INJ INTERNATIONAL NEUROUROLOGY JOURNAL

Diagnostic and Rehabilitative perspective of transcranial magnetic stimulation. A narrative review

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Abstract

Transcranial Magnetic Stimulation is a non-invasive electrical cortical stimulation technique that works on electromagnetic induction principles to achieve neuromodulation and neurostimulation. It has emerged as a promising and enviable technique with excellent tolerance, minimal risk, and unprecedented ability to study neurophysiology and neuroplasticity of the brain for research with a potential in therapeutics. So in conclusion, the use of this technique has shown to be a novel non-pharmacological, diagnostic, and therapeutic tool in a variety of neurological disorders, however, its applicability and use in children is only emerging and is the focus of this review.

Key-words: transcranial magnetic stimulation, post-concussion syndrome, pediatric population, traumatic brain injury, neuroplasticity.

Introduction

Background

Post Concussion Syndrome (PCS) is a clinical condition occurring following direct impact on head. A concussion is defined as a biomechanically induced injury that alters crucial cortical functions. Biomechanical factor includes direct and severe impact to the neck, face, head, and/or by a force transmitted to the head from elsewhere in the body.(1) Headache, dizziness, nausea, vomiting, sensitivity to light and sound, vacant stare, impaired speech, confusion, disorientation, slurred speech over a bust of emotion, frequent loss of consciousness, anxiety, and depression are the most common prevailing signs and symptoms following a concussion injury. (2)(3) A possibility of a concussion episode in a mild Traumatic Brain Injury (mTBI) can be confirmed by a series of symptoms including 'Glasgow Coma Scale' with a score of 13-15, followed by the loss of consciousness for less than 30 minutes (if present), and a post traumatic amnesia of 24 hours (if present). (4) In most cases, symptoms are mild and resolve by itself within 7- 10 days. Only 29.3% of the cases have been seen to advance to PCS.(5) Various brain stimulation techniques have been used for studying these symptoms related to a concussion episode.(6) Transcranial Magnetic Stimulation (TMS) is a non-invasive brain stimulation technique which works on the principles of electromagnetic induction to achieve neuromodulation and neurostimulation. It has emerged to be very promising and enviable technique with minimal risk, excellent tolerance and unprecedented ability to study neurophysiology and neuroplasticity in pediatric research with further scope in therapeutic trials.(7) Clinical trials have posted TMS to be a novel non-pharmacological diagnostic and therapeutic tool in a variety of disorders, for example eating disorders, depression, epilepsy, tinnitus, schizophrenia, migraine, stroke and Parkinson's Disease. (8) However, its applicability and therapeutic use in children for PCS is only very recent and is the focus of this report.

Methods: Use of transcranial Magnetic Stimulation in Post-Concussion Syndrome in pediatric population was searched using the following databases: MEDLINE and PubMed with filters to search article as language in English. Search terms included [(TMS) OR (head injury) OR (post-concussion syndrome). Searches were limited to children under the age eighteen years in any time. The literature review was done in April of 2022.

Neuro-Physiological Correlations for Post-Concussion Symptoms:

The combination of accelerating and decelerating forces following a head trauma result in onset of a neuro-metabolic cascade. Itisduetodisruptionofneuronalmembranewhichresults in calcium accumulation, free radicals generation, mitochondrial dysfunction, and altered glucose metabolism. It causes an increase in level of cellular Adenosine Triphosphate (ATP) creating an energy deficit state causing a decrease in axonal transport and neurotransmission.(9) PCS is also responsible for decreased cerebral blood flow in the regions affected by

concussion, which may further aggravate energy deficiency. This physiological variation cause altered neuronal plasticity that lead to immature myelination and neuro-cognitive symptoms.(10)

Transcranial Magnetic Stimulation:
TMS uses magnetic fields to stimulate nerve cells in the brain. Magnetic pulse is generated through electromagnetic induction using an insulated coil that is placed over the region that needs to be stimulated. The coil can be secured manually or by a mechanical arm. The current passed through the coil generates a magnetic pulse. Several stimulation parameters including pulse intensity, number of pulses, and pulse frequency can be controlled as desired. (11) Additionally, the coil types can also be varied to generate different kinds of magnetic field patterns, and multiple focal points can be employed to induce stronger magnetic fields andtostimulatedeepercorticallayers.Stimulationistypically applied at a sufficient intensity to trigger action potentials in proximate neurons.(7)

Measurements and method of TMS:
TMS is an efficient modality to evaluate functioning and physiological integrity of brain. The strong magnetic pulse generated from the TMS induces electric cur- rent in the brain that flows into the excitable cell membranes which alters the transmembrane potential. This generates an action potential that is transmitted along the neural network. (8) Three TMS protocols have been extensively used to study its diagnostic and therapeutic relevance namely, Single-pulse TMS (spTMS), paired-pulse TMS (ppTMS), and repetitive TMS (rTMS).(10) spTMS is used for a variety of neurophysiological assessment purposes including mapping of various motor cortical out- puts, central motor conduction time, and measuring cortical excitability. In a single pulse method one stimulus is given at a time. Several measurements that are done using spTMS to study excitability of motor cortex and conduction along corticospinal, corticonuclear and callosal fibers are explained as follows. Motor Threshold (MT) In experiments, it is defined as the minimum TMS intensity applied to the motor cortex to elicit MEPs from a resting or activated target muscle that are at least 50 μV peak-to-peak amplitude for more than 50 % of 5 to 10 consecutive trials, when recorded muscles are at rest it is called as resting motor threshold (rMT). The measure of motor threshold can help in evaluating membrane excitability of neurons in the motor cortex, spinal cord, neuromuscular junctions, and the interneuron connecting these motor neurons. An increase in MT is indicative of diseases that affects corticospinal tract, such as brain or spinal cord injury, stroke, and multiple sclerosis.(12)

Motor Evoked Potential (MEP); The amplitude of the MEP will provide information on the integrity of the corticospinal tract. Similar to motor threshold, it is also reflective of motor cortex excitability peripheral motor neurons conduction. If corticospinal tract is affected, the amplitude of MEPs will be altered. A reduction or an absence of MEPs would indicate failure in conduction of central motor neurons, for example, this can happen in a patient suffering brain injury.(13) Silent Period (SP); When a TMS pulse is applied over a motor cortex region linked to a targeted muscle in a contracted state; the electromyogram activity of the muscle is arrested after the MEP for a time period called, as silent period. The neuronal activities that are responsible for this silent period are most likely mediated by μ-amino butyric acid-B (GABA) receptors. If the muscle studied is ipsilateral to the region of cortex where TMS is applied it is called as ipsilateral SP (iSP), if the muscle studied is contralateral, it is called as cortical SP (cSP). Long silent periods are characteristic of patients with brain injury.

Transcallosal Conduction (TC); It is interhemispheric conduction occurring via corpus callosum. On application of a single-pulse TMS to motor cortex, an ongoing voluntary EMG activity in small hand muscle ipsilateral to the side where TMS is applied gets suppressed for a time period. This suppression is called as Transcallosal Inhibition (TI) and is mediated via transcallosal conduction. A higher transcallosal inhibition period can be because of a brain injury. In ppTMS a pair of pulse is applied to the same motor cortex region with variable interstimulus intervals. In ppTMS, a test stimulus is preceded by a conditioning stimulus.(14) This can provide information on intracortical facilitation and inhibition as well as cortico-cortical and transcallosal interactions. In a ppTMS, two sequential stimuli, an initial conditioning stimulus and the subsequent test stimulus are applied with an interstimulus interval. The inhibitory or excitatory effect on motor cortex depends on the conditioning stimulus intensity and the interstimulus interval. Pulses can also be paired with peripheral stimulation such as “paired associative stimulation” or other neuroplasticity protocols. The most common measurements using ppTMS detailed below.(5)

Short-Interval Intracortical Inhibition (SICI); The inhibition of motor evoked potential generated by sub threshold conditioning stimulus on application of a suprathreshold test stimulus after 1–6 milliseconds (ms) in a ppTMS protocol. Long-Interval Intracortical Inhibition (LICI) This outcome is elicited by a suprathreshold

conditioning and test pulses of interstimulus interval of 50–200 ms. Intracortical Facilitation (ICF) It is elicited using a sub- threshold conditioning stimulus followed by suprathreshold test stimulus. Interstimulus interval of 8- 30 ms is required to promote facilitation. A reduction in ICF is reported in patients with cerebellar degeneration.(15)

When several pulses of TMS are applied in a row it is called rTMS.(7) The physiological effects of rTMS on the cortical excitability last for minutes to hours which is in contrast to milliseconds in case of spTMS and ppTMS. The extent of excitability in a simulation depends on the simulation protocol, frequency of rTMS sessions, and the number of times it was repeated. For example, a low frequency magnetic pulse (1 Hz) is inhibitory, while high frequency magnetic field (>5 Hz) is excitatory. The two specific rTMS protocols are, continuous theta burst stimulation (cTBS) and intermittent theta burst stimulation (iTBS). In these protocols a very high frequency of TMS (50 Hz) is applied three times in a interval of 200 ms. If done continuously for a total of 40 seconds it is called as cTBS, or if applied once after every 8 seconds, for about 3 minutes, it is called as iTBS. Both, cTBS and iTBS, are quick, convenient to apply and much thoroughly studied via in vitro stimulation proto- cols. In a healthy brain, rTMS modulates cortical excitability by inducing long term depression like and long term potentiation like activity-dependent metaplasticity. Any abnormality in this cortical output on application of rTMS will suggest altered synaptic plasticity and suggest a neurological problem. rTMS have been used in diagnosis and therapeutics in various neurological disorders including ASD, mood disorders, and depression in pediatric population.(10)

Diagnostic Relevance Of Tms In The Pediatric Population

The use of TMS in pediatric population was performed to explore and treat brain diseases in childhood like Epilepsy, Attention-Deficit/Hyperactivity Disorder (ADHD), Tourette Syndrome, Autism Spectrum Disorder (ASD), Depression, and Schizophrenia. Recently the use of TMS has been reported for treatment of PCS. King, R. (2019) conducted a prospective longitudinal controlled cohort study on children of 8–18 years with mTBI in the first and second month post injury to assess cortical excitability. This study included seventy-eight symptomatic, twenty-nine asymptomatic, and twenty-six control patients. This study was done by eliciting MEPs in the dominant first dorsal interossei muscle in two ways. First, spTMS was used on the contralateral primary motor cortex. The process involved ten single pulse TMS simulations, each of six intensities (100–150% rMT) that were delivered in a random order. As an outcome measure the Post- Concussion Symptom Inventory provided an overall score of PCS symptoms. They found a decrease in cSP and an increase in iSP with an increased TI in the symptomatic group. This is in contradiction to an adult patient with brain injury where cSP is found to be increased. Second, a ppTMS was used with two stimulators that were separated by an interstimulus interval, an initial conditioning stimulus (80 % RMT), and a test stimulus (120 % RMT). Using this way they found a decrease in SICI, ICF, and LICI in symptomatic children. They have also shown that transcallosal tracts were particularly sensitive to the dam- age in mTBI pediatric patients.(11)

A similar work done by Stagg CJ et. al.2011) performed a cross sectional controlled cohort study to measure cortical excitability in children with mTBI. They used multiple TMS paradigms on fifty-three school-aged children from age of 8-18 years who suffered from symptoms which persisted three months post injury. (16)(17) This study included thirty-five symptomatic, twenty-seven asymptomatic, and twenty-eight control patients. They found a reduction in LICI in symptomatic participants compared to healthy controls which is in accordance with the previously mentioned study. (11) The underlying basis to an increased motor cortical excitability in patients with concussion history was proposed by a longitudinal study done by Meehan, SK. (2017) on the adolescent patients of age 19-22 years who suffered concussion at the age of 14-17 years. This study was done on thirty-one patients out of which sixteen patients were with concussion history and fifteen patients were with concussion-like symptoms but no concussion history. (18)(19)(20)

Hadanny A et.al. (2022) also investigated the mechanisms for recovery after mild traumatic brain injury (mTBI) through Neurophysiological measures which included resting-state electroencephalography (EEG) and transcranial magnetic stimulation combined with EEG (TMS-EEG). TMS-EEG findings in the DLPFC indicated that participants showed smaller (more negative) parieto-occipital P60 TEP amplitude when assessed after 4 weeks. N100 amplitude was also found to be persistently larger (more negative) at all time points. It was also concluded that P60 and N100 components have been associated with activation of GABAergic mechanisms. These findings are suggestive of an antagonistic or compensatory E: I relationship between the components that represent stable neuro physiological characteristics.(21)

Similar to other studies, an increased cortical excitability, a decreased facilitation of MEP amplitude, SICI, and ICF in patients with concussion history was found in comparison to ones without it. The decrease in SICI was proposed to be due to additional interneuron's which were recruited as a part of more complex oligosynaptic intracortical networks. These interneurons were susceptible to complex excitatory and inhibitory interactions, and modulation by dopamine and acetylcholine among other neurotransmitters. GABA functions, glutamatergic functions affecting ICF, and rMTs were similar in all populations regardless of the region of concussion.(20)

Conclusions from the above study were further corroborated by Ziemann et al. (2015). This study showed a positive correlation of the measures of glutamate and GABA neurotransmitters with magnetic resonance spectroscopy. They concluded that these neurotransmitters are absent up to three years after concussion. The smaller increase in MEP amplitude and ICF suggested that the injury reduces the ability to modulate intracortical networks by strengthening synapses. Disinhibition in the form of reduced SICI was also correlated to poorer dexterous performance and acts as an early indicator of loss of dexterous ability.(17) They also found slower movement times but similar reaction times as compared to no-concussion groups on a simple response time task. This might be due to the difference in the information processing stage. These conclusions can form the basis for using TMS for improvements in various neuro-cognitive rehabilitation processes.

Tms, A Potent Therapeutic Tool

Applicability and use of TMS therapy on adults with mTBI for the purpose of therapeutics have been thoroughly discussed and reviewed in several studies. All studies concluded alleviating effects of TMS on PCS. The effect of TMS is hypothesized to be different in the pediatric population owing to the difference in physiology between the adult brain and pediatric brain. (16) Applicability of TMS as a therapeutic tool for neuronal plasticity and rehabilitation in the pediatric population with mTBI has been investigated by Hong YH.et.al(2015) using a controlled cortical impact animal (rats) model. This study was performed on twenty-six rats where twenty rats were suffering from mTBI and six were taken as controls. Of the twenty, ten received TMS therapy on 16th-17th postnatal day which is equivalent to a toddler age in humans. This study suggested, a injury results in an altered neuronal hypoactivity in the non-injured primary somatosensory cortex of the brain. They hypothesized reshaping the abnormal post-injury neuronal activity by providing a suitable strategy for use of TMS in rehabilitation. Thus a high-frequency TMS was delivered to the left somatosensory cortex twice a week for a period of four-weeks. The stimulation constituted nine trains of hundred pulses delivered at a frequency of 20Hz with an inter-train rest time of 55 s. This was done to allow an effective cooling of the coil for a total of 9 minutes. Rats that were exposed to TMS therapy achieved significant increase in the evoked fMRI cortical responses (189%), synaptic activity (46%), and neuronal firing (200%). Additionally, there was an increase in the expression of neuroplasticity markers.(22) Further, study also revealed mTBI decreases Ca2+/calmodulin-dependent kinase II (CaMKII) intensity in the non-injured rats suggesting induced post-injury synaptic plasticity. TMS therapy significantly increased number of MUA responses as indicated by increased number of activated pixels in fMRI. They concluded that TMS as a promising approach for reversing the adverse neuronal mechanisms, activated post- TBI, and that this intervention could readily be translated to human studies(22)
Grant Rutherford (2017) attempted to test the efficacy of rTMS towards improving cognitive functioning in humans. They conducted a pilot study on seventeen mTBI patients including teenagers. Eight of them received TMS therapy over the left dorsolateral prefrontal cortex using a standard figure-8 coil. The pulse was applied at a frequency of 20Hz, with each burst comprising 30 pulses over 1.5 s. A total of twenty-five bursts were applied with delay of 28.5 s between each burst on a single day. The session applied 5 days per week for two weeks and alternately in the third week. Resting motor threshold intensity was set at 100%. Cognitive assessment was performed on first day (baseline) and final day of study. No significant improvement was found for visual, language, memory, and cognitive skills, assessed using the Montreal Cognitive Assessment due to its high baseline value. Similarly, no change was observed on the Montgomery-Asberg Depression scale which investigated effect of TMS on depression. In contrast to the above results, there was substantial improvement in the RivermeadPost Concussion Questionnaire for specific PCS symptoms, which concludes that rTMS can be used therapeutically to improve long-term recovery of PCS symptoms in pediatric population.(23)

Another study was performed by Koski L et al. (2015) to test efficacy of rTMS for alleviating PCS symptoms. The study was done on fifteen patients. Twenty sessions of rTMS (5-sec trains of 10 Hz frequency at 110% threshold) were applied over the left dorsolateral prefrontal cortex (DLPFC). A clinical and functional magnetic resonance imaging (fMRI) was conducted before and after the rTMS therapy with a 3-months follow-up period. The outcome measures included PCS scale, cognitive symptoms questionnaire, neuropsychological test performance, and fMRI activity on working memory task-associated activity. The study concluded a decrease in PCS scores and increased task-related activation peaks in the DLPFC after the rTMS therapy.(15)

Another study with the primary objective to determine efficacy of rTMS to treat can persistent post-concussion symptoms (PCS) over DLPFC located through MNI coordinates (-48, 26, 36) vs. (-41, 21, 38) was conducted. The intensity of the rTMS used was 100-120% of resting motor threshold amplitude, with a frequency of 10 Hz, 10 trains of 60 pulses/train (total of 600 pulses) and inter-train interval of 45s were imparted concluded positive outcome on PCS(24)

Recent studies conducted by Stilling JM.et. al. A Sham controlled, to evaluate the effectiveness of high frequency rTMS of prefrontal cortex to improve neurophysiological performance in 26 patients with cognitive complaints with a history of mild to moderate traumatic brain injury. Stimulation of 10 Hz for 20 minutes was given per session for 5 consecutive days. Results of this study indicated that there was no effect of rTMS on cognitive function whereas it may improve Post-Concussion Syndrome and subjective cognitive dysfunction. (24)

Mollica A et al, 2022 in a review stated that the TMS is a potential as well as effective treatment strategy for the post concussive symptoms.(25)

Both studies present a strong evidence for use of TMS as a therapeutic tool for the pediatric population suffering from PCS. Further studies need to be plan and executed to explore how TMS factors can be varied and specifically designed to exact the desired outcome of TMS therapy on the pediatric brain.

Precautions In Pediatric Tms

Side-effects of the TMS therapy are generally mild and majority of the safety data is recorded from the studies done on the adult population. Up to 40% of participants report headache and scalp discomfort after first session.(26) Very few, 1 among 10,000 individuals reported hearing loss and seizures. The risk of hearing loss can be reduced by using appropriate ear plugs and seizures can be prevented by following proper guidelines before initiating the TM. Even in the pediatric population, TMS shows a good tolerability and safety profile from the data collected from 800 normal children and 300 neurologically abnormal children over a period of time. No changes in auditory function were reported in these cases. For single- or paired-pulse TMS no seizures were reported in children, including those with epilepsy or with conditions like cerebral palsy that are associated with increased risk of seizures(27) There was only one case with seizure which was due to depression and was induced from alcohol consumption.(28) In 2009, a consensus conference approved that single-pulse and paired- pulse TMS was safe for children two years and older. However, in the absence of an appreciable volume of data on the potential adverse effects of rTMS, it was suggested children should not be used as subjects for rTMS therapy without compelling clinical reasons to study various psychiatric conditions.(29)(30)

Conclusions

Transcranial Magnetic Stimulation is an underexplored intensive area for various transitional researches in the field of pediatrics. Studies have targeted at identifying and developing therapeutic protocols to diagnose and treat a variety of neurological conditions in children. Safety and efficacy of TMS in diagnosis and rehabilitation in adults and its successful application in treating depression, ADHD and mood disorders in children provides compelling evidence for consideration of TMS for pediatric brain stimulation to treat PCS. However, further research needs to be plan and executed to investigate its safety and efficacy on the developing brain and explore age- related effects on the neurological mechanisms in the pediatric brain. Although, the characteristics of the child's brain pose challenges to the design and execution of TMS protocols, the unprecedented opportunity these modalities offer for studying and modulating pediatric neuropathology and neuroplasticity is unmatched.

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