



Cognitive Enhancement in Neurological and Psychiatric Disorders Using Transcranial Magnetic Stimulation (TMS): A Review of Modalities, Potential Mechanisms and Future Implications

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Cognitive enhancement refers to the improvement of cognitive function related to deficits that occurred as part of a certain illness. However, the term cognitive enhancement does not yet have a definitive meaning, and its connotations often vary depending on the research of interest. Recently, research interests are growing towards enhancing human cognition beyond what has traditionally been considered necessary using various brain devices. The phenomenon of exceeding the cognitive abilities of individuals who are already functional has also introduced new terminologies as means to classify between cognitive enhancing procedures that are part of treatment versus simply supplementary. Of the many devices used to attain cognitive enhancement, transcranial magnetic stimulation (TMS) is a unique neurostimulatory device that has demonstrated significant improvements in various cognitive domains including memory and cognitive processing skills. While many studies have supported the safety and efficacy of TMS in treatment, there has yet to be an optimization in parameter for TMS that is catered to a certain target group. The current paper aims to review with perspective the many studies that have used TMS for the purpose of cognitive enhancement and provide further insight on the development of an optimal stimulation parameter. The paper reviews 41 peer-reviewed articles that used TMS for cognitive enhancement, summarizes the findings that were apparent for each distinct parameter, and discusses future directions regarding TMS as an elective tool for healthy individuals while considering some of the ethical perspectives that may be warranted.

Key words: Transcranial magnetic stimulation, Cognition, Noninvasive, Memory, Neuropsychological tests

INTRODUCTION

The emergence of new and innovative technological tools has become a growing trend in the field of neuroscience, as they provide much insight regarding our knowledge of the brain's capacity [1]. Present day research emphasizes the role of neurological tools as treatment strategies or parts of, such as preliminary screening tools for the future onset of various diseases and disorders [2, 3]. Of the many neurological devices, those that have the ability to

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improve cognitive function have become particularly of interest, as investigating new ways of enhancing human abilities is an ongoing collective goal in neuroscience [4]. Abundant research within the field of neuroscience demonstrate the diverse applicability of neurological devices in enhancing cognitive function, including various diseases and impairments [5-14].

Cognitive enhancement, clinically speaking, refers to intervention strategies that aim to improve cognitive function that has shown deficit as part of a certain illness [15]. However, as the topic of interest in neuroscience research slowly progressed towards enhancing human cognition beyond what is traditionally considered necessary, newer definitions of cognitive enhancement emerged as means to segregate between cognitive enhancing procedures that are treatment-driven versus supplementary [16-18]. There are various approaches to achieve cognitive enhancement such as in forms of therapy [19], pharmacological treatment [20], and the use of a technological device [21]. Among these, noninvasive brain stimulation (NBS) is a technique which emerged in the late 1990s that alters brain activity by changing neural function via intervention [22], and has received much attention in research due to having less generalized side effects. In particular, transcranial magnetic stimulation (TMS) is one of the most utilized methods for the purpose of altering cognitive function. TMS refers to the stimulation of the nerve generated by electrically induced magnetic fields, and is unique and comparable to other NBS technologies due to its neurostimulatory nature [23, 24].

TMS has become popular as it yielded significant findings in the improvement of cognitive function domains [25, 26]. Previous studies have shown that healthy individuals who have undergone TMS treatment demonstrated increased episodic memory [27], working memory [28], and motor learning performance [29-31]. Findings of earlier TMS research also helped elucidate the capability that brain regions can be manipulated to yield altered cognitive function [32]. Recent studies have also introduced the combined application of TMS and neuroimaging techniques such as functional magnetic resonance imaging (fMRI) as well as potential biomarkers for cognitive function [33]. This collective approach of various neuroimaging techniques have enabled us to further understand ways to enhance cognition, manipulate the human brain and categorize by regions of activation in respect to specific cognitive domains.

The purpose of this article is to critically review the usage of TMS in humans for the purpose of cognitive enhancement. The review is divided into sections as follows: a methodology of the data selection process conducted, an introduction of the basic mechanisms of TMS along with the different types of TMS used in clinical trials for cognitive enhancement, a summary of the results

from modern TMS studies and their implications, a discussion to note the possible ways of improvement in the current methodologies for cognitive enhancement using TMS, and concluding with the possible ethical concerns that may follow in the usage of TMS for cognitive enhancement. The paper will focus on reviewing open-label trials and randomized controlled trials that have been performed within recent years, in order to discuss the more long-term effects of TMS treatment, as opposed to the immediate on-line effects of noninvasive brain stimulation.

MATERIALS AND METHODS

This article provides a review of the TMS studies (1999~2018) that primarily focus on the stimulation of the prefrontal cortex, an area of the brain which has reliably shown to influence cognitive function [34]. The current review with perspective is based on a broad spectrum of samples including patients suffering from psychiatric or neurological diseases and healthy volunteers for the purpose of treating cognitive dysfunction and cognitive enhancement, respectively. By performing a literature search in the following databases: PubMed (1999~2018) and MEDLINE (1999~2018), 41 articles were identified and chosen upon a careful review of the content of the articles and were deemed as relative to the current review. The identified articles consist of 10 open-label trials and 31 randomized controlled trials - including within-subject, sham-controlled or crossover designs. Of these, 22 comprised of trials with depression or PTSD, 6 with schizophrenia, 4 with impairment in the cognitive domains, 3 with neurological conditions, 1 with obsessive compulsive disorder (OCD), and 5 studies involving healthy participants only.

MECHANISM OF TMS

Basic mechanism of TMS and emerging trend

The stimulation from TMS is a stored charge that is delivered outside the scalp. The magnetic field generated by the TMS penetrates the skull, and electrical current is generated in the cortical neurons that are located in the area under where the TMS coil is placed [35]. This current then depolarizes the neuronal membranes by mimicking electrical stimulation, thus triggering action potential. Unlike neuromodulatory devices which have low temporal resolution despite similarity in spatial resolution as the TMS, TMS has been noted as a neurostimulatory device as a result of its relatively high temporal resolution [36]. The electrical current from TMS has shown to induce increase in action potentials that are sufficient enough to yield a major mechanic difference [35], suggesting a more long-term alteration in cognitive performance

when used for the purpose of cognitive enhancement [32].

While the general mechanism of TMS has been established over the years as mentioned above, the optimal method and parameters to applying TMS for the purpose of cognitive enhancement has been long debated. During the earlier years of research in cognitive enhancement, TMS was more typically applied to stimulate the peripheral nerves [37]. However, over the last few decades, transcranial magnetic stimulation of the cerebral cortex has received much attention as it turns out the application of TMS over the motor cortex can directly stimulate the corticospinal axon [35]. Furthermore, the application of TMS over non-motor areas of the brain also became of interest as it extended possible research applications with respect to brain-behavior relationships [36]. With direct cortical stimulation, in contrast to peripheral nerve stimulation, both excitatory and inhibitory effects in cognitive function were observed depending on the frequency of the stimulation. In addition, as newer technologies emerged in the field of neuroimaging such as fMRI and neuronavigation, researchers are now able to observe the direct neural effects of TMS by working in tandem with such methodologies, potentially increasing the reliability of these studies [38].

Repetitive TMS

Throughout the years, research also demonstrated that each type of TMS application elicits distinct physiological results. Among these, repetitive TMS (rTMS) has now become the most utilized methodology, due to its ability to alter cortical inhibition and excitation according to stimulation frequency [26]. In particular, recent research emphasize the application of rTMS for the purpose of cognitive enhancement. rTMS applies a certain number of stimulations per session to the area of stimulation over a prolonged period of time – typically between 20 to 40 minutes of treatment time – and its large number of condensed stimulation is what enables alterations in task performance. In the past, fast and repetitive exposure of rTMS was believed to have detrimental negative effects on cognitive processes, due to its disruptive nature [26]. However, studies later clarified that this is only in the case when rTMS is applied while simultaneously performing an online task. On the contrary, studies have indicated that rTMS that is delivered prior to a task or in short periods in between tasks can enhance the overall cognitive task performance [32], and therefore became popularized in the field of cognitive enhancement. Of the many studies that focus on the cognitive enhancing effects of TMS as discussed in the current review, the majority have used rTMS as the primary method of treatment. rTMS may therefore be a promising method of TMS treatment for various deficits and further improvements related to cognition, in both populations of

cognitive deficits such as those with ADHD or dementia, as well as healthy populations.

One of the conventional ways to categorize rTMS is by frequency, which is typically labelled as low or high frequency. Low frequency rTMS (LF-rTMS) refers to a frequency of 1~4 Hz and is known to induce transient suppression or cortical excitability by depolarizing neurons. Studies that utilized LF-rTMS have shown that it indirectly affects emotion and behavior [38], and some improvement in language related tasks [39]. However, there are very few studies that have shown cognitive enhancement using LF-rTMS and as such, high frequency rTMS (HF-rTMS) is the most widely used technique for cognitive enhancement in clinical trials as well as healthy individuals.

HF-rTMS is defined as frequencies that are 5 Hz or higher, and has been found to enhance long-term cortical excitability which sustains up to a month subsequent to the treatment [40]. HF-rTMS was initially thought to have detrimental negative effects on cognitive processes due to its disruptive nature and high magnetic field intensity. However, studies later clarified that HF-rTMS that is applied prior to a task transiently enhances cortical excitability in a more effective manner as compared with LF-rTMS, and have further proven that it has more long-term effects in the cognitive domains than other types of TMS [25].

Brain regions of interest for TMS

One of the factors to note with respect to TMS is its location-specific nature. The neurobehavioral effects from TMS can vary tremendously depending on the particular brain region that is stimulated. Therefore, noting the location of stimulation prior to treatment is essential depending on the treatment group, especially so in the clinical field. For instance, in the case of treatment for motor function in patients with Parkinson's disease, stimulation would more likely be applied to the primary motor cortex in order to treat for the deficits in motor function [41]. In contrast, in the case of patients with psychotic disorders including depression and OCD, stimulation would be applied within the vicinity of the prefrontal cortex to treat for psychological symptoms [42].

One of the key anatomical regions of interest in cognitive enhancement via TMS is the dorsolateral prefrontal cortex (DLPFC). The DLPFC is part of the Brodmann area 9 and is significantly involved in human cognition, particularly in various processing skills including working memory, attentional control, and processing episodic information [34, 43]. Earlier fMRI studies have shown that the left DLPFC is activated during times of task performance, and its activation is increased in correlation with the difficulty of the task [34]. Since the discovery of the function of the DLPFC, many studies have undergone experimental studies to validate

both the safety and efficacy as well as the cognitive enhancing effects of TMS to the left DLPFC. To name a few, numerous randomized, sham-controlled studies have found that applying rTMS to the left DLPFC enhances response inhibition [44-47], working memory [48, 49], delayed improvement in logical memory [50] and verbal fluency [51]. Research have also diversified in methodology, and found that the simultaneous application of rTMS to both hemispheres of the DLPFC improved episodic memory, a finding which revealed that the underlying mechanism involves the alteration in frontal gamma oscillatory activity [52]. While there are several selective studies that found improvement in the cognitive domain by applying TMS elsewhere other than the DLPFC such as the left primary motor cortex to improve associate memory [53], most studies have found that stimulating the left DLPFC via rTMS yields the most effective cognitive enhancement.

COGNITIVE ENHANCEMENT EFFECTS OF TMS

Within recent years, numerous studies have been done as means to validate the safety and cognitive enhancement effects of rTMS treatment. Many of these studies have focused on populations that typically show cognitive deficits as part of a prolonged illness, including depression, schizophrenia, mild cognitive impairment and dementia, and attention deficit hyperactive disorder. Some studies also began to focus on the cognitive enhancement of healthy individuals with normal cognitive abilities for improvement purposes [23, 31, 45, 46, 49].

While these abovementioned studies have explored various cognitive domains using a large spectrum of cognitive rating, the primary cognitive domain that are of interest may be classified into two groups – memory and processing skills. Memory and processing skills are classic examples of the broadly used term ‘intellect’ [54]. Having a large memory capacity and high processing skill are considered valuable intellectual traits among the healthy population, while the lack of brings increasing concern to the aging population and those of cognitive deficit. Here, we review some of the randomized controlled trials that have been conducted over the years using rTMS with the outcome variables of one or both of the abovementioned cognitive domains which are memory and processing skills. We also suggest possible neural pathways of rTMS treatment that may explain for its high efficacy in cognitive enhancement by referring to previous findings regarding brain networks and connectivity. Furthermore, we categorize the outcomes of the studies reviewed according to various samples, including diseased and healthy populations.

Effects-based cognitive domains: memory

In the case of rTMS and cognitive enhancement, studies have primarily focused on the domains of memory that are short-term in that they are not permanent changes to one’s cognitive function (Table 1). Among the various types of memory, those that fit into this description in previous studies have been working memory [6, 8, 9, 48, 49, 51, 56-58, 87], episodic memory [27, 51, 59, 60], and logical memory [27, 55].

Working memory refers to a cognitive system where information is temporarily stored for the purpose of processing, including complex cognitive tasks such as language comprehension, learning, and reasoning [55]. Throughout the years, studies have indicated that certain diseases show cognitive deficits in the working memory spectrum, and therefore affect one’s ability to store and manipulate information online [55]. Within the field of schizophrenia, meta-analyses were performed to confirm this cognitive deficit in working memory in schizophrenic patients [56], and other analyses have also been performed in the field of depression [8], as well as ADHD [6, 9]. While the definitive ways to assess working memory has not yet been stratified and there is a large variety of assessments that can be used, most trial studies have used similar tests to assess working memory. Within the working memory spectrum, many studies have used tasks including digit span, spatial span, and n-back test to measure verbal working memory, as well as spatial span and spatial working memory tasks from the Cambridge Neuropsychological Test Battery (CANTAB) for visual and spatial working memory. In the current review, 15 studies have been chosen collectively which have shown significant improvements in working memory using the above methods of assessment along with rTMS (Table 1). Among these, certain studies have suggested that the improvement in working memory in relation to HF-rTMS may yield greater effect when the working memory load is higher and be related to the reduction of excessive gamma oscillatory activity, as found in Barr and colleagues [57]. In addition, Levkovitz and colleagues (2011) have also noted that certain working memory domains may have greater effects depending on the area of the brain that is activated during the task performance, such as frontal lobe-related tasks in contrast to tasks that activate the striatal-parietal region of the brain [48]. While working memory can be further broken down into spatial working memory and verbal working memory, previous randomized controlled trials have shown significant improvements in both domains of working memory after the treatment of rTMS [58].

Although limited in number, several studies have also indicated improvements in the three pinnacle memory domains, which are episodic, semantic and autobiographical memory after TMS treatment. While these memory domains are primarily related to

Table 1. Studies that have shown increase in memory after rTMS treatment

Group	Reference	N	Location	Session/ Week	Fre- quency (Hz)	Train Dura- tion (s)	Trains per Session	Inter- train- interval (s)	Pulses per session	MT (%)	Cognitive Rating
Healthy	Gagnon et al. (2011)	11	R, L, DLPFC	1/-	-	Paired-pulse	-	0.015	-	90	Remember/Know Task
Healthy	Bagherzadeh et al. (2016)	30	L DLPFC	10/2	10	1	-	5	600	100	Digit span, PRM, DMS
Dep	Triggs et al. (1999)	10	L PFC	10/2	20	2	50	28	2000	80	Digit span, COWA
Dep	Fitzgerald et al. (2003)	60	L DLPFC	20/4	1	6	4	25	300	100	Digit span, Verbal fluency
Dep	Boggio et al. (2005)	25	L DLPFC	10/2	15	5	40	25	1000	110	Semantic & Autobiographical WCST
Dep	Fabre et al. (2004)	11	L PFC	10/2	10	8	20	52	-	100	Hive Test
Dep	Hansen et al. (2011)	30	R PFC	15/3	1	60	2	180	-	110	Digit Symbol, Rey
Dep	Wajdik et al. (2014)	63	L DLPFC	15/3	10	5	32	25	1600	110	RAVLT
PTSD	Boggio et al. (2010)	30	R, L DLPFC	10/2	20	2	40	28	1600	80	WCST, COWA, DSP
Sch	Schneider et al. (2008)	51	L DLPFC	20/4	10	-	-	-	1000	110	WCST
Sch	Barr et al. (2011)*	46	L DLPFC	1/-	20	4	25	25	750	90	N-back test
MCI	Sole-Padullés et al. (2006)	39	L PMC	1/-	5	10	10	2	-	80	10-block design task
MCI	Drumond Marra et al. (2015)	34	L DLPFC	10/2	10	5	-	25	2000	110	RBMT
Apha	Thiel et al. (2013)	24	Posterior IFG	10/2	1	1200	1	-	-	90	Token test, naming, writing
AD	Zhao et al. (2017)	30	Posterior T	30/6	20	10	20	20	-	-	ADAS-Cog

Dep, depression; PTSD, posttraumatic stress disorder; Sch, schizophrenia; MCI, mild cognitive impairment; Apha, aphasia; AD, Alzheimer's Disease; L, left; R, right; DLPFC, dorsolateral prefrontal cortex; PFC, prefrontal cortex; PMC, primary motor cortex; IFG, inferior frontal gyrus; T, temporal; PRM, pattern recognition memory; DMS, delayed matching to sample; WCST, Wisconsin card sorting test; RAVLT, rey auditory verbal learning test; COWA, controlled oral word association; RBMT, rivermead behavioural memory test; ADAS-Cog, Alzheimer's disease assessment scale-cognitive subscale. * Indicates the inclusion of a healthy comparison group.

the medial temporal lobe and the hippocampus as suggested in previous studies [59], rTMS treatment to the DLPFC have yielded significant results. Episodic memory, in particular, have shown to be reduced in individuals with cognitive deficits such as those with amnesic mild cognitive impairment [60], and have been of interest to best prolong and retain in the general population. Gagnon and colleagues (2011) have shown that healthy individuals with normal cognitive abilities have shown increased episodic memory as measured via Remember/Know recognition task, although this was done so using a paired-pulse TMS methodology [23]. Furthermore, Fitzgerald and colleagues (2003) have shown improvements in semantic memory as well as autobiographical memory after the treatment of rTMS, where both low and high frequency rTMS applied to the left DLPFC for 4 consecutive weeks have yielded significant improvements [51].

Effects-based cognitive domains: processing skills

Another beneficial factor that has been suggested as a result of rTMS stimulation is the enhancement of cognitive processing. Cognitive processing is a domain of cognitive function that is distinct from memory, as it is less related to knowledge and more towards non-executive functioning such as selective attention. While the idea of enhancing one's cognitive abilities is generally familiarized as enhancement regarding intellect such as memory domains, processing skills are also a key factor that is significantly associated with intellect. Studies have shown that individuals with higher intelligence quotients tend to have faster processing speed [61], which may arguably be affected by the neural system. Therefore, the electrical current that stimulates the cortical neurons via rTMS may affect the neural pathways in such a way that it leads to a more efficient neural network in terms of processing information.

Within recent years, several studies have demonstrated the effects of rTMS in the improvement of cognitive processing (Table 2). In particular, many of these studies have used the Stroop interference task as the method of assessment for cognitive processing, as it has long been noted as a reliable way of measuring top-down attentional control including attentional vigilance and inhibition [31, 44-47]. While these studies were based on many different target groups including healthy individuals, those with depression, and those with cognitive impairment, all the studies have shown consistency in their findings in that HF-rTMS to the left DLPFC increased the overall performance in the Stroop interference task. The collective findings suggest that the effects of rTMS do not necessarily differ between individuals based on intellect or illness, but rather largely depend on the application process of TMS including the area of stimulation and frequency.

In addition, there are many studies that support the effects of rTMS in enhanced cognitive processing using lesser conventional methods of assessment for cognitive processing including the assessment of psychomotor speed using the Motor Agitation and Retardation Scale [62], the Divided Attention Task [38], and the Letter Cancellation Test [47], all of which demonstrated a significant improvement in task performance.

Group-based cognitive outcome: healthy individuals

Previous studies on cognitive enhancement using rTMS can also be generalized into categories of sample groups. While the application of rTMS has been FDA-approved for the target population of individuals with depression, studies have also shown that healthy individuals show improved cognition after rTMS. In particular, Vanderhasselt and colleagues (2006; 2007) have shown consistent results of the effects of rTMS on the DLPFC in improved performance on the Stroop interference task. The two studies support the efficacy of rTMS in higher performance of attentional control for individuals without any particular neural deficit, and further suggest that the effects are significant regardless of the hemisphere of stimulation [45-46]. Additional studies demonstrated improved attention as a result of rTMS in healthy individuals, using other measures for attentional control including Conner's Continuous Performance Task [31].

Furthermore, numerous rTMS studies on healthy individuals also demonstrated various domains of memory enhancement, including recognition memory and working memory [27, 49]. While rTMS on healthy individuals has not yet proven to improve long-term memory or autobiographical memory as found in a depression model [51], improved recognition memory within healthy individuals may support previous theory that recognition is largely affected by changes in the hippocampus of the brain [63, 64]. Given that the prefrontal cortex is stimulated in rTMS treatment, coupled with the fact that the prefrontal cortex interplays with the hippocampus in human memory [65], rTMS treatment to the DLPFC may indirectly affect the hippocampus in such a way that enhances recognition memory of healthy individuals. Future studies that investigate the connectivity and activation of brain networks that include the area of stimulation in rTMS may contribute to the delineation of the neural pathways of rTMS treatment.

Group-based cognitive outcome: depression and PTSD

In contrast to healthy individuals with a normal range of cognitive function, there is a much higher number of studies that demonstrate the efficacy of rTMS in individuals with disorders including depression and PTSD (Table 1 and 2). While many studies have reported cognitive deficit as a secondary symptom of depres-

Table 2. Studies that have shown increase in processing skills after rTMS treatment

Group	Reference	N	Location	Ses- sion per Week	Fre- quency (Hz)	Train Dura- tion (s)	Trains per Session	Inter- train- interval (s)	Pulses per session	MT (%)	Cognitive Rating
Healthy	Vanderhasselt et al. (2006)	28	L DLPFC	1/-	10	4	40	26.1	1560	110	Stroop task
Healthy	Vanderhasselt et al. (2007)	20	R DLPFC	1/-	10	4	40	26.1	1560	110	Stroop task
Healthy	Hwang et al. (2010)	17	L DLPFC	1/-	10	2	-	10	900	90	Conners' CPT
Dep	Grunhaus et al. (2000)	20	L Motor Cortex	20/4	10	6	-	-	1200	90	TMT-B
Dep	Moser et al. (2002)	19	L MFG	5/1	20	2	20	60	-	80	TMT-B
Dep	Martis et al. (2003)	15	L PFC	15/3	10	5	20	30	1000	110	Stroop task, SCRT, GP
Dep	Hoppner et al. (2003)	30	R DLPFC	10/2	1	60	2	180	-	110	MARS
			L DLPFC		20	2	20	60			
Dep	Hausmann et al. (2004)	41	R, L DLPFC	10/2	1	600	1	-	2600	120	Stroop task
					20	10	10	90	2000	100	
Dep	Boggio et al. (2005)	25	L DLPFC	10/2	15	5	40	25	-	110	Stroop task
Dep	Kedzior et al. (2012)	-	L DLPFC	40/3	10	5	40	25	2000	100	mCST
Dep	Myczkowski et al. (2012)	14	L DLPFC	20/4	5	10	25	20	1250	120	TMT-B, Stroop task
PTSD	Boggio et al. (2010)	30	R, L DLPFC	10/2	20	2	40	28	1600	80	Stroop task
Sch	Levkovitz et al. (2011)	15	R L PFC	20/4	20	-	-	-	-	120	SOC, SSP, SWM
Sch	Guse et al. (2013)*	47	L DLPFC	15/3	10	-	25	30	1000	110	N-back test, DAT
Dem	Antczak et al. (2018)	11	R L DLPFC	10/2	10	5	20	25	3000	90	LCT, Stroop task

Dep, depression; PTSD, posttraumatic stress disorder; Sch, schizophrenia; Dem, dementia; L, left; R, right; DLPFC, dorsolateral prefrontal cortex; MFG, middle frontal gyrus; PFC, prefrontal cortex; CPT, continuous performance task; TMT, trail making test; SCRT, simple and choice reaction time; GP, grooved pegboard; MARS, motor agitation and retardation scale; mCST, modified concept shifting task; SOC, stockings of Cambridge; SSP, spatial span; SWM, spatial working memory; DAT, divided attention task; LCT, Letter Cancellation Test.

* Indicates the inclusion of a healthy comparison group.

sion and/or related emotional distress including PTSD, the precise mechanism that underlie this effect is yet to be elucidated. One of the theories behind this effect that is most agreed upon is the underactivation of the prefrontal cortex of the brain as a response to cope for the psychological distress [66]. The underactivation is coupled with lower cerebral blood flow to the prefrontal cortex, which results in the disturbance of its key function which is higher thinking and executive functioning. The application of rTMS to the left DLPFC may act as an enhancer to the deficit of the prefrontal areas including activation and cerebral blood flow, and has shown to improve memories of those under depression and PTSD in various domains including episodic memory, spatial memory, verbal fluency, and executive function [51, 67-70]. rTMS treatment in depression has also demonstrated improved attentional control including the trail-making test and Stroop interference task [7, 45, 46, 67, 70-74]. While cognitive enhancement through rTMS in models of depression and PTSD has been consistent, further neuroimaging studies that investigate the physiological changes of the brain in response to rTMS may benefit in the understanding of the precise neural mechanisms underlying the magnetic stimulation of the DLPFC.

Potential neurological pathway underlying the effects of rTMS

The current review demonstrates that rTMS treatment has a significant effect in cognitive function across various groups including healthy and diseased populations. However, it is noteworthy that the precise neurological pathway that underlies the effects of rTMS has yet to be elucidated. While the associations between brain regions and their functional roles have been investigated throughout the history of neuroscience, research that directly investigate the neurological pathways in the perspective of rTMS treatment is still limited. Further studies that directly observe the alterations in certain brain network connectivity related to the regions of stimulation in rTMS may help understand its mechanisms, along with the development of novel rTMS parameters. Previous studies in cognitive neuroscience have demonstrated that certain brain networks and their inter-connectivity with other regions of the brain strongly affect cognitive outcomes including memory. A recent study by Bridge and colleagues (2017) have shown the significant association between the hippocampus and the frontoparietal network (FPN) of the brain on retrieval memory [75]. This inter-connectivity relationship between brain regions and networks may help explain the neural pathways that underlie rTMS stimulation, as the DLPFC is one of the main components of the FPN. The magnetic stimulation to the DLPFC may strengthen the connectivity within the FPN, and consequently

increase the inter-connectivity strength between the FPN and hippocampus, yielding an enhancement in memory. This particular mechanism may also be generalizable to other memory domains, and further studies that investigate this process according to different subtypes of memory may help elucidate the validity and generalizability of this potential pathway.

Furthermore, studies have also noted the significant role of the precuneus in cognitive function. The precuneus is another major component of the FPN alongside with the DLPFC, as well as a key modulator of the default mode network (DMN) of the brain [76]. By contributing to two of the major brain networks, the precuneus is involved with a number of important functions including performance of integrated tasks, eye movement, imagery, and self-processing operations [76]. Studies including Utevsky and colleagues (2014) have demonstrated the significance of the precuneus in modulating the default-mode network (DMN), particularly by the optimization or enhancement of the DMN [77]. This optimization of the DMN activity was also found to be in correlation with enhanced resting-state cognition, which can also be interchangeable to attentiveness [77]. Considering these findings, rTMS treatment to the DLPFC may stimulate and optimize the activity of the precuneus within the FPN, resulting in increased connectivity strength between the precuneus and the DMN. The heightened attentiveness that results from this potential neural pathway may explain for the increased processing speed as summarized in the current review (Table 2). A detailed schematic diagram of the two potential neural pathways that underlie as part of the mechanisms of rTMS is also provided (Fig. 1).

Despite these potential mechanisms of TMS, however, it is noteworthy that contradictory findings have also been present. A portion of the previous research that used similar if not identical parameters to those that demonstrated significant cognitive enhancement via rTMS treatment, also demonstrated insignificant findings (Table 3). As many of these studies used both parameters as well as outcome variables that are similar to those described in Tables 1 and 2, this suggests that the cognitive enhancing effects of rTMS should not yet be considered as valid.

ETHICAL CONCERNS OF TMS IN COGNITIVE ENHANCEMENT

The current review demonstrates that the development of neuroscientific tools such as TMS may be an innovative and reliable method of intervention for cognitive enhancement. However, as the application of TMS to healthy individuals with normal cognitive function becomes more prevalent, certain ethical questions arise regarding the accessibility and unknown risks of TMS. For instance, TMS is still under the developmental stages of parameter

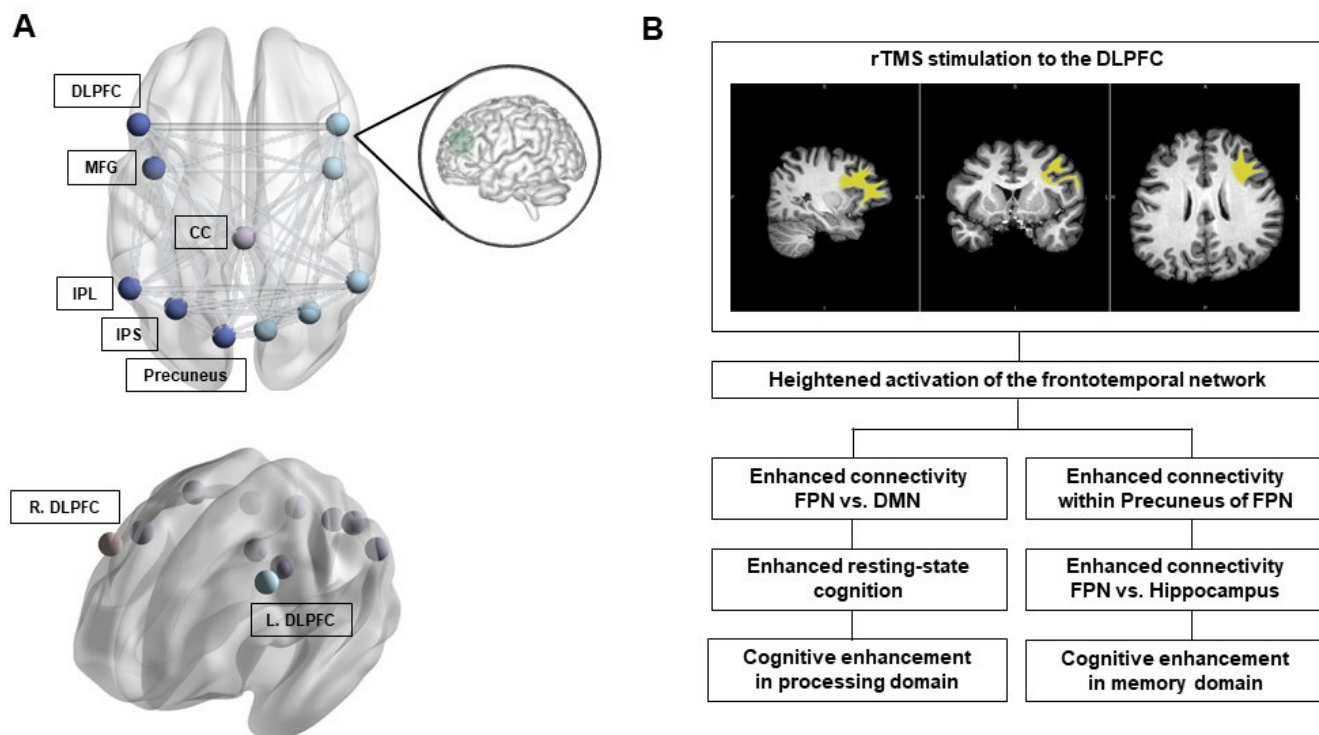


Fig. 1. Schematic diagram of the underlying mechanism of rTMS. (A) Three-dimensional images of the brain that highlight the frontoparietal network of the brain. The top image shows the axial view of the brain, alongside with the area of stimulation for the rTMS treatment summarized in the current review colored in light green. The bottom image shows the sagittal view of the brain. Each circle is a node that represents the region of the brain that is part of the frontoparietal network, and each grey line is an edge that represents the inter-regional connectivity between the nodes. (B) The two potential neural pathways that underlie rTMS treatment to the DLPFC. A T1-weighted image of the brain is shown in sagittal, coronal, and axial view to show the DLPFC as highlighted in yellow. R, right; L, left; DLPFC, dorsolateral prefrontal cortex; MFG, middle frontal gyrus; IPL, inferior parietal lobe; IPS, inferior parietal sulcus; CC, corpus callosum; rTMS, repetitive transcranial magnetic stimulation; FPN, frontoparietal network; DMN, default mode network.

optimization, and adverse effects such as the compromise of tissue within the area of stimulation have not yet been discussed [78]. Although many experiments and patient lesion studies have supported the safety and efficacy of TMS, concerns remain due to a lack of long-term longitudinal studies that investigate the effects of TMS on a tissue-based level. These absences warrant for further ethical discussions which aim to analyze the effects of TMS in cognitive enhancement of healthy individuals who are neurally intact.

First of all, the use of TMS as cognitive enhancers may destroy what is perceived as normal or considered natural in humans. The extent to which science and scientific technologies can intervene with human life, life expectancy, and morbidity have always been accompanied by ongoing discussion regarding ethics and morality [79-80]. One of the difficulties with the debate of the application of TMS in healthy individuals is the lack of consensus around the extent to which an enhancement may be considered acceptable or natural. Scientists who contribute to the development of newer technologies such as TMS need to consider the ongoing moral questions, such as whether cognitive enhancements imply a sense

of hierarchy or deportation from what is considered human nature.

Second, the use of cognitive enhancers that are not yet regulated may lead to discrimination among humans, as disparity in fairness between individuals can arise as a result of the accessibility to TMS. Moreover, if the cognitive enhancing effects of TMS is validated as permanent in the near future, discrimination including negative social backlash may arise, which will warrant for stricter regulations and standards within fields related to cognitive performance, such as test-taking environments [81]. In contrast, there may also be societal pressure to attain cognitive enhancement via neurostimulatory devices, whether this enforcement is a collective familial belief within a household, a provider's belief from an employer's perspective, or cultural belief. The difficult line between consensual and enforcement will then need to be considered, where the enhancement of one's cognitive function may soon be associated with desirability in one's personal or professional life. Considering this, whether one aims to have their cognitive function improved via TMS may not be a personal choice, but rather

Table 3. Studies that have not shown significant differences in cognitive function after rTMS treatment

Group	Reference	N	Location	Session per Week	Frequency (Hz)	Train Duration (s)	Trains per Session	Inter-train interval (s)	Pulses per session	MT (%)	Cognitive Domain
Dep	Speer et al. (2001)	18	L DLPFC	10/2	20	2	40	28	1600	100	Memory (Episodic, Visuospatial, Semantic)
Dep	Loo et al. (2001)	18	L DLPFC	10/2	10	5	30	25	-	110	Working memory Verbal fluency
Dep+ PTSD	Rosenberg et al. (2002)	12	L DLPFC	10/2	1	40	40	20	6000	90	Episodic Memory USC-REMT
Dep	Martis et al. (2003)	15	L PFC	15/3	10	5	20	30	-	110	Attentional control Verbal fluency
Dep	Januel et al. (2006)	27	R DLPFC	16/4	1	60	2	180	-	90	Working memory Attentional control
Dep	Fitzgerald et al. (2009)	27	L PFC	15/3	1	180	4	30	-	110	Executive functioning Memory (Visuospatial, Working)
Sch	Hoffman et al. (2005)	50	L TPC	18/2	1	960	1	-	2000	90	Verbal fluency Attentional control
Sch	Fitzgerald et al. (2005)	33	L TPC	10/2	1	900	1	-	-	90	Memory (Verbal, Working) Verbal fluency
OCD	Kang et al. (2009)	20	R DLPFC	10/2	1	1200	1	-	-	110	Memory (Visuospatial, Working) Verbal fluency
Stroke	Kim et al. (2010)	18	-	10/2	1	300	4	60	900	80	Attentional Control Executive functioning
Aph	Waldowski et al. (2012)	26	R IFG	15/3	1	1800	1	-	-	90	Verbal fluency

Dep, depression; PTSD, posttraumatic stress disorder; Sch, schizophrenia; OCD, obsessive compulsive disorder; Aph, aphasia; L, left; R, right; DLPFC, dorsolateral prefrontal cortex; PFC, prefrontal cortex; TPC, temporoparietal cortex; IFG, inferior frontal gyrus; USC-REMT, University of Southern California repeatable episodic memory test.

an obligation for the purpose of success or meeting the demands of others.

Finally, under the assumption that cognitive enhancement is possible, the matter of fairness may take a toll in the competitive society in which we live. If TMS can in fact provide irreversible cognitive enhancement to neurally intact individuals, the possibility of privatizing TMS as a neurostimulatory tool for societal gains arises, where TMS may be commercialized for economic gains. As demands for TMS increase, there may be a socioeconomic class gap between those who have access to TMS and those who do not, eventually leading to unjust labor standards. In addition, individuals with favorable traits in relation to cognition, such as higher attentiveness or processing skills, may be considered moot as anyone can potentially afford to attain such traits. Furthermore, the stratification between those who can and cannot use this scientific tool may be deepened, where this stratification may not be limited to between socioeconomic classes, but also across cultures and countries, resulting in a global disparity in distribution.

CONCLUSIONS

The current manuscript reviews with perspective the cognitive enhancement effects of TMS that has been demonstrated in recent research. The studies discussed in this review not only confirm the effects of TMS treatment in cognitive improvement, but also suggest that the effects of TMS may be specific to the method of stimulation. Overall, the studies have shown that the enhancing effects of rTMS are not task-specific or specific to the target group, but rather frequency and area-specific, as suggested in previous studies also [48]. Therefore, the use of TMS as treatment may be a valid direction in future research, as it may have universal enhancement effects across individuals regardless of clinical factors such as illnesses including but not limited to depression, schizophrenia, and cognitive impairment.

However, it is important to note that there have been several studies that dispute the cognitive enhancing effects of rTMS as mentioned above (Table 3). Over the years, a number of studies conducted in various target groups including healthy individuals [82], those with depression [51, 83-85], and schizophrenia [86], have demonstrated no significant change in cognitive performance. While most of these studies have used LF-rTMS unlike the studies that demonstrated significant cognitive enhancement via HF-rTMS, the fact that TMS may have no clinical effect in cognition under certain protocols should be noted.

In addition, the studies currently reviewed mostly investigated the short-term and immediate effects of TMS in the enhancement of cognition. While a few studies have undergone a 2-week and

1-month follow-up assessment, respectively, they have suggested that the effects of TMS may be short-term in cognitive domains regarding executive functioning while delayed or sustained in processing skills [48, 50]. To clarify these findings, the development and establishment of a universal protocol in the application of HF-rTMS for the purpose of cognitive enhancement is warranted, as some studies have suggested that a minimum of 4-week treatment may be necessary to see significant effects of TMS [39, 87]. Future studies that are more controlled in the application processes of rTMS are needed to specify the effects of rTMS with regards to cognitive impairment, including the optimal frequency, amount of pulses delivered, intertrain interval, and area of application. Furthermore, many of the TMS studies on cognitive enhancement lack a healthy comparison group as part of the study design. In order to ensure that the cognitive enhancing effects of those with psychiatric or neurological conditions are due to TMS, rather than simply an improvement of psychiatric symptoms, ongoing controlled studies with age- and sex-matched healthy controls are warranted.

It is also noteworthy that having a consistent method of assessment for cognitive function may support in increasing the reliability of the study findings, such as using a test battery that has been well supported over the years including the CANTAB. Through the review of recent TMS studies, it may demonstrate that there are very few number of studies that investigate the cognitive function of individuals as a primary outcome variable. These studies have primarily focused on utilizing neuropsychological tests as means to observe for any deterring of cognitive abilities, and therefore the tests may be less sensitive to detecting improvement.

In conclusion, TMS is a phenomenal technology that has endless potentials to human cognition and enhancement that is alternative to pharmaceutical research. To investigate the effects of TMS beyond the well-established domain of motor function improvement and more towards the cognitive enhancing effects, further clinical trials and optimized protocols are warranted. Future research including randomized controlled trials and clinical trials using various parameters of rTMS may contribute in the development of an optimized protocol for rTMS in the treatment of and enhancement of cognitive abilities, an innovative approach which may open up new directions in the perceptualization of human cognition.

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