Delay'* (MID) taak gebruikt (Pizzagalli et al. 2009).

In hoofdstuk 5 zijn de klinische resultaten van de tPEMF-studie gepresenteerd. De gemiddelde ernst van de depressie tijdens de eerste meting was een HAMD-17-score van 22 punten voor beide groepen. Er was geen verschil tussen de actieve stimulatie en de schijnstimulatie als een gevolg van de stimulatie: deelnemers in beide groepen verbeterden na vijf weken met gemiddeld vijf punten op de HAMD-17. Deze verbetering hield ten minste vijftien weken aan. Ook op andere vragenlijsten zoals de IDS-SR waren er geen verschillen tussen beide groepen na de stimulatie-sessies. Dit resultaat betekent dat er geen effect was van de tPEMF-stimulatie in deze studie. Dit is in tegenstelling tot de eerdere studie uit Denemarken. Qua deelnemersselectie kwamen beide studies overeen, maar mogelijk komen enkele eigenschappen niet overeen. Verder onderzoek zal uit moeten wijzen wat het verschil tussen beide studies

betekent en of tPEMF effectief is voor de behandeling van depressie.

In hoofdstuk 6 zijn de resultaten van de functionele magnetische resonantiescans van de tPEMF studie gepresenteerd. De activeringspatronen vóór en na de behandeling zijn met elkaar vergeleken. Voor de WoF-taak waren er geen significante verschillen tussen beide groepen in de tijd. Dit betekent dat hoogstwaarschijnlijk tPEMF-stimulatie geen effect heeft gehad op emotionele cognitieve verwerking in het brein.

Voor de MID-taak werden verschillen tussen de twee behandelingsgroepen gevonden ná de stimulatiesessies vergeleken met voor de stimulatie-sessies. Het verwerken van beloning gebeurt in twee fases: een beloning voorzien (anticipatiefase) en een beloning ervaren (consumptiefase). Het verschil dat was gevonden trad op tijdens deze tweede fase, de consumptiefase. Het verschil werd gezien in een gebied van het brein dat de linker inferieure frontale gyrus (IFG) heet en in een cluster van het brein dat de rechter linguale gyrus en het achterste deel van de middelste temporale groep omvat. De activatie in beide clusters nam meer af in de groep die actieve stimulatie kreeg in vergelijking met schijnstimulatie. Deze bevindingen zouden kunnen suggereren dat er een effect van tPEMF op de hersenen is in specifiek het beloningssysteem, ondanks dat er geen effect op de depressie werd gevonden.

5. Discussie

In de discussie van dit proefschrift is ten eerste nadruk gelegd op het gebruik van biologische uitkomstmaten naast klinische uitkomstmaten om de werkzaamheid en onderliggende mechanismen van nieuwe neuromodulatie-technieken voor depressie te bestuderen. Ten tweede is er stilgestaan bij het feit dat een depressieve stoornis veel verschillende gezichten kent. De mogelijkheid om de behandeling van depressie te richten op onderdelen van een depressieve stoornis is in de discussie beschouwd. In dit licht is het van belang om bijvoorbeeld therapieresistente depressie beter te begrijpen. Daarnaast is het mogelijk dat behandeling van een depressie middels neuromodulatie meerwaarde kan hebben door deze behandeling te richten op bepaalde symptoomgroepen in plaats van depressie in zijn geheel.

Een belangrijke uitkomst van dit proefschrift is dat het antidepressieve effect van tPEMF voorlopig tegengestelde resultaten geeft. Het is dus nog niet te zeggen of tPEMF werkzaam is voor depressie. Toekomstige studies zouden kunnen bijdragen aan het begrip hierover. Een belangrijke kloof die dan overbrugd moet worden is die tussen het mechanistische effect van tPEMF op het brein en het klinische effect op de depressieve stoornis. Mogelijk dat een studie waarbij tPEMF gericht is op bepaalde symptoomclusters van depressie meer duidelijkheid kan geven over het antidepressieve effect van deze globale neuromodulatie-techniek.

Al met al kunnen we stellen dat er meer onderzoek nodig is naar de mogelijkheid van antidepressieve behandeling met neuromodulatie. Dit geldt specifiek voor globale neuromodulatie-technieken, omdat de uitkomsten van klinische studies tegenstrijdige resultaten vertonen. Verder onderzoek naar verschillende stimulatiemodaliteiten en -parameters zou kunnen zorgen voor een klinisch relevante bijdrage aan de behandeling van depressie. Deze vooruitgang in het psychiatrisch onderzoek naar de behandeling van depressie is hoopgevend voor de klinische praktijk. Het is ten slotte de verwachting dat elektromagnetische energie licht zal brengen in de duisternis van depressie.

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Curriculum Vitae

Sjoerd Marten van Belkum (1986) was born in Leeuwarden, The Netherlands, and grew up in the small town of Wergea. He received his secondary education at '*het Stedelijk Gymnasium*', a grammar school with Latin and Greek. He took his exams in the fields '*Natuur en Techniek*' and '*Natuur en Gezondheid*' with Greek and History as additional courses.

Sjoerd van Belkum chose to study Medicine at the University of Groningen. Additionally he took some courses in Philosophy. During his study he became chairman of the Groningen board of the IFMSA, the International Federation of Medical Students' Associations. He did his clinical rotations in the University Medical Center Groningen (UMCG), in the Medical Center Leeuwarden (MCL), and in the Martini Hospital. His master thesis he wrote on consumerism within market driven health care at the department '*Expertisecentrum Ethiek in de Zorg*' of the UMCG.

After obtaining his medical degree in 2011 he worked as a psychiatric resident at the department of psychiatry of the UMCG. In 2012 he started his training at this hospital to become a psychiatrist. He combined his clinical work with the scientific research described in this PhD thesis. During his training he became chairman of the board of the "SAP", the Dutch association for psychiatric trainees, part of the Netherlands Psychiatric Association (NVvP). He intends to finish his psychiatric training in 2019 and to continue his research on neuromodulation and depression.

In his spare time he enjoys doing watersports, mainly rowing and sailing, but he also enjoys running and cycling. He is an avid photographer and a keen reader. Sjoerd van Belkum is married to Wietske Rienstra. Recently their daughter, Brechtje, was born (2018).