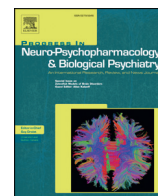




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Treatment of depression with low-strength transcranial pulsed electromagnetic fields: A mechanistic point of view

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ABSTRACT

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 antidepressant 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 antidepressant effect of tPEMF may be specifically attributable to its effects on local brain activity and connectivity.

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1. Introduction

Major depressive disorder (MDD) is a severe mental disorder with an estimated lifetime prevalence of 30% in men and 40% in women (Kruijschaar 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). The 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 T induce an electric current in the underlying brain tissue (Barker et al., 1985).

The antidepressant 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 (HAM-D-17). The overall conclusion was that TMS is an effective treatment of depression (Allan et al., 2011). A more recent systematic review investigating 63 studies concluded that rTMS stimulation has a statistically significant antidepressant 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 et al., 2013).

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“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 et al., 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 preclinically 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 min 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 a 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 et al., 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 antidepressant effects of tPEMF stimulation have also been investigated in both preclinical 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 antidepressant-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 disorder, 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 et al., 2010). After stimulating 50 patients with TRD for 5 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 et al., 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 min 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 et al., 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 antidepressant effects of tPEMF are promising. However, the mechanisms by which electromagnetic fields can produce an antidepressant effect are far from understood. In this paper, we will give an overview of putative mechanisms underlying the antidepressant 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 et al., 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 preclinical 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 et al., 1985; Pell et al., 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 et al., 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 bear 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 et al., 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 et al., 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 an 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, 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 antidepressant 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 et al., 2008; Molendijk et al., 2014; Player et al., 2013; Sen et al., 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 et al., 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, the 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-1 β 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 et al., 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 (T_H1) and an anti-inflammatory group (T_H2 and T_H3). 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 et al., 2009), but results for anti-inflammatory T_H2 cytokines were far less consistent. However, because cytokines influence each other's release, the balance between pro-inflammatory cytokines (T_H1) and anti-inflammatory cytokines (T_H2 and T_H3) might be particularly important (Kim et al., 2007; Sutcgil 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-1 β 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 μ T; 0,48 V/m) reduced levels of the cytokines IL-1 β , IL-6, and TNF- α , as measured in these 9 days (Chang et al., 2004).

In humans PEMF stimulation specifically decreases IL-1 β levels in wound exudate (Rohde et al., 2010). This was shown in a double-blind, placebo-controlled, randomized study applying PEMF stimulation for 20 min every 4 h for the first 3 days, then once every 8 h for the next 3 days, then twice daily (27,12 MHz; 5 μ T; 3,2 V/m) directly after breast reduction surgery. Six hours after surgery, IL-1 β in wound exudate was significantly reduced in the active treatment group compared to placebo. This difference sustained up to 24-h 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-1 β is particularly interesting in view of a head injury study in rats showing significant decreases of IL-1 β levels in liquor following PEMF treatment (Rasouli et al., 2012). Rats were injured under two different conditions. First, they were given head injury and exposed to PEMF treatment in a constant regimen of 5 min stimulation in every 20 min for 6 h (27,12 MHz; 40 V/m). Second, 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-1 β levels in liquor six hours after the injury. However, there was a significant decrease of IL-1 β 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-1 β , 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 antidepressant 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, 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 antidepressant effects of tPEMF are somehow connected with the biological clock.

First, there is circumstantial evidence that weak alternating electromagnetic fields may shorten circadian rhythms in healthy controls (Wever, 1970, 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, 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 h (Wever, 1970, 1973).

Second, 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, 2002) and is thus an intrinsic molecular regulator of the biological clock (Chaves et al., 2011; Emery et al., 1998; Griffin et al., 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 μ T 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 et al., 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 et al., 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 et al., 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. Knock-out flies did not respond to the magnetic fields (Foley et al., 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 antidepressant effect of PEMF. The argument that the antidepressant 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 antidepressant 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 antidepressant 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 antidepressant 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 antidepressant 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. First, 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. Second, 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 we 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 antidepressant effects of tPEMF stimulation did use similar parameters.

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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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