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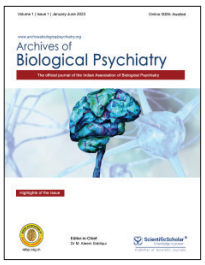

Original Article *Neurophysiology*

Working memory enhancement with transcranial direct current stimulation

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ABSTRACT

Objectives: Transcranial direct current stimulation (tDCS) has been found to enhance working memory (WM) in healthy and diseased populations. Studies have reported the potential role of ethnicity and race in the outcome of neuromodulation. This study aims to evaluate the effects of tDCS on WM performance and its tolerability in healthy volunteers from the Indian population.

Material and Methods: This is an open-label pilot study of 21 healthy volunteers, assessed on the n-Back task before and after anodal stimulation of the left dorsolateral prefrontal cortex using tDCS. The primary measure was the change in the two-back performance (accuracy and reaction time). Furthermore, in this study, the frequency of adverse effects was determined using a questionnaire after each session of tDCS.

Results: The Wilcoxon signed-ranked test showed a significant decrease in the reaction time in the two-back task ($z = 2.02$; $P = 0.04$). The commonly reported adverse effects were itching (52.4%), burning sensation (71.4), tingling (4.8%), skin redness (38.01%), and skin lesions (6.66%). Most of the side effects were observed to be mild in intensity.

Conclusion: This study shows that tDCS is a well-tolerated and safe non-invasive brain stimulation technique that can potentially enhance cognitive performance in healthy individuals.

Keywords: N-Back test, Neuroplasticity, Neuroenhancement, Non-invasive brain stimulation, Neuromodulation

INTRODUCTION

The capacity of holding, processing, comprehending, manipulating, and even simulating information distinguishes homo sapiens from other primates.[1,2] One of the primary regions of the human brain responsible for catering to this information processing and execution is the prefrontal cortex (PFC).[3,4] One of the fundamental processes that enable a person to retain and respond to or act on immediate memory traces falls under the realm of working memory (WM).[2] Given the merits of this cognitive process, which facilitates updating and responding to environmental cues, WM has been widely examined across studies.[5]

The dorsolateral PFC (DLPFC) is one of the substrates of WM function.[6] There is empirical evidence suggesting the role of left DLPFC (L-DLPFC) in the effective functioning of cognitive domains.[7] Two potential research methods have been employed to examine the role of L-DLPFC

in WM functions. First, it is through the examination of neural or electrophysiological correlations of WM performance in neurotypical individuals and in those with WM deficits secondary to neuropsychiatric disorders.[8] Second, it is through focally and locally addressing the left dorsolateral prefrontal cortex (L-DLPFC) aberrance through techniques like region-of-interest specific neuromodulation and evaluating the enhancement in the WM functions from baseline.[9] The second approach would be able to inform more robustly on the causative role of L-DLPFC in the pathophysiology, in contrast to the associative role of the first approach.

In recent years, neuromodulation interventions have gained much attention.[10,11] One of the neuromodulation techniques is transcranial direct current stimulation (tDCS), which is based on the principle that when weak-intensity electric currents are targeted at specific areas of the scalp, they cause polarity-based underlying cortical activation.[12] However, there is a significant heterogeneity in the effects, and substantial evidence implicates ethnic differences in cognitive performance.[13-15] In addition, empirical evidence suggests that factors such as varying skull thickness, hair texture, and brain size may have a bearing on the response to tDCS.[16] As many of these factors are influenced by ethnicities and racial background,[16,17] it becomes imperative to study the effects of this technique on diverse populations, observe for consistency in its outcome, and add to the larger pool of tDCS research.[18] Despite empirical evidence in support of the therapeutic role of tDCS in patients, there is a dearth of knowledge on the investigative effects of tDCS on healthy Indian subjects.

Although various tasks have been used to evaluate WM[19,20] the N-Back task seems to have more ecological validity with better functional implications.[2] One of the experimental protocols looking at the effects of anodal stimulation targeted at the L-DLPFC has been repeatedly proven to enhance the WM functions as tested by cognitive task performance before and immediately after the interventional technique.[1,21]

This was an open-ended study conducted based on the availability of healthy volunteers. The primary aim of the study is to evaluate the applicability of tDCS in enhancing WM task (two-back) performance in healthy Indian volunteers. The secondary aim of the study is to ascertain the tolerability of this technique in this population.

MATERIAL AND METHODS

Healthy volunteers

A total of 21 healthy volunteers between the ages of 18 and 45 years were recruited through convenience sampling. The sample was sufficient to identify any difference in n-back performance with an effect size of Cohen's d of 0.8, at an alpha error of 0.025 (correcting for two outcome measures – reaction time and accuracy of 2-back) with a power of 90%. Subjects with a current or past history of any neurological or psychiatric disorder, pregnancy, developmental disorders, presence of implants, seizures, and family history of any psychiatric disorder (including dementia) in first-degree relatives and use of any psychotropic medications/drugs that are likely to interact with tDCS effects were excluded from the study. The study was conducted after a detailed description of the procedure was given to the subjects, along with a video demonstration, to obtain written informed consent. The study was approved by the Institute's Ethics Committee (No. NIMHANS/EC [BEH.SC.DIV.] 12th MEETING/2018, dated April 24, 2018).

Study protocol

Assessments

All the subjects performed the computerized numerical N-Back cognitive paradigm.[22,23] This was conducted before the start of the tDCS session and after the termination of the tDCS session.

N-Back task

This task comprised three components, zero-back, one-back, and two-back tasks, and was presented in e-prime© stimulation presentation software (v3.0, Psychology Software Tools). The subjects would be presented with a pseudo-randomly arranged sequence of stimuli (one of the digits from 0 to 9 in each trial) in a block. In the zero-back task, the subject had to press the "Yes" button whenever "0" was presented as a stimulus and then had to indicate "No." In one back, the target stimuli were the one which is the same as (repetition of) the one preceding it. In two-back, the patient had to press the "Yes" button if the stimulus (digit) was a repetition of the digit presented two trials earlier.[24] Two separate versions of the task were used for every subject before and after intervention with tDCS in a counterbalanced order. In summary, the N-back task was administered immediately before the tDCS and repeated immediately after. The tDCS was administered for 20 min in a single session. Accuracy and reaction time were calculated for each type of trial and used for further analysis.

Tolerance to tDCS

A structured adverse-effect questionnaire with a severity rating from 1 to 5 and likely attribution to a tDCS rating of 1–4 was used to evaluate the tolerance of the device.[25]

tDCS procedure

tDCS was delivered using an indigenously developed standard transcranial electric current device (WISER tES

Neuromodulator). Rigorous guidelines were followed in the administration of tDCS to maintain safety and consistency in the procedure.[26] The cathode was placed over the right orbitofrontal cortex (r-OFC) with electrode axes horizontally oriented. The anode was placed over the L-DLPFC with vertically oriented electrode axes. L-DLPFC was identified using the Beam F3 software (http://clinicalresearcher.org/F3/calculate.php). r-OFC was determined by locating the area inferior to FP2 and F8 using the universal 10/10 electroencephalogram (EEG) electrode placement system. Single session tDCS was administered to each participant for 20 mins, with 2 mA of current using 5 × 7 cm electrodes.

Statistical tests

The accuracy and reaction time values were calculated using MATLAB© (ver r2012b The MathWorks, Inc). Wilcoxon signed-rank test was applied to compare the changes in N-Back performance with tDCS using IBM® Statistical Package for the Social Sciences® v23.

RESULTS

The participants had a mean age of 29.61 years (Standard deviation [SD]: 3.87), with 9 females and 12 males. The mean years of education was 18.42 years (SD = 2.83). There were no dropouts in the study.

Tolerability

All patients completed a single session of tDCS without any major adverse effects. Among all the side effects, burning sensation, itching sensations, and skin redness were commonly noted, all at mild intensity and none requiring discontinuation due to intolerance. Neither of the subjects reported intra-session or post-session neck pain, scalp pain, sleepiness, nor any phosphenes [Table 1].

Most of the subjects reported the side effects in the mild intensity category. Exceptions to this were headache (n = 3) that was reported in moderate and severe and very severe intensity; trouble in the concentration (n = 2) after tDCS was noted as moderate and severe by two subjects; discomfort (n = 3) was majorly noted to be of moderate intensity [Table 1].

Effect on cognitive task

Wilcoxon signed-rank test showed a significant decrease in the reaction time, specifically in two-back performance across the subjects (z = 2.016, P = 0.04, median = 735.59, inter-quartile range = 686.56 – 936.02). No significant changes were observed in zero-back and one-back performance for both response time and accuracy [Table 2 and Figure 1].

Table 1: Incidence of tDCS-related adverse effects.

Side effects	Single sessions (n=21) (%)
Headache	3 (14.3)
Tingling	1 (4.8)
Itching	11 (52.4)
Burning sensation	15 (71.4)
Skin redness	8 (38.01)
Trouble concentration	2 (9.6)
Acute mood changes	1 (4.8)
Skin lesion	1 (4.8)
Disturbed visual perception	2 (9.6)
Discomfort	3 (14.3)
Giddiness	3 (14.3)

tDCS: Transcranial direct current stimulation

DISCUSSION

The adaptive effect of tDCS on WM in Indian participants was established through this pilot study. This observation supports the contention that tDCS is tolerable. Interestingly, even the tolerability among the healthy Indian population is congruent with data from other studies and populations.[10,25] It is imperative to mention here that the side effects reported by the healthy volunteers in this study were based on a single session of tDCS, who would have been more alert, receptive, and vocal toward the experience of the side effects.

WM performance with N-back

The two-back component in the n-back assesses the WM of the individual, whereas zero-back and one-back primarily evaluate the visual processing and attentional components of executive functions. There was a significant improvement in the average reaction time in two back after a single session of tDCS. This finding is in alignment with other studies.[27] that have reported that anodal DLPFC stimulation with tDCS plays a role in the enhancement of WM tasks. As the accuracy at baseline was more than 90% in almost all the participants, a ceiling effect would have set in, and further improvement could not be evaluated. Furthermore, there is a limitation to the effect of a single session of tDCS, and to examine accuracy-related effects, it may be better to study cognitive performance with multisession tDCS.

Our, results are in alignment with previous studies[27,28] since there is a degree of similarity in the experimental design; however, a contradiction to some other studies[21] where task accuracy has been found to improve but not the response time. However, it is worth mentioning here that there are several aspects related to other studies that differ remarkably from our study. Primarily, the study

Table 2: Comparison of N-back performance before and after tDCS.

	Baseline WM measures		Post-tDCS WM measures		z (df=1.20)	*P*-values
	Median	IQR	Median	IQR		
Zero-back RT (ms)	512.76	493.36–589.55	534.77	486.7–693.57	1.344	0.179
One-back RT (ms)	754.83	586.56–852.48	694.66	623.08–812.70	0.597	0.550
Two-back RT (ms)	735.59	686.56–936.02	727.66	623.45–954.00	**2.016**	**0.044** *
Zero-back accuracy	95.55%	93.33–97.70%	95.55%	93.21–97.77%	1.32	0.187
One-back accuracy	93.95%	90.42–100%	95.23%	95.16–97.61%	0.967	0.333
Two-back accuracy	92.30%	88.43–97.43%	93.09%	89.73–97.43%	1.422	0.155

IQR: Inter-quartile range, tDCS: Transcranial direct current stimulation, WM: Working memory, df: Degrees of freedom, RT: Reaction time, ms: Milliseconds, *: P < 0.05

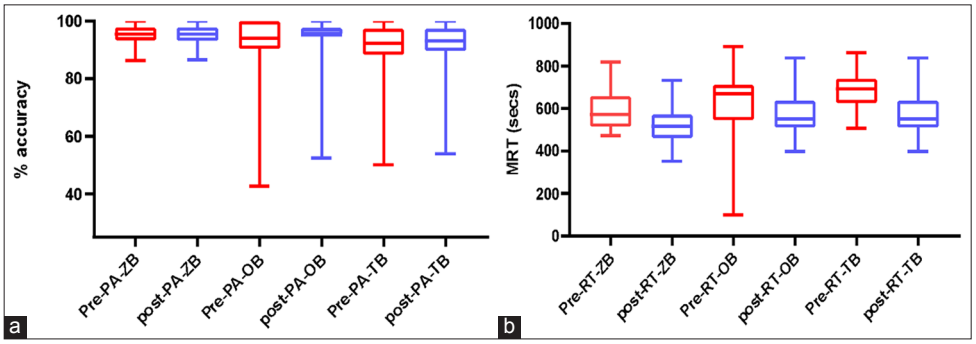

Figure 1: (a) Bar graph depicting the percentage accuracy for zero back (ZB), one back (OB), and two back (TB) at baseline (Pre_PA) and post-transcranial direct current stimulation (tDCS) (Post_PA). (b) Bar graph depicting the mean reaction time (MRT) for ZB, OB, and TB at baseline (Pre_PA) and post tDCS (Post_PA). PA: Performance accuracy

design of our experiment involved tDCS administration during resting state and n-back tested before and after the session, while few studies[21] evaluated the online effects by evaluating the performance during the tDCS session. Since the immediate effect of tDCS is proposed to occur through mechanisms such as axonal modulation and synaptic doctrine.[29] Our interest lies in the post-session effects rather than intrasession effects. These effects may have better translational applications.

The most noteworthy strength of the present study is the data in support of the utility of tDCS in the Indian population. In this study, tDCS has been put to evaluation under the variable functions in addition to providing sufficient data on its tolerability and safety. Although a small sample size limits the study, the preliminary findings are encouraging and underline the need for larger systematic studies. However, one major limitation of this experiment is that a cognitive task precedes and succeeds an intervention like tDCS within a short period, thereby introducing practice effects. To minimize such effects, the study implemented different versions of n-back before and after tDCS. Furthermore, perhaps conducting a study with a larger sample size, with a study design involving more tDCS sessions and exploring the same in a blinded controlled trial, would be better evidence in the application of tDCS for enhancing WM functions in the healthy Indian population.

A major limitation of this study is the small sample size. Nonetheless, it has added valuable evidence regarding the effects of tDCS on cognitive performance and its minimal side effects, which may encourage greater participation by healthy volunteers in the future. Another limitation is the absence of a controlled trial, but the findings from this study could be used to inform future controlled trials exploring the effects of tDCS on healthy volunteers. In addition, since most subjects were recruited using a convenience sampling technique within the campus, it was challenging to assess the influence of years of education on cognitive performance. However, as each subject was observed in a pre-post tDCS design, it allowed for a straightforward interpretation of tDCS effects on the N-back task. The study acknowledges the lack of a sham component but sets up a platform for exploration of the same in a controlled design in the future.

Overall, this pilot study has been able to successfully comment on the usefulness and safety of tDCS in the healthy population. This study has also given evidence of the investigative potential of this neuromodulation technique in examining the role of L-DLPFC in WM functions. Although the results of

this study need to be tested in a more controlled design and the long-term effects of tDCS on WM need to be explored, it is reasonable to say that tDCS is a safe technique that has a promising role in addressing cognitive processes in the Indian population. In light of the evidence of enhancement of WM response time in healthy volunteers, and its tolerability and safety, tDCS may be studied more systematically.

CONCLUSION

The observations made in this study provide a promising platform for the application of tDCS in cognitive enhancement. Further, this study demonstrates the possible use of tDCS in the Indian population for targeting cognitive deficits, especially in disorders such as depression and schizophrenia, where cognitive deficits are one of the many debilitating symptoms. However, the use of tDCS must be exercised with caution since there is a possibility of abuse in healthy individuals. With more optimized protocols, individualized neuro-targeting strategies tDCS can suffice as a promising tool in the realms of non-invasive brain stimulation for both investigative and therapeutic intervention.

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Author contributions

GVS, MK, JCN, VSS, and VS conceptualized the study. GVS and JCN acquired the funding. RP, SS, VHT, and SN were involved in the assessment and tDCS administration. RP and VSS prepared the first draft. All authors reviewed and contributed to the final draft of the manuscript.

Ethical approval: The research/study was approved by the Institutional Review Board at NIMHANS, Behavioral Sciences, number NIMHANS/EC(BEH.SC.DIV.) 12th MEETING/2018, dated 24th April 2018.

Declaration of patient consent: The authors certify that they have obtained all appropriate informed consent from the participants.

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