Efficacy of repetitive transcranial magnetic stimulation (rTMS) in the treatment of major depressive disorder (MDD): a systematic overview of randomized controlled trials
Transcranial magnetic stimulation is the noninvasive technique to induce electrical currents in brain tissue via magnetic fields, proven to have therapeutic effects on depression. The magnetic coil located slightly above the scalp can either excite or inhibit cortical brain areas, depending on the speed of the repetitive cycles. rTMS can be divided into two subtypes; high-frequency rTMS (10-20 Hz) and low-frequency rTMS (≤1 Hz) applied to the left and right dorsolateral prefrontal cortex respectively. The primary objective of this thesis was to identify the clinical efficacy of rTMS, that is the ability to attain remission in MDD patients through repetitive transcranial magnetic stimulation. The electronic search included the databases Cochrane Library and PubMed. Unpublished data was collected through personal communication with researchers. My conclusion is that a substantial body of research supports the efficacy of rTMS in MDD patients. However, optimizing the parameters and identifying the factors which determine successful stimulation is paramount. Combining excitatory and inhibitory stimulation with more efficient frequency protocols, may instigate remission and maintenance rates. With no systemic side effects or drug interactions, this non-invasive brain stimulation technique implies a safe therapy solution for patients suffering from depressive disorders.

Keywords: transcranial magnetic stimulation, rTMS, depression, MDD, neuromodulation, brain stimulation.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>MDD</td>
<td>major depressive disorder</td>
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<tr>
<td>rTMS</td>
<td>repetitive transcranial magnetic stimulation</td>
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<td>dTMS</td>
<td>deep transcranial magnetic stimulation</td>
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<tr>
<td>ECT</td>
<td>electroconvulsive therapy</td>
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<td>mT</td>
<td>millitesla; the unit of magnetic flux density</td>
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<td>TRD</td>
<td>treatment resistant depression</td>
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<tr>
<td>HPA</td>
<td>hypothalamus-pituitary-adrenal cortex</td>
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<td>BDNF</td>
<td>brain-derived neurotrophic factor</td>
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<td>MEP</td>
<td>motor evoked potentials</td>
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<tr>
<td>APS</td>
<td>American Psychiatric Association</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>DSM-V</td>
<td>Diagnostic and Statistical manual of Mental disorders V</td>
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<tr>
<td>ICD-10</td>
<td>International Classifications of Disease 10th ed.</td>
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<tr>
<td>HAMD</td>
<td>Hamilton Depression Rating Scale</td>
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<td>BPRS</td>
<td>Brief Psychiatric Rating Scale</td>
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<td>BDI</td>
<td>Beck Depression Inventory</td>
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<tr>
<td>CGI-S</td>
<td>Clinical Global Impression-Severity of Illness</td>
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<tr>
<td>STAI</td>
<td>State Trait Anxiety Inventory</td>
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<tr>
<td>TCA</td>
<td>tricyclic antidepressant</td>
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<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
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<td>SNRI</td>
<td>selective noradrenaline reuptake inhibitor</td>
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<td>MAOI</td>
<td>monoamine oxidase inhibitors</td>
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<td>MT</td>
<td>motor threshold</td>
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<tr>
<td>cTBS</td>
<td>continuous theta burst stimulation</td>
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<tr>
<td>iTBS</td>
<td>intermittent theta burst stimulation</td>
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<tr>
<td>DLPFC</td>
<td>dorsolateral prefrontal cortex</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>HF-rTMS</td>
<td>high frequency rTMS</td>
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<td>UHF-rTMS</td>
<td>ultra high frequency rTMS</td>
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<tr>
<td>LF-rTMS</td>
<td>low frequency right-sided</td>
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DEFINITIONS

Treatment resistant depression: Patients who do not improve although two adequate trials of antidepressants of different classes, during one episode of depression.

Relapse: Another episode of depression occurring fewer than six months after treatment for acute depression and a fifty percent increase in symptom severity.

Recurrence: Symptoms reoccurring after six months of remission.

Remission: Optimal outcome of treatment for depression (due to the lack of objective biologic markers, significant symptoms may still exist even though patients may have a full response). Measurements are made by various standardized psychiatric rating scales.

Response: Fifty percent reduction in a rating scale of depression [1,2].

BACKGROUND

The neurobiology of affective disorders is yet to be completely understood, but in response to interdisciplinary ingenuity and successful trials new therapeutic modalities are introduced to clinical practice. Direct stimulation of the brain with the aid of magnetic coils is currently advancing treatment strategies for MDD - a common and debilitating psychiatric disorder impacting a large proportion of the global population. Despite a range of antidepressant drugs, there are many patients who fail to obtain an adequate therapeutic effect although completion of trials. Brain stimulation modalities probe an alternative for these patients, as well as a safe solution for antepartum depression.

Transcranial magnetic stimulation is definitely not a new technique, but applied in psychiatry it can be considered a novel approach. The first time rTMS to the left prefrontal cortex was proposed as a treatment method for MDD was in 1993. Thereafter, a multitude of studies have demonstrated clinically meaningful antidepressant effects from rTMS, compared to sham. In 2007 an extended industry-sponsored trial was published, resulting in the US Food and Drug Administration approval of rTMS as a treatment option for MDD in adults [3]. Accumulating approval among neuroscientists, by showing statistically as well as clinically significant antidepressant effects, has made rTMS a rapid growing field of interest even for the general public. Nevertheless, there are numerous unanswered questions. including appropriate scalp location, frequency protocol and adjustments of parameters.
The combination of rTMS and antidepressant drugs is being investigated for the sake of maintenance, however there is promising evidence that rTMS alone can deliver continuous remission [4].

The interest for magnetic stimulation has to a big extent emerged from the ambition to replace ECT. In contrast to ECT the magnetic stimulation does not need to induce a seizure for antidepressant effect, which reduces the risks and side effects fundamentally. There is no need for anesthetic drugs when executing the stimulation, and the much disputed side effect of temporary memory loss after ECT therapy is not reported in any of the rTMS trials. Side effects from rTMS are merely a matter of focal headaches, mild twitching of facial muscles and skin/scalp sensations as the magnetic waves transcend into brain tissue.

Mechanisms of action
Electromagnetic induction is the discovery that a flux in pulse density through a magnetic coil generates an electric field, and that a current through a wire cause a magnetic field around that wire. When discharging current from a powerful electrical condenser into a coil, magnetic fields of 1-10 mT are produced [5]. rTMS takes advantage of these laws of physics, composing a fluctuating magnetic field at a set frequency which induces an electrical current in brain tissue when positioned close to the scalp. The stimulation causes an electric activity in the brain cortex and depending on the placement of the magnetic coil, different effects are provoked by either depolarizing or hyperpolarizing neurons, i.e. affecting the firing of action potentials. The method to stimulate the brain with magnetic coils was developed 1985 to evaluate functions in the central motor system, including the spine. A single pulse from the coil is sufficient to trigger a simple movement of distal limbs. Typically, the thumb is targeted to control and adjust the efficacy of the coil, whereby it is moved to dorsolateral prefrontal cortex regions for psychiatric effects. rTMS is the subcategory of TMS that we come across in clinical practice, primarily executed with antidepressant purpose but also offered to patients suffering from migraine, tinnitus, auditory hallucination in schizophrenia, Parkinson’s and Alzheimer’s disease [6].

The magnetic stimulation is suspected to magnify synthesis of certain nerve growth factors, such as brain-derived neurotrophic factor (BDNF). This factor plays a crucial role in maintaining and regulating neuronal connectivity. Observations that acute and chronic stress in humans suppress endogenous neurotrophic levels, has formulated the BDNF hypothesis.
The decrease in BDNF may lead to atrophy of hippocampus which is a structure known to participate in emotional control. The exact relationship between BDNF and the pathophysiology of depression remains unclear, but there is universal support for taking BDNF into consideration when exploring antidepressant mechanisms [7-9]. Chronic antidepressant medication, ECT, TMS, exercise as well as AMPA receptor potentiators and NMDA antagonists, have all shown to increase mRNA/protein BDNF levels in the rat brain [10-18]. Several antidepressant treatments, either in the medication trials or the brain stimulation labs, have shown to alleviate depressive symptoms through the action of BDNF. BDNF stimulates the development of new hippocampal cells, which is consistent with the line of thought that neuroplasticity has a crucial role in remission. Duman et. al showed in animal studies that the time it takes to induce neurogenesis is equivalent to the time of improvement, namely three to four weeks. The causal sequence postulated from these results, was that raised serotonin levels would increase the cAMP response element-binding (CREB) protein in nerve cells, which in turn augments the level of growth factor BDNF [19,20]. Hence, benefits of rTMS are often explained as enhanced neuroplasticity in certain brain pathways. New theories expand this apprehension when presenting evidence that rTMS resets thalamocortical oscillators, normalize regulatory brain functions, and promote reemergence of intrinsic cerebral rhythms, whereby normal cerebral dynamics are restored. These events may be crucial in engendering neuroplasticity prerequisites, thus placing emphasis on the importance of regenerative aspects of neurons when evaluating antidepressant effects of rTMS. Forcing an oscillatory reset, with the help of theta burst protocol for example, could explain the antidepressant effects achieved with rTMS [21].

It has become apparent, in vivo and in vitro, that rTMS influences immediate-to-early gene expression [22,23]. The mRNA expression changes of monoamine transporter (MAT) genes that rTMS exerts has been proven for dopamine, as well as noradrenaline and serotonin [24-26]. Additionally some studies argue that rTMS affects the neuroendocrine system [27,28].

What impact rTMS has on cortical activity is a revisited question. Observations have noted changes in the prefrontal cortex and paralimbic activity, even after just a couple weeks of rTMS treatment [29]. Brain imaging (fMRI, PET scan etc.) show improved blood circulation and glucose metabolism in human brain regions subject to magnetic stimulation. Activity in the cingulate increases markedly, as well as paralimbic blood flow, following a two-week course of rTMS. The cingulate has a crucial role in the pathophysiology of depression, since it has been recognized as blunted in depressed patients [30]. Some of the alterations in brain
physiology and neurochemistry may be unique to rTMS [31].

**rTMS devices and coil design**

In the beginning the devices differed in moderate ways, the coil (i.e. magnetic field generator) was round and manually positioned by the psychiatrist during treatment. Modern devices are more sophisticated with coil designs varying in material, geometry of the coil configuration and biophysical characteristics of the pulses emitted. Some devices target the brain bilaterally, but most commonly the coil is fixed on the patient’s left side in order to target the left dorsolateral prefrontal cortex (DLPFC). Neuronavigation is the 3D-imaging of the brain based on structural MRI, plotting out the exact areas of the brain thought to be relevant for MDD (for example BA 9 and 46) [32]. Whatever way the coil is positioned, the magnetic field impulses can only reach the outer layers of cortex, approximately 1.5-2.5 cm deep. How to ideally accomplish deeper stimulation is under investigation, as well as the research on what potential benefits it could offer [33]. The figure eight coil emits a more focal activation pattern, whilst the double-cone coil conforms to the shape of the head, which aids deeper stimulation. However, to allow deep transcranial magnetic stimulation (dTMS), some of the focal precision may be compromised [34]. The H-coil has the potential of reaching deeper brain areas such as the cingulate, regions that the more superficial rTMS procedures stimulate as well but indirectly. The geometric shape of the coil governs the focality and depth of cortical penetration, crossing the scalp unimpeded due to the physical nature of electromagnetic induction [35] The H-coil helmet, approved by the FDA (Jan 2013), shows promising impact on deeper brain regions with increased stimulation energy and minimal loss of focal accuracy [33,36].

**Target population**

The patient group earning special priority for this novel form of brain stimulation are individuals whose condition has lacked improvement after several conventional approaches. In contrast to other therapy forms such as TCA, SSRI and other antidepressant medications, rTMS is not associated with the common side effects of weight gain, sexual dysfunction, sedation etc. In another aspect, it is also much less invasive than electroconvulsive therapy (ECT), deep brain stimulation (DBS), vagus nerve stimulation (VNS) and similar treatment solutions. There is an expanding body of scientific evidence supporting the efficacy of rTMS as a treatment option for a wide spectrum of brain disorders; generalized anxiety, schizophrenia (auditory hallucinations and negative symptoms), cognitive impairment,
tinnitus and even nicotine or cocaine addiction. rTMS is still less effective than ECT for the worst afflicted patients, but due to the adverse effects on cognitive function there is reason to opt for rTMS as a treatment choice for individuals suffering from moderate-to-severe MDD [37].

*rTMS administration*

The first TMS devices emitted a single pulse, now modern clinical devices are adjusted to generate a rapid succession of pulses (rTMS). The treatment program typically consists of a four second stimulation, with a subsequent twenty-six seconds of rest. This is repeated for twenty to forty minutes. In order to maintain remission, a patient will need further treatments (five days a week, for four to six weeks). Before the treatment commence, the optimal strength of the magnetic field is calibrated for each patient. This is called the “motor threshold” (MT), which is the strength needed to activate a specific muscle from the motor cortex (typically m. abductor pollicis brevis). From this measurement treatment strength is calculated, commonly between 80 to 120 percent of MT. The standard coil positioning in clinical practice is the so-called “5cm rule” [38], i.e. a 5cm move of the coil from motor cortex to dorsolateral prefrontal areas. Considering natural variations in head circumference, focus of stimulation may be more precise for each individual with more sophisticated methods such as neuronavigation [39]. rTMS passes the skin and skull unimpeded, causing electrical charges within the adjacent cortical brain circuitry.

Many trials have had the aim to find a combination of technical parameters resulting in an improved efficacy. Amongst these parameters are magnetic field frequency, strength and duration of exposure. The left DLPFC is known to be hypoactive in depressed patients, while the right DLPFC tends to be hyperactive. When the coil is positioned on the left side of the DLPFC, the patient is exposed to high-frequency pulses (10-20 Hz) in an attempt to activate this region and stimulate blood circulation. With right-side stimulation low frequencies are operated (1-2 Hz), thought to have an inhibiting effect. The efficacy of high-frequency rTMS, applied to the left DLPFC in MDD treatment, has been established by a wide range of randomized controlled trials including extended multisite trials [4,38,40,41]. These findings have been confirmed by several meta-analyses, and efficacies of other forms of rTMS application have been added to the accumulating evidence base. Low-frequency rTMS applied to the right DLPFC [42], and sequential application of the right and left DLPFC respectively, are the main alternative schemes. The bilateral rTMS trials have been
inconsistent, showing both inferior as well as greater efficacy when compared to unilateral rTMS [43,44].

**Risks and adverse effects**
The known risks of rTMS treatment are mild and transient. Incidences of seizures were reported during the first years of treatment, leading to restrictions and the establishment of safety guidelines [34,45]. Since these measures were obtained, development of seizure activity is eminently unlikely, unless the patient has a history of seizures prior to rTMS treatment [46]. Mild adverse effects, such as discomfort due to facial muscle twitching (14%) and moderate headaches (9%) can be managed by reduction of the stimulus intensity by ten percent for the facial twitches and regular analgesics for the headaches. There are no reports of memory impairment, cognitive derangements or concentration difficulties after rTMS. ECT may exert these side effects, but they are considered acceptable when treating patients with severe MDD due to the pronounced efficacy and short latency period [42]. When rTMS was compared to ECT, no significant differences appeared between these two techniques when the patients did not have psychotic symptoms, but significant differences did appear in favor of the ECT when the patients had psychotic symptomatology [47].

**Depression**
There is a high prevalence of depression on a global scale; approximately fifty percent of women and twenty-five percent of men will suffer a depressive episode at some point [48]. Depression prevalence reflects the difficulty in finding effective treatment for psychiatric disorders, due to the complexity of the brain and interacting body systems. Depression has perpetually earned the epithet “the most common disease and cause of disability world-wide” [49]. Depression is the primary cause of suicide as well as long-term sick leave in private and public sector in Sweden today. Many other countries are facing similar numbers [50-52]. Mild and moderate depression is becoming more common in young and adults, possibly due to the improved methods of diagnosing the condition. Surveys indicate that the age of onset is lower today, and that children and adolescents are more depressed than ever before [53].

Affective mood disorders are commonly classified by the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) [54] and the World Health Organization International Classifications of Diseases 10th edition (ICD-10) [55]. Categories within the classification
systems are depressive episode, recurrent/major depressive disorder, persistent depressive disorder (previously dysthymic disorder), bipolar disorder, schizoaffective disorder, disruptive mood dysregulation disorder (children up to 18 years), and premenstrual dysphoric disorder. A depressive episode can emit in any of these mood disorders. The criteria for a major depression episode diagnose according to DSM-V are the following symptoms (occurring during the same two week period and including at least “depressed mood” or/and “loss of interest”):

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation mad by others.
2. Markedly diminished interest or pleasure in all, or almost all activities, of the day.
3. Significant weight loss or weight gain (> 5% change of body weight in a month), increase or decrease in appetite daily.
4. Insomnia or hypersomnia.
5. Psychomotor agitation or retardation.
6. Fatigue, loss of energy, apathy.
7. Feelings of worthlessness or excessive, inappropriate guilt.
8. Diminished ability to think or concentrate, indecisiveness.
9. Recurrent thoughts of death, recurrent suicidal ideation with or without attempts or plans for committing suicide.

Additional criteria for the diagnose major depressive episode; the symptoms do not meet the criteria of mixed episodes, the symptoms cause clinically significant distress or impairment in social, occupational, or other areas of functioning. Physiological effects of a substance or a general medical condition, causing symptoms of depression, are excluded from this category of mood disorder. The ICD-10 definition of major depression is presented with the same core statements, the two systems do not conflict but rather complement each other. An episode is classified as mild, moderate, severe or severe with psychosis.

Mood deviation is not the only characteristic of depression. When analyzed, a cluster of signs and symptoms emerge. These may be conceptualized as a psychopathological spectrum, ranging from mild to severe in intensity. Major depressive disorder (MDD) is defined by the occurrence of one or more major depressive episodes. These episodes are in turn defined by
their length (minimum of two weeks of depressed mood or loss of interest) and the severity of the depressive state (at least four additional depression symptoms) [54].

The descriptions of depression have been remarkably consistent since the very first psychiatric endeavors. Symptoms have been classified congruously with epithets describing emotional, cognitive, motivational, physical and vegetative manifestations. Biological factors have been of considerable interest, whereby tests have been made of nearly all known constituents of cerebrospinal fluid, urine and blood. The histopathology of the depressed brain has been thoroughly investigated, in tandem with studies of other organs thought to influence moods and emotion [56].

The HPA-axis of hormones is thought to be important since deviations appear in many depressed patients. Stress hormones such as cortisol and adrenaline are elevated. In severely depressed individuals the cortisol is measured at a static maximum, when it normally fluctuates in blood concentration over twenty-four hours (low levels at night, high in the mornings). Disturbances in the HPA-axis are related to chronic stress and depression. The diurnal rhythm and plasma levels of cortisol are controlled by feedback mechanisms, in depressed patients this is seen to be non-functioning [73]. In normal conditions cortisol stimulates parts of the brain necessary for memory and learning, i.e. hippocampus. However, a surplus of cortisol may lead to toxic reactions on the brain tissue, resulting in cognitive impairments. Magnetic resonance imaging performed on certain depressed patients, has revealed actual shrinking of the hippocampus. How the psychoneuroendocrine system confronts social and mental stress is ruled by hereditary dispositions and acquired hypersensitivity, such as early psychosocial trauma. Regulation of noradrenaline receptors in the nervous system appears to be linked to stress sensitivity. People show very different stress tolerance, where the least tolerable are more likely to succumb to depression [57-60].

In addition there are theories addressing disturbances in functional connectivity of the brain as an essential component of the MDD pathophysiology. Brain connectivity is modulated by oscillations of cortical electrical activity, i.e. Alpha (8-13 Hz), Beta (13-30 Hz), Theta (3,5-7 Hz), Delta (0,5-3 Hz) and Gamma (30-70 Hz) with its own set of characteristics. These five different frequency bands coordinate functions across divergent brain areas. Alpha and theta frequency oscillations at the border of 7-8 Hz are thought to play a central role in regulating mood, memory, cerebral blood flow and neurotransmitter levels. New evidence suggests that
depressive disorders may be dependent on brain oscillatory activity. It has been reported that MDD patients exhibit increased oscillatory synchrony in multiple frequency bands across cortical regions. Restoring the normal oscillatory framework is a viable explanation for the efficacy of rTMS [21,61-63].

Although the genetic component of depression is far from deterministic, there is no controversy regarding the gene association with depressive disorders. Depression is frequently discovered in both members of a pair of identical twins. Moreover, the fact that about seventy percent of depressed patients can be treated with an antidepressant drug, strongly indicates abnormal biochemical mechanisms as a component of depressive disorders. The abundance of affected individuals and this success rate has made antidepressants among the most prescribed classes of drugs on a global scale[56]. Granting the majority of MDD patients are helped by an antidepressant drug, a sizeable proportion of patients suffering from this condition fail to respond to monotherapy treatment [64,65]. Genetic vulnerability in combination with a stressful environment may induce a cascade of biochemical events, which eventually propels into destructive conditions in the brain. Although the pathophysiology is not fully understood, it is clear that genetic, environmental and self-inflicted factors interact as a primer for depression [66]. Certain traumas in childhood are linked to depression [67], nevertheless there are people who may cope with recurrent traumas without ever developing depression, which indicates an important genetic aspect. The impact of genetic predisposition is especially noticed in bipolar depression [68], whereas unipolar depression has a genetic component with less impact on the clinical outcome [69]. There are a few established hypothesis offering suggestions for treatment strategies. The monoamine hypothesis advocates that the transmission of monoamines is insufficient [70], serving as evidence base for currently available antidepressants, targeting serotonin and/or noradrenaline reuptake [71]. When monoamine reuptake inhibitors are effective, inhibition is immediate while antidepressant effects occur a month later. Therefore, increasing synaptic availability of monoamines cannot fully explain the efficacy of antidepressants. Monoamine depletion typically only cause a transient depression and ingested precursors such as tyrosine and tryptophan do not improve mood [72].

Neuroplasticity and brain cell turnover are also associated with major depression, which has opted for new approaches in the search for more successful treatments. In animal studies, brain stimulation treatments result in increased cell replication in the amygdala, gyrus cinguli,
hippocampus and the prefrontal cortex – areas crucial for mood and emotion [74].

Repeated relapses and chronicity occur in seventy to eighty percent of MDD patients, and the suicide rate among them is approximately ten percent [75]. Within one year of discharge, thirty percent of inpatients require re-hospitalization [76]. Psychotherapy and extended use of antidepressants may counteract symptom recurrence, however if the affected individual encounters several depressive episodes the risk of relapse remains high albeit treatment [77-79]. Suicide risk among depressed individuals in Sweden has the last decade been up to thirty percent higher than in general population [80]. Patients who are not adequately treated represent the majority of depression-related suicides [81] The suicide rate in Sweden has decreased, closely correlating with the increased prescription of antidepressant medication [82]. Nevertheless, suicide accounts for thousands of deaths in Sweden annually [83]. A vast majority of these victims suffered from depression.

In mild and moderate depression it has been disputed whether treatment is of any gain, since placebo controls have been almost as successful as the treatments tested on these groups of patients [84]. However, major depressive disorder has shown to be of a more resistant kind where active medications offer significantly higher rates of remission than inactive control, i.e. placebo [85]. Selective serotonin reuptake inhibitors (SSRI) dominate the market today, since they come with modest side effects. Tricyclic antidepressant (TCA) is from an older generation of antidepressants, still provided for those who do not improve with SSRI or SNRI. Monoamine oxidase inhibitors (MAOI) are scarcely prescribed, with the more modern options available [86].
OBJECTIVES
To identify the clinical efficacy of rTMS, that is the ability to attain remission in MDD patients through repetitive transcranial magnetic stimulation.

METHODS
Inclusion criteria: Randomized, sham-controlled clinical trials assessing the therapeutic efficacy of rTMS for MDD, during 2010-2015 in English.

Exclusion criteria: Comorbidity when found to be a confounding factor, focus on metabolic and/or anatomical modulations rather than therapeutic remission, medication covariates, lack of sham-control, small sample size (<20), inordinate treatment resistance in study population and dubious study designs motivated exclusion of articles. Incomplete data or studies with more than 1/3 withdrawals in the final quantitative analysis were also excluded, as that could threaten the validity of the results.

Participants: All persons with major depression diagnosed by any recognized criteria, irrespective of gender or nationality, ages 18-75.

Interventions:
1. High-frequency or low-frequency rTMS.
2. Right DLPFC or left DLPFC.
3. Static or theta burst stimulation.
4. Unilateral or bilateral stimulation.
5. Adjunctive rTMS to pharmacotherapy

Search strategy: MeSH terms – Depressive Disorder, Major. Transcranial Magnetic Stimulation, Repetitive. Randomized Controlled Trials as topic. Treatment Outcome.

Databases: PubMed and Cochrane Library.

Outcome measures: Remission, maintenance and relapse rates.
RESULTS

Through electronic database searches I obtained 38 clinical trials that potentially fulfilled my inclusion criteria (abstract study). Out of these, 27 were excluded according to exclusion criteria (full article study). The 11 studies selected for overview were evaluated systematically using a modified version of the SBU protocol from 2009 [87].

1: Ray, S. et al. Efficacy of adjunctive high frequency repetitive transcranial magnetic stimulation of left prefrontal cortex in depression: a randomized sham controlled study [41]
2: Huang, ML. et al. Repetitive transcranial magnetic stimulation in combination with citalopram in young patients with first-episode major depressive disorder: a double-blind, randomized, sham-controlled trial [88]
3: Blumberger, DM. et al. A randomized double-blind sham-controlled comparison of unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant major depression [43]
4: Fitzgerald, PG. et al. A double blind randomized trial of unilateral left and bilateral prefrontal cortex transcranial magnetic stimulation in treatment resistant major depression [89]
6: Janicak, PG. et al. Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: assessment of relapse during a 6-month, multisite, open-label study [40]
7: Nongpiur, A. et al. Theta-patterned, frequency-modulated priming stimulation enhances low-frequency, right prefrontal cortex repetitive transcranial magnetic stimulation (rTMS) in depression: a randomized, sham-controlled study [90]
8: Plewnia, C. et al. Treatment of major depression with bilateral theta burst stimulation: A randomized controlled pilot trial [91]
9: Speer, AM. et al. Antidepressant efficacy of high and low frequency rTMS at 110% of motor threshold versus sham stimulation over left prefrontal cortex [92]
11: Ulrich, H. et al. Ultra-high-frequency left prefrontal transcranial magnetic stimulation as augmentation in severely ill patients with depression: a naturalistic sham-controlled, double-blind, randomized trial [96]
### Efficacy of Repetitive Transcranial Magnetic Stimulation (rTMS) in the Treatment of Depressive Disorders: A Systematic Overview of Randomized and Sham-Controlled Clinical Trials

#### 1) Ray S. et al. (2011)
- **Publication**: [41]
- **Study type**: Randomized (sham-controlled)
- **Patient characteristics**: 45 right-handed patients with moderate/severe depression
- **Intervention**: HF rTMS (10 Hz) at 90% of MT
- **Comparison**: Sham
- **Efficacy measurement**: Hamilton Depression Rating Scale (SIGH-D)
- **Result/Outcome**: High-frequency left prefrontal rTMS was well tolerated and found to be effective as an augmentation to standard pharmacotherapy in first-episode young depressive patients. rTMS can be considered a safe augmentative treatment to SSRI.

#### 2) Huang ML. et al. (2012)
- **Publication**: [88]
- **Study type**: Double-blind (sham-controlled)
- **Patient characteristics**: 60 first-episode young patients with depressive patients
- **Intervention**: HF rTMS (10 Hz) at 90% of MT
- **Comparison**: Citalopram
- **Efficacy measurement**: Hamilton Depression Rating Scale (HAMD-17)
- **Result/Outcome**: rTMS accelerated the rapidity of the antidepressant response in first-episode young depressive patients. rTMS can be considered a safe augmentative treatment to SSRI.

#### 3) Blumberger DM. et al. (2012)
- **Publication**: [43]
- **Study type**: Double-blind (sham-controlled)
- **Patient characteristics**: 74 subjects with TRD
- **Intervention**: Sequential bilateral rTMS to right DLPFC (1 Hz) and left DLPFC (10 Hz) at 120% MT
- **Comparison**: Sham
- **Efficacy measurement**: Hamilton Depression Rating Scale (HAMD-17)
- **Result/Outcome**: The remission rate was significantly higher in the bilateral group than the sham group. The remission rate in the unilateral group did not differ from either group.

#### 4) Fitzgerald PB. et al. (2012)
- **Publication**: [89]
- **Study type**: Double-blind (sham-controlled)
- **Patient characteristics**: 67 patients with TRD
- **Intervention**: Sequential bilateral rTMS and standard HF rTMS to left DLPFC at 120% MT
- **Comparison**: Sham
- **Efficacy measurement**: Hamilton Depression Rating Scale (HAMD-17)
- **Result/Outcome**: Greater antidepressant response to unilateral left-sided rTMS compared with sham or bilateral rTMS.

#### 5) George MS. et al. (2010)
- **Publication**: [4]
- **Study type**: Double-blind (sham-controlled)
- **Patient characteristics**: 199 antidepressant drug-free patients with unipolar nonpsychotic MDD
- **Intervention**: HF rTMS (10 Hz) at 120% MT
- **Comparison**: Sham
- **Efficacy measurement**: Montgomery-Asberg Depression Rating Scale (MADRS)
- **Result/Outcome**: The odds of attaining remission were 4.2 times greater with active rTMS than with sham (95% confidence interval, 1.32–9.24).

#### 6) Janicak PG. et al. (2010)
- **Publication**: [40]
- **Study type**: Double-blind (sham-controlled)
- **Patient characteristics**: 301 patients with unipolar, nonpsychotic MDD
- **Intervention**: HF rTMS (10 Hz) at 120% MT
- **Comparison**: Sham
- **Efficacy measurement**: Montgomery-Asberg Depression Rating Scale (MADRS)
- **Result/Outcome**: Initial data suggest that the therapeutic effects of TMS are durable and that TMS may be successfully used as an intermittent rescue strategy to preclude impending relapse.

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**Note:** This table provides a comprehensive overview of randomized and sham-controlled clinical trials focusing on the efficacy of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depressive disorders.
**Efficacy of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depressive disorders: a systematic overview of randomized and sham-controlled clinical trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Efficacy Measurement</th>
<th>Result/Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>7: Nongpiur A. et al. 2011</td>
<td>Randomized</td>
<td>40 patients with active depression</td>
<td>HF rTMS (490 Hz)</td>
<td>Sham priming</td>
<td>Montgomery-Asberg Depression Rating Scale (MADRS)</td>
<td>Theta range has greater antidepressant effect than low frequency LF rTMS (1 Hz) at 110% of MT</td>
</tr>
<tr>
<td>8: Plewnia C. et al. 2014</td>
<td>Randomized</td>
<td>32 patients with MDD</td>
<td>cTBS and iTBS intensity standardized</td>
<td>Sham</td>
<td>Rating Scale (MADRS)</td>
<td>A significant therapeutic effect of sequential left excitatory and right inhibitory theta burst stimulation was found.</td>
</tr>
<tr>
<td>9: Speer AM. et al. 2014</td>
<td>Randomized</td>
<td>24 acutely depressed patients</td>
<td>HF rTMS (20 Hz) or LF rTMS (1 Hz)</td>
<td>Sham</td>
<td>Rating Scale (HAMD17)</td>
<td>Patients on both frequencies showed greater improvement than on sham. During 7-week continuation of active treatment, additional improvement was observed.</td>
</tr>
<tr>
<td>10: Baeken, C. et al. 2013</td>
<td>Randomized</td>
<td>20 unipolar antidepressant free TRD patients</td>
<td>HF rTMS (20 Hz) at 110% of MT</td>
<td>Sham</td>
<td>Rating Scale (HAMD17)</td>
<td>Intensive HF rTMS protocol was found to be safe and well tolerated.</td>
</tr>
<tr>
<td>11: Ulrich, H. et al. 2012</td>
<td>Randomized</td>
<td>43 severely depressed patients</td>
<td>UHF rTMS (30 Hz) as an add-on to stable antidepressant medication</td>
<td>Sham</td>
<td>Rating Scale (HAMD17)</td>
<td>A 30 Hz left prefrontal rTMS in severely depressed patients was safe, no adverse effects occurred. Improvement of processing speed performance in the UHF group was demonstrated, which covaried with improvement of psychomotor retardation.</td>
</tr>
</tbody>
</table>
DISCUSSION

There is an acute need for novel treatment options for the patients resistant to medication. It is moreover critical to find a replacement for ECT owing the cognitive disabilities the seizures may impose on the patient, as well as effective treatments for antepartum depression. With a four-fold efficacy over sham-control [4], scarce and modest side effects, rTMS may potentially represent a paradigm shift in psychiatric treatment.

My conclusion is that a substantial body of research supports the efficacy of rTMS in patients with depression. However, optimizing the parameters and identifying the factors which determine successful stimulation is paramount. Combining excitatory and inhibitory stimulation with more efficient frequency protocols, may instigate remission and maintenance rates. Padberg et al. indicated early on that high intensity of the magnetic pulses, i.e. high MT, was directly correlated with superior remission rates [97]. These findings ought to be implemented in clinical practice. Neuronavigation performance should be considered in rTMS treatment, in order to coordinate the magnetic pulses to Brodman area 9 and 46. These brain regions are typically targeted in rTMS treatment [32,98], thought to induce the antidepressant effect.

It has been complicated in rTMS research to establish a potent evidence base considering the difficult task of double-blinding the trials, which is imperative to eliminate performance bias i.e. internal validity. rTMS trials differ from pharmaceutical in this matter, where the active compound and placebo drug are identical, making the administration blinded for all participants and professionals in a study. This is impossible for rTMS where placebo has been accomplished by tilting or shielding the coil. Some trials have applied electrodes to the scalp in order to simulate the somatosensory experience of active treatment [99], but the technician setting up the device is inevitably aware of the difference. Although vigorous ingenuity and a disciplined staff, there is a problematic issue of authenticity when labeling these trials as double-blind. It would be judicious to depict these trials as “single-blind with evaluation by external blinded assessors” [47]. There is also issues when creating a convincing sham-control since many patients experience twitching in the scalp and upper face with subsequent headaches. These immediate side effects cannot be artificially achieved or masked during active treatment, since the patient is awake and fully conscious [34,99,100]. The sham-rTMS has been shown to exert some metabolic effects on the brain tissue and MEP, resulting in a diverted placebo effect that may confound results [101].
Principal threats to internal validity of randomized controlled trials are selection bias, lack of strict double-blinding procedures, scant number of patients, heterogeneous pathology and inadequate methods of evaluation. rTMS trials in particular need to address these challenges, owing to the technical circumstances and the complex nature of depression.

Furthermore the variations in coil substance and electronic operation may affect biophysical characteristics of the magnetic pulse, i.e. duration and width of the magnetic field. Attributes of the pulse itself should be considered when comparing the results of different studies, in respect of both safety and efficacy [35]. For maintenance of the acute benefits in clinical practice, antidepressant monotherapy has shown to be a safe strategy [40]. When the rTMS parameters are further optimized, extended remission durability may rule out the need for antidepressants in maintenance therapy.

Methodological improvements in rTMS include high-intensity stimulation (110-120% of MT) [92] with a high number of stimuli (3000 pulses per session) [102], neuronavigation with magnetic resonance imaging for unerring scalp positioning [103] and, if possible, identification of the neurocircuitry and oscillatory dysfunctions associated with the progression of major depressive disorder. Maintenance strategies are critical to ascertain, for the purpose of making rTMS a clinically realistic treatment.

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