Archives of Advances
in Biosciences

Original Article:
Anodal Effects of Transcranial Electrical Stimulation of Right Dorsolateral Prefrontal Cortex on Working Memory of Patients with Multiple Sclerosis

Hamid Alipour[1], Mohammad Nasehi[2*], Mehdi Tehrani-Doost[1], Mohammad Hossein Harirchian[3], Mohammad Reza Zarrindast[1]

1. Department of Cognitive Neuroscience, Institute for Cognitive Science Studies, Tehran, Iran.
2. Cognitive and Neuroscience Research Center (CNRC), Tehran Medical Sciences, Islamic Azad University, Tehran, Iran
3. Department of Neurology, School of Medicine Iranian Center of Neurological Research, Tehran University of Medical Sciences, Tehran, Iran.

Use your device to scan and read the article online

Cite this article as: Alipour H, Nasehi M, Tehrani-Doost M, Harirchian MH, Zarrindast MR. Anodal Effects of Transcranial Electrical Stimulation of Right Dorsolateral Prefrontal Cortex on Working Memory of Patients with Multiple Sclerosis. Archives of Advances in Biosciences. 2022; 13:E37052.

https://doi.org/10.22037/aab.v13i.37052

Article info:
Received: 11 Dec 2021
Accepted: 11 Jan 2022
Published: 05 Mar 2022

*** Corresponding author:**
Mohammad Nasehi
Address: Cognitive and Neuroscience Research Center (CNRC), Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.
E-mail: nasehi@icss.ac.ir

Abstract

Introduction: Multiple Sclerosis (MS) is a chronic, autoimmune and progressive neurological disease that causes a wide range of cognitive deficits in patients by destroying the Central Nervous System (CNS). This study aims to examine the effect of Transcranial Direct Current Stimulation (tDCS) on working memory of patients with MS.

Materials and Methods: For this purpose, a quasi-experimental pre-t-est, post-test design with the control group was considered. In total, 32 patients with relapsing-remitting MS were selected using the convenience sampling method and randomly divided into experimental and control groups. The intervention consisted of 10 sessions of cranial electrical stimulation, during which the participants were divided into two groups receiving real and sham stimulation. N-Back test was employed to evaluate working memory.

Results: The data were analyzed using the independent t-test. The results revealed that working memory was improved in the experimental group compared to the control group ($P<0.05$).

Conclusion: It could be concluded that anodal tDCS over the right dorsolateral prefrontal cortex (R-DLPFC) appears to be a promising therapeutic tool for cognitive dysfunction among patients with MS.

Keywords: Multiple Sclerosis (MS); Transcranial Direct Current Stimulation (tDCS); Working memory

1.Introduction

Multiple sclerosis (MS) is a chronic and progressive neurological disease that leads to physiological and dysfunctional structural changes in the white matter of the brain and spinal cord when the immune system attacks the CNS [1]. This disease has affected 2-2.5 million people worldwide. Approximately 30 out of every 100,000 individuals are diagnosed with MS, which is more prevalent among young people, especially women [2].

In the past, MS was considered a demyelinating disease of the CNS and white matter. However, cortical and deep gray matter demyelination has been recently recog-

nized that may surpass white matter demyelination [3]. One study examined white matter atrophy using imaging techniques and reported some MS symptoms such as epilepsy and depression. Memory, attention and processing speed are among the abilities controlled by the gray matter and these functions are impaired in 40-65% of the patients with MS [4]. Cognitive disorders are among the problems that decrease daily function and quality of life among patients with MS. Approximately 40-70% of the patients with MS experience cognitive impairment [5].

Patients with MS perform attention-demanding tasks more slowly, are more inaccurate and have higher omission errors. Executive functions including conceptual and abstract thinking, ability to plan and organize and verbal fluency are impaired in MS patients. Impaired visual-perceptual function is another prevalent deficit among these patients. This function is not limited to recognizing visual stimuli, but these individuals should be able to accurately determine their characteristics [6]. D'Esposito et al found deficits in the executive control system of MS patients while performing working memory tasks. Slow thinking and processing speed are among the prominent MS symptoms [7].

Some treatment and rehabilitation methods have been recently presented to slow MS progression and reduce its deterioration, one of which is transcranial Direct Current Stimulation (tDCS). tDCS is a non-invasive, painless and safe brain stimulation technique that can modulate cortical excitability. tDCS is used as a treatment for psychiatric and neurological disorders [8]. Human and animal studies have demonstrated tDCS could modulate cortical excitability so that anodal and cathodal stimulation can increase and decrease excitability, respectively. After attaching anodes and cathodes to the scalp in tDCS, the applied current enters the brain from the anode and exits the cathode through the brain tissue [9]. Given that N-methyl-D-aspartate (NMDA) receptor plays an underlying Role in The Neurophysiological Function of Dorsolateral Prefrontal Cortex (DLPFC) in Spatial Working Memory (SWM) and tDCS can provide an NMDA-mediated cortical excitability through tDCS over DLPFC, SWM could be improved [10-12], Hulst et al. examined working memory performance in MS patients. The Right Dorsolateral Prefrontal Cortex (R-DLPFC) was subjected to high-frequency magnetic stimulation, and the brain activity and connectivity in that cortex were simultaneously assessed by Functional Magnetic Resonance Imaging (FMRI). The results showed N-back task accuracy was improved after magnetic stimulation of the mentioned cortex. Moreover, FMRI findings indicated the increased activity associated with R-DLPFC task before stimulation disappeared in MS patients compared to the control group after applying magnetic stimulation. Task-related functional connectivity between the R-DLPFC, right caudate nucleus and bilateral cingulate cortex increased after stimulation [13]. Mattioli et al. conducted a study on patients with MS and found that anodal stimulation of the left DLPFC for 20 min at 2 mA along with performing cognitive training could improve patients' performance in attention-demanding tasks and processing speed compared to the sham stimulation group [14].

Mori et al. examined pain among MS patients and found a significant reduction in pain among the group receiving anodal stimulation over the primary motor cortex (M1) compared to the sham group. Furthermore, no change was observed in patients' depression and anxiety [15]. Chalah et al. investigated MS patients' mood and attention and found anodal stimulation of DLPFC (F3) improved both components [16]. Therefore, the present study aims to evaluate the effect of tDCS of the right DLPFC on working memory among patients with MS.

2. Materials and Methods

This clinical trial was of practical type. The statistical population included 32 patients with relapsing-remitting MS aged 20-45 years old. The participants were selected by a neurologist using the convenience sampling method from those referring to the neurology clinic of Imam Khomeini Hospital, Tehran, based on the Expanded Disability Status Scale (EDSS) of 0-6.5. Inclusion criteria were having MS at least for 5 years, lack of comorbid neurological and psychological disorders and lack of participation in research projects in the past 2 months. Exclusion criteria were the presence of metal implants in the head and neck, having a cardiac pacemaker and a history of seizures, epilepsy and brain tumors. All the participants used drug therapy. The eligible individuals were randomly divided into experimental and control groups. The informed consent was obtained from all the participants. Moreover, they were asked to complete the demographic form and Expanded Disability Status Scale (EDSS). The ethics code was obtained from Ethics Committee of Iran University of Medical Sciences with reference no. IR.IUMS.REC1398.1146. All the participants performed the N-back test. Then, they were divided into two equal groups of active tDCS and sham tDCS (N=16 per group). In the sham tDCS group, the electrodes were placed on the scalp, but the electric current was cut off after a short time (30 sec) without informing the participants. Electrodes with the size of 5*5 were used for stimulation. The sponge pads of electrodes

Archives of Advances
in Biosciences

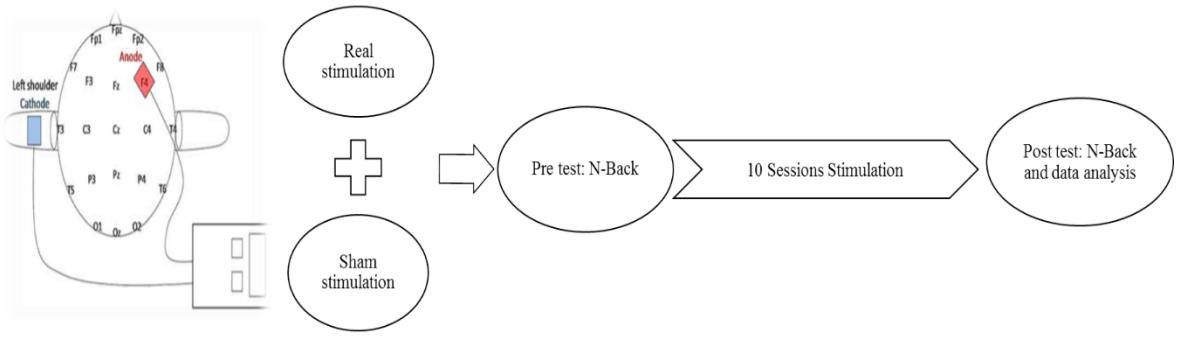

Figure 1. A schematic of the study

were placed in normal saline (10 g of NaCl dissolved in 1000 cc of water) to facilitate current conduction and reduce damage caused by the passage of current. Electrical stimulation protocol was performed at the current intensity of 2 mA and ramp-up period of 20 sec for 20 min in 10 consecutive sessions (5 sessions per week). Finally, the anode and cathode were placed on the right DLPFC and left shoulder, respectively.

Expanded disability status scale (EDSS)

This scale measures the degree of disability of MS patients and examines the functional status of eight systems, including pyramidal, cerebellar, brainstem, sensory, bowel/bladder, visual and cerebral. Finally, the total score ranges from 0 (normal neurological status) to 10 (death due to MS). This scale is implemented by a neurologist and classified into three categories based on Jones' criteria: mild (0-3), moderate (3.5-6.5) and severe (7 and higher) [17].

N-back test

N-back is a computer-based test that was first introduced by Kirchner to assess working memory [18]. In this study, the SWM paradigm was used. SWM is a fundamental executive function, characterized by the short-term maintenance and manipulation of spatial information for organizing more goal-directed behaviors [19]. Visuospatial working memory involves a network of different brain regions. One fMRI study on SWM network demonstrated DLPFC performed higher-level executive processing such as updating information and suppressing distraction [20].

This test includes two visual and auditory aspects. The scores of memory and reaction time in each sensory aspect are calculated separately [21]. In this test, the participant should respond to a set of stimuli based on specific instructions; for example, the participant should respond to the presented stimulus if it is similar to one or more previous stimuli. In this study, N was determined to be 2 (2-back) and memorizing the spatial position of the stimulus was considered. The stimuli were presented visuo-spatially. Validity coefficients ranged from 0.54 to 0.84, indicating high validity of this test. The validity of this test is highly acceptable as a measure of working memory [22].

Statistical analysis

The normal distribution of the data and independence of errors were determined by Durbin-Watson statistic. The data were analyzed using the independent t-test. The significance level was assumed at $P<0.05$. The data were analyzed by SPSS v. 22 software.

3. Results

In this study, 32 patients with relapsing-remitting MS participated, 22 of whom were female and 10 were male. As presented in Table 1, there was no significant difference in age and gender between the experimental and control groups ($P>0.05$), indicating the two groups were matched in terms of these variables. However, a statistically significant difference was observed in EDSS between the two groups ($P<0.05$).

The independence of errors was calculated to be 2.01 using Durbin-Watson statistic. As a general rule, observations are independent if Durbin-Watson statistic is between 1.5 and 2.5. Examining the assumption of error term normality by plotting the residual histogram indicated the normal distribution of the data.

Table 2 presents the effects of anodal tDCS of the R-DLPFC on working memory performance in the N-back test. According to the significance level ($P\leq0.05$) and acceptable level of t-statistic, it can be concluded that there was a significant difference between pre-test and post-test in the experimental group in terms of working memory.

Table 1. Comparing demographic characteristics in experimental and control groups

Variable	Experimental Group			Control Group				
	Mean±SD	Minimum	Maximum	Mean	SD	Minimum	Maximum	P
Age	35.750±3.827	29	42	34.562±4.647		25	41	0.902
EDSS	0.7500±0.683	0	2	0.9375±0.771		0	2	0.472
Variable	Group	Frequency	Percentage	Frequency		Percentage		P
Gender	Female	11(68.8)		11(68.8)				1.000
	Male	5(31.2)		5(31.2)				

Table 2. Results of correlated t-test comparing pre-test and post-test in the experimental group

Experimental Group	Mean±SD	Standard Error of the Mean (SEM)	t	Degree of Freedom (df)	P
Working memory	1.562±5.352	1.338	11.677	15	0.05

Table 3. Results of independent t-test comparing working memory in experimental and control groups

Experimental group	F	t	Degree of Freedom (df)	p-value	Mean Difference	Difference of the Standard Error
Working memory in the pre-test	1.168	1.260	30	0.217	4.000	3.174
Working memory in the post-test	0.016	5.547	30	0.05	16.062	3.174

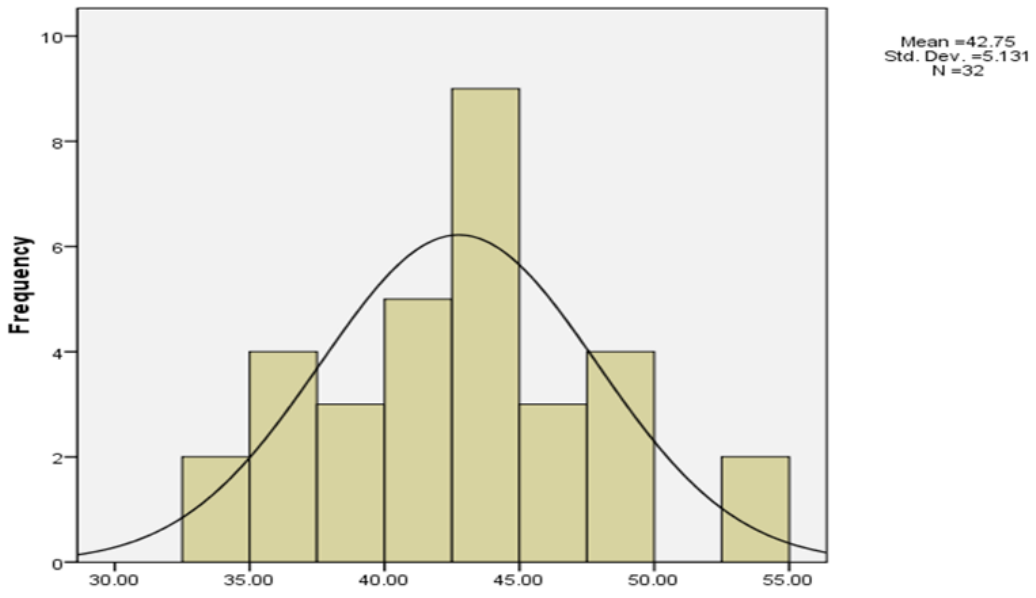

Diagram 1. Histogram of examining the assumption of error term normality

Table 3 compares the performance of the experimental and control (sham) groups. The results revealed no significant difference between the performance of the two groups in the pre-test (P>0.05). However, a statistically significant difference was observed between the two groups in the post-test (P<0.05). Therefore, the anodal tDCS of the right DLPFC improved working memory function among MS patients.

4. Discussion

This study aimed to investigate the effect of tDCS on working memory of patients with relapsing-remitting MS. The results indicated that anodal stimulation of the R-DLPFC improved working memory among MS patients. Consistent with our results, Hulst et al. examined working memory of MS patients. In this study, R-DLPFC was subjected to high-frequency magnetic stimulation, and the brain activity and connectivity in that area were simultaneously assessed by FMRI. The results showed N-back task accuracy was improved after magnetic stimulation of the mentioned cortex. Moreover, FMRI findings revealed that the increased activity associated with R-DLPFC task before stimulation disappeared in MS patients compared to the control group after applying magnetic stimulation. Task-related functional connectivity between the R-DLPFC, right caudate nucleus and bilateral cingulate cortex increased after stimulation [13]. In line with our study, Giglia et al. indicated the effectiveness of anodal stimulation of the R-DLPFC on spatial working memory of the experimental group compared to the control group [23]. Consistent with our work, Hamidi et al. reported the effectiveness of magnetic stimulation of the R-DLPFC on spatial working memory compared to the L-DLPFC. The results showed the delayed-recognition task accuracy increased [24]. Also, the study of Grigorescu et al. was in line with our results. They investigated the effect of electrical stimulation of the bilateral prefrontal cortex on cognitive functions including information processing speed, working memory and attention among MS patients. The anode and cathode were placed on the L-DLPFC (F3) and R-DLPFC (F4), respectively, and excited at 2 mA for 20 min. Interestingly, the task accuracy of working memory was improved in the sham group compared to the experimental group. It was concluded that cathodal stimulation of the R-DLPFC may have led to working memory impairment [25]. Another study revealed the right DLPFC played a key role in dealing with cross-domain motor interference for SWM. Moreover, the anodal tDCS over the right DLPFC enhanced SWM performance, particularly when task difficulty required more complex cognitive manipulations [26].

The mechanism of action of tDCS, despite its widespread use, is still not fully understood. However, researchers have suggested mechanisms such as changes in ion channel function, activation of NMDA receptors and reduction of free GABA in cortical areas affected by anodal or cathodal stimulation, which in turn lead to the enhanced glutamatergic synaptic processes [27]. The Increased Long-Term Potentiation (LTP) via Brain-Derived Neurotrophic Factor (BDNF) is another mechanism of tDCS [28]. BDNF signaling by TrKB receptor directly interacts with synaptic plasticity mechanisms based on NMDA glutamate receptors [29]. A human study focusing on the combined application of pharmacology and fMRI revealed NMDA receptor blockade reduced DLPFC activation and network connectivity and, consequently, impaired SWM performance [30]. Accordingly, Glutamate receptors are critical for synaptic plasticity, and BDNF facilitates glutamatergic synaptic transmission [20]. Therefore, BDNF is directly involved in the repair of the central nervous system and cognitive functions [31].

5. Conclusion

As pointed out in Introduction, cognitive deficits associated with MS are due to white and gray matter demyelination and degradation. It seems that the central nervous system can be repaired and, consequently, the damaged cognitive functions can be improved by tDCS through strengthening synaptic connections and brain networks.

Ethical Considerations

Compliance with ethical guidelines

The ethics code was obtained from Ethics Committee of Iran University of Medical Sciences with reference no. IR.IUMS.REC1398.1146.

Funding

The paper was extracted from the PhD. thesis or extracted from a research project of the first author, Department of Cognitive Neuroscience, Institute for Cognitive Science Studies, Tehran, Iran.

Author's contributions

Conceptualization and Supervision: Mohammad Nasehi, Mehdi Tehranidoost, Mohammad Hossein Harirchian and Mohammad Reza Zarrindast; Methodology: Hamid Alipour; Investigation, Writing – original draft, and Writing – review & editing: All authors;

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

We would like to sincerely thank all those who cooperated with us in conducting this research. Special thanks to Dr. Solmaz Khalifeh for her generous help. We would also like to thank the Cognitive Sciences and Technologies Council for funding this research.

References

[1] Yahia M, Al-Harbi TM, Bashir S. The potential rehabilitation role of transcranial direct current stimulation (tDCS) in multiple sclerosis. Neurol Psychiatry Brain Res. 2018; 30:9-11. [DOI:10.1016/j.npbr.2018.04.003]

[2] Milo R, Kahana E. Multiple sclerosis: Geoepidemiology, genetics and the environment. Autoimmun Rev. 2010; 9(5):A387-94. [DOI:10.1016/j.autrev.2009.11.010] [PMID]

[3] Baecher-Allan C, Kaskow BJ, Weiner HL. Multiple sclerosis: Mechanisms and immunotherapy. Neuron. 2018; 97(4):742-68. [DOI:10.1016/j.neuron.2018.01.021] [PMID]

[4] Rao SM. Neuropsychology of multiple sclerosis. Curr Opin Neurol. 1995; 8(3):216-20. [DOI:10.1097/00019052-199506000-00010] [PMID]

[5] Manca R, Sharrack B, Paling D, Wilkinson ID, Venneri A. Brain connectivity and cognitive processing speed in multiple sclerosis: A systematic review. J Neurol Sci. 2018; 388:115-27. [DOI:10.1016/j.jns.2018.03.003] [PMID]

[6] Trenova AG, Slavov GS, Manova MG, Aksentieva JB, Miteva LD, Stanilova SA. Cognitive impairment in multiple sclerosis. Folia Med (Plovdiv). 2016; 58(3):157-63. [DOI:10.1515/folmed-2016-0029] [PMID]

[7] D'Esposito M, Onishi K, Thompson H, Robinson K, Armstrong C, Grossman M. Working memory impairments in multiple sclerosis: Evidence from a dual-task paradigm. Neuropsychology. 1996; 10(1):51-6. [DOI:10.1037/0894-4105.10.1.51]

[8] Feil J, Zangen A. Brain stimulation in the study and treatment of addiction. Neurosci Biobehav Rev. 2010; 34(4):559-74. [DOI:10.1016/j.neubiorev.2009.11.006] [PMID]

[9] Brunoni AR, Fregni F, Pagano RL. Translational research in transcranial direct current stimulation (tDCS): A systematic review of studies in animals. Rev Neurosci. 2011; 22(4):471-81. [DOI:10.1515/rns.2011.042] [PMID]

[10] Wang M, Yang Y, Wang CJ, Gamo NJ, Jin LE, Mazer JA, et al. NMDA receptors subserve persistent neuronal firing during working memory in dorsolateral prefrontal cortex. Neuron. 2013; 77(4):736-49. [DOI:10.1016/j.neuron.2012.12.032] [PMID] [PMCID]

[11] Monte-Silva K, Kuo MF, Hessenthaler S, Fresnoza S, Liebetanz D, Paulus W, et al. Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. Brain Stimul. 2013; 6(3):424-32. [DOI:10.1016/j.brs.2012.04.011] [PMID]

[12] Nitsche MA, Seeber A, Frommann K, Klein CC, Rochford C, Nitsche MS, et al. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. J Physiol. 2005; 568(Pt 1):291-303. [DOI:10.1113/jphysiol.2005.092429] [PMID] [PMCID]

[13] Hulst HE, Goldschmidt T, Nitsche MA, de Wit SJ, van den Heuvel OA, Barkhof F, et al. rTMS affects working memory performance, brain activation and functional connectivity in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry. 2017; 88(5):386-94. [DOI:10.1136/jnnp-2016-314224] [PMID]

[14] Mattioli F, Stampatori C, Bellomi F, Danni M, Compagnucci L, Uccelli A, et al. A RCT comparing specific intensive cognitive training to aspecific psychological intervention in RRMS: The SMICT study. Front Neurol. 2015; 5:278. [DOI:10.3389/fneur.2014.00278] [PMID] [PMCID]

[15] Mori F, Codecà C, Kusayanagi H, Monteleone F, Buttari F, Fiore S, et al. Effects of anodal transcranial direct current stimulation on chronic neuropathic pain in patients with multiple sclerosis. J Pain. 2010; 11(5):436-42.[DOI:10.1016/j.jpain.2009.08.011] [PMID]

[16] Chalah MA, Riachi N, Ahdab R, Mhalla A, Abdellaoui M, Créange A, et al. Effects of left DLPFC versus right PPC tDCS on multiple sclerosis fatigue. J Neurol Sci. 2017; 372:131-7. [DOI:10.1016/j.jns.2016.11.015] [PMID]

[17] Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology. 1983; 33(11):1444-52. [DOI:10.1212/WNL.33.11.1444] [PMID]

[18] KIRCHNER WK. Age differences in short-term retention of rapidly changing information. J Exp Psychol. 1958; 55(4):352-8. [DOI:10.1037/h0043688] [PMID]

[19] McAfoose J, Baune BT. Exploring visual-spatial working memory: A critical review of concepts and models. Neuropsychol Rev. 2009; 19(1):130-42. [DOI:10.1007/s11065-008-9063-0] [PMID]

[20] Toepper M, Gebhardt H, Beblo T, Thomas C, Driessen M, Bischoff M, et al. Functional correlates of distractor suppression during spatial working memory encoding. Neuroscience. 2010; 165(4):1244-53. [DOI:10.1016/j.neuroscience.2009.11.019] [PMID]

[21] Dehn MJ. Working memory and academic learning: Assessment and intervention. New Jersey: John Wiley & Sons; 2011. https://books.google.nl/books?id=C2uZNzgo29QC&printsec=frontcover&dq=Dehn+MJ.+Working+memory+and+academic+learning:+Assessment+and+intervention.+Joh

n+Wiley+%26+Sons;+2011+Jan+4.&hl=en&sa=X&ved=2ahUKEwjHl52Mzbb2AhXB16QKHdheAisQ6AF6BAgFEAI#v=onepage&q&f=false

[22] Kane MJ, Conway ARA, Miura TK, Colflesh GJH. Working memory, attention control, and the N-back task: A question of construct validity. J Exp Psychol Learn Mem Cogn. 2007; 33(3):615-22. [DOI:10.1037/0278-7393.33.3.615] [PMID]

[23] Giglia G, Brighina F, Rizzo S, Puma A, Indovino S, Maccora S, et al. Anodal transcranial direct current stimulation of the right dorsolateral prefrontal cortex enhances memory-guided responses in a visuospatial working memory task. Funct Neurol. 2014; 29(3):189-93. [PMID]

[24] Hamidi M, Tononi G, Postle BR. Evaluating the role of prefrontal and parietal cortices in memory-guided response with repetitive transcranial magnetic stimulation. Neuropsychologia. 2009; 47(2):295-302. [DOI:10.1016/j.neuropsychologia.2008.08.026] [PMID] [PMCID]

[25] Grigorescu C, Chalah MA, Lefaucheur JP, Kümpfel T, Padberg F, Ayache SS, et al. Effects of transcranial direct current stimulation on information processing speed, working memory, attention and social cognition in multiple sclerosis. Front Neurol. 2020; 11:545377. [DOI:10.3389/fneur.2020.545377] [PMID] [PMCID]

[26] Wu YJ, Tseng P, Chang CF, Pai MC, Hsu KS, Lin CC, et al. Modulating the interference effect on spatial working memory by applying transcranial direct current stimulation over the right dorsolateral prefrontal cortex. Brain Cogn. 2014; 91:87-94. [DOI:10.1016/j.bandc.2014.09.002] [PMID]

[27] Nitsche MA, Kuo MF, Paulus W, Antal A. Transcranial direct current stimulation: Protocols and physiological mechanisms of action. In: Knotkova H, Rasche D, editors. Textbook of neuromodulation. New York: Springer; 2015. NY. [DOI:10.1007/978-1-4939-1408-1_9]

[28] Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: Potential implications for motor learning. Neuron. 2010; 66(2):198-204. DOI:10.1016/j.neuron.2010.03.035] [PMID] [PMCID]

[29] Weinstock-Guttman B, Benedict RH, Tamaño-Blanco M, Ramasamy DP, Stosic M, Polito J, et al. The rs2030324 SNP of brain-derived neurotrophic factor (BDNF) is associated with visual cognitive processing in multiple sclerosis. Pathophysiology. 2011; 18(1):43-52. [DOI:10.1016/j.pathophys.2010.04.005] [PMID]

[30] Driesen NR, McCarthy G, Bhagwagar Z, Bloch MH, Calhoun VD, D'Souza DC, et al. The impact of NMDA receptor blockade on human working memory-related prefrontal function and connectivity. Neuropsychopharmacology. 2013; 38(13):2613-22. [DOI:10.1038/npp.2013.170] [PMID] [PMCID]

[31] Cunha C, Brambilla R, Thomas KL. A simple role for BDNF in learning and memory? Front Mol Neurosci. 2010; 3:1. [DOI:10.3389/neuro.02.001.2010] [PMID] [PMCID]