International Journal of Autism

E-ISSN: 2710-3927
P-ISSN: 2710-3919
IJRSE 2022; 2(1): 06-10

www.rehabilitationjournals.com
Received: 03-01-2022
Accepted: 05-02-2022

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A review of the use of transcranial magnetic stimulation in neurology

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Abstract
Transcranial Magnetic Stimulation (TMS) has been approved by the US Food and Drug Administration (FDA) for the treatment and prevention of severe migraine headaches. Preliminary studies have documented its potential therapeutic benefits in several neurologic diseases. This review, summarizes some of the preliminary studies exploring the potential therapeutic use of TMS for several neurologic disorders such as headaches associated with mild traumatic brain injury, epilepsy, chronic pain, pain associated with fibromyalgia, post–stroke aphasia, spastic cerebral palsy, amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, Alzheimer's disease, dystonia, and Huntington's disease. The efficacy of TMS in treating these conditions is still anecdotal and would require larger randomized placebo controlled sample population, to confirm this minimally invasive and relatively safe brain stimulation technique, as a standard treatment for the neurologic disorders that do not respond to their currently approved clinical interventions.

Keywords: Transcranial magnetic stimulation, repetitive transcranial magnetic stimulation, neurology, neurologic disorders, review, treatment

Introduction
Transcranial magnetic stimulation (TMS), or repetitive transcranial magnetic stimulation (rTMS), is a minimally invasive technique of brain stimulation where a changing magnetic field is used to induce an electric current at specified brain regions through electromagnetic currents. Depending on the equipment used an electric pulse generator, or a stimulator, is connected to a magnetic coil, which in turn is connected to the scalp. A changing electric current within the coil induces a magnetic field which then causes a second inductance of inverted electric charge within the brain itself [1]. Since its FDA approval in 2008, for treatment resistant depression; the scientific and medical community had the opportunity to evaluate TMS and repetitive TMS (rTMS) and found both methods to be relatively safe with minimal adverse effects [2]. The reported adverse effects of TMS include discomfort of scalp muscles, contraction or tingling of the jaw or the face during the procedure. Mild headaches or brief lightheadedness may result. Rare occurrence of syncope and even less commonly seizures [3]. Other adverse effects of TMS include transient induction of hypomania, transient cognitive changes, transient hearing loss, and transient impairment of working memory [2]. Certain populations, including adolescents, pregnant women, older adults and those with metal/electronic implants, require special consideration when prescribing and monitoring treatment courses. With adequate assessment and monitoring processes, TMS can be administered safely to most patients [3].

Diagnostic potential of TMS
Due to TMS minimally invasive method of brain stimulation it has been used as a diagnostic tool for certain neurological conditions. When combined with electroencephalography (EEG), TMS could be a highly relevant technique for exploration of the pathophysiology of epilepsy and could be also used as a biomarker for the diagnosis and the prognosis of epilepsy [4]. The physiological effect of combining TMS with EEG to various cortical regions can also be used for measuring evoked potentials and other EEG-related indices of cortical activation [5]. These TMS properties have been used as an adjunctive tool in diagnosing strokes, multiple sclerosis, amyotrophic lateral sclerosis, movement disorders, motor neuron disease, other disorders affecting the facial and other cranial nerves and the spinal cord, mild traumatic brain injury and in detecting certain areas of the frontal cortex that are activated by visual imagery and information processing [6].

Possible therapeutic potential of TMS

In 2014 the FDA approved TMS for the acute treatment of Migraine headaches, then in 2017, the FDA approval expanded to include its use to prevent migraines in adults. In 2019 the FDA cleared a wearable new device sTMS for acute and prophylactic treatment of migraine in adults and children 12 years of age and older. Several preliminary studies have documented the usefulness of TMS and rTMS for the treatment of several neurological conditions such as headaches associated with mild traumatic brain injury, epilepsy, chronic pain, pain associated with fibromyalgia, post –stroke aphasia, spastic cerebral palsy, amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, Alzheimer's disease, dystonia, and Huntington's disease.

Migraine Headaches

Nearly 1 billion people or approximately 10% of people worldwide suffer from migraine, which is one of the top five the most common neurological disorders in the world. These debilitating headaches affect children and adults, and women are three times more likely to have migraines than men and approximately 18% of women have migraine headaches. Migraine headaches are characterized by intense pulsing or throbbing pain in one area of the head accompanied by nausea and/or vomiting and sensitivity to light and sound. A migraine attack can last anywhere between 4 and 72 hours and about one third of people with migraine headaches experience an aura manifested by visual disturbances such as dots, flashing lights or a blind spot. The aura signals the beginning of the headache. The mechanism of action of TMS is based on its application to the cerebral cortex to induce painless currents in cortical neurons. These currents can lead to neuronal depolarization and then influence cortical excitability by means that are yet not fully understood leading to the relief of the headaches [7]. This ability to modulate cortical excitability could also block waves of cortical spreading depression which are the experimental equivalent of the migraine associated aura [7]. The TMS device is contraindicated in patients who have metals in the head, neck, or upper body that are attracted by a magnet, and in cases with active implanted medical device such as a pacemaker or deep brain stimulator [8].

Headaches associated with mild traumatic brain injury

Mild traumatic brain injury (MTBI) is considered a major public health condition with around 15% of all cases associated with chronic persisting and debilitating headaches (MTBI -HA) [9]. The use of rTMS was found to be beneficial in diagnosing MTBI -HA [9]. Some preliminary studies have suggested rTMS as a clinically feasible and effective treatment option in managing MTBI -HA [6]. In addition to its effects on alleviating MTBI -HA symptoms, rTMS could provide a transient mood enhancing benefit [10]. Further studies are required to establish a clinical protocol balancing both treatment efficacy and patient compliance.

Epilepsy

Epilepsy is a highly prevalent neurological condition characterized by repeated unprovoked seizures with various etiologies. Although antiepileptic medications produce clinical improvement in most individuals, nearly a third of individuals have drug-resistant epilepsy that carries significant morbidity and mortality. There remains a need for non-invasive and more effective therapies for this population. The inhibitory effects of TMS could conceivably reduce cortical excitability associated with epilepsy [11]. Also, TMS is associated with the generation of TMS-induced epileptiform discharges (EDs), could be employed to identify the epileptogenic zone and possibly serve as a biomarker of response to invasive neuromodulator techniques [4]. Studies have also indicated that rTMS exerts a modest but statistically significant antiepileptic effect [12]. More studies are needed to confirm the efficacy of rTMS for seizure reduction, despite reasonable evidence that it is effective at reducing epileptiform discharges [11].

Chronic Pain

Although the exact cause of chronic pain is not known, its presence generates spontaneous pain signals in the nerves which the brain interprets as real pain. Another change also occurs, and that the body's ability to tolerate pain is weakened when chronic pain persists. Chronic pain impairs the quality of life for millions of individuals and therefore presents a serious ongoing challenge into clinical practice. Economically the annual cost of pain treatment is greater than the combined annual costs of heart disease, cancer, and diabetes [13]. Although many analgesics and neurosurgical interventions have been developed for various pain syndromes, they are associated with risks of addiction especially to narcotics and opiates and possible surgical complications. As a result, clinicians have considered TMS due to its minimally invasive nature and fewer complications as an alternative treatment intervention for chronic pain. The use of rTMS have shown to be beneficial for treating neuropathic pain of various origins, such as central pain, pain from peripheral nerve disorders, fibromyalgia, and migraine, but not sufficient for treating orofacial pain, including trigeminal neuralgia, phantom pain, low back pain, myofascial pain syndrome, pelvic pain, and complex regional pain syndromes [14]. There is also some evidence that single doses of high-frequency rTMS applied to the dorsolateral prefrontal cortex may have short-term effects on reducing pain intensity in chronic pain, however there is no evidence that low-frequency rTMS is effective for reducing chronic pain [15]. There remains a need for substantially larger, rigorously designed studies, to confirm the effectiveness of TMS in reducing and relieving chronic pain.

Pain associated with fibromyalgia

Fibromyalgia (FM) is a prevalent chronic pain syndrome with few effective therapeutic options available with rTMS as an emerging therapeutic alternative for this condition; however, results have been mixed [16]. Adequately designed sham-controlled trials have suggested potentially therapeutic benefits of rTMS in improving quality of life (QoL) of patients with FM [17]. The unilateral application of rTMS to the motor cortex of patients with FM, induced a long-lasting decrease in the associated widespread pain and could constitute an effective alternative to analgesic treatment [18]. The use of rTMS in addressing FM's prominent neuropsychiatric symptoms of depression and cognition has also been explored in some studies. The application of rTMS over 10-11 weeks in patients with FM have shown improvement in their attention and executive function compared to the sham group; but there were no differences in overall neuropsychological performance, sleep,

depression, or anxiety scores. Further studies with larger enrollments in assessing neuropsychiatric domains such as fatigue, anxiety, and ability to sustain concentration, will be necessary to confirm rTMS beneficial effects on improving QoL, mood, and cognition in patients with FM.

Post-Stroke Aphasia

Aphasia is among the most debilitating outcomes of stroke. Aphasia is defined as a language disorder occurring in 10-30% of stroke survivors. Speech and Language Therapy (SLT) is the gold standard, mainstay treatment for aphasia, but some patients may not improve with SLT [19]. Using rTMS was shown to improve phrase length during propositional speech, which lasted for up to 2 months, or even as long as 2 years, post- rTMS treatment [20]. When rTMS is combined with SLT, additional improvement has also been observed [21]. Additionally, rTMS could ameliorate post-stroke dysphagic symptoms and improve swallowing [22]. Results to-date have provided promising, but weak to moderate evidence that rTMS could improve or augment the effects of SLT for improving language outcomes in Post –Stroke Aphasia. Recommendations for studying this minimally invasive intervention with multicenter, double-blind, randomized controlled trials are strongly warranted to confirm its wider use in this patient's population.

Spastic cerebral palsy

Spastic cerebral palsy (CP) is the one of most common neurological disorders that is caused by malformation of or damage to the parts of the brain that control movement. Although its precise etiology is children is often unknown, it is believed that CP may be the result of causal pathways, or chains of events that cause or increase the likelihood of brain injury. In most cases children are born with the brain disfunction that caused CP. Several interventions such as medical treatment, surgical intervention and physical therapy rehabilitation have been used to minimize CP disabilities and to improve patients' QoL. The use of r-TMS can reduce muscle spasticity in CP patients who showed significant decrease in muscle tightness for all the muscles selected for the therapy [23].

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), is a progressive, presently incurable, neurodegenerative disorder that causes muscle weakness, disability, and eventually death. Several studies have suggested that rTMS may have positive benefit in ALS [24]. Although none of the trials reported any adverse events associated with the use of rTMS, larger, well-designed trials should be considered, to determine the efficacy and safety of rTMS in ALS and balancing the potential benefit with the impact of conducting these trials on patients with ALS.

Multiple sclerosis

Multiple sclerosis (MS) is a disabling neuropsychiatric condition with fatigue being one of its most common symptoms affecting 75%-90% of patients, and 50%-60% describing fatigue as the worst symptom of their disease [25]. Fatigue is significantly associated with reduced quality of life and is also a major reason for unemployment, especially for patients with otherwise minor disability. The mechanisms underlying abnormal levels of fatigue in MS are poorly understood. The pharmacological treatment of MS has been only partially beneficial in alleviating fatigue, with widely variable effects among patients. The non-pharmacological management of fatigue in MS includes inpatient rehabilitation and endurance training. Various studies into TMS have shown significant improvements in spasticity, fatigue, lower urinary tract dysfunction, manual dexterity, gait, and cognitive deficits related to working memory in patients with MS; however, the exact level of evidence has not been defined as the results have not been replicated in a sufficient number of controlled studies [26]. Depression-related fatigue has also been proposed as one of the etiologies of fatigue in MS, however, further studies with large-scale population are still needed to confirm the effectiveness of rTMS for treatment of fatigue in MS as an independent outcome unrelated to its relief of depression.

Parkinson's disease

Parkinson's disease (PD) affects about 1-2% of the world population, with an estimated 1 million patients in the U.S. alone. It is a degenerative disorder of the central nervous system (CNS), which progresses slowly and is characterized by typical motor deficits, which result from the depletion of the neurotransmitter dopamine. The reason for dopamine depletion is still unknown but has been linked to the degeneration of a very specific group of cells in the substantia nigral. The characteristic motor deficits of PD include a slowing of physical movement, muscle rigidity, involuntary resting tremor, postural instability and gait disturbances. In the progressive stages of the disease, motor disturbances extend to the control of speech and swallowing. Speech becomes slow and soft, and in severe cases is reduced to little more than a whisper. Although various medications are available to ease PD symptoms, they could precipitate many side effects, such as nausea, confusion or psychotic symptoms including hallucinations and paranoid delusions. Additionally, as the disease progresses, these medications eventually lose their effectiveness. Preliminary findings suggest some beneficial effects of rTMS on improving motor symptoms in PD [27]. The associated features of PD which may include depression, sleep difficulties, cognitive impairment and swallowing difficulties could also respond to rTMS treatment [27, 28]. The preliminary findings of rTMS beneficial effects in the treatment of PD are still inconclusive and need to be replicated in controlled trials with more standardized methodology, and adequately sized and well-characterized samples, with the inclusion of multimodal approaches.

Alzheimer's disease

Alzheimer's disease (AD) is considered a major health problem. To date, pharmacological treatments have not achieved desired outcome in reversing its devastating medical, neurocognitive and psychiatric complications, thus prompting growing interest in finding non-pharmacological interventions for this progressive disease. Studies have determined the ability of TMS in detecting synaptic impairment in patients with AD and could be considered an additional diagnostic tool in predicting cognitive decline in the early phases of the disease [29]. Changes and modifications in impaired neural networks could also be induced by rTMS, making it a promising clinical intervention for enhancing performances on several

impaired cognitive functions in AD [30]. However, further well-controlled studies with appropriate methodology in larger patient cohorts are needed to replicate and extend these preliminary findings.

Dystonia

Dystonias represent a heterogeneous group of movement disorders responsible for sustained muscle contraction, abnormal postures, and muscle twists. It can affect focal or segmental body parts or be generalized. Primary dystonia is the most common form of dystonia, but it can also be secondary to metabolic abnormalities, structural dysfunction, side-effect of prescribed medications or genetic predisposition. Patients with primary dystonia could benefit from TMS as a diagnostic tool to test the excitability of connections within and among motor areas of the cortex, and in providing useful information on the dystonia pathophysiology and can potentially be used as a therapeutic tool to treat some forms of dystonia, such as focal hand dystonia, where pharmacological options or injections of botulinum toxin have not been effective [31]. Despite the important value of TMS in improving understanding of the pathophysiology of dystonia, large controlled studies using sham stimulation are still necessary to delineate the place of rTMS in the therapeutic management of dystonia.

Huntington's disease

Several important advances in the pathophysiology of Huntington's disease (HD) have been achieved by means of neurophysiological techniques designed to investigate the excitability and plasticity of brainstem and cortical circuits in patients with the condition including rTMS which is considered a valuable method of evaluating cortical excitability changes in HD [32]. Improvement of choreiform movements by rTMS has been reported in patients with HD, however in those with severe chorea the intensity of choreiform movements where not even transiently reduced. Hence, the proposed role of rTMS in reducing intensity of choreiform movements by altering neuronal plasticity may not beneficial in severe cases of HD.

Conclusion

The potential role of rTMS in treating neurological diseases has been expanding, especially in the past 3 decades. Despite its beneficial therapeutic outcome in the management of migraine headaches. Most of the studies relating to its effects on improving the clinical outcome in various neurological disorders such as headaches associated with mild traumatic brain injury, epilepsy, chronic pain, pain associated with fibromyalgia, post –stroke aphasia, spastic cerebral palsy, amyotrophic lateral sclerosis, multiple sclerosis, Parkinson’s disease, Alzheimer’s disease, dystonia, and Huntington's disease warrant further investigation. Studies with larger sample sizes and control conditions will help confirm some of the preliminary findings on the diagnostic and therapeutic value of this minimally invasive and relatively safe brain stimulation technique.

Disclaimer

The Views described in this manuscript are those of the author and do not reflect the official policy of VA Central California Health Care System (VACCHCS), Fresno, or The Department of Veterans Affairs, or UCSF-Fresno Department of Psychiatry, California, USA.

Acknowledgments

Sincere appreciation family, friends anf colleagues for their support and encouragement.

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