

Research Paper



Effect of Low-intensity Transcranial Magnetic Stimulation on Response Inhibition of Adults With Attention-deficit/Hyperactivity Disorder

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ABSTRACT

Introduction: Response inhibition is an impaired cognitive function in attention-deficit/hyperactivity disorder (ADHD) individuals. This primary deficit during the cancelation of an intended movement is observed even in the minimal demanding cognitive tasks. Studies have shown that transcranial magnetic stimulation (TMS), especially on the dorsolateral prefrontal cortex (DLPFC), can improve response inhibition. Nevertheless, TMS has a low spatial resolution, and its effect may not be observed in a single-session intervention. Studies show that low-intensity TMS has higher spatial resolution. Therefore, in this study, we aimed to evaluate the effectiveness of this method for intervention of response inhibition in ADHD individuals.

Methods: In a double-blind paradigm, the performance of the adults with ADHD while executing a Stroop color and word test (SCWT) was measured during a sham or a real stimulation of the DLPFC. Subsequently, the response inhibitions of the participants were measured before and after the stimulation. The number of correct, wrong, and missed answers to 96 computerized trials and the response times of the answers were measured. In addition, changes in electrocortical activities during the rest phase before and after the stimulation were also evaluated.

Results: After checking for data normality, the paired t-test between behavioral data showed that low-intensity magnetic stimulation of the DLPFC can improve response inhibition (reduce errors) even in a single-session intervention of ADHD individuals. The answering times did not change significantly. The behavioral changes were associated with significant changes in the power of EEG in delta and beta frequency bands at the frontal areas.

Conclusion: The proposed stimulation protocol with low-intensity TMS had a fair effect on the response inhibition in adults with ADHD. Therefore, it could be suggested as a treatment protocol for response inhibition in ADHD individuals.

Keywords:

Attention-deficit/hyperactivity disorder (ADHD), Low-intensity transcranial magnetic stimulation, Stroop color and word test (SCWT), Response inhibition

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Highlights

- Low-intensity transcranial magnetic stimulation reasonably improves response inhibition in adults with attention-deficit/hyperactivity disorder (ADHD).
- Reduction in error rate may not be followed by significant changes in reaction time.
- Low-intensity transcranial magnetic stimulation could significantly change the brain oscillatory pattern toward a desired direction.
- Improving the spatial resolution of transcranial magnetic stimulation, even while decreasing the stimulation level, may enhance its effect.

Plain Language Summary

ADHD individuals have a primary deficit in the cancellation of intended movements. It can be observed while performing even a minimally demanding cognitive task. Studies showed that transcranial magnetic stimulation (TMS), especially on the dorsolateral prefrontal cortex (DLPFC), can improve response inhibition. Because low-intensity TMS has a higher spatial resolution, in this study, we aimed to evaluate the effectiveness of this method for intervention of response inhibition in ADHD individuals. In a double-blind paradigm, the performance of the adults with ADHD during an executive functioning task (color Stroop) was assessed while their DLPFCs were stimulated with a sham or a real low-intensity TMS. The results showed that low-intensity TMS improves response inhibition in adult ADHD and could significantly change the brain oscillatory pattern toward the desired direction.

1. Introduction

Executive functions include various cognitive utilities, such as planning, working memory, attention, and response inhibition. Among them, response inhibition helps an individual avoid pre-planned responses and delay a response while not interfering with other cognitive functions. This function plays an important role in social interactions. Failure in response inhibition causes an inability to sustain attention, be easily distracted, and control behavior. In addition, dysfunction of the response inhibition forces a person to respond to a stimulus before correctly understanding the desired stimulus or making mistakes in searching for a desired goal among the stimuli due to disturbing stimuli. Deficiency in response inhibition can be seen in disorders such as attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (Garavan et al., 1999; Gorfain & MacLeod, 2007; Harnischfeger & Bjorklund, 1993; Tamm et al., 2002).

ADHD is introduced as a neurodevelopmental disorder associated with environmental and genetic factors. ADHD is characterized by three important indicators: attention deficit, hyperactivity, and impulsivity. It was

previously believed that ADHD appears only in childhood and improves during adolescence and adulthood, but recent studies showed that ADHD can continue into adulthood and causes many problems, including deficits in executive functions and social relationships (Barbaresi et al., 2002; Cuffe et al., 2001; DuPaul et al., 1991; Neuman et al., 2005). One of the main problems in the cognitive functioning of ADHD individuals is correct response inhibition. Due to their impulsive behavior, ADHD individuals cannot inhibit a pre-planned (dominant) response and focus on the task. Studies show that ADHD people have a lower response inhibition compared to normal individuals while executing a Stroop color and word test (SCWT) (Barkley, 1997; Barkley, 2000; Fischer et al., 2005; King et al., 2007; Nigg, 2001; Song & Hakoda, 2011). In addition, a lack of proper functioning in response inhibition causes ADHD people to miss the necessary patience in their demands.

Since these cognitive deficits are linked to dysfunction of some brain areas, including the frontal lobe, striatum, and cerebellum, various pharmaceutical and non-pharmaceutical interventions have been introduced. Each method may improve the problem, but non-pharmaceutical treatments, including transcranial electrical and magnetic stimulations, have received more attention due

to the lack of side effects (Breitling et al., 2020; Cosmo et al., 2020). The noninvasive brain stimulation (NIBS) techniques have been effectively used in recent years, and their capability to improve cognitive functions in various mental disorders, including ADHD, has been presented (Acosta & Leon-Sarmiento, 2003; Acosta et al., 2002; Hallett, 2001). Several brain areas showed the potential of targeting NIBS in ADHD people, including stimulation of the dorsolateral prefrontal cortex (DLPFC) for improvement of attention functions and response inhibition (Blasi et al., 2006), the ventromedial prefrontal cortex (VMPFC) for improvement of emotional regulation, and the dorsal anterior cingulate cortex (DACC) for multiple attention and cognitive control.

Considering the mechanism of response inhibition and the functional role of the DLPFC, the target site of NIBS should reduce the number of errors in ADHD people (Barkley, 1997; Croarkin et al., 2011; Jiang et al., 2018; Ridding & Rothwell, 2007; Willcutt et al., 2005).

Studies have reported that electrical stimulation of the DLPFC can improve executive functions in ADHD people (Friebs et al., 2021), even in a single-session stimulation (Dubreuil-Vall et al., 2020). In addition, the effectiveness of repetitive transcranial magnetic stimulation (rTMS) on the DLPFC region has also been discussed (Zaman, 2015), and various parameters such as frequency, intensity, duration of stimulation, and the interval between stimulations have been investigated (Tang et al., 2018). Nonetheless, rTMS has a low spatial resolution between 10 to 30 mm, and the low-intensity magnetic stimulation method has been proposed to be more intensive and improve the spatial resolution to a range between 1 and 5 mm (Colella et al., 2019).

The low-intensity magnetic stimulation is one of the most influential and precise magnetic stimulation methods. Also, its desired effects for improving visual attention (Grosbras & Paus, 2002; Heinen et al., 2014) and treatment of posttraumatic stress disorder by stimulating the prefrontal areas have been indicated (Boggio et al., 2010). Moreover, it has been shown that effective stimulation of the visual cortex can improve the perception of poor visual stimuli that cannot be perceived unconsciously (Abrahamyan et al., 2015). Therefore, we hypothesized that focal stimulation of DLPFC using the micro-TMS approach could be an effective method to improve response inhibition in ADHD individuals. Hence, we aimed to investigate micro-TMS's effectiveness in enhancing response inhibition in ADHD patients while performing the SCWT in a single-session double-blind paradigm.

2. Materials and Methods

Participants and apparatus

Twenty-two sessions of recording were performed for 11 male adults with ADHD (age range: 18-36 years). All participants had a bachelor's or a higher university degree. The inclusion criteria were diagnostic and statistical manual of mental disorders fifth edition (DSM-5), tests and clinical interviews. This study was conducted in accordance with the Helsinki Declaration. In addition, all participants were asked to complete and sign the consent form before entering the study.

Stimuli

Several tests have been introduced to measure response inhibition in ADHD individuals. One of these tests is the SCWT, which measures various parameters by considering the type of response and the duration of the reactions in responding to a group of congruent–incongruent stimuli. This test was first designed and introduced by Ridley Stroop in 1935 to measure the level of attention. The computer-based version of the SCWT test used in the present study consisted of two categories: congruent (matching the word's color with the word's meaning) and incongruent (mismatching of the word's color with the word's meaning) events. The accuracy and validity of the Persian test have been reported to be 80% and 91%, respectively (Khodadadi et al., 2014). The duration of SCWT stimuli was 2000 ms with an interval of 800 ms.

The micro-TMS stimulation was performed using the Beta 1 device by the Parseh-Sanat-Ahouri Company. The stimulation was performed using an intensity of 140 micro-tesla at a frequency of 17 Hz. The sham stimulation was also performed only by putting the related electrode on the target scalp position, and no stimulation was performed.

The participants' brain activities were also recorded using the 19 electrodes placed on the scalp based on the international 10-20 standard arrangement. EEG data were recorded with a sampling rate of 500 Hz using an amplifier made by the LIV technology company, and a reference electrode was placed on the right ear.

Experimental procedure

This study used a control, sham, and real stimulation paradigm. All participants were asked to perform a computer-based SCWT three times. The participants' brain activities were recorded before the experiment started, as

well as before and after the stimulations. The third examiner randomly selected the sequence of the sham or the real stimulation, and participants had 30 minutes of rest after each run of the task. The SCWT test was presented on a 22-inch desktop monitor placed 1 m away from the subject, and the participants answered the test by pressing the arrow key on a QWERTY keyboard.

The participants were asked to sit on a comfort chair in front of a 22-inch monitor, and an EEG cap was placed on the volunteer's head. After calibrating the EEG recording device, EEG was recorded from each candidate in a resting state during eyes open and closed conditions for two minutes. Then, the participants were asked to perform the SCWT and had a 30-minute rest. Subsequently, the EEG recordings were performed again, and the participants were asked to repeat the test while a sham/real micro-TMS was applied to the right DLPFC.

To evaluate the results of this study, criteria such as number of errors, number of correct answers, and reaction times for answering were measured. Consequently, participants' performance at the three phases of the conducted SCWT for 20 minutes was evaluated. The first stage was done before stimulation; the second and third stages were done after sham or real stimulation using micro-TMS.

A standard preprocessing pipeline was performed on the EEG data, including bandpass filtering 1-40 Hz, running independent component analysis, removing a noisy component, visual inspection of the cleaned data, and re-referencing the data to the average of all channels. Subsequently, using the fast Fourier transform analysis, an absolute power of the cleaned EEG data was calculated in the conventional frequency bands. Then, the ratio between each band's powers and the total band's amount was calculated to point to the relative power of each frequency band.

Statistical analysis

To compare the effect of stimulation on response inhibition, the number of errors, correct answers, missed answers, and reaction times were computed in three phases of the experiments. In addition, comparisons were made in both congruent and incongruent words. After the test of normality using the Kolmogorov-Smirnov test, a paired t-test was done to compare the behavioral and relative powers of the two desired conditions. Lastly, the results of EEG data analysis were corrected for multiple comparison effects using the false discovery rate method.

3. Results

The results of this study were categorized into behavioral and neurophysiological findings. In the category of behavioral data analysis of the congruent color words, comparisons between real stimulation and control (no stimulation) and sham stimulation using paired-wise t-test showed that error responses were significantly lower in the real condition as compared to the control condition ($P=0.04$, $t=-2.32$) and slightly improved as compared to sham stimulation ($P=0.13$, $t=-1.61$), with a faster reaction time ($P=0.03$, $t=-2.43$) compared to the control condition, no significant difference with sham stimulation.

While for the incongruent color word, comparisons between real stimulation and control (no stimulation or sham stimulation) showed that error responses were only significantly lower in the sham condition ($P=0.01$, $t=-2.79$ as compared to the control condition), with a faster reaction time ($P=0.02$, $t=-2.64$). Interestingly, no significant differences were observed for other parameters, including missing, wrong, and correct answers. However, the results of real stimulation had a similar trend, but no significant result was observed (error responses in real stimulation compared to the control condition, $P=0.07$, $t=-2.02$).

Regarding the neurophysiology data, statistical analysis of EEG data showed that the spectral power of delta band frequencies at the frontal regions was significantly changed after real stimulation compared to the sham stimulation (Table 1). In addition, the power of brain waves at the beta band frequencies and its sub-bands (beta1 and beta) were also significantly changed in the prefrontal and parietal regions (Table 1).

Changes in spectral power of delta band activities in resting-state EEG data during eyes closed condition showed significant differences between real and sham stimulation at the F8 channel ($P=0.03$, $t=-2.37$).

Significant changes in the resting state EEG of the eyes open condition (Figure 1) are observed in delta band frequencies at the FP1 channel. The real micro-TMS stimulation caused a higher increase in delta band power compared to the sham stimulation ($P=0.02$, $t=2.53$). Moreover, the real stimulation caused a higher decrease in the power of beta band frequencies compared to the sham stimulation (at FP1: $P=0.003$, $t=-3.75$; at P4: $P=0.01$, $t=-3.02$). A similar trend was observed for the sub-bands of beta frequencies only at the prefrontal regions (at FP1 for Beta 1: $P=0.02$, $t=-2.62$; for beta 2: $P=0.02$, $t=-2.74$). Moreover, a significant difference was

Table 1. Comparisons between changes in resting state EEG power spectrum after real or sham stimulations

Condition	Frequency Band	Channel	t	P
Eyes closed	Delta	F8	-2.37 (real<sham)	0.03
Eyes open	Delta	FP1	2.53 (real>sham)	0.02
	Beta	FP1	-3.75	0.00
	Beta	P4	-3.02	0.01
	Beta 1	FP1	-2.62	0.02
	Beta 2	FP1	-2.74	0.02
	Gamma	FP1	-2.77	0.01

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also observed at the lower gamma band frequencies of prefrontal EEG activities ($P=0.01$, $t=-2.77$), t values are presented to compare the effect of real and sham stimulations. In addition, the association between changes in the power of brain activities and behavioral results is presented in [Figure 2](#). The results showed that increased relative power of delta band activities at the prefrontal

regions could increase the error responses to congruent color words. An increase in the relative power of the beta band activities at the prefrontal regions could increase the error responses to incongruent color words.

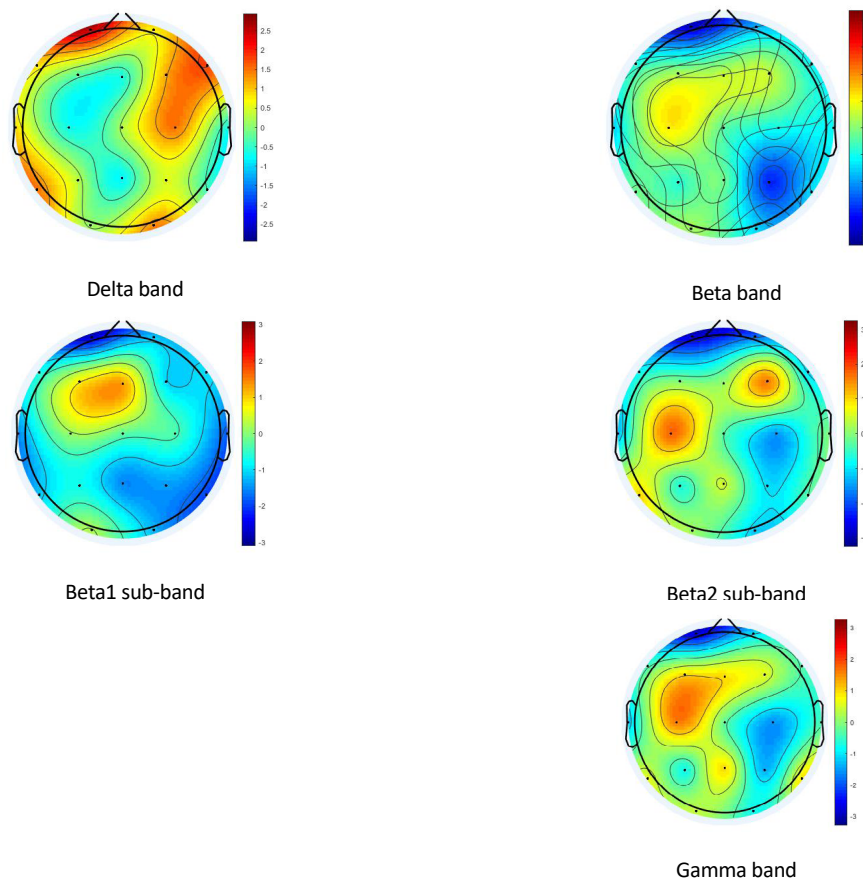


Figure 1. Topographical maps of changes in resting state EEG power spectrum (eyes open condition)

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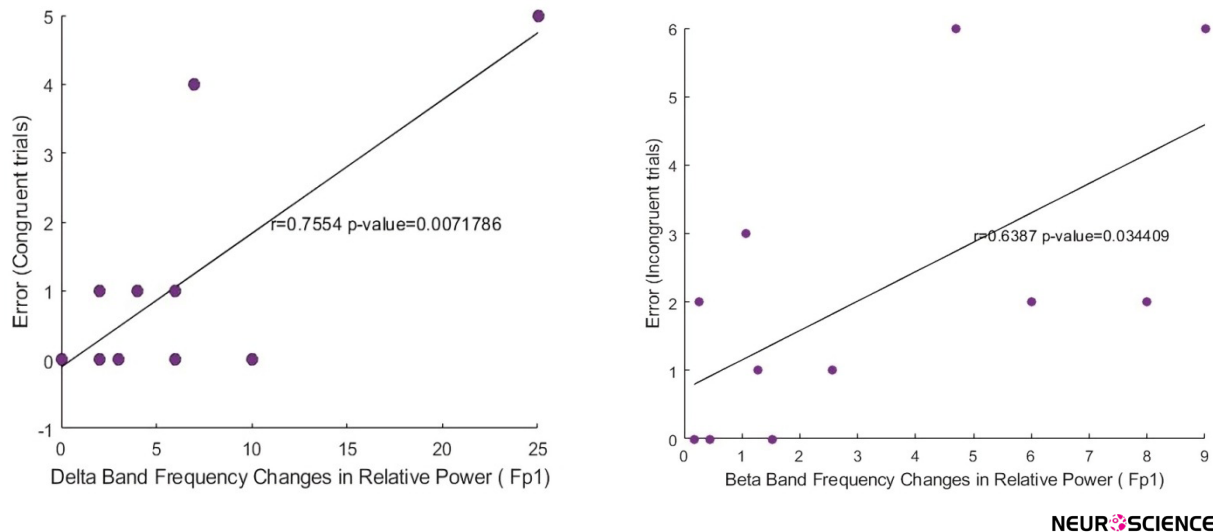


Figure 2. Association between changes of relative power of delta and beta bands at the prefrontal region and error responses to congruent and incongruent color words

4. Discussion

Executive functions are an essential part of the brain's cognitive performance. One of the main parameters of executive functioning is response inhibition. Malfunctions in response inhibition could cause errors in decision-making and planning. In this regard, studies have reported that ADHD individuals suffer from proper function of response inhibition. To improve the response inhibition in ADHD individuals, several studies have been conducted using pharmaceutical and other stimulation techniques.

It has been pointed out that stimulation of frontal areas, such as the DLPFC in ADHD individuals, can compensate for this deficit (Chen et al., 2021; Dubreuil-Vall et al., 2019). Among the NIBS paradigms, electrical and magnetic stimulations showed proper capacity for this purpose. Nevertheless, these methods require multiple intervention sessions to show their effectiveness on individuals with ADHD. It is supposed that improving TMS spatial resolution could enhance the effect of TMS while decreasing the number of intervention sessions. Since the micro-TMS has a higher spatial resolution than the TMS, we aimed to investigate the effectiveness of the single-session low-intensity magnetic stimulation method on the response inhibition of ADHD individuals. Therefore, the participants' performances in SCWT before and after a real or sham stimulation were evaluated. Previous studies show that impairment in inhibition function is presented in the number of error responses to the SCWT.

Consequently, DLPFC was selected as the target region for stimulation with micro-TMS, as described in the method section. The performance of ADHD subjects before and after the stimulation with micro-TMS was compared to quantify the effect of this method.

The results of the behavioral data show that this stimulation protocol can improve response inhibition and decrease the error responses even after a single stimulation session. In addition, an analysis of the EEG data showed that significant changes in the relative power of the delta band at the frontal area were observed after the stimulation. The importance of brain activities in delta and theta frequencies at the frontal regions for proper functioning in response inhibition has been reported in previous studies as well (Ardolino et al., 2005; Clarke et al., 2002; Jacobson et al., 2012; Keeser et al., 2011). Furthermore, significant results of sham stimulation during incongruent trials would need to be further studied.

Previous studies have reported similar findings regarding the results observed in the beta frequency bands. For instance, studies have reported that beta and alpha band activity changes can affect subjects' performance in response inhibition (Liao et al., 2021). Moreover, it has been shown that magnetic stimulation on DLPFC can improve response inhibition (Zrenner et al., 2020). Therefore, changes in the relative power of beta frequency activities after the stimulation with micro-TMS could indicate the proposed paradigm's proper functioning. In addition, a significant correlation observed between error responses and the relative power of delta and beta

bands at the prefrontal region could also be considered a proper marker for protocol effectiveness.

In summary, the results of the present study show that the introduced stimulation protocol can improve response inhibition in ADHD people by changing the brain activities in the frontal regions. In addition, it seems that the introduced single-session stimulation protocol can improve response inhibition and may decrease the intervention sessions. Nevertheless, more investigation on more participants and examination of the method on other disorders considering co-factors such as gender and comorbidities are proposed for future studies.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. The participants were informed of the purpose of the research and its implementation stages. They were also assured about the confidentiality of their information and were free to leave the study whenever they wished, and if desired, the research results would be available to them. A written consent has been obtained from the subjects. Principles of the Helsinki Convention was also observed.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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