Global Scientific JOURNALS

GSJ: Volume 9, Issue 8, August 2021, Online: ISSN 2320-9186
www.globalscientificjournal.com

NEUROPLASTICITY AND TRANSCRANIAL MAGNETIC STIMULATION (TMS) FOR CLINICAL APPLICATIONS

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KeyWords
Neuroplasticity, Brain stimulation, Clinical application, Neurodegenerative disease, Neuropsychiatric disorder, Presurgical mapping, rTMS, TMS

ABSTRACT

Neuroplasticity is the ability of the brain to alter its structure and function. The plasticity impairment of the nervous system leads to neurodegenerative and neuropsychiatric diseases. Transcranial magnetic stimulation (TMS) is the non-invasive brain stimulation approach that functions by enhancing the capacity of brain plasticity. TMS is widely used for disease diagnosis and treatment due to its safety and high therapeutic efficiency. In this study, we aim to review the concept of neuroplasticity and the clinical applications of TMS and rTMS for diagnosis and treatment of neurodegenerative and neuropsychiatric diseases.

Introduction

According to several research and medical exploration for more than 200 years, the hypothesis of Neuroplasticity had always been interesting and be an attractive notion among neuroscientists until recent times. The term “Plasticity” which described molecular and cellular mechanisms was initially introduced to the brain in 1890 by William James and later applied as “Neural Plasticity” by Jerzy Konorski in 1948 [1]. This ability of brain plasticity plays a crucial role in neuroscience and acts as a pivotal key for neurodiagnosis [2]. Impaired neuroplasticity causes neurodegenerative and neuropsychiatric diseases such as depression, obsessive-compulsive disorder (OCD), and Alzheimer’s disease (AD). However, brain plasticity can serve as a paramount factor for therapeutic purposes as well. Currently, this impairment can be cured by supportive care, medications, psychotherapy, and brain stimulation.

Brain stimulation is a powerful clinical approach which is widely used to treat patients with neurodegenerative diseases. This technique modulates the neuroplasticity resulting in the repairment of neuronal synapses and signals, and recovery of brain structure and function [2]. Moreover, it can be use as an alternative option for patients with medical complication or treatment-resistant [2]. By combination with image processing devices (i.e., magnetic resonance imaging (MRI)), the brain stimulation can be used as a diagnostic tool and beneficial for pre-surgical planning and evaluation of prognostic markers [2].

Generally, brain stimulation techniques are categorized into 2 groups: invasive and non-invasive approaches. Invasive brain stimulation requires a surgical procedure which involves implanting electrodes into the target region of the brain. The electrodes are used to deliver electrical impulses to stimulate changes of brain microenvironment and promote brain rewiring. This stimulation aims to modulate the neural plasticity and recovery of the impaired brain [3]. The common invasive approach is deep brain stimulation (DBS) which is typically practiced for debilitating motor symptoms of Parkinson’s disease (PD), dystonia, and tremor conditions [3],[4],[5]. Besides, there are several case reports showing successful treatment for various neuropsychiatric and neurological disorders including Tourette syndrome, obsessive-compulsive disorder (OCD), depression, epilepsy, and stroke recovery [3],[6],[7],[8].

Unlike invasive approach, non-invasive brain stimulation (NIBS) stimulates the brain without using surgical procedure and seems to have less complication compared with DBS or an invasive one [2]. NIBS is associated with a set of technologies and tech-

niques which modulate the excitability of the brain areas and the large-scale networks that are participated, via transcranial stimulation [9]. These modalities include transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial ultrasound stimulation [2]. From several studies and reports, these NIBS techniques, particularly rTMS, are used for treatment of diverse neuropsychiatric conditions such as major depression disorder (MDD), obsessive-compulsive disorder (OCD), migraines, anxiety, schizophrenia, chronic pain, movement disorder, stroke rehabilitation, tinnitus, autism spectrum disorder (ASD), Parkinson's disease (PD), and improvement cognition in Alzheimer's disease (AD) [2],[10],[11],[12].

In this article, the contents are focused on concepts of neuroplasticity and transcranial magnetic stimulation (TMS), especially repetitive transcranial magnetic stimulation (rTMS). Details of its application and clinical uses for neurodegenerative and neuropsychiatric diseases treatment are discussed below in the following main text.

Neuroplasticity

Neuroplasticity can be defined as a capacity of the nervous system to alter its structure, function, and connections in response to intrinsic or extrinsic stimuli. This alteration can occur naturally during human growth and development, gaining experience, and learning. Moreover, it can be induced by emotion, environmental factors, suffering from injuries or diseases, and from clinical therapies [13]. Neural plastic changes can occur throughout human life at diverse levels, for instance alteration in cellular, synapses, brain region's structure, brain function, networks, and behavior [14]. However, neuroplasticity can lead to either positive or negative changes [15]. They can be viewed as adaptive when implying gaining in function, while being considered as maladaptive when relating to negative consequences such as functional loss or increasing in injury [13].

Neuroplasticity and Clinical applications

Neuroplasticity holds a vital functional and ameliorative role across a wide spectrum of brain diseases and also in normal aging and health. Plasticity measurement provides insights into disease pathogenesis, enhances treatment strategies and assists in identifying markers of treatment effects [13].

CNS injuries involving motor deficits include stroke, trauma, and spinal cord injury, while CNS pathologies in neuropsychiatric disorders mostly involve non-motor injury. Both are corresponding to the neuroplasticity [13]. Mental and addictive disorders are associated with the abnormalities in the distributed limbic, prefrontal, and frontostriatal neural circuits that correspond to motivation, perception, cognition, behavior, social interactions, and regulation of emotion [13]. Apart from this, in cellular level of synaptic alteration, particularly the change of the structural and functional phenotype of the presynaptic terminal, is thought to be remarkable significant evidence for several neuropsychiatric conditions such as schizophrenia, autism, intellectual disabilities, and also neurodegenerative diseases, including, Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and drug abuse [16][17].

The dynamic process of brain plasticity is not only valuable for the prognostic biomarker of neurological disorders, but can be significantly beneficial for medication, rehabilitation, and treatment [13]. From the concept of brain's rewiring or rebuilding connections between neurons, pharmacotherapy and brain stimulation techniques have developed to modulate impaired neuroplasticity in the patients who suffer from neurodegenerative conditions, for the purpose of alleviating the symptoms, inducing plasticity, assisting the pateints to regain their normal state, and achieve better quality of lives [1],[2]. Furthermore, by studying the pathology of each neuropsychiatric disease, scientists, physicians, psychologists, and therapeutists can evaluate more precise targets for stimulation during clinical interventions and increase the effectiveness of the treatment.

TMS and rTMS

Magnetic stimulator or Transcranial Magnetic Stimulation (TMS) was first introduced in 1985 by Anthony Barker and his colleagues at the University of Sheffield, United Kingdom [18]. They demonstrated TMS technique showing the effect of magnetic stimulation on the motor cortex in the human brain, in which the magnetic pulses could induce weak electrical current in the brain painlessly [10]. After the coil was placed on the scalp (where was over contralateral motor cortex), the stimulation by the magnetic activated peripheral nervous system made the opposite hand (which was on the opposite side of the activated site) move [10]. Since this discovery, TMS has been used to study brain physiology and provided a significant clinical utility for developing therapeutic tools [19].

Transcranial Magnetic Stimulation (TMS) is a non-invasive or non-surgical form of brain stimulation technique, which has the concept based on two physics principles; Faraday's principle of electromagnetic induction and Ampere's law of circuital law [20]. It involves delivering electrical current through conductive wires encased in insulated coils, which are placed on specific areas of the scalp, in order to induce a local magnetic field [9]. The current from capacitors capable then transfers energy across the skull to in-

duce a secondary electrical current in the brain and alter local electric field in the nerve tissue, leading to depolarize of the underlying superficial neurons or activating a small area of the brain beneath the coil [2],[9],[19],[20]. Moreover, TMS is able to combine with several other devices for quantitative diagnostic and measurement of clinical parameters. Combination with structural brain MRI benefits in TMS targeting. While combination with simultaneous scalp electroencephalogram (EEG), electromyography (EMG) recordings, or motor-evoked potentials (MEPs) are useful for surgical planning and diagnostic applications across various neuropsychiatric disorders [2].

Delivering a single pulse of TMS can transiently trigger an action potential resulting in either activation or inhibition of the neurons underlying cortical region at the site of stimulation [2],[9]. Whereas, when TMS pulses are delivered repetitively, it is known as repetitive transcranial magnetic stimulation (rTMS). These rTMS pulses have potential ability for inducing neuroplasticity effectively and are widely used for therapeutic purposes in order to alter the structural and functional of the impaired brains for patients with neurological and neurodegenerative diseases. Additionally, rTMS is considred to be safe and well tolerated modality and the patients treated with rTMS have shown to have less side effects after the treatment. rTMS pulses either decrease or increase cortical excitability of targeting regions of cerebral cortex depending on the stimulation frequency [10]. Mostly, low frequency rTMS (LF-rTMS) (≤1 Hz) has been inhibitory or shown to reduce cortical excitability, on the contrary, high frequency rTMS (HF-rTMS) (≥5 Hz) has been excitatory or shown to raise cortical excitability [10]. They bring about longer-lasting and enhance plasticity in the brain [2]. Furthermore, in the past 10 years, a new significant form of rTMS protocol has been found to be effective for depression treatment. It was called Theta Burst Stimulation (TBS), which referred to delivery of 3-pulse 50-Hz bursts at a frequency of 5 Hz, that has the efficacy to induce long-term alteration in cerebral cortex excitability in a much shorter period of stimulation [2],[10].

In 2008, the U.S. Food and Drug Administration (FDA) approved TMS therapy device for the clinical depression treatment for the first time.TMS was subsequently approved from National Institute for Health and Care Excellence (NICE) recommendation in 2015, which led to the establishment of rTMS as a frontline treatment for the patients who failed in at least one prior antidepressant medication [10]. Later, FDA also approved TMS for chronic migraine painful treatment in 2013 and for obsessive-compulsive disorder (OCD) in 2018 [10]. At the present time, TMS and rTMS are used worldwide and have shown efficacy for diagnosis and reducing symptoms of various neuropsychiatric diseases.

TMS for Presurgical Mapping

TMS has also been approved by the U.S. FDA for its applications of presurgical motor and language mapping [11]. As the advancement of image processing, TMS-mapping strategies could be performed by combining MRI modalities with TMS using a 3D digitizer to identify the stimulating coil's position and map onto an MRI data set [21]. With the benefit of stereotactically that leaded neuronavigation, this brain mapping modality or known as Navigated Transcranial Magnetic Stimulation (nTMS) can real-time target cortical regions detected by brain MRI and so systematically examine motor responses (which is measured by MEPs induced in various target muscles) [11],[21]. As a consequence, nTMS provides assistance for surgical planning and assesses which cortex's parts could be safely removed during tumor resection or during the removal of an epileptogenic focus, in order to lower the risk of causing postoperative motor deficits or paresis [11],[22]. From many studies revealed that besides tumorous brain lesions, functional mapping with nTMS is also available within hypervascularized cortical areas and serves as a significant tool for presurgical planning and optimizing treatment planning for patients with arteriovenous malformation and cavernous angiomas as well [22].

In terms of language mapping, nTMS can efficiently probe the language network, identify the cortical plasticity induced by intra-hemispheric tumor, and can determine a suitable surgical plan which enables preserving language function after surgery [22]. This non-invasive preoperative protocol for language network mapping can be considered as a significant support for neurosurgeons whenever approaching patients who are affected by suspected language-eloquent brain tumors but not eligible for awake surgery or intraoperative monitoring [23].

rTMS for Treatments

Major Depression Disorder (MDD)

Dorsolateral prefrontal cortex (DLPFC) is the common target that is mostly used during TMS treatment for depression. DLPFC is a significant center of the frontoparietal network which is related to cognitive and multiple behavioral processes such as decision making, attention, working memory, planning, and reward processing [10],[24]. Patients with depression have been found to have this region be hypoactive which may induce negative emotional bias, maladjusted self-referential processing and cogitation [24]. TMS has been used as an alternative treatment for patients with depression who do not respond to existing first-line treatments such as antidepressant medication (e.g., selective serotonin reuptake inhibitors (SSRIs)) and psychotherapy (e.g., cognitive behavioral therapy (CBT)), patients who have problem tolerating side-effects of antidepressant medications, or patients with treat-

ment-resistant depression (TRD) who have been failed from electroconvulsive therapy (ECT) [10],[25],[26],[27],[28].

According to FDA approval, the common procedure of TMS treatment for depression involves applying HF-rTMS over the left DLPFC, which will activate the brain region and induce antidepressant effects, resulting in normalizing the functional balance between neural networks and improve depressive symptoms [10],[24],[25],[27],[28],[29]. Additionally, regarding preliminary evidence, rTMS has shown to be a promising technique for cognitive enhancement in TRD as well [30]. Moreover, in many recent studies, TBS seems to be a potential protocol for TMS treatment as it can increase cortical excitability as effectively as standard stimulation of HF-rTMS. However, TBS requires shorter sessions than HF-rTMS, which can reduce the time burden of treatment for patients [10],[25],[26].

Furthermore, some studies said applying LF-rTMS to the right DLPFC has shown to decrease local activity which also leads to produce antidepressant effects, while significantly lower the risk of seizure induction and may have anti-epileptic properties. This might be preferred for patients with risk factors of seizure and seems to be better tolerated than the standard protocol of HF-rTMS which induces discomfort of the local scalp in a greater degree [10],[26],[31],[32]. However, empirical evidence to date is not supported and the recent studies still less, therefore future research is required [31],[32]. Additionally, some open-label studies have found that rTMS might rapidly improve suicidal thinking and also a pilot study has found that delivering high doses of rTMS over left prefrontal cortex (PFC) for 3 days (54,000 stimuli) to suicidal inpatients is safe and has fewer side effects, while did not worsen suicidal thinking [33]. However, more studies are needed to confirm the effectiveness of rTMS for depression treatment and suicidal thought reduction.

Bipolar Disorder (BD)

Bipolar disorder (BD) is a chronic mood disorder typified by manic, hypomanic and/or mixed or depressive episodes which induce high rates of suicide, functional impairment and lower the quality of patient's life [34]. Recently the treatment of BD is still limited, however some studies and clinical trials reported that rTMS seems to be a promising alternative treatment for both monopolar and bipolar disorder (BD) as well as for BD patients who have failed from pharmacological (ex. lithium and quetiapine) and psychosocial (e.g., psychoeducation) treatment, as it could reduce depressive and mania symptoms and improve cognitive function (working memory and processing speed) mostly without causing adverse effects [34],[35],[36],[37]. Empirical studies mainly focused on the efficacy of rTMS on BD depression episode, whereas the studies on its mania phase are still less and the results are mixed for treating either phase of BD with most of the existing studies [35],[38]. Treatment of BD is challenged since the disease is composed of several phases. Therefore, more studies on larger sample size, stimulation sites, and randomized controlled trials (RCT) are still required to confirm the efficacy of rTMS for the treatment in various phases and more further researches are also needed to elucidate which rTMS protocols and parameters should be practiced in order to proceed the most effective result for BD treatment.

Post-Traumatic Stress Disorder (PTSD) and Anxiety Disorder

According to many researches and meta-analysis studies, rTMS is a promising potential and safe treatment for anxiety related disorders such as generalized anxiety disorder (GAD) and panic disorder, as well as be an effective therapy for post-traumatic stress disorder (PTSD) treatment, without causing severe adverse effects [10],[39],[40],[41],[42]. From the studies, rTMS stimulation mostly at over the right DLPFC resulted in reducing PTSD, anxiety and depressive symptoms [39],[40],[41],[42]. While LF-rTMS over the right DLPFC could reduce ipsilateral motor cortex excitability and improve panic symptoms for patients with panic disorder [43]. Moreover, patients reported LF-rTMS to the parietal cortex (PC) also resulted in reducing fear and anxiety as measured with both predictable fear-potentiated startle (FPS) and unpredictable anxiety-potentiated startle (APS) [44]. rTMS is considered as an effective modality for PTSD, GAD, and anxiety associated disorders treatment, however more larger sample size, RCTs, high quality studies, optimal parameters and assessments are required to confirm the results.

Substance Abuse

Drug addiction is associated with decrease of dopamine function, dysregulation of glutamate homeostasis, and impairment of cognitive function in the brain [45]. According to the precedent studies, rTMS was found to have therapeutic benefit for manipulating drug craving and abuse [45]. HF-rTMS over the DLPFC is a promising alternative treatment for patients addicted with nicotine or tobacco, alcohol, and cocaine [10],[45]. In terms of nicotine and alcohol addiction treatment, it has shown significant reduction in craving level and consumption number for both cigarettes and alcohol as well as decreasing in nicotine dependence, when compared with sham rTMS [10],[45]. And there was a recent study from a randomized and sham-controlled trial state that 10 daily sessions of active MRI-guided-rTMS over the left DLPFC could reduce cigarette consumption, decrease craving for up to one month, and also increase the likelihood of smoking cessation [46]. Regarding cocaine use disorder (CUD), from many studies HF-rTMS mostly over left DLPFC has found to decrease cocaine craving and has therapeutic effects of reduction in cocaine consumption and associated symptoms such as sleep disturbance, anxiety, depression, and other negative effects [10],[45],[47]. rTMS might become a new treatment for alcohol, drugs, and smoking cessation, however future researches still required as the optimal parameters (ex.

targets, intensity, frequency, relationship to cue-induced craving, duration of treatment, neuronavigation, concomitant treatments) are still unclear.

Obsessive-Compulsive Disorder (OCD)

Obsessive-compulsive disorder (OCD) is a chronic and disabling condition with a lifetime prevalence of 2%-3% and has been often found that the patients do not adequately respond to pharmacological treatments or CBT [48],[49]. Based on multicenter sham-controlled pilot studies, deep transcranial magnetic stimulation (dTMS) which is one type of rTMS that referred to the use of special design of H7-coil to induce depolarization in broader and deeper cortical regions in the brain, was approved by FDA for OCD treatment in August 2018 [48]. The main targets of H7-coil are neural networks in the medial prefrontal cortex (mPFC) and anterior cingulate cortices (ACC), in which the impairment in these regions is associated with the pathophysiology of OCD [48],[49]. Applying HF-dTMS using H7 coil has resulted in significant reduction of Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores and reduction in OCD symptoms without causing serious adverse events [48],[49]. Apart from this, a recent meta-analysis stated that stimulation by rTMS over DLPFC also resulted in improvement of OCD symptoms compared with sham rTMS as well [50]. Thus, it has shown that application of LF-rTMS over the supplementary motor area (SMA) was more effective compared to DLPFC [50]. The studies suggest that SMA plays a central role in motor planning, response-inhibition, and extensively connects with cognitive and emotional processing regions, as well as hyperactivity in this area may relate to inhibitory control over repetitive behaviors in OCD patients [50]. Therefore, SMA seems to be an interesting target for inhibition during rTMS stimulation, however larger samples, RCTS, and clinical studies are needed in order to find the most effective stimulation site and optimal parameters for treating OCD.

Migraine and Chronic Pain

TMS and rTMS has shown to be a promising modality for treating neuropathic pain of various origins such as central pain, pain from peripheral nerve disorders, fibromyalgia, and migraine [51],[52]. Single-pulse TMS was approval by U.S. FDA for acute treatment of migraine with aura, while rTMS could be used as a migraine prophylactic therapy both with and without aura by the effects on neurotransmitters and decreasing cortical excitability [53],[54]. According to meta-analysis of RCTs on TMS and migraine treatment, high frequency of 8-shaped coil TMS over the left motor cortex is effective for treatment of migraine with aura and TMS might be a potential option for the patients who failed from drug therapies which include acute therapies (ex. non-steroidal anti-inflammatory drugs, ergotamine preparation, and triptans) and preventive therapies (ex. β-blockers, anticonvulsants, tricyclic anti-depressants, and calcium channel modulators) [52]. However, due to the limitation of small sample size and rising threshold of chronic pathogenic process, the effect of TMS on chronic migraine was not statistically significantly different between active TMS and sham TMS group, and therefore more high quality RCTs are needed to confirm the results [52].

A current study on rTMS and central neuropathic pain has shown that 3 weeks spaced HF-rTMS (20 Hz) over the primary motor cortex (M1) contralateral to the patient's pain using a neuronavigated robotic system, could result in sustained analgesic effect and support clinical treatment towards refractory chronic pain [55]. Moreover, from randomized, double-blind, sham-controlled studies, resulted that HF-rTMS over M1 lead to a long-lasting pain reduction, decrease chronic pain, and improve quality of life in patients with fibromyalgia without affecting mood or anxiety levels [10],[56],[57].

Schizophrenia

Schizophrenia (SZs) is a major psychiatric disorder that has 1.0% prevalence of the world population [58]. Its clinical symptoms present into three major categories as positive symptoms (ex. hallucinations and hearing voices), negative symptoms (ex. social withdrawal, reduction of goal-directed behavior, lack of motivation, and reduced in emotional expression), and cognitive deficits (manifestation of brain dysfunction in cognitive processes ex. attention, working memory, and executive function) [58],[59],[60],[61],[62]. Approximately 20% of patients with SZs have treatment resistance to medication [62]. Although clozapine could be used as a drug of choice for drug-resistant patients and be effective compared to other antipsychotics, it has more side effects (especially potential life-threatening side effect of agranulocytosis which requires close monitoring) and also not all patients achieve remission from SZs symptoms [59],[60],[62].

Auditory hallucinations (AH) and auditory verbal hallucinations (AVH) which are auditive perceptions in the absence of external stimulus, represented a core symptom of SZs and approximately 25%-30% of patients with them are refractory to antipsychotic medication and can chronically persist [60],[63]. According to meta-analysis studies, applying LF-rTMS over left temporoparietal cortex (TPC) revealed significant benefits as compared to sham group and has shown to be safe and effective in AH improvement without causing serious adverse effects [59],[63]. Moreover, according to some studies, LF-rTMS over superior temporal cortex (STC) also has shown to be able to reduce symptom severity and frequency of AVH as well [60]. However, there is still controversial as a systemic review suggested that some studies of rTMS over TPC have high risk of bias and low-quality evidence [64]. Therefore, more studies and larger sample sizes are required to confirm the efficacy of rTMS for AH and AVH treatment, effective stimulation sites, and optimal parameters.

In terms of negative symptoms, conventional approaches with antipsychotics, pharmacological agents, or psychosocial interventions are limited and less effective [61],[65],[66]. Regarding meta-analysis, most of the studies have shown that HF-rTMS over the left DLPFC alone and HF-rTMS combined with antipsychotic treatment can ameliorate negative symptoms with higher rate of mild side effects in SZs patients [61],[65],[67]. However, based on the risk of bias assessment, some studies have rated the efficacy evaluation index as moderate level and cautious is needed when interpreting the results [65]. Apart from this, from a recent study, HF-dTMS bilateral stimulation over the PFC with H-2 coil, which are attributable to antidepressant effects, also induced significant improvements in negative symptoms for both SZs patients with or without depression [66]. Moreover, from recent case series, applying HF-rTMS over DLPFC followed by either LF-rTMS stimuli on Wernicke's area on the left TPC or inhibition of the right DLPFC, could reduce negative symptoms, delusion, and AH, however further studies are recommended to comfirm the efficacy [62].

In terms of cognitive deficits, conventional antipsychotic medication could alleviate the positive and negative symptoms of SZs, but not the cognitive deficits, so rTMS seems to be a potential promising intervention for cognitive deficits treatment in SZs patients [58]. According to meta-analysis reports said that rTMS over DLPFC could improve cognitive enhancing in SZs and HF-rTMS over the left DLPFC with a total number of pulses < 30,000 stimulation could significantly improve working memory in SZs with long-lasting effects, however there is still controversial that rTMS is not associated with a reliable improvement in working memory in SZs as well [58],[68],[69]. Because of many controversial aspects of rTMS towards SZs treatment for positive symptoms, negative symptoms, and cognitive deficits dimensions, more studies are needed to confirm the efficacy of TMS and potential protocol for the treatment.

Tinnitus

Tinnitus refers to auditory symptom characterized by perception of sound such as ringing, buzzing, or hissing in the absence of external source or electromagnetic stimulation [70],[71],[72]. It brings severe psychological stress and lowers the quality of patient's life and also is frequently associated with co-existing symptoms such as depression, anxiety, hearing loss, dizziness, attention and sleep disorder [72],[73]. Unfortunately, there is no curative treatment for tinnitus, so developing new approaches are needed [74]. According to many studies and meta-analysis reports, rTMS is a promising modality for treating tinnitus and chronic tinnitus [72],[73],[75],[76]. It has used to stimulate many regions both unilateral, bilateral, and dual-sites stimulation such as temporal cortex (TC), temporoparietal junctions (TPJ), auditory cortex (AC), dorsomedial prefrontal cortex (DMPFC), PFC, and DLPFC, in the brain for suppressing tinnitus symptoms (ex. loudness, intensity, frequency, awareness and annoyance of tinnitus) and its related symptoms (ex. tinnitus-related depression) [70],[71],[72],[73],[77],[78],[79]. Regarding meta-analysis reports, application of rTMS over AC which is mostly used to treat chronic tinnitus, has been shown to be effective to ameliorate tinnitus symptoms and also generate strongest electric field in the insula [72],[74]. Moreover, from recent research and pilot studies have revealed that rTMS can also be effective to treat tinnitus in patients with vestibular schwannomas (VS) and dual-modulation of TMS with tDCS may increase therapeutic effects of tinnitus treatment, while combining rTMS with repetitive peripheral magnetic stimulation can improve the symptoms of chronic tinnitus and its comorbid disorder of muscular tension in the neck and back [80],[81],[82]. Additionally, in terms of efficacy, stimulation sites and frequency, individualized rTMS treatment has shown to be feasibility approach [83],[84],[85]. However, the effectiveness of rTMS for tinnitus treatment is still controversial [86],[87],[88]. Many more studies are needed to confirm rTMS efficacy for tinnitus treatment, optimal parameters, and potential stimulation sites.

Autism Spectrum Disorder (ASD)

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder which presents as lifelong deficits and characterized in major impairments in social communication and interaction, stereotyped and repetitive behaviors, interests and activities, and deficits in sensory reactivity [89],[90]. Patients with autism have deficits in several dimensions such as attention, emotion recognition and regulation, social skills, cognition, and memory [90]. From preliminary evidences and meta-analysis, rTMS has shown to be a promising intervention for ASD treatment [89],[91]. It has shown the effectiveness to treat some dimensions of ASD such as positive effects on cognitive function, executive and attentional control, improvement in performance of eye-hand integration and confrontational tasks [89],[91],[92]. However, the existing studies are still controversial, have insufficient evidences, and limited for a positive effect of rTMS on some core symptom dimensions of ASD such as stereotyped and repetitive behavior, social behavior, and some aspects of executive function [89],[90]. Therefore, more studies are needed to prove the efficacy of rTMS to various dimensions of ASD as well as optimal stimulation targets, parameters, and protocols.

Alzheimer's Disease (AD), Dementia, and Mild Cognitive Impairment (IMC)

Alzheimer's disease (AD) is a devastating neurodegenerative disorder characterized by cognitive impairment and behavioral derangement and AD is also the most common cause of dementia in older adults [93],[94]. Currently, cholinesterase inhibitors are mainstream pharmacological treatment for AD, thus they have shown limited efficacy on cognitive function and are accompanied by adverse side effects [93],[94]. According to many meta-analysis reports, rTMS is a promising modality for treating patients with dementia, AD, as well as mild cognitive impairment (MCI) which is an early stage of AD or the transitional stage between normal aging

and dementia [95],[96],[97],[98],[99]. Studies suggested that application of rTMS targeting over DLPFC improves behavioral and psychological symptoms of dementia (BPSD) [98],[100]. Regarding meta-analysis, rTMS (mostly HF-rTMS over the left DLPFC and LF-rTMS over the right DLPFC) has shown significantly improvement of global cognitive function and memory in patients with AD and MCI, while HF-rTMS targeting the right inferior frontal gyrus (IFG) enhanced executive performance [94],[95],[96],[97]. Bilateral DLPFC application combined with long term treatment has shown greater efficacy in improvement of AD-associated cognitive performance [101]. Moreover, application of HF-rTMS in elderly patients with mild to moderate AD showed benefit on cognition improvement as well as ameliorate cognitive decline in healthy aging [93],[102].

Parkinson's Disease (PD)

Parkinson's disease (PD) is the second largest progression neurodegenerative disease worldwide, after AD [103],[104]. Its clinical symptoms included both motor symptoms (ex. bradykinesia, resting tremors, rigidity, postural instability, and gait disturbances) and non-motor symptoms (ex. depression, cognitive dysfunction, and autonomic dysfunction) [103],[104]. Conventional treatments (ex. pharmacotherapy, physical exercises, and cognitive therapy), might be beneficial for PD patient's life, however some of these treatments may cause many side effects such as nausea, vomiting, and exercise's aggravation symptoms [104]. Regarding many meta-analysis studies, rTMS is a promising intervention for PD treatment in terms of improving motor deficits, depression, and cognitive function [103],[104],[105],[106],[107]. Application of both HF-rTMS and LF-rTMS over M1, SMA, PFC, DLPFC, or M1+DLPFC have shown significant therapeutic effects on motor deficits in PD patients and a meta-analysis suggested that multi-session of HF-rTMS over M1 (especially bilateral M1) with a total of 18,000-20,000 pulses seems to be the optimal parameters for motor improvement in PD [103],[107],[108]. Moreover, HF-rTMS mostly over DLPFC or PFC appears to have significant positive antidepressive effect in PD with depression and have the effectiveness as SSRIs or fluoxetine which are antidepressants [103],[105],[106],[109]. Furthermore, a recent meta-analysis stated that HF-rTMS over DLPFC might have positive effect on cognition in terms of executive function, however the efficacy of rTMS on cognitive function in PD remains controversial, has few evidences and optimal parameters are still unclear, therefore more studies are needed to confirm the effectiveness of the treatment [104],[108].

Epilepsy

Epilepsy is a highly prevalent neurological condition characterized by a dynamic imbalance between the excitatory and inhibitory impulses in the cortex and are normally shown by repeated unprovoked seizures with diverse etiologies [110],[111],[112]. Nearly one-third of the patients are drug-resistant epilepsy (DRE) or fail to respond to antiepileptic drugs (AEDs) which lead to increase the risk of mortality and other disabilities affecting the quality of life [110],[111],[112]. Regarding meta-analysis, LF-rTMS has shown to be an effective therapy for the treatment of DRE by reducing both the seizure frequency and interictal epileptiform discharges with mild adverse effects and it also seems to be more effective for pediatric patients younger than 21 years old, however the seizure reduction efficacy of rTMS remains controversial and more studies are required [110],[111],[112],[113],[114].

Stroke Rehabilitation

After stroke, it was followed by hemispheric imbalance of excessive inhibitory from healthy to impaired hemisphere and rTMS appeared to be an effective modality for stroke rehabilitation in many dimensions [11]. HF-rTMS has been applied to enhance excitatory in ipsilateral/perilesional cortex, while LF-rTMS is used to suppress contralesional cortex [11]. According to many studies and meta-analysis, LF-rTMS is suggested to be a potential therapeutic tool for patients with aphasia after chronic stroke and language recovery, as well as be a promising intervention for treating dysphagia after stroke [115],[116],[117],[118]. Moreover, rTMS has shown a positive effect on motor function recovery in patients with stroke and improved patients' satisfaction [119],[120],[121]. LF-rTMS mainly affects motor function, whereas HF-rTMS increasesthe amplitudes of MEPs [119]. It appeared to enhance motor recovery in both upper/lower limb and lower extremity motor functions [115],[119],[120],[122],[123],[124]. Apart from this, rTMS also appeared to have efficacy for treating post-stroke depression (PSD), improve cognitive function, attention, memory, and working memory in patients with stroke [125],[126],[127],[128]. However, there is still controversial among the results of the studies, so more studies are needed to draw the conclusion of rTMS efficacy towards stroke rehabilitation.

Tourette Syndrome (TS)

Tourette Syndrome (TS) is a childhood-onset neuropsychiatric disorder manifested by motor and phonic tics, in which tic symptoms might improve during adolescence, however TS symptoms may become chronic or severe when continuation into adulthood [129],[130],[131]. Currently, the conventional treatments are pharmacological and psychological treatment, thus this medical treatment may not always be effective and has many side effects such as weight gain, type 2 diabetes mellitus, hyperlipidemia, myocarditis, and sexual side effects [130]. The preliminary studies and meta-analysis suggested that rTMS is a promising modality for TS treatment and has shown to have efficacy of suppressing TS symptoms and significantly alleviate tics in TS patients

[129],[130],[131],[132],[133]. A meta-analysis revealed that rTMS has remarkedly effects on tic and OCD symptoms and stimulation of bilateral SMA was seen to be more effective in tic symptoms than other areas, while younger age has a better treatment effect [132]. However, the studies of rTMS for TS treatment is less, limited and has controversial results due to various parameters and target regions. Therefore, more studies including larger number of patients, longer follow-up periods are required to confirm the effectiveness of the treatment and elucidate the optimal parameters and stimulation sites.

TMS and Safety

TMS has been shown as an alternative modality used for the patients who have failed from first-line treatment or conventional medication treatment and for the ones who do not prefer medication due to some reasons (ex. side effects of medication, pregnancy, etc.) [10]. It is likely to cause fewer side effects than conventional medication as its most general side effects are headaches, discomfort at stimulation site, and facial muscle twitching, while the rarest side effects of TMS-related seizures are less than 1% which mostly occurred in patients who have risk factors (e.g., vascular, traumatic, tumoral, infectious, or metabolic lesion of the brain, brain damage, congenital epilepsies, patients who have history of epilepsy or seizure, sleep deprivation, and alcoholism) [10],[134],[135].

However, some particular patients must take a serious precaution, especially pregnant women and young children. These patients can be treated with rTMS. Magnetic fields attenuate rapidly with distance does not seem to directly affect the fetus and there are also many reports have shown that pregnant women underwent successful rTMS treatment for depression without side effect to child, however a conservative view of rTMS treatment in pregnancy might be considered in order to balance the benefit and risk ration for individual case [135]. Additionally, direct stimulation on the lumbar spine should be avoided in pregnant women, unless there are justifying compelling reasons and also TMS safety in pediatrics needs special consideration as well since TMS might cause adverse effects due to developmentally-regulated changes in CNS [135]. Furthermore, patients with electronic or magnetic implants for instance, pacemakers, drug pumps, neurostimulators (e.g., cortical or deep-brain electrodes, epidural/subdural, VNS), and cochlear implants must take serious precautions during TMS treatment because there is a risk that magnetic fields may induce malfunctioning of the implanted devices [10],[135].

Conclusion

TMS or rTMS is a non-invasive approach which has less serious side effects and causes no pain when compared to the invasive brian stimulation and other clinical medications. It is usually used for mapping techniques as well as application for the clinical treatment. However, therapeutic advantages of rTMS in some particular diseases such as Tourette Syndrome, epilepsy, and autism are not well elucidated as the number of studies is insufficient. Additionally, sometimes each study used different target brain regions, frequency and intensity of the stimulation, and follow-up period, resulting in the difficulty in the comparison of treatment outcomes. Further studies are required to clarify these diagnostic and therapeutic benefits of both TMS and rTMS, in order to improve neuroplasticity in neurodegenerative and neuropsychiatric patients.

Acknowledgement

I would like to thank and express my very great appreciation to Miss. Natnicha Jiravejchakul from the department of microbiology, faculty of Science, Mahidol University, Thailand for her guidance and feedback when writing this paper.

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