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Published in:
Journal of Affective Disorders

DOI:
10.1016/j.jad.2021.07.087

Publication date:
2021

Journal of Affective Disorders 294 (2021) 679–685

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

No antidepressant effects of low intensity transcranial pulsed electromagnetic fields for treatment resistant depression

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ARTICLE INFO

Keywords:
Depression
MDD
TRD
rTMS
tPEMF
LFMS

ABSTRACT

Background: Noninvasive neurostimulation with transcranial Pulsed Electromagnetic Fields (tPEMF) may be a promising method for treatment resistant depression (TRD). Studies shown substantial improvement of depressive symptoms in patients with TRD, but there is no information on long-term antidepressant 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 in both groups. The improvement continued 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 this type of 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, but a higher magnetic field strength, that reported improvement of depression after treatment with tPEMF compared to sham. An important limitation of our study was the fact that no different dosing regimens were tried.

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 & Mayberg, 2012).

Non-invasive neuromodulation for depression can be categorized into two broad categories: local or global modulation. Local modulation, for example repetitive Transcranial Magnetic Stimulation (rTMS), relies on modulation of local brain regions (Allan, Herrmann, & Ebmeier, 2011). The clinical antidepressant effect of rTMS relies on different

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https://doi.org/10.1016/j.jad.2021.07.087
Received 24 January 2021; Received in revised form 15 April 2021; Accepted 15 July 2021
Available online 22 July 2021

dosing parameters, for example the stimulated brain region or the frequency of the pulses, as well as the strength or intensity of the induced electromagnetic field (Milev et al., 2016). In general, rTMS has become an established treatment for TRD (Lefaucheur, J. P. et al., 2014; Lefaucheur, Jean-Pascal et al., 2020).

Global modulation of the brain refers to weak electromagnetic stimulation at multiple scalp sites simultaneously or with a more or less homogeneous magnetic field (Larsen et al., 2020; Martiny, Lunde, & Bech, 2010; Rohan et al., 2004; Rohan et al., 2013; van Belkum, Bosker, Kortekaas, Beersma, & Schoevers, 2016). Methods that apply this global modulation are dubbed Low Field Magnetic Stimulation (LFMS) (Rohan et al., 2004) or transcranial Pulsed Electromagnetic Fields (tPEMF) (Martiny et al., 2010). There is emerging evidence that weak electromagnetic stimulation may have an antidepressant effect. For example, treatment using tPEMF showed efficacy in treatment resistant depression after 5 weeks of treatment in a double blind Randomized Controlled Trial (RCT) in patients with MDD (Martiny et al., 2010) and in a double blind RCT LFMS had an immediate positive effect on depression severity (Rohan et al., 2013).

Only a few RCTs investigating global stimulation with weak electromagnetic fields have been reported, with no information on the long-term duration of the antidepressant effect. Furthermore, the minimal intensity of the magnetic field is not known, while biological effects of PEMF-exposure of much weaker intensities than previously reported have been described (van Belkum et al., 2016). Using a neurostimulator that previously was found to reduce experimentally induced pain in healthy subjects (Kortekaas et al., 2013), we studied the clinical antidepressant effects of tPEMF, using a similar pulse as Martiny et al. (Martiny et al., 2010) but with a lower intensity. We aimed to show the antidepressant effects of tPEMF in TRD of a low intensity stimulation device. Moreover, we aimed to investigate long-term effects and we aimed 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, from multiple mental health institutions in the north of The Netherlands (Department of Psychiatry of the University Medical Center Groningen (UMCG), the mental healthcare providers Lentis, GGZ Drenthe, GGZ Friesland, and the Department of Psychiatry of the general hospital in Sneek) and we had treatment sites in three of these mental health institutions (Department of Psychiatry of the UMCG, 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 treatment system have previously been published in detail (Kortekaas et al., 2013). In short, a pulse generator was coupled to a treatment cap consisting of a regular EEG cap to which nineteen electromagnets were radially attached and positioned according to the international 10/20 system for EEG electrodes. The electromagnets of the cap consisted of reed relays of which the reed switch was replaced by a steel bolt, transforming them into iron core electromagnets. For the active condition, alternating bipolar square pulses of 2 V were used as input, equal to the bipolar pulses used in the stimulation set of Martiny et al. (Martiny et al., 2010). The stimulation pattern consisted of 3 ms positive and 3 ms negative and 12 ms pause, thus lasting 18 ms in total. The induced magnetic field had a maximum strength of 100 uT at a distance of 1 cm from the coil (for additional measures: see supplemental). 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.

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: 1) a low baseline score and short duration; 2) a low baseline score and a high duration; 3) a high baseline score and short duration: and 4) a high baseline score and high duration. We did not adopt a minimization procedure (Pocock & 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, Gullion, Basco, Jarrett, & Trivedi, 1996), and assessed changes of anxiety symptoms as measured with the Beck Anxiety Index (BAI) (Beck, Epstein, Brown, & Steer, 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 et al., 2009). A higher score is associated with a worse depression outcome (Fekadu et al., 2009; (Fekadu et al., 2009); 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) of 5 points difference between both groups, as reported in a previous publication (Martiny et al., 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 outcome. 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

We included 55 participants, 27 female (49%). The trial ended after the pre-determined 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 at 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 1 shows that the treatment groups were similar in sociodemographic 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 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 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 2). In general, participants did improve significantly over time (F 14.768; p<.001) (Fig. 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 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

Table 1
Sociodemographic and clinical parameters.

Socio-demographics	Active		Sham		P-value	test
N	29		26		-	
Age (years; mean (SD))	49	13	45	12	0.309	2-tailed t-test
Gender (female %)	15	52%	12	46%	0.680	Chi-square
Marital status					0.422	Chi-square
Single (n; %)	10	34%	9	35%	-	
Married (n; %)	15	52%	16	62%	-	
Divorced (n; %)	4	14%	1	4%	-	
Educational background					0.460	Chi-square
Primary (n; %)	2	7%	0	0%	-	
Lower secondary (n; %)	9	31%	11	42%	-	
Upper secondary (n; %)	13	45%	12	46%	-	
University (n; %)	5	17%	3	12%	-	
Presence of somatic complaints (% yes)	18	62%	21	81%	0.127	Chi-square
Clinical						
MDD-type					0.324	Chi-square
MDD first episode (n; %)	14	48%	16	62%	-	
MDD recurrent episode (n; %)	15	52%	10	38%	-	
Number of episodes (median (IQR))	2	(1 - 2,5)	1	(1 - 3)	0.746	Mann-Whitney U
Duration of current episode (mos; median (IQR))	23	(16 - 66)	33	(12 - 107)	0.468	Mann-Whitney U
Presence of comorbidity (% yes)	14	48%	11	42%	0.657	Chi-square
Anxiety Disorders (n; %) (GAD, Panic, Social, OCD, PTSD, NOS)	9	31%	6	23%	0.508	Chi-square
Personality Disorders (n; %) (Avoidant, OCPD, NOS)	5	17%	5	19%	0.849	Chi-square
Miscellaneous (n; %) (Asperger's disorder, ADHD)	2	7%	0	0%	0.173	Chi-square
MSM-score (mean (SD))	7.8	1.60	8.3	2.29	0.402	2-tailed t-test
Study related						
Treatment expectancy (1-10; mean (SD))	5.8	2.3	6.4	2.1	0.373	2-tailed t-test
Correct guess to treatment allocation	12	48%	9	36%	0.254	Chi-square
Stratum					0.986	Chi-square
S1	5	17%	5	19%	-	
S2	20	69%	18	69%	-	
S3	1	3%	1	4%	-	
S4	3	10%	2	8%	-	

sham treatment of 8 points where the tPEMF participants improved and the sham participants worsened on the HAMD-17. However, there were only two participants in this stratum (Table 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 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 3). The interaction time*group for the difference in BAI-score of participants was not statistical significant (F: 2.363; p=.055) (Table 4).

3.4. Reported adverse effects

eTable 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, 2 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.

4. Discussion

In this study we aimed to describe the direct and long-term antidepressant effects of tPEMF of a device utilizing a low intensity magnetic field in patients with treatment resistant depression. 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.

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 et al., 2009). Participants in our sample suffered from moderate treatment resistance (MSM-score: 8), with higher scores indicating a worse depression outcome (Fekadu et al., 2009; (Fekadu et al., 2009); 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 sample of a previous study investigating the effects of tPEMF (Martiny et al., 2010). This does suggest that our negative findings are not likely to be due to the distribution of clinical factors that contribute to treatment resistance.

An important difference between our study and previous investigations of the antidepressant effects of tPEMF and similar global stimulation devices, like Low Field Magnetic Stimulation (LFMS), is the utilized magnetic field strength. For example, the effects of tPEMF have been studied utilizing a magnetic field strength of 1-2 mT (10^{-3} T) half a centimeter from the coil (Martiny et al., 2010). In another set of studies, using LFMS, the induced magnetic field strength encompassed 1 mT in the brain (at an unreported distance from the coil) (Fava et al., 2018; Rohan et al., 2004; Rohan et al., 2013). In contrast, in our study the induced magnetic field had a maximum strength of 0.1 mT measured at a distance of 1 cm from the coil; hypothetically, this may be too low to induce a clinical effect. This alone could be an explanation for the lack of significant results.

A biological effect of PEMF-exposure of similar or even much weaker intensities has however been shown earlier (van Belkum et al., 2016). For example, PEMF exposure of 0.1 mT elevated BDNF mRNA expression in dorsal root ganglion neurons obtained from neonatal rats (Li et al., 2014) and PEMF signals of 0.005 mT (5 uT) increased neurite length and cell body size in three days' time, as opposed to a control and a null condition (Lekhraj et al., 2014). Also, tPEMF stimulation of 43 nT at a distance of 1 cm from the coil was reported to have a clinical analgesic effect in patients with fibromyalgia (Maestu et al., 2013). Additional analyses of data collected in the present trial showed a decrease in brain activation in the left inferior frontal gyrus during reward-outcome processing as a result of tPEMF-stimulation (van Belkum, 2017). It is not to be expected that the static electromagnetic field of the fMRI had an antidepressant effect, as a study in rodents has shown that antidepressant effects depended on low, but oscillating electromagnetic fields instead of strong (3 T) but static electromagnetic fields (Carlezon et al., 2005). In sum, preliminary findings suggest that even

Table 2
change in HAMD-17-scores. Primary analysis time*group interaction: F(3;66) 0,933; p=0,338.
Stratum 1
time*group interaction: F(3;22) 1,069; p=0,383
Stratum 2
time*group interaction: F(3;99) 0,612; p=0,609
Stratum 4
time*group interaction: F(3;13) 0,535; p=0,667

	Active Mean	SD	Sham Mean	SD
HAMD wk0	22	3.2	22	2.5
HAMD wk5	16	5.4	17	5.4
HAMD wk10	15	6.1	14	6.6
HAMD wk20	15	6.6	13	6.2

	Stratum 1				Stratum 2				Stratum 3				Stratum 4			
	Active		Sham		Active		Sham		Active		Sham		Active		Sham	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
HAMD wk0	21	3.0	20	2.1	21	2.3	22	2.1	28	-	26	-	27	2.6	26	0.0
HAMD wk5	13	3.7	13	5.0	16	4.4	17	4.7	24	-	30	-	17	10.4	17	0.0
HAMD wk10	9	8.2	13	7.6	15	4.6	14	7.0	25	-	18	-	20	3.6	13	2.8
HAMD wk20	14	10.0	9	4.0	14	6.0	13	5.0	21	-	23	-	20	2.5	19	1.4

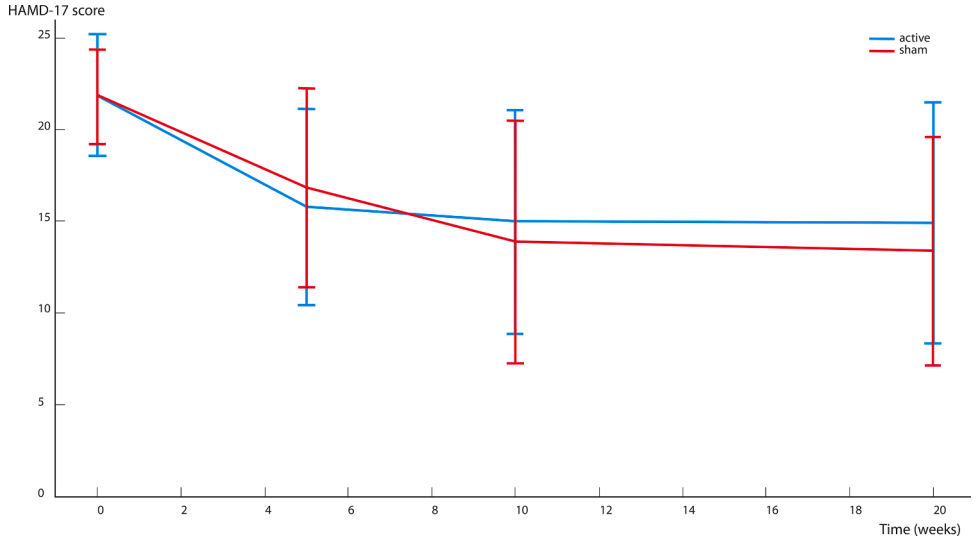

Fig. 2. Decrease of HAMD-17 score over time for both groups.

Table 3
change in IDS-score. Time*group interaction: F(7;340) 0,683; p=0,687.

	Active Mean	SD	Sham Mean	SD
IDS wk0	44	9.8	45	8.9
IDS wk1	41	9.7	41	11.2
IDS wk2	41	10.4	38	11.1
IDS wk3	40	10.5	38	12.8
IDS wk4	37	11.4	36	13.4
IDS wk5	38	13.3	38	12.4
IDS wk10	34	13.3	35	13.2
IDS wk20	38	14.9	33	15.1

Table 4
decrease of BAI-scores; time*group interaction: F(4;192) 2,362; p=0,055.

	Active Mean	SD	Sham Mean	SD
BAI wk0	22	10.3	28	12.4
BAI wk2	20	10.6	21	11.4
BAI wk5	16	9.7	23	11.8
BAI wk10	14	9.7	19	11.7
BAI wk20	18	9.5	18	10.9

magnetic field strengths in orders of magnitudes smaller than previously used may have some biological effects (Fava et al., 2018; Martiny et al., 2010; Rohan et al., 2004; Rohan et al., 2013). Nonetheless, 0.1 mT could be too weak to obtain a clinical antidepressant effect.

There is another aspect of this study that differs from an earlier study investigating the effects of tPEMF (Martiny et al., 2010) and that might explain the differences in findings, which is difference between the stimulation caps used in both studies. In this earlier study the effects of tPEMF have been studied in a double blind RCT in 50 participants suffering from treatment resistant MDD. After five consecutive weeks of stimulation, depression severity decreased significantly more in the active stimulation group compared to sham stimulation (Martiny et al., 2010). In the current study, we applied 2 V over a cap with 19 parallel small iron core coils positioned according to the international 10/20 system (Myslobodsky, Coppola, Bar-Ziv, & Weinberger, 1990). The induced magnetic flux density of this cap is inhomogeneous with a relatively 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 et al., 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 (Martiny et al., 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 et al., 2010). The ACC also plays an important role in affect in general and depression in particular (Groenewold, Opmeer, de Jonge, Aleman, & Costafreda, 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.

An important limitation of our study was the fact that no different dosing regimens have been tried. For example, we did not find an antidepressant effect at 0.1 mT, but we have not been able to test at e.g. 0.5 mT or at 1 mT, i.e., similar to earlier studies (Fava et al., 2018; Martiny et al., 2010; Rohan et al., 2004; Rohan et al., 2013). As a result, the lack of significant results may be attributable to the weakness of the electromagnetic field strength, despite some evidence of possible biological effects of such weak fields, as stated above.

To summarize, we were not able to show an antidepressant effect of tPEMF in a clinical study that was sufficiently powered to find such an effect. More studies will be needed to test if the clinical effects of tPEMF only occur at higher magnetic field strengths. In addition, studies into putative neurobiological mechanisms are needed to clarify which underlying biological mechanisms are at play.

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; TM; FW; RH; HK; AA; RS.

Ethical approval

This study was approved by the Medical Ethical Committee of the University Medical Center Groningen (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.

Funding

This study was funded by: UMCG Innovation Fund, project U-11-221, and Fonds NutsOhra, project 1103-068 (main applicant on both applications was RS).

Declaration of Competing Interest

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.

Acknowledgments

The authors thank Charlotte Kohne, Chris Geraets, Christien van Buuren, Ella Bekhuis, Elroy Doornbos, Esther van Veen, Joyce van Meel, Lotte Staas, Lydia Datema, Maartje Bastiaans, Magda Tasma, Milou van Eldik, Nadine de Jong, Nina Schimmel, Philip Nan, Roelien Anna Vaals, Sjoukje Vroom, Stella Druiven, and Thom Lysen for their assistance in conducting this study and Tjalling Nijboer for essential technical input.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.07.087.

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