Title: Effect of Low-Intensity Transcranial Magnetic Stimulation on Response Inhibition of Adult ADHD

Running Title: Improving Response Inhibition by Low-Intensity TMS

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Abstract

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

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

Results: After checking for data normality, paired t-tests 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. Having said that, the answering times did not change significantly. The behavioral changes were associated with significant changes in 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 adult ADHDs. Therefore, it potentially could be suggested as a treatment protocol on the response inhibition in ADHD individuals.

Keywords: Attention deficit hyper activity disorder, Low-intensity TMS, Stroop color and word test, Response inhibition

Highlights

- Low-intensity TMS has a fair effect on improving response inhibition in adult ADHDs
- Reduce of error rate may not followed by significant changes in reaction time
- Low-intensity TMS could significantly change the brain oscillatory pattern toward a desired direction.
- Improving spatial resolution of TMS even while decreasing the stimulation level may enhance its effect

Plain Language Summary

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

Introduction

Executive functions include a wide range of cognitive utilities such as planning, working memory, attention and response inhibition. Among them, response inhibition helps an individual to 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 the response inhibition causes inability to sustain attention, and easily be distracted and not being able to control a behavior. In addition, dysfunction of the response inhibition is caused a person to respond to stimulus before having a correct understanding of the desired stimulus or making mistakes in searching for a desired goal among the stimuli due to the presence of disturbing stimuli. Deficiency in response inhibition can be seen in disorders such as ADHD and obsessive-compulsive disorder (Garavan et al., 1999; Gorfein & MacLeod, 2007; Harnishfeger & Bjorklund, 1993; Tamm et al., 2002).

ADHD is introduced as a neurodevelopmental disorder linked to environmental and genetic factors. ADHD is characterized by three important indicators of 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 this itself 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 cognitive functioning of ADHD individuals is the correct response inhibition. Due to their impulsive behavior, ADHD individuals are unable to inhibit a pre-planned (dominant) response and focus on the task; and studies reported that ADHD had a lower response inhibition compared to normal individuals while executing a stroop color and word test (Barkley, 1997, 2000; Fischer et al., 2005; King et al., 2007; Nigg, 2000, 2001; Song &

Hakoda, 2011). In addition, lack of proper functioning in response inhibition causes ADHDs to not have the necessary patience in their demands.

Since these cognitive deficits are linked to dysfunctioning of some brain areas including frontal lobe, striatum, and cerebellum; various pharmaceutical and non-pharmaceutical interventions have been introduced. Each of the methods has been able to lead to some improvement, 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 non-invasive brain stimulation (NIBS) techniques have been effectively used in recent years, and their potentials for improvement of cognitive functions in various mental disorders including the ADHD have been presented (Acosta & Leon-Sarmiento, 2003; Acosta et al., 2002; Hallett, 2001; Leon-Sarmiento, 2002). Several brain areas showed the potential to be used as the target of NIBS in ADHDs 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 functional role of the DLPFC, it has been target site of NIBS to reduce number of errors in ADHDs (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 the executive functions in ADHDs (Friehs et al., 2021), even in a single-session stimulation (Dubreuil-Vall et al., 2020). In addition, 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 01 to 30 mm and low-intensity magnetic stimulation method has been proposed to be more focused and improve the spatial resolution to a range between 0- 5mm (Colella et al., 2019) .

The low-intensity magnetic stimulation is one of the effective, and precise magnetic stimulation methods, and its desired effects for improving visual attention (Grosbras & Paus, 2002; Heinen et al., 2014) and treatment of post-traumatic stress disorder by stimulation of 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 ADHDs. Hence, we aimed to investigate effectiveness of micro-TMS for improvement of response inhibition in ADHDs while performing the SCWT in a single-session double-blind paradigm.

MATERIALS AND METHODS

Participants and Apparatus

Twenty two sessions of recording was performed from eleven adults ADHDs (11 male, age: 18-36 years old). All participants had a bachelor or a higher university degree. The criteria for entering this study was DSM-5 test and clinical interviews. This study was conducted in accordance with the Helsinki protocol. In addition, all the participants were asked to complete and sign the consent form before entering in the study.

Stimuli

In order to measure the response inhibition in ADHD individuals, several tests have been introduced. 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 the group of congruent – incongruent stimuli. This test was first designed and introduced in 0395 by Ridley Stroop to measure the level of attention. The computer based version of the SCWT test used in present study, consisted of two categories of congruent (matching the color of the word with the meaning of the word) and incongruent (mismatching of the color of the word with the meaning of the word) events. The accuracy and validity of the Persian test has been reported to be 30-01 percent (Khodadadi et al., 2014). The duration of SCWT stimuli was 0111 milliseconds with an interval of 011 milliseconds.

The micro-TMS stimulation was performed using the Beta1 device made by the Parseh-Sanat-Ahouraian Company (https://www.mytam.ir). The stimulation was performed using intensity of 010 micro-tesla at the 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.

Brain activities of the participants 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 amplifier made by the LIV technology company, and reference electrode was placed on the right ear.

Experimental Procedure

This study was performed based on a control, sham, and real stimulation paradigm. All the participants were asked to perform a computer based Stroop color word test for three times. The brain activities of the participants were recorded prior to start of experiment, as well as before and after of the stimulations. Sequence of the sham or the real stimulation was randomly selected by third examiner and participants had a 30 minutes of rest after each run of the task. The SCWT test was presented on 22 inch a desktop monitor placed 1m away of the subject and participants answered the test by pressing the arrow key on a QWERY keyboard.

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

In order 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, participant's performance at the three phases of the conducted SCWT for 20 minutes were evaluated. Just to remind, the first stage was done before any stimulation, the second and third stage was after sham or real stimulation using micro-TMS.

A standard preprocessing pipeline was performed on the EEG data including band pass filtering 1-40 Hz, running independent component analysis and removing 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, absolute power of the cleaned EEG data was calculated in the conventional frequency bands. Then, ratio between powers of each band to the amount of total band were calculated to point the relative power of each frequency band.

Statistical analysis

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

Results

The results of this study were categorized to 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 error responses were significantly lower in real condition as compared to control condition (p value = 0.04, t value = -2.32) and slightly improved as compared to sham stimulation (p value = 0.13, t value = -1.61), with a faster reaction time (p-value = 0.03, t value = -0.13 as compare to control condition, no significant difference with sham stimulation.

While for the incongruent color-word, comparisons between real stimulation and control (no stimulation), sham stimulation showed error responses were only significantly lower in sham condition (p value = 0.01, t value = -0..3 as compared to control condition), with a faster reaction time (p-value = 0.02, t value = -0..1). Interestingly, no significant result was observed for other parameters including missing answers, wrong answers, and correct answers. However, results of real stimulation had a similar trend but no significant result was observed (error responses in real stimulation compare to control condition, p value = 0.07, t value = -2.02).

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

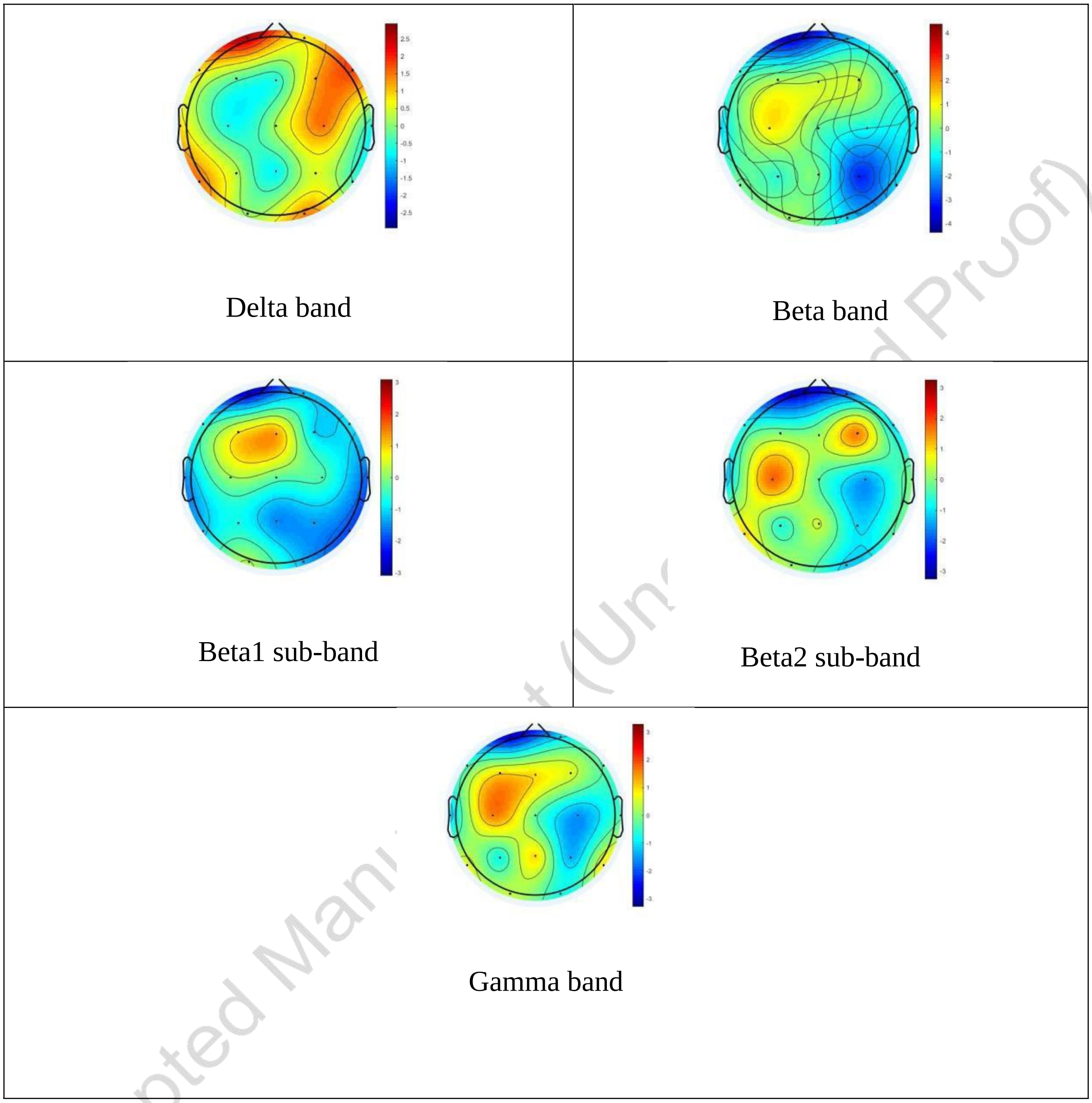
Table1. Comparisons between changes in resting state EEG power spectrum after real or sham stimulations

Condition	Frequency Band	Channel	T-value	P-value
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
		P4	-3.02	0.01
	Beta1	FP1	-2.62	0.02
	Beta2	FP1	-2.74	0.02
	Gamma	FP1	-2.77	0.01

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 value = 0.03 and t value = -0.9.).

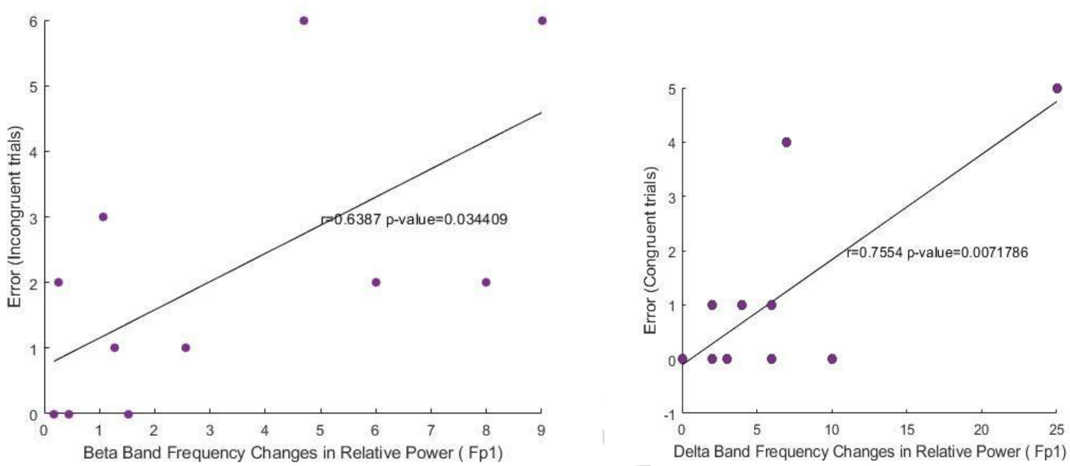
While significant changes in resting state EEG of eyes open condition were observed in delta band frequencies at the FP1 channel. The real micro-TMS stimulation caused a higher increase in delta band power as compare to the sham stimulation (p value = 0.02, t value = 2.53). Moreover, the real stimulation caused a higher decrease in power of beta band frequencies as compare to the sham stimulation (at FP1: p value = 0.003, t value = -3.75; at P4: p value = 0.01, t value = -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 value = 0.02, t value = -2.62; for beta2: p value = 0.02, t value = -2.74). Moreover, a significant difference was also observed at the lower gamma band frequencies of prefrontal EEG activities (p value = 0.01, t value = -2.77)

Figure1: Topographical maps of changes in resting state EEG power spectrum (Eye- open condition). T values of comparison between effect of real and sham stimulations are presented.



In addition, association between changes in power of brain activities and behavioral results are presented in Figure2. The results showed that increase of relative power of delta band activities at the prefrontal regions could increase the error responses to congruent color words. While, increase of relative power of the beta band activities at the prefrontal regions could increase the error responses to incongruent color words.

Figure2. Association between changes of relative power of delta and beta bands at the prefrontal region and error responses to congruent and incongruent color words



Discussion

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

It has been pointed that stimulation of frontal areas such as dorsolateral prefrontal cortex in the ADHD individuals can compensate for this deficit (Chen et al., 2021; Dubreuil-Vall et al., 2019). Among the non-invasive brain stimulation paradigms, electrical and magnetic stimulations showed a proper potential for this purpose. Nevertheless, these methods require multiple intervention sessions to shown their effectiveness on individuals with ADHD. It is supposed improvement of spatial resolution of TMS could potentially enhance the effect of TMS while decreasing number of intervention sessions. Since the micro-TMS has higher spatial resolution as compare to the TMS, in this study we aimed to investigate the effectiveness of single-session low-intensity magnetic stimulation method on the response inhibition of ADHD individuals. Therefore, performances of the participants in SCWT before and after a real, or sham stimulation were evaluated. Previous studies showed 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 and performance of ADHD subjects before and after the stimulation with micro-TMS were compared to quantify the effect of this method.

The results of the behavioral data showed that this stimulation protocol has been able to improve the response inhibition and decrease the error responses even after a single stimulation session. In addition, analysis of the EEG data also showed that significant changes in relative power of delta band at the frontal area is 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.

Regarding the results observed in the beta frequency bands, similar findings have been reported in previous studies. For instance, studies have reported that changes in beta and alpha bands activities can affect the performance of subjects in response inhibition (Liao et al., 2021). Moreover, it has been shown that magnetic stimulation on DLPFC can improve the response inhibition (Zrenner et al., 2020). Therefore, changes in relative power of beta frequency activities after the stimulation with micro-TMS could be an indicator of proper functioning of the proposed paradigm. In addition, significant correlation that was observed between error responses and relative power of delta and beta bands at the prefrontal region could be considered as a proper marker for effectiveness of protocol as well.

In summary, the results of present study showed that the introduced stimulation protocol had the ability to improve the response inhibition in ADHDs by changing the brain activities at the frontal regions. In addition, it seems that the introduced single-session stimulation protocol has a potential to improve the response inhibition and may decrease the intervention sessions. Nevertheless, more investigation on higher number of participants, and examination of the method on other disorders with consideration on co factors such as gender and comorbidities is proposed for future studies.

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