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Transcranial Magnetic Stimulaton: In-Depth Review of Methods, Efficacy and Future Applications

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TRANSCRANIAL MAGNETIC STIMULATION: IN-DEPTH REVIEW OF METHODS, EFFICACY, AND FUTURE APPLICATIONS

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Abstract

Transcranial magnetic stimulation (TMS) has been regarded as a novel technique of neuromodulation with applications that span from the treatment of depression or depression related symptoms to the mapping of cerebral regions. This review takes an in depth look into the different forms of magnetic stimulation including repetitive TMS, theta-burst stimulation, and navigated TMS. The efficacy of these different forms of stimulation is addressed as well as comparisons made to current standards being used. Potential clinically relevant future applications of TMS are also discussed from the treatment of obsessive compulsive disorder to improving motor function after stroke. The purpose of this review is to provide the background information needed to better understand the constructive benefits of TMS and provide evidence for why it has a viable future in clinical settings.

TRANSCRANIAL MAGNETIC STIMULATION:

Introduction

With advances in technology, surgical procedures are becoming more automated and pharmaceuticals are increasing in effectiveness and specificity. The changing mentality of generations opting for more holistic and non-invasive treatments is putting pressure on the medical industry to be innovative and creative in finding new ways to go about treating diseases and disorders [1-4]. There is also a push from the medical industry for more well-developed, minimally invasive procedures. This focus is on decreasing the length of stay for patients as well as costs [5-7]. One form of treatment that is gaining attention is transcranial magnetic stimulation (TMS). A neuro-modularly method of exciting or inhibiting neuronal function with magnetic waves within the brain to elicit specific, intended results.

How it Works

There are numerous forms of neuromodulation but TMS differs from transcranial electric stimulation, another form of neuromodulation. While transcranial electric stimulation excites pyramidal tracts of neurons directly, TMS excites neurons trans-synaptically [8]. This means that the neuromodulation occurring from TMS is happening in the synaptic cleft between neurons, affecting neurotransmitter release.

TMS utilizes magnetic fields produced via currents running through coils in either a circular or a figure of eight pattern. These magnetic fields can induce cortical modulation through excitation or depression of neurons below the application site. Being a non-invasive procedure, it is gaining popularity as an alternative to current pharmaceutical or invasive forms of treatment. It has clinical applications ranging from treatment of depression to cortico-brain mapping with new applications being tested and refined [9]. TMS has come a long way in the past decades, with the initial development being for furthering our understanding of how the brain functions [10], it has since, expanded to new ways of treating diseases previously thought to only be manageable by medications [11].

Two coils are oriented in a figure of eight fashion connected to a power source via a handle. A transformer charges a capacitor which can instantly discharge. Instantaneous discharge generates electrical currents flowing through the coils in opposing directions of one another. The opposing electrical fields generate magnetic fields that last for fractions of a second. The magnetic fields that are then applied over the scalp (figure 1), overlying the cortical area of interest where neuronal synapses are altered, either depressing or exciting cortical excitability depending on the frequency [10, 12].

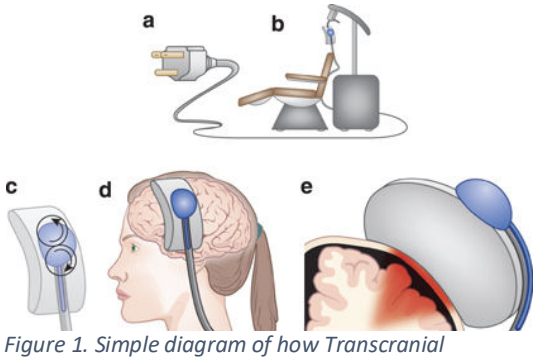

Figure 1. Simple diagram of how Transcranial Magnetic Stimulation works. A source of power (A) charges the capacitors (B). The capacitors are then able to send pulses of electrical current through the coils (C). The coils rest on the scalp (D) and the underlying cortical region is targeted (E) [12].

Generally, TMS, is very well tolerated with reports of minor discomfort at the site of application during treatment being most commonly reported [13]. For patients, treatment requires nothing beyond their presence and patience while the clinician, which can be a doctor, psychiatrist, physiologist, nurse practitioner, or physician assistant with suitable training and certification, applies the magnetic field to the intended region of the brain. Patients can read, converse, or even nap during treatment. The most common and widely

accepted use of TMS is in the treatment of depression and/or depression related symptoms [10]. A course of treatment for depression entails sessions lasting roughly 30-40 minutes, can range from 3-6 times a week and span for three to six weeks. TMS has been found to be especially useful in patients who have had failed results from previous pharmaceutical intervention [14].

Depending on the desired effects of treatment, neurons can either be excited or depressed by TMS. The focus is to promote neuro-modulation in the region of the brain that is associated with the symptoms presented. In other applications, TMS is being used to depress overexcited neurons that can lead to disorders such as epilepsy or obsessive-compulsive disorder (OCD).

Signals originating from the upper regions of the cerebrum start in cortical regions and spread the signal via action potentials down axons, releasing neurotransmitters, and then stimulating the next neuron. This applies to motor functions such as muscle flexion in the distal portion of fingers to stimulation of hormone release resulting in trophic effects throughout the body. TMS has applications beyond motor tract modulation. The treatment of depression is an example of neuro-modulation that does not result in changes to any motor networks.

Based on studies of how TMS evokes electric potentials, it suggests that TMS stimulates the axons of neurons rather than the cell body itself. Accumulation of charge surrounding the body of the neuron protects it from stimulation. Axons have a lower threshold needed for activation/ excitation as compared to the neuron body. The electric fields produced by magnetic stimulation then run parallel to the tissue surface [15].

Different Forms of TMS

Repetitive TMS

There are varying forms of TMS that can be utilized depending on the type and intended outcome of treatment. The most common form of TMS is repetitive TMS (rTMS). rTMS is currently being used in the treatment of depression. The figure-of-eight coils generate a magnetic field creating a stimulus that will last for a short period of time ranging from milliseconds to several seconds followed by intermittent periods of no stimulation. This oscillation of stimulation to rest repeats for the duration of the treatment and results in excitation of the neurons in the targeted portion of the brain [14, 16].

First developed in the mid-1980s, repetitive TMS has been the most popular stimulatory technique for treatment. With constant refinement and specialization it is being used to treat disorders such as depression, psychosis, anxiety, bipolar disorders, obsessions/ compulsions, PTSD; neurological diseases like Parkinson's and epilepsy; and rehabilitation of motor function after stroke. Many applications are still undergoing clinical trials to test efficacy but are beyond proof of principle [14, 17, 18].

Theta-Burst TMS

A more recent form of TMS being researched is Theta-Burst Stimulation (TBS), a form of TMS similar to rTMS but magnetic pulses are applied in bursts of three at 50 Hz with intervals of 200ms of 5 Hz between each burst. One study measured the effects of three types of TBS and the effects of motor evoked potentials (MEPs) [19]. The first of the three was intermittent TBS (iTBS), characterized by 2 seconds of theta-bursts repeated every 10 seconds for 190 seconds total resulting in 600 pulses being delivered. The second was intermediate TBS (imTBS) where 5 seconds of TBS signals were administered every 15 seconds for 110 seconds again resulting in a total of 600

pulses being delivered. The third was continuous TBS (cTBS) where a 40 second, uninterrupted train of theta-bursts were delivered. Upon completion of stimulus, changes in MEP amplitude were measured for twenty minutes. A single pulse of TMS over a motor tract above motor threshold is used to evoke an electromygraphy (EMG) response in small hand muscles to measure the long-term potentiation versus depression of the three TBS patterns. There was a statistically significant difference ($p<0.005$) in amplitude of MEP between each pattern. imTBS failed to evoke significant potentiation or depression of the MEP. cTBS suppressed MEPs for the measured twenty-minute interval after the treatment. Inversely, iTBS facilitated MEPs for the measured time frame post-application [19].

Based upon findings from increasing numbers of studies on safety and efficacy of TBS, reported symptoms and side effects are comparable to or less than that of rTMS in both frequency and severity [20]. A meta-analysis study found that in 4,500 recorded sessions of TBS one reported case of a seizure occurred during treatment. Statistical risk of a seizure associated with TBS is about 0.02%. This data is equivocal with the statistical risk associated with high frequency TMS. In the same meta-analysis it was noted that adverse side effects of high frequency TMS was around 40% while reported adverse effects of TBS were less than 3% [21].

Low versus high frequency TMS

Repetitive TMS can have inhibitory or excitatory effects depending upon the frequency used. When the frequency of stimulation is low ($\leq$1 Hz) neuroinhibitory effects are observed. TMS at 0.1 Hz fails to elicit any change in cortical excitability but at 0.9 Hz, applied for 15 minutes, MEP amplitude was decreased by nearly 20% and lasted for nearly 15 minutes after treatment [22]. Other studies have found that low-frequency rTMS can result in significant suppression of MEPs that can persist for 30 minutes, depressing motor excitability not affecting basic motor behavior[23]. On the inverse side of this, high-frequency rTMS can lead to excitatory effects on MEP[24].

Further studies have been completed comparing low versus high frequency rTMS and the effects it has on cortical excitability. One study comparing 1 and 20 Hz rTMS measured the differences in cortical excitability. The results were congruent with other studies, 1 Hz resulted in decrease of cortical excitability while 20 Hz increased cortical excitability in all tested subjects [25].

CURRENT APPLICATIONS:

Clinical Efficacy

With FDA approval of TMS for the treatment of depression in 2008 [12] there have been numerous studies done testing the safety and efficacy. Currently, TMS is used in the treatment of major depressive disorder (MDD), a common form of depression characterized by frequent, recurrent episodes that lead to impairment and disability [26]. Standard treatment methods for MDD are antidepressant intervention but approximately 20-40% of patients find no relief in symptoms from medications and/ or psychotherapy [27]. It is not uncommon for patients with MDD to develop a treatment-resistant illness which ultimately leads to a need for alternative treatment options. This is where TMS has found its first role in clinical settings.

The most commonly targeted cranial region for TMS in the treatment of depression has been the left and/ or right dorsolateral prefrontal cortex (DLPFC), figure 2. It can be located by its relative location to the motor area of the abductor pollicis brevis [28]. Most trials choose this region based on positive results from early studies. Imaging studies also show that in depressed patients there is decreased blood flow to the left prefrontal cortex. After rTMS of this area increased blood flow was observed [29]. Other studies have also applied low-frequency rTMS to the right prefrontal cortex for the

inhibitory effects. It is theorized that opposing sides of the brain have contrasting function over mood and inhibition of the right prefrontal cortex can achieve the same antidepressant effects as high-frequency application over the left prefrontal cortex [30-32].

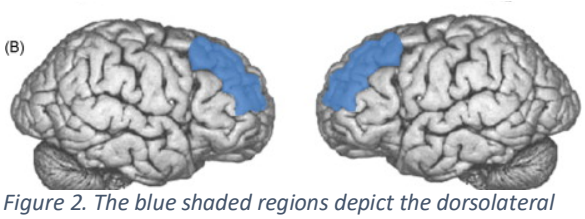

Figure 2. The blue shaded regions depict the dorsolateral prefrontal cortex (DLPRC). The region most commonly targeted by transcranial magnetic stimulation [32].

A study completed by (O'Reardon, et al.) was aimed specifically at measuring safety and efficacy of TMS over the left DLPFC as a treatment for MDD, comprised of 301 diagnosed MDD patients that did not benefit from prior antidepressant treatments. All patients were medication free and going through an MDD episode of 3 years or less upon entering the study. Severity of symptoms were measured on the Clinical Global Impressions Severity of Illness (CGI-S) score, the 17 and 24-item Hamilton Depression Rating Scale (HAMD17), and the Montogomery-Asberg Depression Rating Scale (MADRS). The 301 patients were evenly divided by random assignment between two groups, one group set to receive the active TMS treatment, while the other group received sham treatment. Sham treatment exposes participants to the same initial physical procedures but the electrical current ceases after the initial burst without the knowledge of the patient [33].

Results were measured at two, four, and six weeks. Positive changes were observed in the active group when compared to the sham group at the two-week interval. At four weeks there was a statistical difference observed in the MADRS (p=.038), HAMD17 (p=.006), HAMD24 (p=.012), and CGI-S (p=.009) scores favoring active TMS treatment. Trending positive results of active treatment continued to improve through the six-week evaluation point, figure 3. Remission rates were measured across all three evaluation points with no statistical difference being measured at two or four weeks but a significant statistical difference being measured at 6 weeks. No serious side effects were observed during the study [33].

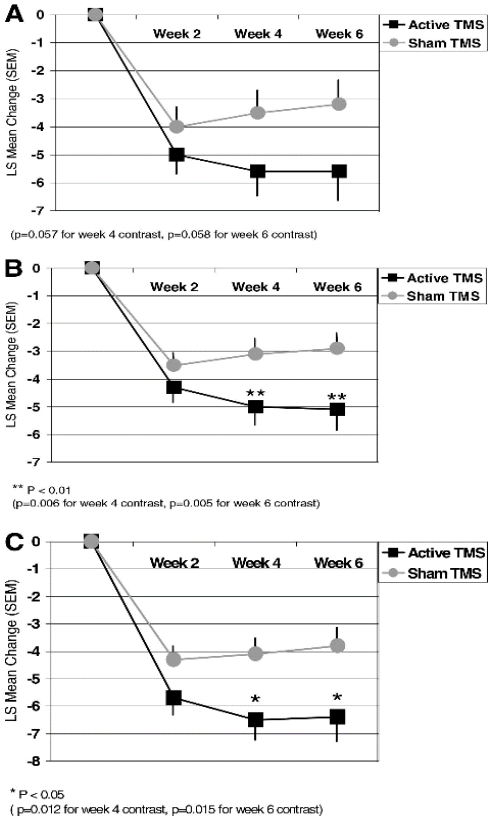

Figure 3. All figures are changes from baseline scores during the acute treatment phase. (A) is the change in Montgomery-Asberg Depreesion Scale (MADRS). (B) Hamiliton Depression Rating Scale (HAMD; 17 Item). (C) HAMD; 24 Item. [33]

A more recent study conducted by (Nathan Bakker, et al. 2015) confirmed the positive antidepressant effects of the O'Reardon study, utilizing rTMS of the dorsomedial prefrontal cortex (DMPFC) for major depression. In this study, 98 patients underwent DMPFC-rTMS. On the Beck Depression Inventory-II scale, response/ remission rates were 40.6%/29.2% respectively [14].

Alternative Applications

Brain Mapping

One of the most recently FDA approved applications of TMS has been the eXimia navigated brain stimulation (NBS) system. This device delivers biphasic TMS pulses used for mapping motor cortices preoperatively to tumor resections. Currently this is the only presurgical, noninvasive method of stimulation mapping of cortical function. The current gold standard for mapping cortical function has been intraoperative direct cortical stimulation (DCS) during craniotomies. The advantage of the current DCS method is that it allows for localization of sub regions of the primary motor cortex in relation to a tumor [34].

Preoperative evaluation using MRI of patient motor cortices has been unsatisfactory due to tumor-related variables. Peritumoral edema, anatomical distortions, and changing vasculature disrupt spatial resolution imaging technology. New advances in TMS coupled with three-dimensional magnetic resonance imaging have produced new and promising brain mapping capabilities. Navigated TMS (nTMS) with optical stereotactic navigation is a feasible method of mapping the peritumoral region of the primary motor cortex.

Early nTMS systems were met with varying levels of success which limited their clinical applicability. More recently, a study utilizing the combination of optically tracked navigation with TMS was conducted. A main advantage of the new system is its improved accuracy being able to account for device position, distance from cortex, and size and shape of the patient's head. In the study nTMS method was used for preoperative mapping in 20 patients with brain tumors scheduled for tumor resection. The goal of the study was to compare accuracy of preoperative nTMS against the current gold standard method of intraoperative DCS. The eXimia NBS system was used to calculate strength, location, and direction of stimulatory electric fields in cortical tissue. Manipulation of placement and orientation of the nTMS device allowed for more accurate mapping of primary motor cortex hotspots. This method had a mean accuracy of 5.7mm [35]. Mapping of the tumor and peritumoral region was performed at 110% of resting motor threshold and 0.25 Hz. Stimulation to the tumor, adjacent gyri and the tumor borders was performed with increased special density and further variation of coil rotation to ensure maximally accurate topography. This whole process can be completed in 30 minutes or less and caused no discomfort for the patients.

Surgical planning and tumor resection were performed by a surgeon separate from who performed preoperative mapping. The operating surgeon received no information about the nTMS mapped "hotspots" but was informed of motor function around the location of the tumor. Intraoperative mapping was done by the surgeon during surgery. The results of the intraoperative mapping of the primary motor cortex "hotspots" were imported to the same coordinate system that was used with the nTMS. Images of intraoperative DCS and nTMS were marked and superimposed, figure 4. DCS and nTMS mapping data was taken in 17/20 patients. Data was not taken for 3 patients due to technical errors or DCS not being performed due to bleeding.

In all but one patient, hotspots were located on the same gyrus. Mean distance between the nTMS hotspots and the DCS hotspots was 7.83± 1.18mm for the motor cortex of the abductor pollicis brevis muscle and 7.07±0.88mm for tibialis anterior muscle. A strong negative correlation was observed between the number of DCS responses and the distance between the nTMS and DCS hotspots. More DCS stimulations resulted in more accurate hotspot mapping and decreased the distance between nTMS and DCS to less than 5mm mean distance difference.

Advantages of TMS are that it is a timelier and equally thorough tool for examining

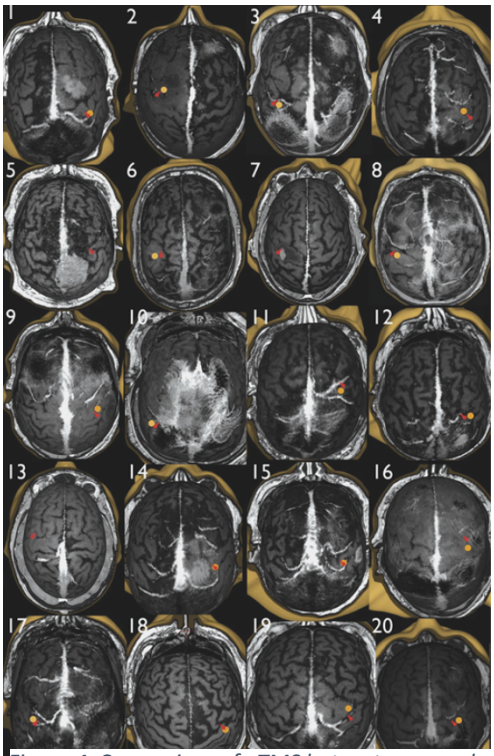

Figure 4. Comparison of nTMS hotspots mapped against DCS hotspots for abductor pollicis brevis muscle. Red points mark the nTMS hotspots while the orange represents the DCS hotspots [35].

motor topography compared to DCS. TMS also allows for cortical mapping in patients who are not suitable for functional MRI techniques. TMS is best utilized for preoperative diagnostics of motor function and its accuracy are comparable to current gold standards [35].

Robotic TMS is another emerging technique for brain mapping. Similar to nTMS, it allows for reliable and accurate detection of the represented motor cortexes for individual muscles or muscle groups. An advantage of this method is that it can be used to detect brain regions that are displaced due to tumor formation [36].

In addition to the mapping of motor regions, TMS can also be used in mapping speech centers of the brain. Patients with lesions of language centers of the brain were scheduled for surgical excision and received mappings via nTMS and traditional intraoperative DCS. The current method of intraoperative mapping, which utilizes an awake surgery approach and is only performed in a select subset of patients, has been highly reliable and a vast amount of information on the variability of cortical language representation has been gathered. The only other preoperative language mapping technique that has been previously utilized has been functional magnetic resonance imagining (fMRI), however the accuracy of this technique has proven to be less than desirable. Since fMRI is reliant on blood flow to regions for mapping, lesions like gliomas can hamper the accuracy by inducing edema and change oxygenation in the peritumoral region [37].

Results from the Tarapore, et al. 2016 study on preoperative brain mapping of language centers using nTMS demonstrated TMS as effective as current DCS methods. Advantages associated with preoperative nTMS also include improved risk-benefit assessment and extend of risk for lesion resection. nTMS also benefits patients not suitable for awake craniotomies, creating safer surgeries with alternatives to intraoperative mapping techniques. Preoperative mapping also creates possibility for smaller, more targeted craniotomies and faster intraoperative mapping. Navigated TMS was well tolerated with no adverse events reported, demonstrating superiority to intraoperative DCS, which can elicit seizures during the craniotomies. All patients that would be subject to awake craniotomies can complete noninvasive language center mapping helping to tailor the craniotomy size, location, and resection trajectory. Results from preoperative nTMS should still be confirmed with intraoperative DCS [38].

Stroke Recovery

Improvements in medicine have greatly increased the survival rates in patients post stroke. Upwards of 70% of patients who survive still experience motor impairment one year after incidence[39]. Patients who have suffered from strokes currently have several treatment options available to them. Most of these treatments

involve the retraining or stimulation of the muscles on the affected side of the body. Bilateral movement training and constraint-induced movement therapy are two treatment methods that work to physically retrain muscle function and are best utilized as close to the stroke incident as possible[40],[41]. Other rehabilitation methods involve brain stimulation, improving upon neuro-plasticity.

Neuromodulation with TMS or transcranial direct current stimulation (TDCS) are emerging as methods with proof of principle benefits in upregulating the excitability in the lesioned hemisphere or downregulating excitability in the intact hemisphere[42]. TMS, as a non-invasive technique, can be used in conjunction with our rehabilitation techniques and can enhance the effects of training and performance motor tasks. These motor tasks can include daily tasks which can allow for patients to better care for themselves and regain functions that would previously have been impaired[43].

Memory Enhancement

A new and rather exciting possible application for TMS is in memory enhancement and presentation of savant like-skills. Savants are commonly associated with individuals with autism, specifically Asperger Syndrome, but these skills have also been observed post traumatic brain injury or encephalitis. It has been hypothesized that the skills and abilities needed to be able to process information like savants are present in everyone but lie dormant from chronically processing information differently.

The cause for presentation of these skills is still unknown but research is being done to see if these traits can be artificially triggered in people who don't otherwise display exceptional talents. Snyder A, et al. 2003 performed small scale, sham controlled, study was done using rTMS to inhibit neural activity of the cerebral cortex in the left anterior temporal lobe and savant-skills were artificially produced [44].

During the study a subset of the participants saw significant improvement in drawing ability, proofreading, and numerosity. All results were compared to pre-treatment baselines and then recorded during and immediately after treatment. All instances of induced, savant characteristics diminished over time, returning to baseline within an hour after completion of rTMS application. No induced changes were observed in participants who received sham stimulation [44].

Associated Risks

Most patients experienced little to no serious side effects associated with TMS. The most commonly reported side effects, according to multiple clinical studies evaluating the efficacy and safety of TMS, was tingling or scalp discomfort around the area of application. Seizures are listed as a possible side effect however multiple large-scale studies have shown that the risk is rather insignificant. Since the updated safety guidelines in 1998, there have been four reported cases of seizures, three of which the patients also took medications that could increase the likelihood of seizures and the fourth may have been a non-epileptic event [16]

Patients with cochlear implants, aneurysm clips, bullet fragments, or any other form of conductive metal objects inserted in their brain and are non-removeable or within 30cm should avoid magnetic stimulation. There is an obvious risk in these cases that the magnetic fields generated by the coils can either disrupt the function of these devices or cause displacement resulting in serious injury or death [16].

Short-Term Side Effects

According to several studies completed, most side effects associated with TMS are short lasting and quickly dissipate with the completion of treatment sessions, rarely lasting longer than the hour following treatment. As previously mentioned, the most commonly reported side effects are mild scalp discomfort at the site of

application, headaches, and neck pain that alleviate immediately after application ceases [45].

Long-Term Side Effects

Studies that have considered potential long-term effects have largely been inconclusive. There has also been a lack of recorded follow up with patients after the treatment period ceases. Alterations in neuroplasticity are theorized to be the most significant long-term side effect. A common concern is the potential negative effect of repetitive electric stimulation on neural tissue. In a 1990 study by Gordon, et al., two epileptic patients received stimulation up to 50 Hz to the anterior temporal lobe for a period, and then the temporal lobes were resected from the patients and studied for histological damage. Using light-microscopy, no damage was observed [46, 47].

Previously mentioned was the concern of effects on neuroplasticity. The concern is electrical stimulus by TMS and the long-term potentiation (LTP) generated. This is where the repetitive nature of electrical brain stimulation at high frequencies can lead to lasting physiological changes in behavior conditioning. For a patient suffering from MDD and receiving TMS treatment, the desired effect is to alter neural function and induce lasting changes that will alleviate associated symptoms [48].

The lack of conclusive evidence to any negative long-term side effects of repeated electrical stimulation should be taken as positive sign for the possibility of further application of TMS but should not be taken as final. There are still a lot of questions that need to be answered about the effects of stimulation on neuroplasticity and what changes it could have years down the line. Further research into long term effects of varying TMS treatments should be a source of interest and discussion if TMS is to be an effectively wide spread source of treatment.

<u>CONCLUSION</u>:

Limitations

While TMS has been shown to be a safe and effective form of treatment for depression as well as useful tool in brain mapping there are still extensive limitations. Current TMS methods are only able to effectively target regions on the outermost layer of the brain. While the scalp is easily permeable to the magnetic fields, the intensity of the magnetic fields is greatly reduced beyond just a few centimeters. The regions of the brain that are most easily targeted by TMS lie in the cortical mantle of the brain, within 2-3cm of the surface [49]. New and novel techniques and improvement in coil technology are being produced and tested to target deeper regions of the brain, but current methods are limited to the outer cranial regions. The area that the magnetic field can induce and provoke change in is also relatively small, a spatial resolution of 0.5-1cm. This limits the ability to study contributions of structures such as cortical columns [50].

Other limitations of TMS are largely associated with the side effects of the treatment. There have been international guidelines [16] set in place that outline parameters for treatment frequency and intensity. Treatment within these guidelines is proven to be safe and effective but not without risk. Seizures and syncope are the two most serious side effects reported but improvements in treatment protocol is resulting in fewer reported incidences. Sensory side effects are among the most commonly reported, unintended consequences of treatment. These include tapping sensations and/ or auditory clicks. These sensory side effects are results from the rapid change of magnetic fields that TMS generates. In studies measuring somatosensory or auditory effects these can influence and interfere with task performance and results [51]. Depending on the location of the treatment the intensity of sensory effects can change, increased auditory clicking being associated with treatment being closer to the auditory region of the brain, lessening as treatment gets further away and similar results

for somatosensory effects. More minor side effects such as headaches, neck pain, and scalp irritations ranging from mild to moderate are associated with TMS and can impact the results of studies and treatment due to patients wishes to cease treatment.

Currently in the United States, the FDA has approved the use of TMS for only a small number of psychiatric and neurological applications. Two TMS devices have been approved for the use of treating depression and depression related symptoms. In neurological applications, Nexstim eXimia Navigated Brain System TMS has been approved for brain mapping [27].

Further research

While these applications of TMS are being widely implemented in clinics across the country there are still relatively new and novel techniques and just begin to scratch the surface of what future applications could be instore. Many possible applications are still in the proof of principle phase or even unknown. Extensive research has been done on the safety and efficacy of noninvasive stimulatory treatments for depression and brain mapping, however, there has been far less research on other applications. A search into possible uses for TMS yields numerous results that range from treatment of psychological disorders like obsessive-compulsive disorder (OCD) and addiction. Other possibilities include applications to better understand interconnectedness of neuronal pathways. Most studies that have been done or are currently being conducted measuring the effectiveness of TMS for uses beyond what has been discussed are mostly still in the proof of principle stage, being conducted with small numbers of individuals taking part and no control or sham groups to compare against.

Areas of research that are gaining popularity are related to the use of TMS techniques in the treatment of psychological disorders. Small scale studies have been done testing the efficacy of low-and high- frequency rTMS over varying cerebral regions to depress obsessive-compulsive symptoms. Since OCD has been characterized by hypermetabolism of orbitofrontal-striatal circuits, using depolarizing magnetic fields can help in decreasing symptoms and returning neural function to a normalized level. In studies that include double-blinded sham control groups, no advantage was found in active treatment over sham treatment. Further research is needed here that accounts for careful consideration of regions to target and stimulate parameters. Novel stimulation methods are also needed, considering the potential effect inhibitory or depressive effect that theta-burst stimulation could have on OCD associated pathways. Other possible uses of TMS, and specifically rTMS, as it relates to OCD may include modulation of obsessive-compulsive symptoms so that brain activity could be measured with functional magnetic resonance imaging and receptor-binding studies[52].

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APPENDICIES:

A. Citations for this review were done using NLM formating.

B. Feeback received from my reviewer, Dr. Chrisophter Bilbao D.O., included information on a push in the medical industry for well developed, minimally invasive procedures. The goals of these being to lessen the length of stay and cost for patients. Other information provided was insight into current methods of mapping brain tumors and how tumor-related variables can complicate this. Other beneficial feedback included better formatting and organizational techniques for the review as a whole and encouragement to clarify or better explain certain topcis. I gladly accepted the feedback received and used it to help guide the review.